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**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 724.01/A1

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

**Support:** NINDS NS29709 (JLN)

**Title:** T-type calcium channel bursting in thalamic association pathways precedes sensory pathways and can be activated by GABAergic input during early postnatal development

**Authors: *Q. MIAO**[1], J. L. NOEBELS[2]
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**Abstract:** Transient-type low-voltage activated calcium channels (T-channels) regulate the intrinsic excitability of thalamic cells and facilitate the genesis of rebound burst firing which enable thalamocortical oscillations and contribute to the modulation of brain states of awareness. The thalamus takes part in sensory, motor and cognitive functions by transmitting information to the cortex via numerous distinct nuclei. These nuclei are divided into two different categories: first order and higher order relays. First order nuclei receive driver input from the periphery or a subcortical source, while high-order nuclei mainly receive descending inputs from the cortex. Precise regulation of T channels is important for healthy thalamocortical processes since abnormal function of T-channels has been implicated in pathological conditions, including epilepsy, neuropathic pain, and sleep disorders. We examined whether different thalamic nuclei develop T-channel expression simultaneously during early development, or whether bursting in these pathways show distinctive stages of maturation? We performed whole-cell recordings in the developing mouse thalamus (postnatal day 3 to 35). We found that across subregions of the lateral thalamus, there is a high-to-low gradient from dorsal to ventral nuclei in the expression of T-channels. Specifically, all laterodorsal thalamic (LD) neurons projecting to associative retrosplenial cortex show a distinctively high expression of T-currents which enable them to fire low-threshold and rebound spikes in as early as one week old C57BL/6 mice. These spikes could be blocked by a T-channel specific blocker, Z944. At this age, a small fraction of neurons in other higher-order nuclei including lateral posterior nucleus (LP), posterior complex (PO) and the dorsal part of medial geniculate complex (dMG) of the thalamus, can fire low-threshold and rebound spikes. In sharp contrast, similar low-threshold and rebound spikes in first-order primary sensory thalamic relay neurons, including visual (lateral geniculate nucleus, LGN), somatosensory (ventral posteromedial nucleus, VPM), and auditory (ventral part of medial geniculate complex, vMG) neurons appeared nearly one week later. Functionally, our preliminary data showed that optogenetic and electrical activations of GABAergic circuit could elicit burst spiking in LD neurons with cell-attached recording. Together, these results indicate

that higher-order thalamic relay neurons utilize firing supported by T-channels earlier than those in the primary sensory pathway and could be recruited by GABAergic inputs.

**Disclosures: Q. Miao:** None. **J.L. Noebels:** None.

**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 724.02/A2

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

**Support:** NHMRC Project Grant APP1099709 2016-2019
NHMRC John Cade Fellowship APP1056929 2014-2018
Rebecca L Cooper Medical Research Grant 2017

**Title:** Rapid modulation of L-type voltage-gated calcium channels during brain development by vitamin D

**Authors: *H. M. GOOCH**, X. CUI, V. ANGGONO, T. H. BURNE, D. EYLES, P. SAH, J. MCGRATH
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**Abstract:** The secosteroid vitamin D [1,25$(OH)_2D_3$] drives ***genomic*** changes in the body via classical steroid hormone pathways. While 1,25$(OH)_2D_3$ is also known to drive ***non-genomic*** effects in some peripheral tissues, most notably the rapid modulation of L-type voltage-gated calcium channels (L-VGCC), its non-genomic effects within the brain remain unexplored. Since accumulating evidence links common L-VGCC genetic variants with neuropsychiatric disorders, and developmental vitamin D deficiency is an established risk factor for schizophrenia, we are investigating the non-genomic effects of 1,25$(OH)_2D_3$ on L-VGCCs in the developing brain. Using wide-field calcium imaging and electrophysiology in the prefrontal cortex (PFC), we found that physiological concentrations of 1,25$(OH)_2D_3$ (0.1 nM) rapidly enhanced L-VGCC activity in a subset of PFC neurons, termed ***vitamin D responsive neurons*** (***I-VDRNs***). 1,25$(OH)_2D_3$ increased activity-dependent somatic cytosolic $Ca^{2+}$ levels by as much as 250% in I-VDRN in both intact (av αF/F increase 29 ± 4%; n=110/1245 cells, 8.8%), and synaptically blocked imaging preparations (av αF/F increase 24 ± 2%; n=53/720 cells, 7.4%). Consistent with this, nucleated patch recordings revealed 1,25$(OH)_2D_3$ enhanced high voltage-activated (HVA) $Ca^{2+}$ channel currents (33 ± 5%, n=5) in a subset of layer 2/3 PFC cells (n=5/21, 24%), suggesting that $Ca^{2+}$ influx through VGCCs contributed to the increased cytosolic $Ca^{2+}$ levels observed during imaging. Further, pre-incubation of imaged slices in the L-VGCC channel blocker nifedipine (10 μM) almost entirely blocked the 1,25$(OH)_2D_3$-induced increase in cytosolic $Ca^{2+}$ levels (av αF/F increase 11 ± 1%; n=8/675 cells, 1.2%), demonstrating that

$1,25(OH)_2D_3$ enhanced L-VGCC activity in a subset of PFC neurons during development. Interestingly, wide-field $Ca^{2+}$ imaging also revealed a second subset of PFC neurons that showed decreases in activity-dependent cytosolic $Ca^{2+}$ levels following bath application of $1,25(OH)_2D_3$ (av αF/F -29 ± 3%; n=38/426 cells, 8.9%), termed ***D-VDRNs***. This effect was not dependent on L-VGCC modulation (av αF/F -22 ± 2%; n=59/675, 8.7%), however pre-incubation with synaptic blockers significantly reduced the proportion of responsive D-VDRN neurons (av αF/F -26 ± 4; n=26/677 cells, 3.6%), suggesting network effects beyond vitamin D responsive neurons. Since L-VGCC activity is required for developmentally critical processes such as neuronal maturation and gene transcription, these findings suggest a significant role for vitamin D during healthy brain development, and suggests potential consequences for developmental vitamin D deficiency.

**Disclosures: H.M. Gooch:** None. **X. Cui:** None. **V. Anggono:** None. **T.H. Burne:** None. **D. Eyles:** None. **P. Sah:** None. **J. McGrath:** None.

**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 724.03/A3

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

**Support:** JPSP KAKENHI JP17K07076
JPSP KAKENHI JP15K15015
JPSP KAKENHI JP25293043
JPSP KAKENHI JP17H04014
Takeda Science Foundation

**Title:** Axonal branches of layer 2/3 dual projection neurons targeting an ipsilateral distant area extend more rapidly than locally targeting branches in mouse neocortex

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**Abstract:** Direct connections between different cortical areas have been shown to be important for sensorimotor integration. Developmental processes of these connections and their underlying mechanisms, however, have not been fully understood. By using a subtype-specific promoter and our new vector for enhancing sparse labeling of cortical neurons combined with tissue clearing of flat-mounted cortices, we visualized a population of layer 2/3 (L2/3) neurons in the mouse primary somatosensory area (S1) that had axons projecting to the contralateral hemisphere as well as to the ipsilateral hemisphere. We analyzed the processes of their axon projections and

found that these neurons first extended the main axonal shaft projecting to the contralateral hemisphere, already crossing the midline before birth. In contrast, collateral branches projecting to the ipsilateral hemisphere emerged around postnatal day 3 at the level of layer 5. Only one among these collateral branches reached the distant areas, such as the primary motor area (M1) and the secondary somatosensory area (S2). Temporal analysis of the branch length suggested that far-reaching branches grew at a higher rate than those projecting to the local targets. This observation raises the possibility that a branch might be selected at a very early stage, if not at the timing of the budding, to target an area distant from the original area of the soma.

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**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 724.04/A4

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

**Title:** Physiological and pathological maturation of cortical neural networks

**Authors: *S. DOMINGUEZ**[1], N. GHANI[1], G. POUCHELON[3], S. COLOMBO[2], M. BOLAND[1], V. LETTS[1], S. PETRI[1], W. N. FRANKEL[5], D. GOLDSTEIN[5], G. J. FISHELL[4], G. BUZSAKI[6], D. KHODAGHOLY[1], J. GELINAS[1]
[2]Inst. for Genomic Med., [1]Columbia Univ., New York, NY; [4]Neurobio., [3]Harvard Med. Sch., Boston, MA; [5]Columbia Univ. Med. Ctr., New York, NY; [6]New York University, Sch. of Med., New York, NY

**Abstract:** The brain's ability to support cognitive processes, such as perception, attention, and memory, represents a critical evolutionary advancement. Neural networks underlying these processes mature over the course of development, and are influenced by ongoing synaptic activity. Modulation of this synaptic activity early in development has the potential to disrupt normal maturation, but the underlying mechanisms of this impairment remain unclear. Here, we examine the properties of cortical neural networks during physiologic development compared to pharmacologic and genetic conditions that alter the excitatory-inhibitory balance. We perform in vivo neurophysiological recordings from mouse pups aged postnatal day 5 to 14 that are cycling through natural waking and sleep epochs. With the use of the NeuroGrid, a high spatiotemporal resolution surface array, we simultaneously record from multiple cortical regions as determined by post-mortem immunohistochemical analysis. We study the effects of acute changes to GABAergic neurotransmission using pharmacologic agonists and antagonists, as well as chronic alteration of excitation-inhibition in a mouse model of pediatric epileptic encephalopathy (KCNT1). Although neural networks exhibit some common responses to these neuromodulatory alterations, expression of oscillatory activity is modified by postnatal age and prior synaptic

experience. These data allow us to better understand the neurophysiologic patterns that characterize normal maturation, and how they can be impacted by aberrant synaptic activity in diseases such as epilepsy.

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**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 724.05/A5

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

**Support:** EMBO Long-term Fellowship
Postdoc.Mobility Fellowship, Swiss National Fundation
NIH R01 NS081297

**Title:** Postsynaptic mGluR signaling controls the development of somatostatin interneurons

**Authors: *G. POUCHELON**[1], E. FISHER[1], R. MACHOLD[2], G. FISHELL[1]
[1]Harvard Med. Sch., Boston, MA; [2]New York Univ., New York, NY

**Abstract:** Our internal representation of the outside world is created within the neocortex. Inhibitory interneurons (INs) sculpt cortical activity and are thus critical in shaping these representations. During development, the inhibitory circuits that allow for the emergence of cortical function are assembled early during the postnatal period. Activity has been increasingly associated with these developmental processes, however the role and the type of activity in IN development remain largely unexplored.
Although Parvalbumin (PV) and Somatostatin (SST)-INs both arise from the same embryonic structure, the medial ganglionic eminence (MGE), they differentiate into two very distinct IN types within the cortex. It seems likely that the afferent activity impinging upon these distinct cells is central to their integration into cortical circuitry. Recent single-cell RNA-seq analyses has revealed that each interneuron subtype expresses a specific set of neurotransmitter receptors, which are potential candidates for activity-dependent controls of their development.
Using in vivo monosynaptic rabies tracing at the postnatal developmental stage when INs settle in their cortical position, we discovered that the earliest presynaptic input to SST-INs is glutamatergic and originate from the thalamus. Analyzing glutamatergic receptors expression during postnatal development revealed that the postsynaptic metabotropic glutamatergic receptor 1 (mGluR1) is specifically expressed in SST-INs and continues to be expressed into adulthood. In addition, we found that mGluR1 is activated by thalamocortical inputs. Therefore we

hypothesize that mGluR1 regulates the integration of SST-INs into cortical networks. Using a combination of mouse genetics, rabies monosynaptic tracing and electrophysiology, we discovered that SST-INs show a defect of maturation upon deletion of mGluR1. Together these findings reveal an activity-dependent postsynaptic mechanism for IN-type differentiation and provide a better understanding of cortical inhibitory circuit development.

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**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 724.06/A6

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

**Support:** NIH Grant R01 NS081297

**Title:** BDNF shapes the functional maturation of cortical interneurons

**Authors: *E. FISHER**[1], G. POUCHELON[1], C. MAYER[2], R. C. BANDLER[3], G. J. FISHELL[1]
[1]Neurobio., Harvard Med. Sch., Boston, MA; [2]Max Planck Inst. of Neurobio., Munich, Germany; [3]NYU Neurosci. Institute, Langone Med. Ctr., New York, NY

**Abstract:** In the mammalian cerebral cortex, inhibitory interneurons sculpt the flow of excitatory information. This complex task is carried out by a wide variety of interneuron subtypes which play distinct roles in cortical function. Two major classes of interneurons, parvalbumin (PV)+ fast-spiking basket cells and somatostatin (SST)+ Martinotti cells, are both derived from a common embryonic origin yet differentiate into highly specialized cell types. Mechanisms that control the diversification of these cell types and specify their integration into their respective circuits are not well understood. Increasing evidence suggests that this process depends not only on initial genetic determinants of cell fate, but also activity-dependent signals once the interneurons invade the cortex and begin to form synapses. One candidate signaling factor to mediate cortical interneuron maturation and synaptic integration is brain-derived neurotrophic factor (BDNF), which is a neurotrophin critical for the development of several cells types and has been shown to regulate inhibition in the developing cortex. However, the contribution of the BDNF high-affinity receptor TrkB to interneuron development has never been tested. Here, we employ a combination of longitudinal fate-mapping, electrophysiology, and synaptic puncta analysis to demonstrate that TrkB controls the circuit integration of SST and PV cortical interneurons.

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**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 724.07/A7

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

**Title:** Early prenatal exposure of rats to homocysteic acid leads to lasting changes in NMDA receptor subunit expression and GABAergic interneuron markers

**Authors: *A. LUNDERBERG**, S. SIMKO, J. ROYER, L. CHASE
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**Abstract:** Homocysteic acid (HCA), a NMDA receptor agonist, is an endogenous metabolite formed from the oxidation of homocysteine. Since hyperhomocysteinemia is a risk factor for several neuropsychiatric disorders, including bipolar disorder and major depressive disorder (MDD), we previously tested the hypothesis that elevated HCA levels in developing rats may induce the development of behaviors associated with MDD and/or bipolar disorder. Our earlier work demonstrated that exposure of postnatal rats to HCA from P3-21 leads to a mixed depressive/manic phenotype that develops post-puberty. Specifically, HCA treated rats exhibit increased risk-taking behavior, reduced social behavior, novelty-induced hyper-locomotion, anhedonia in the saccharine preference test, and reduced spatial learning in the Morris water maze, consistent with a depressive state with manic tendencies. Therefore, in this study, we focused on examining the effects early postnatal HCA exposure had on glutamatergic and GABAergic markers in the hippocampus and the cortex in the adult rat. We hypothesized that early postnatal HCA exposure would lead to excitotoxicity and loss of NMDA-receptor containing GABAergic interneurons which are hypothesized to play an important role in the pathology associated schizophrenia, bipolar disorder and depressive disorder. However, contrary to our hypothesis, we observed that HCA exposure led to an increase in expression of the GABAergic marker, GAD-67 in the cortex of both male and female rats. This finding suggests that perhaps GABAergic interneurons were not appropriately pruned during the critical period. In addition, we observed that HCA exposure led to a significant increase in the NR2A:NR2B subunit expression ratio in the cortex and the hippocampus of male and female rats, but no changes in NR1 subunit expression. Functionally, this would result in NMDA receptors with faster gating kinetics which may be less susceptible to HCA-induced excitotoxicity. Furthermore, we also found that HCA leads to an increase in the expression of BDNF, a neurotrophic factor important for maintenance of GABAergic interneurons. This finding is consistent with the observation that the relative NR2A subunit expression increases as activation of NR2A-specific receptors is associated with an increase in BDNF release. Collectively, these data suggest that early HCA exposure may lead to a shift in the NR2A:NR2B subunit expression, leading to an increase in BDNF expression and GABAergic interneuron survival during the

critical period. *This research was supported by the Hope College Neuroscience Program, Biology Department and Chemistry Department.*

**Disclosures: A. Lunderberg:** None. **S. Simko:** None. **J. Royer:** None. **L. Chase:** None.

**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

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**Program #/Poster #:** 724.08/A8

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

**Support:** NIH Grant MH110438

**Title:** Mechanistic insights into autocrine an paracrine roles of endothelial GABA in the embryonic forebrain

**Authors: Y. CHOI**, A. VASUDEVAN
Dept. of Psychiatry, Angiogenesis & Brain development Laboratory, McLean Hosp., Harvard Med. Sch., Belmont, MA

**Abstract:** The developing cerebral cortex uses a complex developmental plan involving angiogenesis, neurogenesis and neuronal migration. After establishment of the periventricular vascular gradient by embryonic day 11 (E11), neurons and/or neuronal progenitors from ventricular zones navigate along diverse courses, radially and tangentially, to adopt final laminar positions and integrate into specific brain circuits. Our recent studies have shown that the developing periventricular vascular network exquisitely patterned amidst neurons not only acts as a physical substrate for neuronal migration, but also holds the key to several novel developmental mechanisms and pathways. It highlights the importance of endothelial cell secreted GABA signaling in the embryonic forebrain and establishes novel autonomous links between blood vessels and the origin of neuropsychiatric diseases like epilepsy, autism and schizophrenia. Since a common GABA pathway operates in both endothelial cells and GABAergic neurons of the embryonic telencephalon, it is essential to gain further mechanistic insights by segregating this pathway in individual cell types. Our recently generated *Vgat* $^{\Delta Tie2\text{-}Cre}$ or *Vgat* $^{ECKO}$ (endothelial cell knockout; ECKO) mouse model that blocks GABA release from endothelial cells, serves as a new tool to study how endothelial GABA signaling shapes angiogenesis and neurovascular interactions during prenatal development. Here, we isolated individually periventricular endothelial cells and GABAergic neurons from E15 *Vgat* $^{\Delta Tie2\text{-}cre}$ and *Vgat* $^{fl/fl}$ telencephalon and characterized them further by using molecular (RNA seq) and cellular techniques. Our results reveal that the endothelial GABA signaling pathway influences angiogenesis related genes and specific processes like tight junction formation, vascular sprouting and migration. It also shows how components of the neuronal GABA pathway, for

instance receptor mediated signaling and transcription factors are affected in the absence of endothelial GABA release. Taken together, our findings delineate the close relationship between vascular and nervous systems that begin early in embryogenesis establishing their future interactions and interdependence.

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**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 724.09/A9

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

**Support:** FCT - DFA - SFRH/BD/128869/2017

**Title:** Towards molecular connectomics: Proteomic dissection of a specific hippocampal synapse type

**Authors: *N. APÓSTOLO**[1,2], S. N. SMUKOWSKI[4], V. RYBAKIN[3], K. M. VENNEKENS[1,2], S. PORTEGIES[5], N. V. GOUNKO[1,2,6], J. N. SAVAS[4], J. DE WIT[1,2]
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**Abstract:** Neural circuits in the brain communicate through diverse types of synapses. Synapses between different types of neurons can vary widely in their structural and functional properties, and this diversity is required for proper circuit function. Cell adhesion molecules play important roles in synapse development, as they connect pre- and postsynaptic cells and recruit the molecular machinery necessary for synaptic function. However, their potential role in specifying distinct synapse types is still largely unexplored. Single-cell sequencing studies have shown that different neuronal cell types express distinct combinations of adhesion molecules, but whether the structural and functional diversity of different synapse types is reflected in unique adhesion molecule compositions is not known. Typically, the molecular composition of synapses is studied in bulk synaptosome preparations containing many different synapse types. Therefore, the establishment of new methods to elucidate the molecular properties of distinct synapse types is crucial for understanding the molecular basis of synaptic connectivity, function and plasticity. Here, I developed a new method to profile the proteome of a specific hippocampal synapse type, the mossy fiber-CA3 (MF-CA3) synapse, by combining biochemical fractionation, live-labeling for a synapse-specific surface marker, Fluorescence Activated Synaptosome Sorting (FASS) and liquid chromatography-tandem mass spectrometry (LC-MS/MS). Proteomic analysis reveals that

several dozen adhesion molecules are specifically enriched at this synapse. To reveal protein-protein interaction networks within these enriched molecules I am performing a small, unbiased oligomerization-based screen to detect extracellular interactions between individually expressed recombinant extracellular domains. The ultimate goal is to map multiple surface protein complexes at an individual synapse type, the MF-CA3 synapse, and analyze the consequences of synaptic loss of validated adhesion molecules on MF-CA3 synapse structure, function, and plasticity.

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**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

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**Program #/Poster #:** 724.10/A10

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

**Support:** CIHR Grant

**Title:** Patterning of cerebellar inhibitory interneurons by the gamma-Protocadherins

**Authors: *W. X. WANG**[1,2], J. L. LEFEBVRE[1,2]
[1]Neurosciences and Mental Hlth., Hosp. for Sick Children Res. Inst., Toronto, ON, Canada; [2]Dept. of Mol. Genet., Univ. of Toronto, Toronto, ON, Canada

**Abstract:** The developmental events that orchestrate neural circuit formation are dependent on coordinated interactions of neurons with their local environment. Central to these interactions are cell-surface receptors and adhesion molecules, whose concerted actions allow for remarkable specificity in neuronal cell numbers, distributions, and connectivity patterns. Among these are the clustered Protocadherins, which have emerged as key regulators due to their immense capacity for isoform diversity and recognition specificity. The Pcdh locus encodes ~60 different cadherin-like genes, tandemly arrayed into the *–alpha, -beta,* and *–gamma* clusters. This isoform diversity is further amplified through stochastic and combinatorial expression of small subsets of isoforms among single neurons. Genetic ablation of the Pcdh-γs revealed diverse functions in neuronal development, including neuronal survival, dendrite arborization, and synaptic development. However, the temporal timeline of Pcdh function, and how these developmental roles are coordinated in a given cell-type have not been explored. To address this gap in knowledge, we devised genetic strategies for targeting the cerebellar molecular layer interneuron (MLI) population during discrete stages of their development: *prior to, during,* or *post* MLI settlement in the molecular layer. We provide evidence for separate roles of the Pcdh-γs in

regulating interneuron survival and neurite arborization. Early deletion of the Pcdh-γs in MLIs, during the final stages of neuronal migration, leads to reduced survival of MLIs and to reduced neurite arborization. By contrast, late deletion of Pcdh-γs, past the time-point of MLI settlement, did not affect MLI numbers, but led to similar reductions in dendritic and axonal branching. Our results suggest a critical role for the Pcdhs in interneuron survival during a discrete period of MLI integration. We propose a model in which the Pcdh-γs are required for interneuron survival and neurite branching during two windows of development. Further analyses also revealed that survival of a later-born MLI subpopulation, the stellate cells, were preferentially reduced following Pcdh-γ deletion. We are currently using quantitative imaging methods to investigate the expression patterns and roles of Pcdh isoform diversity in mediating these diverse functions.

**Disclosures: W.X. Wang:** None. **J.L. Lefebvre:** None.

**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

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**Program #/Poster #:** 724.11/A11

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

**Support:** CIHR MOP299921
NSERC RGPIN05118

**Title:** Purkinje cell axonal torpedoes are associated with reduced spike propagation failures and enhanced cerebellar-related behaviour

**Authors: *D. LANG-OUELLETTE**, C. A. VAN EITREIM, P. DE VANSSAY DE BLAVOUS, C. ROSEN, M. VIRDEE, A. J. WATT
Dept. of Biol., McGill Univ., Montreal, QC, Canada

**Abstract:** Focal swellings in the axons of Purkinje cells, or torpedoes, have been frequently observed during disease progression, as well as transiently in the developing cerebellum. Given their prevalence in neurodegenerative diseases, current hypotheses suggest that Purkinje cell axonal torpedoes contribute to pathophysiological axonal function.
To elucidate the functional role of Purkinje cell axonal torpedoes in the cerebellum, we used transgenic L7-*tau*-eGFP mice that brightly label Purkinje cells. Using simultaneous dual recordings from visually-identified Purkinje cells and their axons, we measured the properties of spike propagation with and without the presence of axonal torpedoes. Purkinje cell axons propagate action potentials with high fidelity, with low rates of axonal failures. Surprisingly, we found that Purkinje cell axonal torpedoes displayed even lower axonal failure rates compared to axons without torpedoes. We wondered whether an increase in axonal failure rate led to the formation of axonal torpedoes. Using time-lapse two-photon imaging of live cerebellar slices, we

found that Purkinje cell torpedoes were stable over hours, with no new torpedoes formed in ACSF. A non-saturating dose of tetrodotoxin (TTX) caused differential reductions in the firing rate of Purkinje cell somata and axons, thereby mimicking an increase in axon propagation failures. This caused formation of new torpedoes, supporting our hypothesis that torpedoes form when axonal failures are elevated. Finally, we wondered if torpedoes had a functional consequence. To address this, we took advantage of the naturally-occurring variability in motor learning across mice. We found that mice that displayed elevated levels of motor learning had a greater number of Purkinje cell axonal torpedoes, whereas mice that displayed lower levels of motor learning had fewer torpedoes.
Taken together, our results suggest that Purkinje cell axons form torpedoes to improve axonal action potential fidelity. The presence of axonal torpedoes is functionally relevant, as they are associated with enhanced cerebellar-related behaviour. These findings argue that rather than reflecting pathophysiology, axonal torpedoes reflect a homeostatic cellular adaptation that preserves axonal function.

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**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

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**Program #/Poster #:** 724.12/A12

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

**Support:** DoD Grant 66377-RT-REP
W.M. Keck Undergraduate Research Fellowship
James Irvine Foundation Faculty Chair

**Title:** Organophosphate pesticides cause physiological and architectural changes to spinal neurons and somatic muscle in 72-hour zebrafish embryos

**Authors: *E. A. FRADINGER**, T. H. WATANABE, R. C. WILLRICH
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**Abstract:** Organophosphate pesticides inhibit acetylcholinesterase causing an accumulation of acetylcholine at the synapse and hyperstimulation of the cholinergic neurons in both the CNS and PNS. This study seeks to understand the acute effects of organophosphate pesticide exposure on developing neurons. Using the zebrafish model system, we have shown that developmental organophosphate exposure inhibits acetylcholinesterase activity and causes changes to acetylcholine-dependent physiological processes including an increase in spontaneous movement generation at 24 hours-post-fertilization. To further investigate the effects of these pesticides on

neuromuscular development we have utilized wholemount immunohistochemistry to investigate the effects of organophosphate pesticides on the architecture of spinal cholinergic neurons and trunk muscle in 72 hour-post-fertilization embryos. Confocal observations of the trunk spinal region showed that embryos exposed to chlorpyrifos had reduced numbers of cholinergic cell bodies and this effect was amplified in chlorpyrifos-oxon exposed zebrafish. Similarly, changes to trunk muscle architecture were observed in chlorpyrifos exposed embryos and these effects were more pronounced for chlorpyrifos-oxon exposed embryos. Thus, hyperactivity of cholinergic neurons and overstimulation of developing muscle due to acetylcholinesterase inhibition results in structural changes. Interestingly, diazinon did not affect the cholinergic physiology of developing zebrafish embryos. Together, these data highlight the importance of understanding the developmental effects of USDA approved organophosphate pesticides.

**Disclosures: E.A. Fradinger:** None. **T.H. Watanabe:** None. **R.C. Willrich:** None.

**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 724.13/DP01/A13

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

**Support:** NEI (DP1EY024503)
DARPA (BioCon HR0011-17-C-0026)

**Title:** A phase transition in activity of Hydra's nervous system as it reassembles from individual cells

**Authors: *J. LOVAS**, R. YUSTE
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**Abstract:** A growing body of evidence suggests that neural circuits in the cortex and other parts of the brain may operate at a state of self-organized criticality, a concept used to describe the complexity that emerges in systems attracted to dynamics on the verge of a phase transition. Despite the observation of these dynamics and their accompanying power-law scaling in various preparations, there is little *in vivo* experimental evidence for any proposed function of this transition state in the nervous system.
To explore this issue, we work with the small Cnidarian *Hydra vulgaris*, a representative of some of the earliest nervous systems in evolution. *Hydra's* simple nervous system of 300-2,000 neurons is organized in two independent nerve nets in its ectoderm and endoderm and is distributed through the body of the animal without any cephalization or ganglia. Moreover, under the right conditions *Hydra* can reassemble itself into a normal animal after complete dissociation into individual cells. Using transgenic Hydra which express the calcium sensor GCaMP6s in

every neuron (Dupre and Yuste, 2017) we have imaged the neuronal activity of dissociated preparations as they re-aggregate over a period of several days. Our data show how the subcritical activity of dissociated cells transitions to the supercritical state of the reassembled circuitry of the intact animal. The phase transition of *Hydra's* nervous system through a critical regime of activity during the process is reminiscent of the scale-free dynamics of the constantly fluctuating activity of neuronal ensembles of the mammalian cortex. With experimental manipulations to alter the profile of critical dynamics of the process in *Hydra*, we provide *in vivo* experimental evidence in support of the proposed roles of criticality in extending the dynamic range and information capacity of susceptible neural circuits as they form and process information.
Supported by NEI (DP1EY024503) and DARPA (BioCon HR0011-17-C-0026).

**Disclosures: J. Lovas:** None. **R. Yuste:** None.

**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 724.14/A14

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

**Support:** ERC Advanced Grant 694829 "neuroXscales"

**Title:** Spontaneous neuronal activity in developing mouse cerebral organoids

**Authors: M. GIRR**[1], J. BOOS[1], P. MISUN[1], J. BARTRAM[1], M. RENNER[4], M. GAZORPAK[2], A. HIERLEMANN[3], *M. SCHRÖTER[1]
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**Abstract:** Stem-cell (SC) derived brain organoids represent an attractive in vitro model system to study the mechanisms underlying early brain development, and there is a growing body of evidence that cerebral organoids do recapitulate key molecular milestones of early corticogenesis (Di Lullo and Kriegstein, 2017). To what extent cerebral organoids are also capable of giving rise to functional neuronal networks, resembling the structure of in vivo microcircuits, however, remains to be determined. Experimental work, both in vitro and in vivo, suggests that distinct patterns of spontaneous neuronal activity during development represent hallmarks of neuronal network maturation (Blankenship and Feller, 2009). Spontaneous neuronal activity is thought to be involved in key developmental processes, such as neurogenesis and migration, as well as in the formation and refinement of neuronal connectivity (Luhmann et al., 2016). In rodents, sparse intrinsic activity in few cells has already been found at embryonic time points (Owens et al.,

2000), followed by more coherent activity among gap-junction-coupled ensembles around birth (Garaschuk et al., 2000), and early oscillatory patterns in the first postnatal weeks (Crépel et al., 2007), driven by synaptic transmission. Here, we used a genetically encoded calcium indicator to study the trajectories of spontaneous activity in developing cerebral organoids derived from mouse embryonic SCs. Using confocal microscopy, we tracked activity within the same organoid over two weeks in vitro and characterized their intrinsic calcium dynamics. We found that immature neurons showed spontaneous calcium activity already in the second week in vitro. At this stage calcium transients were rare, uncoordinated and of small amplitude. Only few days later, the number of active neurons increased significantly, and spontaneous activity became synchronized over small ensembles of cells; also the amplitude of calcium transients increased strongly during this time. Finally, at three weeks in vitro, the repertoire of activity patterns observed in cerebral organoids was multifaceted, comprising both single-cell and large-scale network-level events. Interestingly, calcium dynamics of developing organoids resembled some of the typical activity patterns observed in acute slice recordings from juvenile cortex. Our results indicate that cerebral organoids also undergo distinct phases of spontaneous activity during neural development, some of which are similar to the patterns reported previously in slices. Thus, cerebral organoids represent a useful tool to explore further the self-organizational principles of neuronal networks.

**Disclosures: M. Girr:** None. **J. Boos:** None. **P. Misun:** None. **J. Bartram:** None. **M. Renner:** None. **M. Gazorpak:** None. **A. Hierlemann:** None. **M. Schröter:** None.

**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 724.15/A15

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

**Support:** 5R01AA021402-06
Schaffer Family Foundation

**Title:** Characterization of novel post-mitotic DNA dynamics in adult neurons

**Authors: *B. A. SIDDOWAY**[1], M.-H. LEE[2], S. E. ROHRBACK[4], R. RIVERA[2], A. CERDA[6], G. E. KAESER[7], B. DILLINGHAM[8], C. LIU[7], C. PARK[7], M. R. MAYFORD[5], J. CHUN[3]
[1]Neurosci., Sanford Burnham Prebys Med. Discovery Inst., Del Mar, CA; [2]Sanford Burnham Prebys Med. Discovery Inst., San Diego, CA; [3]Sanford Burnham Prebys Med. Discovery Inst., La Jolla, CA; [4]Biomed. Sci., Univ. of California San Diego, La Jolla, CA; [5]Psychiatry, Univ. of California San Diego, LA Jolla, CA; [6]Sanford Burnham Prebys UCSD, La Jolla, CA; [7]Univ. of California San Diego and Sanford Burnham Prebys, LA Jolla, CA; [8]Psychiatry, UCSD, San Diego, CA

**Abstract:** Neurons with distinct genomic differences from one another have previously been identified by a number of studies in the frontal cortex and hippocampus, in a phenomenon termed genomic mosaicism. Myriad genomic variations in these brain regions have been identified to date, ranging in size from megabase-scale copy number variations to single nucleotide variants. The majority of large somatic variations appear to occur during neurodevelopment, however, several studies provide evidence that smaller changes can occur to the genome throughout the cellular lifespan of neurons, which in adults, is roughly equal to the age of the individual. The potential physiological role of DNA alterations to adult neuron genomes remains largely unknown, but characterizing the genomic integrity of postmitotic neuronal populations is essential. We developed a novel assay to assess dynamic, postmitotic alterations to the genomes of adult neurons, and characterized postmitotic genomic changes across several brain regions. Surprisingly, we identified an entirely new form of genomic alteration that actively occurs in adult neurons. This phenomenon appears to be highly correlated with behavioral conditioning paradigms in mice and plays an important role in active neuronal circuits. Establishment of a unique sequencing approach allowed us to characterize this process across several brain regions that are involved in learning and memory.

**Disclosures: B.A. Siddoway:** None. **M. Lee:** None. **S.E. Rohrback:** None. **R. Rivera:** None. **A. Cerda:** None. **G.E. Kaeser:** None. **B. Dillingham:** None. **C. Liu:** None. **C. Park:** None. **M.R. Mayford:** None. **J. Chun:** None.

**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 724.16/A16

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

**Support:** CPRIT award RR170010

**Title:** Implication of the spatial position of immediate early genes for the formation of DNAdouble strand breaks

**Authors: *I. DELINT-RAMÍREZ**, R. MADABHUSHI
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**Abstract:** It is known that neuronal activity by the activation of NMDA receptors causes a rapid expression of immediate early genes that play an important role in neuroplasticity. Recently it was reported that this activity stimulation triggers the quick formation of DNA double strand breaks (DSBs) in the promoters of early-response genes, including Fos, Npas4, and Egr1. Surprisingly, these DSBs increase the expression of immediate early genes after NMDA stimulation. Activity-dependent DSB formation is mediated by the type II topoisomerase (Topo

IIβ). Whereas Topo IIβ binds to the promoters of a broad range of genes, neuronal activity induces DSB in only a selective subset of early-response genes. The mechanisms underlying the specificity of DSB formation remain poorly understood. In this work, we examine the signaling mechanisms that affect the formation of activity-induced DSBs in neurons. We further describe how these activity-dependent signaling pathways modulate Topo IIβ activity. Furthermore, we describe the effects of chromatin organizational features in neurons that underlie the positional specificity of activity-induced DSB formation.

**Disclosures: I. Delint-Ramírez:** None. **R. Madabhushi:** None.

**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 724.17/A17

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

**Title:** Optical analysis of functional development of the facial motor nucleus in the embryonic rat brainstem

**Authors: *K. SATO**[1], Y. MOMOSE-SATO[2]
[1]Dept. of Hlth. and Nutr. Sci., Komazawa Women's Univ, Fac. of Human Hlth., Tokyo, Japan; [2]Dept. of Nutr. and Dietetics, Kanto Gakuin University, Col. of Nutr., Yokohama, Japan

**Abstract:** Facial motor neurons of the rat embryo are first generated in rhombomere 4 and then migrate toward the caudo-ventral direction. This migration forms a unique axonal trajectory called the "genu", a loop of facial motor axons around the abducens nucleus. It is still unclear when and how this unique structure is functionally established during ontogenesis. Using voltage-sensitive dye (VSD) recording and the DiI staining method, we identified neural responses evoked by facial nerve (N.VII) stimulation and examined developmental processes of the facial motor nucleus in E12-E17 rat brainstems. We identified two types of fast spike-like signals; a long-duration signal, which corresponded to the action potential in N.VII soma, and a short-duration signal, which reflected the action potential in N.VII axons. The long-duration signal was detected as early as E13, suggesting that the N.VII motor neuron is already excitable at the beginning of cell migration. The response area of the long-duration signal extended caudally at E13-E14, and shifted in a ventral direction at E15. At E16-E17, the long-duration signal was concentrated in the caudo-ventral area, which was comparable to the location of the facial motor nucleus in the adult rat brainstem. These results demonstrate that developmental processes of cell migration and nuclear organization can be visualized and identified functionally with the VSD recording. We discuss the results by comparing functiogenesis and morphogenesis of the N.VII pathway.

**Disclosures: K. Sato:** None. **Y. Momose-Sato:** None.

**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 724.18/A18

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

**Title:** Functional development of the mouse vestibular nucleus revealed by optical recording with a voltage-sensitive dye

**Authors: *Y. MOMOSE-SATO**[1], K. SATO[2]
[1]Dept. of Nutr. and Dietetics, Kanto Gakuin University, Col. of Nutr., Yokohama, Japan; [2]Dept. of Hlth. and Nutr. Sci., Komazawa Women's Univ, Fac. of Human Hlth., Tokyo, Japan

**Abstract:** One major challenge in developmental neurobiology is clarifying when and how the brain is functionally organized during embryogenesis. Although such investigations are significant, they have been hampered by the limited conventional electrophysiological means available for immature neurons and assessing spatio-temporal patterns of neural responses. In the present study, a multiple-site optical recording technique with a voltage-sensitive dye was applied to the mouse embryo, and functional organization of the vestibular nucleus was examined. Stimulation of the vestibular nerve in E12-13 mouse brainstems elicited fast and slow optical signals, which corresponded to the action potential and the excitatory postsynaptic potential (EPSP), respectively. The EPSP was mediated by glutamate and was sensitive to extracellular $Mg^{2+}$, which suppresses the NMDA receptor. In the E13 embryo, the EPSP-related signals were detected from the region extending longitudinally to the levels rostral and caudal to the vestibular ganglion, with high signals concentrated in the caudal region. At E12, the EPSP was lower and generally restricted to the caudal region even when extracellular $Mg^{2+}$ was removed to enhance the glutamate receptor function. These results suggest that the developmental sequence of functional synaptic expression is different between the vestibular subnuclei, and that the EPSP initially appears in the caudal vestibular nucleus in the mouse embryo.

**Disclosures: Y. Momose-Sato:** None. **K. Sato:** None.

**Poster**

**724. Neural Circuit Development: Molecules and Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 724.19/A19

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

**Support:** DFG SFB 1134

**Title:** Structural and functional remodeling of the axon initial segment in a mouse model of autism

**Authors: *M. P. JORDAN**, C. CORCELLI, S. VORWALD, N. JAMANN, C. SCHULTZ, M. ENGELHARDT
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**Abstract:** The classical view of neurons emphasizes the role of dendrites for synaptic signal integration and plasticity. In contrast, the axon has been recognized as a rather static output device. This view is rapidly changing, with recent research revealing a much more active role for axonal microdomains in neuronal signal processing. A key regulator in this regard is the axon initial segment (AIS), strategically positioned at the proximal axon and essential for action potential initiation. It further exhibits significant structural and functional plasticity, depending on network activity. By regulating AIS length and position, neurons can modulate their excitability and therefore contribute to maintain the functional stability of neuronal circuits. Here we asked whether altered network states in a mouse model of autism spectrum disorder (ASD) result in structural and functional remodeling of the AIS. Typically, ASD is characterized by aberrant fronto-striatal circuitry, presumably leading to an imbalance of neuronal excitation/inhibition. In our model, mouse pups were subjected to in-utero exposure with the anticonvulsant valproic acid (VPA), a common rodent model for ASD. Using multi-channel immunofluorescence, confocal microscopy, morphometrical analysis, and electrophysiological recordings, we investigated putative changes in structural maturation and integrity of the AIS in two ASD-relevant anatomical circuits: (i) the dorso-lateral striatum (DLS), mainly controlling automated motor sequences and habitual behaviours and (ii) the barrel field in primary somatosensory cortex (S1BF), which projects to DLS. We found that pyramidal neurons in S1BF layer 2/3 and 5 in VPA-exposed mice display significantly shorter AIS than in saline controls. This decrease in length correlated with a decrease in cellular excitability. Interestingly, inhibitory medium spiny neurons in DLS show significantly longer AIS than saline controls, possibly indicating a higher cellular excitability. In which way these differential cellular responses correlate with the ASD-driven changes in network activity remains to be investigated. Taken together, our results point to a role for AIS plasticity in the development of ASD phenotypes in mice.

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**Poster**

**725. Fragile X Syndrome I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 725.01/A20

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

**Support:** MH60163
NS100050

**Title:** Multiple waves of developmental delays in fragile X cortical circuits *in vitro*

**Authors: *H. MOTANIS**[1], A. GOEL[4], C. PORTERA-CAILLIAU[2], D. V. BUONOMANO[3]
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**Abstract:** Neurodevelopmental delays characteristic of fragile X (FX) syndrome have also been observed in vitro (Motanis et al., 2015). The presence of neurodevelopmental delays in vitro suggests that they are a direct consequence of the *Fmr1* mutation, as opposed to an indirect product of compensatory mechanisms or abnormal sensory experience. Here, we used whole-cell recordings and $Ca^{2+}$-imaging of cortical slice cultures from wild-type (WT) and Fmr1 knockout mice to characterize the development of spontaneous and evoked activity, and determine if they undergo normal network-level homeostatic plasticity. $Ca^{2+}$-imaging of spontaneous activity with GCaMP6f revealed that at 14-16 days in vitro (DIV) mean activity was reduced in FX circuits ($0.051\pm0.006$ vs. $0.130\pm0.032$, $p<0.05$). Recordings at 25-30 DIV revealed no difference in spontaneous activity, confirming the presence of an in vitro developmental delay. Interestingly, whole-cell recordings revealed no significant genotype difference of the input-output functions of evoked EPSPs at 11-15 DIV. But there was a difference at 25-30 DIV ($p<0.01$) as EPSP strength underwent a developmental increase in WT, but not FX circuits. By 35-40 DIV there were no differences in EPSPs strength or evoked network activity between WT and FX circuits. To examine network-level homeostatic plasticity we used chronic optogenetic stimulation (COS-ChR2) to emulate an increase in externally driven activity. Whole-cell recordings revealed that COS-ChR2 (25-30 DIV) induced a significant reduction of evoked EPSP strength ($F_{1,62}=15.56$, $p<10^{-3}$), with no genotype difference—i.e., COS-ChR2 resulted in a decrease in EPSP strength in both WT and FX circuits despite the reduced baseline difference in the FX unstimulated slices. To examine homeostatic plasticity across the network, we used COS together with 2-photon $Ca^{2+}$-imaging in slices co-transfected with GCaMP6f and Chrimson (25-30 DIV). COS-Chrimson induced a significant reduction of both spontaneous ($F_{1,27}=18.75$, $p<10^{-3}$) and light-evoked activity in both genotypes. To begin to understand the nature of the abnormal

development activity we targeted Ca2+ imaging to parvalbumin (PV)_interneurons (PV-Cre mice x ai9 mice, GCaMP6s). Preliminary results indicate normal spontaneous activity of PV neurons in FX circuits. Together these results reveal there were multiple delayed developmental "waves" in FX circuits: first a delay in spontaneous activity, followed by a delay in evoked EPSP strength. In addition, our results indicate that FX circuits exhibit normal homeostatic plasticity, suggesting that some previously described neural phenotypes observed in FX may be compensatory.

**Disclosures: H. Motanis:** None. **A. Goel:** None. **C. Portera-Cailliau:** None. **D.V. Buonomano:** None.

**Poster**

**725. Fragile X Syndrome I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 725.02/A21

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

**Support:** NIH Grant HD 054453-08
The John Merck Fund - Developmental Disabilities Translational Research Program
Simons Foundation Autism Research Initiative (SFARI)

**Title:** Impaired sensory discrimination in fragile X syndrome mice is mediated by abnormal interneuron dynamics

**Authors: *A. GOEL**[1], D. CANTU[1], J. GUILFOYLE[2], G. R. CHAUDHARI[1], A. NEWADKAR[1], B. TODISCO[1], D. DE ALBA[1], N. KOURDOUGLI[1], L. M. SCHMITT[2], E. PEDAPATI[2], C. A. ERICKSON[2], C. PORTERA-CAILLIAU[1]
[1]Neurol. and Neurobio., Univ. of California, Los Angeles, CA; [2]Psychiatry, Cincinnati Children's Hosp. Med. Ctr., Cincinnati, CA

**Abstract:** Fragile X Syndrome (FXS), one of the most common inherited forms of mental impairment, is associated with abnormalities in sensory processing, including a propensity for impaired cognitive performance in the setting of sensory distractors. We investigated the abnormal cortical network dynamics in *Fmr1* knockout (*Fmr1*$^{-/-}$) mice that mediate deficits in learning. Using a go/no-go visual discrimination task for head-restrained mice, we found that, compared to wild-type (WT) mice, *Fmr1*$^{-/-}$ mice take significantly longer to discriminate between gratings drifting in two orthogonal orientations (90$^{o}$ task). Because this delayed learning was associated with higher rates of false alarm responses in *Fmr1*$^{-/-}$ mice in early sessions, which could result from an abnormal state of hyperarousal, we tested whether *Fmr1*$^{-/-}$ mice were more susceptible to sensory distraction. We found that introduction of visual or auditory distractors, after mice learned the basic 90$^{o}$ task, significantly impaired performance in *Fmr1*$^{-/-}$, but not WT

mice. These deficits are consistent with an inability of *Fmr1*$^{-/-}$ mice to "tune out" sensory distractors and focus on the task, a hallmark of FXS symptoms that could be mediated by alterations in cortical sensory processing and/or decision making. We next used in vivo two-photon calcium imaging (with rAAV-syn-GCaMP6s) to record network dynamics in layer 2/3 of primary visual cortex (V1) and found a significantly lower fraction of and broader tuned orientation tuned pyramidal (Pyr) cells in V1 in *Fmr1*$^{-/-}$ mice compared to WT mice, which correlated with task performance. Dysfunction in parvalbumin (PV) neurons have been implicated in FXS. PV interneurons in sensory areas sharpen orientation tuning of Pyr cells and indirectly modulate attention via alterations in cortical gain, both of which can affect visual feature detection and sensory discrimination. Thus, we recorded from PV neurons by expressing AAV-flex-GCaMP6s in PV-Cre x LSL-TdTom (ai9) WT and *Fmr1*$^{-/-}$ mice and, found a decrease in functional output of PV cells in *Fmr1*$^{-/-}$ mice. Pharmacogenetic manipulation of PV cell activity using designer receptors exclusively activated by designer drugs (DREADDs) restored both normal PV cell dynamics and orientation selectivity, and rescued the visual sensory discrimination deficit. Interneurons expressing vasoactive intestinal polypeptide (VIP) also dynamically regulate sensory responses and plasticity as a function of the behavioral brain state of the animal, thus affecting arousal and attention during learning. Hence, we are currently examining the contribution of VIP cell activity during presentation of sensory distractors in *Fmr1*$^{-/-}$ and WT mice.

**Disclosures: D. Cantu:** None. **J. Guilfoyle:** None. **G.R. Chaudhari:** None. **A. Newadkar:** None. **B. Todisco:** None. **D. de Alba:** None. **N. Kourdougli:** None. **L.M. Schmitt:** None. **E. Pedapati:** None. **C.A. Erickson:** None. **C. Portera-Cailliau:** None.

**Poster**

**725. Fragile X Syndrome I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 725.03/A22

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

**Title:** Fmr1 gene transplacement in cultured primary neurons for rapid assessment of rare mutations identified in psychiatric disease patients

**Authors: *M. M. NAGIEC**[1], M. FITZPATRICK[1], J. M. MADISON[1], K. DUONG[1], M. KOST-ALIMOVA[2], E. M. SCOLNICK[1], J. R. COTTRELL[1]
[1]Stanley Ctr. for Psychiatric Res., [2]Ctr. for Develop. of Therapeut., Broad Inst. of MIT and Harvard, Cambridge, MA

**Abstract:** Fragile X Syndrome (FXS), the most common inherited form of intellectual disability and a leading genetic cause of autism, is predominantly caused by silencing of *FMR1* gene expression and the loss of FMRP protein. Two hallmark cellular manifestations of the loss of

FMRP in brain tissue are (i) changes in dendritic spine morphology related to altered cytoskeletal remodeling and (ii) the increased rate of mRNA translation resulting from the loss of translational repressor function of FMRP. We adopted CRISPR- and siRNA-based approaches to achieve robust gene ablation in cultured primary neurons. Single *Fmr1* directed guide RNA transduced into rat hippocampal neurons by lentivirus alongside the SpCas9 resulted in efficient gene inactivation, with 77% of *Fmr1* gene copies acquiring a damaging lesion as assessed by Surveyor nuclease assay and confirmed by deep sequencing and >80% reduction of Fmrp protein as measured by ICC and immunoblotting by DIV21. Treatment of hippocampal neurons with 1μM Accell siRNA on DIV1 also resulted in robust (80-90%) reduction of *Fmr1* expression on DIV16 as measured by RT-qPCR as well as by ICC and immunoblotting. The Accell siRNA modality of Fmrp depletion was more reproducible and was therefore chosen for gene replacement experiments. Using a plate-based fluorescent noncanonical amino acid tagging (FUNCAT) assay, we found that inactivation of *Fmr1* in rat hippocampal neurons in culture results in elevation of the rate of mRNA translation. In addition, it caused an increased phosphorylation of the actin depolymerizing factor cofilin (pS3) and its regulators LIMK (pT508) and Slingshot L1 (pS978). Both cellular phenotypes were reversed by reintroduction of the human *FMR1* by recombinant AAV8 transduction. Using this *in vitro* primary neuron gene eviction and transplacement system, we are assessing the impact of rare *FMR1* mutations found in psychiatric disease patients on FMRP function. Our data show that the hallmark FXS cellular phenotypes can be studied in the plate based systems amenable for high throughput approaches.

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**Poster**

**725. Fragile X Syndrome I**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 725.04/A23

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

**Support:** NIH Grant F31NS101932-01
NIH Grant R21NS089080

**Title:** Role of Cdh1-APC as a regulator of FMRP and protein synthesis at the synapse

**Authors: *A. VALDEZ**[1], A. LAI[2], G. J. BASSELL[2]
[1]Cell Biol., [2]Emory Univ., Atlanta, GA

**Abstract:** For learning and memory to occur, neurons synthesize synaptic proteins in response to stimulation. This process of protein synthesis is tightly regulated to ensure that the optimal amount of proteins is made to strengthen or weaken the connection between two neurons. One of

the ways that cells regulate this process is ubiquitination, a mechanism by which proteins are targeted for degradation through the attachment of a smaller protein, ubiquitin, to specific amino acid residues. Disrupted ubiquitination can lead to multiple debilitating forms of human disease, such as a neurodevelopmental disorder known as Angelman Syndrome and several genetic forms of Autism Spectrum Disorder. Dysregulated ubiquitination may be a shared mechanism amongst other neurodevelopmental diseases.
One neurodevelopmental disease with no FDA-approved treatment is Fragile X Syndrome (FXS). Patients with FXS experience a wide variety of symptoms such as severe intellectual disability, sensory disorders, hyperactivity, reproductive issues, and seizures. FXS is caused by the loss of one protein, the Fragile X Mental Retardation Protein (FMRP). Despite lacking only FMRP, symptoms of FXS are complex and multifaceted. This suggests that FMRP must play a vital role in multiple cellular processes. FMRP has been observed to repress mRNA translation; however, it is unclear how the repressive activity of FMRP is regulated.
Neuronal stimulation has been shown to increase the ubiquitination of FMRP. This suggests that ubiquitination may be a mechanism of regulating the repressive activity of FMRP. Here we demonstrate that the Cdh1 subunit of the E3-ubiquitin ligase anaphase-promoting complex (APC) associates with FMRP, and thus may play a role in ubiquitinating FMRP. Mass spectrometry analysis reveals that Cdh1 interacts with known components of FMRP granules, such as FXR1. FMRP granules have been observed to induce translational repression. Thus, this data suggests a novel function of Cdh1 as a translational regulator through the association of FMRP granules beyond its well-characterized role in ubiquitination during mitosis. The biological relevance of this data is emphasized as expression of Cdh1-APC increases steady-state protein synthesis.
Our data identify a novel role of Cdh1-APC as a regulator of translation and support the novel hypothesis that ubiquitination serves as a dynamic mechanism to regulate FMRP.

**Disclosures: A. Valdez:** None. **A. Lai:** None. **G.J. Bassell:** None.

**Poster**

**725. Fragile X Syndrome I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 725.05/A24

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

**Support:** Ben and Catherine Ivy Foundation
Stanford Bio-X
NIH Grant HD084214

**Title:** A cross-sectional investigation of fragile X syndrome neurodevelopment in a neonatal FMR1 knockout mouse model using diffusion weighted MRI

**Authors: *S. G. GUO**[1], S. T. REYES[2], C. LEUZE[3], J. A. MCNAB[4], F. T. CHIN[5]
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**Abstract: Background:** Fragile X syndrome (FXS) is a genetic condition affecting neurodevelopment. Humans with FXS down to 6 months old demonstrate abnormal white matter microstructure[1]. A previous *ex vivo* diffusion weighted MRI (dMRI) study found delayed cerebellar myelination in neonatal FXS mice[2]. We aim to acquire high-resolution *in vivo* dMRI scans using wild type (WT) and *FMR1* knockout (KO) mice to identify connectivity patterns in the living neonatal mouse brain for selected regions of interest (ROI) to correlate with published human dMRI data. This preclinical tool will further contribute to our understanding of FXS neurodevelopment. **Methods:** P5 & p10 *FMR1* KO and WT male mice (n=3-5 mice/age group) were used. Anesthesia protocols were optimized for p5 & p10 mice using 45 mg/kg and 70 mg/kg of ketamine respectively plus 0.9 mg/kg dexmedetomidine. DTI used a Bruker 7T MRI with a CryoProbe. We customized an imaging setup and protocol to accommodate the limited possible scan time and small scan area inherent to imaging p5 mice. We used a segmented 3D dMRI Echoplanar Imaging (EPI) sequence at resolution 0.44 x 0.47 x 0.36 mm, TE = 24.9 ms, TR = 600 ms, 2 segments, 1 average, b = 1000 s/mm$^2$, 25 diffusion directions, 3 b = 0 s/mm$^2$ images, diffusion pulse duration of $\delta$ = 4 ms, a diffusion separation of $\Delta$ = 10 ms (total scan time of 35 mins). Fractional anisotropy (FA) and mean diffusivity (MD) values at 3 ROIs (cortex, caudoputamen, and thalamus) were quantified using FSLView. **Results & Discussion:** FA and MD values were compared (table 1). No significant differences were found in p10 mice. In p5 mice, KO mice had significantly lower FA values (thalamus) and higher MD values (cortex & caudoputamen)—consistent with decreased FA values in the thalamus of human FXS infants. **Conclusion:** This pilot study overcame challenges with imaging neonatal FXS mice, demonstrating significant differences in thalamus (FA) and cortex and caudoputamen (MD) regions in p5 mice. These results are consistent with recently published results in human FXS infants.
[1] Swanson Meghan R. et al, Development of White Matter Circuitry in Infants With Fragile X Syndrome, May 2018, *JAMA Psychiatry* [2] Pacey Laura K. et al, Delayed myelination in a mouse model of fragile X syndrome, June 2013, *Human Molecular Genetics*

Table 1. FA and MD metrics of p5 and p10 mice

| | | **Fractional Anisotropy** | | **Fractional Anisotropy** | | **Mean Diffusivity ($10^{-4}$mm$^2$/s)** | | **Mean Diffusivity ($10^{-4}$mm$^2$/s)** | |
|---|---|---|---|---|---|---|---|---|---|
| **Age** | **Brain Area** | **KO** | **95% Confidence Interval** | **WT** | **95% Confidence Interval** | **KO** | **95% Confidence Interval** | **WT** | **95% Confidence Interval** |
| **p5** | Cortex | 0.224 | (0.204, 0.229) | 0.232 | (0.196, 0.238) | 10.1* | (9.91, 10.2) | 8.52* | (8.66, 9.52) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **p5** | Caudoputamen | 0.204 | (0.190, 0.218) | 0.183 | (0.152, 0.205) | 8.64* | (8.57, 8.84) | 8.04* | (7.95, 8.27) |
| **p5** | Thalamus | 0.164* | (0.160, 0.169) | 0.202* | (0.174, 0.213) | 8.95 | (8.81, 9.28) | 8.62 | (8.16, 8.93) |
| **p10** | Cortex | 0.226 | (0.195, 0.256) | 0.219 | (0.189, 0.227) | 9.32 | (8.39, 9.90) | 8.21 | (7.73, 8.49) |
| **p10** | Caudoputamen | 0.191 | (0.153, 0.219) | 0.162 | (0.120, 0.176) | 9.16 | (8.48, 9.81) | 8.40 | (8.26, 8.53) |
| **p10** | Thalamus | 0.242 | (0.147, 0.233) | 0.165 | (0.163, 0.171) | 10.0 | (9.31, 10.7) | 8.21 | (8.18, 9.62) |

FA and MD values were quantified in 3 ROIs (cortex, caudoputamen, and thalamus). n=4 mice were used for both p5 WT and KO. n=5 mice were used for p10 KO, and n=3 for p10 WT. *$p<0.05$

**Disclosures: S.G. Guo:** None. **S.T. Reyes:** None. **C. Leuze:** None. **J.A. McNab:** None. **F.T. Chin:** None.

**Poster**

**725. Fragile X Syndrome I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 725.06/A25

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

**Support:** CIHR
Fragile X Canada
FRAXA

**Title:** FMRP regulates mossy fiber-granule cell synaptic plasticity by modulating the Cav3-Kv4 complex

**Authors: *X. ZHAN**[1], H. ASMARA[1], N. CHEN[2], G. SAHU[3], C. SZALAY[3], F. ZHANG[4], G. W. ZAMPONI[4], R. W. TURNER[3]
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**Abstract:** The excitability of cerebellar granule cells is strongly regulated by an ion channel complex consisting of Cav3 (T-type) calcium and Kv4 (A-type) potassium channels (Cav3-Kv4). Our previous studies found that long-term potentiation of mossy fiber input to granule cells involves a dramatic increase in postsynaptic excitability through a reduction in A-type current invoked by a hyperpolarizing shift in steady-state inactivation (Vh) of Kv4. This study examined

how regulation of Cav3 and Kv4 channels could contribute to disruption of synaptic plasticity in a Fragile X Syndrome (FXS) mouse model. We found that mossy fiber LTP and the associated left-shift in Kv4 Vh is absent in FMRP-/- mice but rescued by infusing FMRP(1-298) through the patch recording electrode *in vitro*. FMRP was found to co-immunoprecipitate (coIP) with Cav3.1 and Kv4.3 with an association close enough to support FRET in tsA-201 cells. Introducing a short N-terminal fragment of FMRP either through the recording electrode or by bath applying a tat-FMRP construct left-shifted the Vh of either Cav3.1 or Kv4.3 expressed in tsA-201 cells, and the Cav3-Kv4 Vh in granule cells *in vitro*. Moreover, tail vein injection of tat-FMRP into FMRP-/- mice promoted widespread uptake into neurons across the CNS within 1 hr. Behavioral tests reveal a concentration-dependent reduction of hyperactivity in the Open Field test, and restoration of syllable duration in ultrasonic recordings of vocalizations between male and female FMRP-/- mice. These findings are important in revealing a previously unrecognized association between FMRP and Cav3 calcium channels that affects the properties of a Cav3-Kv4 complex at the plasma membrane level to control synaptic plasticity. Early behavioral results with tat-FMRP introduction in vivo suggest a new therapeutic approach to reduce aberrant behavioral symptoms of Fragile X Syndrome. Supported by grants from the CIHR, Fragile X Canada, FRAXA and SFARI Explorer award (RWT) a Harley Hotchkiss Studentship (CS), a UoC Eyes High and AI-HS PDF (GS), and Cumming School of Medicine, Hotchkiss Brain Institute, Fragile X Canada and FRAXA PDF support (XZ).

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**Poster**

**725. Fragile X Syndrome I**

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

**Support:** NIH Grant HD 054453-08
Amgen Foundation

**Title:** Pupil fluctuations track deficits in perceptual learning in Fragile X Syndrome mice

**Authors: *G. CHAUDHARI**, A. NEWADKAR, B. TODISCO, D. DE ALBA, A. GOEL, C. PORTERA-CAILLIAU
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**Abstract:** Fragile X Syndrome (FXS), a leading inherited form of mental impairment and single-gene cause of autism, is a complex disorder with a wide variety of symptoms, including learning impairment, atypical sensory processing, hyperarousal, and hyperactivity. In this study, we

sought to determine if these symptoms are interrelated and, specifically, whether hyperactivity and hyperarousal contribute to learning disability in a mouse model of FXS. We used a go/no-go visual discrimination task for head-restrained mice that requires them to preferentially lick for a water reward in response to a preferred visual stimulus, namely gratings drifting in one of two orthogonal orientations. We discovered that wild-type (WT) mice learn to associate the preferred stimulus with the water reward within 4 sessions, whereas *Fmr1* knockout (*Fmr1*$^{-/-}$) mice take significantly longer to master the task. Inspired by a recent study showing that WT mice slow down for the preferred visual stimulus, we hypothesized that *Fmr1*$^{-/-}$ mice's hyperactivity might affect their ability to modulate their running speed, thus impairing their ability to discriminate between the orientations. Using a custom MATLAB video analysis algorithm, we found that there were no differences between the absolute running speeds of *Fmr1*$^{-/-}$ and WT mice, both before and after learning the task (before: 50 ± 8 cm/s vs. 48 ± 6 cm/s, p=0.86; after: 61 ± 6 cm/s vs. 59 ± 8 cm/s, p=0.82). However, after learning the task both groups of mice exhibited a significant reduction in running speed when presented with the preferred stimulus. This suggests that *Fmr1*$^{-/-}$ mice are not hyperactive in this paradigm and that locomotion does not contribute to the learning deficit in *Fmr1*$^{-/-}$ mice as they too learn to slow down for the preferred stimulus. Next, we examined the role of hyperarousal in task performance. Recent studies suggest that changes in pupil size in mice reflect different brain states and correlate with the activity of excitatory and inhibitory neuron subtypes. Hence, we hypothesized that persistent hyperarousal in *Fmr1*$^{-/-}$ mice, reflected by enlarged pupil size, impairs their visual discrimination. We used an infrared camera coupled with custom MATLAB code to monitor pupil dynamics of *Fmr1*$^{-/-}$ and WT mice during both the basic visual discrimination task and a modified task, in which auditory and visual distractors are presented at random. The latter paradigm shows that, whereas the performance of WT mice is unaffected by sensory distractors, *Fmr1*$^{-/-}$ mice that have learned the basic task can no longer discriminate in the presence of distractors. We will present data on the effects of distractors on pupil size during the task in both genotypes.

**Disclosures: G. Chaudhari:** None. **A. Newadkar:** None. **B. Todisco:** None. **D. de Alba:** None. **A. Goel:** None. **C. Portera-Cailliau:** None.

**Poster**

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**Location:** SDCC Halls B-H

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**Program #/Poster #:** 725.08/A27

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

**Support:** Simons Foundation

**Title:** Enhancement of mitochondrial efficiency causes synaptic metabolic maturation, reversing the abnormal protein translation in Fragile X syndrome

**Authors: *P. LICZNERSKI**[1], H.-A. PARK[1], P. MIRANDA[1], V. K. GRIBKOFF[1], R. CHEN[1], M. GRAHAM[2], R. J. LEVY[3], E. A. JONAS[1]
[1]Intrnl. Medicine/Section Endocrinol., [2]Ctr. for Cell. and Mol. Imaging, Yale Univ. Sch. of Med., New Haven, CT; [3]Dept. of Anesthesiol., Columbia Univ., New York, NY

**Abstract:** Fragile X syndrome is caused by loss of function of the gene encoding Fragile X mental retardation protein (FMRP), an RNA-binding protein. Loss of FMRP leads to abnormally elevated protein synthesis and high survival rates of neurons in the brain. This is associated with excessive numbers of neurons, immature synapses and aberrant synaptic plasticity. There is a significant elevation in levels of Bcl-xL, the anti-apoptotic mitochondrial protein. Bcl-xL targets to mitochondria and depletion of Bcl-xL disrupts mitochondrial membrane potential and decreases ATP content of neurons. We now show that there is a close functional relationship between FMRP, Bcl-xL and mitochondria and that absence of FMRP alters mitochondrial structure and function, causing a proton leak across the inner mitochondrial membrane, resulting in inefficient mitochondrial respiration and decreased ATP production. We also find that the elevated levels of protein translation in FMRP KO mouse neurons can be reduced by treatment with two specific modulators of the ATP synthase, which closes an inner membrane leak within the ATP synthase c-subunit, increasing the efficiency of mitochondrial metabolism. One of these modulators also increases LTP in FMRP KO mouse hippocampal slice recordings. We suggest that FMRP is not only an mRNA binding protein but also normalizes the association between the ribosome and the mitochondria. This relationship is crucial for correct synaptic development and plasticity.

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**Poster**

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

**Support:** R01MH106490
FRAXA Research Foundation

**Title:** Abnormal neuronal exosomal miRNA signaling to astroglia contributes to glutamate transporter GLT1 dysregulation in FXS mouse models

**Authors: *Y. MEN**, J. YELICK, S. JIN, Y. YANG
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**Abstract:** Fragile X syndrome (FXS) is a neurodevelopmental disorder caused by the loss-of-function of fragile X mental retardation protein (FMRP). We previously showed that astroglial glutamate transporter subtype GLT1 and glutamate uptake is significantly reduced in cortex of $Fmr1^{-/y}$ mice, leading to dysregulated extracellular glutamate homeostasis and enhanced neuronal excitability. We also showed that the reduced GLT1 expression is resulted from the decreased mGluR5 expression and signaling in Fmr1-deficient astrocytes. Here, we uncovered an exciting new pathway, the exosome-mediated transfer of miR-124 from neurons to astroglia, that up-regulates GLT1 expression. In this pathway, neuron-specific miR-124 as well as a number of other miRNAs are selectively and abundantly packed into neuronal exosomes and transferred into astroglia. Transferred miR-124 significantly up-regulates GLT1 protein expression by suppressing GLT1-inhibiting downstream miR-132 and miR-218. In addition, exosomally transferred miR-124 also suppresses the expression of miR-128 which binds to mGluR5 mRNA and decreases its protein expression in astrocytes. We found that the levels of miR-124 are increased 15 fold in wild type (WT) astrocytes co-cultured with WT neurons compared to that in WT astrocyte cultures alone without altering the levels of pri-miR-124, the precursor of miR-124. In contrast, miR-124 levels in Fmr1 KO astrocytes co-cultured with wild type neurons are increased only 6 fold when compared to that in Fmr1 KO astrocytes alone. Interestingly, expression levels of both primary miR-124 (pri-miR-124) and the mature miR-124 are increased 6 fold in Fmr1-deficient astrocytes alone compared to that in WT astrocytes alone. These results suggest an increased basal endogenous miR-124 transcription in Fmr1 KO astrocytes alone while the transferred miR-124 levels from neurons to Fmr1 KO astrocytes are substantially reduced. We also found that downstream miR-128 levels are increased 19 fold, corresponding to the reduced mGluR5 levels observed in Fmr1 KO astrocytes, while miR-132 and miR-218 levels in Fmr1 KO astrocytes are not altered. Exogenously introduced miR-124 is sufficient to suppress miR-128 and restores GLT1 expression. Our findings reveal a potential role of miRNA-mediated pathological mechanisms in the GLT1 dysregulation in mouse models of FXS, which may identify new modulators to restore normal extracellular glutamate environment and attenuate FXS symptoms.

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**Poster**

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**Program #/Poster #:** 725.10/A29

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

**Support:** HD082013

**Title:** Behavioral assessment of mice with cell type-specific deletion of FMRP in somatostatin and parvalbumin interneurons

**Authors: *M. KALINOWSKA**[1], E. KLANN[2]
[1]Ctr. for Neural Sci., New York Univ., New York, NY; [2]Ctr. for Neural Sci., New York Univ. Ctr. for Neural Sci., New York, NY

**Abstract:** Fragile X syndrome (FXS) is a common genetic cause of autism spectrum disorder (ASD) and intellectual disability that results from silencing of the *FMR1* gene, resulting in the loss of its protein product, fragile X mental retardation protein (FMRP). FMRP is an mRNA binding protein with functions in mRNA transport, localization, and translation. It is well known that mRNA translation is altered in FXS and many studies strongly link this dysregulated translation to the pathophysiology of FXS. The function of FMRP in excitatory synapse morphology and function has been widely studied in *Fmr1* KO mouse, a rodent model of FXS. In contrast, the function of FMRP in GABAergic neurons has been less characterized. Both pre- and post synaptic components of the GABAergic system are dysregulated in *Fmr1* KO mice, where multiple GABA receptor subunits and synthesizing enzymes show altered expression in several brain regions. In addition, alterations in inhibitory neurotransmission were found in *Fmr1* KO mice in a number brain regions including amygdala, hippocampus, and cortex. Inhibitory neurotransmission plays a fundamental role in shaping circuit development and function, and imbalances between excitatory and inhibitory transmission have been implicated in ASD. The consequence of FMRP deletion in different interneuron subtypes and their specific contributions to behavioral deficits observed in *Fmr1* KO mice have not been examined. Using Cre -lox recombinase technology, we generated mice with cell type-specific deletion of *Fmr1* in parvalbumin (PV)- and somatostatin (SOM)-expressing interneurons, two of the major interneuron subtypes in the central nervous system. To elucidate the complex interaction between GABAergic dysfunction and behavioral phenotypes in FXS, we assessed anxiety-like behaviors, motor function, memory, repetitive and social behaviors in *PV-Fmr1*$^{-/y}$ *SOM-Fmr1*$^{-/y}$ mice. Our preliminary findings suggest novel, cell type-specific functions for FMRP in distinct behavioral features associated with this neurodevelopmental disorder.

**Disclosures: M. Kalinowska:** None. **E. Klann:** None.

**Poster**

**725. Fragile X Syndrome I**

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**Program #/Poster #:** 725.11/A30

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

**Support:** FRAXA Fellowship
NIH Grant R01 MH092877

**Title:** Activation of autophagy rescues cognitive deficits in Fragile X mice

**Authors: *J. YAN**[1], M. W. PORCH[1], B. COURT-VAZQUEZ1[1], M. V. BENNETT[2], R. ZUKIN[3]
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**Abstract:** Fragile X syndrome (FXS) is the most frequent form of heritable intellectual disability and autism. Autophagy is a catabolic process of programmed degradation and recycling of proteins and cellular components *via* the lysosomal pathway. However, a role for autophagy in the pathophysiology of Fragile X syndrome is, as yet, unclear. Here we show that autophagic flux, a functional readout of autophagy, and biochemical markers of autophagy are downregulated in hippocampal neurons of Fragile X mice. We further show that enhanced mTOR complex 1 (mTORC1) activity and translocation of Raptor, a defining component of mTORC1, to the lysosome coincides with and is causally related to reduced autophagy. Activation of autophagy by delivery of shRNA to Raptor directly into the CA1 of living mice *via* the lentivirus expression system corrects aberrant spine structure, synaptic plasticity and cognition in Fragile X mice. Finally, we show that postsynaptic density protein (PSD-95) and Activity-regulated cytoskeletal-associated protein (Arc), synaptic proteins implicated in spine structure and synaptic plasticity, respectively, are elevated in neurons lacking FMRP and are degraded, at least in part *via* the lysosomal/autophagy pathway. Activation of autophagy corrects PSD-95 and Arc abundance, identifying a potential mechanism by which downregulated autophagy is causally related to the Fragile X phenotype and reveals a previously unappreciated role for autophagy in the synaptic and cognitive deficits associated with Fragile X syndrome.

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**Poster**

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**Program #/Poster #:** 725.12/A31

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

**Support:** NIH/NIMH R01 MH092877-07

**Title:** Genetic rescue of fragile X by conditional knockdown of Rictor

**Authors: *S. ROUDABUSH**, J. YAN, J.-Y. HWANG, B. COURT-VAZQUEZ, R. S. ZUKIN
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**Abstract:** Fragile X syndrome (FXS) is the most common heritable form of intellectual disabilities and the leading genetic cause of autism. The neuroanatomical hallmark of Fragile X is an increased density of immature spines, a factor thought to underlie synaptic dysfunction and impaired cognition in Fragile X mice. Our laboratory identified cofilin, an actin depolymerizing agent that regulates spine structure, and its upstream effector Rac1, a Rho GTPase and identified target of FMRP in *Drosophila,* factors critical to spine abnormalities and cognitive dysfunction, to be dysregulated in Fragile X mice. Whereas a role for overactivated mTORC1 signaling in pathophysiology of Fragile X syndrome is well-established, a role for aberrant mTORC2 signaling is, as yet, unclear. Because mTORC2 is upstream of Rac/cofilin signaling and actin polymerization, we hypothesized that genetic reduction of Rictor, a defining component of mTORC2 and binding partner critical to mTOR function and stability, might rescue synaptic defects in Fragile X mice. Because Rictor-null mice are embryonically-lethal, we created *Fmr1* KO mice in which *Rictor* could be conditionally knocked out by means of CRISPR/Cas9 technology and the Cre-loxP system, *Fmr1* KO *Rictor* cKO. In preliminary experiments, we showed that delivery of lentivirus synapsin-Cre into the somatosensory cortex of neonatal Rictor cKO mice successfully knocked out Rictor protein. We further showed that conditional knockout of Rictor in Fragile X mice restored components of Rac/PAK and cofilin signaling to near wild-type values. Preliminary findings indicate that cKO of *Rictor* in layer V of the somatosensory cortex of juvenile/neonatal *Fmr1* KO mice is sufficient to rescue aberrant dendritic spine morphology and density, as assessed by dual DiI and immunofluorescence labeling. Future studies will determine whether cKO of Rictor can rescue aberrant synaptic plasticity and behavioral phenotypes in FXS mice.

**Disclosures: S. Roudabush:** None. **J. Yan:** None. **J. Hwang:** None. **B. Court-Vazquez:** None. **R.S. Zukin:** None.

**Poster**

**725. Fragile X Syndrome I**

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

**Support:** NIH 1U54HD082008
US Army Medical Research W81XWH-15-1-0436

**Title:** Cell-specific deletion of Fmr1 from excitatory neurons increases MMP-9 activity and contributes to abnormal development of mouse auditory cortex

**Authors: *M. RAIS**[1], A. PALACIOS[1], X. SHUAI[1], O. POPA[1], K. A. RAZAK[2], I. M. ETHELL[1]
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**Abstract:** Fragile X Syndrome (FXS), a genetic condition that is linked to autism, is characterized by intellectual disabilities, language deficiencies, behavioral challenges and auditory processing deficits. The *Fmr1* knockout (KO) mouse model replicates most of these associated behavioral and auditory processing deficits. We recently showed that elevated levels of Matrix Metalloproteinase-9 (MMP-9) contribute to the hyper-responsiveness of auditory cortex in *Fmr1* KO mice by affecting perineuronal net (PNN) formation around parvalbumin (PV)-expressing inhibitory interneurons. We also showed that genetic reduction of MMP-9 levels restores PNN formation around PV cells and normalizes auditory responses. However, how different cell types contribute to elevated MMP-9 levels and impaired development of PV cells and PNNs seen in *Fmr1* KO mice is not known. Increased cortical excitability (UP state) is present with deletion of *Fmr1* only from excitatory neurons, suggesting that FMRP expression in excitatory cortical neurons is required for normal cortical responses. In this study, we show that cell-specific deletion of *Fmr1* from excitatory neurons also affects PV and PNN development and MMP-9 activity in mouse auditory cortex. This was achieved through Cre-mediated deletion of floxed *Fmr1* gene in excitatory neurons of forebrain using Nex1 ($Cre^{Nex1}$) promoter. At P21, PV cell density and PV/PNN co-localization were significantly reduced in L2-3 and L4 auditory cortex of conditional KO mice, suggesting that these deficits develop during the early postnatal period. PNNs around PV cells also remained impaired in the adult auditory cortex of conditional KO mice. Furthermore, MMP-9 activity was also significantly increased in the adult auditory cortex of $Cre^{Nex1}/Fmr1^{Flox}$ KO mice compared to WT. Together, these findings suggest that *Fmr1* deletion from excitatory neurons may contribute to impaired development of PV expressing inhibitory interneurons via MMP-9-dependent regulation of PNNs, leading to abnormal auditory processing.

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**Poster**

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

**Support:** MH099114

**Title:** Metaplasticity mediated by Kv4.2 is altered in the hippocampus of Fmr1 KO mice

**Authors: *T. NOMURA**[1], C. MORTON[2], A. CONTRACTOR[3]
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**Abstract:** Fragile X syndrome (FXS) is a neurodevelopmental disorder that causes intellectual disability and is the most common known cause of autism. Studies using the mouse model of FXS (Fmr1 KO) have uncovered synaptic deficits including alterations in several forms of synaptic plasticity. CA1 hippocampal long-term potentiation (LTP) is still observed in Fmr1 KO mice, but there is evidence that the threshold for LTP induction is elevated. Metaplasticity, the "plasticity of synaptic plasticity", sets the state dependence of synapses to be either more or less likely to undergo LTP after a "priming" stimulus. Importantly, this priming induced change in LTP threshold is relevant to memory consolidation. However, it is not known if this important form of plasticity is altered in FXS mice. We found that priming of synapses with low frequency stimulation suppresses subsequent induction of LTP in the CA1 region of the hippocampus as previously described. This NMDA receptor-dependent metaplasticity was enhanced in Fmr1 KO mice. There was no significant difference in the relative NMDA receptor component of transmission in Fmr1 KO mice. Based upon the known alteration in the voltage gated potassium channel Kv4.2, a key molecule for LTP induction, we hypothesized that this important K+ channel might contribute to the altered metaplasticity in CA1 neurons in Fmr1 KO mice,. Consistent with this hypothesis, the enhanced metaplasticity in Fmr1 KO mice was restored by treatment of the slices with heteropodatoxin, a selective blocker of Kv4.2. Therefore, our results indicate that 1) Priming stimuli trigger modulation of Kv4.2 in CA1 neurons in NMDA receptor dependent manner, which results in LTP inhibition 2) The ability of NMDA receptor activation during priming to modulate Kv4.2 activity is altered in Fmr1 KO mice. This study provides novel insight into the mechanisms that underlie changes in the threshold for synaptic plasticity in FXS and may provide potential therapeutic targets for cognitive deficits linked with this disorder.

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**Poster**

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**Support:** NICHD R01 HD084214
Ben & Catherine Ivy Foundation
GE Healthcare

**Title:** Gaba in fragile x syndrome: A study using magnetic resonance spectroscopy

**Authors: *S. GADE**[1], M. GU[1], T. HJOERNEVIK[2], J. H. PARK[1], B. SHEN[1], S. HALL[1], D. SPIELMAN[1], F. T. CHIN[1]
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**Abstract:** Fragile X syndrome (FXS) is the result of a mutation on the FMR1 gene and is the leading heritable cause of cognitive disability[1]. Recently, research has implicated gamma-aminobutyric acid (GABA) dysfunction in learning, memory and normal neuronal function[2,3,4]. Magnetic Resonance Spectroscopy (MRS) allows for in vivo quantification of neurotransmitters to study disease state. Understanding the differences in neuro-metabolites such as GABA can be crucial in the development of precision medicine for patients with FXS. A total of 5 participants (age 24.6 ± 2.7 years) enrolled in the study, 3 young adult males with FXS and 2 young adult males with idiopathic intellectual delay (matched on age and IQ). A comprehensive neuropsychology battery of assessments for cognitive function (Stanford-Binet Intelligent Scales), adaptive skills (Vineland-II) and autism spectrum symptoms (ADOS-2) were completed. MRS data was acquired on a GE MR750 3T scanner using MEGA-SPECIAL sequence for GABA editing with TE= 80ms, TR=2s, 10 min acquisition[5]. This study presents a preliminary analysis of GABA/Creatine ratios and intellectual impairment. Using MRS, we quantify GABA/Creatine levels for potential differences between FXS and IDD participants. The current study is a first of its kind to quantify neuronal information in the population of FXS. Findings may indicate GABA levels correlate with behavioral measures of inhibition and predict atypical information processing. The quantification and analysis of GABA in FXS can suggest a disruption in inhibitory signaling in the brain and lead to a translational path for precision medicine.

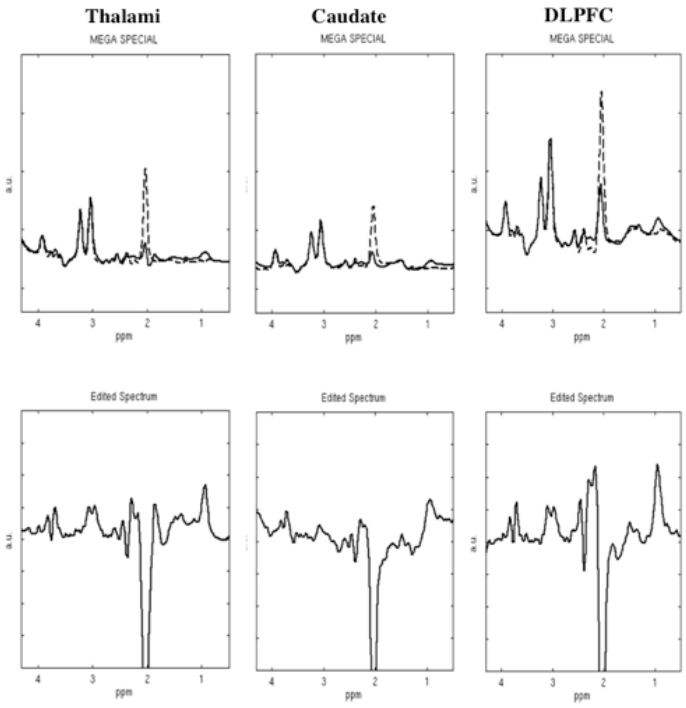


*Figure: 1 Representative 1H-MRS spectra for GABA editing.*

| IQ & GABA/Cre Ratios |
|---|

| | IQ Score (SB-5, FSIQ) | GABA/Creatine Ratios | | |
|---|---|---|---|---|
| Condition | | Thalamus | Caudate | DLPFC |
| FXS | 40 | 0.1155 | 0.0572 | 0.0784 |
| FXS | 40 | 0.0582 | 0.0766 | 0.0772 |
| FXS | 40 | 0.0791 | 0.0984 | 0.0541 |
| IDD | 56 | 0.1057 | 0.0965 | 0.0482 |
| IDD | 66 | 0.0863 | 0.0701 | 0.0751 |

**Disclosures: M. Gu:** None. **T. Hjoernevik:** None. **J.H. Park:** None. **B. Shen:** None. **S. Hall:** None. **D. Spielman:** None. **F.T. Chin:** None.

**Poster**

**726. Fragile X Syndrome II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 726.01/B1

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

**Support:** NSFC Grant 81771488

**Title:** Calsyntenin-1 implicates in dendritic spine abnormalities and hippocampus-dependent memory deficits in Fragile X Syndrome mice

**Authors: *Z. ZHANG**[1,2], Z. ZHANG[2], K. CHENG[1], Y. PEI[1], J. LIU[1], G. HAN[1], G. LIU[1], X. ZHU[2], S. JIN[2], L. WANG[2], F. XU[2], Y. ZENG[1]
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**Abstract:** Calsyntenin-1 (CLSTN1), a transmembrane cargo-docking protein of the cadherin superfamily localized in the postsynaptic membrane, is important for dendritic spine maturation during postnatal development. It was previously identified as one of the targets of fragile X mental retardation protein (FMRP). FMRP loss-of-function causes fragile X syndrome (FXS) and autistic features. However, the implication of CLSTN1 in dendritic spine abnormalities and the underlying neuropathologic processes in FXS remain to be investigated. In this study, using a transgenic mouse model and in vitro approach, we demonstrated that CLSTN1 mediates the dendritic redistribution of neuron-specific intercellular adhesion molecule-5 (ICAM5, telencephalin), subsequently affecting the maturation of dendritic spines in *Fmr1* KO mice, an animal model of FXS. We found that CLSTN1 protein is reduced in the postnatal brains of *Fmr1*

KO mice and that this reduction correlates with increased ICAM5 levels on the surface of synapses and excessive filopodia-like spines. Normalization of CLSTN1 levels in *Fmr1* KO neurons reduces ICAM5 expression on the surface of synapses and rescues impaired dendritic spine phenotypes. Using virus-mediated neural morphology labeling, we further found that normalization of CLSTN1 in the dentate gyrus in *Fmr1* KO mice restores the abnormal dendritic spine morphology of granule cells, and further improves spatial memory, fear memory and social memory. To investigate the mechanistic link between CLSTN1 and ICAM5, we conducted in vitro experiments and found that CLSTN1 immunoprecipitates, co-localizes, and co-transports with ICAM5 in neurons. In conclusion, this study demonstrates that CLSTN1 plays a critical role in dendritic spine formation and maturation by regulating ICAM5 redistribution in neurons. In *Fmr1* KO mice, CLSTN1 dysregulation contributes to excessive dendritic ICAM5 distribution and promotes abnormal spine formation and maturation. Thus, CLSTN1 may serve as a potential biomarker as well as therapeutic target for FXS.
**Key words:** Calsyntenin-1 (CLSTN1); Fragile X Syndrome; ICAM5; hippocampus-dependent memory; dendritic spine

**Disclosures: Z. Zhang:** None. **Z. Zhang:** None. **K. Cheng:** None. **Y. Pei:** None. **J. Liu:** None. **G. Han:** None. **G. Liu:** None. **X. Zhu:** None. **S. Jin:** None. **L. Wang:** None. **F. Xu:** None. **Y. Zeng:** None.

**Poster**

**726. Fragile X Syndrome II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 726.02/B2

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

**Support:** 2017XZZX002-13
31490590

**Title:** Mismatch between synapse elimination and synapse consolidation during early development in a mouse model of fragile X syndrome

**Authors: *X. WU**, Y. LIU, H. WANG
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**Abstract:** Synapse refinement, a process of elimination the unwanted synapses and consolidation of wanted ones, plays a crucial role in the early development of central nervous system. However, if this process was disrupted by either genetic mutations or environmental changes, is thought to be involved in many developmental disorders including autism. Loss of fragile X mental retardation protein (FMRP) in human causes intellectual disability and accompanies with features of autism such as problems with social interactions and delayed

speech. Although previous studies have shown that FMRP deficits cause seriously impaired synaptic plasticity, the role of this protein in developmental synapse refinement has not been investigated yet. Using whole cell patch recording in acute slices from fragile X mental retardation 1 gene knockout (*Fmr1* KO) mice, we explored the developmental synapse elimination and synapse consolidation respectively at the VPm relay synapse in the somatosensory system. We found the loss of FMRP did not affect synaptic connectivity at P7-8, but caused a decrease in the strength of the synapse, as indicated by very small evoked AMPAR-EPSCs and NMDAR-EPSCs in Fmr1-KO mice. Later at P12-13, the synaptic properties became comparable between WT and Fmr1-KO mice, but the synapse elimination was disrupted in the mutants. At the age of P15-P16, the synaptic connectivity returned to normal, as indicated by the majority of VPM neurons only received one Pr5 input in Fmr1-KO mice, but the synaptic strength showed a significant decrease again. Our results uncovered that synaptic elimination and synaptic strengthening do not match during development in *Fmr1* KO mice.

**Disclosures: X. Wu:** None. **Y. Liu:** None. **H. Wang:** None.

**Poster**

**726. Fragile X Syndrome II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 726.03/B3

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

**Support:** Nebraska Stem Cell Grant

**Title:** Probing astrocyte function in Fragile X syndrome using human induced pluripotent stem cell derived astrocytes

**Authors: *B. REN**[1], P. RAGUNATHAN[1], Y. JUNG[1], V. SAINI[1], B. OLDHAM[1], A. ARMSTRONG[1], N. RAJ[2], G. BASSELL[2], A. DUNAEVSKY[1]
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**Abstract:** Fragile X syndrome (FXS) is an X linked neurodevelopmental disorder related to intellectual disability and the most common monogenic cause of autism spectrum disorder. FXS results from an expansion of CGG repeat in the 5'-untranslated region of FMR1 gene, leading to the absence of fragile X mental retardation protein (FMRP), an mRNA binding protein. Recently, the absence of FMRP in astrocytes has been implicated in structural and functional synaptic deficits in FXS mouse models. However, the contribution of human astrocytes to such impairments remains unclear. To investigate whether astrocyte dysfunction contributes to the pathogenesis of FXS, we generated a human-based FXS model via differentiation of human induced pluripotent stem cells (hiPSC) to astrocytes. We observed delayed developmental

pattern from immature to the mature stage in FXS derived astrocytes with altered expression of astrocytic proteins. FXS astrocytes also have altered functional properties displaying enhanced ATP-induced calcium signaling. In ongoing experiments other canonical astrocyte function such as glutamate uptake capacity as well as regulation of synaptogenesis is being investigated. To examine the phenotypes of FXS astrocytes in vivo, we generated chimeric mouse brains by neonatal implantation of FXS and control hiPSC-derived immature astrocytes. The transplanted human astrocytes expressed the astrocyte markers, exhibited morphology distinct from the human astrocytes in culture and acquired the long and complex processes in the mouse brain 3 months post engraftment. We are currently examining the astrocyte morphologies, their distribution in different regions in the mouse brain and their effect on structural synaptic plasticity in vivo. Our studies suggest a role of human astrocytes in FXS pathogenesis and provide therapeutic targets for the personalized FXS treatment.

**Disclosures: B. Ren:** None. **P. Ragunathan:** None. **Y. Jung:** None. **V. Saini:** None. **B. Oldham:** None. **A. Armstrong:** None. **N. Raj:** None. **G. Bassell:** None. **A. Dunaevsky:** None.

**Poster**

**726. Fragile X Syndrome II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 726.04/B4

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

**Support:** NIMH, NICHD U54 HD082008-01

**Title:** Inhibition of matrix metalloproteinase-9 activity to correct auditory hypersensitivity in fragile X syndrome

**Authors: *P. PIRBHOY**[1], J. W. LOVELACE[2], T. WEN[1], K. RAZAK[2], D. K. BINDER[3], I. M. ETHELL[4]
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**Abstract:** Most individuals with Fragile X Syndrome (FXS) and autism spectrum disorders (ASD) experience improper processing of sensory stimuli (McDiarmid et al., 2017). Auditory cortical neurons of *fragile X mental retardation-1* gene knock-out (*Fmr1* KO) mice exhibit abnormally sustained responses to sounds and impaired sound selectivity (Rotschafer et al., 2013). Notably, genetic reduction of matrix metalloproteinase-9 (MMP-9) rescued altered event-related potential (ERP) habituation responses in *Fmr1* KO mice implicating MMP-9 as a target for reversing auditory processing deficits in FXS (Lovelace et al., 2016). Both FXS patients and *Fmr1* KO mice exhibit high levels of MMP-9, but how this impairs sensory processing and

neuronal circuits remains unclear. To test the hypothesis that excessive activity of MMP-9 leads to increased degradation of perineuronal nets (PNNs) and altered parvalbumin (PV) interneuron development, the auditory cortex (AC) of *Fmr1* KO C57BL/6 mice and their wild-type (WT) counterparts were treated with a selective MMP-2/9 inhibitor, SB-3CT (250 µM or 25mg/kg), or vehicle at P14 or P22. Immunohistochemistry was used to determine the density of PV-positive interneurons and PNNs in the AC one day after treatment. Results revealed enhanced PNN formation in layer 4 of the AC in *Fmr1* KO mice treated with SB-3CT at P14 compared to saline-treated *Fmr1* KO mice. To determine whether enhanced PNN formation following treatment of *Fmr1* KO mice with the MMP-9 inhibitor reverses auditory processing deficits we measured resting state and evoked neuronal oscillations in freely moving mice implanted with electroencephalography (EEG) electrodes. Results show that acute treatment of SB-3CT (25mg/kg) reduces excessive resting gamma power and normalizes sound-evoked responses in *Fmr1* KO mice compared to vehicle. Together, results reveal that inhibition of MMP-9 may serve as a potential therapeutic to ameliorate auditory cortical processing deficits in FXS.

**Disclosures: J.W. Lovelace:** None. **T. Wen:** None. **K. Razak:** None. **D.K. Binder:** None. **I.M. Ethell:** None.

**Poster**

**726. Fragile X Syndrome II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 726.05/B5

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

**Support:** NIMH 1R01MH109026
NINDS R0INS065992

**Title:** Homeostatic intrinsic plasticity is not operating normally in FMR1 KO cortical neurons

**Authors: *P. BUELOW**[1], Y. KWON[2], R. H. PURCELL[3], G. J. BASSELL[4], P. A. WENNER[5]
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**Abstract:** Fragile X Syndrome (FXS), the most common cause of heritable intellectual disability and autism spectrum disorder, is associated with a wide range of debilitating symptoms, such as sensory hypersensitivity. Foundational studies in a mouse model of FXS, the *FMR1* KO, suggest that an impaired cortical excitatory/inhibitory (E/I) balance may underlie symptoms associated with FXS. The E/I balance would be expected to depend on homeostatic plasticity mechanisms, which act to stabilize network activity levels. One type of homeostatic plasticity is homeostatic intrinsic plasticity (HIP), which regulates the expression of voltage-gated ion channels to maintain a stable membrane excitability (e.g. through Na channel insertion following spike

blockade). FMRP has previously been shown to regulate a subset of ion channels, some of which overlap with ion channels known to be involved in HIP. Surprisingly, there have been no prior studies of whether HIP is intact in the *FMR1* KO cortex. Here we show that some, but not all, aspects of HIP are intact in ~ DIV12 primary cortical excitatory neurons following 48 hr activity deprivation with TTX (Na channel blocker) and APV (NMDA receptor blocker). We show that in KO and WT control basal conditions, there is an equal proportion of neurons that spike once (single-spiking) or more than once (multi-spiking). Following TTX/APV, all WT neurons become multi-spikers. However, this conversion fails to occur in the KO, suggesting a loss of HIP function in KO neurons. On the other hand, we observed a greater increase in firing rate in KO neurons compared to WT when we measured the action potential firing frequency of the multi-spiking neurons following TTX/APV. This finding suggests a gain of HIP function specific to the multi-spiking neurons. These findings were recapitulated these findings following 48 hr activity reduction using the AMPA receptor antagonist NBQX. The recovery of network-wide activity patterns was tested following NBQX using multi-electrode arrays. Surprisingly, our preliminary findings suggest that KO networks recover activity similarly to WT despite altered expression of HIP. Together, these results highlight the importance of HIP mechanisms in establishing the homeostatic capacity of WT and KO networks, but suggest homeostasis is achieved using different mechanisms in the KO. Ongoing work is testing how altered HIP regulation of ion channels may underlie the loss and gain of HIP function in *FMR1* KO neurons.

**Disclosures: P. Buelow:** None. **Y. Kwon:** None. **R.H. Purcell:** None. **G.J. Bassell:** None. **P.A. Wenner:** None.

**Poster**

**726. Fragile X Syndrome II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 726.06/B6

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

**Support:** DBT
MRC
Simons Foundation

**Title:** Fronto-amygdala connectivity in a rat model of fragile X syndrome

**Authors: *A. D. JACKSON**[1,2,3,4], S. M. TILL[1,2,3], D. J. A. WYLLIE[1,2,3,4], S. CHATTARJI[2,4,5], P. C. KIND[1,2,3,4]
[1]Ctr. for Discovery Brain Sci., [2]Simons Initiative for the Developing Brain, [3]Patrick Wild Ctr., Univ. of Edinburgh, Edinburgh, United Kingdom; [4]Ctr. for Brain Develop. and Repair, Inst. for Stem Cell Biol. and Regenerative Med., Bangalore, India; [5]Natl. Ctr. for Biol. Sci., Bangalore, India

**Abstract:** Fragile X syndrome (FXS) is a common form of heritable intellectual disability and autism spectrum disorder caused by the loss of FMRP. Some of the key symptoms associated with FXS are social anxiety, abnormal emotional behaviour as well as mood disorders. Similarly, studies using animal models of FXS, including both the mouse and the recently generated rat model, have also revealed changes in fear and anxiety behaviours. Fronto-amygdala circuitry has been strongly implicated in emotional regulation and its disruption has been associated with anxiety-related disorders. Therefore, we aimed to determine if neuronal function and plasticity in medial prefrontal cortex (mPFC) and basolateral amygdala (BLA), as well as their interactions are altered, potentially explaining the deficits in fear learning and expression in a novel rat model of FXS.

Here, we show that mGluR-dependent long-term potentiation (LTP) at both cortical and thalamic inputs to the lateral amygdala are absent in *Fmr1* KO rats. We also observed age-dependent LTP deficits in the prelimbic area of mPFC. Finally, we used retrograde tracers to identify a neuronal subpopulation in layer 5 mPFC that projects to the BLA. Whole-cell *in vitro* electrophysiology recordings revealed these cells are hypoexcitable in the absence of FMRP, due at least in part, to a significant shortening of the axon initial segment, the site of action potential initiation. This effect on cellular excitability was not observed in the subpopulation of mPFC layer 5 neurons that project to the contralateral mPFC. Conversely, principal neurons in the BLA that project to the mPFC exhibited strong hyperexcitability compared to control neurons. These data reveal that the loss of FMRP results in alterations in the subnetworks that mediate fronto-amygdala transmission which may have significant effects on how these circuits process fear information.

**Disclosures: A.D. Jackson:** None. **S.M. Till:** None. **D.J.A. Wyllie:** None. **S. Chattarji:** None. **P.C. Kind:** None.

**Poster**

**726. Fragile X Syndrome II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 726.07/B7

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

**Support:** NIH Grant 1U54 HD082008-01
US Army Medical Research W81XWH-15-1-0436
FRAXA Research Foundation Fellowship

**Title:** Pharmacological rescue of translation-relevant EEG phenotypes in a mouse model of fragile X syndrome

**Authors: *J. W. LOVELACE**[1], K. ESPINOZA[2], I. M. ETHELL[3], D. K. BINDER[4], K. A. RAZAK[5]
[1]Psychology Dept., [2]UC Riverside, Riverside, CA; [3]Univ. California Riverside Sch. of Med.,

Riverside, CA; [4]Univ. of California Riverside Div. of Biomed. Sci., Riverside, CA; [5]Univ. California, Riverside, Riverside, CA

**Abstract:** Identification of comparable biomarkers in humans and validated animal models will facilitate pre-clinical to clinical therapeutic pipelines to treat neurodevelopmental disorders. Fragile X Syndrome (FXS) is a leading known genetic cause of intellectual disability with symptoms that include increased anxiety, social and sensory processing deficits. Recent EEG studies in humans with FXS have identified neural oscillation deficits that include enhanced resting state gamma power and reduced inter-trial coherence of sound evoked gamma oscillations. To determine if analogous phenotypes are present in an animal model of FXS, we recorded EEGs in awake, freely moving *Fmr1* knock out (KO) mice using similar stimuli as in the human studies. We report remarkably similar neural oscillation phenotypes in the *Fmr1* KO mouse including enhanced resting state gamma power and reduced evoked gamma synchronization. These deficits suggest a form of enhanced 'resting state noise' that interferes with the ability of the circuit to mount a synchronized response to sensory input, predicting specific sensory and cognitive deficits in FXS. These observed deficits are either reduced or completely rescued after pharmacological treatment which include acute (1 day) or chronic (10 day) treatment with Minocycline. We also report on the effectiveness of acute and chronic CTEP on these same deficits. The abnormal gamma oscillations are consistent with parvalbumin neuron and perineuronal net deficits seen in the *Fmr1* KO mouse auditory cortex indicating that the EEG biomarkers are not only clinically relevant, with evidence of pharmacological intervention, but could also be used to probe cellular and circuit mechanisms of sensory hypersensitivity in FXS.

**Disclosures: K. Espinoza:** None. **I.M. Ethell:** None. **D.K. Binder:** None. **K.A. Razak:** None.

**Poster**

**726. Fragile X Syndrome II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 726.08/B8

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

**Support:** FRAXA Foundation
FRQS 33140

**Title:** Neurophysiological changes induced by a combined intervention with lovastatin and minocycline in patients with fragile-X-syndrome: A TMS study

**Authors: *A. LACROIX**[1], F. MORIN-PARENT[2], C. CHAMPIGNY[3], F. CORBIN[3], J.-F. LEPAGE[4]
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Sherbrooke, QC, Canada; [3]Dept. of biochemistry, [4]Pediatrics, Sherbrooke Univ., Sherbrooke, QC, Canada

**Abstract:** Animal models of Fragile-X syndrome (FXS) show the presence of imbalance between excitatory and inhibitory intracortical mechanisms. This imbalance is thought to be at the root of several features typical of the disorder, such as anxiety, seizures, hypersensitivity, and hyperactivity. Preclinical studies show that Minocycline and Lovastatin have positive impacts on neurophysiological markers of the disorder, including neuronal hyperexcitability, while open label clinical studies show improvement in hyperactivity and anxiety. Here, for the first time, we assessed the effects of a 20-weeks pharmacological intervention combining Lovastatin and Minocycline (LOVAmix trial) on the main inhibitory and excitatory circuits using transcranial magnetic stimulation (TMS) in 16 patients with FXS. We measured the resting motor threshold (rMT), short interval intracortical inhibition (SICI), long interval intracortical inhibition (LICI), cortical silent period (CSP), and intracortical facilitation (ICF). Before treatment, individuals with FXS presented significantly altered SICI, LICI, and ICF compared to age and sex matched controls. Preliminary analyses show that LOVAmix intervention normalized SICI in FXS, implying an improvement in GABAa mediated inhibition. These results suggest that combined therapy with Lovastatin and Minocycline is a promising approach to correct the neurophysiological alterations involved in cortical hyperexcitability in FXS.

**Disclosures: F. Morin-Parent:** None. **C. Champigny:** None. **F. Corbin:** None. **J. Lepage:** None.

**Poster**

**726. Fragile X Syndrome II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 726.09/B9

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

**Title:** Modeling fragile x syndrome (fxs): gsk-3β, a promising therapeutic target for fxs

**Authors: *M. CIAMPOLI**, P. PORCEDDU, A. MISTO, A. M. REGGIANI
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**Abstract:** Fragile X syndrome (FXS) is a neurodevelopmental disorder, resulting from the loss of expression of the fragile X mental retardation (FMR1) gene. Individuals affected by FXS display many behavioral problems, including hyperactivity, cognitive impairment and autistic-like behaviors. The focus of our study was to understand more on the biological mechanism involved in FXS. To do that we initiated by progressing the behavioral characterization of FMR1 KO mice, a widely used experimental model to mimic FXS in rodents since they carry the same mutation as in the human disease. Key FXS associated phenotypes were investigated, i.e.

locomotor activity, sensorimotor gating, cognitive abilities and social behavior. Moreover, since our mice are derived from FVB genetic background the comparison was made with respect to corresponding wild type (WT) of such a strain. Our main findings were that FMR1 KO mice have significantly increased level of hyperactivity in the open field test, altered startle responses and strong sociability deficits as shown by the reduced social interaction attitude when they meet an unknown mouse. In contrast, a very mild cognitive deficit was observed by using different specific behavioral test.Hardly anything is known about the pathological mechanisms leading to FXS symptoms and we focused our interest on the glycogen synthase kinase 3 beta (GSK-3β) system since there is growing evidence showing an increased activity of this kinase in the mouse model of FXS. GSK-3β regulates a variety of developmental processes, such as neurogenesis, glycogenesis, cell migration, cell morphology and axonogenesis through interaction with a variety of signaling pathways. The possible link with FXS could be that FMRP is known to play a critical role in adult hippocampal neurogenesis and regulation of adult neural stem cell fate by modulating the translation of GSK-3β. Therefore, we decided to test the GSK3β hypothesis in our characterized FMR1 KO mice. We chronically treated FMR1 KO mice with a GSK-3β inhibitor (TDZD-8) and we looked at the effect on the behavioral phenotypes development. Highly remarkably we found that GSK-3β inhibitor is able to rescue the different behavioral alterations typical of FMR1 KO mice.These findings strongly suggested a role of GSK-3β in the specific behavioral patterns associated with FXS.

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**Poster**

**726. Fragile X Syndrome II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 726.10/B10

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

**Support:** NIH F31MH115656-01
Seaver Foundation
NIMH T32

**Title:** Disruption of the KH1 domain of Fmr1 leads to transcriptional alterations, impairments in white matter integrity, and attentional deficits in rats

**Authors: *C. E. GOLDEN**[1], M. BREEN[2], L. KORO[2], M. G. BAXTER[3], H. HARONY-NICOLAS[2], J. D. BUXBAUM[4]
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**Abstract:** Fragile X Syndrome (FXS) is a neurodevelopmental disorder that is the leading monogenic cause of autism spectrum disorder and a frequent form of inherited intellectual disability. FXS is caused by mutations in the Fragile X mental retardation 1 (*FMR1*) gene. In most cases, the mutation is an expansion of a microsatellite CGG triplet repeat, which leads to suppression of the expression of the fragile X mental retardation protein (FMRP), an RNA-binding protein involved in multiple aspects of mRNA metabolism. In some cases, individuals with FXS carry a point mutation in FMR1. Interestingly, we found that the previously published *Fmr1* knockout rat model of FXS expresses a transcript with a deletion of the KH1 domain, an RNA-binding domain where one of the few known point mutations associated with FXS is found. This deletion of the Fmrp-KH1 domain leads to attention deficits in both males and females, reminiscent of those observed in individuals with FXS. Deletion of the KH1 domain also leads to alterations in the transcriptional profiles within the medial prefrontal cortex (mPFC), which are of potential translational value for FXS, and deficits to white matter integrity in the neocortex and subcortical regions, measured with diffusion tensor imaging. These findings indicate that attentional testing and magnetic resonance imaging might be reliable cross-species tools for investigating the pathophysiology of FXS and potential readouts for pharmacotherapy testing.

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**Poster**

**726. Fragile X Syndrome II**

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**Program #/Poster #:** 726.11/B11

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

**Support:** ZIA-MH000889

**Title:** Amino acid starvation: Differential response to DHPG stimulation in hippocampal slices from WT and Fmr1 KO mice

**Authors: S. COOKE**, J. RUSSIN, I. LOUTAEV, *C. B. SMITH
Section on Neuroadapatation and Protein Metabolism, NIH, NIMH-SNPM, Bethesda, MD

**Abstract:** Fragile X syndrome (FXS) is the most common inherited form of intellectual disability, resulting from loss of the protein FMRP. Although the origin of FXS is known, the cellular and molecular consequences of this loss are still being uncovered. As FMRP is an RNA-binding protein, an impairment in protein synthesis is hypothesized to be a core phenotype. We developed an *in vitro* method to measure rates of protein synthesis in hippocampal slices with [$^{3}$H]leucine as a tracer. Preliminary results show no differences in protein synthesis between WT

and *Fmr1* KO mice, despite previous observations *in vivo* (Qin et al., *J Neurosci* 25:5087, 2005) and *in vitro* (Osterweil et al., *J Neurosci* 30:15616, 2010). Our protocol differs from other *in vitro* methods through inclusion of a full complement of amino acids in the incubation medium. Amino acid starvation (AAS) has been shown to have widespread, powerful effects on activation and translation of proteins involved in regulating protein synthesis. We used Western blotting to measure phosphorylation and abundance of signaling molecules following mGluR5 stimulation (100 μM DHPG, 5 min) during amino acid repletion (AAR) and AAS. The most striking results were found with proteins p-p70S6k, p-eIF2α, and p-Akt (Ser 473). In AAR conditions, p-p70S6k increased (50%) with DHPG treatment in WT but not in *Fmr1* KO. This finding is consistent with protein synthesis dependence of mGluR5-activated LTD (Huber et al., *Science* 288:1254, 2000) in WT but not in *Fmr1* KO (Nosyreva & Huber, *J Neurophys* 95:3291, 2006). In contrast, DHPG increased p-p70S6k (60%) in *Fmr1* KO, but not in WT, under AAS conditions. Following DHPG treatment, p-eIF2α tended to decrease (20%) in WT and significantly increased (40%) in *Fmr1* KO under AAR and was unaffected by DHPG under AAS. These genotype-specific differences in phosphorylation of eIF2α under AAR and AAS may point to a deficiency in this important regulatory site of protein synthesis in *Fmr1* KO mice. Lastly, p-Akt was not affected by DHPG in either genotype under either condition, whereas in both genotypes levels of p-Akt were significantly elevated by AAS, regardless of DHPG stimulation. Elevated phosphorylation of Akt in response to AAS illustrates the potential for AAS to alter the activity of proteins involved in cellular growth pathways. No known defects in whole body amino acid metabolism have been reported in FXS, making AAR the physiologically relevant condition for its study. The response of hippocampal slices to amino acid conditions provides a new domain for understanding the consequences of FMRP loss in cellular signaling pathways.

**Disclosures: S. Cooke:** None. **J. Russin:** None. **I. Loutaev:** None. **C.B. Smith:** None.

**Poster**

**726. Fragile X Syndrome II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 726.12/B12

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

**Support:** NIH MH084989
NIH MH096832
NIH 5T32MH065215-15

**Title:** FMRP-NBEA-PKA pathway actin cytoskeleton misregulation in a fragile X syndrome model

**Authors: *J. C. SEARS**, K. S. BROADIE
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**Abstract:** Fragile X syndrome (FXS) is the leading monogenic cause of autism and intellectual disability, resulting from loss of Fragile X Mental Retardation Protein (FMRP) encoded by the *Fmr1* gene. FMRP acts as a repressor of protein translation during activity-dependent synapse refinement in early-use critical periods. FMRP loss causes neural circuit hyperexcitation and hypoinhibition. Here, we employ the *Drosophila* FXS model to explore molecular mechanisms underlying these defects within the central brain Mushroom Body (MB) learning and memory circuit. We first discovered FMRP binds the mRNA transcript for Neurobeachin (NBEA; *Drosophila* Rugose(Rg)), with protein levels increased in the disease model. NBEA/Rg is an A-Kinase Anchoring Protein that regulates neuronal PKA localization/activity and modulates short-term memory formation. In parallel, we discovered striking neuronal actin cytoskeleton alterations during the early-use critical period in the FXS disease model, with increased filamentous-actin (F-actin) in MB axon lobes. Proposing a FMRP-Rugose-PKA-actin pathway, we hypothesize Rg gain-of-function (GOF) should phenocopy FMRP loss-of-function (LOF). Consistently, Rg GOF increases F-actin in MB axon lobes, and correcting Rg levels in the FXS disease model prevents the F-actin defect. Thus, elevated Rg is sufficient to increase axonal F-actin, and Rg is necessary for F-actin accumulation in the disease state. We hypothesized this mechanism operates via PKA activity, and so tested if modulating PKA would phenocopy Rg GOF and FMRP LOF. Consistently, over-expression of the PKA catalytic subunit causes a striking F-actin increase in MB axon lobes. Using a PKA activity assay with brain homogenates, we find ~2-fold increased PKA activity in the FXS disease model, comparable to the effect of PKA catalytic subunit over-expression. Moreover, correcting Rg levels in the FXS model prevents this elevated PKA activity phenotype, indicating that Rg is necessary for the observed PKA hyperactivity. Ongoing experiments are testing this new pathway both in downstream and feedback signaling mechanisms, and in single MB neurons. Taken together, our data indicate hyperactive PKA activity through a loss of FMRP-Rugose regulation in the FXS disease state, resulting in excessive F-actin accumulation in learning and memory center neurons during the critical period. To ensure rigor, sample sizes of at least 10 brains per group in imaging experiments were used, dissections/protein isolations were conducted on the same day, and female/male numbers were kept constant. When possible, analyses were conducted blind, and compared groups were labeled simultaneously.

**Disclosures: J.C. Sears:** None. **K.S. Broadie:** None.

**Poster**

**726. Fragile X Syndrome II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 726.13/B13

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

**Support:** US Army Medical Research grant W81XWH-15-1-0436

**Title:** Effect of sound exposure on developing auditory cortex in fragile X syndrome mouse model

**Authors: *A. KULINICH**[1], S. M. REINHARD[2], K. A. RAZAK[2], I. M. ETHELL[1]
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**Abstract:** Fragile X syndrome (FXS) is the most common genetic cause of autism and intellectual disability. FXS is associated with a loss-of-function mutation in the Fragile X mental retardation (*Fmr1)* gene. The *Fmr1* knock out (KO) mice display the core deficits of FXS, including sensory hypersensitivity and abnormal cortical processing. Our previous study revealed abnormal responses to sound in the developing auditory cortex (AC) of *Fmr1* KO mice during the critical period plasticity (CPP) window, a postnatal window of circuit re-organization driven by sensory input. We also observed a delayed development of parvalbumin (PV) interneurons and perineuronal net (PNN) formation around GABAergic cells, suggesting that the auditory processing deficits may arise from altered CPP during development. To test whether developmental plasticity is abnormal in *Fmr1* KO mice, KO and WT mice were exposed to a 14 kHz tone during CPP (from P9 to P20). Control WT and KO mice were raised in the same sound-attenuated chamber from P9 until P20 without the exposure to 14 kHz tone. We obtained *in vivo* event related potentials recordings from AC of control and sound-exposed P21-P23 WT and KO mice. Significant changes in response amplitude evoked by 14 kHz tone were observed between control and sound-exposed *Fmr1* KO groups. We also performed dendritic spine analysis in L2/3 and L5/6 AC in control and sound-exposed P21 WT and KO mice. Spine density was found to be higher in AC of sound-unexposed *Fmr1* KO mice compared to WT; however it decreased dramatically in both groups following sound exposure. Immunohistochemical analysis also showed a reduced PV and PNN cell density in P21 *Fmr1* KO mice compared to WT. However, sound exposure lead to increased PV cell density in *Fmr1* KO mice, but no change in WT mice. Our studies provide a novel mechanistic insight into the auditory processing deficits in FXS and suggest a developmental period for therapeutic applications.

**Disclosures: A. Kulinich:** None. **S.M. Reinhard:** None. **K.A. Razak:** None. **I.M. Ethell:** None.

**Poster**

**726. Fragile X Syndrome II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 726.14/B14

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

**Support:** NIH Grant MH085324

**Title:** Dendritic spine alterations of striatal spiny projection neurons in the mouse model of fragile X syndrome

**Authors: *J. A. BEATTY**, B. A. GREGORY, M. J. RAILING, T. P. O'MALLEY, A. M. NIETO, C. L. COX
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**Abstract:** Fragile X syndrome (FXS) is the most common form of inherited intellectual disability and the leading genetic cause of autism spectrum disorder. Symptoms include hyperactivity, social phobia, impaired cognition, and repetitive/compulsive behaviors. FXS is caused by a repeating CGG mutation in the fragile X mental retardation 1 (*FMR1*) gene leading to a decrease in fragile X mental retardation protein (FMRP). FMRP is highly expressed in neurons, especially in dendritic spines, the primary site of synaptic connections. Neocortical neurons from FXS patients and *Fmr1* knock-out (KO) mice have an increased density of abnormally elongated dendritic spines, suggesting that the decrease of FMRP is linked to abnormal spine development, leading to alterations in synaptic transmission. The striatum is the input nucleus of the basal ganglia, a group of subcortical brain regions implicated in voluntary motor control and learning. Although basal ganglia dysfunction has been linked to repetitive/compulsive behaviors, few studies have investigated the spine morphology of striatal spiny projection (SP) neurons in FXS. In this study we performed two-photon laser scanning imaging of fluorescently labeled SP neurons from male and female WT and *Fmr1* KO mice (approximately 3 weeks of age). Image series in the z-plane of proximal and distal dendrites from SP neurons were used to count and classify dendritic spines into distinct subtypes based on shape and overall length. *Fmr1* KO mice displayed a reduced population frequency of mature, mushroom-type spines on SP neurons compared to WT controls. In addition, *Fmr1* KO mice had a lower density of total spine and mushroom-type spines on SP neurons compared to WT controls. Based on the altered dendritic spine morphology seen in this study, we hypothesize that SP neurons from *Fmr1* KO mice may also possess alterations in excitatory synaptic transmission.

**Disclosures: J.A. Beatty:** None. **B.A. Gregory:** None. **M.J. Railing:** None. **T.P. O'Malley:** None. **A.M. Nieto:** None. **C.L. Cox:** None.

**Poster**

**726. Fragile X Syndrome II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 726.15/B15

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

**Support:** Fonds de recherche du Québec (FRQS) Grant 33140
FRAXA Researcg Foundation
Faculté de médecine de l'Université de Sherbrooke (FMSS)

Canadian Institutes of Health Research (CIHR)

**Title:** fMRI in clinical research for fragile X syndrome:Preliminary results from the LOVAmix trial

**Authors: *A. LOUDGHI**, F. MORIN-PARENT, S. GHUMMAN, C. CHAMPIGNY, F. CORBIN, J.-F. LEPAGE
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**Abstract:** Fragile X syndrome (FXS) is the primary hereditary cause of autism spectrum disorder and intellectual disability. Recent clinical trials have highlighted the need for objective outcome measures to quantify response to treatment, including neuroimaging techniques such as resting-state functional magnetic resonance imaging (rs-fMRI) to assess potential changes in cerebral functioning. Here, we report the preliminary results of 11 participants who took part in the LOVAmix trial, the first clinical trial investigating the effects of a combined pharmacological intervention (lovastatin + minocycline) for patients with FXS. Preliminary analyses show that the intervention modulates connectivity within the salience network, a circuit at the interface of other networks that play a crucial role in task switching. These results demonstrate the feasibility of using rs-fMRI as an objective outcome measure in clinical research with FXS patients, and suggest that the combined administration of lovastatin and minocycline modifies brain circuits related to core domains of cognitive dysfunctions that are characteristic of the condition.

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**Poster**

**726. Fragile X Syndrome II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 726.16/B16

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

**Support:** NIH Grant R15S088776

**Title:** Cytokine expression and sickness behavior following lipopolysaccharide stimulation in the Fmr1 knockout mouse

**Authors: *S. L. HODGES**[1], S. 0. NOLAN[2], L. TOMAC[2], I. MUHAMMED[2], P. WOMBLE[2], J. N. LUGO[1]
[1]Inst. of Biomed. Studies, [2]Psychology and Neurosci., Baylor Univ., Waco, TX

**Abstract:** Fragile X syndrome (FXS) is a neurodevelopmental disorder caused by a single genetic mutation in the Fragile X mental retardation 1 (*FMR1*) gene. In addition to behavioral

and physiological symptoms, evidence has suggested that individuals with FXS may have altered immune function. In the present study, we investigated how *Fmr1* knockout (KO) mice would respond to an innate immune stimulus by administering a single injection of the bacterial mimetic lipopolysaccharide (LPS) (0.33mg/kg, i.p.) or 0.9% physiological saline. Four hours after injections, brains were dissected, followed by RNA isolation and qRT-PCR on hippocampal tissue. As expected, we found LPS significantly increased proinflammatory cytokines in *Fmr1* KO and wild type (WT) mice (IL-1beta, TNF-alpha, IL-6, MCP-1), with no effect on anti-inflammatory cytokine IL-10. Additionally, *Fmr1* KO mice given LPS had trending elevations in proinflammatory cytokine expression compared to WT LPS mice. A separate cohort of mice were tested in a burrowing paradigm with a single injection of LPS or saline prior to the testing phase, however, no differences were detected between genotypes in the behavioral sickness response following an immune stimulus. Twenty-four hours following injections, we examined cytokine expression again to determine whether differences detected at 4hr. post-LPS injections were similarly altered at 24hrs. This study provides insight into whether dysregulated immunity could be playing a broader role in the pathophysiology of FXS.

**Disclosures: S.L. Hodges:** None. **S.0. Nolan:** None. **L. Tomac:** None. **I. Muhammed:** None. **P. Womble:** None. **J.N. Lugo:** None.

**Poster**

**726. Fragile X Syndrome II**

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**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 726.17/B17

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

**Support:** NIH Grant R15S088776

**Title:** Dietary rescue of adult behavioral deficits in the Fmr1 knockout mouse

**Authors: *S. O. NOLAN**[1], S. L. HODGES[2], J. OKOH[1], M. BINDER, 76708[1], S. CONDON, 76708[1], P. WOMBLE, 76708[1], J. N. LUGO, JR[1]
[1]Psychology and Neurosci., [2]Inst. of Biomed. Studies, Baylor Univ., Waco, TX

**Abstract:** Previous work has supported the role of omega-3 fatty acids in the attenuation of the behavioral phenotype of the male *Fmr1* knockout mouse model. Given the association of earlier interventions with better prognoses in children with neurodevelopmental disorders, this study aims to expand upon the current knowledge through the inclusion of a prenatal treatment of omega-3 fatty acids. In the present study, male FVB/129 *Fmr1* wildtype and female *Fmr1* heterozygous breeding pairs were assigned to one of three diet conditions one week prior to pairing: standard lab chow, EPA/DHA enriched chow, and a diet controlling for the fat increase. On postnatal day (PD) 9, isolation-induced ultrasonic vocalizations were recorded from pups.

Upon reaching PD60, the same subjects were tested in several behavioral assays, including open field, elevated plus maze, social partition, nose poke assay, delay fear conditioning, and pre-pulse inhibition. Preliminary analyses of the results indicate that prenatal dietary treatment with omega-3 fatty acids reduces hyperactivity, normalizes anxiety levels and enhances fear learning in the delay fear conditioning task in adulthood. To date, clinical trials for children with neurodevelopmental disorders have been largely ineffective, and studies suggest most parents of these children will try at least one alternative therapy during their child's lifetime. As such, studies like these are important for assessing the impact of such an intervention on the development of autistic behaviors.

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**Poster**

**726. Fragile X Syndrome II**

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**Program #/Poster #:** 726.18/B18

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

**Support:** Michael Smith Foundation for Health Research
Canadian Institutes for Health Research (CIHR MOP 125888)
Fragile X Research Foundation of Canada

**Title:** Loss of FMRP leads to NMDAR dysfunction and dendritic atrophy in a specific subpopulation of hippocampal neurons

**Authors: *L. BETTIO**[1], S. YAU[2], J. CHIU[1], C. CHIU[1], B. R. CHRISTIE[1]
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**Abstract:** Fragile X Syndrome (FXS) is the most common inherited intellectual disability. This neurological condition is caused by silencing of the Fmr1 gene, which encodes the Fragile X Mental Retardation Protein (FMRP). FMRP is an RNA-binding protein that has been shown to repress the translation of a large number of mRNAs, including many of which encode proteins that are important for synaptic structure and function. The excessive protein synthesis induced by lack of FMRP in the hippocampus has been associated with an abnormal number of immature dendritic spines, and deficits in synaptic plasticity. Within this context, we have previously reported that a dysfunction in N-methyl-D-aspartate receptors (NMDARs) in the hippocampal dentate gyrus (DG) is associated with some of the behavioral changes induced by the lack of FMRP. Since NMDARs contribute to dendritic arborization during neuronal development, the present study investigated whether the hypofunction of these receptors is associated with

alterations in dendritic complexity in the hippocampal DG in Fmr1 KO mice. This subregion of the hippocampus is constantly producing new neurons in the adult brain, which migrate from its deeper layer (subgranular zone) to its granule cell layer (GCL). Here, we examined how the lack of FMRP affects NMDAR function in two subpopulations of neurons: those with a single primary dendrite that reside in the inner portion of the GCL (more immature), and those that present multiple primary dendrites and are located in the outer portion of the GCL (more mature). Our findings demonstrate that neurons with both a single primary dendrite and multiple primary dendrites from Fmr1 KO mice present a reduction in NMDAR excitatory postsynaptic currents (EPSCs) and a higher level of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR)/NMDAR ratio in comparison with their wild-type counterparts. However, we only found a significant change in dendritic arborization of neurons with multiple primary dendrites. Our study indicates the NMDAR-associated dendritic atrophy in Fmr1 KO mice affects a specific subpopulation of GCL neurons, that may represent a more mature neuronal phenotype.

**Disclosures: L. Bettio:** None. **S. Yau:** None. **J. Chiu:** None. **C. Chiu:** None. **B.R. Christie:** None.

**Poster**

**726. Fragile X Syndrome II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 726.19/B19

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

**Support:** HD082013

**Title:** Genome-wide measurement of mRNA translation in fragile X syndrome

**Authors: *S. ARYAL**, F. LONGO, E. KLANN
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**Abstract:** Fragile X syndrome (FXS) is the most prevalent inherited form of intellectual disability and the leading monogenic cause of autism. FXS is caused by loss of expression of the fragile X mental retardation protein (FMRP), an mRNA-binding protein whose primary function is to regulate translation in neurons. Correspondingly, mouse models of FXS exhibit increased steady-state protein synthesis in multiple brain regions. Precise control of translation is especially critical in neurons because rapid *de novo* protein synthesis is required for long-lasting synaptic plasticity, which is impaired in FXS mice. Indeed, there is widespread agreement that aberrant translation underlies a majority of the phenotypes, including autism-like behaviors, exhibited by FXS model mice. Consistent with these observations, genetic deletion of the translation-stimulating p70 S6 kinase 1 (S6K1) rescues a range of phenotypes, including

excessive translation, aberrant synaptic plasticity, and autism-like behaviors in FXS model mice. In this study, we sought to determine the identities of the messenger RNAs that exhibit eccentric translation in FXS model mice brains, and to investigate whether genetic deletion of S6K1 normalized their altered synthesis to levels comparable to those in wild-type (WT) littermates. Toward this end, we carried out ribosome profiling on cortical lysates of ~ P30 WT, *Fmr1* knockout (KO), *Rps6kb1*(S6K1) KO, and double knockout (DKO) mice. Ribosome profiling uses deep sequencing of ribosome-protected mRNA fragments to identify precise positions of translating ribosomes on individual mRNAs. We used DeSeq2 on quality-controlled sequencing datasets to identify mRNAs that registered differential normalized ribosome footprint counts across the four genotypes.
To our surprise, we observed that the majority of genes with differential ribosome loading have decreased overall ribosome footprint counts in FXS. One possible explanation for these results is that the loss of FMRP causes ribosomes to elongate at increased velocities, which in turn decreases the number of ribosomes bound to FMRP-regulated mRNAs at steady-state, ultimately reducing ribosome loading. Indeed, using a novel biochemical method that measures the number of translating ribosomes remaining after defined periods of runoff elongation, we observed excessive elongation in primary cortical neurons derived from FXS model mice. We are currently conducting ribosome profiling after multiple time-points of runoff elongation to identify mRNAs that exhibit excessive elongation in FXS. Our findings reveal systems-level insights on translational dysregulation in the cortex of FXS model mice.

**Disclosures: F. Longo:** None. **E. Klann:** None.

**Poster**

**727. Angelman and Other Developmental Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

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

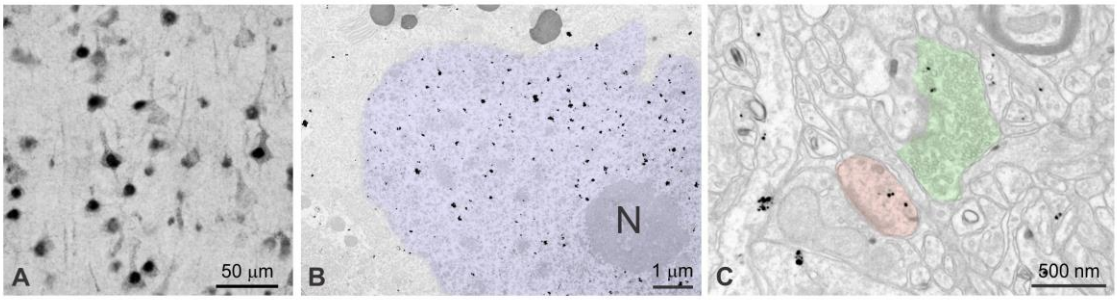
**Support:** NIH Grant NS039444 to R.J.W.
NIH Grant R56NS097831 to B.D.P.
the Angelman Syndrome Foundation to B.D.P.

**Title:** Subcellular organization of the autism-associated protein UBE3A in human cerebral cortex

**Authors: *A. C. BURETTE**[1], M. C. JUDSON[2], A. N. LI[3], E. F. CHANG[4], W. W. SEELEY[5], B. D. PHILPOT[6], R. J. WEINBERG[7]
[1]Cell and Developmental Biol., Univ. of North Carolina, Chapel Hill, NC; [2]Dept. of Cell Biol. and Physiol., UNC-CH, Chapel Hill, NC; [3]Memory and Aging Ctr., [4]Neurosurg., UCSF, San

Francisco, CA; [5]Memory and Aging Ctr., UCSF, San Mateo, CA; [6]Cell Biol. and Physiol., [7]Cell Biol. & Physiol., Univ. North Carolina, Chapel Hill, NC

**Abstract:** Loss of the E3 ubquitin ligase UBE3A causes Angelman syndrome, whereas excess UBE3A activity (through gene duplication or gain-of-function mutation) greatly increases the risk for autism. Despite this strong association with neurodevelopmental disorders, the functional role of UBE3A in the brain is still unclear, and its cellular and subcellular organization in the human brain is almost completely unknown. We used light and electron microscopic immunohistochemistry to study the distribution of UBE3A in in the adult human cerebral cortex. We demonstrate here that UBE3A is expressed throughout the layers of cortex. It is present at high levels in both excitatory and GABAergic neurons, and at lower levels also in glial cells. We find that UBE3A in neurons has a broad, but nonuniform, subcellular distribution, concentrating preferentially in axon terminals, and in euchromatin-rich domains within the nucleus (see figure). UBE3A in terminals is likely to help regulate transmitter release at individual synapses, consistent with published evidence in a mouse model. In contrast, we speculate that by regulating gene activity, UBE3A in the nucleus may exert cell-wide effects. By identifying the subcellular compartments in which UBE3A concentrates, our data provide insight into the diverse functional capacities of this E3 ligase in the neocortex, which may help to illuminate mechanisms of human neurodevelopmental disease.




A, UBE3A concentrates in neuronal nuclei; B, immunogold particles associate with euchromatin but not the nucleolus (N); C, signal is also visible in axon terminals (green) and dendritic spines (pink).

**Disclosures: A.C. Burette:** None. **M.C. Judson:** None. **A.N. Li:** None. **E.F. Chang:** None. **W.W. Seeley:** None. **B.D. Philpot:** None. **R.J. Weinberg:** None.

**Poster**

**727. Angelman and Other Developmental Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 727.02/B21

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

**Support:** Ontario Rett Syndrome Association
Jessica Carr Fund
CHEO Foundation

**Title:** The enteric nervous system in Rett syndrome

**Authors: *S. C. SCHOCK**[1], G. WAHBA[4], P. HUMPHREYS[2], E. NIZALIK[3], W. STAINES[4], D. GRYNSPAN[3]
[1]Res. Inst., [2]Div. of Neurol., [3]Pathology, Children's Hosp. of Eastern Ontario, Ottawa, ON, Canada; [4]Cell. and Mol. Med., Univ. of Ottawa, Ottawa, ON, Canada

**Abstract:** Background: Rett syndrome is a neurodevelopmental disorder characterized by cognitive impairment, motor dyspraxia and seizures which develop during early childhood in girls. MeCP2, the gene mutated in Rett syndrome, is an important mediator of synaptic development and is essential in regulating neuronal homeostatic synaptic plasticity. Clinical reports disclose that patients with Rett syndrome suffer from gastrointestinal (GI) dysmotility. We hypothesize that this could be due to impaired synaptic function in the enteric nervous system (ENS).
Methods: We have shown by immunohistochemistry that MeCP2 is present in neurons within the GI tract of humans and mice. We then carried out in vivo studies to determine whether MeCP2 knockout mice reproduced the GI dysmotility seen in Rett syndrome. Following this, homeostatic synaptic plasticity was induced in mouse enteric neuronal cultures by exposure to an excitatory stimulus (45mM KCl). The expression of the inhibitory neurotransmitter precursor nitric oxide synthase was then measured, an increase in expression being indicative of plasticity. This same experiment was performed on enteric neuronal cultures derived from MeCP2 knockout mice to determine if plasticity is altered in these neurons.
Results: MeCP2 knockout mice reproduced the GI dysmotility observed in Rett syndrome. We found that control enteric neuronal cultures underwent homeostatic synaptic plasticity in response to a prolonged excitatory stimulation. However, enteric neurons cultured from MeCP2 KO mice failed to show this induction of plasticity.
Conclusions: MeCP2 plays an important role in proper GI motility. Neurotransmitter imbalances likely mediate the GI pathology seen in Rett syndrome. These imbalances may be due to dysfunction in homeostatic plasticity mechanisms.

**Disclosures: S.C. Schock:** None. **G. Wahba:** None. **P. Humphreys:** None. **E. Nizalik:** None. **W. Staines:** None. **D. Grynspan:** None.

**Poster**

**727. Angelman and Other Developmental Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 727.03/B22

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

**Title:** Creatine transporter disorder: New insights into epileptic phenotype and diagnostic biomarkers

**Authors: *L. BARONCELLI**[1], F. CACCIANTE[2], G. SAGONA[3], M. GENNARO[1], L. LUPORI[2], R. MAZZIOTTI[3], E. PUTIGNANO[1], T. PIZZORUSSO[3]
[1]Neurosci. Institute, CNR, Pisa, Italy; [2]Scuola Normale Superiore, Pisa, Italy; [3]Univ. of Florence, Florence, Italy

**Abstract:** Creatine (Cr) transporter (CrT) deficiency is an orphan disorder (CTD, OMIM #300352) characterized by intellectual disability, epilepsy and autistic-like behavior. Epilepsy is one of the symptoms with the greatest impact on everyday life of patients and families. Animal models are crucial tools to analyze disease mechanisms and to develop new therapeutic strategies. Four murine models of CTD are available so far. However, they have been analyzed only at the behavioral, neurochemical and anatomical level. To expand our knowledge about the face validity of the murine model, we monitored brain excitability and seizure susceptibility in the CrT knockout mice using video-EEG recording sessions. Our data show that CrT loss-of-function results in higher susceptibility to kainic acid (KA)-induced seizures, as assessed both at behavioral and electrophysiological level. Accordingly, we detected a prominent reduction of parvalbuminergic synapses in the cerebral cortex. This activity allowed us to fill a substantial gap in the current literature and to provide a more comprehensive set of normative data for the evaluation of potential therapeutic approaches. In addition, since CTD patients show impaired activity of cerebral cortex, we monitored visual responses in CrT ko mice throughout the disorder progression using longitudinal transcranial intrinsic optical signal (IOS) imaging and visual evoked potential (VEP) recordings. A peculiar increase of IOS and VEP response was detected in CrT ko mice, indicating that integrated visual assessment could be used as a classifying biomarker for CTD diagnosis and treatment assessment with high reliability. Importantly, VEP recordings and IOS imaging can be readily applied to humans, increasing the translational value of the visual biomarker.

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**Poster**

**727. Angelman and Other Developmental Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 727.04/B23

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

**Support:** American Thyroid Association Research Grant

**Title:** Ectopic brain-derived insulin-like growth factor-1 partially rescues neuroanatomical defects associated with developmental hypothyroidism

**Authors: *A. GROND**[1], K. E. SAATMAN[2], D. S. SHARLIN[1]
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**Abstract:** Insufficient thyroid hormone (TH) during development results in permanent neurological deficits. These deficits are the result of neuroanatomical defects that include smaller brain, fewer parvalbumin neurons, and hypomyelination. Interestingly, insufficient insulin-like growth factor 1 (Igf-1) during development results in similar neuroanatomical defects to those reported for developmental hypothyroidism. Thyroid hormone is known to indirectly influence serum Igf-1 levels through its regulation of pituitary growth hormone (GH) secretion which stimulates hepatic Igf-1 production. Our lab and others have observed decreases of local brain-derived Igf-1 in the developing hypothyroid mouse brain. This observation suggests that deficits associated with low TH during development may be the result of altered brain-derived Igf-1. Considering this, we sought to determine whether ectopically expressing Igf-1 in the developing brain could rescue neuroanatomical defects associated with low TH. To accomplish this, the tet-off transgenic system was used where mice harboring the tetracycline transactivator protein driven by the human GFAP promoter (tTA-GFAP) were crossed with mice containing the human Igf-1cDNA under the control the TET response element (Igf1-pTRE) transgene. Double transgenic (dTg) offspring carrying both the tTA-GFAP and Igf1-TRE genes overexpress Igf-1 specifically in brain astrocytes. Timed-pregnant mice were treated with thyroid gland inhibitors from embryonic day 14.5 (E14.5) until postnatal day 14 (P14) to induce a hypothyroid state in pups. At P14, pups were weighed and sacrificed, trunk blood was collected, and brains were dissected, weighed, and immediately frozen. Hippocampal structure, known to be disrupted by developmental hypothyroidism, was assessed by fluorescent imaging using DAPI staining. Our initial results indicate that ectopic expression of Igf-1 in the brain (dTg mice) rescues hypothyroidism-induced reductions in brain weight without increasing body weight. In addition, the ectopic expression of Igf-1 restored hypothyroidism-induced perturbations in dentate gyrus size. Ongoing studies are using quantitative real-time PCR on micro-dissected cortical and hippocampal samples to quantify myelin associated glycoprotein and parvalbumin mRNAs. Taken together, our findings support the idea that ectopic brain-derived Igf-1 rescues neuroanatomical defects caused by hypothyroidism and implicates TH in the regulation of brain Igf-1.

**Disclosures: A. Grond:** None. **K.E. Saatman:** None. **D.S. Sharlin:** None.

**Poster**

**727. Angelman and Other Developmental Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 727.05/B24

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

**Support:** Sage Therapeutics, Inc.

**Title:** A Novel GABA receptor-positive allosteric modulator ameliorates motor dysfunction in an Angelman syndrome mouse model with maternal deletion from Ube3a to Gabrb3

**Authors: *H. YAN**[1], Z. PEI[1], R. RODRIGUIZ[2], X. WANG[1], M. LEWIS[5], M. ACKLEY[5], F. SALITURO[5], A. ROBICHAUD[5], J. DOHERTY[5], W. WETSEL[3], Y.-H. JIANG[4]
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**Abstract:** Angelman syndrome (AS) is a severe neurodevelopmental genetic disorder characterized by motor incoordination, absence of speech, epilepsy, intellectual disability, and autistic behaviors. Approximately 70% of AS patients harbor a maternal deletion in chromosomal region 15q11-q13 and ~15% of these patients bear mutations in the *UBE3A* gene. Notably, AS patients with maternal deletion of 15q11-q13 also have haploinsufficiency in a cluster of GABA receptor subunit genes (*GABRB3*, *GABRA5*, *GABRG3*) and their symptoms are typically more severe than in patients carrying only a *UBE3A* mutation. We have previously characterized two different lines of AS-like mutant mice that harbor an exonic deletion in the *Ube3a* gene ($Ube3a^{m-/p+)}$ or have a 1.6 Mb deletion from *Ube3a* through *Gabrb3* ($UGD^{m-/p+}$). Both lines of AS-like mutant mice recapitulate the major clinical features of AS patients including a robust impairment in motor performance. Despite substantial progress in understanding the molecular basis of AS, it remains a significant challenge to develop effective pharmacological therapies for the disorder. A recent study has shown that tonic inhibition is specifically decreased in cerebellar granule cells of $Ube3a^{m-/p+}$ mice and this impairment is believed to contribute to impaired motor function. Recently, novel synthetic neurosteroid positive allosteric modulators (PAMs) of $GABA_A$ receptors have been described that have potent effects on both synaptic and extrasynaptic receptors (SGE-516) and preferential effects on extrasynaptic receptors (SGE-872). We hypothesized that SGE-872 would enhance tonic currents in cerebellar granule cells and correct the motor dysfunction in an AS mouse model. We performed whole-cell voltage clamp recordings in cerebellar brain slices and behavioral analyses in the AS $UGD^{m-/p+}$ mouse model treated with SGE-872 and SGE-516, both *in vitro* and *in vivo*. Tonic $GABA_A$ receptor-mediated currents were evaluated by application of bicuculline in cerebellar granule cell brain slice preparations. We found that $GABA_A$-receptor mediated tonic

current ($I_{tonic}$) is decreased in both UGD $^{m-/p+}$ and Ube3a$^{m-/p+}$ mice compared with wild-type mice. Pre-incubation of cerebellar slices in SGE-872 corrected the tonic current defects in UGD $^{m-/p+}$ mice. Both acute treatment with SGE-872 (i.p.) in adulthood and chronic treatment with chow containing SGE-516 beginning at weaning partially corrected the impaired motor performance on the rotarod with UGD $^{m-/p+}$ mice. These data suggest a role for GABAergic dysfunction in the motor phenotypes in AS and support the potential use of GABAergic neurosteroids for the treatment of the disorder.

**Disclosures: H. Yan:** None. **Z. Pei:** None. **R. Rodriguiz:** None. **X. Wang:** None. **M. Lewis:** None. **M. Ackley:** None. **F. Salituro:** None. **A. Robichaud:** None. **J. Doherty:** None. **W. Wetsel:** None. **Y. Jiang:** None.

**Poster**

**727. Angelman and Other Developmental Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 727.06/B25

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

**Support:** NIH Grant #P01NICHD033113

**Title:** Reduction of cholinergic interneurons in the striatum of humans with williams syndrome

**Authors: *D. CUEVAS**[1], K. L. HANSON[1,2], K. M. GROENIGER[1], C. F. HORTON LEW[1], D. GREINER[1], B. C. HRVOJ-MIHIC[1], U. BELLUGI[5], E. HALGREN[1,3], K. SEMENDEFERI[1,4]
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**Abstract:** Williams syndrome (WS) is a rare neurodevelopmental disorder caused by a hemideletion of approximately 25-28 genes at 7q11.23. Its unusual social and cognitive phenotype is most notably characterized by the disinhibition of social behavior, in addition to reduced global IQ, with a relative sparing of language ability. Increased social approach behavior in WS may represent a unique deficit in the ability to inhibit responses to specifically social stimuli, which may be rooted in part in abnormalities of frontostriatal circuitry. Here, we examined the density of excitatory cholinergic and inhibitory parvalbumin-positive interneurons in the striatum of seven postmortem cases with WS and age-, sex-, and hemisphere-matched controls. Previous research has suggested that the selective ablation of cholinergic interneurons in mice led to significant increases in exploratory social behavior toward novel conspecifics. Interestingly, we found a significant reduction in the density of cholinergic interneurons in the medial caudate nucleus, an important region receiving cortical afferents from the orbitofrontal and ventromedial prefrontal cortex in circuitry involved in language and reward systems. This pattern of decreased cholinergic interneuron density in WS is contrasted by findings in other

disorders, including Tourette syndrome and schizophrenia, where unique patterns of decreased cholinergic interneuron density are also found. Taken together with findings from neuroimaging, differences in the brains of individuals with WS at both the macro- and microstructural level further indicate a role for frontostriatal dysfunction in the disorder's distinctive behavioral phenotype.

**Disclosures: D. Cuevas:** None. **K.L. Hanson:** None. **K.M. Groeniger:** None. **C.F. Horton Lew:** None. **D. Greiner:** None. **B.C. Hrvoj-Mihic:** None. **U. Bellugi:** None. **E. Halgren:** None. **K. Semendeferi:** None.

**Poster**

**727. Angelman and Other Developmental Disorders**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 727.07/B26

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

**Support:** NIH Grant #P01NICHD033113

**Title:** Parvalbumin-positive interneurons of the basolateral amygdala in Williams syndrome: A postmortem histological study

**Authors: *D. GREINER**[1], K. L. HANSON[1,2], C. F. HORTON LEW[1], K. M. GROENIGER[1], D. CUEVAS[1], B. HRVOJ-MIHIC[1], U. BELLUGI[4,2], E. HALGREN[2,5], K. SEMENDEFERI[1,3]
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**Abstract:** The amygdala is an important site of reorganization in recent human evolution, particularly in the lateral nucleus, which is larger in humans and contains significantly more neurons than would be predicted for an ape brain of its size. The amygdala is critically involved in the processing of social stimuli and reward, and is a site of impairment in many disorders of social cognition. Williams syndrome (WS) is a rare neurodevelopmental disorder characterized by unusual hypersociality and disinhibition of social behavior, as well as atypical features of elaborated language use, in addition to visuospatial deficits and moderate intellectual impairment. Unlike many other disorders of social cognition, WS is characterized by a well-described genetic etiology, involving the hemideletion of 25-28 genes in a region of the seventh chromosome known to be a site of recent adaptive selection in the genome. Interestingly, segmental duplications of the deleted region in WS have been noted in a subset of cases of Autism Spectrum Disorder (ASD). Our research has found a significantly greater number of neurons in the lateral nucleus of the amygdala in WS as compared to typically-developing subjects, in contrast to findings of decreased neuron number in this region in ASD. We have

additionally utilized immunohistochemical staining methods in conjunction with unbiased stereological methods in a sample of seven postmortem subjects with WS and age-, sex-, and hemisphere- matched typically developing subjects to quantify the density of parvalbumin-positive interneurons in the amygdala. We suggest that modifications to the amygdala's microcircuitry in WS, and particularly imbalances in the ratio of excitatory neurons to inhibitory interneurons, may contribute to increased drive for social engagement, reduced threat detection, and social disinhibition characteristic of the disorder.

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**Poster**

**727. Angelman and Other Developmental Disorders**

**Location:** SDCC Halls B-H

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

**Support:** NIH Grant P01 NICHD033113
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**Title:** A stereological study of glia density in the cortex in Williams syndrome

**Authors: *L. WILDER**[1], K. HANSON[1], C. HORTON LEW[1], C. BROWN[2], D. CUEVAS[1], D. GREINER[1], K. GROENIGER[1], U. BELLUGI[3], K. SEMENDEFERI[1]
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**Abstract:** Williams Syndrome (WS) is a rare neurodevelopmental disorder, resulting from a hemideletion of approximately 25-28 genes on chromosome band 7q11.23. It is characterized by a specific and well defined cognitive and behavioral phenotype, including anxiety and altered social behavior, specifically hypersociability and lack of social inhibition. Investigation of neuroanatomical alterations in WS provides an excellent opportunity to study the links between genes, brain and behavior. Our previous postmortem histological studies of WS revealed decreased neuron density in the prefrontal cortex (PFC), layer V/VI in the orbitofrontal cortex in particular (Lew et al. 2017a), increased neuron number in the lateral nucleus of the amygdala (Lew et al. 2017b), and increased glia density in the caudate nucleus of the striatum, with increased oligodendrocyte density in the medial caudate (Hanson et al. 2017). These findings suggest abnormalities in frontostriatal and frontoamygdala circuits, which may underlie the anxiety and atypical social behavior observed in WS.
In the present study, we used five adult WS subjects and five typically developing controls,

matched for age, sex, and hemisphere, to examine glia distribution in the cortex. We targeted five Brodmann areas (BA 25, 10, 3, 4, and 18) to determine if differences in glia density, and oligodendrocyte density specifically, are restricted to frontostriatal regions. Blocks of tissue containing each cortical area were cut at either 40um (BA 25) or 60um (BA 10, 3, 4, and 18), and stained for Nissl substance. Cell density for all glia, and also for oligodendrocytes, was estimated with StereoInvestigator software for infragranular (V/VI) and supragranular layers (II/III). Glial cells were distinguished from neurons by their lack of stained cytoplasm surrounding the nucleus. Oligodendrocytes were identified by their small, round shape, darkly stained euchromatin, and distribution of nuclear heterochromatin (García-Cabezas et al. 2016). Preliminary results demonstrate the greatest increase in density, in both oligodendrocytes and other glia, in WS in BA 25, 3, and 4, and a smaller increase oligodendrocyte density, but not density of other glial cells, in BA 10 and 18. These increases in glia density were observed in all layers examined. Oligodendrocyte density demonstrated a layer specific pattern, with the greatest increases found in layers V/VI, in all cortical areas examined. These results suggest that neuroanatomical alterations in WS are not limited to particular cortical areas, and that increases in oligodendrocyte density may be a systemic feature of the disorder.

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**Poster**

**727. Angelman and Other Developmental Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 727.09/B28

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

**Title:** Alterated circadian rhythm in the Snord116-deleted mouse, an experimental model of Prader-Willi syndrome

**Authors: *M. BOLLA**[1], M. FALAPPA[2], L. CANCEDDA[3,4], V. TUCCI[5]
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**Abstract:** Prader-Willi syndrome (PWS) is a genomic imprinted disorder that is characterized by brain developmental, behavioral and metabolic abnormalities. *Snord116* is a small nuclear RNA that controls the expression of many genes, including different clock genes in the suprachiasmatic nucleous. *Snord116* is also a main regulator of sleep symptoms associated with PWS. Here, we analyzed the effects of the loss of paternal expression of *Snord116* in the circadian rhythms of mice during light-dark (LD) and dark-dark (DD) where they express the

capability of entrainment and free-running respect to external events, respectively. We found that loss of paternal expression of *Snord116* in mice alters the circadian period during free-running, when the animals run according to their internal clock. In particular, mutant mice present with a reduced shortening of their circadian period in DD in comparison to their wild-type littermates. On the other hand, the circadian period during LD shows an unalterated circadian rhythm in mutants compared to wild-type mice. Our study indicates that *Snord116* is involved in the regulation of circadian rhythms in mice and points out a new endophenotype for pre-clinical investigation into the pathomechanisms of PWS. Moreover, this research promotes the knowledge of how imprinted genes can contribute to the alteration of circadian rhythms.

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**Poster**

**727. Angelman and Other Developmental Disorders**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 727.10/B29

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

**Support:** NIH Grant R21E023377
Simons Foundation Grant 495112

**Title:** Spatiotemporal tracking of human neurodevelopmental genes with cerebral organoids

**Authors: *D. SEN**
Chem. and Biomolecular Engin., North Carolina State Univ., Raleigh, NC

**Abstract:** Epigenetic mechanisms play essential roles in mammalian neurodevelopment. Genomic imprinting is a process causing the mono-allelic expression of a gene in a parental origin specific manner, and it is controlled by a hierarchy of epigenetic events. Although they are small in number, many imprinted genes are expressed in the human brain and hold important roles in development and disease. As a key example, the imprinted gene UBE3A is an important nexus in neurodevelopment and complex brain disorders where deletion of the maternal or paternal alleles of UBE3A differentially leads to Angelman Syndrome or Prader-Willi Syndrome, respectively. In addition, duplication of maternal UBE3A occurs in some forms of Autism Spectrum Disorder. These three diseases share some common neurological comorbidities strongly suggesting UBE3A's role in neural function; yet, it is still unclear when, where, and how UBE3A is regulating or disrupting normal neurodevelopment or adult brain function. Therefore, mapping the spatiotemporal localization of UBE3A expression in neurons and other cell types in the brain could provide key insights into the underlying mechanisms of UBE3A-related disorders and suggest key cell types and brain regions for further study. However, due to technical and ethical limitations, such maps have yet to be generated in humans. Here we aim to

map UBE3A expression throughout early prenatal brain development by using human cerebral organoids. Human cerebral organoids are model systems that exhibit most cell types of the human brain as well as polarized tissue structures, and have been temporally correlated with early fetal neurodevelopment. Through this human system, we connect molecular processes to tissue-level properties by spatiotemporally mapping UBE3A. This map suggests several specific brain regions, cell types, developmental time windows, and mechanistic hypotheses to pursue in understanding UBE3A's role in the human brain and in neurodevelopmental disorders.

**Disclosures: D. Sen:** None.

**Poster**

**727. Angelman and Other Developmental Disorders**

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

**Support:** ISF Grant 287/15
ASF

**Title:** Selective α1-NaKA inhibition rescues hippocampal CA1 activity dependent calcium dynamics and hippocampal deficits in a mouse model of Angelman syndrome

**Authors: *P. RAYI**, H. KAPHZAN
Univ. of Haifa, Haifa, Israel

**Abstract:** We previously showed that increased expression of alpha1 subunit of Na/K-ATPase (α1-NaKA) is the precipitating event actuating the hippocampal LTP deficits, AIS abnormalities in CA1 pyramidal neurons (PNs) and memory impairment in Angelman Syndrome (AS) mice (Kaphzan et al., 2011). However, the mechanistic role of α1-NaKA in AS pathophysiology is not fully understood. Because NaKA is known to affect excitability and modify Calcium ($Ca^{+2}$) dynamics, we hypothesized that activity dependent $Ca^{+2}$ dynamics in CA1 PNs in AS mice is altered, and thus induces the observed hippocampal deficits. Hence, we aimed to: 1. Determine the activity dependent $Ca^{+2}$ dynamics in CA1 PNs in AS mice. 2. Determine whether the pharmacological inhibition of α1-NaKA pump activity will normalize this aberrant AS mice activity dependent $Ca^{+2}$ dynamics, and subsequently rescue any of the hippocampal dependent deficits.
**Results:** *Ex-vivo* 2-Photon calcium imaging in secondary apical dendrites of CA1 PNs showed a faster $Ca^{+2}$ evacuation and lower peak $Ca^{+2}$ levels compared to their WT littermates. Moreover, inhibition of α1-NaKA pump activity with Marinobufagenin (MBG) normalized this aberrant activity dependent $Ca^{+2}$ dynamics in the AS mice. Furthermore, our results show that MBG treatment rescues the LTP deficits observed in the CA3-CA1 pathway of AS mice, and whole-

cell recordings showed normalization of the increased excitability of hippocampal CA1 cells in AS mice. Finally, we show that chronic inhibition of α1-NaKA by MBG (10 μg/Kg/day) using osmotic mini-pumps rescued the spatial learning deficits of AS mice seen in the Morris water maze test. Taken together, our study brings new insights into the aberrant $Ca^{+2}$ dynamics in AS mice. Additionally, these results suggest the use of pharmacological α1-NaKA inhibition as a therapeutic strategy for alleviating AS hippocampal deficits.

**Disclosures: P. Rayi:** None. **H. Kaphzan:** None.

**Poster**

**727. Angelman and Other Developmental Disorders**

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**Program #/Poster #:** 727.12/B31

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

**Support:** NINDS 1R21MH104252-01A1

**Title:** A novel cyclic peptide facilitates learning and memory in Angelman syndrome

**Authors: *J. MARSHALL**, K. LAU, M. RIOULT-PEDOTTI, M. YAO, C. MARINO, P. MIGANI
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**Abstract:** Angelman syndrome (AS), is a severe cognitive disorder caused by loss of expression of the maternally inherited allele of the Ube3A gene. The Ube3A gene encodes an ubiquitin ligase that regulates synaptic strength, learning, and memory. Using biochemical, electrophysiological and mouse behavioral methods we explore the efficacy of a novel compound, CN2097, to treat Angelman syndrome. Our studies in an Angelman syndrome (AS) mouse model, suggest that the reported reduction in alpha-$Ca^{2+}$/calmodulin-dependent kinase II (αCaMKII) activity that produces learning deficits, is the result of defective BDNF signaling. Brain-derived neurotrophic factor (BDNF) plays a key role in long-lasting increases in synaptic strength (long-term potentiation; LTP), a synaptic basis of learning and memory. We found that the impaired LTP observed in the Angelman mouse model occurs because of a reduction in the interaction between TrkB and the synaptic scaffold protein PSD-95, leading to attenuated BDNF-induced CaMKII and PI3K (Akt/mTOR) signaling. We designed a novel cyclic peptide, CN2097, that binds with high affinity to the PDZ domains of PSD-95 to enhance the association of PSD-95 with TrkB and restore signaling that is sufficient to reduce the LTP impairment observed in the CA1 region of the hippocampus. Assessing behavioral paradigms, we found that CN2097 restored contextual fear memory and improved rotarod performance in AS mice. These studies demonstrate that CN2097 can rescue deficits in CaMKII and Akt signaling and reverse the LTP impairment to ameliorate learning deficits. The use of drugs based on enhancing BDNF-

TrkB signaling provide a novel treatment approach that has the potential to lead to the first effective therapy for Angelman syndrome.

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**Poster**

**727. Angelman and Other Developmental Disorders**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 727.13/B32

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

**Title:** Small molecule inhibitors of G9a reactivate the maternal PWS locus genes in Prader-Will-syndrome patient derived neural stem cells and differentiated neurons

**Authors: *H. WU**[1], C. NG[1], V. VILLEGAS[1], S. CHAMBERLAIN, 02139[2], A. M. CACACE[3]
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**Abstract:** Prader-Willi syndrome (PWS) is a congenital developmental disorder in which boys and girls present with developmental delays, including muscle hypotonia, short stature at infancy, intellectual impairment and various behavioral problems during childhood. Most PWS patients exhibit poor feeding habits and lose appetite control, leading to obesity and type II diabetes. This combination of traits indicates dysfunction of the neuroendocrine system. In healthy individuals, the maternal copies of genes situated on chromosome 15q11-q13 are silenced by hypermethylation and repressive histone modulation of the PWS imprinting center (IC). Because the vast majority of PWS patients have genetic deletions on their paternal chromosome 15q11-q13, there is loss of gene expression including SNORD116, SNORD115 snoRNA clusters, SNURPN, SNURF, NDN and MAGLE2 (PWS genes). A recent report demonstrated that inhibition of the epigenetic enzyme G9a (also known as EHMT2) by small molecules could reactivate SNORD116 and other PWS genes in both PWS patient fibroblasts and a PWS mouse model (Kim et al., 2016). This is consistent with the key role that G9a, a histone methyltransferase, plays in catalyzing H3K9 dimethylation at the maternal PWS IC to silence PWS genes. However, it is not known if inhibition of G9a could have similar impact on PWS neural progenitors and neurons, the cell types of direct pathophysiological relevance for PWS.
In this study, we derived neural progenitor cells (NPCs) and NGN2-induced glutamatergic neurons from induced pluripotent stem cells from a PWS patient with a ~ 5.1 Mb deletion on the paternal PWS locus (PWS1-7). We found that 1 uM 5-azacytidine reactivated maternal SNORD116 and other PWS genes to ~20%-100% of a WT control line (MCH2-10) in NPCs but has no effect in neurons. This is consistent with the hypothesis that the antagonizing effect of

DNA methylation for 5-azacytidine is only limited to mitotic cells. Multiple small molecule inhibitors of G9a reactivate maternal PWS genes in a dose dependent manner from 0.1 uM to 3 uM in both NPCs and neurons, albeit less effectively in neurons. Interestingly, G9a inhibition does not induce the methylation of the maternal PWS IC, indicating that disruption of the histone repressive complex alone is sufficient to drive an open chromatin state of the IC that leads to PWS gene reactivation. Finally, we found that GNRH1 and HTR2C, the downstream genes impacted by the deleted PWS genes in neurons, are partially rescued by G9a inhibitors. Using disease relevant cellular models, this study provided *in vitro* support for potential epigenetic intervention as an approach to PWS treatment.

**Disclosures: C. Ng:** A. Employment/Salary (full or part-time):; full time, Fulcrum Therapeutics Inc. **V. Villegas:** A. Employment/Salary (full or part-time):; full time, Fulcrum Therapeutics Inc. **S. Chamberlain:** None. **A.M. Cacace:** None.

**Poster**

**727. Angelman and Other Developmental Disorders**

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**Program #/Poster #:** 727.14/C1

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

**Support:** Murine Behavioral Neurogenetics Facility
Institute for Brain and Cognitive Sciences
Provost's Initiative University of Connecticut

**Title:** Language-related assessments in a mouse AS model

**Authors: *P. A. PERRINO**[1], S. J. CHAMBERLAIN[4], I.-M. EIGSTI[2], R. H. FITCH[3]
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**Abstract:** Angelman syndrome (AS) is a neurodevelopmental disorder characterized by motor deficits, seizures, and some autistic-like behaviors. AS stems from dysfunction of the maternally-imprinted *UBE3A* gene, with the paternal copy silenced. Located on human chromosome 15q11.2, *UBE3A* encodes for ubiquitin-protein ligase E3A that acts in the ubiquitination pathway to identify substrates for degradation in the proteasome. *UBE3A* also appears necessary for the maturation of neural circuits and experience-dependent plasticity in the cerebral cortex. Over the last several years, mouse models with a full or conditional deletion of the maternally-imprinted *Ube3a* mouse-homolog have been used to study the mechanisms and behavioral phenotypes associated with AS. These studies suggest that a loss of the *UBE3A* protein results in up-regulation or down-regulation of many other genes involved in key cellular pathways (e.g.,

cellular signaling, regulation of cell death, and neurogenesis). Although several research groups have conducted extensive behavioral phenotyping on the transgenic *Ube3a* model (using various background strains), findings to date do not provide particular insight on the profound language disabilities associated with AS. Our lab has built upon evidence that auditory processing deficits can be linked to speech and language delays, and early indices of rapid auditory processing can predict later language outcomes in typically developing and at-risk human populations, specifically to develop comparable tasks for use in mouse models. We also use vocalization analysis, an area where other labs have already shown atypical results in the *Ube3a* KO mouse. Finally, we can tap cognitive and memory processing particularly relevant to language (e.g., sequential and rule learning) as well. The current results show behavioral features of a transgenic mouse model with a dysfunction of the maternally-imprinted *UBE3A* mouse-homolog (*Ube3a*$^{m-/p+}$), using tasks that might specifically relate (in humans) to atypical language abilities (rapid auditory processing, processing of conspecific ultrasonic communications, complex sequential processing, rule learning). We also present data from social-communication and related tasks to validate the autistic-like phenotype as seen in AS, as well as tactile and repetitive behavioral assessments. Overall, we expect AS mice to show a pattern of specific acoustic and sensory processing deficits, as well as learning impairments, that could contribute to the language phenotype in humans with AS.

**Disclosures: P.A. Perrino:** None. **S.J. Chamberlain:** None. **I. Eigsti:** None. **R.H. Fitch:** None.

**Poster**

**727. Angelman and Other Developmental Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 727.15/C2

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

**Support:** Departmental Start-Up Funds

**Title:** Microglia regulates molecular factors related to brain arteriovenous malformation in endothelial cells

**Authors: *E. PARK**[1], P. R. CHEN[2], E. KIM[1]
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**Abstract:** Brain arteriovenous malformation (bAVM) is a congenital disease caused by abnormal development of the capillary network connecting arteries and veins in the brain. It often leads to cerebral hemorrhage in young patients however the underlying molecular mechanism is not clear yet. Endothelial dysfunction is representative pathology of bAVM and angiogenic molecular factors have been related to the focal bAVM formation. On the other hand,

previous studies have shown immune cells including microglia are highly distributed around endothelium of blood vessel in human bAVM. It suggests the interaction between endothelial cells and microglia is critical in the bAVM pathology. Therefore we determined if microglia regulate molecular factors related to bAVM in endothelial cells. We stimulated BV2 microglia cell line with soluble endoglin (sENG) which is expressed in endothelial cells and elevated in human bAVM, and the conditioned media (CM) from sENG-treated BV2 cells (BV2-CM) treated to mouse primary endothelial cells. Real time quantitative-PCR exhibits increased mRNA expression of inflammatory cytokines (TNFα and IL-6) and angiogenic mediators (MMP-9 and VEGF-A) in BV2 cells by sENG treatment. Endothelial cells incubated with sENG-treated BV2-CM significantly increased molecular factors (Notch-1 and TGF-β) that have been related to bAVM formation. To test if the effect is related to pro-inflammatory activation of microglia, the BV2 cells were stimulated with lipopolysaccharide (LPS) and the CM was treated to endothelial cells. LPS induced inflammatory cytokines (TNFα and IL-6) and angiogenic mediators (MMP-9 and VEGF-A) in BV2 cells and the LPS-treated BV2-CM significantly increased TGF-β and VEGF-A in endothelial cells, but not increased Notch-1 which is induced in sENG-treated BV2-CM. The results suggest that microglia may interact closely with endothelial cell in the bAVM pathology with different route of inflammation.

**Disclosures: E. Park:** None. **P.R. Chen:** None. **E. Kim:** None.

**Poster**

**727. Angelman and Other Developmental Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 727.16/C3

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

**Support:** NIMH RO1 MH104324
NIMH U01 MH110274

**Title:** Temperament, language and social development in infants and toddlers with agenesis of the corpus collosum

**Authors: *J. TURNER**[1], J. ELISON[2], S. SUNG[2], R. ADOLPHS[1], L. K. PAUL[1]
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**Abstract:** Approximately 1 in 2000 infants under age 1 are diagnosed with agenesis of the corpus callosum (AgCC) annually in the United States. Accumulating evidence suggests that CC development is critically involved in the emergence of behavioral and cognitive skills during the first two years of life, that structural abnormalities of the CC are associated with a variety of neurodevelopmental disorders, and ~30% of individuals with AgCC later show phenotypic features consistent with an autism spectrum disorder. With modern availability of high-resolution

ultrasound imaging, an increasing number of AgCC cases are being identified in utero, making it imperative to provide data that can guide medical and psychological support to infants with AgCC.
Longitudinal behavior ratings of children with AgCC, acquired at ~ 6, 12, 18 and 24 months of age, were compared with ratings of normative comparison children (HC), using Infant Behavior Questionnaire-Revised (AgCC=17, HC=18), MacArthur-Bates Communicative Development Inventories (AgCC=9, HC=34) and Video-Referenced Rating of Reciprocal Social Behavior 2.3 (AgCC=16, HC=80).
*Temperament:* Positive and negative emotionality ratings were similar in AgCC and control groups at 6 months. By 12 months, both emotionality ratings had increased minimally in the AgCC group and increased significantly in control children, resulting in significantly lower emotionality scores in AgCC at 12 months. Groups did not differ in duration of orienting at either 6 or 12 months.
*Language Development:* Gesture use was lower in AgCC than controls at 12, 18 and 24 months, despite similar rates of age-related improvement. In contrast, groups had similar total vocabulary scores at 12 months, but vocabulary expansion was slower in the AgCC group with resulting in significantly smaller vocabulary by 24 months.
*Social Skills:* At 18 months, the AgCC group was significantly more atypical than the control group. Although the AgCC group exhibited more marked improvement than the control group over time, their social skills remained somewhat more atypical than the control group at 24 months.
These findings suggest that interventions for children with AgCC should target emotional expression during the first year of life and language development during the second year.

**Disclosures: J. Turner:** None. **J. Elison:** None. **S. Sung:** None. **R. Adolphs:** None. **L.K. Paul:** None.

**Poster**

**727. Angelman and Other Developmental Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 727.17/C4

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

**Title:** Effects of Ube3a overexpression in sprague dawley rats

**Authors: *A. W. NENNINGER**, M. M. PETERS, E. J. WEEBER, K. R. NASH
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**Abstract:** Angelman syndrome (AS) is a disease characterized by severe intellectual disability, speech and movement problems, abnormal personality, seizures, and disrupted LTP. Interruption in expression or function of the paternally imprinted Ube3a gene is thought to be the sole cause

in many cases of AS. The Ube3a gene encodes a member of the HECT domain containing E3 ubiquitin ligases. Ube3a has been shown to interact with a number of proteins in the CNS in addition to functioning as a ubiquitin ligase and coactivator of steroid receptors. Due to this single gene alteration and lack of changes in brain structure during development it is believed that a gene therapy approach could offer a therapeutic treatment. We have previously shown that introduction of the full length Ube3a gene using Adeno-associated virus (rAAV) using stereotactic surgery recovers the deficits present in AS mouse and rat models. Although gene therapy is a promising potential treatment there is some concern that supraphysiological levels of Ube3a may cause a separate set of cognitive deficits. This evidence comes from studies of a syndrome closely related to AS known as chromosome 15q11.2-13.1 duplication syndrome, or Dup15q. This syndrome results from a duplication of the region containing the UBE3A gene resulting in increased levels of the Ube3a protein. Therefore, to investigate the effects of overexpression of Ube3a 2 month old sprague dawley rats were injected with rAAV either expressing Ube3a or GFP as a control. After aging the rats for 3 months, behavioral tests including Morris water maze, novel object, rotarod, fear conditioning and digi-gait were performed. We also present electrophysiological characterization of these rats.

**Disclosures: A.W. Nenninger:** None. **M.M. Peters:** None. **E.J. Weeber:** None. **K.R. Nash:** None.

**Poster**

**727. Angelman and Other Developmental Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 727.18/C5

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

**Title:** De novo mutations in the RNA Helicase DDX6 disrupt P-body assembly and cause intellectual disability, microcephaly, and dysmorphic features

**Authors: *C. BALAK**[1], M. BENARD[2], E. SCHAEFER[3], K. RAMSEY[1], M. ERNOULT-LANGE[2], F. MATTIOLI[4], N. BELNAP[1], V. GEOFFROY[5], M. COUREL[2], J. MULLER[6], M. NAYMIK[1], K. BACHMAN[7], M. CHO[8], R. RICHHOLT[1], A. LE BECHEC[9], W. M. JEPSEN[1], M. DE BOTH[1], S. RANGASAMY[1], J.-F. DELEUZE[10], A. BOLAND[10], S. SZELINGER[11], H. DOLLFUS[3], I. PIRAS[1], J. CHELLY[4], D. W. CRAIG[12], J.-L. MANDEL[4], V. NARAYANAN[1], M. HUENTELMAN[1], D. WEIL[2], A. PITON[4]
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**Abstract:** The RNA helicase *DDX6* is a member of the DEAD-box protein family and plays vital roles in RNA metabolism processes such as translational repression, decapping and RNA decay. Previous *in vitro* and lower *in vivo* models have implicated altered *DDX6* in cellular dysfunction but clinical consequences and pathogenesis in humans have not yet been described. Here we report the identification of multiple unrelated patients carrying *de novo* missense mutations in *DDX6,* all presenting with non-epileptic intellectual disability (ID), developmental delay (DD), microcephaly and overlapping dysmorphic features of unknown etiology. All missense variants reside in exon 11 which encodes the highly-conserved C-terminal RecA domain of *DDX6,* involved in RNA binding, helicase activity and protein partner binding. Comprehensive *in vitro* functional studies performed on *DDX6* p.Arg373Gln and p.Cys390Arg variants demonstrated that both mutations lead to significant defects in P-body assembly and interactions with protein partners involved in translation repression (and mRNA degradation). Additionally, study of patient-derived fibroblasts carrying the p.Cys390Arg mutation demonstrated a significant reduction in total P-body number when compared to an unrelated age-matched control individual. Transcriptomic studies revealed among the genes up-regulated in patient cells an enrichment of mRNA excluded from P-bodies, targets of *DDX6,* and in mRNA encoding protein involved in regulation of translation. Two additional patients with *de novo* mutations affecting the same or adjacent amino acid to p.Cys390 were also identified. Collectively, our clinical and molecular data define a novel role for *DDX6* mutations in human neurodevelopmental dysfunction and confirm the implication of this gene in an autosomal dominant form of intellectual disability with developmental delay and dysmorphic features.

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**Poster**

**727. Angelman and Other Developmental Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 727.19/C6

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

**Support:** FAST TRAC PROGRAM GRANT NUMBER FT2017-002
R01NS097808 (JLS) The MIND Institute's Intellectual and Developmental Disabilities Research Center (IDDRC) HD079125

**Title:** Automated motor outcomes in genetic models of ubiquitin protein ligase E3A gene (UBE3A) mediated neurodevelopmental disorders

**Authors: *M. C. PRIDE**, J. L. SILVERMAN
UC Davis Sch. of Med., Sacramento, CA

**Abstract:** Clinically-relevant outcome measures are required to demonstrate the test utility of innovative drug designs (like gene therapy or stem cells), as well as to validate other traditional medicinal therapies that may be in the drug discovery pipeline by biotechnological and pharmaceutical companies. However, a major rate-limiting step, is that sophisticated, well-validated, tools that provide precise, translationally relevant (i.e., the same measures in animal models and human patients) outcome parameters are underdeveloped. Our studies utilized automated treadmill walking and pressure sensitive equipment to allow for the collection of a substantial number of quantitative motor parameters such as gait, coordination, stride length, stance width, and pressure of feet (~paws). These innovative quantifiable outcomes revealed 30 metrics of posture, gait and locomotion, stride length, force development, loading, symmetry, and gait variability. Each of these measures are analogous to those being collected by clinics at the MIND Institute, Baylor and UCLA for rare genetic neurodevelopmental disorders characterized by developmental delay and ataxia, such as Angelman and Dup15q Syndromes. Both of these genetic disorders have substantial characteristic motor dysfunction. We collected digital paw prints of each of the four limbs assessed by the Mouse Specifics software. Our studies revealed mutant mice had deficits in numerous parameters on the treadmill assay, including stride and swing length, as well as in the other more commonly used motor assays. Advantages for our focused study on motor phenotypes resulting from *Ube3a* deletion or overexpression are the a) strong correlation between motor and social communication abilities, b) motor is highly translatable between preclinical models and human studies, making associated outcome measures extremely useful in a clinical trial, and c) these motor markers could all be used as preclinical screening outcomes for therapeutic development.

**Disclosures: M.C. Pride:** None. **J.L. Silverman:** None.

**Poster**

**727. Angelman and Other Developmental Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 727.20/C7

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

**Support:** NIH Grant T32GM099608
CIRM Grant DISC2-09032
FASTFIRE Grant

**Title:** Reactivation of Ube3a in mouse models of Angelman syndrome following transplantation of engineered mesenchymal stem cells secreting zinc finger artificial transcription factors

**Authors: *P. DENG**[1], U. BEITNERE[1], R. LEE[2], N. A. COPPING[2], J. A. HALMAI[3], H. O'GEEN[1], A. A. ADHIKARI[2], B. P. PYLES[1], S. DEL CAMPO[3], S. P. PETKOVA[2], M. PRIDE[2], J. L. CARTER[3], S. S. CARTER[1], J. NOLTA[4], J. L. SILVERMAN[2], D. SEGAL[1], K. FINK[3]
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**Abstract:** Angelman Syndrome (AS) is a genetically inherited neurodevelopmental disorder characterized by impaired cognitive development, lack of speech, seizures, and motor ataxia. The genetic cause for AS is usually due to a *de novo* deletion of the maternal *UBE3A* gene. Additionally, brain-specific postnatal imprinting of the intact paternal *UBE3A* gene results in complete loss of UBE3A in mature neurons due to the presence of a long antisense transcript driven by the neighboring *SNURF/SNRPN* promoter. Our group has previously shown reactivation of the paternally silent *Ube3a* gene in the brains of a mouse model of AS following i.p. injection of a KRAB-fused Zinc Finger artificial transcription factor (S1K) targeted to the *Snurf/Snrpn* promoter. This treatment effectively silenced expression of the antisense transcript, allowing paternal UBE3A to be expressed. As an alternative delivery method, we have engineered S1K-secreting bone-derived mesenchymal stem cells (MSC). The ability of MSC to transfer larger molecules such as organelles are suggestive of their potential usefulness as delivery vehicles for artificial transcription factors such as zinc fingers.
Here we show a series of *in-vitro* and *in-vivo* AS model experiments that demonstrate highly efficient *Ube3a* reactivation by the reprogrammed MSCs. We engineered mouse MSCs to secrete S1K as confirmed by uptake into Neuro2a cells with MSC-S1K conditioned media via fluorescent microscopy. We then bilaterally transplanted MSC-S1K into the hippocampus of 8-week old *Ube3a:YFP* reporter mice. Brains were examined at 3-, 6-, and 10- weeks following transplantation. Interestingly, we observed significant reactivation of the silenced *Ube3a:YFP* gene compared to controls via IHC and western blotting in the hippocampus, cerebellum, and

cortex 3-weeks following transplantation and stable reactivation up to 6-weeks. Additionally, in vivo experiments comprehensively characterized the functional effect of MSC-S1K in E6:AP AS mice. Compared to wild type littermate controls and sham transplanted MSC, we measured for improvements in behavioral phenotypes reported in previous reports of AS mice and in unpublished findings of our collaborators (using gross and fine motor skills assays (e.g., open field, beam walking, rotarod, DigiGAIT); learning and memory assays (e.g., novel object recognition, spontaneous alternation, contextual and cued fear conditioning); and polyspike analysis via electroencephalography (EEG). We report the first-of-its-kind use of MSCs as a delivery platform for epigenetic modifiers in neurologic disease – expanding the therapeutic potential of both systems for future genetic diseases.

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**Poster**

**727. Angelman and Other Developmental Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 727.21/C8

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

**Support:** HD079125
R01NS097808
FT2017-002
FT2016-001

**Title:** Expression of UBE3A via lentivector delivery in hematopoietic stem cells to treat Angelman syndrome

**Authors: *J. L. SILVERMAN**[1,3], A. A. ADHIKARI[3,1], N. A. COPPING[3,1], R. D. LEE[1], J. R. BEEGLE[2], H. NELSON[2], H. O'GEEN[3], D. J. SEGAL[3], J. S. ANDERSON[2]
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**Abstract:** The ubiquitin protein ligase E3A gene (*UBE3A*) encodes for enzyme responsible in the ubiquitination of target substrates for degradation, spanning almost all cell types. A deletion or mutation in *UBE3A* causes Angelman syndrome (AS), a neurodevelopmental genetic disorder associated with severe cognitive impairments, poor motor coordination, and epilepsy. One of our laboratory's goals is to develop a hematopoietic stem cell (HSC) gene therapy to deliver an artificial transcription factor (Bailus et al., 2016) for the treatment of AS. To evaluate the use of

HSC therapy as a treatment option for AS, we have generated lentiviral vectors expressing modified Ube3a proteins that contain both secretion signals and single amino acid changes which create N-glycan sites for increased cell uptake. We have also generated immune deficient mouse models of AS, lacking either *Rag1, IL2,* and/or *Rag2* genes, that are capable of receiving HSCs to evaluate the efficacy of the lentiviral vector transduced cells. *In vitro* experiments confirmed expression of the modified Ube3a proteins in human HSCs and their immune cell progeny. We evaluated the ability of the modified Ube3a proteins to function properly by ubiquitination of target proteins. *In vivo* experiments generated and characterized novel mouse models of AS with maternally inherited deletions of *Ube3a* and that are capable of transplantation of human CD34+ HSC. We comprehensively characterized the immune deficient *Rag1-/-*, *IL2-/-* and *Rag2-/-* mice to ensure that there were no confounding effects of immunodeficiency compared to control C57BL/6J prior to transplantation with HSCs. We measured behavioral phenotypes reported in previous *Ube3a*$^{m-/p+}$ models (Jiang et al., 2010; Born et al., 2017) using anxiety-like behavior assays (e.g., elevated plus-maze); motor assays (e.g., open field, beam walking, rotarod); learning and memory assays (e.g., novel object recognition, spontaneous alternation, contextual and cued fear conditioning); and seizure threshold assays (measuring seizure severity and latency to first jerk post-pentylenetetrazole-induced seizures). In the *Rag1-/-* and *IL2-/-* mice, we did not find any pronounced anxiety-like phenotypes, motor deficits, or global learning/memory phenotypes; however, we did observe deficits in novel object recognition. Taken together, our data show that an Ube3a lentiviral vector-transduced human CD34+ HSC gene therapy could be a possible safe and efficacious delivery method for gene therapeutics in AS. Future directions will be to transplant Ube3a lentiviral vectors in our humanized mouse model and to evaluate its efficacy and safety as a therapeutic.

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**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 728.01/C9

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

**Title:** Deep brain stimulation for Gilles de la Tourette syndrome in children and youth: A meta-analysis with individual participant data

**Authors: *M.-A. COULOMBE**[1], L. ELKAIM[2], N. M. ALOTAIBI[4,7], D. A. C. GORMAN[5,9], A. G. WEIL[3,11], A. FALLAH[12,13], S. KALIA[6,8], N. LIPSMAN[6,14], A. M. LOZANO[6,7], G. M. IBRAHIM[6,10]

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**Abstract: Background**: Gilles de la Tourette syndrome (GTS) is a disorder characterized by motor and vocal tics. Although by definition the onset of GTS is before age 18 year, clinical trials of deep brain stimulation (DBS) have been conducted only in adults. Using individual participant data (IPD) meta-analysis methodology, the current study investigated the safety and efficacy of DBS as a treatment for GTS in children and youth. **Methods**: A systematic review with no date or language restrictions was performed according to the PRISMA statement. From 843 articles screened, the IPD of 58 children and youth (ages 12-21) extracted from 21 articles were collected and analysed. A mixed-effects univariable analysis followed by multivariable hierarchical regression were performed using change in the Yale Global Tic Severity Scale (YGTSS) score as primary outcome and reported measures of comorbidities as secondary outcomes. **Results**: Our results showed an average improvement of 57.5 ± 24.6% across studies on the YGTSS. We also found that comorbid depression and stimulation pulse width each correlated negatively with outcome ($p<0.05$). In patients with less severe GTS, greater improvements were evident following thalamic stimulation. Over one-quarter (n=16, 27.6%) of participants experienced side effects, the majority of which were minor. **Conclusion**: DBS in the pediatric population may be an effective option with a moderate safety profile for treatment of GTS in carefully selected children and youth. Large prospective studies with long-term follow-up are necessary to understand how DBS influences tic symptoms and may alter the natural course of GTS in children.

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**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 728.02/C10

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

**Support:** PICT 0892

**Title:** Cyclin-dependent kinase 5 regulates dopamine transporter surface expression and internalization, clues to understand the dopaminergic system of p35 knock-out mice

**Authors: *G. FERNANDEZ**, M. MARI, F. KRAPACHER, G. PAGLINI
INIMEC-CONICET-UNC, Cordoba, Argentina

**Abstract:** Dopamine transporter (DAT) catalyzed the Dopamine (DA) reuptake from the synaptic cleft. This process is the major regulator of dopamine signaling strength, limiting pre and postsynaptic DA receptors activation. Desregulation in DA signaling is common in a broad of psychiatric Disorders such as Parkinson disease, Schizophrenia, Attention Deficit hyperactivity Disorder (ADHD), etc. Therefore, DAT has been one of the most studied proteins in order to understand the neurobiology mechanism underlying these disorders. Previous studies from our lab have demonstrated that transgenic mice lacking p35 protein (p35KO), the specific activator of Cyclin dependent kinase 5 (Cdk5) exhibit behaviors resemble those described in animal models of ADHD. p35 KO mice display hyperactivity which is reverted by Methylphenidate and d-Amphetamine, drugs targeting DAT. Although we have shown that p35KO mice have an altered Dopaminergic system, the trafficking and activity of Dopamine Transporter (DAT) still remain unknown. In this work we studied the implications of Cdk5 inhibition in DAT expression and trafficking in P35KO mice and N2a cell line. Through Biotinylation assay, we observed that p35KO mice have a normal DAT expression levels in Striatum synaptosomes but the superficial expression of the transporter is diminished in these mice. On the other hand, using the antibody feeding method, we demonstrated that, in N2a cell line, the genetically and pharmacologically inhibition of Cdk5 augment the constitutive endocytosis rate of DAT. These results suggest that Cdk5 activity modulates DAT trafficking from the plasma membrane, and its superficial levels. These findings may help us to elucidate DAT function in the hyperdopaminergic system of p35KO animal, model of ADHD.

**Disclosures: M. Mari:** None. **F. Krapacher:** None. **G. Paglini:** None.

**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 728.03/C11

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

**Support:** L.I.F.E. Foundation Grant

**Title:** Targeted deletion of latrophilin-3 in Sprague-Dawley rats results in hyperactivity and reduced anxiety-like behavior: A new model of ADHD

**Authors: *S. L. REGAN**
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**Abstract:** Attention deficit hyperactivity disorder (ADHD) is a persistent developmental disorder characterized by inattention, impulsivity, and hyperactivity. ADHD is partially heritable, with monozygotic twin concordance of 70-80%. Recently, Latrophilin-3 (*LPHN3)* polymorphisms have been associated with a subtype of ADHD, but how it translates to ADHD is unknown. We created a null mutant of *Lphn3* in Sprague Dawley rats using CRISPR/Cas9 to excise exon-3. We compared wildtype (WT) and knockout (KO) progeny of het x het crossings using home-cage activity, elevated zero maze, and the acoustic startle response. We also assessed monoamines, mRNA expression, and protein levels. *Lphn3* KO rats were hyperactive as adolescents and adults in the home-cage test, showed decreased anxiety in the elevated zero-maze, and had increased acoustic startle responses compared with WT. Norepinephrine was increased in the hippocampus and HVA was increased in the neostriatum. Increased protein levels were found for the dopamine transporter (DAT) in neostriatum. The L*phn3* KO rat offers a new approach to understanding variant LPHN3 leads to ADHD and may help elucidate the CNS function of this poorly understood adhesion protein. (Supported by a grant from the L.I.F.E. Foundation.)

**Disclosures: S.L. Regan:** None.

**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

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

**Support:** Natural Science Foundation of China Project nos. 31700977, 31671151, 31600896, 31521063, and 31271187
Fundamental Research Funds for the Central Universities 2017XTCX04

**Title:** Cognitive training combining numerosity with visual perception promotes arithmetic fluency in children with dyscalculia

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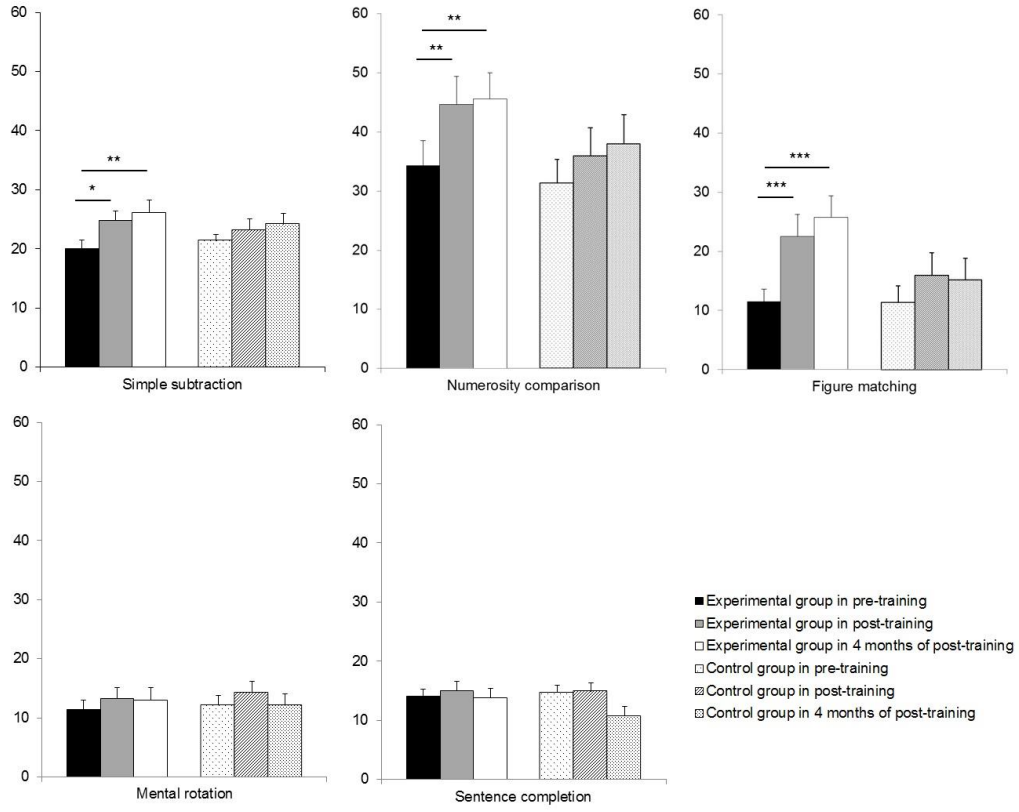
**Abstract:** Developmental dyscalculia (DD) is a disorder in the development of mathematical abilities that afflicts approximately 5% of school-age children. Although the effect of numerosity

training on symbolic mathematics performance have been proved, the mechanisms underlying this effect remain unclear. The goal of the current study was to test the hypothesis that numerosity training (with an apple-collecting computer game) enhances arithmetic fluency through the improvement of visual perception. 96 children with developmental dyscalculia (DD) were identified Chinese primary school children and they were randomly divided into the interventional group and the control group. The interventional group received training with an apple-collecting game, whereas the control group received an English dictation task. Children were tested in cognitive and mathematical abilities before and after 8days of training, 15 minutes per day, and four months later. Results showed that the interventional group showed significant improvement in simple subtraction, numerosity comparison, and figure matching, but not in mental rotation and sentence completion, whereas the control group did not show significant improvements in any areas. Analysis of covariance further showed that the improvements in numerosity and arithmetic performance could be accounted for by the improvement in figure matching (a measure of visual perceptual ability). The results suggest that numerosity training with an apple-collecting computer game enhances arithmetic fluency in DD children by improving their visual perceptual ability.




**Disclosures: D. Cheng:** None. **X. Zhou:** None. **Q. Xiao:** None.

**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 728.05/C13

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

**Support:** R21 DA040228
T32 DA017637

**Title:** Multigenerational transmission of developmental nicotine exposure-induced ADHD-like phenotypes is modulated by the D397N polymorphism of CHRNA5 in adolescent mice

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**Abstract:** Developmental nicotine (NIC) exposure (DNE) is associated with increased NIC use and ADHD, a neurodevelopmental disorder characterized by inattention, impulsivity, hyperactivity and sleep disturbances, increased amplitude of rest-wake activity rhythms, eveningness, and increased NIC use. The alpha-5 nicotinic acetylcholine receptor (nAChR) subunit (CHRNA5) is important for ADHD-relevant phenotypes such as attentional behaviors, and constitutive knockout of CHRNA5 alters the effects of DNE on neuronal morphology. The human D398N polymorphism of CHRNA5 is associated with increased risk for NIC dependence and has been shown to alter the function of ADHD-implicated neuronal populations in-vitro. We have previously demonstrated that DNE elicits multigenerational NIC preference, ADHD-like hyperactivity and risk-taking, and aberrant rhythmicity of home cage (HC) activity in wild-type mice. However, no previous research has explored the potential role of the D397N polymorphism (mouse equivalent of the D398N polymorphism in humans) in the transmission of DNE-induced ADHD-like phenotypes. We thus characterized the behavioral and rhythmometric consequences of DNE in the F1 (D F1 NIC and N F1 NIC) and F2 (D F2 NIC and N F2 NIC) generation adolescent offspring of D397 and N397 mice exposed to NIC prior to and throughout breeding. To this end, we assessed HC activity rhythms as well as open field (OF) activity and risk-taking behaviors at baseline (BL) and in response to voluntary NIC consumption and withdrawal (WD). D397 and N397 DNE mice exhibit a multigenerational predisposition to NIC consumption, HC hyperactivity during the inactive phase at BL, and increased risk-taking behaviors in the OF at BL. However, only D F2 NIC and N F1 NIC mice display active phase HC hyperactivity and hyperactivity in the OF at BL. Similarly, only D F2 NIC and N F1 NIC mice exhibit anomalous rhythmicity of HC activity, including increased MESOR, global amplitude, and orthophase estimates, which indicate general hyperactivity, increased magnitude

of daily variation in activity, and phase-delayed peak activity which resembles eveningess, respectively. Collectively, these data suggest that the D397N polymorphism exerts an apparent lineage-switching effect on the multigenerational transmission of certain ADHD-like phenotypes, wherein only second-generation D397 and first-generation N397 adolescent DNE progeny display the entire spectrum of ADHD-like phenotypes assessed. Taken together, our findings underscore the need for human research exploring the multigenerational link between DNE and ADHD and warrant consideration of the role of the D398N polymorphism therein.

**Disclosures: J.M. Buck:** None. **J.A. Stitzel:** None. **H.C. O'Neill:** None.

**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 728.06/C14

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

**Support:** 2017R1C1B5018076

**Title:** Atypical attentional bias to emotional faces in children with ADHD

**Authors: J.-H. SONG**[1], N. KWON[1], *S.-Y. KIM[2]
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**Abstract:** Emotional faces involuntarily bias attention regardless of one’s current goal possibly due to its ecological value. Recent studies showed that involuntary attentional bias to negative emotion was positively related to one’s level of anxiety in neurotypical adults, whereas children with typical development (TD) did not show the modulation effects. Children with ADHD often report high levels of anxiety as well as atypical attentional functions. However, it has been unspecified whether children with ADHD would also show attentional bias to emotional faces. Thus, we investigated 1) whether task-irrelevant emotional faces can bias attention in children with ADHD, and 2) effects of anxiety levels on the attentional bias to threats in ADHD. In Study 1, 20 children with ADHD (mean age (M) = 13.2) and 26 children with TD (M = 13.4) performed a task to detect an orientation of red “T” (a target) presented at the upper right position on the computer screen. While performing the task, a distractor (either a picture of angry face or place) appeared for 4 seconds and disappeared for 5-8 seconds. Attentional capture effects (ACE) were defined by RT differences between targets presented with onset of a distractor (T1) and targets without distractors (TBaseline). Attentional holding effects (AHE) were defined by how long the ACE lasted (e.g., until T2, T3, or T4, where “T2” was defined by targets appearing 2 seconds after the onset of a distractor). A three-way ANOVA with Group (TD/ADHD), Emotion (Angry/Neutral), and Order (T1/T2/T3/T4/TBaseline) showed significant 3-way interaction, driven by significant ACE in TD [Angry: $t(25)=6.65$, $p<.001$; Place :

*t*(25)=6.33, *p*<.001]. However, ACE was not significant by either distractor in ADHD. In study 2, 21 children with ADHD (M = 12.6) and 25 children with TD (M = 12.6) performed the same task as in the Study 1, but distractors were all faces (i.e., Angry face/Neutral face). The same three-way ANOVA and subsequent post-hoc analyses revealed that TD showed ACE by both faces [Angry: *t*(24)=7.22, *p*<.001; Neutral : *t*(24)=4.95, *p*<.001], whereas ADHD showed ACE only by angry faces [*t*(20)=2.85, *p*<.01]. Notably, correlation analyses with ACE, state anxiety, and trait anxiety in ADHD revealed a significant positive correlation between the magnitude of ACE and levels of trait anxiety [*r*=.606, *p*<.01]. Overall, our findings suggest that ADHD reveal atypical mechanisms of attentional bias to emotional faces, and their attentional orienting functions are modulated by their anxiety levels rather than ecological values of external stimulus. Upcoming neuroimaging studies will help to elucidate underlying neural mechanisms of attentional bias to threats in ADHD.

**Disclosures: J. Song:** None. **N. Kwon:** None. **S. Kim:** None.

**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 728.07/C15

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

**Title:** Improving working memory by applying the newly designed story grammar marker in children with specificlanguage impairmentof northern Taiwan

**Authors: H.-C. YANG**[1], D.-X. LIN[1], C.-M. YANG[2], D.-H. HUANG[2], D.-Y. HSU[2], *S.-M. WENG[1]
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**Abstract:** Specific language impairment (SLI) is diagnosed as delayed or abnormal language development in kids without apparent pathologic mechanisms, such as poor neurodevelopment, physical abnormality of the speech apparatus, autism spectrum disorder, apraxia, acquired brain damage or hearing loss, etc. Previous studies have shown the link between working memory (WM) and language development in young children with SLI. Most SLI cases have deficits in both verbal short-term and WM, and with limited abilities to simultaneously store and process verbal information that may also constrain their acquisition of linguistic skills. Hence, intensive WM training may be effective for enhancing the weakest aspects of short-term memory in children with SLI; WM training may also be of value as the aim of developing compensatory therapeutic strategies for SLI. Since telling stories puts a tremendous load on WM, especially for children been found to have difficulties with oral language expression and organization, story

grammar marker (SGM) which reduces the load on WM by externalizing the global structure and sequence of components in stories might be introduced for improving WM in SLI kids. Here we introduced a newly designed pyramidal shape SGM consists all elements of traditional SGM and we recruited twenty SLI kids aged from 7 to 12 years old to be randomized distributed into two groups with either traditional or newly designed pyramidal shape SGM for WM training for 4 weeks. Our data showed this newly designed pyramidal shape SGM has equivalent effects on WM training as traditional one and also the advantage as an user-friendly tool for its toy-like interface design.

**Disclosures: H. Yang:** None. **D. Lin:** None. **C. Yang:** None. **D. Huang:** None. **D. Hsu:** None. **S. Weng:** None.

**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 728.08/C16

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

**Title:** Early development of speech network before birth and their prediction to language performance of 2 years later

**Authors: *M. ZHU**, Y. LIU, Y. HE
State Key Lab. of Cognitive Neurosci. and, Beijing, China

**Abstract:** Resting-state functional connectivity (RSFC) approaches offer a novel tool to delineate functional networks in the brain. The aims of the present study were: 1) to explore the task-based hierarchical speech-processing networks on adults in a non-task resting state and how the networks emerge and change on babies before birth; 2) to find the relationship between the network properties before birth and the language performance at 2 years old. With three cohorts of participants - 105 adult participants from HCP, 20 full-term neonates from dHCP, and 40 preterm neonates with 31-42 weeks gestational age, we examined their intrinsic functional connectivity pattern by defining networks based on six regions of interest (ROI). The results confirmed that the resting functional connectivity patterns on adults were also organized in a hierarchical way, which corresponding to the levels of acoustic input, phonemic analysis and articulation, semantic processing and information integration. The similarity of each network on neonates to adults decreased from low to high-level networks. We also found that the functional connectivity between the cortex of HG and mSTS and that of primary motor and inferior frontal gyrus increased with gestational age. Moreover, multivariate pattern analysis using support vector regression revealed that the language performance of 2 years old could be predicted by the functional connectivity strength within some language networks. Collectively, we highlighted the

hierarchical language network in human brain and the relatively development order in the very early age.

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**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

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

**Support:** University of Missouri Department of Radiology Mission Enhancement Fund
University of Missouri Summer Medical Student Internship Program

**Title:** The effects of methylphenidate on verbal creativity, verbal fluency, and problem-solving abilities in individuals with attention deficit hyperactivity disorder

**Authors: *B. M. KILLE**[1], B. J. FERGUSON[2], M. M. MCBRIDE[2], D. C. WANG[2], D. Q. BEVERSDORF[3]
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**Abstract:** Creativity, or the ability to generate ideas that are both novel and useful, is associated with a decreased signal-to-noise ratio in the brain that results in defocused attention. Reductions in attention are the hallmark of attention deficit hyperactivity disorder (ADHD), which may facilitate divergent thinking that is essential to the creative process. One of the most common treatments for ADHD is methylphenidate (MPH), a psychostimulant that targets the dopamine and noradrenergic systems, which increases attention in ADHD. However, the effects of MPH on convergent and divergent thinking in ADHD are unclear. Therefore, the present study examined effects of MPH on convergent and divergent thinking in individuals with ADHD. Participants (N=9, range=18-40, mean age=26.3, SD=7.01, 3 females, all Caucasian) with a diagnosis of ADHD and who are currently taking MPH for their ADHD were recruited for this ongoing study. Participants attended one session while on their MPH and another where they withheld their MPH. During both sessions, participants completed problem-solving tasks (anagrams, compound remote associates) letter & category fluency assessments, and the Verbal Torrance Test for Creative Thinking (V-TTCT). Initial analyses indicate significant reductions in solution latency time for the anagrams task ($p = 0.008$), and significant increases in originality on the V-TTCT ($p = 0.049$) for the MPH session. Furthermore, trends toward significance were revealed for flexibility and the total battery score on the V-TTCT. Thus, initial results from this ongoing

study suggest that MPH may increase some domains of verbal creativity and problem-solving abilities in those with ADHD.

**Disclosures: B.M. Kille:** None. **B.J. Ferguson:** None. **M.M. McBride:** None. **D.C. Wang:** None. **D.Q. Beversdorf:** None.

**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

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**Program #/Poster #:** 728.10/C18

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

**Support:** Boğaziçi University BAP project no: 6747S

**Title:** Vibrotactile adaptation and Weber's Law in children with Tourette syndrome

**Authors: Ü. EŞEN**[1], H. DOKTUR[2], D. YıLDıZ[2], C. TANıDıR[3], M. TOMMERDAHL[4], *B. GUCLU[1]
[1]Bogazici Univ., Istanbul, Turkey; [2]Bakirkoy Res. and Training Hosp. for Psychiatry, Neurol. and Neurosurg., İstanbul, Turkey; [3]İstanbul Gelişim Univ., İstanbul, Turkey; [4]Dept. of Biomed. Engin., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

**Abstract:** Tourette syndrome (TS) is a developmental neuropsychiatric disorder which is characterized by multiple motor tics along with at least one vocal tic present at least for one year. It was previously suggested that neurotransmission, especially regarding the inhibitory neurotransmitter γ-aminobutyric acid (GABA), is altered in patients with TS and neuroanatomical changes such as increased volume in dorsal prefrontal and parieto-occipital brain regions were documented. According to these findings, the chronic tics and premonitory urges are thought to be due to hyperexcitability caused by reduced GABA concentrations; and TS patients do not adapt to vibrotactile stimuli as much as healthy controls. In the current study, we aim to extend the GABAergic dysfunction hypothesis by testing vibrotactile intensity/amplitude discrimination with and without adaptation based on different standard and adapting stimuli. Twenty-nine TS patients (age range: 9-17, 7 female, 22 male) participated in psychophysical experiments. Vibrotactile stimuli (25 Hz, duration: 0.5 s) generated by a portable device (CM-4, Cortical Metrics) were applied on the fingertips of the participants. The test battery consisted of measuring choice reaction time (amplitude: 200 μm), dynamic detection threshold (amplitude ramp: 2 μm/s), static detection threshold, amplitude discrimination, and amplitude discrimination with single site adaptation (adapting duration: 1 s). Our analyses show that the dynamic thresholds were still higher than the static thresholds (averages 11 μm vs. 8 μm; $p<0.001$) indicating some adaptation due to ramping subthreshold stimuli. ANOVA was performed on difference limen (DL) values with standard stimulus amplitude (levels: 50, 100,

200 µm) and adapting stimulus amplitude (levels: 0, 100, 300 µm) as factors. DL values increased as a function of the standard stimulus amplitude as predicted by the Weber's Law ($p<0.001$), and there was a main effect of adaptation by increasing DLs ($p<0.001$). However, there was also a significant interaction between the amplitudes of the standard and adapting stimuli ($p=0.014$). Increasing the adapting stimulus amplitude did not cause an additional increase in DLs. These preliminary data suggest that reduced adaptation due to GABAergic dysfunction in TS may be more prominent at higher adapting stimulus levels. We are currently studying normal children to characterize their vibrotactile discrimination capacity for comparison with the TS group.

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**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

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

**Support:** IMPRS for Language Sciences Fellowship
Max Planck Research Group Grant

**Title:** Probing neuronal and molecular underpinnings of language-related disorders using human stem cell-derived neuronal networks

**Authors: *M. V. ANIJS**[1], F. M. S. DE VRIJ[2], S. A. KUSHNER[2], S. C. VERNES[3,4]
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**Abstract:** Human language is a fascinating and complex trait and the genetics of related disorders can help us to identify its underlying biological processes. Given that language is unique to humans, species-specific neurogenetic mechanisms are likely involved, highlighting the importance of studying language-related genes such as *CNTNAP2* in human model systems. To do this, we have generated electrophysiologically mature neuronal networks from human stem cells. The differentiation protocol that we use generates forebrain neural progenitor cells from stem cells that subsequently give rise to both neurons and astrocytes in a consistent 60:40 ratio. The resulting neuronal networks include neurons representative of both upper and deep cortical layers and we have demonstrated the activity and connectivity of the networks by calcium imaging. We aim to understand the neuronal phenotypes observed in neuronal networks

derived from normal ‘wild-type’ cells and compare these with isogenic lines carrying CRISPR/Cas9-induced mutations in key language-related genes. We are developing lines that allow to investigate consequences of coding mutations (e.g. in the *CNTNAP2* gene) and non-coding mutations (e.g. in microRNAs or 3'UTR regulatory sequences). These models also allow interrogation of the underlying molecular state of the differentiated human neurons and how these pathways are perturbed in mutant-derived networks. In our molecular studies, we place a particular focus on the role of microRNAs, since they are important modulators of gene regulation, have evolved relatively rapidly, and have been implicated in several neurodevelopmental disorders such as autism and specific language impairment. To understand not only the genes, but also the related microRNA regulatory pathways important for normal network function, we are profiling total and small RNA expression patterns across neuronal differentiation and network development. This work will demonstrate molecular pathways involved in normal network development and function. Integrating these findings with equivalent studies in isogenic mutant-derived networks will provide new insight on how coding and non-coding mutations lead to disrupted neuronal development/function and ultimately language-related disorders.
Taken together these investigations will connect known language-related genes via shared pathways and implicate new players in neuronal network development and language-related disorders. In this way, we will gain a more complete understanding of the genetic components of neuronal development that underpin language, with the potential of detecting processes that are unique to our species.

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**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 728.12/C20

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

**Support:** R01 CA74177
R01 MH065702
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**Title:** Guanfacine decreases impulsivity in a mouse model of Neurofibromatosis type 1

**Authors: *J. L. LUKKES**[1,2], S. D. FITZ[1,2], H. P. DROZD[3,2], D. W. CLAPP[4,5,2], A. I. MOLOSH[1,2], A. SHEKHAR[1,3,6,7]
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[5]Microbiology and Immunol., [6]Pharmacol. and Toxicology, [7]Indiana Clin. and Translational Sci. Inst., Indiana Univ. Sch. of Med., Indianapolis, IN

**Abstract:** Neurofibromatosis type 1 (NF1) is an autosomal dominant disease with mutation in one copy of the NF1 gene and has a prevalence of approximately 1 in 3000 individuals. Children with NF1 suffer from a significant incidence of learning disabilities and cognitive difficulties associated with symptoms of attention deficit hyperactivity disorder (ADHD). Even though approximately 40-60% of children with NF1 meet criteria for ADHD, very few preclinical studies, if any, have investigated alterations in impulsivity and risk-taking behavior. Mice with deletion of a single *Nf1* gene (*$Nf1^{+/-}$mice)* recapitulate many of the phenotypes of NF1 patients. Therefore, we compared wild type (WT) and *$Nf1^{+/-}$* mouse strains to investigate differences in impulsivity, risk-taking, and locomotor activity using the delayed discounting task (DDT), cliff avoidance reaction (CAR) test, and open field. For DDT, mice were trained to differentiate between a small and large reward in a t-maze. Once criteria were met, a 10 s or 20 s delay was administered prior to the large reward. *$Nf1^{+/-}$* mice choose a higher percentage of smaller rewards when both 10 s and 20 s delays were administered compared to WT mice, suggesting *$Nf1^{+/-}$* mice are more impulsive. When treated with the alpha-2A adrenergic receptor agonist guanfacine (0.3 mg/kg, i.p.) daily across the six day testing phase of DDT, *$Nf1^{+/-}$* mice exhibited decreased impulsive choice by waiting for the larger, delayed reward. In the CAR test, mice were placed on an elevated, circular platform for 60 min. *$Nf1^{+/-}$* mice exhibited increased risk-taking and impulsivity compared to WT mice in the CAR test by repetitively entering the outer edge of the platform where they risk falling. Treatment with guanfacine ameliorated deficits in behavioral inhibition by reducing the amount of exploration *$Nf1^{+/-}$* mice made along the outer edge of the platform. In addition, *$Nf1^{+/-}$* mice exhibited increased distance travelled and mean speed compared to WT controls in a 1 hr open field test. Hyperactivity in *$Nf1^{+/-}$* mice was reduced with guanfacine pre-treatment. Overall, our study confirms that *$Nf1^{+/-}$* mice exhibit an ADHD phenotype. These data suggest that *$Nf1^{+/-}$* mice can be used to identify drug targets and alterations in neural circuitry associated with symptoms of ADHD.
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**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

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NHMRC Centre of Research Excellence (CRE) in Child Language #1023493
NHMRC CRE in Speech & Language Neurobiology #1116976
NHMRC CRE Moving Ahead #1023043
NIH Grant R01HD081720

**Title:** Altered gray matter volumes in language-associated regions in children with developmental language disorder and speech sound disorder

**Authors: *F. KURTH**[1], E. LUDERS[1,2], L. PIGDON[2], G. CONTI-RAMSDEN[3,2], S. REILLY[2,4], A. T. MORGAN[2]
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**Abstract:** Developmental language disorder (DLD) and speech sound disorder (SSD) are common, and although scientific evidence for structural and functional alterations in DLD / SSD is accumulating, current neuroimaging studies provide an incongruent picture. Here, we hypothesized that children affected by DLD and SSD present with gray matter (or gray matter asymmetry) aberrations in brain areas associated with language processing compared to typically developing (TD) children. To assess this hypothesis, we enhanced MRI-based information with microscopically defined cytoarchitectonic probabilities of Broca's area (BA 45, BA 44) as well as an auditory area (TE 3.0). Left and right gray matter volumes in addition to gray matter volume asymmetry were investigated in 18 children with SSD, 13 children with DLD, and 18 TD children within these regions of interest. We observed significantly larger gray matter volumes in right BA 45 in DLD compared to TD children and also compared to SSD children. These findings suggest an altered development of language processing areas, specifically BA 45, in children with DLD that is in agreement with previous interpretations of procedural deficits. Furthermore, we detected a larger rightward gray matter asymmetry in BA 45 in children with DLD and with SSD compared to TD children, albeit only on a trend level. This may suggest an altered hemispheric lateralization of language processing in DLD and SSD consistent with previous reports.

**Disclosures: F. Kurth:** None. **E. Luders:** None. **L. Pigdon:** None. **G. Conti-Ramsden:** None. **S. Reilly:** None. **A.T. Morgan:** None.

**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 728.14/C22

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

**Support:** IMSS Grant FIS/IMSS/PROT/G15/1483

**Title:** Atomoxetine prevents working memory loss in hyperactive rats, mediating plastic changes in prefrontal cortex pyramidal neurons

**Authors: *N. I. MARTINEZ TORRES**[1,2], D. GONZÁLEZ-TAPIA[3], N. VÁZQUEZ-HERNÁNDEZ[1], I. GONZÁLEZ-BURGOS[1]
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**Abstract:** Attention Deficit Hyperactivity Disorder (ADHD) causes impaired visuospatial working memory (VWM), which primarily maps to the prefrontal cortex. However, little is known about the synaptic processes underlying cognitive loss in ADHD, or those ultimately involved in the preventive effect observed through theclinical use of Atomoxetine (ATX). To investigate the plasticity underlying ADHD related cognitive loss, and that potentially involved in the preventive action of Atomoxetine. Allocentric VWM was assessed, as well as the dendritic spine number and proportional density on pyramidal neurons in the prefrontal cerebral cortex layer III of neonatal 6-hydroxydopamine-lesioned rats. The effect of acute ATX treatment was also assessed at 28 days of age. 6-OHDA induced lesions produced increased motor activity and a loss ofVWM, concomitant with a reduction in thin spine density. ATX administration reversed cognitive loss, in conjunction with a decrease in thin spines and an increase in mushroom spines. A reduction in the proportion of spines involved in learning in hyperactive animals could account for the loss in cognitive function observed. Considering thin spine density was also reduced after ATX administration, we hypothesized that the restoration in cognitive function recorded could be brought about by an increase in memory related mushroom spines.

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**Poster**

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**Location:** SDCC Halls B-H

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**Program #/Poster #:** 728.15/C23

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

**Support:** NIH Grant T32GM007288
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**Title:** Deletions in the ANKS1B gene encoding AIDA-1 cause synaptic dysfunction and human disease

**Authors: *A. CARBONELL**[1], J. O. TINDI[4], H. ERDJUMENT-BROMAGE[5], C. CHO[2], T. A. NEUBERT[6], B. A. JORDAN[3]
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**Abstract:** AIDA-1, the product of the gene *ANKS1B*, is a synaptic protein previously implicated in amyloid precursor protein processing and nuclear function. Previous work in our lab demonstrated that AIDA-1 regulates the synaptic localization of the NMDA receptor subunit GluN2B, and that postnatal deletion of AIDA-1 impairs synaptic plasticity and reduces anxiety-like behaviors in mice. Published studies link *ANKS1B* to neuropsychiatric diseases, including autism spectrum disorder (ASD) and schizophrenia. We recently identified several families harboring heterozygous deletions in the *ANKS1B* gene detected by chromosome microarray. Probands suffer from diverse conditions including ASD, attention-deficit hyperactivity disorder, speech apraxia, and motor impairments. Using blood samples from two of these families, we confirmed the presence of the heterozygous deletion by quantitative PCR and reprogrammed peripheral mononuclear cells to generate human induced pluripotent stem cells (hiPSCs). To model the functional and behavioral implications of embryonic loss of AIDA-1, we generated an animal model by crossing AIDA-1 floxed mice to a Nestin-Cre mouse line. In several cohorts of conditional heterozygous AIDA-1 mice, behavioral analysis reveals reduced anxiety, increased startle response and reduced prepulse inhibition, reduced sociability, and impaired fine motor function compared to littermate Nestin-Cre controls. To probe the mechanisms by which AIDA-1 regulates neuronal function, we immunoprecipitated AIDA-1 from mouse brain lysates and identified the AIDA-1 interactome using tandem mass tag-based quantitative mass spectrometry. Our analyses revealed proteins involved in ER to Golgi transport, endosomal recycling, and small GTPase regulation. We are currently characterizing induced neurons from proband and control hiPSCs using imaging, biochemical analyses, and functional electrophysiology. Moreover, we are testing neural substrates in AIDA-1 heterozygous mice to identify the cellular and synaptic dysfunction underlying behaviors relevant to neuropsychiatric disease.

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**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 728.16/C24

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

**Support:** NICHD 1R15HD087937
Alan & Wendy Pesky Resesarch award

**Title:** Decoding Dyslexia

**Authors: *L. A. GABEL**[1], E. JOHNSON[3], D. T. TRUONG[4], E. MURRAY[2], E. ESCH[2], K. VOSS[2], O. GRIGAUX[2], S. PANIAGUA[5], J. R. GRUEN[6]
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**Abstract:** Reading disorder (RD, a.k.a. Dyslexia) is a specific learning disability that affects reading. If learning disabilities remain untreated, a child may experience long term social and emotional problems which 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. The complete explanation of a complex neurodevelopmental disorder requires an understanding across multiple levels, including, but not limited to, cognition, behavior, and genetics. Although our understanding and treatment for dyslexia has greatly increased in the last 20 years, a significant percentage of children with dyslexia are either identified too late, or have a specific manifestation of the disorder that is not understood well enough to design and deliver a successful remediation. This outcome is exacerbated when the child is non-native speaker. Research examining the connection among genetic, cognitive and behavioral aspects of reading disorder offers promise for early identification and intervention to successfully address specific phenotypes of RD. Recently we demonstrated the 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. This deficit is consistent across language orthographies (i.e. transparent and non-transparent languages). In this study we examined the link between maze performance, phonological processing, family history of dyslexia, and genetic risk in a longitudinal study. We examined reading ability and maze performance at 5-6 and 8-9 years of age and determined whether early reading measures, maze performance or genetic risk is a better predictor of reading ability by the third-grade.

**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:** None. **D.T. Truong:** None. **E. Murray:** None. **E. Esch:** None. **K. Voss:** None. **O. Grigaux:** None. **S. Paniagua:** None. **J.R. Gruen:** None.

**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 728.17/C25

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

**Support:** NARSAD AWARD FOR YOUNG INVESTIGATOR

**Title:** Cerebral organoids as a new way to model ADHD pathophysiology

**Authors: *C. A. SARAIVA LOPES**[1], S. KO[2], J. R. COPPETA[3], B. M. COHEN[2], M. TEICHER[2], K.-S. KIM[2]
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**Abstract:** Attention deficit hyperactivity disorder (ADHD) is a heterogeneous neurodevelopmental disorder with a devastating impact on the quality of life of millions of children, adolescents and adults. While ADHD is thought to be highly heritable and its etiology largely unknown, it is likely to involve a combination of environmental factors and the contribution of multiple genes defects. To understand the molecular underpinnings of ADHD, we hypothesize that 3D neuralized structures (organoids) derived from patient-specific induced pluripotent stem cells (iPSCs) can be used as a potential platform. In particular, the Prefrontal Cortex (PFC) is emerging to be of central relevance to the neural pathways of ADHD, as it connects extensively to sensory and motor cortices, as well as to the basal ganglia and cerebellum. These areas are intricately interconnected and modulated by a mesh of neurons that in ADHD display heavy deficits in dopaminergic and noradrenergic transmission. Thus, it is critical to understand the molecular influences modulating PFC's function in order to develop novel medications for patients afflicted with the disorder. We have started to generate and characterize iPSCs-derived cortical organoids from ADHD patients and healthy siblings controls to study the molecular and cellular differences in corticogenesis between diseased and control brains. Particularly, we propose that the root cause of the PFC's smaller structure involves a limited progenitor pool and impaired radial migration. To achieve these long-term goals, we used our novel and non-viral reprogramming methods to generate high quality control and ADHD-iPSCs lines to optimize in vitro organoid generation, and apply this technology to fusion organoid models. Our approach will facilitate examination of how disease risk is translated at the cellular and tissue levels through comparative studies of processes such as progenitor cell proliferation, migration and connectivity during development.

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**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 728.18/C26

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

**Title:** Human ADHD gut microbiota induces ADHD-like features in mice

**Authors: A. C. TENGELER**[1], S. A. DAM[2], M. WIESMANN[1], J. NAAIJEN[2], B. FRANKE[3], *T. L. KOZICZ[4], A. ARIAS VASQUEZ[2], A. J. KILIAAN[1]
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**Abstract:** Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by attention disabilities, hyperactivity and impulsiveness. Neuroimaging studies have shown alterations in several brain regions in children and adults with ADHD, including the hippocampus and internal and external capsule. ADHD is considered multifactorial and involves genetics and environmental factors. Additionally, gut micro-organisms (i.e., the gut microbiota) might contribute to the pathobiology of ADHD because a divergent microbiota is found in people with ADHD compared to healthy controls. Increasing evidence suggests a role for the gut micro-organisms in neurodevelopment, including brain function and structure. Therefore we hypothesize that the gut microbiota from persons with ADHD might influence brain function and structure similar to what has been reported in ADHD. In this confirmatory, double-blind and randomized study we investigated the impact of the gut microbiota on behavior and brain structure/function by colonizing young male germ-free wild-type C57BL/6JOlaHsd mice with microbiota from three human males with ADHD and three male age-matched healthy controls. Mice (n=14 per experimental group) were housed in gnotobiotic isolators, in which the behavioral tests were conducted as well. Linear discriminant analysis effect size (LEfSe) showed that nineteen bacterial genera were significantly different between the ADHD and control mice. In addition, a significant difference in β-diversity between the mice colonized with ADHD or control microbiota was found. Mice colonized with ADHD microbiota did not differ in locomotion activity, but were more anxious than control mice in the open field test. In the larger human sample (n=135 with ADHD and n=134 controls) we also found a positive correlation between ADHD scores and anxiety scores. Colonization with ADHD-microbiota affected brain structure as well: increased functional connectivity between right motor cortex and right visual cortex and differences in DTI measures in hippocampus (decreased FA and increased MD and RD) and right internal capsule (decreased FA and increased RD) as obtained with an 11.7 T Bruker MR scanner. This study demonstrates that ADHD microbiota is able to induce anxiety and brain structure abnormalities in mice that are similar to alterations found in humans with ADHD. Our data also suggests that the microbiota might be a potential target in alleviating

ADHD symptoms. The microbial composition can be manipulated by diet, therefore nutritional interventions could be a promising therapy to mitigate ADHD symptoms.

**Disclosures: A.C. Tengeler:** None. **S.A. Dam:** None. **M. Wiesmann:** None. **J. Naaijen:** None. **B. Franke:** None. **T.L. Kozicz:** None. **A. Arias Vasquez:** None. **A.J. Kiliaan:** None.

**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 728.19/C27

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

**Title:** Multimodal imaging of occipitotemporal cortex in children with dyslexia

**Authors: *C. WANG**, M. MANDELLI, C. WATSON, E. CAVERZASI, M. GORNO-TEMPINI
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**Abstract:** Individuals with developmental dyslexia have been demonstrated to show atypical neural response to printed words and faces, but the nature of those abnormal processes remains unclear. To explore the possible mechanisms, we acquired neuropsychological measures and multimodal imaging data from 25 children with dyslexia (age mean = 12.6 years, SD = 2.2) and 16 age-matched typically developing controls (age mean = 12.2 years, SD = 1.7) to investigate neural response during implicit tasks with words and cartoon faces in dyslexics and the related structural characteristics. In a cluster in the left occipitotemporal cortex showing the strongest word selectivity in controls, dyslexics showed reduced activation and lack of gradient in word response relative to controls. In the same area, the neural response for faces was greater than for words in both controls and dyslexics. Furthermore, analyses of high-resolution structural anatomy also revealed gyrification abnormalities of this region in a sub-group of dyslexic children. Our findings suggest that children with dyslexia show a complex pattern of functional and structural abnormality in the occipitotemporal cortex.

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**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 728.20/C28

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

**Title:** Genetic polymorphisms of HTR1A and -1B and serotonin transporter binding measured by PET allow for accurate classification of ADHD: An imaging-genetics machine learning model

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**Abstract:** Objective: High heritability rates above 70% have been reported for ADHD. While the norepinephrine and dopamine transporters represent a main treatment target for attention deficit and hyperactivity disorder (ADHD), single nucleotide polymorphisms (SNPs) associated with serotonergic transmission might impact ADHD etiology and pathology [1]. Here, we strove for a multivariate prediction model for ADHD based on SNPs as well as SERT binding potential ($BP_{ND}$) measured with [$^{11}$C]DASB and positron emission tomography (PET).
Methods: 16 patients with ADHD and 18 healthy control subjects (HC) were scanned by PET and genotyped for 30 SNPs within *SLC6A4, HTR1A, HTR1B, HTR2A* and *TPH2* genes using Sequenom iPLEX. The collective and the genotyping technique has been described previously [2, 3]. 18 cortical and subcortical regions of interest (ROI) were defined. The cerebellum was used as reference region for computation of $BP_{ND}$. 18 cortical and subcortical regions of interest (ROI) were defined. RandomForest (RF) was used to select the most informative set of predictors in a nested cross-validation approach [4]. The inner loop was used for model optimization, the outer loop for validation.
Results. Variable selection produced consistent results and highlighted the putamen, anterior cingulate cortex and midbrain ROI as well as SNPs rs1328684 of *HTR2A* and rs130058 of *HTR1B* as most discriminative between HC and ADHD patients. Mostly, the feature selection algorithm chose 2-3 predictors for optimal performance. The mean accuracy for the validation sets across the ten repeats was 0.81 (±0.05) and the models yielded balanced sensitivity and specificity.
Conclusion. A prediction accuracy above 0.8 allows for clinically relevant classification. Therefore, our results advocate the relevance of the two SNPs within *HTR2A* and *HTR1A* genes and epistasis within these genes in ADHD and might contribute to the generation of a

multimodal, imaging- and genetics-based classification tool for ADHD. Regarding the high rates of co-morbidities and difficult differential diagnosis in this disorder, a reliable classification model would be of significant clinical value.

**References:**

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3. Vanicek, T., et al., Hum Brain Mapp, 2017. **38**(2): p. 792-802.
4. Varoquaux, G., et al., Neuroimage, 2017. **145**(Pt B): p. 166-179.

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**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 728.21/C29

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

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

**Title:** Brain and behavioral consequences of developmental nicotine exposure in a GAD67-GFP mouse model

**Authors: *M. M. MARTIN**, M. X. TRUPIANO, D. M. MCCARTHY, P. G. BHIDE
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**Abstract:** Cigarette smoking during pregnancy is a major public health concern because it can have detrimental effects on both the mother and her child. For example, developmental nicotine exposure (DNE) is associated with increased risk for ADHD, conduct disorder, aggression, learning disabilities, depression, and epilepsy. The GABA neurotransmitter system is known to be altered in many of these developmental disorders raising the possibility that DNE may target the GABA system in the developing brain. Here we examined the effects of DNE on the GABA system using a GAD67-GFP knock-in mouse model. Female mice were exposed to plain drinking water or water containing nicotine (200 µg/ml) beginning 3 weeks prior to conception and continuing throughout pregnancy and up to 3-weeks postpartum when the offspring were weaned. We found that DNE produces a significant increase in the number of GABA neurons in the intermediate and marginal zones of the dorsal forebrain in 15-day old embryos, suggesting that DNE alters the GABA neuron migration from the basal to the dorsal forebrain. Since perturbation of developmental pathways can lead to lasting changes in the mature brain and

behavior, we examined behavioral phenotypes as well as the number and location of GABA and non-GABA neurons in the prefrontal and medial prefrontal cortex in the adult mouse brain. We found significant changes in the behavioral phenotype (deficits in working memory and impaired approach-avoidance behavior) as well as significant changes in neuron numbers suggesting long-term behavioral and structural consequences of developmental nicotine exposure.

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**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

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

**Support:** The Jim and Betty Ann Rodgers Chair Funds
Avekshan LLC

**Title:** Norbinaltorphimine, a selective κ-opioid receptor antagonist, alleviates behavioral and neurotransmitter phenotypes in a mouse model of attention deficit hyperactivity disorder

**Authors: L. ZHANG**[1], J. BIEDERMAN[2], T. J. SPENCER[2], K. L. JAUNARAJS[3], D. G. STANDAERT[3], D. M. MCCARTHY[1], *P. G. BHIDE[1]
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**Abstract:** Kappa opioid receptor (KOR) antagonists improve stress resilience and have therapeutic potential in mood disorders and drug addiction. However, whether they can alleviate non-stress related neurobehavioral deficits is not known. Since KORs negatively regulate dopamine and noradrenaline release from synaptic terminals, KOR antagonists have the potential to alleviate the frontal cortical hypo-dopaminergic state associated with attention deficit hyperactivity disorder (ADHD), and provide therapeutic benefit. To test this possibility, we administered norbinaltorphimine (nor-BNI; 20 mg/kg; i.p.) to a perinatal nicotine exposure (PNE) mouse model of ADHD. The PNE mouse is an excellent ADHD model because it shows significant decreases in frontal cortical dopamine and noradrenaline content, and attention and working memory deficits. Following a single nor-BNI administration to the PNE mice, we assayed frontal cortical dopamine and noradrenaline levels by *in vivo* microdialysis and HPLC at 30 min intervals over a 48 hr period. We observed two dopamine peaks at 3 and 5 hr post nor-BNI, and two noradrenaline peaks at 4 and 6 hr post nor-BNI. Additionally, the nor-BNI administration significantly improved attention and working memory in the PNE mice at 2.5 and

5.5 hr post nor-BNI. By 24 hr after the nor-BNI administration, both the behavioral parameters returned to pre-nor-BNI levels. These observations suggest that nor-BNI produces bi-phasic elevation of dopamine and noradrenaline levels in the frontal cortex that begin approximately 2-3 hr after the nor-BNI administration and last up to 24 hr. Nor-BNI produces significant improvements in attention and working memory in the PNE mouse model. The improvements are evident up to 5.5 hr after the single nor-BNI administration but not at 24 hr. In summary, our data suggest that nor-BNI may have therapeutic potential for ADHD related phenotypes, and enlarge the neuropsychiatric landscape in which KOR antagonists may have clinical benefit.

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**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

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**Program #/Poster #:** 728.23/C31

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

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

**Title:** A selective κ-opioid receptor antagonist alleviates behavioral phenotypes in Fmr1 knockout mouse

**Authors: *D. M. MC CARTHY**[1], M. TRUPIANO[1], E. CARRAZANA[2], L. ZHANG[1], J. BIEDERMAN[3], T. J. SPENCER[3], P. G. BHIDE[1]
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**Abstract:** Fragile X mental retardation syndrome (FX) is an inherited condition that causes a range of developmental disabilities, including delayed speech and language development, mild to moderate intellectual disability, anxiety, attention deficit, hyperactivity, communication and social deficits associated with autism spectrum disorder, and seizures FX is the result of a mutation in the Fragile X mental retardation 1 (*FMR1*) gene. The mutation expands a DNA segment, known as the CGG triplet repeat, beyond its normal range of 5 to 40 repeats. An expansion in the 55-200 range constitutes a premutation, whereas an expansion beyond 200 repeats causes a full mutation or FX. FX is the number one inherited cause of intellectual disabilities, and the most common known cause of autism worldwide. Therefore, new methods for the treatment are needed. We examined spontaneous locomotor activity, attention, anxiety, social interaction and cliff avoidance reflex in the *Fmr1* knockout mouse (B6.129P2-*Fmr1*$^{tm1Cgr}$/J). Adult male and female *Fmr1* knockout mice showed hyperactivity, impaired social

interaction (tube test), increased time in the open arms of the elevated plus maze and impaired cliff avoidance reflex. We have shown that the selective kappa opioid receptor antagonist norbinaltorphimine (nor-BNI) attenuates hyperactivity in a developmental nicotine exposure mouse model and increases frontal cortical dopamine and noradrenaline levels (Zhang *et al*, 2018 Soc. Neurosci. Abstr.). Since the phenotypes observed in the *Fmr1* knockout mouse could be mediated at least in part via impaired frontal cortical monoamine neurotransmitter signaling mechanisms, we examined the effects of nor-BNI on the behavioral phenotypes in the *Fmr1* knockout mouse. A single administration of nor-BNI (20mg/kg; i.p.) significantly reduced hyperactivity in male *Fmr1* knockout mice and partially rescued impaired social interaction in the tube test in both males and females. Our observations suggest that nor-BNI can alleviate behavioral phenotypes in the *Fmr1* knockout mouse and that it could have therapeutic potential in management of FX.

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**Poster**

**728. ADHD, SLI, Dyslexia, and Other Disorders**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 728.24/C32

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

**Title:** Adolescent stress and hypofrontality: Towards a rodent model of ADHD

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**Abstract:** The estimated worldwide prevalence of Attention-Deficit/Hyperactivity Disorder (ADHD) is approximately 1.2% to 7.3%. The etiopathogenesis of this disorder remains controversial, although symptoms are well characterized: hyperactivity, impulsivity and inattention. Given its role in the regulation of high-level executive functions, consensus interpretation considers hypofrontality is critical in the emergence of ADHD. Adolescent male rats were subjected to chronic unpredictable mild stress for 3 consecutive weeks starting from the post-weaning phase. The stress procedure was a combination of a series of unpleasant situations, repeated over the week. The control rats were handled daily but were not subjected to any stress. Then the rats were exposed to a series of behavioral experiments. A set of rats were sacrificed immediately after the stress procedure and the prelimbic pyramidal neurons were tested electrophysiologically. Another set of rats were used for in vivo brain imaging using Functional Magnetic Resonance imaging technology. Stressed rats exhibited an attenuated corticosterone

response to acute stress compared to control mates. They spent a significantly higher time exploring the open arms of the elevated plus maze and travelled longer distances in the open field test indicating a disinhibited behavior. They also displayed higher number of premature responses and a lower number of correct responses on the 5-Choice Serial Reaction Time Task reflecting a motor impulsivity. They displayed higher number of premature responses on the Differential Reinforcement of Low rate responding and showed increased delay discounting, reflecting a cognitive impulsivity as well, behaviors partially restored following DREADD activation of the Prelimbic Cortex. They demonstrated a lower number of correct responses on the cognitive flexibility task, higher motivation and compulsivity for saccharine and increased preference for cocaine as compared to saccharine. Finally, the stress procedure also decreased *ex vivo* intrinsic excitability of deep layer pyramidal neurons in the prelimbic cortex of the rats as evidenced by a higher threshold for inducing action potential, a lower input resistance and a higher action potential latency, observations also confirmed using fMRI analyses. In brief, we have successfully developed a preclinical model of ADHD after subjecting adolescent rats to chronic mild stress. This model shows the behavioral hallmarks of ADHD, namely, disinhibition, hyperactivity, impulsivity and inattention, that correlates with decreased excitability of pyramidal neurons of the prelimbic cortex.

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**Poster**

**729. Calcium Channels: Regulation and Modulation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 729.01/C33

**Topic:** B.04. Ion Channels

**Support:** PICT-2015 3330

**Title:** Ghrelin selectively inhibits CaV3.3 subtype of low voltage activated Ca2+channels

**Authors: *E. R. MUSTAFA**, S. CORDISCO GONZALEZ, S. S. ROGRIGUEZ, J. RAINGO
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**Abstract:** Voltage-gated $Ca^{2+}$ ($Ca_V$) channels are instrumental in coupling changes in membrane voltage to $Ca^{2+}$ influx that, in turn, regulates numerous critical neuronal functions. In particular, low voltage activated $Ca^{2+}$ channels ($Ca_V3$) are involved in the generation of burst firing and pacemaker activity. Knowing that G-protein coupled receptors can modulate $Ca_V3$ activity, here we investigated the ghrelin effect on $Ca_V3$ currents through its receptor, GHSR. Previously, we have showed that ghrelin evoked GHSR activity inhibits high voltage activated $Ca_V$, particularly $Ca_V2.1$ and $Ca_V2.2$. Whole cell patch recordings on transfected tsA201 cells reveal that

activation of GHSR by ghrelin application has an inhibitory effect on $Ca_V3.3$ currents but no effect either on $Ca_V3.1$ or $Ca_V3.2$. Application of ghrelin has no impact on $Ca_V3.3$ voltage dependency parameters ($V_{1/2}$ and *k* of activation and $V_{rev}$). On the other hand, ghrelin accelerates the $Ca_V3.3$ activation and inactivation kinetics at hyperpolarized voltages (from -40 to -20 mV), while the kinetics of recovery from inactivation remains similar to control values. Based on this data, we hypothesized that ghrelin application could reduce the calcium entry by $Ca_V3.3$ channels in response to physiologically relevant stimuli, such as action potentials. In order to study the isolated efficacy of $Ca_V3.3$ to calcium entry during action potential train we measure $Ca^{2+}$ currents using a hippocampal CA1 neuron firing recording as a voltage command in tsA201 cells expressing $Ca_V3.3$ and GHSR. We found that ghrelin reduces the calcium entry through $Ca_V3.3$ evoked by this stimulation paradigm. Similar to previous reports, $Ca_V3.3$ displayed current facilitation, and we found that this phenomenon is slightly reduced by ghrelin application. Next, we explore the signaling cascade implied in the effect of ghrelin on $Ca_V3.3$ and we found that co-expression of a $G_q$ dominant negative mutant or co-expression of the regulator of G-protein signaling 2 (RGS2, an effector antagonist for $G_{q/11}$) completely occlude the inhibitory actions of ghrelin on $Ca_V3.3$. The data presented here allow us ascribing a ghrelin control of the firing activity in neurons expressing GHSR and $Ca_V3.3$, but further experiments are necessary to explore this possibility.

**Disclosures: E.R. Mustafa:** None. **S. Cordisco Gonzalez:** None. **S.S. Rogriguez:** None. **J. Raingo:** None.

**Poster**

**729. Calcium Channels: Regulation and Modulation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 729.02/C34

**Topic:** B.04. Ion Channels

**Title:** Leptin promotes cellular differentiation and increases ionic currents in cells of neuroblastoma n1e115

**Authors: *B. DOMINGUEZ MANCERA**, R. I. VERGARA-REYES, P. CERVANTES-ACOSTA, A. HERNANDEZ-BELTRAN, M. BARRIENTOS-MORALES
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**Abstract:** The study of the development and neural function has been favored with the establishment and use of cell lines such as N1E-115 (neuroblastoma), which proliferates unlimitedly and develops neurites when is exposed to different agents. To determine the chronic effect (48-72 hrs) of the anorexigenic hormone Leptin -LEP- on N1E-115 cells, it was applied alone or in combination with Dimethylsulfoxide - $Me_2SO$- (agent promoting the development of neurites). Cells were grown at in Dulbecco's modified Eagle's medium (DMEM) containing

0.12% with 10% fetal calf serum. The cultures were maintained under a humidified atmosphere containing 5% $CO_2$. After the cultures were in confluent phase, cells were trypsinized and seeded at a density of 5 X $10^5$ per 35 mm dish in 2 ml of growth medium. The treatments were Control, LEP (10nM), $Me_2SO$ (1.5%) and LEP (10nM) + $Me_2SO$ (1.5%). The cells were subjected to electrophysiological study with the Patch clamp technique in Whole Cell Recording; cells with capacitance higher than 40 pF were used. The statistical analysis was by one-way ANOVA and the post hoc comparisons were by Tukey ($p<0.05$). The results show that the cells maintained in standard culture medium (DMEM + SFB10%) without treatment, do not show neuritic development; LEP, $Me_2SO$ and LEP + $Me_2SO$ stimulate cells to produce neurites and neural networks. An increase in inward (1.4 folds) and outward currents (1.3 folds) is observed in the analysis of total currents in LEP treated cells, LEP + $Me_2SO$, and in cells treated with $Me_2SO$ respect to the control value (~2 nA inward and ~1.5 nA outward currents). The inwards currents ($Ca^{2+}$, $Na^+$) increased ($p <0.05$) ~ 1.5 ± 0.5 folds in the three treatments; as well as the neuritic development with respect to the control. In conclusion, Leptin promotes differentiation and electrical activity.

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**Poster**

**729. Calcium Channels: Regulation and Modulation**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 729.03/C35

**Topic:** B.04. Ion Channels

**Support:** DGAPA-PAPIIT Grants IN218016, IA206317 and IV100116
CONACyT Grant 255635

**Title:** Neural voltage-independent regulation of voltage-gated calcium channels in pancreatic β-cells

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**Abstract:** The islets of Langerhans are innervated by sympathetic and parasympathetic terminals. Voltage-independent regulation of calcium channels is crucial for intracellular calcium concentration and insulin secretion. Voltage-gated calcium (CaV) channels are regulated by G proteins via voltage-dependent and independent mechanisms. Phosphatidylinositol-4,5-bisphosphate ($PIP_2$) is a membrane phosphoinositide feasibly regulating the activity of ion

channels and transporters. $PIP_2$ has been hypothesized to be responsible for voltage-independent regulation of CaV channels. However, whether CaV channels are regulated by $PIP_2$ in pancreatic β-cells, it is still scarcely understood. At present, $PIP_2$ depletion through activation of a muscarinic pathway induced by oxotremorine methiodide (Oxo-M) can be readily performed to assess voltage-independent regulation in pancreatic β-cells. Conversely, noradrenaline (NA), a voltage-dependent Gβγ activator, can be applied to detach voltage-dependent regulation by means of a prepulse paradigm. Therefore, the purpose of this study was to investigate the voltage-independent regulation of CaV channels, by cholinergic and adrenergic receptor activation in pancreatic β-cells of the rat. By using patch clamping and biochemical methods we recorded CaV currents and separated voltage-independent and voltage-dependent counterparts. CaV current amplitude was inhibited by activation of the muscarinic receptor 1 ($M_1R$) in the absence of kinetic changes. Oxo-M-induced inhibition exhibited the hallmarks of voltage-independent regulation and did not involve PKC activation. This inhibition was mimicked or occluded by diC8-$PIP_2$ dialysis supporting mediation of native $PIP_2$ into the plasma membrane. On the other hand, both NA exposure and cell dialysis with GTPγS, a nonspecific activator of G proteins, significantly inhibited CaV current in pancreatic β-cells. Interestingly, this inhibition persisted despite of a strong depolarizing prepulse. Taking together, CaV channels in rat pancreatic β-cells are regulated mostly by a voltage-insensitive mechanism. However, further experiments should be addressed to elucidate the nature of a double-controlled inhibition of CaV channels exerted by the autonomic nervous system on pancreatic β-cells.

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**Poster**

**729. Calcium Channels: Regulation and Modulation**

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**Program #/Poster #:** 729.04/C36

**Topic:** B.04. Ion Channels

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CONICET
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**Title:** Dopamine receptor type 1 modulates $Ca_V2.2$ current density

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**Abstract:** D1R interacts with $Ca_V2.2$ and modulates its trafficking to the plasma membrane. This effect has been shown to regulate $Ca_V2.2$ density at postsynaptic sites in the prefrontal cortex (Kisilevsky et al. 2008). Here we studied the cellular mechanisms involved in $Ca_V2.2$ regulation by D1R using a heterologous expression system. We manipulated the concentration of transfected $Ca_V2.2$ and YFP-tagged D1R cDNA in HEK293t cells and measured D1R expression levels by fluorescence signal. There was a linear correlation between the amount of D1R transfected and YFP signal level, as expected. We recorded whole-cell calcium currents in cells expressing $Ca_V2.2$, its auxiliary subunits and increasing concentrations of D1R. We found a positive correlation between $Ca_V2.2$ current density and D1R expression levels at low D1R/$Ca_V2.2$ cDNA molar ratios (D1R/$Ca_V2.2$ MR) ($Ca_V2.2$ alone= 79.31 ± 11.04 pA/pF, 0.1 D1R/$Ca_V2.2$ MR= 114.3 ± 9.42 pA/pF; P=0.023). Moreover, this effect was occluded by Cholero Toxin, a Gs protein inhibitor. To evaluate if this effect was due to an increase in functional channels at the plasma membrane, we measured total charge movement during ON gating current evoked by steps from -100 mV to the reversal potential. We found that the charge movement increased from 7.6 ± 1.2 fC/pF ($Ca_V2.2$ alone) to 12.6 ± 0.22 fC/pF (0.1 D1R/$Ca_V2.2$ MR). At D1R cDNA concentrations above 0.1 D1R/$Ca_V2.2$ MR, the $Ca_V2.2$ current density was reduced, reaching values below the control condition without D1R ($Ca_V2.2$ alone= 79.31 ± 11.04, 1 D1R/$Ca_V2.2$ MR= 43.35 ± 4.88 pA/pF; P=0.0008). This current reduction was insensitive to Cholero Toxin. We hypothesized that high D1R expression levels could promote the formation of D1R homodimers. We therefore assayed the effect of adding equimolar cDNA concentrations of other receptors that are able to form heterodimers with D1R (ghrelin receptor and D2R) and found that this maneuver occluded the calcium current increase. Finally, we compared the acute inhibitory effect of dopamine mediated activation of D1R on $Ca_V2.2$ currents. We found a shift in the EC50 (3.28 ± 0.32 µM at 0.1 D1R/$Ca_V2.2$ MR versus 0.79 ± 1.5 µM at 1 D1R/$Ca_V2.2$ MR) without changes in the maximum inhibitory effect (~50 % of inhibition). This result suggests that D1R expression level impacts its activation mode. In summary, we found a biphasic effect of D1R co-expression on $Ca_V2.2$ current: at low D1R expression levels, a stimulation of traffic that implicates Gs protein activity, and in contrast, at high D1R expression levels, a reduction in current and increased sensitivity to dopamine-mediated inhibition, possibly due to the formation of D1R dimers and involving a different signaling pathway.

**Disclosures: J. Raingo:** None. **C. Chou-Freed:** None. **V. Martinez Damonte:** None. **S. Rodriguez:** None. **C. McCarthy:** None.

**Poster**

**729. Calcium Channels: Regulation and Modulation**

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**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 729.05/C37

**Topic:** B.04. Ion Channels

**Support:** NIH grant NS055251 (DL)

**Title:** Cell-specific epigenetic modification of the CACNA1B gene in nociceptors controls calcium channel function in normal and neuropathic pain

**Authors: *E. J. LOPEZ SOTO**, D. LIPSCOMBE
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**Abstract:** Voltage-gated $Ca_V2.2$ calcium channels control transmission of noxious stimuli at nociceptor terminals in dorsal horn spinal cord. $Ca_V2.2$ channels are the targets of many drugs and neurotransmitters that activate G-protein coupled receptors to down regulate nociception. Nociceptors express a unique form of the $Ca_V2.2$ channel, through cell-specific pre-mRNA splicing, which influences the sensitivity of $Ca_V2.2$ channels to inhibition by mu-opioid receptors. Here, we elucidate the mechanism of cell-specific selection of *CACNA1B* exon 37a during alternative pre-mRNA splicing. The multi-zinc finger DNA binding protein CCCTC-binding factor (CTCF) is a master regulator of gene expression. A few reports, based on studies in non-neuronal cell lines, suggest that CTCF may also promote exon recognition of weak splice junctions. Based on publicly available ChIP-seq data, we identify that CTCF binds a region of *CACNA1B* close to exon 37a in several (although not all) human and mouse cell lines. By electrophoretic mobility shift assay, we confirm that recombinant CTCF binds a 60 bp region in exon 37a of Cacna1b, but not the neighboring homologous exon 37b. We have applied several methods, *in vitro* and *in vivo* using cell lines and neurons from mouse dorsal root ganglia (DRG), to show that CTCF promotes Cacna1b exon 37a inclusion in Trpv1-lineage neurons during pre-mRNA splicing. Using the DRG-derived F11 cell line as a model we show: 1) by ChIP-qPCR, that CTCF binds in exon 37a of Cacna1b *in vivo*, but not in exon 37b; 2) CTCF overexpression increases, and CTCF siRNA knockdown decreases exon 37a inclusion; 3) pharmacological inhibition of gDNA methylation (58.75 ± 6.644 % reduction as measured by 5-mC DNA ELISA) results in a 2.0 ± 0.1 fold-increase in exon 37a expression, an increase in CTCF binding to exon 37a, and a decrease in 5-mC in exon 37a; 4) siRNA knockdown of DNA methyltransferase DNMT3a, but not DNMT1 or DNMT3b, promotes exon 37a inclusion; 5) active DNA demethylating enzymes TET1 and TET2, but not TET3, when overexpressed, increase exon 37a inclusion. *In vivo*, we show that DRG Trpv1-lineage neurons, but not Trpv1-negative neurons, express exon 37a, have less 5-mC in locus 37a compared to DRG neurons that do not express Trpv1. Additionally, we find that in a peripheral nerve injury model, known to alter global methylation, exon 37a inclusion is reduced. Collectively, our results show that cell specific epigenetic factors change alternative splicing exon selection in Cacna1b gene, thereby regulating transmission of nociceptive information in the primary afferent pain pathway in normal and neuropathic pain.

**Disclosures: E.J. Lopez Soto:** None. **D. Lipscombe:** None.

**Poster**

**729. Calcium Channels: Regulation and Modulation**

**Location:** SDCC Halls B-H

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**Topic:** B.04. Ion Channels

**Support:** NIH R01NS-044163
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**Title:** $PIP_2$ depletion inhibits N-type $Ca^{2+}$ channels in acutely dissociated oxytocin neurons of rat supraoptic nucleus

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**Abstract:** Oxytocin (OT) and vasopressin (VP) neurons of supraoptic nucleus express high-voltage-activated L-, N-, P/Q-, and R-type $Ca^{2+}$ channels that prompt transmitter release, intracellular signaling, and plasticity. These channels also serve a critical role in triggering the $Ca^{2+}$-dependent afterhyperpolarization (AHP) activated during repetitive firing. Previous work from our lab has demonstrated that the second messenger phosphoinositol PtdIns(4,5)P2 ($PIP_2$) is required for AHP generation in OT, but not VP neurons. Depletion of $PIP_2$ results in AHP abolishment, lowered somatic $[Ca^{2+}]_i$, and decreased whole-cell $Ca^{2+}$ currents. Furthermore, we determined the AHP was reduced after blocking N-type channels, but not after blocking L, P/Q, or R channel types in OT neurons. To determine the mechanism by which $PIP_2$ modulates $Ca^{2+}$ channels, we studied isolated $Ca^{2+}$ currents in voltage clamp from acutely dissociated supraoptic neurons using Wistar-Kyoto rats containing the OXT-mRFP1 fusion transgene to label OT neurons (Yoichi Ueta, Kitakyushu, Japan). Wortmannin, a compound that obstructs $PIP_2$ production by targeting the rate-limiting enzyme PI4Kα, significantly inhibited whole cell $Ca^{2+}$ currents in OT but not VP neurons. This effect was abolished when cells were supplemented intracellularly with the $PIP_2$ analogue, di$C_8$-$PIP_2$. Wortmannin also caused a hyperpolarizing 4.6 mV shift in the voltage activation curve, but this shift did not account for the total inhibition of the current. Activation and deactivation time constants were unaffected. When isolating N-type $Ca^{2+}$ currents with 5 μM nifedipine (L-type), 0.5 μM agatoxin-IVA (P/Q-type), and 0.3 μM SNX-482 (R-type), wortmannin significantly inhibited the isolated N-type current, but had little effect when examining the reciprocal family of $Ca^{2+}$ currents available after only N-type channels were blocked using 1 μM conotoxin GVIA. The results suggest that $PIP_2$ selectively and constitutively modulates N-type channels in OT neurons, which are in turn coupled to $Ca^{2+}$-dependent AHPs.

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**Poster**

**729. Calcium Channels: Regulation and Modulation**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 729.07/D1

**Topic:** B.04. Ion Channels

**Support:** CIHR Grant to Ray Turner

**Title:** A tri-protein complex of Cav1.3, RyR2 and KCa3.1 channels contributes to the slow AHP in hippocampal pyramidal neurons

**Authors: *G. SAHU**[1], R. WAZEN[2], P. COLARUSSO[2], G. ZAMPONI[1], S. CHEN[3], R. TURNER[1]
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**Abstract:** Calcium entry mediated by L-type voltage gated calcium channels (Cav1 family) plays a vital role in controlling the firing pattern of hippocampal pyramidal neurons. We recently found that Cav1.3 functionally couples with the intermediate conductance calcium-activated potassium channel (KCa3.1) to contribute to a long lasting slow afterhyperpolarization (sAHP) that determines the pattern of spike discharge in pyramidal cells (Sahu et al., 2017, PMID 29038242). IsAHP in pyramidal neurons is preferentially activated by Cav1.3 calcium entry and accentuated by Cav1.3 facilitation. However, the full range of molecular mechanisms that support IsAHP generation over a 10 sec time span has not been determined. We employed Stochastic Optical Reconstruction super resolution microscopy (STORM) and patch clamp recordings to define the relationship between Cav1.3, KCa3.1 and ryanodine receptor 2 (RyR2) calcium release channels. STORM in total internal reflection fluorescence (TIRF) mode (30-40 nm precision) revealed a close apposition between Cav1.3 and KCa3.1 channels when expressed in tsA-201 cells or as native channels in cultured hippocampal pyramidal cells. Cav1.3 and KCa3.1 channels were observed throughout neuronal somata and dendrites in isolation or as distinct clusters in close apposition. Similarly, clustered patterns were reliably detected between Cav1.3 and RyR2 and between KCa3.1 and RyR2, suggesting a tri-protein complex. In a separate set of experiments IsAHP-like tail currents were recorded in tsA-201 cells expressing Cav1.3 and KCa3.1 following a 0 mV depolarizing step (100 msec). The IsAHP-like outward tail current was blocked after internal perfusion with 200 µM ryanodine and potentiated after perfusion with 10 mM caffeine, which decreases or increases RyR-mediated store calcium release, respectively. Removing extracellular calcium further blocked KCa3.1-mediated tail currents, indicating that Cav1.3 -mediated calcium entry is required for inducing RyR2-mediated calcium release that prolongs the IsAHP.
These data establish a close functional coupling among Cav1.3, KCa3.1 and RyR2 channels as a

tri-protein complex, where calcium entry through Cav1.3 channels results in a long lasting KCa3.1-mediated component of the sAHP by activating RyR2.
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**Poster**

**729. Calcium Channels: Regulation and Modulation**

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**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

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**Topic:** B.04. Ion Channels

**Support:** NINDS T32 NS086750
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**Title:** L-type calcium channels cooperate with NMDA receptors to signal to the nucleus

**Authors: *N. MANDELBERG**[1], B. LI[2], S. D. SUN[3], R. W. TSIEN[1]
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**Abstract:** Neurons and synapses are plastic, with the remarkable ability to change their physiology based on the inputs they receive. Excitation-transcription (E-T) coupling refers to the control of gene transcription by electrical activity across the cell membrane – the process by which a neuron translates external inputs into a language that the nucleus can understand. The transcription factor calcium- and cAMP response element binding protein (CREB) is a well-studied linchpin of E-T coupling in neurons, and its role in learning and memory has been firmly established across organisms. L-type voltage-gated calcium channels ($Ca_V1$) play a disproportionally large role in CREB-mediated E-T coupling because of their privileged relationship with downstream signaling molecules. While plasticity can exhibit remarkable synapse specificity, the role of E-T coupling in linking specific synapses, rather than whole-cell somatic events, to the nucleus remains poorly understood. Specifically, it is unknown where in the neuron $Ca_V1$-mediated E-T coupling is initiated, and how $Ca_V1$ channels cooperate with other mediators of E-T coupling.
Recent work from our lab has suggested that $Ca_V1$ channels signal not only through calcium flux, but also via a voltage-dependent conformational change (VDC) that synergizes with calcium signals. This synergy extends to both the calcium flux through the channel itself, but also through *N*-methyl-D-aspartate receptors (NMDARs), raising the possibility of local cooperation between $Ca_V1$ channels and other synaptic calcium sources. We show that quantal

events in the absence of whole-cell spikes can influence CREB, suggesting that localized, synaptic stimuli are capable reaching the nucleus. We have also begun to explore the spatial profile of $Ca_V1$ influence on nuclear events by restricting the activation of $Ca_V1$ to specific portions of the neuron during stimulation. To determine how $Ca_V1$ channels and NMDA receptors could synergistically contribute to neuronal E-T coupling, we pharmacologically isolated $Ca_V1$ VDC and ionic flux from NMDA receptors. We provide evidence that NMDA receptor stimulation works with $Ca_V1$ VDC to activate neuronal CREB, and that this synergy is exaggerated in a model of Timothy Syndrome, a genetic form of autism spectrum disorder. Furthermore, we used different calcium chelators to show that this functional relationship is based on a close spatial relationship. Together, these results suggest that $Ca_V1$ channels can exert control over neuronal transcription from the dendrite based on local signals that interact not only with downstream signaling partners, but also other channels at the dendritic spine.

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**Poster**

**729. Calcium Channels: Regulation and Modulation**

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**Program #/Poster #:** 729.09/D3

**Topic:** B.04. Ion Channels

**Support:** CIHR (RWT)
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AI-HS PDF (GS)
Cumming School of Medicine and Hotchkiss Brain Institute PDFs (XZ)
Harley Hotchkiss Studentship (CS)

**Title:** A dynamic T-type calcium-calmodulin interaction activates a signaling cascade for CaM kinases and CREB

**Authors: *H. ASMARA**, X. ZHAN, C. SZALAY, G. SAHU, P. K. STYS, G. ZAMPONI, R. W. TURNER, T2N 1N4
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**Abstract:** Calmodulin (CaM) is an important signalling molecule that regulates high voltage-activated calcium channels and second messenger cascades that activate CaM kinases and gene transcription. Calcium channels of the Cav3 family (T-type) mediate low threshold calcium influx, but were not believed to interact with CaM. We reported a constitutive association between CaM and the Cav3.1 channel at rest that is lost through an activity- and Cav3 calcium-dependent CaM dissociation, followed by activation of αCaMKII (Asmara, PMID 28800734). Recent work has revealed a Cav3.1 channel-dependent LTP of parallel fiber input to Purkinje

cells that we find can be triggered by optogenetic stimulation of ChR2 expressed in relation to promotor activity of parvalbumin or L7 in Purkinje cells in in vitro tissue slices. We used a theta-burst pattern of light pulses (470 nm) over 5 min (25 Hz for 200 ms at 1 Hz) to trigger a ChR2-mediated depolarization in Purkinje cells to selectively evoke Cav3 calcium influx in the presence of high voltage-activated calcium channel blockers. Slices were fixed to detect immunolabel for phosphorylation sites specific to either αCaMKII or CaMKIV from a condition of rest or 5 min after an LTP-inducing optogenetic burst pattern. We further examined phosphorylation of CREB using antibodies specific to phosphorylation at site serine 133 (αCaMKII-mediated) and serine 142 (αCaMKII or CaMKIV-mediated). We found under resting conditions that Purkinje cells in lobule IX / X exhibit a higher level of activated CaMKIV than αCaMKII, with membrane optogenetic stimulation increasing immunolabel intensity for αCaMKII but not CaMKIV. Optogenetic stimulation further triggered nuclear CREB activation, as signified by immunolabel for CREB Ser-133 and Ser-142. Phosphorylation of αCaMKII and CREB Ser-133 were blocked by the Cav3 channel blocker TTA-P2 (1 μM), but not CaMKIV and CREB Ser-142. Together these results indicate that Cav3 calcium influx is sufficient to trigger αCaMKII and phosphorylation of CREB Ser-133. Cav3-mediated calcium influx thus differentially regulates αCaMKII and CaMKIV levels during activation of a signaling cascade that triggers CREB in Purkinje cells following stimuli capable of activating long term plasticity of parallel fiber input.

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

**Poster**

**729. Calcium Channels: Regulation and Modulation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 729.10/D4

**Topic:** B.04. Ion Channels

**Support:** NIH Grant NS084190
NIH Grant DC009433
DoD grant MR130438

**Title:** CaBP1 regulates $Ca_v1$ L-type $Ca^{2+}$ channels and their coupling to neurite growth and gene transcription in mouse spiral ganglion neurons

**Authors: *A. LEE**[1], T. YANG[2], J.-E. CHOI[2], D. SOH[2], K. TOBIN[2], M.-L. JOINER[2], M. HANSEN[2]
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**Abstract:** CaBP1 is a $Ca^{2+}$ binding protein that is widely expressed in neurons in the brain, retina, and cochlea. In heterologous expression systems, CaBP1 interacts with and regulates voltage-gated $Ca_v$ $Ca^{2+}$ channels but whether this is the case in neurons is unknown. Here, we investigated the cellular functions of CaBP1 in cochlear spiral ganglion neurons (SGNs), which express high levels of CaBP1. Consistent with the role of CaBP1 as a suppressor of $Ca^{2+}$-dependent inactivation (CDI) of $Ca_v1$ (L-type) channels, $Ca_v1$ currents underwent greater CDI in SGNs from mice lacking CaBP1 (C-KO) than in wild-type (WT) SGNs. The coupling of $Ca_v1$ channels to downstream signaling pathways was also disrupted in C-KO SGNs. Activity-dependent repression of neurite growth was significantly blunted and unresponsive to Cav1 antagonists in C-KO SGNs in contrast to WT SGNs. Moreover, $Ca_v1$-mediated $Ca^{2+}$ signals and phosphorylation of cAMP-response element binding protein were reduced in C-KO SGNs compared to WT SGNs. Our findings establish a role for CaBP1 as an essential regulator of $Ca_v1$ channels in SGNs and their coupling to downstream pathways controlling activity-dependent transcription and neurite growth.

**Disclosures: A. Lee:** None. **T. Yang:** None. **J. Choi:** None. **D. Soh:** None. **K. Tobin:** None. **M. Joiner:** None. **M. Hansen:** None.

**Poster**

**729. Calcium Channels: Regulation and Modulation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 729.11/D5

**Topic:** B.04. Ion Channels

**Support:** NIH Grant EY026817
NIH Grant EY020542

**Title:** Cav1.4 calcium conductance is dispensable for presynaptic ribbon development in photoreceptors

**Authors: *S. A. BAKER**[1], V. KEROV[2], J. G. LAIRD[1], J. HARDIE[2], M.-L. JOINER[2], B. WILLIAMS[2], S. GARDNER[1], M. ZIMMERMAN[3], A. LEE[2]
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**Abstract:** Determining the roles of proteins present in the synaptic terminal of the retina is essential to further efforts to prevent and cure blindness. $Ca_v1.4$ is a photoreceptor specific, voltage-gated calcium channel clustered at the presynaptic active zone or 'ribbon'. $Ca^{2+}$ influx via $Ca_v1.4$ is essential for communication across the first visual synapse. $Ca_v1.4$ channels are also required for synaptic development, but the mechanism for this aspect of $Ca_v1.4$ function is unknown. We used *in vivo* electroporation to transiently express $Ca_v1.4$ in a subset of $Ca_v1.4$ KO

rods and demonstrated rescue of synaptogenesis using morphological markers, electrophysiological recordings of bipolar neurons, and a behavioral assay for vision. We designed a complimentary pair of $Ca_v1.4$ mutants lacking the ability to conduct $Ca^{2+}$, and found that either could rescue pre-synaptic development of $Ca_v1.4$ KO rods but post-synaptic development was incomplete. We propose that $Ca_v1.4$ serves two roles in synaptogenesis; as a scaffold to organize development of the pre-synaptic ribbon complex, and as a mediator of $Ca^{2+}$ signaling to complete the process. The scaffolding role of $Ca_v1.4$ may serve as a primer to ensure that structural framework is in place prior to the requirement for dynamic $Ca^{2+}$ signaling in response to changing lighting conditions.

**Disclosures: S.A. Baker:** None. **V. Kerov:** None. **J.G. Laird:** None. **J. Hardie:** None. **M. Joiner:** None. **B. Williams:** None. **S. Gardner:** None. **M. Zimmerman:** None. **A. Lee:** None.

**Poster**

**729. Calcium Channels: Regulation and Modulation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 729.12/D6

**Topic:** B.04. Ion Channels

**Support:** NIH Grant GM 58055

**Title:** Effect of isoflurane on axonal endoplasmic reticulum $Ca^{2+}$dynamics in hippocampal neurons

**Authors: *V. OSMAN**[1], H. C. HEMMINGS, Jr.[2]
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**Abstract:** General anesthetics are essential to modern medicine, but despite their widespread clinical use, their precise cellular and molecular mechanisms of action remain unclear. Anesthetics depress synaptic transmission with both pre- and post-synaptic effects including inhibition of activity-dependent $Ca^{2+}$ influx into the presynaptic nerve terminal. However, the principal presynaptic sites of action upstream of $Ca^{2+}$ entry are unknown. Axonal endoplasmic reticulum (ER) $Ca^{2+}$ controls presynaptic $Ca^{2+}$ through sequestration, and decreased ER $Ca^{2+}$ has been linked to a reduction in presynaptic $Ca^{2+}$ influx. ER $Ca^{2+}$ efflux and influx mechanisms are essential for $Ca^{2+}$ regulation and provide possible targets for anesthetic action. **Isoflurane, a common volatile anesthetic, inhibits presynaptic $Ca^{2+}$ entry and synaptic vesicle (SV) exocytosis, which we hypothesize involves effects on ER $Ca^{2+}$ dynamics**. Primary cultures of rat hippocampal neurons were used to test isoflurane-induced changes in ER $Ca^{2+}$ concentration using fluorescent biosensors and pharmacological modulators of ER $Ca^{2+}$ regulators. This project

will further our understanding of isoflurane's neuronal mechanisms of action. Ultimately, this understanding will aid in the development of more-selective anesthetics decreasing patient risk.

**Disclosures: V. Osman:** None. **H.C. Hemmings:** None.

**Poster**

**729. Calcium Channels: Regulation and Modulation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 729.13/D7

**Topic:** B.04. Ion Channels

**Support:** NIH Grant R15GM119099
NIH Grant R15DK102092

**Title:** Functional modulation of the Cav3.1 calcium channel by alternative splicing at the C-terminus

**Authors: *R. WANG**, Z. WANG, F. SHAKOLA, E. KALONTAR, M. HOSSAIN, Y. YU, M. RUGGIU
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**Abstract:** The CACNA1G gene encodes for Cav3.1, the alpha-1G subunit of a low-voltage-activated T-type calcium channel, which plays crucial roles in cardiac and smooth muscle cells and neurons by influencing the transmembrane potentials and regulating intracellular $Ca^{2+}$ signaling. Heterozygous missense mutations in the CACNA1G gene cause spinocerebellar ataxia-42 (SCA42), and mice that are null for this gene are unable to generate spike-and-wave discharges in thalamocortical relay neurons in response to GABA-B receptor activation, a hallmark of absence seizure. Different splice variants of Cav3.1 have been described, and alternative splicing of Cav3.1 channel transcripts can alter channel kinetics, localization, and cytosolic $Ca^{2+}$ trafficking, which create a complex and diverse system of electrical conduction and signal transduction. In this work, we analyze the function of two exons, termed E34 and E35, that are alternatively spliced *in vivo* in all possible combinations. These exons are found immediately after domain IV in the intracellular C-terminus, but their function is still largely unknown. To examine the physiological properties of these splice variants, we recorded channel activity with two-electrode voltage clamp on *Xenopus* oocytes injected with mRNAs corresponding to specific splice variants. Our data show that the Cav3.1 variants that include either or both E34 or E35 produce much larger channel currents than that of the variant skipping both exons, suggesting that the protein sequences encoded by E34 and E35 may facilitate the channel trafficking, or increase the channel open probability or signal channel conductance. We also analyzed the expression of these C-terminal splicing variants by RT-PCR in the mouse. The results show that E34 and E35 are preferentially included in nerve tissue postnatally, while they

are mostly skipped in embryonic tissues. By generating minigene constructs, we investigated the mechanism of E34 and E35 splicing regulation in a cell line, and tested whether specific splicing factors contribute to their inclusion and/or skipping. Taken together, our data indicate that the alternative splicing at exon 34 and 35 of Cav3.1 may regulate neuron excitability and modulate the intrinsic firing pattern by changing the $Ca^{2+}$ influx through the channel.

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**Poster**

**729. Calcium Channels: Regulation and Modulation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 729.14/D8

**Topic:** I.06. Computation, Modeling, and Simulation

**Support:** Next Generation Ultrasonic Transduction for Medicine and Imaging Project Strategic Importance (Hng Kong, Hong Kong SAR China)
Study the mechanism of ultrasound induced brain stimulation Post-doctoral Fellowship (Hong Kong, Hong Kong SAR China)

**Title:** Ultrasonic sensitivity of neurons targeted by gene encoded nano-scale gas vesicles

**Authors: *T. ZHU**, X. HOU, Z. QIU, J. GUO, L. SUN
The Hong Kong Polytechnic Univ., Hong Kong, Hong Kong

**Abstract:** Ultrasound brain stimulation shows great potential for probing brain function and treating brain disorders with unique advantages as both noninvasive and good spatiotemporal resolution. However, it lacks cellular selectivity which is critical for precisely targeting neurons for understanding brain functions and treating brain dysfunction. Nano-scale gas vesicles, with a gene encoded biogenic ultrasound responsive protein structure, can scatter sound waves and thereby produce ultrasound contrast which is considered as the GFP in ultrasound. We wondered that whether the oscillations of nano-scale gas vesicles can localize acoustic energy to induce targeted perturbations to the selected neurons. Here we report our findings on nano-scale gas vesicle enabled acoustic sensitivity both in vitro and ex vivo. In cellular level, the nano-scale gas vesicles were targeted to different domains of various membrane proteins such as Piezo1, TRPV1, CFTR etc, as well as simply mixing with the cells in the solution. Calcium imaging on primary culture neurons and CHO cells were utilized to characterize the performance of nano-scale gas vesicles to ultrasound stimulation. Our results show nano-scale gas vesicles can enhance the effects of what low-intensity ultrasound activates primary culture neurons, whereas the neurons would keep silent at the absence of nano-scale gas vesicles under the same ultrasound stimulation. In addition, cell targeting experiments showed different responses when

targeting to different domains of the same mechanosensitive ion channels. Finally, this effect was tested in brain slices targeted by RGD to integrin. Similar result was also observed in the ex vivo experiment, demonstrating a novel targeting strategy for ultrasound brain stimulation. Collectively, we demonstrated a novel targeting strategy for ultrasound stimulation with gene encoded nano-scale gas vesicles. It is a promising tool in targeting neurons on account of combining noninvasive, good spatiotemporal resolution of ultrasonic stimulation and enhancement effect plus good biocompatibility of nano-scale gas vesicles together.

**Disclosures: T. Zhu:** None. **X. Hou:** None. **Z. Qiu:** None. **J. Guo:** None. **L. Sun:** None.

**Poster**

**730. HCN Channels**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 730.01/D9

**Topic:** B.04. Ion Channels

**Support:** NIH Grant EY020542

**Title:** A role for 14-3-3 in the downregulation of HCN1 channels

**Authors: *C. K. LANKFORD**[1], J. HOUTMAN[2], S. BAKER[1]
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**Abstract:** Hyperpolarization activated HCN1 channels function to control neuronal excitability and timing and are abundantly expressed in the cortex, hippocampus, cerebellum, brainstem, and retina. HCN1 dysregulation in these systems can result in hyperexcitability as well as saturation of downstream neural circuits. HCN1 activity has been shown to be modulated by multiple factors with dopamine, neuropeptide Y, and nitric oxide signaling all resulting in reduced HCN1 activity. It has also been shown that phosphorylation by protein kinase C reduces HCN1 activity by downregulating the number of channels at the cell surface. The mechanism underlying this controlled HCN1 downregulation remains poorly understood. We recently identified an interaction between HCN1 and the 14-3-3 family of proteins, a highly conserved family of phosphopeptide binding proteins abundantly expressed in the brain. We hypothesize that 14-3-3 binding is involved in the phosphorylation dependent downregulation of HCN1. To test this hypothesis, we mapped the 14-3-3 binding site on HCN1 and determined that a site near the C-terminus serves as the principle site for 14-3-3 recruitment. Loss of this site significantly disrupts the 14-3-3/HCN1 interaction as assessed by co-immunoprecipitation and results in an increase in the steady-state levels of HCN1 in a heterologous expression system. Pulse-chase experiments using SNAP-tag labeled HCN1 revealed that loss of 14-3-3 binding extends the half-life of HCN1. These results suggest that 14-3-3 binding is involved in HCN1 turnover.

**Disclosures: C.K. Lankford:** None. **J. Houtman:** None. **S. Baker:** None.

**Poster**

**730. HCN Channels**

**Location:** SDCC Halls B-H

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**Topic:** B.04. Ion Channels

**Support:** National Institute of General Medical Sciences (GM084854
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National Institute on Minority Health and Health Disparities (8G12-MD007600)
NSF Partnershups in International Research an Education (PIRE) Program Neural Mechanism of Reward & Decision (OISE-1545803)

**Title:** $I_H$ current modulates bicuculline-induced increased in rebound excitation of vta da neuron

**Authors: *K. Y. BOSQUE CORDERO**[1], R. VÁZQUEZ-TORRES[2], C. A. JIMENEZ-RIVERA[3]
[1]Biol. Dept., Univ. of Puerto Rico Rio Piedras Campus, San Juan, Puerto Rico; [2]Physiol. Dept., Univ. of Puerto Rico, San Juan, PR; [3]Physiol., Univ. of Puerto Rico, Physiol. Dept., San Juan, PR

**Abstract:** The hyperpolarization-activated cation current ($I_h$) is a major determinant of neuronal intrinsic excitability in many cells including dopaminergic neurons of the Ventral Tegmental Area (VTA DA). In contrast to other cellular conductances, the $I_h$ current is activated by hyperpolarizing voltage steps to potentials negative to -55 mV. $I_h$ current modulates the electrophysiological properties of neurons in the Mesocorticolimbic (MCL) system. Neuroadaptations in this network are hypothesized to trigger drug addiction. Rebound excitation is the increase in firing rate following hyperpolarizing inputs. Changes in the intrinsic properties of the cell related to rebound excitation are still poorly understood. We used ZD7288 (ZD)(an $I_h$ blocker) in whole cell patch-clamp recordings to evaluate rebound excitation in VTA DA neurons. Rat brain slices were also incubated with bicuculline (BIC) (30 or 120 minutes) as a mechanism to enhance excitability and promote rebound excitation through GABAergic disinhibition. In addition the effect of ZD in the increase rebound excitation after BIC treatment was investigated. It was found that ZD administration reduced rebound excitation in naïve slices. After 30 minutes of BIC incubation there was a significant increase in the number of action potentials (AP) within the rebound excitation (No BIC, AP 1±0.22 vs. BIC 30 minutes, AP 18±11) and a 69% $I_h$ reduction (No BIC, -465pA vs. BIC 30 minutes, -144pA, ****p<0000.1) with a left shift in the activation curve. There was a reduction in rebound excitation after 2 hours BIC incubation but it was still enhanced compared to control (No BIC AP 1±0.22 vs. BIC 120 min AP 5±1.4). A 25% $I_h$ current reduction was found with no apparent change in the

activation curve after BIC treatment (No BIC, -465pA vs. BIC 120 minutes, -351pA, *p>0.01). ZD administration reduced the rebound excitation of 2-hour BIC treated slices to baseline level (No BIC AP 1±0.22 compared to BIC 120 minutes +ZD AP 1±0.4). Taken together, our data suggest that the $I_h$ current may play an important role in the modulation of rebound excitation and in drug-induced excitability in the MCL system.

**Disclosures: K.Y. Bosque Cordero:** None. **R. Vázquez-Torres:** None. **C.A. Jimenez-Rivera:** None.

**Poster**

**730. HCN Channels**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 730.03/D11

**Topic:** B.04. Ion Channels

**Support:** CNPq - 306087/2016-2 (Brazil)
CAPES - PROEX (Brazil)
FAPEMIG - APQ-02013-15 (Brazil)

**Title:** Activation of group-I mGluR receptors increases $I_h$ in mouse MNTB neurons

**Authors: *A. B. CORREA**, C. KUSHMERICK
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**Abstract:** Metabotropic glutamate receptors play physiological roles in the control of neuronal excitability, modulation of synaptic transmission and regulation of synaptic efficacy. These receptors can be classified into three groups according to their structure and signaling pathways. Group-I is composed of the isoforms $mGlu_1$ and $mGlu_5$ that couple through the G protein $G\alpha_q$. Activation of postsynaptic Group-I mGluR receptors generates an inward (depolarizing) current in mouse Medial Nucleus of the Trapezoid Body (MNTB) neurons through an unknown mechanism. Here, we investigated the contribution of HCN channels to the inward current activated by the Group-I mGluR agonist (S)-3,5-dihydroxyphenylglycine (DHPG, 10 μM) in mouse MNTB neurons from C57BL wildtype (WT) or $mGlu_5$ knockout (KO) animals. Brainstem slices containing the MNTB were obtained from juvenile mice (p20-30) and membrane currents were measured under whole-cell voltage clamp at 33-34 °C. HCN current ($I_h$) was measured as the difference between the steady-state and instantaneous currents evoked by voltage steps from -60 mV to different test potentials. To calculate conductance, we measured the reversal potential of $I_h$ as the intersection of the I-V relationship of tail currents obtained with or without prior depolarization to -120 mV. No significant differences were observed between WT and $mGlu_5$ KO MNTB neurons for $I_h$ current amplitudes or maximum conductance ($G_{max}$). Application of DHPG did not affect the midpoint or the steepness of the $I_h$ activation curve, but

significantly increased $G_{max}$ by 9.1%. The effect of DHPG to increase $I_h$ was not significantly different in WT vs. $mGlu_5$ KO animals. We conclude that $I_h$ contributes to the inward current evoked by DHPG in the MNTB neurons from WT and $mGlu_5$ KO mice.

**Disclosures: A.B. Correa:** None. **C. Kushmerick:** None.

**Poster**

**730. HCN Channels**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 730.04/D12

**Topic:** B.04. Ion Channels

**Support:** Marie Sklodowska-Curie Grant

**Title:** Exploring HCN channels in primary cortical neurons

**Authors: *Y. IACONE**[1,2], C. STAMPE JENSEN[1], T. BENNED-JENSEN[1], T. JESPERSEN[2], T. NYGAARD JØRGENSEN[1]
[1]H. Lundbeck A/S, Valby, Denmark; [2]Copenhagen Univ., Copenhagen, Denmark

**Abstract:** Imbalance in excitatory and inhibitory activity (E/I imbalance) has been linked to the pathophysiology underlying several neuropsychiatric disorders, such as epilepsy and schizophrenia. Genetic studies have linked hyperpolarization-activated cyclic nucleotide-gated (HCN) channels to both disorders. More recent studies have linked improper trafficking of the channels to the neuronal cell surface to depression, overall making it an attractive drug target. HCN channels are believed to have multiple functions on neuronal activity and are expressed in both excitatory and inhibitory neurons with different subcellular localization. However, the exact distribution between specific cell populations and how this distribution effects the overall E/I balance is still unclear. Using in situ hybridization in primary cortical cultures, we confirm that HCN1 is expressed in both GABAergic and glutamatergic neurons, although only in a subpopulation of each cell type. To further address this, in situ hybridization as well as immunocytochemistry combined with various cell specific markers is applied. Besides, we aim at studying the effect of HCN inhibition on neuronal activation looking at c-fos induction, both in individual cell types and at the overall network level.

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**Poster**

**730. HCN Channels**

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**Topic:** B.04. Ion Channels

**Support:** NIH Grant RO1NS083402
NIH Grant RO1NS097610

**Title:** Reduced seizure propensity and enhanced function of hyperpolarization-activated cyclic nucleotide channels (HCN) in mice deficient in striatal enriched protein phosphatase (STEP)

**Authors: *S. JANG**, H. CHUNG
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**Abstract:** STriatal Enriched Protein Phosphatase (STEP) is a brain specific tyrosine phosphatase that regulates Hebbian and homeostatic plasticity by negatively regulating NMDA- and AMPA-subtype glutamate receptors at excitatory synapses. Previously, our lab reported that prolonged manipulation of hippocampal network activity changes STEP61 expression and activity, resulting in modulating synaptic weight against altered network activity in a homeostatic manner. Despite a well-established role of STEP61 in regulating synaptic activity, it is unclear whether STEP regulates the function of other ion channels that contribute to intrinsic excitability of hippocampal neurons. Our findings show that (1) STEP knock-out (KO) mice display prolonged latency to convulsion, reduced cumulative seizure scores, and decreased death rate following I.P injection of Kainic acid (30 mg/kg), suggesting that STEP KO mice are resistant to Kainic acid-induced status epilepticus (SE). In electrophysiology experiment, (2) lack of STEP leads to elevated voltage sag (mV), rebound potential (mV), hyperpolarization-induced inward currents (pA) and tail currents (pA) in hippocampal neurons located at CA2 regions where STEP61 is highly enriched in wild-type (WT) mice. Consistently, (3) acute inhibition of endogenous STEP activity into cultured hippocampal neurons enhances Ih (pA) and voltage sag (mV). (4) Lastly, over-expression of STEP WT gene into CHO cells transfected with HCN2 gene leads to reduction of the total expression of HCN2 channels and Ih currents while STEP expression is not altered. Taken together, STEP is a negative modulator for the function of HCN channels, contributing to determining the severity of SE following i.p injection of KA.

**Disclosures: S. Jang:** None. **H. Chung:** None.

**Poster**

**730. HCN Channels**

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**Topic:** B.04. Ion Channels

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**Title:** A unique subcellular distribution of HCN channels accelerates action potential propagation in GABAergic interneuron axons

**Authors: *F. C. ROTH**, J. F. STORM, H. HU
Div. of Physiol., Univ. of Oslo, Inst. of Basic Med. Sci., Oslo, Norway

**Abstract:** Fast-spiking parvalbumin-expressing basket cells ($PV^+$-BCs) produce rapid feedforward and feedback inhibition in cortical neuronal networks and play a key role in a wide range of higher brain functions. These operations critically depend on a complex axonal signaling machinery that translates action potentials (APs) initiated in the proximal axon to a highly divergent GABAergic synaptic output with minimal temporal delay. In many types of axons, repetitive firing produces afterhyperpolarizations (AHPs) that slow down AP propagation. By contrast, our previous direct recordings from rat $PV^+$-BC axons revealed a stable AP propagation velocity during high-frequency repetitive firing, but the underlying mechanism remains unclear. We propose that hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in $PV^+$-BC axons reduce the AHP and are a critical determinant of axonal AP propagation velocity during sustained firing. To test this idea, we performed simultaneous soma-axon recordings in rat hippocampal $PV^+$-BCs with the confocal targeted patch-clamp method to measure the latency between somatic and axonal APs during long trains of APs at 20 Hz, which mimic the activity pattern of $PV^+$-BCs during locomotion in rodents. Under control conditions, the latency remained nearly constant during the AP train. Bath application of the HCN channel blocker ZD7288 increased the latency of all axonal APs in the train and unmasked a large slow AHP. Interestingly, the AP latency increased progressively during repetitive firing in the presence of ZD7288 (n = 8), suggesting that HCN channels are critical for maintaining high AP propagation velocity during repetitive firing in $PV^+$-BC axons. In close agreement, ZD72288 also prolonged temporal delays between presynaptic APs in $PV^+$-BCs and inhibitory postsynaptic currents in dentate gyrus granule cells (n = 7). Together, these results imply a high density of HCN channels in the interneuron axon. To directly test this idea, we mapped the HCN channel subcellular distribution in $PV^+$-BCs with outside-out patches. In stark contrast to pyramidal neurons, HCN channels in $PV^+$-BCs were confined to the axon (median density 11.0 pS $\mu m^{-2}$, 50 patches) and almost undetectable at the soma and dendrites (5 and 6 patches,

respectively). Simulations with simplified BC compartmental models suggest that this unique HCN channel distribution increases axonal AP propagation velocity by counterbalancing AHPs during repetitive firing.

**Disclosures: F.C. Roth:** None. **J.F. Storm:** None. **H. Hu:** None.

**Poster**

**730. HCN Channels**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 730.07/D15

**Topic:** B.04. Ion Channels

**Title:** Downregulation of HCN channels in mouse hippocampal neurons by virus delivered gene-interfering tools

**Authors: *M. DEUTSCH**[1], A. GÜNTHER[2], A. BAUMANN[1]
[1]Inst. of Complex Systems (ICS-4), Res. Ctr. Juelich, Juelich, Germany; [2]Brain Sci. Inst., RIKEN, Wako, Japan

**Abstract:** Pacemaker ion channels, also known as hyperpolarization- and cyclic nucleotide-gated (HCN) ion channels, are expressed in a wide range of neuronal tissue. On the cellular level they contribute to the regulation of the resting membrane potential, integration of synaptic input at the dendrites, regulation of presynaptic neurotransmitter release, as well as generation of rhythmic activity. Thus HCN-channel dysfunction or altered gene expression levels might lead to several pathologic conditions like epilepsy, neuropathic pain, Parkinson´s disease or an age-related decline in the working memory. To investigate consequences of HCN-channel dysfunctions in single neurons and neuronal networks, we interfered with HCN-channel expression.
Therefore, we specifically targeted the different channel isoforms using two independent gene-interfering techniques. First, we took advantage of a cell-autonomous RNA-interference process. It mediates the breakdown of target mRNA by the application of short-hairpin RNAs. As a second approach we used an enzymatically inactive Cas9 variant. This protein binds specifically to transcriptional start regions of *hcn* genes, thereby directly interfering with the gene transcription. Both techniques were delivered to hippocampal neurons by recombinant adenoassociated viruses. We monitored the specificity and efficacy of *hcn* gene knockdown by immunological, and quantitative PCR assays. By electrophysiological recordings of virus transduced neurons we validated changes of neuronal activity. The knowledge achieved by these experiments provides further insight in HCN-channel functions, in particular their contribution to the activity of neuronal networks.

**Disclosures: M. Deutsch:** None. **A. Günther:** None. **A. Baumann:** None.

**Poster**

**730. HCN Channels**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 730.08/D16

**Topic:** B.04. Ion Channels

**Support:** Brains and Behavior Seed Grant

**Title:** Chronic inflammation increases SUMOylation of the hyperpolarization activated cyclic nucleotide gated channel 2 (HCN2), which mediates the hyperpolarization activated current ($I_h$), is altered in rat dorsal root ganglion (DRG) neurons

**Authors: *L. A. FORSTER**[1], L. A. JANSEN[2], V. RYU[2], A. Z. MURPHY[1], D. J. BARO[2]
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**Abstract:** Previous studies showed that injection of Complete Freund's Adjuvant (CFA) into a rodent's paw elicited inflammatory pain behavior that lasted for 14 days. Chronic inflammatory pain was prevented by genetic ablation of HCN2 from primary sensory afferent neurons in the DRG. Immunohistochemistry (IHC) on sectioned lumbar 4-6 (L4-6) DRG from injected animals showed that HCN2 immunoreactivity (IR) in ipsilateral relative to contralateral DRG increased at post-injection (pi) days 1 and 7 but not 4. *In vivo* DRG recordings showed that $I_h$ and the number of cells expressing $I_h$ was increased at days 5-7. We interpreted these data to mean that multiple mechanisms acted over distinct time courses to produce a persistent HCN2 mediated increase in primary sensory afferent neuron $I_h$. We are testing the hypothesis that HCN2 SUMOylation is altered during chronic pain. Small Ubiquitin like Modifiers (SUMO) are peptides that are post-translationally added to lysine residues in target proteins to alter protein-protein interactions. Previously, we have shown HCN2 channels are SUMOylated in the mouse nervous system. Increased HCN2 SUMOylation is associated with increased HCN2 surface expression and $I_h$. SUMOylation likely regulates HCN2 interactions with auxiliary proteins that control channel surface expression and stability. Using proximity ligation assays (PLA), SUMOylated HCN2 channels were visualized as fluorescent puncta that varied in size from 1-45 pixels. Control experiments showed that the number of puncta/DRG neuron was significantly increased in positive (antibodies included) vs negative (antibodies omitted) sections (t-test $p=0.019$). In order to examine changes in HCN2 IR and SUMOylation in adult male rats, CFA was injected into one hindpaw and L4-6 DRG were obtained at 1d and 3d pi and sectioned at 20 µm. At 1d pi IR increased in all small (<30µm), medium (30-40 µm) and large (>40 µm) diameter neurons ipsilateral relative to contralateral levels (n=1 rat), and the number of small cells expressing HCN2 increased by 55%. We are currently examining HCN2 SUMOylation at 1d pi. At 3d pi, IR intensity was the same in ipsilateral and contralateral DRG, and the number of neurons expressing HCN2 was increased by 87% in small diameter neurons and was unchanged

in medium and large diameter neurons. SUMOylation was significantly increased in small but not medium or large diameter neurons from ipsilateral vs. contralateral DRG at 3d pi. Puncta size was not significantly different, however, the average number of puncta/cell increased by 78% (n=1 rat). In sum, our work suggests that HCN2 SUMOylation is increased in primary sensory afferent neurons during chronic inflammatory pain.

**Disclosures: L.A. Forster:** None. **L.A. Jansen:** None. **V. Ryu:** None. **A.Z. Murphy:** None. **D.J. Baro:** None.

**Poster**

**730. HCN Channels**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 730.09/D17

**Topic:** B.04. Ion Channels

**Support:** NINDS Grant RO1-NS059934

**Title:** TRIP8b phosphorylation is altered in epilepsy and affects HCN1 channel binding

**Authors: *K. FOOTE**[1], R. J. HEUERMANN[1], J. S. TRIMMER[3], G. T. SWANSON[2], D. M. CHETKOVICH[4]
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**Abstract:** Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are expressed within the distal dendrites of CA1 pyramidal neurons in the hippocampus, where they reduce dendritic integration and dampen neuronal excitability. Channel gating and trafficking is modulated by direct interactions with an auxiliary subunit, tetratricopeptide repeat-containing Rab8b-interacting protein (TRIP8b). Interactions between hippocampal TRIP8b and HCN1 are reduced in animal models of temporal lobe epilepsy (TLE), leading to a redistribution of HCN1 away from the distal dendrites of CA1 pyramidal neurons. The mechanistic basis for decreased association of TRIP8b and HCN1 in models of TLE is unknown. In this project, we test the hypothesis that the phosphorylation state of TRIP8 modulates the affinity of the auxiliary protein for HCN1 and that dephosphorylation contributes to TLE-associated redistribution of channels. We first carried out mass spectrometry analysis to identify relevant phosphorylation sites on TRIP8b. Our data confirmed the phosphorylation of previously published residues, as well as identified novel sites. We then generated rats with kainic acid-induced seizures and identified six phosphorylation sites on TRIP8b that are modulated after seizures. At least one of these residues is located in a region of TRIP8b that influences HCN channel function. In order to study the significance of individual phosphorylation sites, we performed cell-based assays such as co-immunoprecipitation and fluorescence polarization. Our results demonstrate that the

phosphorylation state of TRIP8b impacts the binding interaction between TRIP8b and HCN1 channels. We propose that reestablishing the phosphorylation state of TRIP8b in epilepsy will aid in restoring HCN channel properties in the epileptic hippocampus.

**Disclosures: K. Foote:** None. **R.J. Heuermann:** None. **J.S. Trimmer:** None. **G.T. Swanson:** None. **D.M. Chetkovich:** None.

**Poster**

**730. HCN Channels**

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**Program #/Poster #:** 730.10/D18

**Topic:** B.04. Ion Channels

**Support:** NRF-2017M3C7A1025602
NRF-2016M3A9 B6021209

**Title:** Locus coeruleus activation inhibits HCN currents via alpha 2 adrenergic receptor in mesencephalic trigeminal neurons

**Authors: *J. WON**[1], S. OH[2], Y. KANG[3]
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**Abstract:** Masticatory function is coordinated by trigeminal proprioceptive inputs relayed by the mesencephalic trigeminal nucleus (MTN) neurons, which are exceptional in that they are located in the central nervous system. MTN neurons are known to show rigorous hyperpolarization induced-inward current ($I_h$) through HCN channels to control resting membrane potential, membrane resonance, and firing patterns of MTN neurons. Despite these important roles, how HCN channels are intrinsically regulated has not been elucidated. As MTN neurons receive projections from the noradrenergic locus coeruleus (LC) neurons, we investigated whether noradrenergic inputs inhibit HCN current in MTN neurons by using patch clamp analysis combined with pharmacological approaches. When MTN neurons were exposed to a2AR agonist guanabenz (GBZ), $I_h$ was significantly reduced in a dose dependent manner. This inhibition was blocked by atipamezole, an a2AR antagonist. The reduction in $I_h$ was insensitive to barium, an inward rectifying potassium channel blocker, implying that the affected $I_h$ is mainly HCN current. The activation curve of GBZ sensitive current was similar to those of sensitive to ZD7288, indicating that the affected $I_h$ is indeed from HCN channel. GBZ also induced negative shifting of the activation curve of HCN currents ($I_{HCN}$). $I_{HCN}$ inhibition was reversed by a2A AR specific blocker BRL44408, and immunohistochemical analysis further confirmed the molecular expression of a2A AR expression in MTN neurons. As DiI-labeled MTN neurons were found to receive projections from TH-positive LC neurons by immunohistochemical analysis, we

activated either multiple or single LC neurons to see if $I_{HCN}$ are reduced in adjacent MTN neurons. Microstimulation and single LC neuron firing resulted in increase of intracellular calcium in LC neurons, which was accompanied by inhibition of $I_{HCN\ in}$ MTN neurons. The inhibition of $I_{HCN}$ was positively correlated to the firing frequency of LC neurons. Our results suggest that noradrenergic input induces $I_{HCN}$ inhibition in MTN neurons. These results indicate that LC activation due to exogenic factors may alter the excitability of MTN neurons, which can lead to altered proprioceptive transmission from the masticatory system and masticatory dysfunctions.

**Disclosures: J. Won:** None. **S. Oh:** None. **Y. Kang:** None.

**Poster**

**731. Network Interactions: Signal Propagation**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 731.01/D19

**Topic:** B.09. Network Interactions

**Support:** NIH Grant R01 NS052233

**Title:** Coding of information in live neuronal networks reconstructed from the hippocampus

**Authors: D. POLI**[1], Y. S. VAKILNA[1], T. B. DEMARSE[2], *B. C. WHEELER[3], G. J. BREWER[4]
[1]Biomed. Engin., Univ. of California Irvine, Irvine, CA; [2]Neurol., Univ. of North Carolina, Chapel Hill, NC; [3]Bioengineering, Univ. of California San Diego, LA Jolla, CA; [4]MIND Inst. and Biomed. Engin., UC Irvine, Irvine, CA

**Abstract:** Our goal is to determinate the nature of information coding and transmission between hippocampal regions (the circuit comprised of the dentate gyrus (DG), CA3, CA1, and entorhinal cortex) to bridge the gap in understanding between the synaptic (molecular) and macroscopic (EEG or fMRI) levels. We reconstruct the trisynaptic circuit in vitro, culturing neurons dissociated from the hippocampal subregions on a multichamber device over a micro-electrode array (MEA). Micro-tunnels connect the compartments allowing axonal growth but not somata migration. We found DG axons spontaneously form connections to and drive input-dependent repeatable motifs of activity in CA3 reminiscent of in vivo network topology (Bhattacharya et al., Front. Neural Circuits, 2016). We also observed that strong axonal inputs transmitted via micro-tunnels in the native feed-forward direction (e.g., from EC into DG) evoked more target activity than that induced by feed-back propagation during site specific electrical stimulation in individual chambers (Poli et al., EMBEC & NBC, 2017). Further, the sparse temporal-spatial pattern of the highest spike rates evoked by stimulation sites in DG region at 3-5 recording sites coupled to CA3 neuron specifically coded information identifying the stimulation sources

induced in the opposite chamber. (Poli et al., Front. Neural Circuits, 2017). Functions ascribed to the hippocampal sub-regions for encoding pattern separation of the EC axonal inputs transmitted into the dentate gyrus (DG) via micro-tunnels and pattern completion from DG into the CA3 region intrinsically emerged from the networks and were passed on to downstream subregions (Poli et al., Journal of Neural Engineering, 2018). The development of the multichamber system provides a new paradigm for directly measuring axonal communication and spiking within all sub-regions simultaneously with regional specificity. Feed-forward and feedback connectivity were inferred from the direction of spike times within tunnels over two electrodes. The proportions of feed-forward and feed-back varied by subregion as did the spike dynamics. Low frequency delta, theta and gamma oscillations emerged from the networks, surprisingly robust in the axons between subregions. Thus, each stage of the hippocampal trisynaptic loop provides detailed data for understanding hippocampal computation.

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**Poster**

**731. Network Interactions: Signal Propagation**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 731.02/D20

**Topic:** B.09. Network Interactions

**Support:** BMBF Grant "Funktion reziproker Synapsen"

**Title:** From local to global signaling in olfactory bulb granule cell dendrites

**Authors: *M. MÜLLER**[1], O. BOSCH[1], V. DARIA[2], V. EGGER[1]
[1]Univ. Regensburg, Regensburg, Germany; [2]The Australian Natl. Univ., Canberra, Australia

**Abstract:** The inhibitory axonless olfactory bulb granule cells (GCs) form reciprocal dendrodendritic synapses with mitral and tufted cells (MTCs), the main projection neurons of the olfactory bulb (OB), via large spines. These synapses mediate self inhibition of and lateral inhibition between MTCs and are substantially involved in odor signal processing. GC dendrites are highly excitable in multiple ways: Synaptic inputs to individual GC spines can generate $Na^+$ spikes that are localized to the spine head, and stronger activation results in globally propagating dendritic signals that encompass both low-threshold $Ca^{2+}$ spikes (LTS) and $Na^+$ spikes.
To optimally investigate the transition from local to global signaling, we implemented a holographic two-photon uncaging system which allows simultaneous photostimulation of multiple spines in 3D in acute brain slices. We first tested the function of the holographic system via photolysis of caged glutamate at spines along basal dendrites of cortical pyramidal cells (PC) in juvenile rat brain slices. Cells were recorded from and filled with calcium-sensitive

fluorescent dye (OGB-1) via somatic patch pipettes.
Next, we investigated the conditions for $Na^+$ spike generation. Although GC resting potentials are hyperpolarized compared to PCs by approx. -10 mV, their $Na^+$ spike threshold potential requires similar numbers of simultaneously activated spines (9 ± 2, n = 24 in 23 GCs vs 10 ± 1, n = 7 in 4 PCs). Within the subthreshold regime GCs can display both sub- and supralinear integration of inputs, depending on the relative distance between the stimulated spines and their proximity to the mitral cell layer. As to low-threshold $Ca^{2+}$ spikes, activation of a significantly lower number of spines already suffices to elicit dendritic $Ca^{2+}$ transients as detected by two-photon $Ca^{2+}$ imaging in dendritic sections remote from the stimulated spines (5 ± 2 spines, n = 24 in 23 GCs, $P < 0.001$ vs $Na^+$ spike). We show that these $Ca^{2+}$ signals are able to propagate far along the dendrite and thus might correspond to the previously observed LTS. Occasionally, the somatic membrane potential showed so-called spikelets that indicate dendritic $Na^+$ spikes (n = 4 GCs).
These findings highlight the broad computational power of GC dendrites and elucidate the precise conditions underlying the transition from local to global signaling.

**Disclosures: M. Müller:** None. **O. Bosch:** None. **V. Daria:** None. **V. Egger:** None.

**Poster**

**731. Network Interactions: Signal Propagation**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 731.03/D21

**Topic:** B.09. Network Interactions

**Support:** HHMI

**Title:** Inhibitory control of the prefrontal cortex by the claustrum

**Authors: *J. C. JACKSON**[1], M. M. KARNANI[2], B. V. ZEMELMAN[3], D. BURDAKOV[2], A. K. LEE[4]
[1]Ashburn, VA; [2]The Francis Crick Inst., London, United Kingdom; [3]Ctr. for Learning and Memory, Univ. of Texas, Austin, TX; [4]HHMI Janelia Res. Campus, Ashburn, VA

**Abstract:** The claustrum is a small subcortical nucleus that has extensive excitatory connections with many cortical areas. While the anatomical connectivity from the claustrum to the cortex has been studied intensively, the physiological effect and underlying circuit mechanisms of claustrocortical communication remain elusive. Here we show that the claustrum provides strong, widespread, and long-lasting feedforward inhibition of the prefrontal cortex (PFC) sufficient to silence ongoing neural activity. This claustrocortical feedforward inhibition was predominantly mediated by interneurons containing neuropeptide Y, and to a lesser extent those containing parvalbumin. Therefore, in contrast to other long-range excitatory inputs to the PFC,

the claustrocortical pathway is designed to provide overall inhibition of cortical activity. This unique circuit organization allows the claustrum to rapidly and powerfully suppress cortical networks and suggests a distinct role for the claustrum in regulating cognitive processes in prefrontal circuits.

**Disclosures: J.C. Jackson:** None. **M.M. Karnani:** None. **B.V. Zemelman:** None. **D. Burdakov:** None. **A.K. Lee:** None.

**Poster**

**731. Network Interactions: Signal Propagation**

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**Program #/Poster #:** 731.04/D22

**Topic:** B.09. Network Interactions

**Support:** Human Frontier Science Program (RGY0073/2015)
Korea Health Technology R&D Project through Korea Health Industry Development Institute (KHIDI) (HI17C0212)
Korea University Grant

**Title:** *In vivo* evidence of spatio-temporal spike pattern propagation in feedforward network of vibrissal primary somatosensory cortex

**Authors: *H. JANG**, J. KWAG
Dept. of Brain and Cognitive Engin., Korea Univ., Seoul, Korea, Republic of

**Abstract:** Spikes transduced from whisker movement in the vibrissal primary somatosensory cortex (vS1) *in vivo* have spatio-temporally complex spike patterns composed of neural codes such as rate code (firing rate) and temporal code (precise spike timing) to encode somatosensory information. For such information to be useful, *in vivo* complex spike pattern should be preserved in the downstream neurons across layers of canonical feedforward network (FFN, Layer (L)4->L2/3->L5->L6). To directly investigate whether whisker-evoked spatio-temporally complex spikes can propagate across the canonical FFN, single-unit activities were recorded from L1 to L6 of vS1 using a multi-electrode probe (NeuroNexus) during 3s whisker stimulation (12 Hz) in anesthetized mice. The propagation of *in vivo* spike pattern was quantified by analyzing the coherence and instantaneous similarity between spike patterns in L4, the main recipient of sensory inputs, and that in other downstream layers (L2/3, L5, and L6) of the canonical FFN. Through coherence analysis, we found that a subset of downstream units in L2/3, L5, and L6 preserved *in vivo* spike pattern of L4, indicating reliable propagation of whisker-evoked *in vivo* spike pattern. To further investigate whether rate and temporal structure of the spike pattern were propagated, we analyzed the instantaneous firing rate and instantaneous similarity and found that both rate and temporal structure of spikes were preserved in

downstream layers. Our results demonstrate for the first time that the whisker-evoked neural codes propagate across the canonical FFN of vS1, suggesting that such propagation of neural code might serve as a key mechanism for somatosensory information processing.

**Disclosures: H. Jang:** None. **J. Kwag:** None.

**Poster**

**731. Network Interactions: Signal Propagation**

**Location:** SDCC Halls B-H

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**Topic:** B.09. Network Interactions

**Support:** DFG(SFB 958)
BMBF (01GQ1001A)
BMBF SmartAge grant (01GQ0972)

**Title:** Involvement of hilar mossy cells in the functional coupling between CA3 and dentate gyrus during sharp wave-ripple activity

**Authors: *A. SWAMINATHAN**[1], I. WICHERT[2], D. SCHMITZ[1,2,3,4,5], N. MAIER[1]
[1]Neurosci. Res. Center, Charité Universitäts, Berlin, Germany; [2]Bernstein Ctr. for Computat. Neurosci., Berlin, Germany; [3]Berlin Inst. of Hlth., Berlin, Germany; [4]Ctr. for Neurodegenerative Dis. Berlin, Berlin, Germany; [5]Einstein Ctr. for Neurosciences, Berlin, Germany

**Abstract:** The dentate gyrus (DG) is considered as the hippocampal input gate for the information arriving from the entorhinal cortex. Embedded into the DG network are two excitatory cell types – granule cells, which project to the CA3, and hilar mossy cells (MCs), which receive input from both, granule cells and feedback projections from CA3 pyramidal cells (PCs). Postsynaptic targets of MC projections include granule cells and various interneurons in both the same and in the contralateral hemisphere of the brain. The role of MCs during rhythmic population activity, and in particular during sharp-wave/ripple complexes (SWRs), has remained largely unexplored. SWRs are prominent field events in the hippocampus during slow wave sleep and quiet wakefulness, and they are involved in memory consolidation and future planning. We used an *in vitro* approach to investigate MC activity and -activation during SWRs. With simultaneous CA3 field potential– and cell-attached recordings from MCs we find that a significant fraction of MCs (47%) is recruited into the active neuronal network during SWRs. Moreover, MCs receive pronounced, compound ripple-associated synaptic input where both excitatory and inhibitory components are phase-coherent with and delayed to the CA3 ripple. Finally, we demonstrate that a significant fraction (66%) of tested granule cells receive SWR-associated excitatory inputs that are delayed compared to MCs, indicating an indirect activation of granule cells by CA3 PCs via MCs. Together, our data suggest a role for MCs in the

distribution of SWR-associated synaptic activity from the CA3 area onto diverse targets in the ipsi- and contralateral DG network.

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**Poster**

**731. Network Interactions: Signal Propagation**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 731.06/D24

**Topic:** B.09. Network Interactions

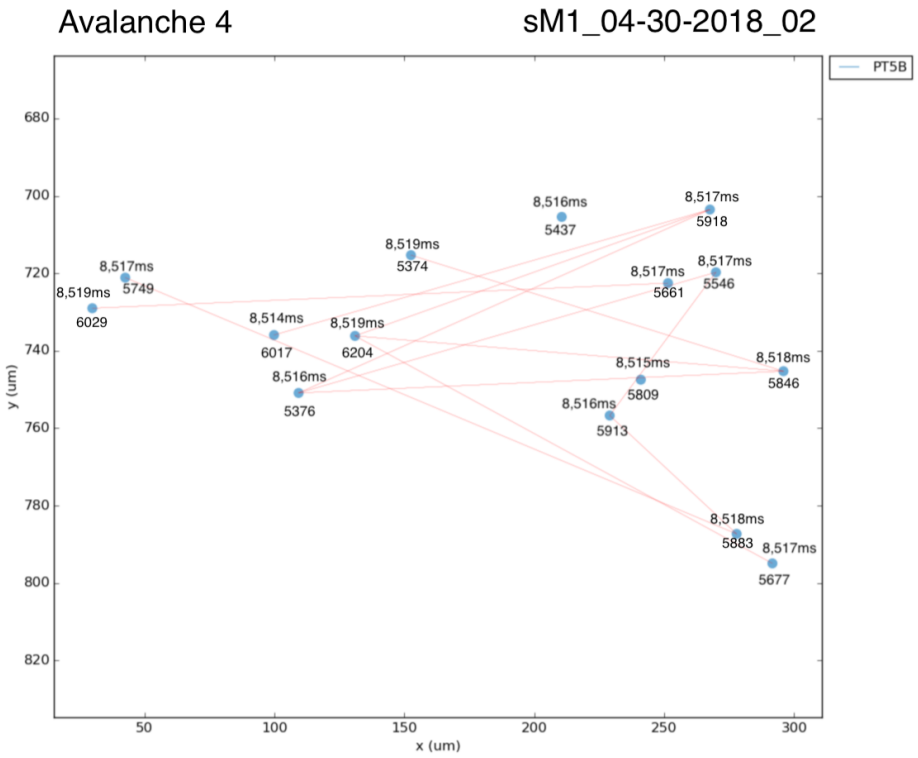
**Support:** NIH U01EB017695

**Title:** Identifying avalanches in simulated mouse primary motor cortex (M1)

**Authors: *D. W. DOHERTY**[1], S. DURA-BERNAL[2], S. A. NEYMOTIN[3], W. W. LYTTON[4]
[1]SUNY Downstate Med. Ctr., Pittsburgh, PA; [2]Physiol. and Pharmacol., State Univ. of New York Downstate Med. Ctr., Brooklyn, NY; [3]Dept. Neurosci., Brown Univ., Providence, RI; [4]SUNY Downstate, Brooklyn, NY

**Abstract:** Connectivity among the neurons participating in avalanches recorded in vitro and in vivo has been unknown. We set out to observe avalanches in a realistic simulation of a cortical column from the mouse primary motor cortex (M1) and to investigate mechanisms underlying the generation of avalanches. We applied sustained 0.23nA current to a 40um x 1350um x 40um volume of a 300um x 1350um x 40um simulated cortical column. About 2.2s after stimulus onset, self-sustained asynchronous irregular (AI) activity appeared. We binned spikes into 1ms bins during AI activity and found no gaps in spiking when all of neurons were included. We decided to look for avalanches in populations by cell type. Using the same stimulus protocol, Pyramidal Tract neurons in layer 5B (PT5B) were responsive only after the onset of AI activity across the simulated cortical column. PT5B activity in raster plots resembled avalanches so we binned PT5B responses into 1ms bins and computed avalanches as continuous activity every millisecond from one neuron to next until activity stoped for 1ms or more. The PT5B population power law value was -1.97 from 7.2s of AI activity. The total number of avalanches observed was 1,122 and the longest duration was 50ms.We applied 0.22nA for 5s to the simulated cortical column in the same manner as above to see if PT5B avalanches remained if the stimulus was turned off. AI activity appeared at 8s or 3s after the stimulus was turned off. PT5B responses were placed into 1ms bins from a 2s period resulting in 249 avalanches, 32ms longest duration avalanche, and power law value of -2.22. The same experiment with 180s runtime resulted in 172s of AI activity, 27,938 avalanches, 50ms longest duration avalanche, and power law value of -2.74. Avalanche number 4 shown in the accompanying diagram has a duration of 6ms (from 8,514ms to 8,519ms) and size of 15 unique neurons. The red lines in the diagram show direct

connections between the PT5B neurons. Our ability to record from every neuron in our simulated M1 enables us to investigate connectivity underlying avalanche activity in normal and diseased brain.




**Disclosures: D.W. Doherty:** None. **S. Dura-Bernal:** None. **S.A. Neymotin:** None. **W.W. Lytton:** None.

**Poster**

**731. Network Interactions: Signal Propagation**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 731.07/DP02/D25

**Topic:** B.09. Network Interactions

**Support:** NIH 1R24MH109060-01

**Title:** Peak activation of the CA2 subregion of the hippocampus precedes peak activation of CA3 following perforant-path stimulation

**Authors: *C. A. WILHITE**[1], R. S. WITTE[2], S. L. COWEN[3]
[1]Physiological Sci., [2]Med. Imaging, [3]Psychology, The Univ. of Arizona, Tucson, AZ

**Abstract:** Episodic memory formation requires accurate information processing by the entorhinal-hippocampal network. Recent studies using single recording electrodes in guinea pigs and in slice preparation have shown that the CA2 subregion of the hippocampus receives direct input from the entorhinal cortex (EC), indicating a distinct role of CA2 in the processing of signals within the entorhinal-hippocampal circuit. Here we used multiple penetrations of high-density silicon probes to analyze evoked potentials and current source density (CSD) in the hippocampus of an anesthetized rat. Penetrations were performed across the entire transverse axis of three cross-sections of the dorsal hippocampus, and local-field measurements were acquired in response to electrical stimulation of the medial entorhinal afferents (medial perforant-path). We found that the peak of the CSD response in CA2 preceded the peak response in distal CA3 (Student's *t* test, $p < 0.001$, $d > 1.0$, $n = 10$ trials) across all sections. Cross-correlation measures between regions revealed a > 1 ms lag between the peak source in CA2 and the peak source in distal CA3 across all sections. Furthermore, this lag in time of the peak CSD between CA2 and distal CA3 was larger at low (300 µA) compared to high (750 µA) stimulation intensities. Lastly, the amplitude of the peak CSD in CA2 was larger than the peak CSD in distal CA3 for low and high stimulation intensities ($p < 0.001$, $d > 1.0$) across all sections. Such fast and robust activation of CA2 upon stimulation of the entorhinal afferents *in vivo* supports the claim that information processing in CA2 may occur in parallel with the classical trisynaptic circuit (EC --> DG --> CA3 --> CA1). Further studies are needed to determine whether these CA2 activation patterns are behaviorally significant in the waking animal.

**Disclosures: C.A. Wilhite:** None. **R.S. Witte:** None. **S.L. Cowen:** None.

**Poster**

**731. Network Interactions: Signal Propagation**

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**Program #/Poster #:** 731.08/D26

**Topic:** B.09. Network Interactions

**Support:** NEI R01-EY024067
NEI 5R01EY024067-05
Simons Foundation SCGB 325548

**Title:** Visuomotor planning increases the magnitude of synaptically-mediated evoked potentials in macaque frontal cortex during optogenetic stimulation in parietal cortex

**Authors: *B. FERRENTINO**[1], R. A. SHEWCRAFT[1], B. PESARAN[2]
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**Abstract:** The frontoparietal pathway plays a role in flexible, cognitive behaviors such as attention, decision making, and movement planning. Coherent neuronal dynamics in frontal and parietal cortex vary with task demands. Furthermore, frontoparietal networks are both functionally and anatomically connected in primates. Additionally, we have shown evidence of effective connectivity in frontoparietal circuits from measurements taken in frontal cortex during optogenetic stimulation of posterior parietal cortex. However, whether behaviorally driven changes in frontal cortical dynamics result from changes in frontoparietal effective connectivity is unknown. Here we optogenetically stimulate PPC while simultaneously recording from frontal cortex in an awake macaque during both reach and saccade tasks and quiet sitting without controlled behavior and show that frontoparietal effective connectivity varies across conditions. We implanted one rhesus macaque with a semi-chronic, 96-channel array of movable electrodes placed over frontal cortex. We also added a chamber system over PPC, allowing for injection of AAV-hSyn-ChR2(h134R)-EYFP. We stimulated PPC with 500 ms long pulse trains of 10 ms wide pulses at a rate of 20 pulses/s with Poisson distribution. We performed stimulation during the delay period of a delayed reach and delayed saccade tasks and while the animal was sitting quietly without being engaged in an explicit task. To assess how frontoparietal effective connectivity changes with task engagement, we compared the stimulation-pulse-triggered, synaptically-mediated evoked potentials in frontal cortex across both conditions. We found that stimulation of the superior parietal lobule generated synaptically-mediated evoked potentials in frontal cortex on 34 of 96 total electrodes. The driven responses were located in motor cortex, consistent with known anatomical and functional connectivity of frontoparietal circuits. The amplitude of pulse-triggered evoked potentials in the frontal cortex significantly changed by -23.01 - 834.19% on 12 out of 34 electrodes with evoked potentials when synaptic input from PPC arrived during the delay period of the task compared to quiet rest ($p<0.05$; permutation test). This increase in evoked response magnitude across a large-scale circuit suggests that effective connectivity of the frontoparietal network is strengthened when the subject is engaged in preparing a visually guided movement.

**Disclosures: B. Ferrentino:** None. **R.A. Shewcraft:** None. **B. Pesaran:** None.

**Poster**

**731. Network Interactions: Signal Propagation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 731.09/D27

**Topic:** B.09. Network Interactions

**Support:** NIH Grant MH109091

**Title:** Voltage imaging in brain slices using genetically encoded voltage indicators

**Authors: M. M. MILOSEVIC**[1], E. J. MCKIMM[2], *S. D. ANTIC[3]
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**Abstract:** Genetically encoded voltage indicators (GEVIs) enable longitudinal monitoring of neuronal circuit dynamics of identified cell populations. GEVI's membrane delimited signals arise largely from the neuropil where dendritic and axonal membranes of many cells intermingle, hence optical signals from densely-labeled neuronal processes cannot be allocated to individual neurons. It was previously established that optical signals arising from population imaging with externaly applied voltage-sensitive dyes do not report neuronal action potentials, but rather they report compound synaptic potentials. Optical signals in GEVI-labelled animals are also dominated by synaptic potentials. Here, we take advantage of the synaptic-potential-bias in GEVI optical recordings to analyze the synaptic connectivity of subplate neurons of developing cerebral cortex. Subplate neurons are the oldest and most mature (pioneer) cortical cells residing in a transient subplate zone. The zone is transient because the entire zone with subplate neurons disappears after birth. During the in utero development, before cortical layers 4, 3 and 2 have been formed, the subplate neurons are thought to receive and nurture young thalamocortical projections. In neonatal (P02-P06) mice, we analyzed the spread of synaptically-evoked depolarization across the subplate zone using synaptic stimulations delivered in three characteristic locations: A) white matter; B) subplate zone and C) cortical plate (where migrating neurons assume their positions at this age). The multi-site experimental measurements are analyzed to determine the strength and spatial propagation of synaptic inputs projecting from cortical plate into the subplate zone and compare it against those projecting from the white matter into the subplate zone (putative thalamocortical). We discuss the use of GEVI brain slice imaging as an experimental tools for dissection of brain circuits. Support, MH109091.

**Disclosures: M.M. Milosevic:** None. **E.J. McKimm:** None. **S.D. Antic:** None.

**Poster**

**731. Network Interactions: Signal Propagation**

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**Program #/Poster #:** 731.10/DP03/D28

**Topic:** B.09. Network Interactions

**Support:** NINDS R3721135

**Title:** Spatiotemporal coupling of slow-wave and spindle activity during sleep

**Authors: *L. D. HARRIGER**[1], M. A. YASSA[2], B. A. MANDER[3], R. T. KNIGHT[5], J. J. LIN[4]
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**Abstract:** Slow waves (high power waveforms 0.5-2 Hz for at least one cycle) [SW] are a defining feature of EEG for NREM sleep, occurring more frequently with increasing sleep depth - none being observed during epochs of NREM1, while >20% of NREM3 epochs consist of SW activity. The SW is related to neuronal activity, whereby one phase of the oscillation is associated with neuronal quiescence, and the other an increase in neuronal activity, referred to as down- and up-states, respectively. Spindles (high power waveforms 10-16 Hz lasting several cycles) are another prominent feature of sleep during NREM2-3. Not only are both of these waveforms characteristic of sleep, but increases in the occurrence of SWs and/or spindles are associated with improvements in memory, and similarly the relative occurrence of these waveforms decreases with age and in subjects with various cognitive disorders. Furthermore, there is a strong temporal coupling between these two waveforms whereby spindles tend to occur during the up-state of SWs. Interestingly, the more synchronized spindles are to the up-states the better memory dependent task performance is, and likewise, this phase-locking becomes less synchronized with age. Studies have also revealed that each waveform exhibits a spatial structure, propagating as traveling waves with preferred directions. In this respect, the spindle has been shown to occur primarily as a rotational wave beginning in the temporal lobe and spiraling in a posterior-to-anterior fashion towards the frontal lobe. In contrast, while the topographical structural of the SW has been studied in less detail, it is often characterized as propagating in the reverse - anterior-to-posterior - direction. Given the importance of SW-spindle phase-locking it seems counter-intuitive that these waveforms should propagate along opposite trajectories, so to investigate how these waves might be decoupled in space, and yet still be synchronized in time, we present a method to compare the propagation of these waveforms. We hypothesize, that during instances of SW-spindle coupling, an extended portion of brain becomes transiently synchronized in a SW downstate propagating in an anterior-to-posterior manner; this SW is then focally disrupted at the distal wavefront by a spindle, while the down-state is prolonged in more anterior regions until the spindle reaches its location.

**Disclosures: L.D. Harriger:** None. **M.A. Yassa:** None. **B.A. Mander:** None. **R.T. Knight:** None. **J.J. Lin:** None.

**Poster**

**731. Network Interactions: Signal Propagation**

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**Topic:** B.09. Network Interactions

**Support:** CIHR MOP-142447

CIHR PJT-156054
NSERC 342292

**Title:** Input-specific synaptic location and function of the alpha5 GABAA receptor subunit in the mouse CA1 hippocampal neurons

**Authors: *S. AMALYAN**, E. MAGNIN, R. FRANCAVILLA, L. DAVID, L. TOPOLNIK
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**Abstract:** Hippocampus-dependent memory and learning processes are coordinated by GABAergic inhibition, which is provided by a heterogeneous population of interneurons via activation of specific sub-types of GABA receptors. The alpha5-$GABA_AR$ subunit (α5-$GABA_AR$) is highly expressed in the hippocampus of the mouse, monkey and human brain. It has been reported that, in the CA1 pyramidal cells, this subunit is predominantly located at extrasynaptic sites, where it is responsible for the generation of tonic inhibitory conductance. However, little is known about the synaptic expression of the α5-$GABA_AR$ and its location site-specific function. We examined the cell- and synapse-specific distribution of the α5-$GABA_AR$ in the CA1 stratum oriens/alveus (O/A) using a combination of immunohistochemistry, whole-cell patch-clamp recordings, and optogenetic stimulation in hippocampal slices. In addition, the input-specific role of the α5-$GABA_AR$ in spatial learning and anxiety-related behavior was studied using behavioral testing. Using optogenetic activation of distinct inhibitory inputs to O/A interneurons, we demonstrate that the vasoactive intestinal peptide (VIP+) and calretinin (CR+)-expressing inputs are sensitive to the α5-$GABA_AR$ inverse agonists (L-655,708 and MRK-016). These results were validated by immunohistochemical labeling, showing that the α5-$GABA_AR$ subunit was preferentially targeted to the inhibitory synapses made by the VIP+ and CR+ inputs onto somatostatin (SOM+)-expressing interneurons. In contrast, synapses made by the parvalbumin (PV+)-positive inhibitory inputs to O/A interneurons showed no or little α5-$GABA_AR$. Finally, chemogenetic silencing of VIP+ inputs showed that the α5-$GABA_AR$ expressed at this input is dispensable for spatial learning but may play a role in the anxiety-like behavior. In summary, our results show that the α5-$GABA_AR$ subunit exhibits a cell- and input-specific expression in the CA1 hippocampus, being mainly expressed in SOM+ interneurons and targeted to synapses formed by the VIP+ and CR+ inputs. Furthermore, phasic inhibition via VIP+ input to interneurons plays a predominant role in the regulation of the anxiety-like behavior, whereas the α5-$GABA_AR$ subunit tonic inhibition may control spatial learning.

**Disclosures: S. Amalyan:** None. **E. Magnin:** None. **R. Francavilla:** None. **L. David:** None. **L. Topolnik:** None.

**Poster**

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**Topic:** B.09. Network Interactions

**Support:** CIHR Grant PJT-156054
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NSERC Grant 342292

**Title:** Synaptic mechanisms underlying the network state-dependent recruitment of the interneuron-specific interneurons in the mouse CA1 hippocampus

**Authors: A. GUET MCCREIGHT**[1], X. LUO[2], R. FRANCAVILLA[2], V. VILLETTE[2], F. SKINNER[1], *L. TOPOLNIK[2]
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**Abstract:** In the hippocampus, a highly specialized population of interneuron-specific (IS) inhibitory cells coordinates the activity of local inhibitory circuits. While disinhibition is thought to play a critical role in hippocampal learning, the contribution of IS cells to network activity remains unclear. Here we reveal the synaptic properties of CA1 type 3 vasoactive intestinal peptide/calretinin-co-expressing IS cells (IS3) and demonstrate their recruitment during different network states in awake mice. Using patch-clamp recordings and two-photon glutamate uncaging, we found that IS3 cells fire spikes in response to repetitive or spatially clustered excitatory inputs. In particular, both the Schaffer collateral and the temporoammonic pathways could drive IS3 cell firing in vitro. Using synaptic models of these layer-specific inputs and a computational IS3 cell model with in vivo-like levels of synaptic activity, we predicted that IS3 cells could be driven to spike rhythmically during theta oscillations, as well as transiently during sharp-wave ripples. We also predicted inhibitory populations that could reduce or silence IS3 cell recruitment during these network states. Furthermore, two-photon calcium imaging in awake mice revealed a range of IS3 cell activities across the behavioral states. As a rule, somatic calcium transients (CaTs) increased with locomotion, often at specific running speeds, which persisted across recording sessions. In addition, significant CaTs were detected during immobility but not coupled to sharp-wave ripples. Thus, while synaptic properties of IS3 cells are predicted to generate a particular output, additional factors may modulate the cell recruitment during different behavioral and network states.

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**Poster**

**731. Network Interactions: Signal Propagation**

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**Topic:** B.09. Network Interactions

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**Title:** Hippocampal long-range VIP-GABAergic neurons projecting to subiculum comprise a heterogeneous population of cells that may coordinate contextual learning

**Authors: *R. FRANCAVILLA**, X. LUO, E. MUNOZ, O. CAMIRÉ, L. TOPOLNIK
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**Abstract:** The formation and recall of cognitive representations require fast coordinated communication among multiple cortical areas. Interestingly, anatomical data point to the existence of long-range GABAergic circuit elements that could account for cross-regional disinhibition between the hippocampus and functionally connected regions. Despite their potentially important role in coordinating rhythmic activity among relevant brain areas, very little is known about the cell types, their connectivity and their functional role in hippocampus-dependent memory. Here, using a combination of retrograde tracing, anatomical analysis, and optogenetics we have identified several distinct types of hippocampal GABAergic cell projecting to subiculum that express vasoactive intestinal peptide (VIP-LRPs). First, retrograde tracing using *cre*- and combinatorial *cre-/flp*-dependent strategies showed that VIP-LRPs represent a heterogeneous population with cells located in different CA1 hippocampal layers and expressing different markers such as *m2* muscarinic receptor, calretinin and enkephalin. Channelrhodopsin2-based mapping of VIP-LRP targets revealed that these cells are interneuron-selective in the CA1 region but target both pyramidal cells and interneurons in the subiculum. To further study their functional role in hippocampus-dependent memory, such as the novel object recognition task and the contextual fear conditioning, we applied the optogenetic antidromic activation of VIP-LRPs validated in vitro to in vivo experiments. Our data showed that activation of VIP-LRPs had no impact on the recognition memory but impaired the fear learning in the context-dependent manner. Together, these results identify the VIP-LRP neurons as a heterogeneous cellular population, which, through its region- and target-specific innervation, may control the information flow along the hippocampo-subicular axis and coordinate mnemonic processing associated with contextual learning.

**Disclosures: R. Francavilla:** None. **X. Luo:** None. **E. Munoz:** None. **O. Camiré:** None. **L. Topolnik:** None.

**Poster**

**732. Oscillations and Synchrony: Unit Studies**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 732.01/D32

**Topic:** B.09. Network Interactions

**Support:** CIHR
NSERC

**Title:** The coordinated activity of the cortical slow oscillation and the reuniens nucleus of the thalamus in anesthetized mice

**Authors: *D. BASHA**[1,2], S. CHAUVETTE[1], J. SEIGNEUR[1], I. TIMOFEEV[1,2]
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**Abstract:** **Background:** During sleep, the electrophysiological activity of the hippocampus and the medial prefrontal cortex (mPFC) becomes coordinated, which is likely a physiological basis for the transition of short-term memory into long term storage. The hippocampus sends direct but limited excitatory afferents to the mPFC although no direct feedback connections from the mPFC to hippocampus have yet been described and no reliable brain functions can be executed without feedback activity. The ***nucleus reuniens*** of the ventral midline thalamus receives mPFC afferents and projects to the hippocampus, suggesting that it may serve as a conduit for mPFC control of hippocampal activity during sleep. Therefore, we hypothesized that the cortical slow oscillation in mPFC could drive synaptic activity in reuniens neurons. **Methods:** Using sharp glass micropipettes and tungsten microelectrodes, we obtained intracellular recordings of identified reuniens neurons together with local field potential recordings of the mPFC and the hippocampus in mice anesthetized with ketamine-xylazine. **Results:** All recorded reuniens neurons revealed membrane potential depolarization with progressive buildup of synaptic activities during the active states of the mPFC slow oscillation. During these states, the recordings of most reuniens neurons displayed sharp rising depolarizing events, likely driver EPSPs occasionally accompanied with spikes. **Conclusions:** The results confirm our hypothesis that the cortical slow oscillation effectively drives neurons of the nucleus reuniens of the thalamus. The cortical drive to the reuniens is likely the main source of frontal cortical activity mediating feedback to the hippocampal formation during the slow oscillation.

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**Poster**

**732. Oscillations and Synchrony: Unit Studies**

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**Program #/Poster #:** 732.02/D33

**Topic:** B.09. Network Interactions

**Support:** This study was supported by Russian Science Foundation grant (contract number: 17-11-01273)

**Title:** Intrinsic and synaptic properties determine macroscopic phase response curves and coherence states of inter-communicating gamma oscillatory neural circuits

**Authors: *G. D. DUMONT, ESQ**[1], B. S. GUTKIN[2]
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**Abstract:** Macroscopic oscillations of different brain regions show multiple phase relations that are persistent across time. Such *phase locking* is believed to be implicated in a number of cognitive functions and is key to the so-called Communication Through Coherence (CTC) theory for neural information transfer. Multiple cellular level mechanisms influence the network dynamic and structure the macroscopic firing patterns.
Key question to identify the biophysical neuronal and synaptic properties that permit such motifs to arise and how the different coherence states determine the communication between the neural circuits.
We use a semi-analytic modeling approach to investigate the emergence of phase locking within two bidirectionally delayed-coupled spiking circuits with global gamma band oscillations. Internally the circuits consist of excitatory and inhibitory quadratic integrate and fire cells coupled synaptically in an all-to-all fashion. The circuits can show global the pyramidal-interneuron (PING) or interneuron gamma (ING) rhythms. Multiple circuits can also be intercoupled together with reciprocal synaptic connections with variable delays and targeting excitatory and/or inhibitory neurons.
Using mean-field approach together with an exact reduction method, we break down each spiking gamma network into a low dimensional nonlinear system. We then derive the macroscopic phase resetting-curves (mPRCs) that determine how the phase of the global oscillation responds to incoming perturbations. We find that depending on the gamma type (PING or ING) and perturbation target (excitatory of inhibitory neurons), the mPRC can be either class I (purely positive) or class II (by-phasic).
Hence we show analytically how incoming excitation can either promote spiking (advancing the phase) or retard the global oscillation.
We then study the emergence of macroscopic coherence states (phase locking) of two weakly

synaptically-coupled gamma-networks by deriving a phase equation for the coupled system. This phase equation links the synaptic mechanisms to the coherence state of the system; notably the determinant part played by the delay and coupling strength in the emergent variety of coherence modes. We show that the delay is a necessary condition for symmetry breaking, i.e. a non-symmetric phase shift between the macroscopic oscillations and that the effect is controlled by the synaptic weights of the pyramidal neurons. Using this analysis we find that a whole host of phase-locking relationships can exist, depending on the coupling strength and delay, potentially giving an explanation to the experimentally observed variety of gamma phase-locking modes.

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**732. Oscillations and Synchrony: Unit Studies**

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**Program #/Poster #:** 732.03/D34

**Topic:** B.09. Network Interactions

**Title:** Measured connectivity of bursting neuronal networks with and without inhibition

**Authors: *H. LEMKE**, A. NANTWI, T. NGUYEN
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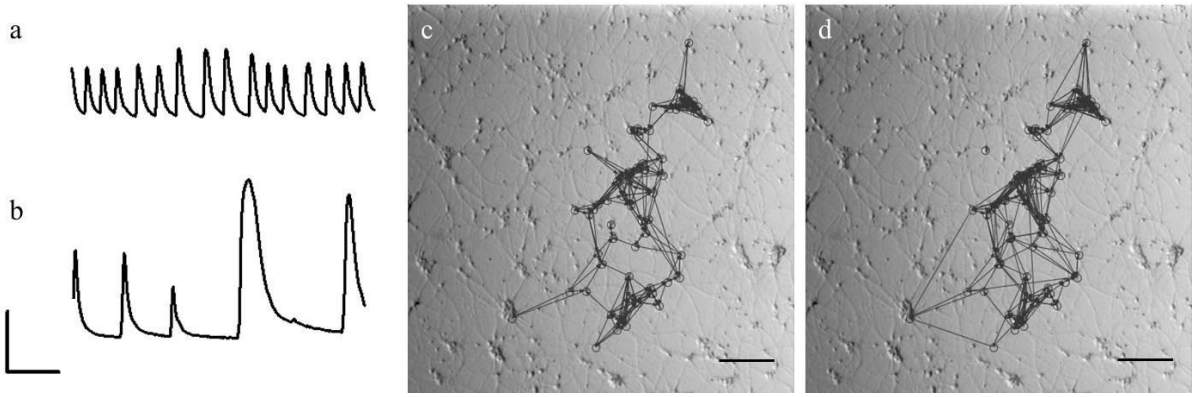
**Abstract:** Neuronal networks in dissociated cultures spontaneously generate synchronous activity known as network bursting, which is characterized by the firing of nearly all neurons every 30−100 seconds. There has been much research directed toward understanding the initiation of bursts, as well as the role of underlying network topology. Previously, we used a novel approach [1] that combines laser scanning photostimulation (LSPS) with calcium (Ca) imaging of a large cell-population to directly measure the functional connectivity of bursting neuronal networks. This approach permits rapid mapping of excitatory connections in networks consisting of 150-200 neurons and 1500-2000 connections. From these connectivity maps, various network properties are extracted.
In the present study, we used this approach to explore the role of inhibitory connections in network bursting. Bursting activity was recorded for 5 minutes before mapping the connectivity of 60 neurons. Next, bicuculline, a $GABA_A$ receptor antagonist, was added to the bath to block inhibitory connections. Activity was recorded for ten minutes, after which connectivity was mapped again. In accord with other reports, we observed that with the addition of bicuculline, fluorescence amplitudes increased while bursting rates decreased (see Fig. 1a and 1b). Analysis of connectivity maps (see Fig. 1c and 1d) revealed that both the number of excitatory connections and the average degree increased. Interestingly, the modularity coefficient and clustering coefficient stayed relatively the same, suggesting that community structure does not depend on network type.

[1] Nguyen T., O'Connor K., Sheth K., Bolle N.: Mapping functional connectivity of bursting neuronal networks. Applied Network Science 2(15), 1-15 Figure 1. Network bursting of a neuronal network composed of (a) both excitatory and inhibitory connections and (b) only excitatory connections (40 µM bicuculline added). Scale bars: delta F/F= 10%(vertical), 50 sec (horizontal). Corresponding connectivity maps (c) with and (d) without inhibition. Scale bar: 200 µm.

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**Poster**

**732. Oscillations and Synchrony: Unit Studies**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 732.04/D35

**Topic:** B.09. Network Interactions

**Title:** Spike-timing-dependent plasticity effect on the temporal patterns of neural synchronization

**Authors: J. ZIRKLE**[1], *L. L. RUBCHINSKY[2,1]
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**Abstract:** Synchronization of neural activity has been associated with several neural functions. Abnormalities of neural synchrony may underlie different neurological and neuropsychiatric diseases. Neural synchrony in the brain at rest is usually very variable and intermittent. Experimental studies of neural synchrony in different neural systems report a feature which appears to be universal: the intervals of desynchronized activity are predominantly very short (although they may be more or less numerous, which affects average synchrony). This kind of short desynchronization dynamics was conjectured to potentially facilitate efficient creation and break-up of functional synchronized neural assemblies.

Cellular, synaptic, and network mechanisms of the short desynchronizations dynamics are not fully understood. In this study we use computational neuroscience methods to investigate the effects of spike-timing-dependent plasticity (STDP) on the temporal patterns of synchronization. We employed a minimal network of two simple conductance-based model neurons mutually connected via excitatory STDP synapses. The dynamics of this model network was subjected to the time-series analysis methods used in prior experimental studies.
We found that STDP may alter synchronized dynamics in the network in several ways depending on the time-scale of action of plasticity. However, in general, the action of STDP tends to promote dynamics with short desynchronizations similar to those observed in experiments. Complex interplay of the cellular and synaptic dynamics may lead to the activity-dependent adjustment of synaptic strength in such a way as to facilitate short desynchronizations in the activity of synaptically coupled intermittently synchronized neurons.

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**Topic:** B.09. Network Interactions

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ministère enseignement supérieur et recherche (O. Dubanet)
INSERM (X.leinekugel)

**Title:** Probing the polarity of perisomatic GABAergic transmission in the adult mouse hippocampus *in vivo*

**Authors: *O. DUBANET**[1], A. BEYELER[2], K. LECORF[2], A. FRICK[2], H. HIRASE[3], X. LEINEKUGEL[2]
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**Abstract:** Pathological alterations in the balance between excitation and inhibition have been suspected for a long time to be responsible for aberrant neuronal processing in adult cortical circuits. Accordingly recent publications have proposed the implication of defective inhibition in the etiology of various pathologies including epilepsy, depression, schizophrenia and autism. In vitro experiments have suggested that defective function of the K-Cl co-transporter KCC2 was responsible for a reversed polarity of GABAergic synaptic transmission from inhibitory to excitatory, participating in epileptogenesis in animal models as well as in human epileptic tissue. However, this hypothesis is not clearly demonstrated in vivo. Treatment with the diuretic

bumetanide, which also reduces the accumulation of $Cl^-$ ions in neurons through the inhibition of NKCC1, was found to reduce seizures in epileptic animal models. But first, the relevance of in vitro assessment of the polarity (i.e. excitatory vs inhibitory) of GABAergic transmission for the in vivo condition has been put into question. And second, bumetanide has a limited bio-availability in the brain due to poor blood brain barrier penetration, and it is therefore unclear if its action was indeed due to a restoration of neuronal $Cl^-$ gradient. In order to test the hypothesis of excitatory GABAergic transmission in epilepsy with a direct approach in vivo, we use multi-site silicon probe recordings and investigate the mono-synaptic interactions between pyramidal cells and interneurons in the hippocampus of adult mice in vivo, after induction of seizures by injection of the convulsant kainic acid (KA). Our preliminary results suggest that the perisomatic GABAergic inhibition of pyramidal cells is indeed deficient in a subset of neurons and KA-treated mice. Therefore, excitatory effects of GABA might not be a general phenomenon in epilepsy, but rather affect the synaptic transmission between specific neuronal populations in cortical circuits, which may have serious implications for the identification of therapeutical targets against epilepsy.

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NIH Grant R01-MH-099645
US Office of Naval Research Grant N00014-13-1-0672

**Title:** Human sleep spindles are associated with a phase-dependent upregulation of unit activity that is consistent with spike-timing dependent plasticity

**Authors: *C. DICKEY**[1], A. SARGSYAN[2], J. MADSEN[4], E. N. ESKANDAR[5], S. S. CASH[6], E. HALGREN[3]
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**Abstract:** Sleep spindles are waxing and waning 10-16 Hz neural oscillations that last for 0.5-2 s during non-REM sleep. These network events are associated with memory consolidation but little information is available regarding how they may coordinate unit activity to facilitate

plasticity. We investigated whether sleep spindles modulate unit activity with timing that may facilitate spike-timing dependent plasticity, a mechanism that leads to long-term potentiation when the pre-synaptic spike occurs 25 ms before the post-synaptic spike. We analyzed local field potentials and unit activity in human intracranial microelectrode recordings. Spikes were sorted into units, which were then classified as putative excitatory, inhibitory, or multi-units based on waveforms, autocorrelation, and burstiness. We found that during sleep spindles there is a phase-dependent upregulation of unit spiking that varies across cell types. Furthermore, we discovered that during sleep spindles a given unit pair is more likely to fire within the 25 ms window that facilitates spike-timing dependent plasticity, and that this effect is not explained simply by the increased firing rate. Together, these results may suggest that sleep spindles modulate unit activity in an organized manner to facilitate spike-timing dependent plasticity, a critical neuronal mechanism underlying memory consolidation.

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**Poster**

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Tampere University of Technology Graduate School
Finnish Brain Foundation sr

**Title:** Computational analysis of cortical networks: The role of network structure, cellular and synaptic mechanisms in initiation, maintenance and suppression of network activity

**Authors: *J. ACIMOVIC**[1], H. TEPPOLA[1], T. MÄKI-MARTTUNEN[2], M.-L. LINNE[1]
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**Abstract:** We summarize our theoretical and computational work that addresses mechanisms responsible for initiation, maintenance and suppressing of spontaneous population activity in cortical networks. The models are primarily motivated by in vitro studies, however the examined mechanisms have more general implications. Three aspects of this work are emphasized: 1) a framework connecting properties of neuronal morphology with graph theoretic concepts of connectivity, 2) a study examining effects of structured connectivity to spontaneous activity in neuronal population, 3) the most recent work integrating these previous results with more detailed models and experimental data. Part 1) describes our work on structural organization of

connectivity, deriving the relation between morphometric properties of individual neurons and the graph theoretic description of network structure both in approximative models with mean-field-type characterization of neuron morphology (Aćimović et. al, 2015) and models with statistically accurate neuronal morphology (Aćimović et. al, 2011). Starting from a homogeneous population, we show how neurite morphology alone constrains the connectivity. More recent analysis also considers non-homogeneities that lead to structures like hub networks and networks containing clusters of strongly coupled neurons. Part 2) incorporates these models of connectivity into spiking neuronal networks to examine the effect of structured connectivity on network activity. The activity consists of spontaneous network bursts (e.g. like those recorded in dissociated in vitro cultures), the periods of intensive synchronized activity spreading across neuronal population, separated by low-activity intervals. Network bursts are quantified by their frequency and internal structure. Our previous work (see Mäki-Marttunen et. al; 2013) examines how connectivity and neuronal model complexity affect internal burst structure. Our recent unpublished work includes the properties of connectivity that support bursting initiation. Part 3), our most recent study, combines these previous results with more precise description of neuronal dynamics and suitable model fitting protocols to quantitatively reproduce statistics of experimental data. The role of cellular model complexity, short-term presynaptic activity, the contribution of most common glutamatergic and GABAergic synaptic receptors, as well as the details of network connectivity are included in the model. The obtained results are discussed and compared to the relevant models from the literature summarized in our recent publication (Manninen et. al, 2018).

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**Poster**

**732. Oscillations and Synchrony: Unit Studies**

**Location:** SDCC Halls B-H

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**Topic:** B.09. Network Interactions

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**Title:** Gamma oscillation gate basal forebrain cholinergic modulation of mPFC neuron ensemble

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**Abstract:** The acetylcholine system plays important behavior function including learning & memory and attention. Basal forebrain cholinergic neurons are the major source of cortical acetylcholine; its projection is widely projected and form different types of synapse with the cortical neurons. We combined with in vivo optogenetics and multi-channel electrophysiological techniques, selective specific regulation of basal forebrain cholinergic neuron activity in transgenic CHAT-Cre mice, while using multi-electrophysiological techniques to record medial prefrontal cortex neurons activities and field potential oscillations. We first Identified three different types of the cholinergic modulated cortex neurons types: excited pyramid neurons, inhibited interneurons and excited interneurons based on the cortical neurons response when the light stimuli of the BF cholinergic neurons. The cortical neurons responses modulated by the acetylcholine release were also state dependent only present during wake state not in sleep stage. Further analysis demonstrated that the excited interneurons response only occurs during high 30-100Hz Gamma oscillations. Our data provide the general neuronal mechanism that how the cortical neuron ensembles modulated by the acetylcholine release during different states in free moving animals. Suggestion that the gamma oscillation is the gate of the interneuron activation of the acetylcholine release in mPFC.

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**Poster**

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**Topic:** B.09. Network Interactions

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European Research Council (Grant No. StG 715043)

**Title:** Medial septal pacemaker neurons synchronize in phase not in frequency during hippocampal theta generation

**Authors: *B. KOCSIS**[1], R. FIÁTH[2], A. DOMONKOS[1], P. BARTHO[3], T. FREUND[1], S. KÁLI[1], I. ULBERT[2], V. VARGA[4], B. HANGYA[1]
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**Abstract:** The hippocampal theta oscillation typically occurs during exploratory behaviours and REM sleep and has been linked to learning and memory. The medial septal region of the basal forebrain has been identified as responsible for theta generation. According to the leading theory, rhythmically active individual 'pacemaker' cells, firing at their own frequencies, are synchronized to a common frequency and thus give rise to the hippocampal theta. However, experiments in which multiple septal neurons were recorded concurrently are rare and therefore the mechanisms of septal theta synchronization are still debated.
To address this, we aimed to decipher the network mechanisms of rhythm genesis in the medial septal circuit by analysing multiple simultaneously recorded medial septal neurons from an anesthetized rodent model of hippocampal theta oscillation including both rats and mice. Anaesthetized mouse recordings were performed with state-of-the-art high density silicon probes. Additional recordings were performed in awake drug-free mice. We analysed the emergence of theta-synchrony evoked by sensory stimulation (anesthetized) or forming spontaneously (awake) within the medial septal network. A group of medial septal neurons showed theta rhythmic firing irrespective of the dominant hippocampal oscillation and exhibited increased phase synchrony during theta (putative 'pacemaker' neurons), sustaining their original frequency. This contradicts to the aforementioned theory of frequency-synchronization of septal units as a key mechanism underlying theta generation. As an alternative, increased timing precision of action potentials within the theta cycle may be responsible for the observed stronger synchrony. A second group of neurons fired synchronously at lower delta frequencies while a third group of cells followed the dominant hippocampal oscillation.
To better understand the roles of the different rhythmicity groups described above, we also built a minimal network model. The building blocks were neurons that exhibited rhythmic activity in either delta or theta frequency range and showed a characteristic H-current known to be expressed by septal pacemaker neurons. We showed that a minimal network model of inhibitory pacemaker neurons and excitatory 'follower' neurons can capture multiple features of the septal theta generating network.

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**Poster**

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**Support:** NIH R01 EB016407
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**Title:** Neuronal population activity underlying difference of spontaneous wakefulness and anesthesia network dynamics in layer 2/3 somatosensory cortex

**Authors: *B. RAHSEPAR**, J. NOUEIHED, F. R. FERNANDEZ, J. A. WHITE
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**Abstract:** Although the behavioral effects of anesthetics are obvious, the neuronal network mechanisms underlying this difference remain elusive. To understand how network activity is changed under anesthesia compared to spontaneous awake state, we imaged calcium dynamics of different neuronal populations in layer 2/3 of mouse somatosensory cortex in both states. Our preliminary data shows that firing rate of excitatory cells are significantly lower under Ketamine-Xylazine anesthesia whereas the maximum cross-correlations between the neurons are significantly higher. From an information theory perspective, the decorrelation observed during wakefulness may maximize the information that the population of the neurons could encode neuronal activity during waking and sensory processing periods. Our goal is to track calcium activity using two-photon microscopy in excitatory and inhibitory neurons simultaneously during wakefulness and under anesthesia. The calcium activity will be used to investigate how changes in the firing properties of these two population contributes to enhanced cross-correlation between neurons under anesthesia. By tracking both the output in both cells types, our hope is to elucidate the mechanisms decorrelating neuronal spike activity during wakefulness.

**Disclosures: B. Rahsepar:** A. Employment/Salary (full or part-time):; Boston University. **J. Noueihed:** A. Employment/Salary (full or part-time):; Boston University. **F.R. Fernandez:** A. Employment/Salary (full or part-time):; Boston University. **J.A. White:** A. Employment/Salary (full or part-time):; Boston University.

**Poster**

**732. Oscillations and Synchrony: Unit Studies**

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**Topic:** B.09. Network Interactions

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**Title:** Structured thalamocortical dynamics in monkeys during loss and recovery of consciousness

**Authors: *J. YANAR**, J. A. DONOGHUE, M. LUNDQVIST, M. MAHKNE, E. N. BROWN, E. K. MILLER
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**Abstract:** While the mechanism of general anesthetics have been detailed at the molecular level, a systems-level description is largely lacking. It remains unknown if top-down or bottom-up processing is affected differently in anesthesia, or even if subcortical structures may play an initiating role in the transition across conscious states. We utilized a non-human primate model of general anesthesia to investigate how various cortical and subcortical networks mediate the transition into and out of anesthesia-induced unconsciousness. We simultaneously recorded local field potential (LFP) and spiking activity from chronic multielectrode arrays in prefrontal (PFC), posterior parietal, and auditory cortex, as well as from probes in the thalamus of two monkeys during intravenous administration of the GABAergic anesthetic propofol. In line with previous work, loss of consciousness (LOC) was followed by global decreases in spike rates and widespread cortical slow (0.1 - 1.2 Hz) oscillations—a hallmark of GABA-modulating anesthetics. However, not all brain regions were affected contemporaneously. PFC was the most sensitive to drug onset with beta power increasing across multiple PFC regions soon after propofol administration. This beta oscillation was tightly coherent between PFC and thalamus. This coupling was specific to particular thalamic subnuclei. On the other hand, slow oscillations appeared first and most prominently in parietal cortices. They moved anteriorly to frontal cortex during induction into LOC. Remarkably, different cortical areas simultaneously exhibited differentiated depths of anesthesia. Burst suppression, a marker of deep anesthesia, was present in parietal and temporal cortices while frontal cortex was in a lighter stage characterized by cross-frequency coupling of slow oscillations with high frequency activity. During regaining of consciousness (ROC), cortical areas exhibited a different sequence in returning to the conscious state. Whereas PFC was the first region to be affected during induction, it was the last area to return to pre-induction state, in terms of LFP power and spiking responses to auditory and somatosensory stimuli. Overall, these data suggest that general anesthetics such as propofol impact the brain in a highly structured manner and disrupt higher cognitive areas quite differently from sensory areas.

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**Poster**

**733. Oscillations and Synchrony: LFP Studies I**

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**Topic:** B.09. Network Interactions

**Support:** Georgetown University 2018 Dean’s Toulmin Pilot Award

**Title:** Disproportional local field potential and GCaAMP-6 signals of hippocampal neuronal population activities

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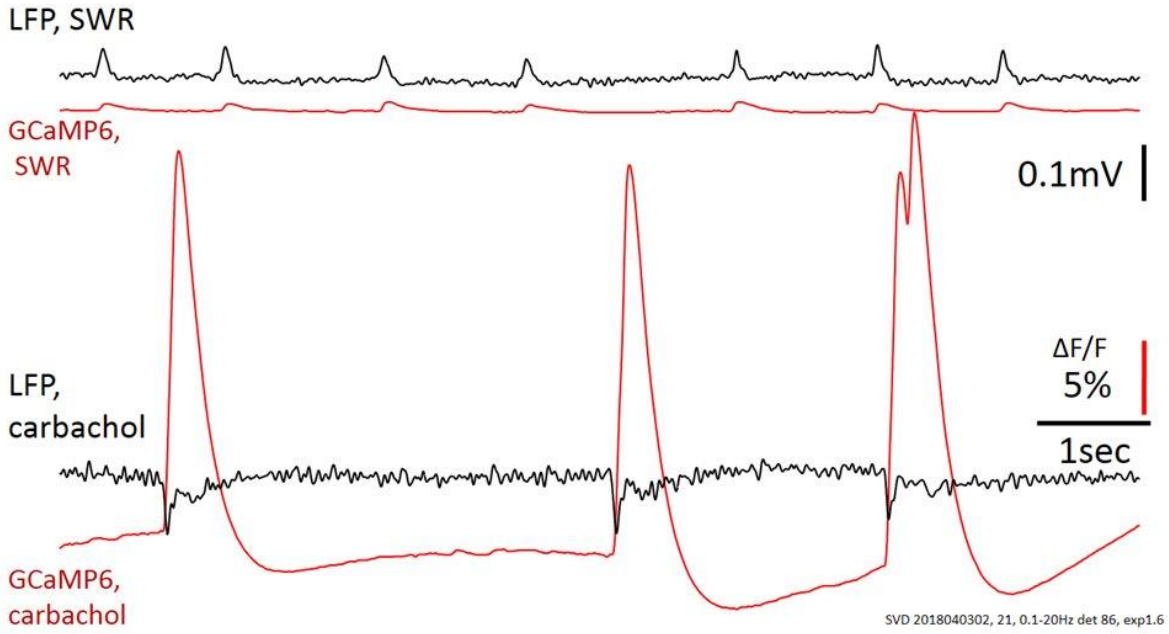
**Abstract:** We compared the local field potential (LFP) and GCaAMP-6 fluorescent signals in mouse hippocampal slices. During spontaneous sharp wave ripples (SWRs) and carbachol induced theta oscillations, the LFP amplitude was similar but the GCaMP-6 signal was disproportionally large, by a factor of 80. The LFP signal of the SWRs was about 50 μV in the striatum radiatum of CA1 (Fig 1, top black trace), and the GCaAMP-6 signal of the same tissue was about 0.3% (dF/F, 470nm excitation, 520 nm emission, measured as a population summation from an area of 60 μm in diameter by a 20x objective and a photodiode array, Fig 1 top red trace). When the tissue was perfused with 60 μM carbachol, the SWRs stopped and were replaced by episodic theta oscillations. The amplitude of the episodic oscillation was ~100 μV (Fig 1 bottom black trace), and the GCaAMP-6 signal was disproportionally large, about 26% of dF/F (Fig 1 bottom red trace). We used C57BL/6J-Tg (Thy1-GCaMP6f) GP5.5Dkim/J. mice (Jax 024276) mouse and the Ca signals are presumably reflecting neuronal Ca influx. SWRs and carbachol induced oscillations represent two active states in the hippocampus, both comprised of large numbers of moderately depolarized neurons with sparse spiking. Our data suggest that the LFP and GCaAMP population signals were not linearly correlated during population neuronal events.




**Disclosures: P. Li:** None. **A. Caccavano:** None. **S. Vicini:** None. **J. Wu:** None.

**Poster**

**733. Oscillations and Synchrony: LFP Studies I**

**Location:** SDCC Halls B-H

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**Topic:** B.09. Network Interactions

**Support:** DFG-SPP 1665
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**Title:** Layer-specific networks in the developing prefrontal cortex

**Authors: *S. H. BITZENHOFER**, J. A. PÖPPLAU, I. L. HANGANU-OPATZ
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**Abstract:** Coordinated activity in neuronal networks shapes the refinement of cortical networks during brain development. Thereby, it is critical for the maturation of cognitive and behavioral abilities. Dysfunction of early network activity disturbs the maturation of cortical networks, leading to life-long disruptions of cortical function and the emergence of neurodevelopmental disorders. We elucidated the layer-specific cellular mechanisms underlying rhythmic activity in the developing prefrontal cortex with a combination of in utero electroporation, optogenetics and electrophysiology. We show that optogenetic activation of layer 2/3 pyramidal cells in the prefrontal cortex induces rhythmic spiking and drives local network activity in beta frequency at neonatal age. Furthermore, we show that the frequency of this driven activity increases with age driving activity in gamma frequency in juvenile mice. Chronic stimulation of layer 2/3 pyramidal cells during early postnatal development alters the functional maturation of cortical networks and disrupts behavioral abilities at older age.

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**Poster**

**733. Oscillations and Synchrony: LFP Studies I**

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**Title:** An electrophysiological marker of arousal level in humans during sleep and general anesthesia

**Authors: *J. D. LENDNER**[1], R. F. HELFRICH[1], J. LIN[2], M. P. WALKER[1], B. A. MANDER[3], P. G. LARSSON[4], R. T. KNIGHT[1]
[1]Univ. of California Berkeley, Berkeley, CA; [2]Dept. of Neurol., [3]Psychiatry and Human Behavior, Univ. of California, Irvine, Irvine, CA; [4]Univ. of Oslo, Oslo, Norway

**Abstract:** Although sleep and general anesthesia are prominent states of reduced arousal, it remains unclear if they share a common mechanism. So far, comparative research mostly focused on oscillatory dynamics like slow waves which can be observed during non-rapid eye movement (NREM) sleep and under general anesthesia with propofol. However, it is unclear how reduced arousal level is mediated during rapid eye movement (REM) sleep where no such oscillations are present. For this study, we utilized the spectral slope as an electrophysiological metric of non-oscillatory neural activity to delineate wakefulness from states of reduced arousal. The spectral slope represents the decay of the electrophysiological power spectrum in log-log space and is thought to index the local balance between excitation and inhibition. Here, we demonstrate in four independent datasets including scalp EEG and intracranial EEG that the spectral slope tracks arousal levels in both NREM and REM sleep as well as under general anesthesia with high temporal precision. For anesthesia, we found a significant decrease in spectral slope with departure from wakefulness in both EEG and intracranial EEG, evident in the majority of electrodes. These results confirm that anesthesia is a global brain state of increased inhibition. Moreover, we also observed decreased slope values in NREM and REM sleep compared to wakefulness in both recording groups - compatible with a higher rate of inhibition in sleep. In the scalp EEG the main effect of slope was concentrated around frontal electrodes F3, Fz, F4 consistent with a focus in medial prefrontal cortex. Consequently, the intracranial regions that were driving this effect were localized in medial prefrontal cortex and medial temporal lobe structures. When training a classifier to differentiate between sleep stages, both spectral slope and slow oscillation power performed comparatively well when differentiating NREM sleep from wakefulness. When discriminating between REM and wake, however, the spectral slope showed a significantly better performance of 79.06 % ± 3.10 (mean ± SEM; $p = 0.002$) compared to slow oscillation power (59.95 % ± 2.19; chance level: 50%). These findings indicate that enhanced inhibition might be the underlying principle of reduced arousal states, emphasize the role of non-oscillatory dynamics in brain activity and thus, resolve the paradox of decreased arousal during REM sleep.

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**Poster**

**733. Oscillations and Synchrony: LFP Studies I**

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**Topic:** B.09. Network Interactions

**Support:** Marie Curie Postdoctoral Fellowship

**Title:** Distinct activity patterns in neuromodulatory centers are associated with differential modulation of cortical low and high gamma oscillations

**Authors: *N. K. TOTAH**, S. VAN KEULEN, N. LOGOTHETIS, O. ESCHENKO
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**Abstract:** Neuromodulatory systems are thought to gate cortical neuronal excitability – a generalized state consisting of high frequency (20 to 200 Hz) local field potential (LFP) oscillations. Stimulating neuromodulatory centers evokes a non-specific response across all components of the excited cortical state (beta and gamma band LFP oscillations). The non-specificity of neuromodulation is at odds with the fact that neuromodulators regulate distinct cognitive functions that are affiliated with different cortical LFP oscillations. For example, various dopamine and norepinephrine-dependent cognitive functions (e.g., working memory, spatial navigation, and top-down attention) are each accompanied by power increases within different LFP frequency bands. How can neuromodulators contribute to cognitive processes associated with different LFP frequency bands if they non-specifically modulate cortical LFP? Here, rather than perturbing neuromodulatory systems with stimulation, we recorded spontaneous unit activity from two primary sources of cortical neuromodulators (the noradrenergic locus coeruleus, LC, and dopaminergic ventral tegmental area, VTA) and correlated it with LFP power fluctuations in the prefrontal, visual, and somatosensory cortex of urethane-anesthetized rats. We found that neuromodulatory population spike rate rhythmically fluctuates at 1 – 2 Hz (delta band) in both LC and VTA. But, in the LC, an additional 5 – 7 Hz (theta band) fluctuation of spike rate occurred. While neuromodulatory delta oscillations non-specifically regulated the power of all cortical LFP oscillations over 20 Hz, theta spike rate oscillations were exclusively associated with cortical high gamma band (60 – 200 Hz) activity. As LC population spiking rhythmically rose and fell, two types of LC single units (characterized by narrow or wide action potentials) fired in phasic opposition, potentially providing differential cortical state regulation. Our results demonstrate that the noradrenergic system is a unique neuromodulatory center that can affect specific cortical activity patterns, rather than merely gate a generalized state of cortical excitability.

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**Title:** Enhanced cerebello-cortical coherence of local field potentials during patterned stimulation of the cerebellar vermis

**Authors: *S. TREMBLAY**[1], C. A. CHAPMAN[2], R. COURTEMANCHE[1]
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**Abstract:** The cerebellum is involved in sensorimotor, cognitive and emotional functions through cerebello-cerebral connectivity. Non-invasive cerebellar neurostimulation has been used to treat neurological disorders and has positive functional effects on frontal oscillations, cognition, and mood. Here, we explored the effects of rhythmic cerebellar stimulation at various frequencies on oscillations and coherence across a cerebello-cortical network in the rat. We predicted that slow frequencies (< 30 Hz) would synchronize large networks, and that faster frequencies (> 30 Hz) would synchronize more local networks. In addition, 25 Hz cerebellar stimulation has been shown to modulate prefrontal gamma activity. We therefore hypothesized that cerebellar stimulation in the theta and beta ranges would be effective in modulating rhythmic activity in the prefrontal cortex. Local field potentials (LFPs) were recorded continuously with bipolar electrodes in the lateral cerebellum (crus I/II), and in both hemispheres of the prefrontal cortex (frontal association cortex), in three adult male Sprague-Dawley rats anesthetized with urethane. Stimulation patterns were delivered to the cerebellar vermis in a randomized order: single pulses (0.2 Hz), and repeated pulses at 1 Hz (delta), 4 Hz (theta), 25 Hz (beta), and 50 Hz (gamma). Coherence between sites, in seven frequency bands (covering 0.1 Hz to 200 Hz), was analyzed before, during, immediately after, and 30 sec after stimulation. The effects of stimulation frequency and intensity were analyzed using a repeated measures ANOVA for each coherence comparison (Cb-Cx, Cx-Cx). Beta-frequency stimulation had the strongest enhancing effect on Cb-Cx coherence (in 8-14 and 14-30 Hz bands) and Cx-Cx coherence (80-200 Hz), with a main effect of stimulation in each of the three rats. Few studies have looked at the effects of cerebellar stimulation on oscillations and coherence across cerebello-cerebral networks. We have found here that cerebellar beta-frequency stimulation can drive synchronization of large cerebellar-cerebral and cerebral-cerebral networks. The present results could provide basic mechanisms underlying the therapeutic effects of cerebellar stimulation by promoting large-scale synchronization of neural networks.

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668863, SyBil-AA
SEV- 2013-0317
PVE 88881.068077/2014-01

**Title:** Different theta rhythms in the hippocampus synchronized with layer-specific gamma oscillations via cross-frequency coupling

**Authors: *V. LÓPEZ-MADRONA**[1], E. ALVAREZ-SALVADO[2], D. MORATAL[3], O. HERRERAS[4], E. PEREDA[5], C. MIRASSO[6], S. CANALS[1]
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**Abstract:** A prominent feature of brain activity is the presence of oscillations in neuronal recordings. Interactions between brain rhythms have been demonstrated at different space and time scales, and are believed to play an important role in neuronal communication. One such interactions is the cross-frequency coupling (CFC) between the phase of the theta rhythm and the amplitude of gamma oscillations in the hippocampus. However, how this idea copes with the co-existence of multiple theta rhythm generators and layer-specific gamma oscillations is not yet understood.
We used multichannel silicon recordings in freely exploring animals and source separation tools to analyse theta and gamma oscillations in CA1 and the dentate gyrus originating in CA3 and entorhinal cortex (EC) layers II and III. Synchronization between theta generators was computed, showing epochs of high and low theta coherence, supporting the idea of several rhythms coexisting in the hippocampus. An increase of the theta frequency was found in the activity generated in the EC correlated with higher synchronization, but not in CA3, suggesting that EC neurons have an active role binding the rhythms of different populations.
Moreover, the interaction between layer-specific gamma oscillations and theta rhythms was measured through CFC analysis, finding the strongest coupling between signals with the same origin and during events of high theta synchronization. In order to investigate the directionality

of these interactions, systematic analysis of cross-frequency directionality was performed, indicating that the higher frequencies drive the theta oscillation in each layer.
These results suggest that layer- and band-specific gamma-oscillations coordinate theta rhythms. This mechanism may explain how anatomically distributed computations, organized in theta waves, can be bound together.

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**Poster**

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**Topic:** B.09. Network Interactions

**Support:** NSERC
OGS

**Title:** Toward cellular-based explanations of LFP theta-gamma rhythm generation in the hippocampus

**Authors: A. CHATZIKALYMNIOU**[1,2], *F. K. SKINNER[1,3]
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**Abstract:** One of the most studied examples of cross-frequency coupling (CFC) in the rodent hippocampus, is phase-amplitude coupling (PAC) of theta and gamma rhythms. CFC has been implicated in various cognitive roles and specific CFC changes may be an early biomarker for neurological disease. However, underlying cellular-based mechanisms are difficult to determine. In large part, this is due to CFC analyses being performed using population activity recordings such as local field potentials (LFPs), and cellular contributions to LFPs are challenging to determine. These challenges arise because of the many overlapping pathways and multiple cellular subtypes that exist to influence PAC in LFPs. To obtain a cellular-based understanding of theta-gamma PAC, we are leveraging insights from existing simple (Ferguson et al. 2017, 4 (4) ENEURO.0131-17.2017) and detailed (Bezaire et al. 2016, eLife Sciences 5, e18566) models that are connected to a whole hippocampus preparation. The simple models provide an explanation for theta rhythm generation as dependent on spike-frequency adaptation and post-inhibitory rebound but only include fast-firing parvalbumin (PV+) interneuron types and pyramidal (PYR) cells and ad-hoc LFP representations. The detailed models include PYR cells and 8 different interneuron subtypes, produce theta-gamma rhythms using biophysical LFP models, and show that only some interneuron subtypes contribute to theta power. However,

mechanistic explanations of theta/gamma generation still need to be developed. We use a MATLAB-based program, SimTracker (Bezaire et al. 2016 bioRxiv 81927), to design, execute, organize, and analyze the simulations. From analyses of the existing detailed models, we find that the removal of connections from PV+ basket cells or PYR cells, but not other cell types, lead to a tripling of LFP gamma at ~30 Hz and ~70 Hz power respectively. Further, we have developed reduced versions of the detailed models and we find that they also exhibit theta-gamma rhythms. These reduced models increase computational efficiency and allow us to perform many sets of biophysical LFP simulations. Analysis of these simulations allows us to extract explanations using insights from the simple models. Subsequently, we can explain how extra-hippocampal inputs from medial septum and entorhinal cortex modulate PAC in the hippocampus and possibly predict critical balances for CFC disease biomarkers.

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**Program #/Poster #:** 733.08/D50

**Topic:** B.09. Network Interactions

**Title:** The effect of transcranial magnetic stimulation to the prefrontal cortex in a non-human primate model

**Authors: *S. SHIRINPOUR**[1], A. Y. FALCHIER[2], G. LINN[2], M. P. MILHAM[2], C. E. SCHROEDER[2,3], A. OPITZ[1]
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**Abstract:** Transcranial magnetic stimulation (TMS) to the dorsolateral prefrontal cortex (PFC) is currently clinically administered as a non-invasive neuromodulation tool for the treatment of depression. Nonetheless, basic mechanisms underlying TMS effects on prefrontal neural circuitry are largely unknown. Several studies have investigated TMS effects using non-invasive imaging modalities such as electroencephalography (EEG). However, EEG suffers from low signal to noise ratio and low spatial specify due to volume conduction. Therefore, in our study we investigate the effect of prefrontal TMS in a non-human primate model with implanted depth electrodes arrays spanning the left hemisphere from frontal to occipital brain regions. This allows us to record neural activity from the stimulation region and connected brain areas with high spatiotemporal resolution. Several sessions of single-pulse TMS to the prefrontal cortex together with baseline as control condition were recorded (monkey under anesthesia). Data preprocessing involved removal of TMS artifacts such as pulse artifact and muscle activity. Neural activity

could be fully recovered at least 10 ms after stimulation. As shown in fig 1, we found decreased power shortly after the stimulus and recovery in low frequency oscillations (2-4 Hz) roughly one second after offset. This effect was strongest in prefrontal electrodes. In conclusion, we provide evidence that TMS is modulating intrinsic brain activity under anesthesia through the suppression of low frequency oscillations. Future research will involve investigating the effect of changing TMS parameters in further detail. Our research can lead to a better understanding on how TMS affects neural activity in the prefrontal cortex and eventually more efficient treatment protocols to a variety of disorders such as depression.

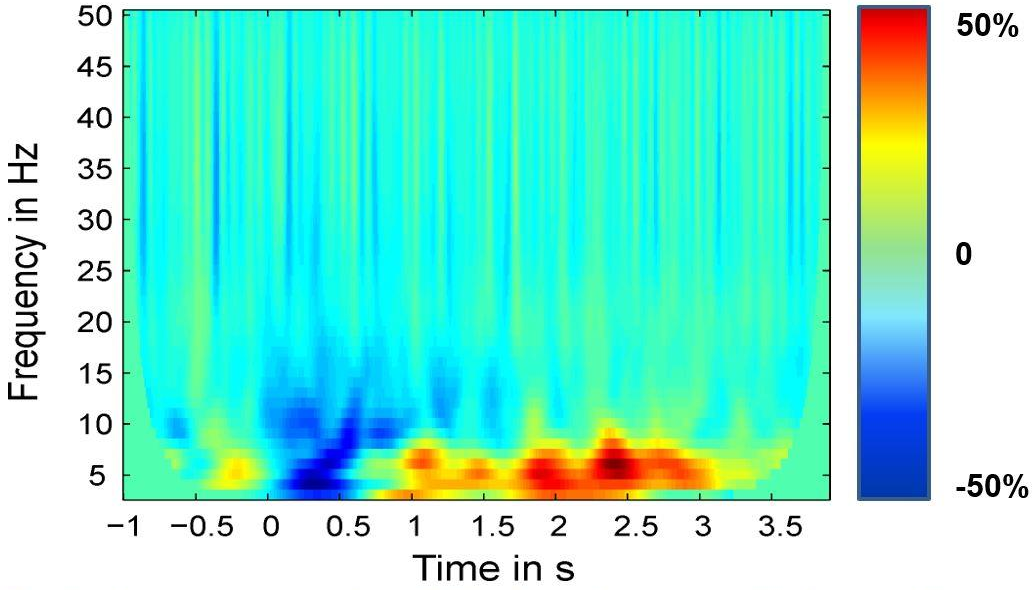


*Fig 1. Time-frequency response to single-pulse TMS (applied every 5s, average over 500 pulses) to the PFC contrasted to no-stimulation baseline shows reduced neural activity and recovery afterward for low frequency oscillations with respect to stimulus.*

**Disclosures: S. Shirinpour:** None. **A.Y. Falchier:** None. **G. Linn:** None. **M.P. Milham:** None. **C.E. Schroeder:** None. **A. Opitz:** None.

**Poster**

**733. Oscillations and Synchrony: LFP Studies I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 733.09/D51

**Topic:** B.09. Network Interactions

**Support:** NIH R01 NS092760

**Title:** Evaluating phase-synchrony dynamics in epilepsy patients using EMD-based mean-phase coherence analysis

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**Abstract:** Spatiotemporal synchrony dynamics between neuronal populations play an important role in decoding complicated brain functions such as in normal cognitive processing as well as during pathological conditions such as epileptic seizures. It has been widely shown that the synchrony level can be altered in several neurological disorders such as epilepsy, which itself may promote epileptic seizures. Therefore, evaluating synchrony dynamics may not only reveal crucial components essential to clinical EEG interpretation but may also provide a key insight into the dynamics of seizures as they evolve. A variety of mathematical methods have been proposed to identify the instantaneous synchrony changes among neuronal networks in the brain. However, many of them rely on several assumptions regarding properties of brain electrophysiological signals that render them inappropriate for this purpose: cross-correlation, Fourier spectrum-based coherence, wavelet methods, and mutual information measures are among them. These methods, while useful, suffer from assumptions of time-series linearity and/or stationarity, and may possibly detect spurious levels of synchrony as a result of utilizing bivariate measures, while original signals themselves may consist of several oscillatory components. Furthermore, it has been shown that phase synchronization can be detected among non-linear, coupled, chaotic oscillators even if their amplitudes are not synchronized. Therefore, it is crucial to employ non-linear methods to measure instantaneous phase-synchrony changes. Empirical mode decomposition (EMD) provides localized time-frequency representation of a signal via adaptively decomposing it into a finite group of narrowband, oscillatory components without making any assumptions of its linearity and stationarity features. This study reports on developing a non-linear, adaptive, analytical methodology that merges the EMD, Hilbert transform, mean-phase coherence analysis, and eigenvalue decomposition technique to evaluate the dynamical evolution of phase-synchrony in three epilepsy patients with temporal lobe epilepsy and one patient with frontal lobe epilepsy. Although a different phase-synchrony dynamics was detected between both types of epilepsy, the synchrony levels achieved a maximum at seizure offset during the ictal periods as seizures evolved. This result suggests that hypersynchronization of the epileptic network may be an essential self-regulatory mechanism by which the brain terminates seizures.

**Disclosures: S. Farahmand:** None. **T. Sobayo:** None. **D.J. Mogul:** None.

**Poster**

**733. Oscillations and Synchrony: LFP Studies I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 733.10/E1

**Topic:** B.09. Network Interactions

**Support:** NIH Grant DC015780
NIH Grant MH111439

**Title:** Loudness effects on the spectral composition of stimulus-related activity in the macaque auditory cortex

**Authors: *Y. KAJIKAWA**[1], J. J. ORZYK[1], C. E. SCHROEDER[2]
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**Abstract:** Brain signals often exhibit prominent power/amplitude in particular frequency bands, as indexed by spectrotemporal decompositions of both ongoing and event-related activity. Specific frequencies of ongoing activity have been linked to a number of behavioral and cognitive conditions. For sensory responses, spectral analyses have mostly been applied to responses at higher stimulus intensities. Resulting frequency compositions usually include both "evoked" components (those clearly phase-locked to stimulation) and "induced" components (those that are poorly phase-locked to stimuli). However, the magnitude and timing of sensory responses depend on the strength of sensory stimuli (e.g. sound level, cutaneous indentation pressure, visual contrast and brightness). When stimuli are weak, sensory responses are both smaller and slower. Similarly, the spectral composition of sensory responses is likely to be dependent on the stimulus strength, and there is some evidence for this idea. We examined how the spectrotemporal patterns of auditory cortical responses to broad-band noise changed depending on the sound intensity in awake macaques. We indexed the spectral composition of stimulus-related activity using both field potentials and current source density. At high stimulus intensities, evoked responses occur with brief onset peaks with broad band characteristics, followed by slower temporal components with lower frequency composition. At lower stimulus intensities, evoked responses occurred with similar but blunt peak patterns, and corresponding spectrotemporal peaks both delayed and limited to lower frequency bands. Induced (poorly phase-locked) components' spectral composition was defined by single trial spectral decomposition followed by averaging of resultants across trials. At high stimulus intensities, induced activity generally began with a spectral peak at ~150 Hz and rapidly shifted down to ~60 Hz within 50 ms. At lower stimulus intensities the spectral peak of trials-asynchronous peak started at lower frequencies with more delays, even after accounting for the delay of the evoked response peak components. Thus, both evoked and induced response components may change their frequency bands depending on the sensory input strength in sensory cortex.

**Disclosures: Y. Kajikawa:** None. **J.J. Orzyk:** None. **C.E. Schroeder:** None.

**Poster**

**733. Oscillations and Synchrony: LFP Studies I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 733.11/E2

**Topic:** B.09. Network Interactions

**Support:** ERANET EuroTransBio9 InHEALTH
BMBF #031B0010B

**Title:** Slow-wave oscillations in cultured neuronal networks reflect bursting and single spiking

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**Abstract:** Microelectrodes implanted in human or animal brain tissue record electrophysiological signals from neurons. These signals have two components: slowly varying local field potentials (LFP), associated with the spatial average of many sub-threshold post-synaptic currents (“input”), and multi-unit activity in form of action potentials (MUA, spikes, “output”). In two-dimensional neuronal cultures, so far only spike-bursts have been associated with LFPs (Leondopoulos et al, J Neural Eng. 2012). In order to examine this input-output relationship, we cultured networks of 1—5 x $10^5$ cortical, hippocampal or striatal neurons from P0 rats on planar microelectrode arrays (MEAs) with 60 electrodes (30 µm diameter, 200 µm distance, Multichannel Systems, Germany). Using the MEA2100 system, we obtained stable 30-minute recordings of both slow extracellular voltage fluctuations above 0.1 Hz and spike activity corresponding to neuronal action potentials. To control for potential phase shifts between spikes and slow waves, we carefully applied linear-phase FIR filters, down-sampled the data from 25 kHz to 1 kHz and verified that spikes were only minimally distorted or time shifted. Conversely, spikes did not distort low frequency signals obtained by band-pass filtering. We calculated normalized power spectral densities of 6-minute long segments using the Welch method with an 8.2-second long sliding window of 8,192 points, 50% overlap and a frequency resolution of 0.12 Hz. In each of the traditional delta (1—4 Hz), theta (4—11 Hz), beta (11—30 Hz) and gamma (30—55 Hz) frequency bands, we aggregated spectral power and determined spike-phase histograms reflecting the percentage of spikes at a specific phase of slow wave activity. After approximately 3 weeks in vitro, networks developed synaptically mediated spontaneous spiking activity organized in synchronous network bursts that were associated with slow LFP oscillations at the respective bursts frequency. Power spectral densities showed clear peaks at the network burst rates. However, after pharmacologically suppressing synaptically mediated synchronous network bursting, neurons on several electrodes exhibited tonic spike firing at individual but constant frequencies. These tonic single spikes preferentially occurred at the rising flanks of

same-frequency gamma oscillations. In conclusion, cultured networks exhibited slow delta and theta LFP oscillations corresponding to synaptically mediated burst events, but also gamma oscillations at the precise frequency of tonic single spike firing in the absence of network bursts. These results may have relevance for the interpretation of DBS electrode signals.

**Disclosures: S. Theiss:** None. **S. Illes:** None.

**Poster**

**733. Oscillations and Synchrony: LFP Studies I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 733.12/E3

**Topic:** B.09. Network Interactions

**Title:** Signs of cortical electrical activity after death

**Authors: *P. PANI**[1], F. GIARROCCO[1,2], E. BRUNAMONTI[1], M. GIAMUNDO[1], M. MATTIA[3], S. FERRAINA[1]
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**Abstract:** It is known that brain activity can persist for minutes or even return in mammals after a cardiac arrest of limited duration. At the same time, other observations have shown the possibility to fully recover cognition after longer times (up to 40 min). This suggests that what happens to the brain after cardiac arrest is mostly unknown. Recordings of brain activity around cardiac arrest have been typically conducted by using electroencephalography or electrocorticography that record neural activity as relatively large voltage fluctuations from sensors located outside the brain. From these measures, smaller electrophysiological phenomena cannot be detected. To bridge this gap, we recorded intraparenchymal local field potentials (LFPs) by means of a multi-electrode array (MEA) in the frontal cortex of a male monkey, during a standard euthanasian procedure. The LFPs were recorded starting from a deep sedated state (induction by Ketamine; mixture Isoflurane/Oxygen to effect), displaying supra-threshold fluctuations well after the cardiorespiratory arrest caused by the intravascular bolus injection. Cardiac activity was also recorded. We found that cortical LFPs displayed a regime of burst suppression by the anesthesia, followed by a strong drop-down once cardiac arrest occurred. However, after few minutes, bursts of LFPs distributed and coordinated across the MEA, emerged sparse in time up to about 120 minutes, each displaying a peak of power at 1-3 Hz in the Fourier spectrograms. Although confined to a single subject, our results show that the dying brain can still show signs of electrophysiological activity: a persisting excitability of the cortical tissue occurring after some minutes of apparent silence. We think that this finding stimulates fundamental scientific, ethical and clinical questions.

**Disclosures: P. Pani:** None. **F. Giarrocco:** None. **E. Brunamonti:** None. **M. Giamundo:** None. **M. Mattia:** None. **S. Ferraina:** None.

**Poster**

**733. Oscillations and Synchrony: LFP Studies I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 733.13/E4

**Topic:** B.09. Network Interactions

**Support:** NEI R01-EY024067
Simons Foundation Grant SCGB 325548

**Title:** Only sub-gamma coherence predicts long-range, parietal-frontal effective connectivity in macaques

**Authors: *R. SHEWCRAFT**[1], B. PESARAN[2]
[1]Ctr. for Neural Sci., New York Univ., New York, NY; [2]New York Univ. Ctr. for Neural Sci., New York, NY

**Abstract:** Coherent neural activity plays a role in flexible behaviors that require hand-eye coordination (Dean 2012), attentional control (Buschman & Miller 2007), visual perception (Womelsdorf 2006), working memory (Pesaran 2002) and decision making (Wong 2016). The causal relationship between coherent neuronal dynamics and inter-regional interactions has not been previously examined. Here we optogenetically stimulate neurons in the posterior parietal cortex while simultaneously recording spike-field activity in the frontal cortex to provide causal evidence of functional connections. We then compare parietal-frontal functional connectivity, measured by LFP coherence, with causally determined maps of parietal-frontal effective connectivity. We injected AAV5-hSyn-ChR2(h134r) in the PPC of two rhesus macaques and measured synaptically driven responses to optogenetic stimulation on an array of 96 electrodes implanted over frontal cortex. The electrodes covered approximately 180 $mm^2$ of cortical surface. We also implanted a single electrode at the stimulation site in PPC. We measured LFP activity on all electrodes during a baseline period prior to stimulation. We also measured synaptically mediated LFP responses in frontal cortex that were driven by stimulation in PPC. We used 1 s long pulse trains, with 10 ms wide pulses and Poisson distributed inter-pulse intervals with a mean rate of 20 pulses/s. We estimated functional connectivity by computing the coherence between the PPC electrode and each frontal electrode during the baseline period. Larger stimulation-driven responses in frontal cortex may be due to greater synaptic connectivity with the stimulation site. Therefore, we quantified the strength of synaptic interaction as the maximum Z-score of the pulse-triggered evoked potential at each frontal site. Next, we compared the functional connectivity with the stimulation-based effective connectivity by computing Spearman's rank correlation coefficient ($\rho$) across all electrodes. In each animal,

coherence at frequencies below 35 Hz was significantly and positively correlated with evoked potential magnitude (p < 0.05, FWER corrected). Coherence at 35-100 Hz was not positively correlated with synaptic interactions. Furthermore, we found animal specific frequency structure. For Monkey H, the correlation had peaks at 5 Hz ($\rho$=0.70) and 14 Hz ($\rho$=0.57), with a trough at 11 Hz ($\rho$=0.40). Monkey J had peaks at 4 Hz ($\rho$=0.38) and 25 Hz ($\rho$=0.26), with a trough at 15 Hz ($\rho$=0.0). These results show that neural coherence measures the strength of synaptic interactions between populations of PPC neurons and individual frontal neurons.

**Disclosures: R. Shewcraft:** None. **B. Pesaran:** None.

**Poster**

**733. Oscillations and Synchrony: LFP Studies I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 733.14/E5

**Topic:** B.09. Network Interactions

**Support:** NIH Grant MH099085

**Title:** Investigating the ventral hippocampal-prefrontal anxiety circuit: Sexual dimorphisms and effects of estrous stage

**Authors: *K. J. SCHOEPFER**[1], A. A. WILBER[2], W. WU[3], M. KABBAJ[1]
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**Abstract:** Synchronized oscillations in the local field potentials (LFPs) between interconnected brain structures are hypothesized to play a role in the regions' communications. In mice and rats, the ventral hippocampus (vHPC) monosynaptically projects to the medial prefrontal cortex (mPFC) ipsilaterally and bilaterally. As members of the corticolimbic system, the vHPC and mPFC serve 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. Inappropriate overrepresentation of the anxiety response can classify an anxiety disorder. Women are ~60% likelier than men to be diagnosed with an anxiety disorder, yet possible neural correlates to this sex difference have not been explored. 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. Phase-locked theta (4-12 Hz) oscillations between the vHPC and mPFC have been shown to directly underlie innate anxiety-like behaviors in male rodents. Surprisingly, however, the vHPC-mPFC circuit's role in anxiety-like behavior remains to be investigated in females. Here, we aim to determine how the vHPC-mPFC circuit differs between both sexes of rat and identify the degree of female

estrous stage modulation therein. Rodents are implanted with electrodes in vHPC CA1, prelimbic mPFC, infralimbic mPFC, and dorsal HPC (dHPC) CA1 (as a negative control) and are acclimatized to a square arena. LFPs are recorded daily in this familiar arena, and theta parameters are analyzed as a function of sex and of estrous stage. Rodents are then recorded on the elevated plus maze (EPM), a validated behavioral test for innate anxiety-like behavior; females are tested either in diestrus (low E2/P4) or proestrus (high E2/P4) stages. We predict that between vHPC-mPFC (but not dHPC), theta coherence, theta power correlations, and EPM zone-specific LFP profiles may exhibit sexual dimorphisms which are most polarized in high-E2 female estrous states. This project aims to extrapolate a validated electrophysiological endophenotype of innate anxiety-like behavior (vHPC-mPFC theta synchrony) in males to both sexes. Results are expected to delineate sexual dimorphisms and similarities in a functional neural circuit that mediates innate anxiety expression.

**Disclosures: K.J. Schoepfer:** None. **A.A. Wilber:** None. **W. Wu:** None. **M. Kabbaj:** None.

**Poster**

**733. Oscillations and Synchrony: LFP Studies I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 733.15/E6

**Topic:** B.09. Network Interactions

**Support:** Hungarian Brain Research Program - Grant No. 2017-1.2.1-NKP-2017-00002
VEKOP-2.3.2-16-2017-00013

**Title:** Auditory evoked neural responses in the auditory cortex of the cat during slow wave sleep and anesthesia

**Authors: *D. A. HORVATH**[1,2,3], A. JUHASZ[2], R. FIATH[1,2], K. TOTH[1], G. KARMOS[2], I. ULBERT[1,2]
[1]RCNS HAS, Budapest, Hungary; [2]Fac. of Information Technol. and Bionics, Pazmany Peter Catholic Universtiy, Budapest, Hungary; [3]Sch. of PhD Studies, Semmelweis Univ., Budapest, Hungary

**Abstract:** Aims
Changes of auditory cortical evoked potentials depending on vigilance are well known. However, the underlying cellular and circuit level processes are still unclear. We aimed to characterize single unit firing properties in relationship to the sleep slow wave (SW) phase.
Methods
We implanted chronically metal linear array multielectrodes into the auditory cortex (AC) of cats. We recorded spontaneous local field potential (LFP), multiunit and single unit activity and the same signals evoked by single or pairs of clicks from the AC of freely moving and behaving

animals. To describe the firing properties of single units related to the SWs, we detected the LFP phase of the SWs and computed the preferred phase for firing of each single unit using circular statistics. We also characterized the extracellularly recorded and separated single units based on their firing autocorrelograms and waveform properties. We determined the cortical layer for each extracellularly recorded single unit based on the current source density (CSD) diagram of the click evoked average responses.
Results
We found that while both putative principal cells and interneurons prefer to fire at the initial phase of the up state, circular statistics reveals that interneurons are more locked to the up-state phase than principal cells. Adding the cortical layer of each single unit to the data analysis revealed that neurons in the different cortical layers have different preferred firing phases during the SW.
Conclusions
We can conclude that each cortical neuronal type has its own contribution the SW recorded in naturally sleeping cats.

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**Poster**

**733. Oscillations and Synchrony: LFP Studies I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 733.16/E7

**Topic:** B.09. Network Interactions

**Support:** NIH #R01NS101108

**Title:** Decreased phase amplitude coupling across laminar hippocampal CA1 following traumatic brain injury

**Authors: *C. COTTONE**, K. GAGNON, C. ADAM, M. SERGISON, H.-C. I. CHEN, A. ULYANOVA, J. A. WOLF
Univ. of Pennsylvania, Philadelphia, PA

**Abstract:** Traumatic brain injury (TBI) is caused by mechanical insults to the head, often resulting in prolonged or permanent brain dysfunction including disruption of cognitive functions. The hippocampus is one of the most studied brain regions following TBI due to its central role in short-term and spatial memory and its demonstrated vulnerability during TBI. We hypothesize that TBI may disrupt the timing between ensembles of neurons in these networks, and that this may underlie aspects of post-TBI cognitive dysfunction. Preliminary results demonstrated that TBI leads to a disruption of oscillatory organization in the hippocampus and

dysfunctional entrainment to theta, potentially due to a compensatory response to loss of afferent input due to axonal injury. Cross-frequency coupling (CFC) and spike-local field potential (LFP) entrainment may support the organization of these neurons assembles and are present during a range of cognitive functions, including learning and memory. While CFC and spike-LFP interactions have been studied in detail both within a brain region and across brain regions, little is known about their short-range interactions within the laminar architecture of the hippocampus and how they may be affected following TBI. Using 64-channel silicon probes, we simultaneously recorded laminar hippocampal field structure and CA1 neurons in behaving rats during an open field paradigm. Recordings were divided into moving and non-moving periods, and then phase-amplitude coupling (PAC) was calculated for every possible pair of channels using the 1-20 Hz band as the phase of the lower frequency oscillation and 1-300 Hz band as the power of the coupled higher frequency oscillation (64x64 permutations). The entrainment of the neurons was calculated for each single neuron's firing properties, with every channel's local field potential oscillations on the laminar probe for each frequency in 1-300 Hz band. As such, we can now visualize to which frequencies the cell is attuned, as well as where these oscillations are located in the laminar structure. Results show a reduction in PAC in injured subjects relative to sham, predominantly between radiatum and pyramidal layers in theta-gamma and delta-theta-ripple coupling, thus reflecting a loss of encoding synchrony between CA1-CA3 (low gamma (~ 30-60 Hz)), EC-CA1 (high gamma (~ 60-110 Hz)) and a disruption of the Sharp waves-ripples (~ 140-240 Hz) generation. One interpretation of these results is that laminar afferent inputs into CA1, both from CA3 and entorhinal cortex, are no longer properly coupled to lower frequencies, leading to disrupted entrainment and the consequent disruption of neuron ensemble formation.

**Disclosures: C. Cottone:** None. **K. Gagnon:** None. **C. Adam:** None. **M. Sergison:** None. **H.I. Chen:** None. **A. Ulyanova:** None. **J.A. Wolf:** None.

**Poster**

**733. Oscillations and Synchrony: LFP Studies I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 733.17/E8

**Topic:** B.09. Network Interactions

**Support:** São Paulo Research Foundation, FAPESP (2012/06122-4)
Coordination for Improvement of Higher Education Personnel, CAPES (PNPD 1645824)
São Paulo Research Foundation, FAPESP (2016/17882-4)

**Title:** Reactivity of prefrontal and thalamic spontaneous oscillations to hippocampal high-frequency stimulation

**Authors: *L. S. BUENO-JUNIOR**, R. N. RUGGIERO, J. P. LEITE
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**Abstract:** Rodent synaptic plasticity experiments are traditionally focused on stereotyped responses - field postsynaptic potentials (fPSPs) - evoked by afferent electrical stimuli at innocuous frequencies (e.g., 0.05 or 0.1 Hz). Through measuring a given feature of fPSPs, such as amplitude or slope, one can analyze how they react to conditioning manipulations, for example high-frequency stimulation (HFS). A less common approach is to evaluate how spontaneous oscillations between fPSPs react to HFS. This approach is the one we report here. In chronically implanted rats, we examined local field potentials (LFP) in 8-second inter-stimulus epochs before and after HFS. Also unlike most of the literature, we probed a three-node circuit: the stimulated area, i.e., hippocampus (intermediate CA1/subiculum), and two recorded areas, i.e., medial prefrontal cortex (mPFC) and mediodorsal thalamus (MD), allowing functional connectivity measures. Ongoing analyses indicate a long-lasting (>2 h) increase in power spectral densities across low- and high-gamma frequencies after HFS, both in the mPFC and MD. In addition, these areas showed stronger power and coherence around a 6 Hz-peaked theta activity, but this effect was specific to the initial 3 minutes after HFS. These preliminary findings may reflect the different stages of fPSP long-term potentiation, which requires further analysis. Considering that electroencephalography is increasingly used for monitoring the effects of deep-brain stimulation in humans, future studies like the present one could further explore spontaneous oscillations in their relationship with synaptic plasticity, both in health and disease.

**Disclosures: L.S. Bueno-Junior:** None. **R.N. Ruggiero:** None. **J.P. Leite:** None.

**Poster**

**734. Oscillations and Synchrony: LFP Studies II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 734.01/E9

**Topic:** B.09. Network Interactions

**Support:** NIH Grant R01MH101547
NIH Grant R01MH111889
Department of Psychiatry at UNC Chapel Hill

**Title:** Transcranial static magnetic field stimulation of the dorsolateral prefrontal cortex has region specific effects on neural oscillations

**Authors: *A. G. SHEFFIELD**[1], S. AHN[2], S. ALAGAPAN[3], F. FROHLICH[4]
[1]UNC Chapel Hill, Chapel Hill, NC; [2]Dept. of Psychiatry, UNC at Chapel Hill, Chapel Hill, NC; [3]Psychiatry, Univ. of North Carolina At Chapel Hill, Chapel Hill, NC; [4]Psychiatry, Univ. of North Carolina, Chapel Hill, NC

**Abstract:** Transcranial static magnetic field stimulation (tSMS) is a novel non-invasive brain stimulation technique that has been shown to locally increase alpha oscillations in the parietal and occipital cortex. We investigated if tSMS locally increased alpha oscillations in the left or right prefrontal cortex, as the balance of left/right prefrontal alpha oscillations (frontal alpha asymmetry) has been linked to emotional processing and mood disorders. Therefore, altering frontal alpha asymmetry with tSMS may serve as a novel treatment to psychiatric diseases. We performed a crossover, double-blind, sham-controlled pilot study to assess the effects of prefrontal tSMS on neural oscillations. The DLPFC was chosen as the site of stimulation as frontal alpha asymmetry has been localized to this region. 24 right-handed healthy participants were recruited and received left DLPFC tSMS, right DLPFC tSMS, and sham tSMS in a randomized order. EEG data were recorded using a 128-channel Hydrocel Geodesic Sensor Net and Netamps 410 amplifier (EGI Inc., Eugene, OR). EEG data were collected before (2 minutes eyes-closed, 2 minutes eyes-open), during (10 minutes eyes-open), and after (2 minutes eyes-open) stimulation. After standard signal preprocessing, power spectral density (PSD) was computed by Welch's method with a 2-second window and a 12.5% overlap resulting in a PSD with 0.5 Hz resolution. Alpha was defined as 2 Hz on either side of the individual alpha frequency (IAF), and exploratory analyses were performed for the fixed frequency bands delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), and gamma (30-50 Hz). Frequency power during- and post-stimulation were log-normalized to the eyes-open pre-stimulation period. Finally, channels were grouped and averaged for 8 locations for statistical analysis: left/right frontal, temporal, parietal, and occipital. In contrast to our hypothesis, neither left nor right tSMS locally increased frontal alpha oscillations. However, IAF alpha oscillations were higher in occipital cortex relative to other brain regions during left DLPFC tSMS. Both left and right DLPFC tSMS increased post-stimulation global theta oscillations relative to sham, with a greater increase in response to right stimulation. Beta oscillations in the left hemisphere increased post-stimulation for left and right DLPFC tSMS compared to sham. We concluded that DLPFC tSMS modulated the network oscillations in regions distant from the location of stimulation and that tSMS has region specific effects on neural oscillations.

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**Poster**

**734. Oscillations and Synchrony: LFP Studies II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 734.02/E10

**Topic:** B.09. Network Interactions

**Support:** NIH Grant R01MH111889
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**Title:** Entrainment of alpha oscillations by transcranial alternating current stimulation in the ferret

**Authors: *E. NEGAHBANI**[1], I. M. STITT[1], S. RADTKE-SCHULLER[1], T. DOAN[6], M. DANNHAUER[6], A. V. PETERCHEV[6,7,8], F. FROHLICH[1,2,3,4,5]
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**Abstract:** Despite the growing number of applications of transcranial alternating current stimulation (tACS), the underlying mechanisms remain largely unknown due to the lack of technical feasibility of simultaneous electroencephalography (EEG) and tACS. Previously, our simulations showed that tACS entrains neuronal firing and that the entrainment depends on the match of stimulation frequency to the endogenous frequency as a function of stimulation amplitude (Arnold tongue). Yet, experimental confirmation has been lacking. Here, we tested the hypothesis that tACS modulates alpha oscillations by entraining single neurons as described by the Arnold tongue. We used the head-fixed ferret (*Mustela putorius furo*) as the animal model since it displays robust thalamo-cortical alpha oscillations.
We implanted multielectrode arrays in a 3-node thalamocortical network including the lateral posterior (LP)/Pulvinar nuclear complex of the thalamus, the posterior parietal cortex (PPC) and the primary visual cortex (VC, area 17). tACS electrodes were placed on the left frontal (above the eye) and the medial occipital regions. Animals (n = 3) received 12 stimulation sessions, each including 54 stimulation trials drawn randomly from combination of 6 different amplitudes (all subthreshold) and 9 frequencies (centered on the individual endogenous alpha frequency). We also developed a computer model of the distribution of the tACS electric field in the ferret head to guide and validate the stimulation protocol.
Neurons at PPC and VC but not LP/Pulvinar phase synchronized to the tACS waveform as characterized by Arnold tongues centered on the endogenous peak frequency (~ 14 Hz), thus confirming the predictions of the computational models. tACS synchronized the PPC neurons stronger than the ones in VC. Further delineation indicated that tACS synchronized the narrow-spiking neurons more strongly than wide-spiking neurons in both PPC and VC. Further analysis showed that narrow spiking neurons were also more strongly phase-locked to the endogenous oscillations.
Together, our results represent the first in-vivo demonstration of entrainment of alpha oscillations by tACS that is characterized by an Arnold tongue. This experimental confirmation of the theoretical predictions from computational modeling paves the way for future, mechanistic investigations of how tACS modulates network oscillations, including how plasticity enables effects of tACS to be maintained after stimulation.

**Disclosures: E. Negahbani:** None. **I.M. Stitt:** None. **S. Radtke-Schuller:** None. **T. Doan:** None. **M. Dannhauer:** None. **A.V. Peterchev:** None. **F. Frohlich:** A. Employment/Salary (full or part-time):; University of North Carolina, Chapel Hill. E. Ownership Interest (stock, stock

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**Poster**

**734. Oscillations and Synchrony: LFP Studies II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 734.03/E11

**Topic:** B.09. Network Interactions

**Support:** NIMH Grant R01MH101547
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**Title:** Development of functional connectivity in the fronto-parietal network in ferrets

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**Abstract:** Synchronized activity in the fronto-parietal network plays a crucial role in attention and other cognitive functions, and is disrupted in schizophrenia and other psychiatric disorders. Recent studies have begun to investigate the development of fronto-parietal functional interactions. However, these studies use EEG or fMRI, two methods which are limited by their spatio-temporal resolution. To fill the knowledge gap between very early network activity patterns in local networks[1] and the mature network synchronization patterns that are linked to cognitive function, we performed microelectrode electrophysiological recordings in developing ferrets (*Mustela putorius furo*), an altricial animal model system with a long history in the study of development. We implanted multielectrode arrays into the frontal (prefrontal and premotor, PFC/PMC) and posterior parietal cortex (PPC) for simultaneous recordings of single-units and local filed potentials (LFPs). We recorded from freely-moving animals from postnatal day 26 to 77 (P26-P77). To probe functionally and translationally relevant network activity patterns, we used an auditory oddball test which is commonly used to detect pathologically altered network activation in schizophrenia.
A total of fourteen sessions were recorded from seven animals. Coherence analysis revealed that, similar to a previous finding in adult ferrets during a sustained attention task[2], the LFP signals in PFC/PMC and PPC were synchronized in theta band (4-8 Hz) during the oddball test as early as P26. The theta coherence was higher in trials with the deviant tone compared to trials with the standard tone (t-test, $p < 0.05$, $n = 14$ sessions). The action potentials in both brain regions were phase-locked to the LFP in the theta band; and the phase-locking value was higher for the deviant than the standard tone (PFC/PMC, $p < 0.01$, $n = 160$ single-units; PPC, $p < 0.05$, $n = 37$). When assessed as a function of age, the enhancement of theta coherence by the deviant tone

became shorter in duration and less delayed to the tone onset.
Together, our results suggest that fronto-parietal interactions track circuit maturation and may represent an attractive target for future network-based interventions during development for the prevention and treatment of neuropsychiatric disorders.
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[2] Sellers KK, et al. Oscillatory dynamics in the frontoparietal attention network during sustained attention in the ferret. Cell reports. 2016 Sep 13;16(11):2864-74.

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**Poster**

**734. Oscillations and Synchrony: LFP Studies II**

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**Topic:** B.09. Network Interactions

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National Institute of Mental Health of the National Institutes of Health under Award Number R01MH101547
North Carolina Translational NC TraCS 2KR721505

**Title:** Characterizing social and cognitive development in nrem sleep and risk for asd

**Authors: *J. PAGE**[1], C. LUSTENBERGER[2], F. FROHLICH[3]
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**Abstract:** Early childhood is characterized by rapid development and pronounced changes in both early brain function and learning. Both are thought to be fostered by sleep [1], specifically non-rapid eye movement (NREM) sleep. NREM sleep is characterized by the presence of slow wave activity (SWA) and sleep spindles (10-16 Hz) [2], which are related to intelligence and general learning traits in adults, school aged children [3], and cognitive and social development in infants/toddlers [4]. Sleep spindle characteristics are widely studied in young adults and school aged children, and show clear developmental changes [5]. Furthermore, spindle features are altered in several neurodevelopmental disorders, such as autism spectrum disorder (ASD) in both adults [6] and children [7]. Sleep spindles may, therefore, represent a useful biomarker to distinguish typical from atypical development. However, the topographical and spectral

characteristics of sleep spindles has yet to be examined in infants/toddlers with risk for autism and moreover it is unknown how these features are associated with outcomes of early cognitive and social development.To do address this gap, we conducted a study to characterize the topography of sleep spindles in 12 - 30 month typically developing (TD) infants/toddlers and risk for ASD (meeting diagnostic criteria based on the ADOS-2) and examined associations with cognitive and social development. Here, we report preliminary nap data in TD and ASD group with high density electroencephalogram (hdEEG, 128 electrodes) and associations with cognitive and social development. Initial findings show decreased spectra power in theta (4-7 Hz), slow (10-12Hz) and fast (14-16Hz) spindles, and increased beta (20-25Hz) activity, in infants/toddlers in the ASD group. Infants/toddlers at-risk of ASD showed negative correlations with theta, slow and fast spindles, and beta on measures of cognitive and social development. Autism severity was negatively correlated with frontal sleep spindles, and positively correlated with beta oscillations. Thus, participants with increased symptom severity showed decreased spindles and increased beta activity. These findings suggest an important role of network dynamics of NREM sleep in cortical maturation and the associated development of both cognitive functioning and risk for neurodevelopmental disorders.

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**Poster**

**734. Oscillations and Synchrony: LFP Studies II**

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**Topic:** B.09. Network Interactions

**Support:** NIMH Grant R01MH101547
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NCTrACS KR941707

**Title:** Target engagement of alpha oscillations by transcranial alternating current stimulation (tacs) in patients with chronic low back pain

**Authors: *J. PRIM**[1,6], S. AHN[2,6], M. ALEXANDER[2,6], M. DAVILA[2], K. MCCULLOCH[1], F. FROHLICH[2,6,3,4,5]
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**Abstract:** Chronic low back pain (LBP) is the second most prevalent cause of disability in US adults. Although extensively studied, current therapeutic options for chronic pain are limited. The development of a new, safe, scientifically-supported, low-cost treatment for chronic pain is imperative for helping the millions of people with chronic pain who suffer from physical handicaps and common psychiatric comorbidities such as opioid addictions and depression. Chronic pain ultimately is a disorder of the central nervous system, which is manifested in aberrant activity patterns such as network oscillations in the thalamo-cortical system. We hypothesized that transcranial alternating current stimulation (tACS), which is a non-invasive brain stimulation tool developed to modulate brain rhythms, can be used as a treatment option in patients with LBP by modulating abnormal neuronal activity. Here, we evaluated the efficacy and feasibility of tACS in 20 patients with LBP by conducting a double-blind, randomized, placebo-controlled cross-over single site study. We hypothesized that 10Hz-tACS would modulate abnormal alpha oscillations and automatic nervous system (ANS) regulation resulting in pain relief. We applied a single session of 10Hz-tACS for 40 minutes and recorded electroencephalography (EEG) and heart rate variability (HRV). We measured pain severity assessed by the Defense and Veterans Pain Rating Scale (DVPRS), Pressure Pain Threshold (PPT), and Oswestry Disability Index (ODI). Changes in alpha oscillations from EEG data and high frequency component (HF) (known as respiratory sinus arrhythmia) from HRV data were presented as primary outcomes. Changes in pain severity were secondary outcomes.
We found that baseline alpha oscillations were negatively correlated with pain severity ($p$<0.05, FDR corrected). and 10Hz-tACS enhanced alpha oscillations in the somatosensory region ($p$<0.05, FDR corrected). Importantly, the enhancement of alpha oscillations were significantly correlated with pain relief (normalized pain changes) in the frontal and somatosensory regions ($p$<0.05, FDR corrected) in the active tACS condition while no correlation was seen in the condition. We found a significant treatment effect in the HF of HRV (Linear mixed-effects model, $F(1,56)=8.61$, $p<.01$) and a negative correlation between HF and pain severity ($r=-0.47$, $p<.01$). There was a treatment effect using the nonparametric signed rank test for normalized pain changes. These findings suggest that 10Hz-tACS could be a network-level approach for treating patients with LBP. Further studies with larger sample sizes are needed to better understand the effect of tACS on chronic pain.

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**Poster**

**734. Oscillations and Synchrony: LFP Studies II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 734.06/E14

**Topic:** B.09. Network Interactions

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NC TraCS 2KR961706

**Title:** Physiological correlates of the ANS and HPA-axis in active and passive music therapy interventions

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**Abstract:** Music therapy (MT) is an innovate multicomponent intervention that has been shown to treat major depressive disorder (MDD), yet specific components that drive efficacy remain unknown. Rhythm has emerged as a component that is hypothesized to be critical for MT. Active MT requires patients to engage rhythmically with music, embodying a pulse by coordinating their playing with the music. In contrast, passive MT only requires patients to listen to music, omitting the sensorimotor engagement that is central to active MT. This differential impact of rhythmic engagement in MT interventions remains unexplored. Dysregulation of the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis have been implicated in MDD. MT has been shown to modulate heart rate variability (HRV) and stress hormone levels, physiological correlates of the ANS and HPA-axis, respectively, suggesting that MDD could be treated with MT. Here we contrasted the effects of active and passive MT interventions to examine the differential impact of rhythmic engagement on the ANS and HPA-axis in healthy control participants.Healthy participants (N=16) participated in both an active and a passive 40 minute MT intervention session on separate days spaced at least one-week apart. HRV recordings and saliva samples were collected both before and after each intervention session. The high frequency component (HF) and the low frequency divided high frequency components (LF/HF) were calculated (HRV markers of parasympathetic and sympathetic ANS activation, respectively) and saliva samples were analyzed for alpha-amylase and cortisol (endocrine markers of the sympathetic ANS and HPA-axis, respectively). Normalized change scores over the duration of the interventions—log(post/pre)—were calculated for each correlate. ANOVA of change rate was used to compare the effects of session order (1st and 2nd) and condition (active and passive) on these change scores. A main effect was found for condition in LF/HF

(F(1,27)=8.206, p=0.00783, ηp2=0.227), where active MT decreased LF/HF power (mean change, -0.3872), while passive MT increased LF/HF power (mean change, 0.3731). There was no effect of condition for alpha-amylase (F(1,27)=1.216, p=0.280, ηp2=0.0416), cortisol (F(1,27)=0.054, p=0.817, ηp2=0.00194), or HF (F(1,27)=0.004, p=0.952, ηp2=0.000132). These results indicate that MT effectively targets the ANS and suggests that differences in rhythmic engagement between active and passive MT leads to a differential modulation of the sympathetic ANS.

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**Poster**

**734. Oscillations and Synchrony: LFP Studies II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 734.07/E15

**Topic:** B.09. Network Interactions

**Support:** R21MH105574
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**Title:** Targeting impaired neural oscillations in patients with schizophrenia by transcranial alternating current stimulation

**Authors: *S. AHN**[1,5], J. M. MELLIN[1,5], S. ALAGAPAN[1,5], M. L. ALEXANDER[1,5], J. H. GILMORE[1], L. F. JARSKOG[1,6], F. FROHLICH[1,5,2,3,4]
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**Abstract:** Neural oscillations are a fundamental mechanism that organizes the temporal relationship of activity patterns in large-scale brain networks. Several psychiatric disorders have been associated impairment of neural oscillations [1]. In particular, patients with schizophrenia exhibit impaired neural oscillations involved in sensory and cognitive processing [2]. Therefore, strategies to target and modulate impaired neural oscillations may serve both as tool to investigate the causal relationship between oscillation abnormalities and symptom manifestations and, ultimately, to treat patients by restoring physiological oscillation dynamics. Transcranial

alternating current stimulation (tACS) is a non-invasive brain stimulation modality that applies oscillating electrical currents to the brain via scalp electrodes. A single session of tACS enhances posterior alpha oscillations (8-12 Hz) in healthy humans [3]. Yet, it has remained unknown if tACS, and in particular repeated application of tACS, can alter or modulate network in disorders associated with dysfunction of neural oscillations such as schizophrenia.
In this study, we performed a randomized, double-blind, sham-controlled clinical trial to contrast tACS with transcranial direct current stimulation (tDCS) and sham (i.e., placebo) stimulation in 22 schizophrenia patients with auditory hallucinations. Clinical results were recently reported in a separate paper [4]. We used high-density electroencephalography to investigate if a five-day, twice-daily 10Hz-tACS protocol enhances alpha oscillations and modulates network dynamics that are impaired in schizophrenia. We found that 10Hz-tACS enhanced alpha oscillations ($F$6,57=3.49, $p$=0.005) on day 5 of stimulation and modulated the strength of global functional connectivity to 10Hz. In addition, 10Hz-tACS enhanced the 40Hz auditory steady-state response (ASSR, $F$6,57 =4.20, $p$=0.001), which is impaired in patients with schizophrenia.
Importantly, clinical improvement of auditory hallucinations correlated with enhancement of alpha oscillations and the 40Hz-ASSR. Together, our findings suggest that tACS has potential as a network-level approach to modulate impaired neural oscillations related to clinical symptoms in patients with schizophrenia.
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**Poster**

**734. Oscillations and Synchrony: LFP Studies II**

**Location:** SDCC Halls B-H

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**Title:** Pilot double-blind, placebo-controlled clinical trial of transcranial alternating current stimulation (tacs) for the treatment of major depressive disorder (mdd)

**Authors: *M. L. ALEXANDER**[1,2], S. ALAGAPAN[1,2], C. E. LUGO[1], J. M. MELLIN[1,2], C. M. LUSTENBERGER[1], D. R. RUBINOW[1], F. FROHLICH[1,2,3,4,5]
[1]Psychiatry, [2]Carolina Ctr. for Neurostimulation, [3]Neurol., [4]Cell Biol. and Physiol., [5]Neurosci. Ctr., Univ. of North Carolina, Chapel Hill, NC

**Abstract:** Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders, but existing pharmacological treatments are non-specific and associated with poor remission rates and undesirable side effects. Safer, more effective, targeted treatments are urgently needed. Here, we evaluated the efficacy and feasibility of transcranial alternating current stimulation (tACS), which we hypothesized would improve clinical symptoms by reducing alpha oscillations in the left frontal regions. (NCT02339285)25 participants were randomized to one of three arms (10Hz-tACS, 40Hz-tACS, or active sham stimulation) and received daily 40 minute sessions over five consecutive days. We measured change in clinical symptoms using the Montgomery-Åsberg Depression Rating Scale (MADRS) as the primary outcome, and change in alpha oscillations as measured by high-density electroencephalography (hdEEG) as the secondary outcome. Exploratory analyses were performed on the Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI), and Montreal Cognitive Assessment (MoCA).Although there was no significant interaction between treatment condition (10Hz-tACS, 40Hz-tACS, sham) and session (baseline to four weeks after completion of treatment), exploratory analyses showed significance at 2 weeks following completion of treatment, with more participants in the 10Hz-tACS group responding to treatment as measured by the MADRS and HDRS in comparison to the 40Hz-tACS and sham groups. Furthermore, we found a significant reduction in alpha power over the left frontal regions in EEG after completion of the intervention for only the group that received 10Hz-tACS. Importantly, the treatment was safe and feasible, with the majority of patients completing all sessions and no adverse events, mania, or hypomania during the course of the study.To our knowledge, this is the first clinical trial of tACS for the treatment of MDD. Additional studies with larger sample sizes are needed to better understand the effect of tACS on depression.

**Disclosures: M.L. Alexander:** A. Employment/Salary (full or part-time):; University of North Carolina. **S. Alagapan:** A. Employment/Salary (full or part-time):; University of North Carolina. **C.E. Lugo:** A. Employment/Salary (full or part-time):; University of North Carolina. **J.M. Mellin:** A. Employment/Salary (full or part-time):; University of North Carolina. **C.M. Lustenberger:** A. Employment/Salary (full or part-time):; University of North Carolina. **D.R. Rubinow:** A. Employment/Salary (full or part-time):; University of North Carolina. **F. Frohlich:** A. Employment/Salary (full or part-time):; University of North Carolina. E. Ownership Interest

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**Poster**

**734. Oscillations and Synchrony: LFP Studies II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 734.09/E17

**Topic:** B.09. Network Interactions

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**Title:** Higher-order visual thalamus orchestrates cortico-cortical synchronization during sustained attention

**Authors: *W. A. HUANG**[1,2], S. RADTKE-SCHULLER[1], Z. C. ZHOU[1,2], F. FROHLICH[1,2,3,4,5]
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**Abstract:** Sustained attention, the continuous allocation of processing resources to respond to infrequent but behaviorally relevant stimuli[1], is impaired in many psychiatric disorders and represents an important aspect of cognitive control[2]. Sustained attention requires engagement with the external world and is modulated by thalamo-cortical rhythms[3]. Despite the extensive behavioral characterization of sustained attention, very little is known about the underlying thalamo-cortical oscillations and their potential role as a stimulation target for enhancing sustained attention. Here, we studied this question by simultaneous recording from three reciprocally connected nodes in the thalamo-cortical visual circuit: pulvinar complex (lateral aspect of lateral posterior nucleus, LPl) - posterior parietal cortex (PPC) - primary visual cortex (V1) circuit, in ferrets (*Mustela putorius furo*). To probe visual sustained attention, we employed a widely used paradigm: the five-choice serial reaction time task (5-CSRTT)[4], in ferrets, as ferrets have a relatively well-developed higher-order visual thalamus. In this task, animals need to pay attention to a computer screen during a delay period with random length until a visual stimulus is presented, which the animal touches for reward. We found that (1) theta-band (4-8 Hz) functional connectivity (eg. coherence) between LPl, PPC and V1 dominates and increases during the delay period before the animal touched the correct stimulus location, (2) this functional connectivity is directed from LPl to PPC and V1, and (3) the LPl theta phase couples to the local gamma amplitude (40-80 Hz) and PPC/V1 gamma coherence (30-60 Hz). As a whole, our study determines the role of thalamic theta in coordinating cortical functional connectivity of the LPl-PPC-V1 during sustained attention and provides targets for subsequent

optogenetic circuit interrogation. Our work will ultimately provide a circuit-level mechanistic explanation on how a higher-order visual thalamic structure modulates cortical communication, and may represent a fundamental link between neural network activity and behavior.

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**Poster**

**734. Oscillations and Synchrony: LFP Studies II**

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**Topic:** B.09. Network Interactions

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**Title:** Pilot double-blind, placebo-controlled clinical trial of the effect of transcranial alternating current stimulation (tacs) on the stress-immune response

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**Abstract:** Stress is evolutionarily important to survival; however, high levels can lead to adverse health outcomes. Stress responses are characterized by the activation of two pathways: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic division of the autonomic nervous system (SNS). These pathways are regulated via a top-down mechanism, where reflexes in the brain produce physiological changes elsewhere in the body. Additionally, immune activity is closely related to stress, with cytokine markers reacting to SNS activation and entering a negative feedback loop with the HPA axis. This research sought to target the top-down mechanism of the stress pathways using 10Hz bifrontal Transcranial Alternating Current Stimulation (tACS) (NCT03178344).

20 participants underwent 40 minutes of tACS or an active sham condition at two separate sessions in a double-blind, randomized, crossover study design. Saliva samples were collected before and after stimulation to test for alpha amylase (indicator of SNS), cortisol (indicator of HPA axis), and a cytokine panel (indicator of immune functioning) as the primary outcomes, and change in alpha oscillations was measured by high-density electroencephalography (hdEEG) as the secondary outcome. Exploratory analyses were performed using the State-Trait Anxiety Inventory (STAI), Perceived Stress Scale (PSS), Connor-Davidson Resilience Scale (CDRISC), and the Behavioral Inhibition and Activation Scales (BIS/BAS).

Results demonstrated an effect of stimulation in reducing alpha amylase activity as well as two markers of the cytokine panel, indicating a decreased stress and immune response in the verum stimulation condition. Furthermore, exploratory analyses indicated a positive relationship between interleukin 1-beta and scores on the PSS, and a similar inverse relationship between the same cytokine marker and scores on the CDRISC, suggesting a mediating effect of resilience on responses to tACS. Finally, there were no adverse events or negative effects of verum stimulation on any of the markers, supporting other evidence of tACS as a safe and effective method for use in human populations.

This research adds to the understanding of the physiological effects of tACS, as well as provides a basis for tACS as a possible treatment for individuals with chronic stress and anxiety. To our knowledge, this is the first clinical trial exploring the effect of tACS on the stress-immune response. Additional studies involving larger sample sizes and clinical populations are needed to further expand on these findings.

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**Poster**

**734. Oscillations and Synchrony: LFP Studies II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 734.11/E19

**Topic:** B.09. Network Interactions

**Support:** NIH Grant R01MH111889
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**Title:** Optically-resolved posterior parietal cortex neural populations show NMDA receptor-dependent visual deviance detection

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**Abstract:** Disorders such as schizophrenia and attention deficit hyperactivity disorder (ADHD) are characterized by impairments in context-dependent sensory processing (i.e., the inability to distinguish between frequent and rare stimuli) [1]. Such sensory processing impairment may arise from the lack of cognitive control from higher-order brain areas, for example, the parietal cortex which is involved in both sensory processing and stimulus history [2,3]. However, little is known about how single neuron activity gives rise to population dynamics that distinguishes if a stimulus has been present frequently or infrequently. In human electroencephalography (EEG) studies, the sensory response amplitude is modulated by the frequency of stimulus presentation, a phenomenon that is termed deviance detection (DD). To address this gap in knowledge, we recorded 2-photon calcium activity in parietal cortex of the head-fixed ferret during a visual oddball paradigm. We hypothesized that a distinct subnetwork of neurons shows DD which is impaired by blocking NMDA receptors with MK801. During the recordings, we presented to the animals drifting grating stimuli with differing motion directions. In each recording block, one stimulus was presented frequently (standard - 90% occurrence) and the other infrequently (deviant - 10%). We found that a DD effect arose from neurons that showed enhanced activity in the deviant context at trend level (2-way ANOVA; saline: 51/322 neurons, $F(2, 341) = 2.82$, $p = 0.06$); in MK801 sessions, the DD diminished (34/124 neurons, $F(2, 203) = 1.03$, $p = 0.36$). Ninety neurons were found to enhance activity to the standard context, and 57 enhanced to the deviant context. Interestingly, there was heavy overlap of these neurons that enhanced to both contexts (44 neurons); further we found that these neurons contributed the most to the DD effect. Importantly, these results suggest that the parietal cortex differentiates oddball context, and that the mechanism of such context distinction relies on NMDA-receptor function of specific subpopulations. With these findings, we hope to ultimately gain a mechanistic understanding of context-dependent cognitive deficits by bridging the gap between single neurons and population-

level dynamics. 1) Lee M, et al. Neural mechanisms of mismatch negativity dysfunction in schizophrenia. Mol Psychiatry. 2017 Nov;22 2) Kremláček J, et al. Visual mismatch negativity in the dorsal stream is independent of concurrent visual task difficulty. Front Hum Neurosci. 2013 Jul 30 3) Akrami A, et al. Posterior parietal cortex represents sensory history and mediates its effects on behaviour. Nature. 2018 Feb 15

**Disclosures: Z.C. Zhou:** None. **Y. Yu:** None. **Y. Li:** None. **F. Frohlich:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PulvinarNeuro, Elsevier. F. Consulting Fees (e.g., advisory boards); PulvinarNeuro, Tal Medical.

**Poster**

**734. Oscillations and Synchrony: LFP Studies II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 734.12/E20

**Topic:** B.09. Network Interactions

**Support:** MH107239
MH112505

**Title:** Bidirectional closed-loop optogenetic control of gamma oscillations reveals their role in memory consolidation

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**Abstract:** Gamma oscillations are local field potential (LFP) fluctuations between 30-100 Hz that occur throughout the brain. They are thought to coordinate neuronal interactions not only locally, but also between regions. Testing the role of gamma oscillations had so far not been possible because previously available techniques did not allow for up- or down-regulation of gamma without substantial off-target effects. Here, we introduce a novel approach for detecting and modulating spontaneous gamma oscillations. Specifically, we achieved real-time control over these oscillations by combining optogenetics with programmable multi-channel signal processors, known as “field programmable gate arrays” (FPGAs). Unlike computers, FPGAs allow nearly instantaneous signal analysis and conditional light stimulus delivery, providing unprecedented control over fast neuronal events like gamma. This method has allowed us to track gamma burst cycles with millisecond accuracy and deliver optogenetic stimuli with both frequency and phase specificity. As a test-bed for our method, we examined whether gamma oscillations in the basolateral amygdala (BLA) mediate the facilitation of memory consolidation by emotions. It was previously shown that manipulations which increase or decrease BLA

activity after training respectively enhance or impair subsequent memory recall. Moreover, it was reported that emotionally arousing stimuli elicit prominent gamma oscillations in the BLA. We first tested whether gamma oscillations were present during the consolidation of emotional memories in Long Evans rats implanted with electrodes in the BLA. We found that the power of mid-gamma oscillations (40-70 Hz) is increased in the BLA immediately after training on aversive and appetitive spatial memory tasks, and that this increase correlates with subsequent memory strength. Next, we used our closed-loop gamma detection algorithm to deliver 2 ms light pulses either in-phase (trough) or out-of-phase (peak) with ongoing gamma. These tests were carried out in subjects that had received AAV infusions in the BLA, driving the expression of the excitatory opsin Chronos. By timing light pulses to particular oscillatory phases, we could boost or diminish oscillations, specifically in mid-gamma. When these manipulations were carried out immediately after training in a spatial task, subsequent memory strength was respectively enhanced or impaired. This study introduces a novel closed-loop optogenetic method to modulate fast oscillatory rhythms in real time. Importantly, our results directly link gamma oscillations in the BLA with the emotional modulation of memory consolidation.

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**Poster**

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**Topic:** B.09. Network Interactions

**Support:** NIMH R01MH087755

**Title:** Gamma oscillations in the basolateral amygdala - A computational perspective

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**Abstract:** The basolateral nucleus of the amygdala (BL) supports a plethora of psychological processes, from emotional behaviors to memory consolidation. Recent experimental work in the lab of our collaborator has successfully developed a closed-loop real-time optogenetic control system that reliably detects and modulates gamma-oscillatory bursts in the BL with frequency and phase specificity (Kanta et al., 2017), and more importantly, that this modulation affects memory consolidation.
However, how gamma modulation affects the functioning of specific neuronal microcircuits in BL is not clear. In this study, we investigate this using a large scale biophysical computational

model of the BL. We first replicate several features of gamma oscillations seen in *in vivo* local field potential recordings from BL (Amir et al., 2018), including their spectral composition, entrainment of unit activity and spatial heterogeneity. Our network model also produces gamma as transient, several cycle long bursts, mimicking the fine structure of gamma rhythmogenesis seen *in vivo*. We then add expression of channelrhodopsin in selected neuron subpopulations, with the aim of seeking a deeper understanding of the mechanisms of optogenetic control on gamma oscillations in BL. The model is used to study various aspects of the control of oscillations including specificity, optimal conditions, and limitations.

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**Poster**

**734. Oscillations and Synchrony: LFP Studies II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 734.14/E22

**Topic:** B.09. Network Interactions

**Title:** Artificial neural networks for prediction of the local field potential

**Authors: *B. LATIMER**[1], Z. CHEN[1], T. BANKS[1], D. HO[1], V. KANTA CHANTZI[2], D. B. HEADLEY[3], D. PARE[4], S. S. NAIR[1]
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**Abstract:** Predicting the future of a time series given past measurements is an open problem in machine learning. This is applicable to neuroscience when one wants to use statistical models to predict upcoming patterns in the local field potential (LFP) or electroencephalogram (EEG). With these models, experimenters can create closed loop control systems that provide more accurate feedback to the brain via optogenetic or transcranial magnetic stimulation. In this study, we trained different statistical models to use past values in the LFP to predict its future state. In particular, we are interested in predicting the occurrence of bursts of gamma-band activity (64-84 Hz), and the time domain values of the LFP out to 10 ms in the future. To accomplish this task, we examined the performance of four different models: autoregressive linear prediction (AR), feed forward artificial neural networks (ANN), convolutional neural networks (CNN), and recurrent neural networks (RNN). Preliminary results show that the AR model does not perform significantly better than chance in predicting gamma bursts, suggesting nonlinear dependency in the data. Averaging the raw LFP data for 50 ms prior to the burst (similar to a spike triggered average) did, however, show an interesting trend of higher mean voltage level ending with a rising slope. ANN prediction of the gamma-band filtered signal 10 ms ahead in time has an

accuracy approaching 70% on testing data, with accuracy improving to 85% with the addition of a low-pass filtered version and the raw LFP signal. We are presently exploring Long Short Term Memory (LSTM), and evolutionary learning algorithm approaches to enhance accuracy. One of our goals is to implement the best performing algorithm in a field programmable gate array (FPGA) to enhance the prediction of gamma bursts in real-time.

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**Poster**

**734. Oscillations and Synchrony: LFP Studies II**

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**Topic:** B.09. Network Interactions

**Support:** NIMH R01 grant MH107239
NIMH R01 grant MH112505

**Title:** Gamma oscillations in the basolateral amygdala: Regional specialization, microcircuit mechanisms, and behavioral correlates

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**Abstract:** The basolateral amygdala (BLA) is a cortical-like structure that mediates a variety of emotional behaviors. Like cortex, it generates gamma oscillations, which are local field potential (LFP) fluctuations at 30-100 Hz. In the BLA, gamma oscillations are most prominent in conditions of emotional arousal, when they coordinate the activity of fast-spiking interneurons and pyramidal cells, similarly to what has been reported in cortex. However, many properties of gamma oscillations in the BLA remain unclear. For instance, we do not know if they are similarly expressed in the basolateral (BL) and lateral (LA) nuclei, whether they coordinate local microcircuits similarly across nuclei, and if they are differentially recruited by positively or negatively valenced events. The present study explores these questions. Long Evans rats were implanted with silicon probes in the BLA to record LFPs and unit activity. They were then trained to respond to a light CS that depending on its position signaled either reward availability or an impending footshock. The footshock could be avoided passively or actively, depending on the rats' position in relation to the CS. During the inter-trial interval, spontaneous gamma oscillations were only observed in the BL nucleus (mid-gamma, ~55 Hz). Moreover, principal and fast-spiking cells in BL had substantially higher entrainment to gamma compared with those in LA. Further analyses revealed that this disparity was associated with differences in the

prevalence of fast-spiking cells and in their connectivity with principal neurons. Compared to LA, BL had a higher proportion of fast-spiking interneurons, paralleling the higher incidence of parvalbumin expressing cells in BL than LA. We also found that BL had a higher probability of connections between principal cells and fast-spiking interneurons, a connection known to be crucial for gamma genesis. During task events, mid-gamma power increased in BL and LA, particularly at the onset of the conditioned stimuli and active behaviors, such as active avoidance and reward approach. Moreover, gamma power gradually ramped up during behavioral freezing, until the rat either avoided or was shocked. Together, these results suggest that gamma oscillations are differentially expressed in BL and LA, likely because of differences in their intrinsic connectivity. Moreover, our findings indicate that gamma oscillations are similarly engaged during positively and negatively valenced stimuli or behaviors, suggesting that they act as a general mechanism for coordinating ensemble activity. This material is based upon work supported by NIMH R01 grants MH107239 and MH112505 to Denis Paré.

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**Poster**

**735. Network Interactions**

**Location:** SDCC Halls B-H

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**Topic:** B.09. Network Interactions

**Support:** KAKENHI 16K13017

**Title:** Identification of functional brain networks recruited by acute treadmill running at different intensities

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**Abstract:** Accumulating evidence suggested that physical exercise improves various brain function, including memory and learning, emotion and cognitive/executive functions. The multiple effects of exercise on the brain function may be due to interaction of neural activation of multiple brain regions stimulated by exercise. Furthermore, previous studies have suggested that the beneficial effects of exercise on brain functions are different depending on intensity of the exercise. Thus, it is possible that physical exercise forms exercise-specific functional brain network, which is defined by co-activation of multiple brain regions, and that the functional brain network recruited by exercise may depend on intensity of the exercise. However, the functional brain networks underlying the beneficial effects of exercise remain unclear. In the present study, we tried to identify the functional brain network recruited by acute treadmill

running at different intensities (30 min; high speed, 25 m/min; low speed, 15 m/min; control, 0 m/min) in male Wistar rats, using c-Fos immunohistochemistry and correlation analysis. We selected 23 brain regions as ROI, including cortex, limbic system, hypothalamus, and brainstem, which are regions associated with mental or motor functions. We mapped functional brain network recruited by each physical exercise, using correlation analysis to the inter-regional c-Fos expression data obtained after each exercise condition. Furthermore, we characterized properties of the functional brain networks, using graph theoretical analysis. Acute treadmill running increased c-Fos expression of motor cortex, sensory cortex, amygdala and hippocampus, regardless of exercise intensity. On other hand, high speed group showed significantly more c-Fos-positive cells in medial prefrontal cortex, the hypothalamic paraventricular nucleus, nucleus accumbens, caudate putamen and the locus ceruleus nucleus, compared to control group. Low speed group showed significantly more c-Fos-positive cells in the dorsal raphe nucleus and cingulate cortex, compared to control group. These results suggests that the effects of exercise on brain functions are different depending on intensity of the exercise. Furthermore, the functional brain network in low speed group had more connection expressing inter-regional negative correlation than that in control group, whereas the functional brain network in high speed had no connection expressing inter-regional negative correlation. These results suggest that acute physical exercise at different intensities could form intensity-specific functional brain networks.

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**Poster**

**735. Network Interactions**

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**Topic:** B.09. Network Interactions

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**Title:** Critical dynamics in resting state oscillatory brain activity is associated with dopamine-related polymorphism

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**Abstract:** Human resting state (rs) brain activity is characterized by temporal fluctuations across variety of timescales. In the sub-second timescales, activity is characterized by neuronal

oscillations in many frequencies. In timescales of seconds to tens of minutes, scale-free fluctuations and power-law long-range temporal correlations (LRTCs) characterize the amplitude envelopes of neuronal oscillations. Scale-free dynamics and LRTCs are suggestive of critical neuronal dynamics, which endows the brains with an optimal information processing capacity. LRTCs in neuronal activity have high inter-individual variability. Twin studies have indicated a strong genetic inheritance of this variability. Cortical signal variability affects both neuronal oscillations and scale-free fluctuations. These result of changes in neuronal firing patterns which in turn are affected by dopaminergic (DA) neurotransmission. We investigated whether scale-free dynamics as evidenced by LTRCs in oscillation amplitude envelopes could be modulated by DA transmission. DA is regulated by the Catechol-O-methyltransferase (COMT, rs4680). The greatest variance in COMT activity is explained by a single nucleotide polymorphism (Val/Met) at codon 158. Val/Met substitution results in reduction in enzyme activity and higher cortical DA-levels. We hypothesized that COMT polymorphism and DA-levels could influence LRTCs and brain critical dynamics in rs oscillatory activity. We recorded rs magnetoencephalography (MEG) data from 83 healthy volunteers (18-55 years of age; 6 left-handed; 44 female), genotyped using Infinium PsychArray-24 v1.1 (Illumina). The sample consisted of 18 Val/Val, 49 Val/Met, and 16 Met/Met carriers. We estimated oscillation amplitude envelopes between 3-120 Hz for cortically source-reconstructed MEG data and used detrended fluctuation analysis (DFA) to quantify the LRTCs. The genotypes differed in brain dynamics in gamma (30-60 Hz) band. Compared to Met/Met and Val/Val homozygotes, Val/Met heterozygotes exhibited greater scaling exponents, especially in the frontal, insular, limbic, parietal and temporal regions. These genotype differences in LRTC scaling exponents were not explained by the amplitude of the gamma oscillations. As the Val allele is associated with less synaptic dopamine compared to Met allele, our data suggest that intermediate brain DA-levels are associated with the strongest LRTCs in rs oscillatory activity.

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**Poster**

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**Topic:** B.09. Network Interactions

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**Title:** Excitation/inhibition balance in the aMCC influences resting state activity in the CEN

**Authors: *L. V. DANYELI**[1,2,3,4], L. COLIC[1,3], D. DENZEL[6,3], F. VON DÜRING[3], L. R. DEMENESCU[3], M. LI[3,6], M. WALTER[1,2,3,6,5]
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**Abstract:** *Background:* Excitation/inhibition balance can be used as a predictor not only for the functional regional response in the task-based functional magnetic resonance imaging (fMRI) but also for functional connectivity (FC) strength measured within and between networks. Previous studies reported that both Glutamate (Glu) and γ-Aminobutyric acid (GABA) levels can predict within network connectivity patterns. However, the results were inconsistent and they were mainly focused on the default mode network confirming that there is a need for more robust and extensive measurements. Therefore, we investigated whole brain associations between the main excitatory - Glu - and inhibitory neurotransmitter - GABA - with the FC of the anterior mid cingulate cortex (aMCC), a node of the salience network (SN), with a particular focus on regions of the central executive network (CEN). We additionally explored how these metabolites influence basic neuronal measurements such as fractional amplitude of low frequency fluctuation (fALFF).
*Methods*: 78 healthy subjects (39 females, age = 26.97 ± 6.53) completed a research paradigm that included a resting-state fMRI and a magnetic resonance spectroscopy (MRS) session in 7T. An MRS voxel was placed in the aMCC, and Glu, GABA and Creatine (Cr) levels were acquired using a stimulated-echo acquisition mode (STEAM) sequence. A regression analysis was conducted in SPM8 between metabolites and aMCC voxel-seed FC maps with age, sex and grey matter ratio as covariates of nuisance. Additionally, the same regression analysis was performed for fALFF. Results are reported on FWE < 0.05 cluster level significance with an initial threshold of $p < 0.001$, uncorrected.
*Results*: Glu/Cr and aMCC voxel FC showed a strong negative association in the left posterior frontal gyrus and several nodes of the visual cortex. A regionally converging positive correlation was found between fALFF and GABA/Cr in the left posterior frontal gyrus.
*Conclusion*: Both GABA and Glu levels measured in the aMCC predict the strength and the basal activity of the posterior frontal gyrus, which is a node of the CEN.

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**Poster**

**735. Network Interactions**

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**Topic:** B.09. Network Interactions

**Support:** NSERC Grant 435843

**Title:** Role of the parafacial respiratory group in the recruitment of abdominal expiratory activity during sleep

**Authors: *A. PISANSKI (HERNANDEZ ABAD)**[1], N. KOCH[2], X. DING[1], S. PAGLIARDINI[2]
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**Abstract:** In resting conditions, breathing is typically characterized by an active inspiratory phase and a passive expiratory phase. Expiration may become active through abdominal (ABD) muscle recruitment during periods of increased inspiratory requirements. This respiratory rhythm is thought to be controlled by three coupled oscillators in the ventral medulla: preBötzinger complex (preBötC) for generating inspiration, the parafacial respiratory group (pFRG) for generating active expiration, and the post-inspiratory complex (PiCo) which is thought to control the post-inspiratory phase. Although there exists abundant evidence linking preBötC activity to the generation of respiratory rhythm, research addressing the role of pFRG in ventilation and rhythm generation across sleep states is limited. Recent work in our laboratory reports the occurrence of ABD recruitment during REM sleep, despite the induction of muscle paralysis during this sleep state. This ABD recruitment was associated with a stabilization of breathing in healthy rats. Because pFRG generates active expiration through the engagement of ABD muscles, we hypothesize that the expiratory oscillator is also responsible for the ABD recruitment observed during REM sleep in healthy rats. To test this hypothesis, we inhibited and activated the pFRG oscillator using a chemogenetic approach (DREADDs) while simultaneously recording EEG, airflow, ABD and neck EMG of transfected rats across sleep/wake cycles. Our results suggest that manipulation of pFRG activity influences expiratory ABD recruitment events during REM sleep. Inhibition of pFRG significantly reduced the number of REM events with ABD recruitment, whereas activation of this oscillator resulted in an increase of the number of REM events in which ABD recruitment was observed. Interestingly, modulation of pFRG activity did not seem to affect ABD recruitment during NREM sleep. These results suggest that ABD recruitment may occur through different mechanisms across states.

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**Title:** Phase-specific effects of alpha tACS on functional resting-state connectivity in the motor network

**Authors: *K. F. HEISE**, E. BOKKEN, B. KING, G. ALBOUY, D. MANTINI, S. P. SWINNEN
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**Abstract: Background:** Transcranial alternating current stimulation (tACS) has been shown to modulate endogenous neural rhythms in a frequency-specific way. Our aim is to investigate whether tACS induced modulation of resting-state (RS) connectivity. To do so, tACS was applied bilaterally centred over primary motor cortex in combination with functional magnetic resonance imaging acquisitions. Our analyses specifically focused on the effect of stimulation phase on RS connectivity of the Motor Network (MN) and Default Mode Network (DMN). **Material & Methods:** 12 young (range 20-28 years of age, 4 females) healthy volunteers were tested in a double-blind cross-over design. Peri-rolandic individual alpha frequency was derived from resting-state EEG prior to MRI scanning. TACS was applied using a high-density electrode montage to homologues primary motor cortices with either 0° phase lag, 180° phase lag, or sham stimulation (order counterbalanced across subjects) during task-free MRI (eyes open). Two RS functional sequences of 5 minutes (baseline without, 2$^{nd}$ with tACS) were acquired in each session using multiband factor imaging method (TR= 1000 ms; TE= 33 ms). fMRI data was co-registered to the high-resolution T1-weighted image. 20 seeds for regions of interest (ROI) were chosen to define MN and DMN. Connectivity analysis was performed on the z-transformed correlation coefficients of each ROI pair. Baseline normalized z-scores for connectivity measures were subjected to separate linear mixed effects (LME) models for each ROI pair within subject contrasting stimulation conditions (0°, 180°, sham) modelled as fixed effect. **Results:** LME results revealed that relative changes in RS connectivity (stimulation - baseline) were significantly different for 180° phase lag compared to sham condition ($p<.01$) and for 180° phase lag compared to 0° phase lag ($p<.01$), but not for the contrast of 0° and sham. Specifically, our results show a strong relative within hemisphere increase and between hemisphere decrease in connectivity of primary motor, premotor, and somatosensory cortices but an increase in

connectivity within regions of the DMN for 180° phase lag compared to sham. Comparison of 180° to 0° phase lag condition showed a relative intrahemispheric increase in MN connectivity and a decrease in connectivity within the DMN within and between hemispheres for 180° phase lag (p-corrected <.05). **Discussion:** Our results reveal a phase-specific modulation of connectivity within the MN, in particular primary motor, somatosensory, and premotor cortices but which is also extending beyond the site of stimulation as it also affects distant connectivity patterns in the DMN.

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**Poster**

**735. Network Interactions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 735.06/E29

**Topic:** B.09. Network Interactions

**Support:** NIH Grant MH60163

**Title:** Characterization of excitatory and inhibitory neuron activity during up states *in vitro*: Up states are resilient to optical activation of PV neurons

**Authors: *D. V. BUONOMANO**[1], J. L. ROMERO-SOSA[2], H. MOTANIS[3]
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**Abstract:** Many computations the brain performs emerge from the neural dynamics of local cortical circuits. The dynamics in these circuits are governed in part by the interaction between recurrently connected excitatory and inhibitory neurons. An example of neural dynamics that emerges from local circuits are Up states—which reflect network-wide patterns of activity. Here we examine the role of inhibition and resilience of Up states in cortical organotypic slices.Simultaneous recordings from pyramidal (Pyr) neurons and parvalbumin-positive (PV) neurons, revealed that PV neurons exhibited an intrinsic excitability profile marked by a low spike adaptation index (AI=0.01±0.01) compared to pyramidal neurons (AI=0.122±0.015), and that during Up states the firing rate of PV neurons was higher than Pyr (18±2.5 Hz) vs (7±2.2 Hz). Interestingly, $Ca^{2+}$-imaging revealed no difference in mean activity which may reflect differences in $Ca^{2+}$ buffering. Of 30 paired recordings, 12 exhibited detectable Pyr→PV connections, 8 pairs had PV→Pyr connections, and 7 pairs were reciprocally connected—thus reciprocity was present at higher than chance levels. The correlation between Pyr and PV activity during Up states was higher in reciprocally connected pairs (0.67±0.01 vs 0.82±0.008, $p<10^{-10}$). Paradoxically we observed that, on average, PV neurons fired before the Pyr neurons by

16.9±5.71ms—indicating that events driving Up states may initially preferentially activate PV neurons, or that PV neurons respond significantly quicker to these triggering events.Experimental and theoretical studies suggest that local neural circuits may store information in locally stable patterns of neural activity—i.e., neural trajectories. Critical to this hypothesis is the notion that these trajectories are robust to perturbations. We performed perturbation experiments in which PV neurons were optically activated after the initiation of spontaneous Up states. While brief optical activation of PV neurons decreased intracellularly evoked spikes, it did not change the mean duration of Up states (1.91±0.17 vs 1.99±0.19 sec).These results establish that Up states are robust to perturbations produced by broad light activation of PV neurons, and that local connectivity shapes neural dynamics—as evidenced by the increased correlation between reciprocally connected neurons. Furthermore, the presence of Up state *in vitro* reveals that the learning rules that lead to these dynamic regimes are intact, thus providing an opportunity to study how Up states emerge from local cortical circuits.

**Disclosures: D.V. Buonomano:** None. **J.L. Romero-Sosa:** None. **H. Motanis:** None.

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**Topic:** B.09. Network Interactions

**Title:** Quantification of spine density in the rat default mode network

**Authors: *S. DAVANGER**[1], L.-M. VALENCIA-PESQUEIRA[2], R. HOLST[3]
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**Abstract:** The default mode network (DMN) underlies important aspects of mental function, such as self-generated thoughts and mind wandering. These thoughts have autobiographical and social-oriented content and are important for future planning and adapting to a changing environment. In humans, the posterior and the anterior cingulate cortices are included in a set of central hubs, receiving and integrating information from other DMN areas. In rat brain, the cingulate cortex is a key DMN area. Due to the complex nature of processing and predicting events in a continuously changing social environment, we hypothesized that high computational demands on the DMN hubs are reflected in a high synaptic density. We investigated dendritic spine density of layer V cortical pyramidal neurons in 5 female rats, after Golgi staining. Imaging was performed with a Leica Microscope and Application Suite X. Images were subjected to deconvolution. Imaris software was used to produce 3D reconstructions from Z-stacks and to quantify spine density along basal dendrites. 14 cortical areas were selected for analysis and classified as belonging to the DMN, lateral cortical network (LCN; a task-positive network), or primary cortex. The cingulate cortex had the highest spine density of the 14 areas, at

1.64 spines/µm (SD: 0.55, 95% CI: 1.38 - 1.90), while primary sensory cortex (S1) and the jaw region of the primary sensory cortex (S1J) had the lowest, at 1.05 spines/µm (SD: 0.43, 95% CI: 0.83 - 1.27) and 1.03 spines/µm (SD: 0.21, 95% CI: 0.92 - 1.14), respectively. Two mixed models were estimated. The first consisted of a comparison between the cingulate cortex and all other regions. This approach showed that the spine density levels are significantly higher in the cingulate cortex with $p < 0.0005$. The second model split the non-cingulate class into three groups: the DMN, LCN and primary cortices. This model showed higher levels of the cingulate cortex spine density compared to the three groups, with $p < 0.0005$. Thus, the cingulate cortex of the DMN has the highest spine density of the rat cerebral cortex. Investigations of DMN synapses in rat brain may complement fMRI studies of functional connectivity in humans, demonstrating the neuroanatomical basis for complex neuropsychological processes.

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**Poster**

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**Topic:** B.09. Network Interactions

**Support:** NWO Veni grant 451-12-021
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**Title:** EEG power predicts laminar specific fMRI connectivity

**Authors: *R. SCHEERINGA**[1,2], P. KOOPMANS[3], T. VAN MOURIK[1], O. JENSEN[4], D. G. NORRIS[5], M. BONNEFOND[2]
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**Abstract:** In general, feedforward anatomical connections between brain regions originate in supragranular layers of lower order regions and project to layer IV while feedback projections originate deep layers and project to both deep and superficial layers of the lower order regions. LFP recordings have related these feedforward and feedback projections to gamma and alpha-beta band synchronization respectively. With the development of high resolution fMRI we can now measure laminar level neural activity non-invasively in humans. In a recent study we related laminar fMRI activity in V1, V2 and V3 to simultaneously recorded EEG power in the alpha, beta and gamma bands. For this we used a visual attention task in which subjects had to respond to a speed increase in inward contracting gratings. A cue indicated whether a speed increase was

likely to occur, or would not occur (attention contrast). In line with invasive electrophysiology we observed that EEG gamma band power correlated positively to middle and superior cortical layers, beta power correlated negatively with deep layers while alpha power correlated negatively with BOLD in all layers. Here we reanalyze this data and explore whether fMRI based laminar specific connectivity between lower (V1/V2) and higher order (V2/V3) regions is related to frequency specific power effects. For this we first estimated the single trial BOLD amplitudes. For both 'attention on' and 'attention off' conditions we calculated laminar connectivity between all regions and layers but observed no laminar specific differences related to attention. If we, however, correlate this attention effect over subjects with attention effects in EEG power we do find laminar specificity. Gamma power correlated with connectivity strength of lower order superficial layers with all higher order layers, but especially with superficial-superficial layer connectivity. For beta we observe a negative correlation between EEG power and connectivity of higher order deep layers and all layers in the lower order region. This correlation is substantially stronger for the deep layers. This suggests gamma synchronization relates to the neural response of the entire cortical column to bottom-up input, while beta relates to how it responds to top-down input.

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**Poster**

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**Topic:** B.09. Network Interactions

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**Title:** The role of NMDA conductance in average firing rate shifts caused by external periodic forcing: A computational study

**Authors: *N. NOVIKOV**[1], B. GUTKIN[2]
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**Abstract:** Many processes occurring in the brain involve prolonged modulation of neural firing rates. The examples are working memory retention [1], motor planning [2], or sustained attention [3]. Alongside with the firing rates, neural oscillations are usually modulated. In many cases, there is a theoretical understanding of mechanisms via which the level of neural activity affects the oscillations [4]. At the same time, the effects of oscillations on the mean firing rates are less explored. However, investigation of these effects is important for understanding the functional

role of oscillations in controlling excitability of cortical regions and stability of neural representations.In the present work, we theoretically investigated the role that slow voltage-dependent NMDA currents could play in shifting the mean firing rates of an excitatory-inhibitory system in the presence of external zero-mean harmonic forcing. We analyzed a low-dimensional system with linearized neural gain functions, and non-linear NMDA conductance.
First, we provided analytical expressions that link parameters of the model with the forcing-induced shift in the average firing rates. Next, we considered a model with NMDA receptors located on the excitatory neurons only (Model 1) or both on the excitatory and the inhibitory neurons (Model 2). For both models, we used our analytical results to find the initial and the shifted (by the external forcing) time-averaged steady-states on the phase plane. We geometrically demonstrated that the excitatory firing rate shift is strongly limited by stability conditions in the Model 1, while in the Model 2 it is possible to overcome these limitations. Predictions of our phase-plane analyses were confirmed by direct numerical simulations of the corresponding models. Finally, we performed bifurcation analysis, and demonstrated that there is an optimal combination of excitatory-to-inhibitory AMPA and NMDA weights that result in the strongest possible shift of the excitatory firing rate without loss of stability.
1. Funahashi, S. (2017). Working Memory in the Prefrontal Cortex. Brain Sci, 7(5), 49. 2. De Lafuente, V., Jazayeri, M., & Shadlen, M. N. (2015). Representation of Accumulating Evidence for a Decision in Two Parietal Areas. J Neurosci, 35(10), 4306-4318. 3. Busse, L., Katzner, S., & Treue, S. (2008). Temporal dynamics of neuronal modulation during exogenous and endogenous shifts of visual attention in macaque area MT. PNAS, 105(42), 16380-16385. 4. Buzsáki, G., & Wang, X.-J. (2012). Mechanisms of Gamma Oscillations. Annual Review of Neuroscience, 35, 203-225.

**Disclosures: N. Novikov:** None. **B. Gutkin:** None.

**Poster**

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**Topic:** B.09. Network Interactions

**Support:** Early Postdoc.Mobility
NIH Supplemental visiting fellow

**Title:** Optogenetic stimulation-induced plasticity of orbitofrontal-striatal circuits *in vivo*

**Authors: *S. BARISELLI**[1], A. V. KRAVITZ[2]
[1]NIDDK, NIH, Bethesda, MD; [2]NIDDK, Natl. Inst. of Hlth., Bethesda, MD

**Abstract:** The dorso-medial striatum (DMS) is a brain region at the interface between excitatory inputs, mainly from cortex and thalamus, and dopaminergic afferents to control the selection of appropriate actions. While *ex vivo* studies have provided detailed mechanistic information about cortico-striatal plasticity and its dopaminergic modulation, it is unclear how these mechanisms operate in living mice to shape on-going behavior. Thus, we studied, optogenetic-mediated theta-burst stimulation (TBS) and low-frequency stimulation on orbitofrontal cortex-evoked local field potentials (OFCe LFPs) and multi-unit neuronal activity in DMS of awake mice. We found that while TBS induced potentiation, LFS did not induce cortico-striatal plasticity. Considering that motor, compulsivity and cognitive disorders have been linked to impairments in cortico-striatal plasticity, studying circuit plasticity *in vivo* in awake mice will provide realistic insights to develop refined circuit therapies for such diseases.

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**Program #/Poster #:** 735.11/E34

**Topic:** B.09. Network Interactions

**Title:** Think globally, act locally (and vice versa): The perils and neuroprotective features of topology in seizures and cognition

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**Abstract:** It has long been known that disturbances to brain anatomy can lead to seizures. Investigations of these changes have mostly centered on the properties of cells and synapses. Recently there has been increased interest in the contributions of network structure. For example, network changes following post-traumatic injury and neurodegeneration in aging can be accompanied by an increased prevalence of seizures. However, even these models miss some of the most profound implications of network structure as they are often driven by "small world" graph theory and the disproportional contribution of "hubs". Similarly, the conclusions are often based on the availability (and limitations) of current imaging data provided by MRIs, fMRIs and, more recently, tractography. Together these models correctly draw our attention to the importance of networks but can miss the relation between simple local changes and global activity. Here we illustrate through a range of computational network models how local changes can introduce a variety of unexpected and rich neural patterns. The models include large recurrent network lattices (up to 100,000 units) as well as random networks. In both cases we show how small changes in local topology can modulate system dynamics including activity persistence and the geometric features of the activity. For example, local damage -- akin to post-

traumatic injury -- can act as a "seed crystal" in a chemical lattice and generate spiral waves. These patterns, once generated, can be then be projected onto intact networks and shown to be persistent. Beyond pathology, the models suggest important roles for local and global heterogeneity in generating and maintaining the persistent activity that is so necessary for healthy cognition. The observations thus have broad implications for how we consider network topology -- both locally and globally -- in conditions such as epilepsy and Alzheimer's disease, as well as their potentially critical role in healthy development. Moreover, we demonstrate how these concepts may translate to cognitive and behavioral output through the application of embodied autonomous agents modeling.

**Disclosures: E.L. Ohayon:** None. **A. Lam:** None.

**Poster**

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**Topic:** B.09. Network Interactions

**Support:** IRP, NIMH, NIH, DHHS

**Title:** Dissecting a prefrontal-striatal-temporal lobe circuit in rhesus macaques via retrograde vector-mediated expression

**Authors: *K. E. DASH**[1], W. LERCHNER[1], T. SETOGAWA[2], J. N. TURCHI[3], V. MINASSIAN[5], M. A. ELDRIDGE[4], V. D. COSTA[6], B. B. AVERBECK[2], B. J. RICHMOND[2]
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**Abstract:** We are interested in the connectivity between regions of the brain that support goal-oriented behavior. Prior monkey behavioral experiments from our group have shown that medial temporal lobe (MTL), orbital prefrontal cortex (OFC), and ventral striatum (VS) play roles in the integration of visual and reward value information. In a preliminary study, we injected the OFC with a lentivirus virus expressing anterogradely transported green fluorescent protein (GFP and visualized strong projections to both, VS and the MTL. To identify reciprocal connections, we injected 4 x 5 µl of a retrogradely transported Lentivirus (Lenti-FuGE-syn::GFP) into the OFC of one monkey at an injection rate of 0.5 µl /min. In a second monkey, a retrogradely transported Adeno-Associated Virus (AAV-retro-hSyn-GGaMP) was injected bilaterally into VS (3 x 10 µl in the left hemisphere and 11 x 1 µl in the right hemisphere). Antibody staining for the GFP reporter expression, followed by immunohistochemistry as well as confocal microscopy revealed common regions of afferent VS and OFC projections from the basolateral amygdala (BLA), and

perirhinal cortex (PR). It also showed that area TE, in the anterior temporal lobe, projects strongly to the OFC while there were few cell projecting to the VS. Conversely, there is a dense entorhinal cortex projection to the VS but not to the OFC. In future studies we plan use a two-component retrograde virus system expressing chemogenetic receptors to examine the functional properties of the projections reported above.

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**Poster**

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**Topic:** B.09. Network Interactions

**Title:** Local circuit regulation via gap junctions and self-inhibition in the locus coeruleus

**Authors: *A. M. MCKINNEY**, X. JIANG
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**Abstract:** The locus coeruleus (LC) is the source of ~90% of the brain's noradrenergic projections. It participates in diverse behaviors and cognitive processes crucial for survival, including sleep/wake states, attention, and the fight/flight response, and its dysfunction is closely associated with diverse neuropsychiatric disorders such as depression, post-traumatic stress disorders, Alzheimer's disease, and autism spectrum disorders. Despite its importance, our current understanding of the LC is largely restricted to its long-range projection and diverse effects on its postsynaptic targets, though little is known about how LC neurons interact each other to coordinate their functions within the local circuit. Utilizing an *ex vivo* brain slice preparation that allows simultaneous intracellular recording of up to 8 LC neurons (targeted by expression of dopamine β-hydroxylase, DBH+), we examined the functional interactions between LC neurons at the single-cell level in order to uncover the general principles governing the functional organization of LC local circuits. Our profiling of LC neurons and their connections so far revealed several unexpected mechanisms regulating the excitability of adult LC neurons: (1) a strong (>15mV) self-inhibition lasting tens of seconds that following phasic firing and persists in the presence of the α2 adrenoreceptor blockers yohimbine and idazoxan, (2) prevalent gap junction coupling, which was previously believed to be abolished during late adolescence, and (3) that single LC neurons do not communicate with each other via ionotropic synaptic connections or α2 adrenoceptor-mediated mechanisms, as was previously reported. More LC neurons recordings are currently underway to validate these finding and uncover how molecular and genetic variation underlies the unique organization of the LC local circuits.

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**Poster**

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**Topic:** B.09. Network Interactions

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**Title:** Inter-hemispheric effective connectivity predicts chronic subjective fatigue and motor corticospinal excitability in stroke survivors

**Authors: *S. ONDOBAKA**, A. KUPPUSWAMY
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**Abstract:** Chronic post-stroke fatigue (PSF) has a significant impact on stroke survivors' morbidity, disability, quality of life and mortality. Yet, it remains elusive what the neuronal mechanisms are that underlie PSF, a risk factor for development of depression in many neurological and psychiatric disorders. PSF has been associated with increased corticospinal excitability, as indexed by resting motor thresholds (RMTs). We recently proposed that PSF is a result of poor sensory attenuation, i.e. inability to withdraw attention from a sensory stream. In this study, we employed spectral dynamic causal modelling (spDCM) of resting state fMRI signals of non-depressed stroke survivors and measured their RMTs. We assessed their chronic fatigue level by using a validated and commonly used Fatigue Severity Scale (FSS-7). We reasoned that the patterns of inter-hemispheric connectivity could provide a mechanistic explanation for the inter-individual variability in chronic PSF severity and the associated corticospinal excitability. Our reasoning was motivated by the previous neuronal findings that link inter-hemispheric balance (IB; a measure of [L>R-R>L] connectivity) with both attentional control and cortical excitability. We hypothesised that the deviation from the naturally occurring left-hemisphere inhibitory dominance would be positively associated with both severity of persistent self-reported PSF and the associated corticospinal excitability.
The result from the linear regression analysis showed that the individual IB in the motor cortex (M1) predicts reported levels of chronic fatigue ($p = 3.09e^{-05}$, $R^2 = 0.673$) and corticospinal excitability ($p = 5.07e^{-04}$, $R^2 = 0.541$). We observed a positive association between L>R M1 connectivity and both FSS scores ($R^2 = 0.278$) and RMTs ($p = 0.0188$, $R^2 = 0.299$). There was a negative association between both RMTs and FSS and the strength of R>L M1 connectivity (FSS: $p = 0.0057$, $R^2 = 0.388$, RMTs: $p = 0.0379$, $R^2 = 0.242$). As previous report showed, we observed a significant correlation between the subjectively reported FSS scores and the physiologically measured RMTs ($p = 0.0026$, $R^2 = 0.443$). There was a negative association between FSS and the strength of R>L M1 connectivity ($p = 0.0057$, $R^2 = 0.388$). The findings

support the idea that the individual inter-hemispheric neural dynamics between primary motor regions influence corticospinal excitability and underpin chronic post-stroke fatigue. The strong explanatory power of resting IB dynamics make it a promising target for new intervention protocols using brain stimulation to change corticospinal excitability and ameliorate chronic fatigue symptoms.

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**Title:** Cortical propagation of slow wave activity unveiled by fast line fMRI scanning and optic-fiber calcium recordings

**Authors: *F. AEDO-JURY**[1,2], M. SCHWALM[1,2], A. STROH[1,2]
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**Abstract:** Slow-oscillation-associated slow wave activity (SWA) represents a default cortical state, occurring e.g. during deep sleep and anesthesia. Individual slow waves occur spontaneously, but can be evoked by sensory stimulation, generating a propagating wave of activity. Using optic-fiber calcium recordings in two sensory cortical areas and fMRI fast line-scanning in anesthetized rats, we explored temporal dynamics of SWA which was reliably induced and maintained by deep isoflurane anesthesia.Slow calcium waves were recorded in somatosensory (S1) and visual cortex (V1) with an optic fiber upon neural staining with the synthetic calcium indicator Oregon-Green BAPTA-1 (OGB-1). Visual stimulation was employed to induce stimulus-locked slow waves. Stimulus-induced slow calcium waves were reliably detected with characteristic delays, first in V1 and with a latency of approx. 100 ms in S1, yielding a propagation speed of approx. 50 mm/s.Line scanning fMRI (FLASH pulse sequence, TR: 50 ms, spatial resolution: 0.6 mm) revealed visually-evoked BOLD responses during SWA occurring first in the occipital lobe and exhibiting an increasing delay along the posterior-anterior axis, suggesting activity propagation from V1 towards other cortical areas with a velocity similar as determined with optic-fiber calcium recordings. Data was analyzed measuring individual voxel rise-time of the BOLD signal versus distance to V1.As previously shown in recordings of spontaneous activity by conventional multislice fMRI, during SWA BOLD

activation of the entire cortex occurs. Here we resolve the cortical propagation of slow waves using fast fMRI line scanning, while unambiguously controlling for the origin of the wave from the V1 upon visual stimulation.With this technique spatiotemporal propagation dynamics of SWA can be investigated on the mesoscale, with an imaging modality applicable both in rodents and humans. This will allow for translational studies probing SWA propagation in the context of neurological disorders in which SWA dynamics may be altered or disrupted.Thereby fMRI line scanning methods can bridge the apparent gap between the high temporal resolution of optical and electrophysiological methods and brain-wide fMRI methods, enabling a cross-scale investigation of defined neurophysiological phenomena as e.g. slow wave activity.

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National Science Foundation (1736028)

**Title:** Homeostasis and oscillatory modulation

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**Abstract:** Neuromodulators like dopamine, serotonin, and acetylcholine alter membrane excitability, but prolonged modulation leads to homeostatic corrections. Neural oscillations also modulate excitability and can be sustained for prolonged periods, though whether oscillations also engage homeostatic mechanisms is an open empirical and theoretical question. In a series of numerical experiments, we study the interaction between homeostasis and oscillations in a feed-forward population of pyramidal cells driven by a constant stimulus, with varying levels of oscillatory modulation. We show that sustained oscillations can engage Calcium-dependent homeostatic mechanisms, to surprising effect. For example, excitatory oscillations---which typically increase excitability--begin instead to inhibit firing. In contrast, short (4-cycle) bursts of excitatory oscillations synchronize firing just as well as sustained oscillations, but return to increasing excitability. Based on these results we suggest that the stability of an oscillation in any brain area can, via homeostatic mechanisms, profoundly affect the role that an oscillation will play in shaping the neural code.

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**Title:** Firing activity of protrudor and retractor XII motor neurons are differentially altered in 22q11.2DS

**Authors: *X. WANG**[1], C. BRYAN[2], A. LAMANTIA[2], D. S. MENDELOWITZ[3]
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**Abstract:** Pediatric dysphagia often results in aspiration into the naso-pharynx and lungs and is associated with respiratory distress. These feeding and swallowing difficulties, and their consequences, are seen in up to 80% of children with developmental disorders including infants with DiGeorge/22q11.2 Deletion Syndrome (22q.11.2DS). The tongue, essential for the peripheral execution of swallowing as well as respiratory control, is innervated by the hypoglossal nerve (CnXII). Our initial work has found the neurobiological properties of hypoglossal motorneurons (MNs) change in *LgDel* mouse pups that carry an orthologous heterozygous deletion of 28 contiguous genes on murine chromosome 16 that are orthologues of these deleted in 22q11.2DS. We asked whether CnXII MNs that innervate key classes of extrinsic tongue muscles: protrudors move the tongue forward while retractors pull the tongue backwards, differ in their physiological properties, and potential phenotypic divergence in *LgDel* versus wild type (WT) pups. We also asked whether CnXII MNs innervating tongue protrudors and retractors receive different synaptic inputs during different phases of the fictive respiratory cycle in the two genotypes. Our current results show that retractor CnXII MNs are more dominant in *LgDel* than WT pups and have a higher firing rate during both tonic and respiratory related phasic phases. In contrast, protrudor MN activity is more prominent in WT pups and in WT, firing of protrudor MNs is increased both during and between inspiratory bursts. These observations provide a foundation for understanding the pathophysiological changes in functionally and anatomically distinct CnXII MNs and their contribution to swallowing and breathing abnormalities that occur in DiGeorge/22q11.2 Deletion Syndrome.

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**Poster**

**735. Network Interactions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 735.18/E41

**Topic:** B.09. Network Interactions

**Title:** Tuning cortical network state from criticality to balanced dynamics by strengthening inhibition

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**Abstract:** According to many experimental observations, the neurons in cerebral cortex tend to fire independently of each other, sometimes referred to as the asynchronous state. In contrast, many other experimental observations reveal relatively coordinated and synchronous cortical population dynamics. These discrepant observations have naturally led to competing hypotheses to explain them. A commonly hypothesized explanation of asynchronous firing is that excitatory and inhibitory neurons are precisely correlated, nearly canceling each other, resulting in the so-called 'balanced state'. On the other hand, a prominent hypothesis to explain the more coordinated state is that the system operates at the tipping point of a phase transition, in a state called 'criticality'. Both hypotheses claim the same qualitative mechanism - properly balanced excitation and inhibition. Thus, natural questions arise: how are the balanced state and criticality related, how do they differ? Here we propose an answer to these questions based on investigation of a simple, network-level computational model. We found that the strength of inhibitory synapses relative to excitatory synapses can be tuned from weak to strong to generate a family of models that spans a continuum from 'criticality' to the 'balanced state'. When inhibition was strong (balanced by strong excitation) the dynamics were clearly inconsistent with predictions for criticality; avalanche distributions were not power-laws, branching functions were not flat, etc. Rather, the dynamics for strong inhibition matched expectations for the "balanced state"; perfectly canceling E and I synaptic inputs, weak pairwise correlations, synaptic strength scaling like square root of network size, etc. At criticality (weak inhibition) E and I currents were loosely balanced, pairwise correlations were higher, and synaptic strength scaled like inverse of network size. Our results reconcile two long-standing competing hypotheses and offer a possible explanation of discrepant experimental observations: neuromodulatory mechanisms that act at inhibitory synapses could cause shifts in cortical state from criticality to the balanced state, or vice versa.

**Disclosures: J. Li:** None. **W.L. Shew:** None.

**Poster**

**735. Network Interactions**

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**Topic:** B.09. Network Interactions

**Support:** FQXi Grant FQXi-RFP3-1343
Human Frontier Science Program

**Title:** The fractal cortex: Reconciling cortical network dynamics across scales of observation

**Authors: *W. L. SHEW**[1], S. CHAKRABORTY[2], T. KNOPFEL[3], V. AGRAWAL[2]
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**Abstract:** Current understanding of the cerebral cortex is synthesized from observations acquired at diverse spatial scales. How do the governing principles of cortical neural network dynamics vary when observed at different scales? As experimental tools approach larger and larger measurement volumes with finer and finer resolution, answering this question directly becomes plausible. Here we developed a systematic approach to quantify how a change in scale of observation results in an apparent change in the rules governing cortical network dynamics. We expect our methodology to be useful for studying multi-scale measurements of diverse neural systems. Here, we applied our approach in two different network-level computational models and voltage imaging measurements of mouse cortex.

Our approach was motivated by a growing number of experiments which suggest that the cortical network operates in a dynamical regime near 'ciriticality'. Here, criticality refers to the boundary between an ordered, synchronous regime and a disordered, asynchronous regime of population neural activity. Interestingly, theory suggests that, if the system operates in a dynamical regime near criticality, then the rules governing the system dynamics could manifest with a special fractal symmetry - dynamic rules that are similar across different scales of observation. Here we first confirmed this prediction in two computational models. The first model was a network of simple binary excitatory neurons. The second model included more realistic details of cortical neural networks, including adaptation, inhibitory neurons, distance-dependent connectivity, and more. To our knowledge this is the first demonstration of scale-invariance of the dynamical rules that govern a neural system at criticality.

Next, we applied our approach to analyze voltage-imaging recordings of cortical network dynamics from a mouse as it awoke from anesthesia. Because this imaging technique provided wide coverage (the dorsal surface of nearly one hemisphere) with good resolution (33 microns per pixel), we could directly resample the same data at different scales to compare how dynamical rules vary across scales. We found that the dynamical rules governing mouse cortex

exhibited a distinct shift, becoming more scale-invariant as the mouse awakens from anesthesia. Considered together with our models, this finding suggests that conscious cortex is closer to criticality than unconscious cortex.

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**Poster**

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**Program #/Poster #:** 735.20/E43

**Topic:** B.09. Network Interactions

**Support:** Arkansas Biosciences Institute Grants 0055 and 0070

**Title:** Cortical network dynamics exhibit longest-ranged temporal correlations for critically-balanced excitation and inhibition

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**Abstract:** Growing experimental evidence supports the hypothesis that the cerebral cortex often operates close to a special dynamical regime, called criticality, at the tipping point between synchronous and asynchronous population neural activity. Typically, this evidence is based on the statistics of population activity, focusing on bouts of elevated collective activity called neuronal avalanches, cascades, or population events. At criticality, theory predicts that these events are very diverse in spatiotemporal size, with the probability of different event sizes following a particular power-law distribution. However, in humans it is difficult to reliably measure spatiotemporal sizes of population activity events using typical noninvasive measurement tools, which have severe limitations on spatial resolution. One alternative approach is to focus on temporal statistics of recordings with good temporal resolution (e.g. EEG and MEG). Theory predicts population dynamics with diverse temporal scales at criticality which manifest as long-range temporal correlations. Away from criticality in the asynchronous regime or synchronous regime, distributions of event sizes are expected to deviate from power-law and temporal correlations become shorter in duration.
This predicted relationship between temporal correlations and event size distributions has yet to be directly verified in experiments. Here we show, using multi-electrode recordings in rat somatosensory cortex, that power-law distributed events coincide with the longest-range temporal correlations. We generated a wide range of cortical states by pharmacologically altering inhibition. Comparing across these different cortical states, we found, that the asynchronous state (excessive inhibition) and the synchronous state (reduced inhibition) exhibit shorter range of temporal correlations and deviation from power-law event size distributions compared to the

balanced state. Our findings demonstrate that studies of long-range temporal correlations based on noninvasive human brain recordings can reveal changes in the balance of excitation and inhibition. Our results also suggest that sufficiently long-range temporal correlations are consistent with power-law distributed population events, as predicted at criticality.

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**Poster**

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**Topic:** B.09. Network Interactions

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CAPES grant PVE 88881.068077/2014-01
FAPESP Center for Neuromathematics (grant #2013/07699-0, S. Paulo Research Foundation FAPESP)

**Title:** Neuronal avalanches and long-range temporal correlations at the emergence of collective oscillations: What is the relation with branching processes?

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**Abstract:** The critical brain hypothesis has emerged in the last decades as a fruitful theoretical framework for understanding collective neuronal phenomena. Lending support to the idea that the brain operates near a phase transition, Beggs and Plenz were the first to report experimentally recorded neuronal avalanches, which are bouts of neuronal activity with both sizes (*s*) and durations (*d*) distributed according to power laws: $P(s) \sim s^{-3/2}$ and $P(d) \sim d^{-2}$. The exponents governing these distributions coincide with those of a critical branching process or, more generally, with the mean-field exponents of the directed percolation (DP) universality class, which comprises a variety of models in which a phase transition occurs between an absorbing (silent) and an active phase. This class of models, however, failed to reproduced other signatures of criticality observed experimentally, most notably long-range time correlations observed at both small (microelectrode arrays) and large (M/EEG) spatial scales. The CROS ("CRitical OScillations") model was proposed by Linkenkaer-Hansen et al. as an attempt to reproduce both classes of phenomena (avalanches and time correlations). With excitatory and inhibitory stochastic neurons locally connected in a two-dimensional disordered network, they showed that the model exhibited a transition from an active to an oscillating state. Precisely at the transition, the network activity had long-range time correlations and power-law distributed avalanches.

From the theoretical point of view, however, the model raises several questions, which we investigate here. Firstly, we introduce a tentative order parameter to better characterize the phase transition, while also simulating larger system sizes (*L=300*) than in the original results (*L=50*). Secondly, we point out that it is highly counterintuitive to have a two-dimensional system exhibiting mean-field exponents. That could be due to an insufficiently small ratio between connection range and system size (which is addressed here, again, by increasing *L*). We argue that, if the onset of oscillations in a two-dimensional network is to be reconciled with DP critical exponents, then the DP exponents for dimensionality *D=2* should also be tested. Finally, we explore parameter space in more detail around the transition line, allowing the exponents to be adjusted by a maximum-likelihood estimator (MLE) and testing whether the model satisfies other scaling relations which have been observed experimentally.

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**Poster**

**735. Network Interactions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

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**Topic:** B.09. Network Interactions

**Support:** M-GATE ETN H2020
CNRS iNFInITI

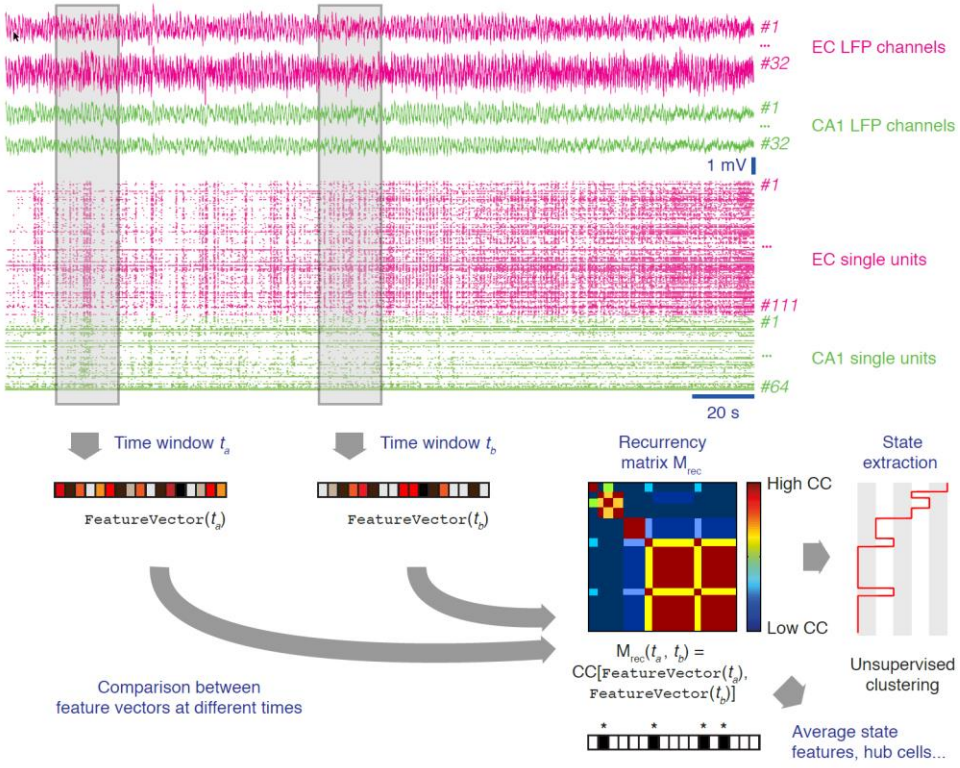
**Title:** Switching states of network connectivity in rat recordings during anaesthesia and sleep

**Authors: *W. CLAWSON**, D. BATTAGLIA, A. F. VICENTE, C. BERNARD, P. P. QUILICHINI
INSERM U1106 INS, Marseille, France

**Abstract:** Oscillations pace neuronal firing and coordinate communication between neuronal populations. However, how a given neuronal network can support different operations is still unclear. In this study, we compare 4 different global brain states: theta vs slow oscillations during anesthesia and REM vs non-REM in natural sleep through analysis of LFPs and single unit recordings in the entorhinal cortex and hippocampus in rats.
We find that changes in the dominant oscillatory state have a complex impact on neural computations. Each of the global brain states we examine can be subdivided into computing microstates and are characterized by different methods of information processing within the neural population based on firing pattern, information sharing and information storage. We show

that the global brain state modulates the temporal statistics of computing microstate switching. This results in varying levels of complexity of computational state transitions, measured through a minimum description length approach. This demonstrates that changes in the global brain state impact both the repertoire from which the computing microstates are sampled and the transitional rules between these states.

Within each computing microstate we identify functional hubs as neurons that are actively involved in specific primitive operations such as information sharing and storage. Importantly, these hubs are not simply neurons with a high firing rate but exhibit these operations as an effect of the current computing microstate. We show that different computing microstates within each global brain state lead to the recruitment of different hub neurons. Interestingly, only a few neurons are hubs during a given state but approximately 70% of all neurons can be hubs within other computing microstates. Therefore, being a functional hub is not a permanent property, but depends on the current computing microstate.

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**Poster**

**735. Network Interactions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 735.23/E46

**Topic:** B.09. Network Interactions

**Title:** Spatio-temporal organization of cell assemblies in nucleus reuniens during slow oscillations

**Authors: *P. P. QUILICHINI**[1], D. ANGULO-GARCIA[2], M. FERRARIS[1], A. GHESTEM[1], C. BERNARD[1]
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**Abstract:** The nucleus reuniens (NR) is an important anatomical relay between the medial prefrontal cortex (mPFC) and the hippocampus (HPC) and growing evidences suggest that it has a role in orchestrating the information flow between the HPC and the mPFC. However, the network mechanisms supporting such function are still unknown. We used silicon probe implanted in the NR, HPC and mPFC in rats during anesthesia, which reproduces some network dynamics of slow-wave sleep, to extract long-lasting stable recordings of local field potentials and large numbers of single units simultaneously. At the beginning of UP states, we identified a reliable sequential activation of NR neurons, which moreover present a spatial organization whereas this nucleus is apparently a non-layered region. Using chemical inactivation of the NR, we show that NR seemed necessary to support the sequences concurrently found in the mPFC at the onset of UP states as well as the robust generation of neuronal sequences during Sharp-Wave Ripples in the HPC. We propose that NR actively binds mPFC and HPC during slow oscillations and appears to participate to the stability of neuronal assemblies that are formed in these regions, which are known to support memory transfer/consolidation.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 736.01/E47

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH/NIA R01 AG056478
NIH/NIA R01 AG055865
The Saban Family Foundation
The Maurice Marciano Family Foundation

**Title:** Retinal amyloidosis, gliosis and inflammatory biomarkers in mild cognitive impairment and Alzheimer's disease patients

**Authors: *A. RENTSENDORJ**[1], Y. KORONYO[1], D.-T. FUCHS[1], J. SHEYN[1], G. REGIS[1], J. DOUSTAR[1], C. A. MILLER[2], K. L. BLACK[1], M. KORONYO-HAMAOUI[1,3]
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**Abstract:** The retina, a CNS tissue, displays numerous abnormalities in Alzheimer's disease (AD), including the presence of Aβ deposits, pTau, nerve fiber layer (NFL) thinning and retinal ganglion cell (RGC) degeneration. Yet, the possible inflammatory processes associated with the pathological hallmarks of AD in this tissue are poorly understood. We investigated retinal pathology including amyloidosis, macro- and microgliosis, and analysis of RGCs in mild cognitively impaired (MCI) and AD patients as compared to age- and gender-matched controls. We assessed load and distribution of macrogliosis (Vimentin, Müller glia), astrogliosis (GFAP, s100β), and microgliosis (Iba1) surrounding retinal Aβ (4G8 and 12F4) in predefined retinal layers and sub-geometrical regions. RGCs and various inflammatory biomarkers were further quantified. Analysis of retinal cross sections spanning from the Ora Serrata to the optic disc in the supro-temporal and inferior-nasal quadrants revealed a wide spectrum of pathological changes in retinal tissues isolated from patients as compared to controls. Aβ deposits were more abundant in inner retinal layers (~90%), with up to a 7.5-fold increase in $A\beta_{42}$ (12F4)-immunoreactive area in peripheral regions of the AD retina. Importantly, retinal Aβ burden was tightly associated with gliosis, including reactive astrocytes, activated microglia, and other infiltrating myelomonocytes. Most early observed changes were related to astrogliosis, especially noted in far peripheral regions with a 3.3-fold change in AD compared to controls. In MCI, and moreover in AD patients, S100β+ astrocytes were not confined to the inner retina but propagated into the outer layers. Vimentin-expressing Müller glias were increased by 1.7-fold in the AD retina, though not in MCI. The peripheral regions of the retina appear more sensitive to damage associated with AD than the central regions. Triggering receptor expressed on myeloid cells2 (TREM2) and immunomodulatory factor osteopontin (OPN/Spp1) expressions were also upregulated in AD retinae. Levels of retinal OPN, a neuronal intrinsic factor that can promote neuronal survival and regeneration following injury and may be involved in glial cell activation and neuroprotection, were tightly associated with retinal Aβ load. Taken together, our findings suggest the occurrence of early and progressive pathological processes related to Aβ and associated inflammation in the retina of MCI and AD patients. A better understanding of this pathology in AD patients may help in the design of novel targeted therapies to treat or prevent AD in the future.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 736.02/E48

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH/NIA R01 AG056478
NIH/NIA R01 AG055865
Saban Family Foundation
Maurice Marciano Family Foundation

**Title:** Immunomodulation therapy targets large to medium Aβ deposits and surrounding inflammatory cells in old late-stage mouse models of Alzheimer's disease

**Authors: *J. DOUSTAR**[1], T. TORBATI[1,5], G. C. REGIS[1], D.-T. FUCHS[1], Y. KORONYO[1], J. SHEYN[1], A. RENTSENDORJ[1], P. K. SHAH[2,3,4], K. BLACK[1], S. LI[6], M. KORONYO-HAMAOUI[1,2]
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**Abstract:** Previously, we have shown that immunomodulation with glatiramer acetate (GA) in 8-13 month old mouse models of Alzheimer's disease (AD) leads to substantial attenuation of neuropathology and preservation of synapses and cognitive function. However, adult AD mouse models have been argued to correspond to the pre-clinical human disease, presenting limited aspects of aging-related processes linked to clinical manifestations of AD. In the current study, we explored the impact of GA immunization on old, late-stage double-transgenic $APP_{SWE}/PS1_{\Delta E9}$ mice (ADtg; 21-24 months old), an age more comparable with clinical stages of the human disease. Treatment included weekly subcutaneous injections of either GA or PBS for 8 weeks, compared to age-matched naïve wild-type littermates (n=7 mice/group). Brain and retinal tissues were analyzed for soluble and insoluble amyloid-beta (Aβ) levels, inflammatory biomarkers, and synaptic integrity. In spite of the late disease stage, Aβ plaque burden was significantly reduced in the entorhinal cortices and retinae of immunized mice. Additional assessment of plaque phenotype revealed a targeted response to large- and medium-sized plaques determined by their area, length and width. These differences can be attributed to an increased recruitment of myeloid cells to sizable plaque populations. Diffused plaques were more impacted by the

immunization as compared with mature fibrillar plaques. In comparison to PBS-treated controls, brains of GA-immunized mice displayed a significant decrease in $GFAP^+$ astrogliosis. In-depth analysis of astrocyte morphology and functional biomarkers showed lower reactive astrocytes with reduced expression of glutamine synthetase (GS), an astrocyte-associated enzyme involved in degradation of extracellular synaptic glutamate, in GA-treated ADtg mice. GA immunization restored astrocyte homeostatic GS levels, comparable with levels measured in WT mice. GA also altered patterns of innate immune cells surrounding medium to large plaques. Further, analysis of synaptic density in these aged mice indicated enhanced postsynaptic PSD95 biomarker expression following GA immunization in areas of reduced Aβ pathology. This study demonstrates the specific neuroprotective effects of GA immunomodulation in old, late-stage ADtg mice and provides the foundation to translate GA for AD treatment in humans.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 736.03/E49

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH/NIA R01 AG056478
NIH/NIA R01 AG055865
The BrightFocus Foundation Award
The Coins for Alzheimer’s Research Trust (C.A.R.T) Fund
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The Maurice Marciano Family Foundation

**Title:** Synaptic protection, immune regulation, and oligomeric amyloid-β clearance by bone marrow-derived macrophages

**Authors: *D.-T. FUCHS**[1], S. LI[1,3], J. SHEYN[1], A. RENTSENDORJ[1], E. Y. HAYDEN[4], T. TORBATI[1,5], K. L. BLACK[1], D. B. TEPLOW[4], Y. KORONYO[1], M. KORONYO-HAMAOUI[1,2]
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**Abstract: Background:** Synaptic loss accurately predicts cognitive decline in Alzheimer’s disease (AD) patients. Accumulation of soluble amyloid β-protein ($Aβ_{42}$) oligomers appears to

be detrimental to synapses, yet oligomers are difficult to study due to their constant dynamic state. Previous work has shown the feasibility to generate and study photochemically stabilized oligomers via photo-induced cross-linking of unmodified proteins (PICUP). We have further demonstrated the therapeutic effects of bone marrow (BM)-derived macrophages in partially attenuating disease progression in murine models of AD via the involvement of infiltrating macrophages in cerebral Aβ plaque clearance. **Methods**: Here, we sought to investigate the ability of BM-derived macrophages, either pre-stimulated with glatiramer acetate (GA) or genetically targeted to overexpress ACE (ACE10), to uptake and degrade $A\beta_{42}$ oligomers and preserve synapses. **Results:** Our studies indicated that peripheral immune activation in $APP_{SWE}/PS1_{\Delta E9}$ transgenic mice, either with GA or adoptive transfer of BM-monocytes, profoundly reduced cerebral Aβ burden and increased synaptic density. In postnatal day 1 cortical neurons, overnight exposure to 100nM of pure $A\beta_{42}$ fibrils, and moreover, defined and photochemically stabilized oligomers, but not monomers, triggered substantial pre-VGluT1 and post-PSD95 synaptic loss and neuritic retraction. Co-culturing primary neurons in vitro with BM-derived GA-prestimulated or ACE-overexpressing macrophages, as compared with WT macrophages, resulted in enhanced synaptic and neuritic protection as well as increased clearance of synaptotoxic $A\beta_{42}$ assemblies. Synaptic rescue by curbing oligomeric $A\beta_{42}$ species tightly correlated with macrophage anti-inflammatory phenotype, high surface expression of Scara-1, TREM-2 and CD36, and efficient extracellular Aβ degradation. **Conclusion:** Overall, our studies indicate that activated BM-derived macrophages can effectively protect neurons against the synaptotoxicity of Aβ oligomers associated with AD.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 736.04/E50

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH/NIA R01 AG056478
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The Saban Family Foundation
The Maurice Marciano Family Foundation

**Title:** Inner retinal hallmark pathology and inflammation in Alzheimer’s disease patients

**Authors: *Y. KORONYO**[1], A. RENTSENDORJ[1], E. BARRON[3], D.-T. FUCHS[1], J. SHEYN[1], C. A. MILLER[4], K. L. BLACK[1], G. MELI[6], D. R. HINTON[5], M. KORONYO-HAMAOUI[1,2]

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**Abstract:** In Alzheimer's disease (AD) patients, the retina displays a wide spectrum of abnormalities, including nerve fiber layer thinning, vascular changes, and retinal ganglion cell (RGC) degeneration. We previously reported the first-ever identification of key pathological hallmarks, Aβ plaques, in the retina of AD patients, including those at early stages. Other groups further demonstrated $A\beta_{1-42}$ peptides, Aβ deposits, and tauopathy in postmortem retinas of AD patients. Here, we explored novel pathological hallmarks of AD along with associated inflammation and degeneration in retinal flatmounts and cross sections and in the corresponding brain sections from mild cognitively impaired (MCI) and AD patients. The ultrastructure and presence of specific amyloid deposits in glial cells were investigated using transmission electron microscopy (TEM). We identified the existence of intracellular Aβ oligomers in cells within the innermost retinal layers of MCI and AD patients, with 2-3-fold increases in confirmed patients versus controls. We further found various pathological changes in retinal tissues of AD patients, such as retinal vascular Aβ deposits, $A\beta_{40}$- and $A\beta_{42}$-containing plaques, (p)tau, paired helical filaments (PHF) tau, and neurofibrillary tangles (NFTs). These AD-related pathologies were more abundant in the inner retina, and especially in the peripheral regions of the superior and inferior quadrants. A 4.7-fold increase in retinal $A\beta_{42}$-containing plaques was noted in the superior temporal regions of AD patients (n=8) as compared to age- and sex-matched controls (n=7; $p<0.001$, t-test). Strong associations between retinal and brain plaque load in the same set of patients were found, in particularly for the primary visual cortex and the entorhinal cortex. Inner retinal Aβ deposits were tightly associated with local inflammation, similar to brain pathology, including astrogliosis, activated microglia, and changes in other non-neuronal glial cells. TEM analysis revealed the existence of $A\beta_{42}$ deposits in certain sub-cellular compartments of Muller glial cells. These pathological changes were linked to a significant 30% retinal neuronal loss with enhanced susceptibility of a certain RGC subset. Utilizing a noninvasive retinal imaging developed by our team enabled us to monitor with high spatial resolution individual amyloid deposits and infiltrating immune cells. Our findings indicate the existence and distribution of pathological hallmarks and associated inflammation and degeneration in the inner retinae of MCI and AD patients, which provide the incentive to develop noninvasive high-resolution retinal imaging to diagnose and monitor AD.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 736.05/E51

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant AG049952
DFG German Research Foundation

**Title:** High fat diet exacerbates brain blood flow reductions caused by stalled capillaries in a mouse model of Alzheimer's disease

**Authors: O. BRACKO**, J. C. CRUZ HERNANDEZ, L. K. VINARCSIK, M. ALI, M. SWALLOW, J. ZHENG, B. N. NJIRU, N. NISHIMURA, *C. B. SCHAFFER
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**Abstract:** Cerebral blood flow (CBF) reductions have been long observed in patients and mouse models of Alzheimer’s disease (AD). Obesity is associated with increased risk for developing AD as well as with increased severity of AD symptoms. Using *in vivo* multiphoton microscopy we have shown that ~1.6% of cortical capillaries are transiently stalled in APP/PS1 mice, leading to a ~20% reduction in CBF that can be restored by administering antibodies against the neutrophil-specific cell surface protein, Ly6G. This blood flow improvement also led to an immediate improvement in performance on spatial and working memory tasks. Wildtype (wt) mice showed a much lower rate of capillary stalling of ~0.4%. This study explores if a western high fat diet (HFD; 42% kcal fat, 42.7% kcal Carbohydrates and 15.2% Protein; Fig. 1A) exacerbates this capillary stalling phenomena in APP/PS1 mice. The number of capillary stalls was elevated in 18-month old AD mice (0.9% on control diet; 1.1% on HFD) as compared to wt (0.3% on control diet; 0.6% on HFD) (Fig. 1B). Thus, capillary stalling increased by 20%, and CBF also decreased by 27%, in both AD mice and wt mice receiving HFD compared to AD and wt mice receiving a control diet, respectively (Fig. 1C-G). AD-HFD animals displayed an enhanced motor and cognitive deficit compared to AD animals after 6 month of HFD whereas wt-HFD animals display cognitive deficits after 9 month HFD compared to wt controls. Impaired short-term memory was restored using anti-Ly6G treatment in APP-HFD animals, however deficits seen in wt-HFD animals were not (Fig. 1H). The onset of cognitive decline did not change between AD control and AD-HFD groups; however at 16 months, AD-HFD animals had larger short-term memory deficits and reduced CBF compared to AD control animals. Anti-Ly6G treatment released stalls, improved CBF to control levels and restored short-term memory deficits in AD and AD-HFD mice. We demonstrated that capillary stalling contributes to enhanced AD progression in obese APP/PS1 mice, suggesting that this mechanism isone potential link between obesity and AD risk and severity.

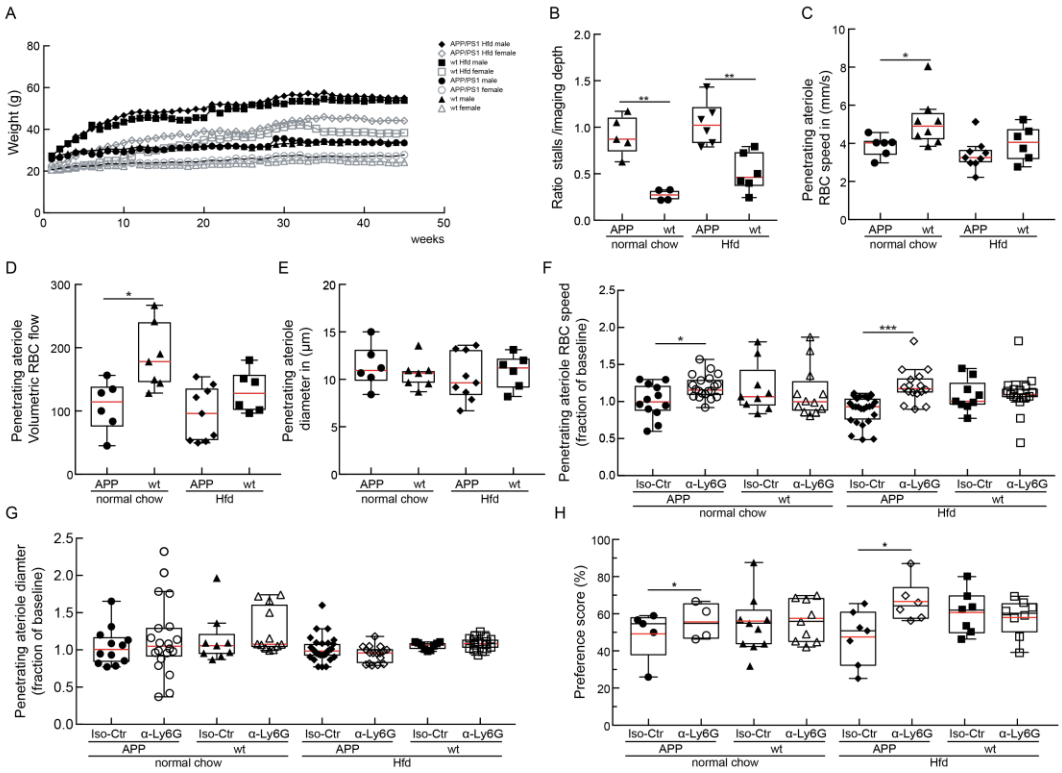


Figure 1: Stalled capillaries causing reduced CBF in AD and wt mice on a western high fat diet. (A) Graph shows the body weights of wild-type (wt) and AD mice on a HFD or normal chow. (B) Number of capillaries with stalled blood flow in AD-HFD AD, wt-HFD and wt. (C) RBC speed (D) Volumetric RBC flow and (E) diameters at 10 month of age (5-month on HFD) AD-HFD, AD, wt-HFD and wt. (F) RBC speed and (G) capillary diameter of AD-HFD, AD, wt-HFD and wt mice, measured 60-90 min after α-Ly6G or Iso-Ctr antibody administration in 13-month old mice (9 month on HFD). (H) Preference score in object replacement task for AD-HFD, AD, wt-HFD and wt mice analyzed 3-6 hr after a single administration of α-Ly6G or Iso-Ctr antibodies compared to baseline measurements.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 736.06/F1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant 1R21AG052860
NIH Grant 1R21EB024694
NSF Grant IOS-1453339

**Title:** Time lapse tracking with intravital imaging in an Alzheimer's disease mouse model reveals highly dynamic plaques after vascular occlusions

**Authors: *Y. ZHANG**, N. NISHIMURA
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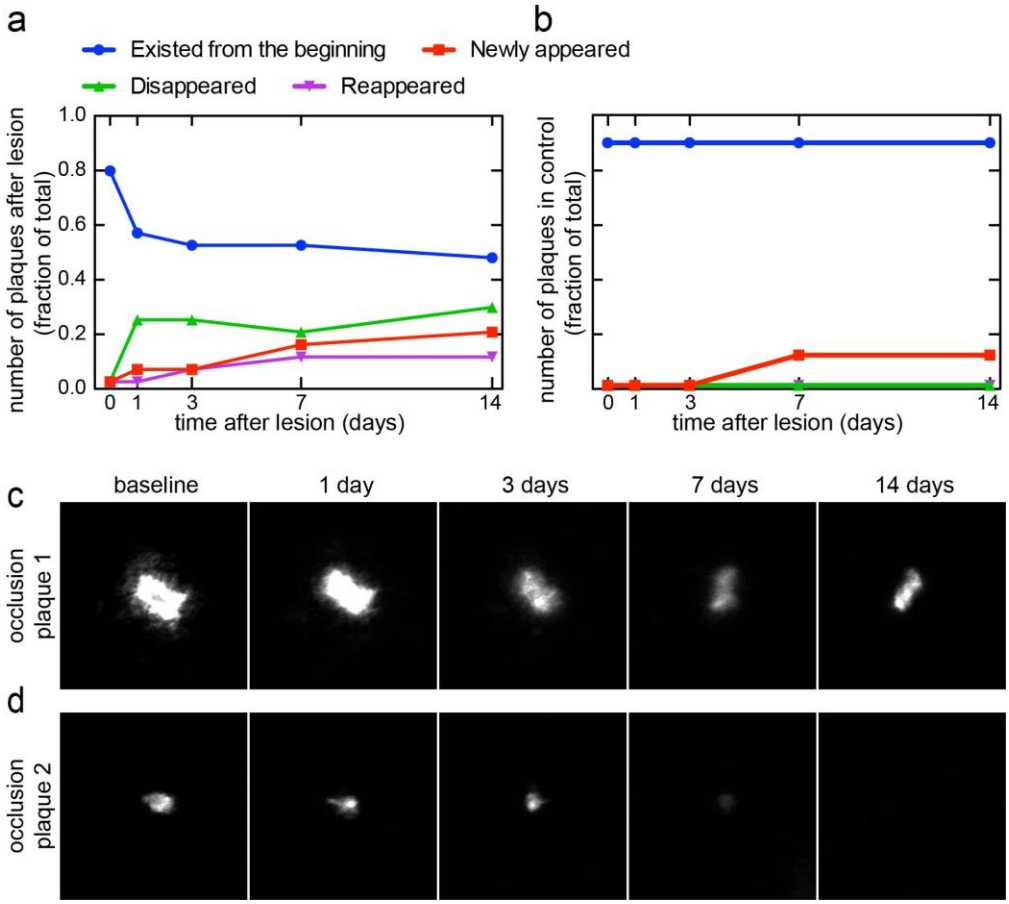
**Abstract:** Alzheimer's disease (AD) is a common neurodegenerative disease that currently has no cure. The progression of AD is characterized by the formation of amyloid plaques consisting of amyloid-beta (Aβ). Although vascular risk factors are correlated with AD incidence and progression, previous studies conflict on how vascular occlusions alter Aβ plaque accumulation. We used two-photon microscopy to image plaque dynamics in APP/PS1 mice expressing green fluorescent protein in microglia. To model microvascular occlusions that mimic small lesions found frequently in AD patients, we injected rose bengal and irradiated with a green laser through a cranial window to occlude cortical penetrating arterioles. Vessels were labeled with Texas-Red dextran and plaques were visualized with methoxy-X04 and animals were imaged on before and after lesioning on day 1, 3, 7, and 14 (n = 3 lesions in 3 animals,12 months old). One day after the lesion, about 30% of previously existing plaques disappeared, but about half of these reappeared over the course of two weeks (Fig. a). Plaque morphologies near lesions also changed over time (Fig. c and d). Control regions on the contralateral side showed no change in pre-existing plaque numbers (Fig. b). In both the lesion and control regions, new plaques appeared within the two-week period at similar rates. From 3 to 14 days post lesion, we observed a steep increase in the number of microglia surrounding the lesion with enlarged cell bodies and short processes that were consistent with activation.
These results suggest that microvascular lesions can alter Aβ plaques, causing both appearance and disappearance in response to injury. An increase in the number of activated microglia correlated with stabilization of plaque numbers, indicating a potential role of microglia in driving plaque dynamics.




**Disclosures: Y. Zhang:** None. **N. Nishimura:** None.

**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 736.07/F2

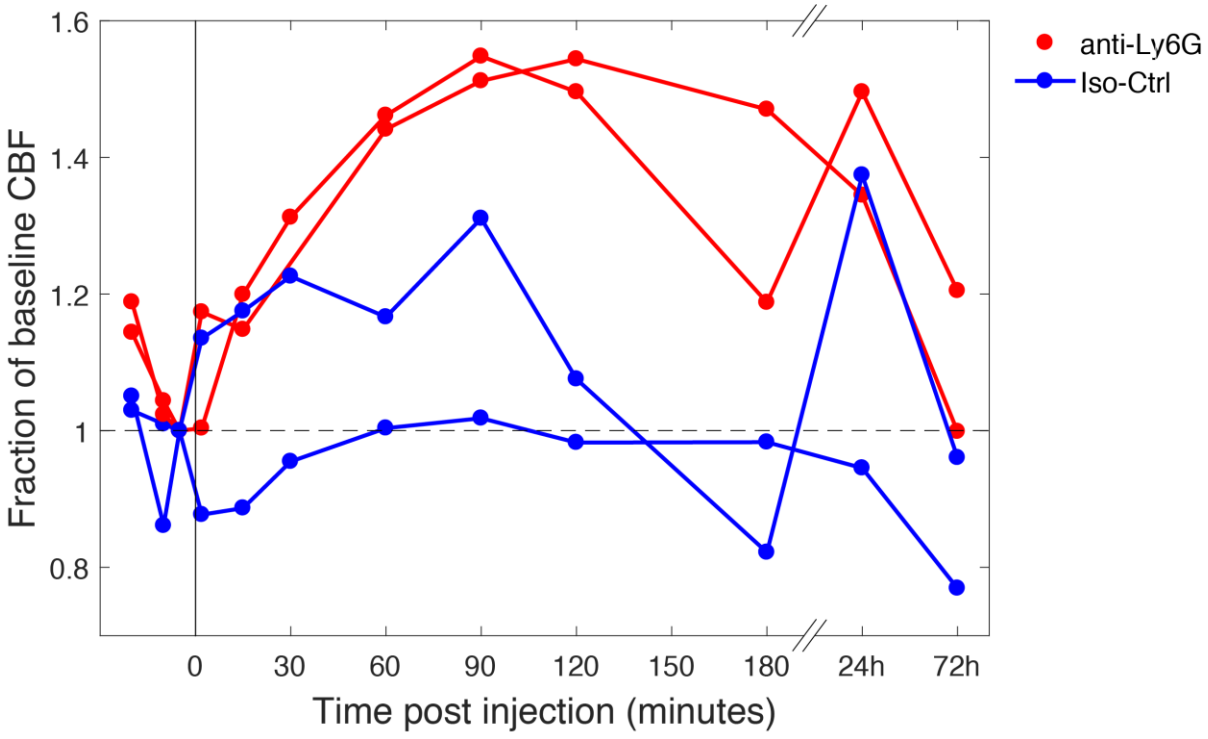
**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH grant AG049952
BrightFocus Foundation

**Title:** Multi-exposure speckle imaging to measure the cerebral blood flow recovery associated with blocking leukocyte adhesion in mouse models of Alzheimer's disease

**Authors: *D. A. RIVERA**, O. BRACKO, N. NISHIMURA, C. B. SCHAFFER
Cornell Univ., Ithaca, NY

**Abstract:** Human patients and mouse models of Alzheimer's disease (AD) exhibit a cerebral blood flow (CBF) deficit of ~30%. Using two-photon excited fluorescence (2PEF) microscopy in AD mice, we recently discovered that this blood flow deficit was caused by an increased number of capillaries with stalled blood flow. Administration of antibodies against Ly6G, a cell surface protein on neutrophils, eliminated the capillary stalls and led to CBF increases of ~30% and improved performance on short term memory tasks. Measuring CBF changes with 2PEF microscopy is tedious, however, so here we evaluate the use of multi-exposure speckle imaging (MESI). MESI uses the degree of blurring of a laser speckle pattern, caused by moving red blood cells, across various camera exposure times to quantify fractional CBF changes. We used MESI to measure CBF changes in mouse models of AD (APP/PS1, 12-18 months) after treatment with anti-Ly6G (4 mg/kg, injected IP) or isotype control antibodies in isoflurane anesthetized mice. We averaged the MESI signal across the full 3 x 3-mm imaging window, which included measurements from multiple surface arterioles and venules as well as the capillary bed. We found that CBF gradually increased in AD mice to ~140% of the baseline value over 1 hr after injection of anti-Ly6G (see Figure), but remained closer to baseline in animals receiving isotype control antibodies. The measured increase in CBF after anti-Ly6G administration was comparable to vessel-by-vessel measurements made using 2PEF. By 72 hrs. after anti-Ly6G administration flow had decreased to near baseline levels, consistent with the time scale for neutrophil replacement. Our work shows that MESI is a viable method for assessing CBF changes in AD mice, while providing higher time resolution and much reduced experimental and data analysis effort. We plan to use this method to test whether drugs that have already passed safety trials in humans and that target the leukocyte adhesion pathway lead to improved cortical blood flow in AD mice, with the goal of identifying potential therapies for improving brain blood flow in AD patients.



**Disclosures: D.A. Rivera:** None. **O. Bracko:** None. **N. Nishimura:** None. **C.B. Schaffer:** None.

**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

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**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** European Research Council grant 615102
NIH grant AG049952
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**Title:** DeepVess: Automated, open-source segmentation and centerline extraction of 3D, *in vivo*, multiphoton images of cortical vasculature in Alzheimer's mouse models using deep convolutional neural networks

**Authors: *M. HAFT JAVAHERIAN**[1], L. FANG[1], V. MUSE[1], C. B. SCHAFFER[1], N. NISHIMURA[1], M. R. SABUNCU[1,2]
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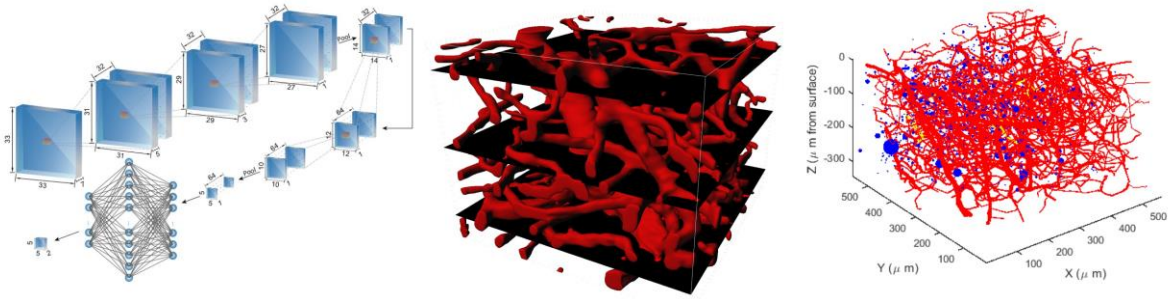
**Abstract:** There is a strong correlation between neurodegenerative diseases, e.g. Alzheimer's disease (AD), brain microvascular dysfunction, and reduced brain blood flow. Therefore, a functional understanding of the changes in structure and function of vascular network in the brain with age and AD is essential. Imaging methods such as multiphoton microscopy can generate 3D images of the cortical vascular network with micrometer resolution in vivo from animal models. However, the quantitative analysis of these complex structures requires imaging segmentation and is hampered by features of live animal imaging such as motion and poor contrast. The segmentation of vessels is a primary bottleneck that has prevented the systematic comparison of 3D vascular architecture across experimental populations. We explored the use of convolutional neural networks to segment fluorescently-labeled vessels in volumetric multiphoton microscopy images of the mouse cortex. We evaluated different artificial neural network architectures and machine learning techniques in the context of this segmentation problem. We show that our optimized convolutional neural network architecture, which we call DeepVess (Fig. A), yielded a segmentation accuracy that was better than both the current state-of-the-art and a trained human annotator (Fig. B), while also being orders of magnitude faster. Additionally, we implemented a centerline extraction algorithm as a post-processing step to enable comparisons of topological properties of the vascular networks (vessels in red, blue

indicates amyloid plaques, Fig. C). To explore the effects of aging and AD on capillary structure, we applied DeepVess to 3D images of cortical blood vessels in young and old mouse models of AD and wild type littermates. We found little difference in the distribution of capillary diameter or tortuosity between these groups, but did note a decrease in the number of longer capillary segments (>75 μm) in aged animals as compared to young, in both wild type and Alzheimer's disease mouse models.




(A) (C) (D)

**Disclosures: L. Fang:** None. **V. Muse:** None. **C.B. Schaffer:** None. **N. Nishimura:** None. **M.R. Sabuncu:** None.

**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 736.09/F4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Research Grants Council of Hong Kong SAR (SAR (16103017)
the Collaborative Research Fund (C6003-14G)
the Area of Excellence Scheme of the University Grants Committee (AoE/M-604/16)
the Shenzhen Knowledge Innovation Program (JCYJ20151030140325152, JCYJ20151030154629774, JCYJ20160428145818099, JCYJ20170413173717055)

**Title:** Regulation of osteopontin expression in disease associated microglia in Alzheimer's disease

**Authors: *W.-Y. FU**[1,2,3], S.-F. LAU[1,2,3], X. ZHOU[1,2,3], C.-Y. CHUANG[1,2,3], Y. WANG[1,2,3], A. K. FU[1,2,3,4], N. Y. IP[1,2,3,4]
[1]Div. of Life Sci., [2]Mol. Neurosci. Ctr., [3]State Key Lab. of Mol. Neurosci., The Hong Kong Univ. of Sci. and Technol., Hong Kong, China; [4]Guangdong Key Lab. of Brain Science, Dis. and Drug Develop., HKUST Shenzhen Res. Inst., Shenzhen, China

**Abstract:** Innate immunity contributes to the pathogenesis of Alzheimer's disease (AD). It has recently been reported that the subpopulation of microglia transit from a homeostatic state to a disease-associated state in AD transgenic mouse brains. Specifically, various gene markers are induced in the disease-associated microglia. Among them, *secreted phosphoprotein 1* (*SPP1*) encodes a pro-inflammatory immune protein, osteopontin (OPN), which is secreted by immune cells including macrophages and dendritic cells. While OPN regulates the secretion of various cytokines to mediate inflammation, its precise physiological and pathological functions in microglia are unclear. Understanding the regulation of *SPP1* in microglia may elucidate the molecular control underlying the transition of microglia upon AD progression. Here, we show that *SPP1* is aberrantly upregulated in the cortex of aged APP/PS1 mice (an AD mouse model) and restrictively expressed in disease-associated microglia. Immunofluorescence analysis showed that in aged wild-type mice, OPN was mainly expressed in neurons and weakly expressed in a few glial cells. Remarkably, OPN expression was significantly induced in microglia associated with amyloid plaques in aged APP/PS1 mice. Furthermore, we found that epigenetic modification of *SPP1* was correlated with its gene regulation in the microglia of APP/PS1 mice. These findings suggest that the epigenetic modulation may regulate the induction of marker genes in disease-associated microglia upon AD progression. Thus, understanding the regulation of the epigenetics and gene expression of *SPP1* may enhance our understanding of the change of microglial state in AD.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 736.10/F5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Research Grants Council of Hong Kong SAR 16103017
Collaborative Research Fund C6003-14G
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**Title:** IL-33 ameliorates Alzheimer's disease-like pathology by modulating the transcriptome signature of microglia

**Authors: *S. LAU**[1,2,3], W.-Y. FU[1,2,3], Y.-P. LAM[1,2,3], A. C. SHUI[1], T. H. CHEUNG[1], A. K. FU[1,2,3], N. Y. IP[1,2,3]
[1]Div. of Life Sci., [2]Mol. Neurosci. Ctr., [3]State Key Lab. of Mol. Neurosci., The Hong Kong Univ. of Sci. and Technol., Hong Kong, China

**Abstract:** Alzheimer’s disease (AD), the most common form of dementia, has no effective treatment. Emerging evidence suggests that microglia, the major myeloid cell type in the brain, may contribute to AD pathogenesis. During AD progression, the microglia transit from their homeostatic state to a disease-associated state. However, it is unclear how this state transition is regulated and how the disease-associated microglia (DAM) are involved in AD pathology. We previously demonstrated that interleukin 33 (IL-33) administration rescues impaired cognitive functions and pathology in an AD transgenic mouse model, in part through enhancing amyloid phagocytosis by microglia. Here, we report that IL-33 administration regulates the gene signature of microglia in AD transgenic mice using single-cell RNA sequencing. While IL-33 administration did not significantly affect the proportion of homeostatic microglia in APP/PS1 mice, it modulates the transcriptome signature of DAM. Furthermore, immunofluorescence staining showed that there are more microglia co-localized with amyloid plaques after IL-33 treatment. Thus, our results collectively suggest that transition of microglial state may play a role in mediating the beneficial effects of IL-33 in AD.

**Disclosures: S. Lau:** None. **W. Fu:** None. **Y. Lam:** None. **A.C. Shui:** None. **T.H. Cheung:** None. **A.K. Fu:** None. **N.Y. Ip:** None.

**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

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**Topic:** C.02. Alzheimer's Disease and Other Dementias

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NIA 5R00AG029726-04
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NINDS 1R01NS076794-01
ZEN-10-174633
AFAR/Ellison Medical Foundation Julie M11472
NSF DGE 1418060

**Title:** Innate immunity sex differences in STAT3 signaling in Alzheimer’s disease

**Authors: *R. OSEAS**[1], M. F. UCHOA[1], K. R. DOTY[1], A. W. VESLING[1], B. P. LEUNG[1], R. RAZI[1], A. M. QUIHUIS[1], M.-V. GUILLOT-SESTIER[2], T. C. TOWN[2]
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**Abstract:** Alzheimer’s disease (AD) is pathologically defined by deposition of amyloid-β (Aβ) peptides as senile plaques, neurodegeneration, and neuroinflammation. Recent evidence suggests that failure in Aβ clearance, rather than overproduction, is etiologically linked to sporadic AD.

Our group previously demonstrated that genetic deletion of the anti-inflammatory cytokine, interleukin10 (IL-10), ameliorates AD-like pathology in APP/PS1 transgenic mice and increases mononuclear phagocytic Aβ clearance. We hypothesize that mononuclear phagocytes are the major responders to IL-10 via STAT3 signaling. To test this, we conditionally and inducibly deleted STAT3 in monocytes by tamoxifen-treating Csf1r-Cre $Stat3^{f/f}$ APP/PS1 mice and wildtype littermates after onset of AD-like pathology (at 6 months of age), and analyzed mice at 12 months. Ablation of STAT3 signaling in mononuclear phagocytes did not affect overall spatial learning and memory in APP/PS1 mice. However, pathological assessment of gliosis (GFAP and CD68) and plaque load (ThioS and 6E10) strikingly revealed greater severity in Csf1r-Cre $Stat3^{f/f}$ APP/PS1 females than in males. Furthermore, biochemical analysis revealed increased Aβ40 and Aβ42 abundance in brain homogenates from $APP/PS1^{+}Csf1r\text{-}Cre^{+}Stat3^{fl/fl}$ vs. $APP/PS1^{+}Csf1r\text{-}Cre^{-}Stat3^{fl/fl}$ mice. Interestingly, these differences were exquisitely sex-specific; stratification by sex revealed that Aβ40 and Aβ42 levels in guanidine- and detergent-soluble brain compartments, as well as Aβ oligomers, were increased in female STAT3 monocyte-deleted mice, but no effect was observed in males. Importantly we show that the most potent female sex-hormone, estradiol, interacts with the STAT3 pathway. Continuation of this work is expected to help elucidate how innate immunity is differentially affected by sex in the context of AD.

**Disclosures: R. Oseas:** None. **M.F. Uchoa:** None. **K.R. Doty:** None. **A.W. Vesling:** None. **B.P. Leung:** None. **R. Razi:** None. **A.M. Quihuis:** None. **M. Guillot-Sestier:** None. **T.C. Town:** None.

**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

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**Topic:** C.02. Alzheimer's Disease and Other Dementias

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NINDS 1R01NS076794-01
ZEN-10-174633
AFAR/Ellison Medical Foundation Julie Martin Mid-Career Award in Aging Research
M11472
NSF DGE 1418060

**Title:** Metabolic changes in immunologically tolerant macrophages treated with amyloid-beta

**Authors: *M. F. UCHOA**[1], K. W. IM[2], A. W. VESLING[2], C. J. MILLER[2], R. RAZI[2], R. OSEAS[2], B. P. LEUNG[2], T. C. TOWN[3]
[1]Physiol. and Neurosci., USC, Culver City, CA; [2]Physiol. and Neurosci., USC, Los Angeles, CA; [3]Physiol. and Neurosci., Zilkha Neurogenetic Inst., Los Angeles, CA

**Abstract:** Failed Aβ clearance is emerging as a key etiological factor in late-onset Alzheimer's disease (AD), and the role of the innate immune system in this process has recently taken center stage after multiple top hits in genome-wide association studies. The anti-inflammatory innate immune cytokine, interleukin-10 (IL-10), is genetically linked to increased risk of late-onset AD. Data from our lab confirms that IL-10 signaling is pathologically elevated in AD brains and in the APP/PS1 mouse model of cerebral amyloidosis. Furthermore, genetic deletion of IL-10 activates Aβ clearance. Others have shown that IL-10 treatment inhibits the mTOR complex master energy sensor, and pharmacological inhibition of this complex promotes immunological tolerance. *We hypothesize that IL-10 inhibits the mTOR pathway to promote Aβ immune tolerance in macrophages*. IL-10 induces macrophage Aβ tolerance, earmarked by reduced Aβ phagocytosis, decreased cytokine expression, and failure to activate NF-κβ. Aβ tolerized macrophages show increased phosphorylation of AMPK (an mTOR complex suppressor), and exhibit decreased isocitrate dehydrogenase and increased lipoprotein lipase (Lpl) expression. This phenotype suggests a deviation from TCA to lipid metabolism. Intriguingly, IL-10 treatment does not induce mitochondrial polarization; instead, it decreases mitochondrial activity similar to Aβ or bacterial lipopolysaccharide treatment. IL-10 treated macrophages have enhanced lipid storage in the form of lipid droplets, which suggests anabolism rather than catabolism of lipids. Increased expression of glycolytic genes and inhibition of the tricarboxylic acid cycle in brain macrophages from the $APP_{swe}/PS1_{\Delta E9}$ mouse model of cerebral amyloidosis provides *in vivo* validation for these findings. Further, APP/PS1 brains have increased lipid droplets inside brain macrophages and altered expression of lipid metabolism genes including *Lpl*. Moreover, transcriptomics analysis demonstrates that the mTOR signaling pathway is decreased in $APP_{swe}/PS1_{\Delta E9}$ brains. IL-10 deletion restores brain mTOR signaling, which correlates with increased Aβ phagocytosis. This study reveals how IL-10 impacts innate immune tolerance to Aβ by altering lipid metabolism and AMPK-mTOR signaling.

**Disclosures: M.F. Uchoa:** None. **K.W. Im:** None. **A.W. Vesling:** None. **C.J. Miller:** None. **R. Razi:** None. **R. Oseas:** None. **B.P. Leung:** None. **T.C. Town:** None.

**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 736.13/F8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** DGE 1418060
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1R01NS076794-01
ZEN-10-174633
M11472

**Title:** Trem $2^+$ peripheral macrophages targeted with nanoparticles inhibits TGF-Beta signaling and mitigates Alzheimer pathology in TgF344-AD rats

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**Abstract:** Transforming growth factor-beta (TGF-beta), a prominent immunosuppressive cytokine regulator, increases in abundance in the brains of Alzheimer disease (AD) patients as well as in rodent models of the disease. Our group has shown that genetic ablation of TGF-beta-Smad 2/3 signaling in peripheral mononuclear phagocytes (macrophages) causes brain recruitment and resolution of cerebral amyloidosis, combined with associated cognitive disturbance in AD-like mouse models. We bridged this genetic approach into the pharmacological domain by utilizing next-generation nanoparticle technology to block TGF-beta signaling in peripheral macrophages. The concept is to 're-balance' innate immunity and neuroinflammation in the pre-clinical TgF344-AD rat model, which manifests the full spectrum of age-dependent AD pathologies and cognitive impairment. To specifically target peripheral macrophages, we developed PEG-PLGA nanoparticles encapsulating a small molecule TGF-beta-Smad 2/3 inhibitor and the non-toxic fluorescent tracker, Coumarin-6 (designated nano-C6/SB). We conducted two long-term peripheral treatment studies with nano-C6/SB-one beginning prior to plaque accumulation and the other starting after established disease. We cognitively/behaviorally tested aged TgF344-AD rats and controls, and subsequently analyzed their brains for evidence of peripheral macrophage infiltration and AD-like pathology. We show that peripheral nano-C6/SB treatment: 1) promotes brain infiltration of C6 and Trem2 double-positive peripheral mononuclear phagocytes that localize to amyloid plaques; 2) attenuates cerebral amyloidosis and tauopathy; and 3) partially remediates cognitive deficits. Nano-C6/SB directly targets peripheral macrophages, effectively inhibiting TGF-beta signaling and increasing Abeta phagocytosis. These cells are almost exclusively Trem2 positive, as opposed to Trem2 negative brain-resident microglia. We conclude that PEG-PLGA nanoparticles encapsulating small molecule TGF-beta-Smad 2/3 inhibitors hold pre-clinical promise to directly target Trem$2^+$ peripheral macrophages for cerebral Abeta clearance.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 736.14/F9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant AG048205 to AZ
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**Title:** Glia maturation factor (gmf) mediated overexpression of voltage-dependent anion channel 1(vdac1) promotes mitochondrial dysfunction through oxidative stress and apoptosis in alzheimer's disease

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**Abstract:** Mitochondria, central to basic life functions due to their generation of cellular energy, also serve as the place for cellular decisions leading to apoptosis. A key protein in mitochondria-mediated apoptosis is the voltage dependent anion channel (VDAC), which also mediates the exchange of metabolites and energy between the cytosol and the mitochondria. We hypothesized that Glia maturation factor (GMF) a pro-inflammatory molecule changes the mitochondrial permeability and induces apoptosis through overexpression of VDAC1 in amyloid beta (Aβ 1-42) peptide treated SH-SY5Y human neuronal cell line in an in vitro model of AD. Our results showed that GMF- treated SH-SY5Ycells showed higher expression of VDAC1, increased release of cytochrome c and apoptosis compared with control group. We also checked the co-localization of GMF with VDAC1, Aβ and phosphorylated-tau (p-tau) expression in post-mortem human AD brains. Results showed higher co-localization of GMF with VDAC1, Aβ and phosphorylated-tau (p-tau) in AD brains compared with age matched control brains. We propose that enhanced level of GMF in AD brain leads to the overexpression of VDAC1 and release of cytochrome c and subsequently apoptosis. Our data suggest that overexpression of VDAC1amplifies and regulates the significant function of GMF in the pathogenesis of AD.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 736.15/F10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH/NIA grant 1R21AG052321
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**Title:** Myeloid cell-specific p38 MAP kinase deficiency exacerbates amyloid pathology: Potential link to altered gut microbiome

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**Abstract:** Studies with animal models of Alzheimer's disease (AD) have shown that in addition to neuroinflammation, systemic immune challenge/inflammation can influence AD pathology and AD-like cognitive changes in complex ways. Such effects are most likely mediated by peripherally activated innate immune cells (i.e., monocytes and other myeloid cells) and/or their products that signal though compromised blood brain barrier. One of the key pathways that signals innate immune cell activation and hence, their expression of multiple mediators is p38a MAP kinase. In this study, we tested the effect of Cre-loxP mediated myeloid cell specific knockout of the kinase (mp38cko) on AD pathology in the APP-PS1 Tg mice. Contrary to expectation, mp38cko resulted in increased (over 2-fold) rather than decreased levels of beta-amyloid accumulation in the brain (-as determined by ELISA) and plaque load relative to wt p38/APP-PS1 Tg mice. This was accompanied by an increased neuroinflammatory response i.e., increased expression of IL-1b, TNFa and iNOS. Interestingly, an analysis of intestinal microbiota indicated significant changes in certain species in the mp38cko mice relative to controls in particular, a down-regulation of Bifidobacterium choerinumand Bacteroides acidifaciens that are known to produce beneficial and anti-inflammatory factors i.e., small chain fatty acids such as butyrate. In line with these microbial changes observed, mp38cko mice displayed increased susceptibility to high fat diet/low-dose streptozotocin-induced type-2 diabetes. These findings point to the potential role of gut microbiota in homeostatic counterbalancing of host immune response and hence, their influence/impact on systemically administered anti-inflammatory approaches to treat AD and other neurodegenerative and neuroinflammatory diseases.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 736.16/F11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Modulation and trafficking of amyloid-β by microglia-derived microvesicles

**Authors: *M. R. NICHOLS**, L. GOUWENS, M. ISMAIL, V. ROGERS, N. ZELLER, E. GARRAD, F. AMTASHAR, N. MAKONI, D. OSBORN
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**Abstract:** Microvesicles (MVs) and exosomes comprise the overall larger group of cell-secreted extracellular vesicles (EVs). These cargo-holding vesicles mediate cell-to-cell communication and have recently been implicated in neurodegenerative diseases such as Alzheimer's disease (AD). While the bulk of the literature focuses on the smaller exosomes (10-100 nm diameter), several reports have also tied the larger MVs (100 nm-1 μm) to AD. This evidence points to an increase in MVs in AD and suggests that MVs may be linked with amyloid-β (Aβ), the primary protein component of the neuritic plaques in the AD brain. Since microglial cells play such an important role in AD-linked neuroinflammation, we sought to characterize MVs shed from microglial cells, better understand MV interactions with Aβ, and determine whether internalized Aβ may be incorporated into secreted MVs. Multiple strategies were used to characterize MVs shed from microglia after ATP stimulation. Confocal images of isolated MVs bound to fluorescently-labeled annexin-V via externalized phosphatidylserine revealed a polydisperse population of small spherical structures. Dynamic light scattering measurements yielded MV diameters ranging from 150-600 nm (mean of 350 nm). Electron microscopy of resin-embedded MVs cut into thin slices showed well-defined uranyl acetate-stained ring-like structures with diameters ranging from 50-300 nm. The use of a fluorescently-labeled membrane insertion probe, NBD C6-HPC, combined with an Aβ ELISA effectively showed a strong interaction between MVs and Aβ protofibrils, but not Aβ monomers. Despite the lesser monomer interaction, MVs had an inhibitory effect on monomer aggregation. Microglia rapidly internalized Aβ protofibrils, and subsequent stimulation of the microglia with ATP resulted in the release of MVs containing the Aβ protofibrils. The role of MVs in neurodegeneration and inflammation is an emerging area and further knowledge of MV interaction with Aβ may shed light on extracellular spread and influence on neurotoxicity and neuroinflammation.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 736.17/F12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Cure Alzheimer's Fund

**Title:** Characterization of the human antimicrobial peptides Aβ and amylin in a 3 D blood brain barrier cell culture infection model

**Authors: *D. VIJAYA KUMAR**, T. I. MITCHELL, W. A. EIMER, N. NAVALPUR SHANMUGAM, E. KIM, S. CHOI, R. E. TANZI, R. D. MOIR
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**Abstract:** OBJECTIVES; Here we show that the human amylin peptide of type 2 diabetes, like amyloidogenic amyloid-beta (Abeta) protein of Alzheimer's disease (AD), is an antimicrobial peptide (AMP). As with Abeta, amylin's AMP activity is mediated by oligomerization and fibrillization triggered by binding of microbial cell surface carbohydrate moieties. Antimicrobial activity involves agglutination and entrapment pathways that parallel the AMP actions of Abeta. Previous studies report amylin/Abeta co-localization in post-mortem human brain tissues. We characterized amylin and Aβ for cooperative synergistic antimicrobial activities in a 3D blood brain barrier (BBB) cell culture model
METHODS; Minimal inhibitory concentration of amylin's was assayed by spot tests and plating. Binding, fibrillization and bacterial membrane disruption were confirmed by electron microscopy. In-house developed competitive inhibition ELISA's were used to characterize specificity of amylin for microbial surface binding. A 3D ReN cell based BBB model was used to test infection induced Abeta/amylin mediated antimicrobial activity.
RESULTS; Data shows amylin-mediated disruption of bacterial membranes is consistent with established pathways mediating antimicrobial activities of classical AMPs. Competitive inhibition ELISA data shows surface carbohydrate binding mediates amylin's AMP activities. 3D cell culture data are consistent with synchronous and synergistic AMP action of Abeta and amylin against bacterial pathogens.
CONCLUSION; Findings from this study suggest amylin plays a protective immune role in pancreas, entrapping pathogens in amyloid deposits. Pancreatic plaques that accumulate in diabetes may be generated as an innate immune response to genuine, or incorrectly perceived, infection. Data from 3D BBB cell culture system suggest possible synchronous antimicrobial actions of amylin and Abeta may also generate the amylin/Abeta deposits reported for human brain.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

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**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** The Helmsley Charitable Trust
Cure Alzheimer's Fund
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**Title:** Aβ42 is an antimicrobial peptide against neurotropic viruses

**Authors: *W. A. EIMER**[1], D. VIJAYA KUMAR[3], N. N. SHANMUGAM[3], S. CHOI[3], A. RODRIGUEZ[3], T. MITCHELL[3], K. J. WASHICOSKY[3], B. GYORGY[4], X. O. BREAKEFIELD[2], R. E. TANZI[3], R. D. MOIR[3]
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**Abstract:** INTRODUCTION; Late-Onset Alzheimer's disease (LOAD) is a complex disease involving interacting genetic and environmental etiologies. There is growing evidence that neuropathic pathogens, such as Herpes simplex virus type 1 (HSV-1), are associated with AD pathology and may contribute to initiating the disease. Our lab has reported that Amyloid-Beta 42 protein (Aβ42) is an antimicrobial peptide (AMP) with protective properties against bacterial and fungal infections in transgenic mice, *C. elegans*, and Drosophila. HSV-1, a neurotropic virus that has near ubiquitous infection in the elderly population, is capable of upregulating Aβ42 production and causing abnormal tau phosphorylation *in* vitro. These properties make it a strong candidate for impacting AD pathology. Our research found that Aβ42's antimicrobial properties extend to protection against multiple families of neurotropic virus infection in both animals and cultured cells. Our model involves Abeta-mediated agglutination of viral particles via surface glycolproteins, preventing membrane fusion and infection. METHODS; Anti-viral properties were assayed by cell culture infectivity, electron microscopy, and *in vitro* binding assays. Mouse mortality, brain tissue analysis, and 3-D cell culture model of the brain characterized physiological Abeta antimicrobial activity. RESULTS; Abeta *in vitro* assays show significant infection protection from HSV1 through binding of amyloid to viral envelope surface glycoproteins. The 5XFAD AD mouse challenged with HSV1 demonstrates increased survival against HSV1 intracranial challenge, reduced viral titers, and advanced development of amyloid

plaques. These properties are also replicated in our 3-D cell culture model and with other neurotropic viruses, developing viral entrapping amyloid plaques in under 3 days. CONCLUSION; Aβ42's antimicrobial properties are expanded to include anti-viral protection against the neurotropic viruses including HSV1. Our model of anti-viral activity is consistent with our previous findings against bacterial and fungal infections, and further solidifies Abeta's roll as an AMP in the immunoprivileged brain. These findings are not only significant for understanding AD, but provide novel pathogen driven amyloidosis model systems for further study.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 736.19/F14

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH R01ES026057
R01ES026067-S2

**Title:** Sex-and genotype differences in astrocyte reactivity in humanized apoe mice

**Authors: *A. EID**[1], I. MHATRE[2], Y. HAN[1], J. R. RICHARDSON[1]
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**Abstract:** Alzheimer's disease (AD) is a progressive neurodegenerative disorder, and is characterized by the presence of pathological hallmarks including amyloid beta (Aβ) plaques, and neurofibrillary tangles. Patients diagnosed with AD also experience neuronal loss in the hippocampus and regions of the cerebral cortex, specifically the frontal cortex. This loss is thought to be facilitated by the pathological products themselves, as well as chronic neuroinflammation. It has been classically accepted that microglia are involved in mediating this neuroinflammatory response, but recent evidence has also shown that astrocytes play a prominent role, particularly as it pertains to generation of nitric oxide. Aging, family history, sex, particularly female, and APOEe4 genotype have been shown to play prominent roles in increasing AD risk. The prominent expression of APOE in astrocytes suggests a potential link between APOE genotype and neuroinflammation. However, it is not currently known whether there are intrinsic sex and genotype differences in astrocytes that may influence the inflammatory response. To address this question, we isolated mixed and sex-specific primary

microglia and astrocytes from postnatal day (PND) 0-3 humanized APOE3 and APOE4 and measured their response to either LPS (microglia) or a mix of pro-inflammatory cytokines (astrocytes). In the mixed and sex-specific microglial cultures, we observed few differences in pro-inflammatory cytokine mRNA levels. However, APOE4 primary astrocytes generated higher levels of media nitrite, an indicator of nitric oxide production compared to APOE3 astrocytes. We also found increased expression of the pro-inflammatory cytokines TNFα, IL-6, iNOS and IL-1B mRNA in APOE4 astrocytes. In our sex-specific studies in primary astrocytes, we observed higher expression of TNFα, iNOS, and IL-6 following cytokine treatment in female APOE4 astrocytes compared to male APOE4 astrocytes. Taken together, these data demonstrate significant differences in response of astrocytes to inflammatory stimulus based on sex and APOE genotype, which may provide insight sex and APOE genotype differences in AD.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 736.20/F15

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Regulation of metabolic genes in microglia in a murine model of Alzheimer’s disease

**Authors: *J. F. CODOCEDO**, G. E. LANDRETH
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**Abstract:** Microglia, the resident macrophages of the CNS, act in a homeostatic capacity to maintain the brain microenvironment. In the murine models of AD it has been demonstrated that plaque-associated microglia exhibit a distinct gene expression profile that include the up-regulation of several genes associated with lipid metabolism. Analogous changes are observed in other degenerative diseases and are reflective of microglial metabolic reprograming. Recent discoveries on the role of metabolic pathways in immune cell function has supported the idea that metabolic reprograming may govern the phenotype of immune cells by controlling transcriptional and posttranscriptional events that are central to their phenotypic activation. However, the microglial metabolic changes that occurs during AD progression, and their impact in their activation, remain largely unknown. We evaluated the expression of genes related to glucose and lipid metabolism during the development of the disease in the cortex and hippocampus of 5XFAD mice model. In agreement with previous reports, we observed a time dependent increase in expression of genes related to lipid metabolism, LPL and FABP5. In addition, we observed an increase in the levels of glucose transporter 5 (GLUT5) and hexokinase 2 (HK2) which are critical for the uptake and metabolism of glucose. Interestingly, the increase in HK2 seem to be dependent on the disease progression whereas the increase in Glut5 is only

dependent on the disease status. We determined that the increase in HK2 is expressed selectively within activated microglia associated with amyloid plaques by immunohistochemical analyses. This could explain the regional increase in HK2 which at 4 month is only detected in hippocampal microglia and at later stages is also observed in the upper layers of the cortex, following the spread of Aβ plaques. These data suggest a unique metabolic signature in AD that can be important in the development of biomarkers for early diagnostics and also could allow the establishment of metabolic intervention strategies to rescue microglial function.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 736.21/F16

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Cure Alzheimer's Fund

**Title:** Aβ peptide binds, agglutinates and neutralizes endotoxins released during infection

**Authors: *T. I. MITCHELL**[1], D. VIJAYA KUMAR[2], W. A. EIMER[2], N. NAVALPUR[3], R. E. TANZI[3], R. D. MOIR[3]
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**Abstract:** OBJECTIVES; We previously showed amyloid-beta (Aβ) protein of Alzheimer's disease (AD) is an antimicrobial peptide (AMP), and demonstrated this in cell culture, worms and animal models. Here we demonstrate that the broad-spectrum activity of Aβ also encompasses binding and neutralization of bacterial endotoxins (LPS). Like many classical AMPs that also neutralize microbial virulence factors, Aβ possesses this property that might enable it to thwart microbial toxins that gain access into the brain. Endotoxin and other virulence factor neutralization are particularly important for the immune privileged brain that primarily combats infection through local innate immune pathways. In this study we demonstrate bacterial endotoxin neutralization activities of Aβ.
METHODS; Experiments tested binding and neutralization actions of Aβ against bacterial lipopolysaccharide (LPS), an archetypal microbial endotoxin. Aβ-mediated anti-LPS activities were tested in in vitro assays such as the LAL test, and cultured human neuroglioma, microglia and mouse macrophage cells.
RESULTS; Data is consistent with binding and potent inhibition of LPS activities by Aβ, including suppression of various proinflammatory cytokines key to mediate harmful neuroinflammation in infection. Monomeric and oligomeric forms of Aβ first target specific

carbohydrate domains on LPS. Aβ binding leads to agglutination and protective sequestration of soluble LPS.
CONCLUSION; Findings from this study suggest Aβ may play a protective role by neutralization of virulence factors like endotoxins in brain. Also endotoxin neutralization is mediated by Aβ binding, oligomerization and fibrillization and parallels LPS-agglutination activities of classical AMP. Our findings are consistent with the emerging Aβ-mediated antimicrobial protection hypothesis in AD.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

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**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH R56AG05755501 to L.X., M.E.F.-P., P.R., P.S.
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**Title:** Age-dependent crosstalk between prostaglandin D2 receptor DP2 and microglia activation as a potential neurodegeneration mechanism in the transgenic rat model of Alzheimer’s disease

**Authors: C. H. WALLACE**[1], R. SHRESTHA[1], A. RASHID[1], A. ALLIGER[2], L. XIE[3], P. SERRANO[2], *P. ROCKWELL[1], M. E. FIGUEIREDO-PEREIRA[1]
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**Abstract:** Chronic inflammation plays a central role in Alzheimer’s disease (AD) and in accelerating AD pathology. Multiple mechanisms link neuroinflammation to AD. Our studies focus on a particular pathway of neuroinflammation, the cyclooxygenase (COX) pathway, which is relevant to AD. COX-2 is highly induced in AD and negatively impacts neuronal function. The COX pathway is key to the conversion of arachidonic acid to bioactive prostaglandins (PGs), which are lipid compounds with hormone-like effects. Prostaglandins are implicated as playing vital roles in AD. Our goal is to characterize factors of the prostaglandin D2 (PGD2) signaling pathway that have biomarker potential. Our hypothesis is that these biomarkers of neuroinflammation can be used to diagnose early stages of AD. We focus on the PGD2 pathway in conjunction with the microglial activation known to occur in AD. PGD2 is the most abundant prostaglandin in the brain, and the one that increases the most under pathological conditions. DP2 receptor activation by PGD2 leads to a decrease in cAMP and an increase in calcium, and promotes neuronal loss. In this study we analyzed the levels of the DP2 receptor and microglia

activation in wild type (WT) and TgF344-AD (Tg-AD). Tg-AD rats express mutant human "Swedish" amyloid precursor protein (APPsw) and Δ exon 9 presenilin-1 (PS1ΔE9) driven by the prion promoter. Tg-AD rats present the full array of AD pathology including cerebral amyloidosis, tauopathy, gliosis, neuronal loss in the cerebral cortex and hippocampus, and cognitive impairment at 16 months of age. Changes in DP2 levels and microglia activation were assessed in the rat brains at pre-pathology (4 months of age) and when signs of neuroinflammation are significant (11 months of age) by immunohistochemistry. Our results demonstrate an age-dependent increase in DP2 receptor levels in three areas of the hippocampus: CA1, CA3 and dentate gyrus (DG). Microglia activation was prevalent in CA1 and DG but not in CA3 areas of the hippocampus in 11 month TG-AD rats. Our results support a microglia-PGD2-DP2 receptor crosstalk as a contributor to hippocampal neurodegeneration in Tg-AD rats. These results provide new information for developing potential new diagnostic biomarkers and therapeutic strategies for asymptomatic early stages of AD.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

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**Title:** Effect of APOE lipoproteins on microglial response to intracranial infusion of Aβ - *in vivo* two-photon imaging and transcriptomic analysis

**Authors: *I. M. LEFTEROV**[1], F. LETRONNE[1], B. IORDANOVA[2], N. FITZ[1], C. WOLFE[1], K. NAM[1], B. PLAYSO[1], T. KOZAI[2], R. KOLDAMOVA[1]
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**Abstract:** In brain Apolipoprotein E (APOE) is secreted mainly by astrocytes, and is the major lipid carrier. Only properly lipidated APOE can efficiently function in brain but the differential role of APOE isoforms in the context of their different lipid composition is poorly understood. APOE affects Aβ clearance and deposition in isoform-dependent manner, and *in vitro*, it was

demonstrated that APOE affects Aβ aggregation and its phagocytosis by microglia. We hypothesize that, based on their different lipidation, APOE3 and APOE4 native lipoproteins impact microglial response in isoform-dependent manner. We used Cx3cr1 mice infused bi-laterally into cortex with Hilyte™-labeled Aβ42 pre-incubated with native APOE3 (Aβ+APOE3) or APOE4 (Aβ+APOE4) particles. We used *in vivo* time-lapse two-photon microscopy to investigate the microglia barrier around Aβ infusion site. In separate experiments, the injected mice were perfused at different time points, microglia sorted by FACS and used for RNA-seq. Flow cytometry was used to determine the proportion of the microglia cells that have or have not engulfed Aβ. The two-photon images acquired during the first 2 hours, demonstrated that microglia cells extended their processes faster towards the Aβ+APOE3 infusion site than towards the Aβ+APOE4. Flow cytometry determined that Aβ uptake by microglia was higher in mice injected with APOE3 than in those injected with APOE4 native lipoproteins. Using RNA-seq approach we compared the transcriptome of two microglia populations, namely microglia that have engulfed Aβ (double positive) and microglia without Aβ (single positive) separately for the mice injected with APOE3+Aβ or APOE4+Aβ. In the dual positive microglia from both APOE3 and APOE4 groups, the genes that were significantly upregulated were recently identified as disease associated microglial genes. In contrast, genes important for the normal microglia function, the homeostatic microglia genes, were upregulated in single positive cells. Interestingly, we also identified a significant number of genes and Gene Ontology categories uniquely up-regulated in mice injected either with APOE3+Aβ or APOE4+Aβ. Altogether, two-photon imaging results demonstrate that infusion of Aβ together with native APOE3 induces a more rapid response by microglia than with native APOE4 thus isolating the infused Aβ and suggesting a protective mechanism for diminishing the spread of Aβ. In regard to the transcriptome, we postulate that native APOE3 and APOE4 infused with Aβ affect the transcription of common as well as unique microglial genes and pathways. The study highlights isoform-specific effect of APOE on microglia response to Aβ.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

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**Program #/Poster #:** 736.24/F19

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant R21AG048498

**Title:** Toll-like receptor 4 antagonism as therapeutic for AD-associated neuroinflammation

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**Abstract:** Alzheimer's disease (AD) is the most common form of dementia with no cure and only palliative therapeutics. The rare familial form of AD (FAD) is caused by autosomal dominant mutations that increase the peptide amyloid-β (Aβ), which aggregates to form both amyloid plaques and soluble oligomers (oAβ), the latter considered a proximal neurotoxin. *APOE4* is the greatest genetic risk factor for AD, compared to the common *APOE3* and the rare but protective *APOE2*. The mechanism underlying *APOE* modulation of AD risk remains unclear. Even less understood is the critical link between female sex and *APOE4*-induced AD risk. A common and early symptom of AD pathology is Aβ-induced neuroinflammation enhanced by *APOE4*. Importantly, oAβ-induced neuroinflammation is mediated by the Toll-like receptor-4 (TLR4), a key component in the innate immune response. Thus, our hypothesis is that blocking the TLR4 pathway will reduce AD pathology, particularly in female *APOE4* carriers. To test this hypothesis, we used the EFAD-Tg mice, which overexpress specifically Aβ42 and express human *APOE4* (E4FAD) or human *APOE3* (E3FAD). Both male and female E4FAD mice and female E3FAD mice were treated with IAXO101 (TLR4 antagonist) using prevention (4-6 month/M) and reversal (6-7M) paradigms. Efficacy of the drug was assessed in behavioral tests. ELISAs were run to determine Aβ levels in TBS, TBSX and FA sequential protein extraction fractions, and IL-1β levels in TBS fraction. Immunohistochemical measures include total Aβ deposition and astrogliosis. Amyloid deposition was measured by area covered in plaques via Thio-S staining. In the reversal paradigm, IAXO induced a significant increase in learning and memory, and a decrease in soluble Aβ in the female E4FAD mice. In the male E4FAD mice, amyloid deposition and astrogliosis were reduced, effects less pronounced in the female E3FAD mice. There were no significant effects with the prevention paradigm. Thus, inhibition of the TLR4 pathway by IAXO101 affected selective readouts for both neuroinflammation and Aβ solubility/deposition, two components of AD-related pathology. Further investigation is needed to understand the mechanism of the sex difference and the role of age and level of pathology for the use of TLR4 inhibitors as a therapeutic for AD.

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**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 736.25/F20

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant R01 AG051437-01
HHMI Gilliam Fellowship for Advanced Studies
T32-AG052354
T32-GM95412

**Title:** Microrna miR-155 modulates inflammation inAlzheimer's disease

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**Abstract:** Alzheimer's Disease (AD) is a progressive age-related neurodegenerative disorder characterized by the accumulation of extracellular amyloid beta (A*β*) as well as CNS and systemic inflammation. Innate immune cells like CNS resident microglia and circulating monocytes use microRNAs to rapidly respond to inflammatory signals, such as A*β* exposure. MicroRNA (miRNA) profiles are altered in tissue, circulating monocytes, and serum of AD cases. MiR-155 is a miRNA that modulates the phasic inflammatory responses of immune cells, driving pro-inflammatory responses. However, the role of miR-155 in modulating neuroinflammation in AD remains unknown. *We hypothesize that miR-155 participates in AD pathophysiology by modulating inflammatory cell function, gene expression and Aβ equilibrium*. We generated trigenic mouse models of AD to investigate the role of miR-155 in microglia alone or in microglia and monocytes during disease progression. $APP^{swe}/PS1^{\Delta E9}$ mice were crossed with mice containing homozygous floxed miR-155 alleles and expressing Cre recombinase from the CX3CR1 locus. For *in vivo* acute and microglia-specific deletion of miR-155, mice express a tamoxifen inducible Cre recombinase directing miR-155 deletion to microglia, while a constitutively active Cre is expressed in the microglia and monocyte deletion model. Microglia specific deletion of miR-155 was achieved by a one-time tamoxifen treatment via oral gavage at 8 weeks of age. At 6 and 9 months of age microglia were isolated by *ex vivo* FACS and miR-155 deletion was assessed by endpoint PCR. We observed deletion of floxed miR-155 alleles, substantially reduced miR-155 expression and changes in inflammatory gene expression in microglia by qPCR. Targets of miR-155 including cMAF, CSF1R, SOCS1, and SHIP1 were upregulated at both time points. We observed that acute miR-155 deletion in microglia increases mortality ($p=0.0009$) in the $APP^{swe}/PS1^{\Delta E9}$ line, compared to vehicle animals that maintained miR-155 expression. We observed cohorts over 72 hours using the Noldus Phenotyper System and determined that increased mortality in this model may involve seizures. Concentrations of soluble and insoluble A*β* in cortical, striatal and hippocampal lysates were assessed using Luminex. *In vivo* continuous miR-155 deletion in microglia and monocytes also altered survival, and changes in soluble and insoluble A*β* were detected. Our results support the hypothesis that miR-155 deletion alters survival, innate immune gene expression and *Aβ* equilibrium in an AD model further elucidating the molecular pathways regulating neuroinflammation in AD and supporting a critical role for inflammatory cells in AD pathogenesis.

**Disclosures: K.E. Prater:** None. **S.L. Davidson:** None. **S. Jayadev:** None. **G.A. Garden:** None.

**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 736.26/F21

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH grant R15NS091934

**Title:** Platelet derived growth factors disrupt the blood-brain barrier and elevate amyloid pathology in 5xfad mice

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**Abstract:** Alzheimer’s disease (AD) is the most common neurodegenerative disorder affecting 5.4 million people in the United States. Currently only symptomatic medicines are available but the search for novel therapeutic treatments continues. Previous evidence has shown the beneficial effects of growth factors in the treatment of AD pathology. Based on reported positive results obtained with the product Endoret®, the aim of this study was to in vitro and in vivo investigate the beneficial effects of platelet-derived growth factors (PDGFs) against AD pathology with a focus on the blood-brain barrier (BBB) function. For the in vitro studies, a cell-based BBB model was used to evaluate the effect of PDGFs on the monolayer intactness and amyloid-β (Aβ) transport. For the in vivo studies, 5xFAD mice were divided into 3 groups (n=7/group, 4 months old, males). Mice received intranasal PDGFs at 10% (group 1) and 100% (group 2) and normal saline (group 3 as control) every other day for 4 weeks. At the end of treatment, mice were sacrificed and brains were collected. Our results from in vitro studies showed that 24-hour treatment of PDGFs enhanced the monolayer tightness and increased Aβ transport across the monolayer in a concentration dependent manner. Findings from the in vivo studies, however, demonstrated 10 and 100% PDGFs exacerbated the amyloid pathology in 5xFAD brains. PDGFs at both doses disrupted the BBB integrity and functionality, increased brain amyloid deposit as confirmed by ELISA and immunostaining, which was associated with increased caspase-3, and neuroinflammatory markers such as IL-1β and TNF-α. In conclusion, the adverse effects observed in this study suggest PDGFs may not provide beneficial effect against AD, and the consideration to utilize growths factors derived from platelets should be further investigated.

**Disclosures: Q.A. Duong:** None. **A. Kaddoumi:** None.

**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 736.27/F22

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant RF1 AG051495

**Title:** Characterizing amyloid pathology-driven heterogeneity of the astrocyte response in a mouse model of Alzheimer's disease

**Authors: *D. TUMBLESON-BRINK**[1], A. OBLAK[2], S. PUNTAMBEKAR[3], B. T. LAMB[4]
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**Abstract:** Alzheimer’s disease (AD), characterized by progressive memory loss and dementia, brain atrophy and death, is associated with rampant neurodegeneration due to extracellular deposition of neurotoxic amyloid (Aβ) plaques and hyperphosphorylation of tau, resulting in intraneuronal neurofibrillary tangles (NFTs). Extracellular Aβ deposition stimulates microglial and astrocytic localization and process extension toward plaques. This is associated with a shift to an inflammatory or reactive state, characterized by upregulation of cytokine/chemokine expression and heightened surface expression of Iba1 in microglia and GFAP in astrocytes. Recent research suggests that pro-inflammatory microglia may drive neurotoxic astroglial responses, indicating that microglial-astrocyte interactions can shape neurodegenerative pathology. Although astrocytes also play a direct role in neuronal homeostasis and synapse function, relatively little is known about their roles in modulating pathology and neurodegeneration/regeneration in AD. Historically, GFAP has been used to identify astrocyte populations in the CNS, however, many astrocyte populations, including those in the cortex of C57BL/6 mice, do not typically express GFAP. In this study, we use the pan-astrocytic marker S100B in conjunction with GFAP to define the heterogeneity of the astrocyte population within the CNS, and analyze how these populations shift towards a reactive phenotype in response to the neuroinflammatory environment of Aβ plaques in AD. In the 5XFAD mouse model of AD, cortical astrocytes near plaques typically transition from a homeostatic S100B+/GFAP- state to a reactive S100B+/GFAP+ state. Between 4 and 6 months in 5XFAD cortex, the percentage of GFAP+ astrocytes increases with plaque pathology. However, using immunohistochemistry and confocal imaging, we have identified a previously uncharacterized, small population of astrocytes in close proximity to plaques that retain their homeostatic, S100B+/GFAP- phenotype. These findings highlight the phenotypic heterogeneity of the plaque-associated astrocyte response in the cortex of 5XFAD mice through disease progression and suggest that distinct

signaling mechanisms may be necessary to skew astrocytes towards reactive vs. homeostatic phenotypes. Our data also provides further evidence that GFAP should not be used as a pan-astrocytic activation marker in AD research. Understanding the heterogeneity of the astrocyte population will help better understand how the interactions between distinct subpopulations of plaque-associated astrocytes and microglia drive AD-associated pathology and/or neuronal health.

**Disclosures: A. Oblak:** None. **S. Puntambekar:** None. **B.T. Lamb:** None.

**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 736.28/F23

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Characterization of the neuroinflammatory response in Alzheimer's disease

**Authors: *A. C. FEVGA**[1], V. VAN DIS[2], T. M. LUIDER[3], D. A. MUSTAFA[2], J. M. KROS[2]
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**Abstract:** Alzheimer’s disease (AD) is the most common neurodegenerative disorder and the most prevalent type of dementia. Its enigmatic pathogenesis currently hampers the attempts to identify diagnostic biomarkers that would contribute to early detection along with a therapeutic approach that would halt the disease progression. Alongside the most widely accepted hypothesis that implicates the accumulation of senile plaques and neurofibrillary tangles, a growing body of evidence entangles immunological mechanisms in AD pathogenesis. However, the exact function of the neuroinflammatory response in the disease mechanism remains elusive, as it appears in both beneficial and detrimental guises. These opposing effects appear to be largely dependent on the phasic progression of the disease. With the present study, we aim at portraying the role of the neuroinflammatory process involved in different stages of AD. To that aim, we examined post-mortem formalin-fixed paraffin-embedded (FFPE) human brain tissue of early and advanced AD patients in comparison to age-matched controls. We performed gene expression profiling using the nCounter® neuroinflammation panel of NanoString technology, which enables the comprehensive multiplex gene expression analysis of 770 genes and the identification of 23 neuroinflammatory pathways. RT-PCR and immunohistochemistry were subsequently utilized for the validation of our findings. Considering the pivotal position of neuroinflammation in AD, our study endeavors to provide further insight not only into the underlying mechanisms of the disease pathogenesis, but also into strategies for the modulation of AD progression.

**Disclosures: A.C. Fevga:** None. **V. van Dis:** None. **T.M. Luider:** None. **D.A. Mustafa:** None. **J.M. Kros:** None.

**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 736.29/F24

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Office of Student Scholarship, Creative Activities and Research Undergraduate Research Program at George Mason University

**Title:** Analysis of inflammatory biomarkers in a novel mouse model of Alzheimer's disease

**Authors: *M. SOBESKI**[1], S. L. P. LIPPI[2], J. M. FLINN[2]
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**Abstract:** Alzheimer’s disease (AD) is a neurodegenerative disorder that affects more than 5 million people in the United States. There is currently no known cure available. Mouse models of AD are used to study behavioral degradation as well as the plaque and tangle pathology that develops. Many models, however, only focus on amyloid or tau. A new mouse containing mutations in human amyloid precursor protein (hAPP) and microtubule-associated protein tau (MAP tau) has been developed in our lab (Lippi et al., 2017 SfN poster). This mouse has undergone behavioral characterization and the brains of these mice have been probed for plaque and tangle pathology. One area of particular interest is that of inflammation, since the AD brain is seen to be in a state of chronic inflammation. Inflammatory proteins, such as tumor necrosis factor alpha (TNFα) are common markers of microglial activation and play key roles in the inflammatory response pathway. Preliminary data show transgenic (Tg) mice have higher levels of TNFα, on average, than those with no AD mutations. In addition, increased levels of TNFα were seen to significantly correlate with the nesting score, which is indicative of deterioration activities of daily living (ADL) (Deacon, 2012). It is possible that glycogen synthase kinase 3 (GSK3) may be affecting inflammation increases in the Tg mice (Hooper, 2008) and future work will probe for GSK3 protein levels in this new model. An improved understanding of the inflammatory activation process and how this is perturbed in a mouse model containing both amyloid and tau pathology may lead to new therapies for AD.

**Disclosures: S.L.P. Lippi:** None. **J.M. Flinn:** None.

**Poster**

**736. Alzheimer's Disease and Other Dementias: Neuroinflammation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 736.30/F25

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** 2016 APA Dissertation Research Award
Osher Lifelong Learning Institute Scholarship
Phi Kappa Phi Love of Learning Award
GMU Dissertation Completion Award

**Title:** Assessment of brain pathology in a novel hAPP/Tau mouse model of Alzheimer's disease: Effects of zinc supplementation

**Authors: *S. L. LIPPI**, K. M. CRAVEN, M. L. SMITH, M. A. SOBESKI, J. M. FLINN
George Mason Univ., Fairfax, VA

**Abstract:** Alzheimer's disease (AD) is a progressive neurodegenerative condition that is characterized by the presence of amyloid plaques and tau tangles in the brain. Mouse models of AD aim to recapitulate not only behavioral deficits of AD but also plaque and tangle pathology; however, many models only focus on amyloid or tau. In the present study, a new hAPP/Tau mouse was developed from a cross of the J20 (hAPP) and rTg4510 (Tau P301L) mice, and the impact of Zinc (Zn) supplementation was explored. The hAPP/Tau mice were compared to mice with TauP301L, with a CaMKIIa promoter to drive tau expression, CaMKIIa promoter only mice, and mice with no mutations present. The brains were assessed for plaque and tangle pathology, free Zn levels, and inflammatory and tau protein levels. Only hAPP/Tau mice displayed insoluble plaques as detected by Congo Red staining. In addition, an increased amount of tangle pathology in the infralimbic region (IL) and hippocampus (HP) was noted through Thioflavin-S staining. Zinc water exacerbated tangle pathology in the HP and IL of hAPP/Tau mice. There was no significant difference between hAPP/Tau mice and single tau mice for the phosphorylated tau epitope, AT8, or total tau. Zinpyr-1 staining showed that hAPP/Tau mice had significantly lower free Zn in the dentate gyrus and CA3 regions of the HP, possibly due to Zn binding to AD-protein species in the region. hAPP/Tau mice displayed significantly higher GFAP levels than CaMKIIa promoter mice and had higher levels on average than mice with no mutations present. This increase in GFAP inflammation correlated with several behavioral measures. Mice with lower nesting scores (Smith et al., 2017 SfN Poster), had higher levels of GFAP and mice that spent less time in the target quadrant of the Barnes maze had higher levels of GFAP. Brain pathology seen in this novel hAPP/Tau mouse mimics that seen in the brains of AD patients. This hAPP/Tau mouse should be considered as a potential model to test future therapeutics or to analyze brain pathology's influence on behavior.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 737.01/F26

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** FWF Special Research Program (F4413-B23)

**Title:** Microglia prevent peripheral immune cell invasion and promote an anti-inflammatory environment in the brain of APP-PS1 transgenic mice

**Authors: *M. S. UNGER**[1,2], P. SCHERNTHANER[1,2], J. MARSCHALLINGER[1,2,3], H. MROWETZ[1,2], L. AIGNER[1,2]
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**Abstract:** Undoubtedly, neuroinflammation is a major contributor to disease progression in Alzheimer´s disease (AD). Neuroinflammation is characterized by the activity of brain resident glial cells, in particular microglia, but also by peripheral immune cells, which infiltrate the brain at certain stages of disease progression. The specific role of microglia in shaping AD pathology is still controversially discussed. Moreover, a possible role of microglia in the interaction and recruitment of peripheral immune cells has so far been completely ignored. Here, we ablated microglia cells in 12 months old WT and AD transgenic mice (APP-PS1) for 4 weeks using the Colony stimulating factor 1 receptor (CSF1R) inhibitor PLX5622 (Plexxikon, Inc.) and analysed its consequences to AD pathology and in particular to peripheral immune cell infiltration. First, PLX5622 treatment successfully reduced microglia numbers. This was, however, compensated by the appearance of a treatment resistant infiltrating macrophage population ($Iba1^+/TMEM119^-$) highly expressing the phagocytosis marker CD68 and the lymphocyte activation, homing, and adhesion molecule CD44, specifically at sites of amyloid-beta plaques in the brains of APP-PS1 mice. In consequence, ablation of microglia significantly raised the number of $CD3^+/CD8^+$ T-cells and reduced the expression of anti-inflammatory genes specifically in the brains of APP-PS1 mice. We conclude that in neurodegenerative conditions chronically activated microglia might limit T-cell recruitment to the brain and that macrophages connect innate with adaptive immune responses. Investigating the role of peripheral immune cells, their interaction with microglia and understanding the link between innate and adaptive immune responses in the brain might be a future directive in treating AD pathology.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 737.02/G1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Influenza A virus infection in a mouse model of Alzheimer’s disease

**Authors: *S. HOSSEINI**[1,2], K. MICHAELSEN-PREUSSE[1], A. HOLZ[1,2], K. SCHUGHART[2], M. KORTE[1,2]
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**Abstract:** Influenza viruses until today are a leading cause of worldwide severe pandemics and represent a major threat to human and animal health. Although the primary target of influenza viruses in mammals is the lung, infection can cause neurological disorders, including delirium and encephalopathy. We could show previously that a peripheral influenza A virus infection caused by a non-neurotropic virus variant leads to long-term neuroinflammation and synapse loss together with impaired memory formation in young adult mice (Hosseini et al. 2018, JNS). Processes of neuroinflammation have indeed been associated with neurodegenerative diseases such as Alzheimer’s disease (AD) and prolonged or excessive innate immune responses are considered a risk factor for AD. Therefore, in order to investigate the role of influenza infection for the development and progression of AD two months old APP/PS1 mice were infected intranasally with non-neurotropic H3N2 (maHK68) influenza A virus. Whereas the infection had no effect on neuronal cell number in the CA1 region analysis of spine density revealed a reduction 120 days post infection in comparison to WT and also to non-infected APP/PS1 mice. A detailed analysis of microglia density and morphology revealed neuroinflammation in the hippocampus already of uninfected APP/PS1 mice but microglia activation was even more pronounced in APP/PS1 mice upon H3N2 infection. Taken together these results demonstrate that influenza infection as a peripheral immune stimulation may exacerbate AD possibly by triggering microglia hyperactivation.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 737.03/G2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** W.M. Keck Foundation grant 1021RR549507

**Title:** Modeling glycosylation in Alzheimer's disease using patient-derived stem cells

**Authors: *K. ROSENBALM**, D. NIX, M. TIEMEYER
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**Abstract:** The pathology of Alzheimer's disease (AD) is complex and involves incompletely understood inflammatory responses. The contributions of inflammatory cells, either resident in the brain (microglia) or recruited from peripheral sources (monocytes/macrophages), are an emerging interest with regard to the initiation and progression of AD. Glycoprotein and glycolipid glycans regulate inflammatory cell differentiation, activation, trafficking, and survival. For each of these glycan-mediated activities, immune cells express glycan binding proteins, such as Siglecs, that recognize glycans within the cell's environment triggering subsequent responses, which can be pro- or anti-inflammatory depending on the glycan structure, receptor specificity, and cell type involved. To investigate whether glycomic changes accompany and/or contribute to the pathology of AD, we characterized the glycome of AD patient-derived induced pluripotent stem cells (iPSCs) and differentiated neural cultures, including glycosphingolipids as well as N-linked and O-linked glycoprotein glycans. We observed alterations in the abundance of sialylated and sulfated O-glycan structures in differentiated neural cultures. In addition, given CD33/Siglec-3's involvement as a risk factor for AD, we also analyzed the expression of anti-inflammatory glycan ligands for Siglec receptors in these tissues. In both our mouse and human iPSC AD models, we have observed an upregulation of Siglec-F ligands as well as a concomitant reduction of Siglec-9 ligand in AD iPSCs. The glycome of AD iPSCs was largely unchanged in comparison to normal control iPSCs, indicating the specificity of glycosylation alterations for these Siglec ligands. Using 5xFAD mouse brain immunohistochemistry, we observed that the increased expression of Siglec-F ligands occurs in a cell type specific manner at the brain's immune barrier, the choroid plexus epithelium. Naïve derived 3-D choroid plexus tissue ("chorganoids") have demonstrated a comparable amount of Siglec ligand expression between normal control and AD tissues, where we have observed increased expression of Siglec ligands after challenging chorganoids with Toll-like receptor ligands. Future combinatorial co-culture experiments will provide a novel opportunity to assess cell-specific glycomic and functional responses in AD.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 737.04/G3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Differences in dietary inflammatory index in individuals with Alzheimer's dementia, mild cognitive impairment, and controls

**Authors: *A. K. HALT**[1], B. E. SUTTON[1], T. SHADRICK[1], D. DRYSDALE[2], M. MCBRIDE[1], D. Q. BEVERSDORF[3]
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**Abstract:** More than 5 million Americans are currently living with Alzheimer's dementia (AD). Studies have identified chronic inflammation as a key feature of AD. Whether inflammation is a cause or byproduct of AD is not known. However, chronic inflammation appears to be important to the pathophysiology of AD. As there is no cure for AD, research to explore modifiable risk factors that could potentially reduce inflammation and the likelihood of developing AD is vital. One such factor is diet. Using the dietary inflammatory index (DII), we can map an individual's diet on a continuum from -1, being highly anti-inflammatory, to 1, being highly pro-inflammatory. Our current research aims to investigate the inflammatory index of the diets of individuals with AD, Mild Cognitive Impairment (MCI), and healthy controls. Mild cognitive impairment is a significant risk factor in the development of dementia, as Alzheimer's disease may already be pathologically present. Although individuals with MCI experience decline in memory and cognitive ability, they have preserved daily living activities. Participants with AD, MCI, and healthy controls completed food frequency questionnaires assessing consumption of various foods over the past month. Preliminary analysis revealed, in agreement with other work, that healthy controls consumed significantly greater amounts of omega-3 rich foods, a potent anti-inflammatory, than did participants with AD ($p<0.001$). Additionally, we found that although participants with MCI did not significantly different from control participants, participants with MCI trended towards significance in consuming greater amounts of omega-3 rich foods than participants with AD ($p=0.06$). Next, we are analyzing the pro- and anti-inflammatory effects of foods assessed in the food frequency questionnaire. We hypothesize that individuals with AD will have diets with a DII score closer to 1, meaning they are highly pro-inflammatory; whereas, control individuals will have a DII score closer to -1, meaning they are highly anti-inflammatory. Additionally, we hypothesize that individuals with MCI will consume diets with a DII more similar to those with AD than controls due to the antecedent presence AD pathology and subsequent inflammation. Further research is needed to understand the interplay

between diet and AD/MCI, specifically in terms of how anti-inflammatory and pro-inflammatory components of foods consumed influence the course of neurodegeneration and dementia.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 737.05/G4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** AARF-16-442963
NIEHS R01-ES024331

**Title:** Inflammatory cytokine IL-1beta downregulates LRP1 via microRNA-mediated gene silencing in endothelial cells

**Authors: *H.-W. HSU**, C. RODRIGUEZ-ORTIZ, J. ZUMKEHR, M. KITAZAWA
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**Abstract:** Abnormal buildup of amyloid-beta (Aβ) species is a prominent pathological hallmark for Alzheimer’s disease (AD), but its underlying mechanisms by which toxic Aβ species accumulates in the brain remain to be elucidated. Recent evidence from in vivo and in vitro studies suggests that the buildup of toxic metabolites in the brain is primarily mediated by impaired clearance mechanisms, rather than overproduction. Low density lipoprotein receptor-related protein 1 (LRP1) in the endothelial cells mediates Aβ clearance from the brain parenchyma. Aging as well as certain environmental factors have shown to decrease its expression in endothelial cells, and genetic ablation of endothelial LRP1 in mice significantly accumulated soluble Aβ in the brain. We have previously demonstrated that blocking IL-1 signaling ameliorated Aβ and tau buildup in the brain and rescued cognition in the mouse model. Recent studies also show that IL-1β, together with IL-6 and TNFα, plays a critical role in age-related inflammation and cellular responses. Therefore, we hypothesize that sustained IL-1β promotes the loss of LRP1 in endothelial cells. We first examined the exposure to IL-1β (1 ng/ml) for 24 hrs significantly downregulated LRP1 in the human primary microvascular endothelial cells (MVECs), and its effect was long-lasting after removal of IL-1β from the media. The IL-1β-induced reduction of LRP1 was not mediated by the proteasome- or lysosome-dependent degradation mechanisms. Instead, we found that IL-1β significantly upregulated microRNA-205-5p, -200b-3p, and -200c-3p in MVECs. These microRNAs were predicted to bind LRP1 mRNA to halt its translation. The application of synthetic microRNA-205-5p, -200b-3p, or -200c-3p mimic effectively downregulated LRP1, and pre-treatment with antagomirs

against these microRNAs restored LRP1 in IL-1β-exposed MVECs. These results strongly suggest that miRNA-205-5p, -200b-3p, and -200c-3p are directly involved in the LRP1 regulation in MVECs. The expression of these microRNAs appeared to be controlled by NF-kB as NF-kB inhibitor, BMS-345541, inhibited the IL-1β-mediated increased expression of these three microRNAs and rescued LRP1. Our study provides novel mechanisms addressing that inflammation is a key triggering event for AD pathogenesis. These three candidate miRNAs involved in the regulation of LRP1 might lead to therapeutic applications of miRNA inhibitor and NF-kB inhibitor to treat AD in the future.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 737.06/G5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant AG050471

**Title:** Modulation of the inflammatory response by RNA-binding protein TIA1 in the P301S mouse model of tauopathy

**Authors: *C. LEBLANG**[1], B. WOLOZIN[2], J. LUEBKE[1]
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**Abstract:** Tauopathies such as Alzheimer’s Disease and Frontotemporal Dementia are characterized by aggregation of hyperphosphorylated tau protein, widespread neuro-inflammation and neuronal death. We have recently shown that the RNA-binding protein TIA1 regulates tau pathophysiology and toxicity in part through sequestering phospho-tau oligomers in pathological stress granules (Vanderweyde et al., 2016; Apicco et al., 2017). Haplo-insufficiency of TIA1 in the P301S mouse model of tauopathy reduced the accumulation of tau oligomers, as well as the development of downstream cognitive deficits, cortical thinning, and synapse loss. In the healthy brain TIA1 acts as a regulator of the innate immune response and of cell death by sequestering TNFα and COX2 mRNA transcripts in normal stress granules (Ash et al., 2014; Lopez de Silanes et al., 2005). The putative role of TIA1 in the immune response led us to hypothesize that full TIA1 knockout would increase the immune response in the P301S mutant mouse model. Here, we characterized the inflammatory response in P301S vs. WT mice that were TIA1+/+, TIA1+/- or TIA1 -/-. Immunohistochemistry and 3D cell counting techniques were used to assess microglial morphology and MHCII antigen presentation in the CA1 and

Dentate Gyrus regions of the dorsal hippocampus. Microglial activation was significantly greater in all P301S groups compared to WT, confirming that tauopathy induces neuro-inflammation in this model. There was a significantly higher number of activated microglia in the P301S TIA1 -/- compared to P301S TIA+/+ and P301S TIA+/-, which did not differ. The inflammatory response was not observed in the WT TIA1 -/- group, indicating that the inflammatory phenotype seen in the P301S TIA-/- group requires the presence of tau and/or downstream neuropathological insults. Gross atrophy of the hippocampus was observed in P301S TIA1 -/- mice, but not in the other genotypic groups, perhaps reflecting the severe inflammation selectively present in P301S TIA1-/- mice. Immuno-electron microscopy was used to assess microglial ultrastructure and neuronal interactions, to quantify synapse loss, and to characterize colocalization of tau with TIA1. These studies suggest that TIA1 plays an important role inhibiting inflammation in the context of tauopathy, but that this role is only apparent with full TIA1 deletion. Ongoing studies are quantifying levels of inflammatory cytokines and phagocytic markers to determine the mechanisms by which TIA1 regulates neuro-inflammation.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 737.07/G6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Alzheimer’s association Grant AARF-16-443213
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**Title:** Transcriptomic profiling of microglia reveals distinct gene expression changes in response to aging and APOE isoform

**Authors: *K. NAM**, N. F. FITZ, C. M. WOLFE, F. LETRONNE, I. LEFTEROV, R. KOLDAMOVA
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**Abstract:** Alzheimer’s disease (AD) is a progressive neurodegenerative disorder with a significantly increased risk for carriers of E4 allele. Aging is the strongest risk factor for AD and tightly associated with impaired brain homeostasis. Microglia play a crucial role in maintaining brain homeostasis and microglial dysfunction is linked to neurodegeration. However, APOE

isoform specific effects and its association with age- and AD-related changes in the microglial transcriptome still remain poorly understood. To get further insight in the specific effects of APOE isoform in response to aging, we performed RNA-seq using isolated microglia from WT and APP/PS1 mice expressing human APOE3 and APOE4 (WT/E3, WT/E4, APP/E3, APP/E4). The transcription profiles of younger (3.5 month), young (7.5 month) and older mice (13.5 month) were further analyzed to identify microglia specific genes affected by aging or APOE isoform. We found commonly affected genes associated with aging in both APP transgenic and WT mice regardless of APOE isoform including disease-associated microglial genes (DAM). Surprisingly, our data show that microglia from APOE3 expressing mice showed higher number of differentially expressed genes with aging compared to APOE4 expressing mice, but differential expression was stronger in APP transgenic mice. We also identified a number of commonly affected genes by aging in APOE3 or APOE4 expressing mice regardless of amyloid phenotype. The conclusions from this study are: a) aging is the strongest factor that affects brain transcriptome; b) APOE isoform-specific effect on brain transcriptome correlates to amyloid phenotype and is less pronounced in WT mice; c) the microglia transcriptome is affected by amyloid pathology, aging and APOE isoform.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 737.08/G7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** This study was supported by the National Institute On Aging of the National Institutes of Health in the United States (R01AG051674).

**Title:** The effects of stem cell factor and granulocyte colony-stimulating factor on removal of β-amyloid deposits in aged APP/PS1 mice

**Authors: *L.-R. ZHAO**[1], Y. LIU[2], S. LONGO[2]
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**Abstract:** Alzheimer’s disease (AD) primarily affects older adults. Amyloid-beta (Aβ) accumulation is associated with the pathological progression of AD. Emerging evidence shows that innate immune system dysfunction plays a key role in Aβ accumulation. Improving the function of innate immune system to enhance Aβ clearance has been proposed to be an important strategy for restricting the development of AD. This study aimed to determine the effects of two hematopoietic growth factors, stem cell factors (SCF) and granulocyte colony-stimulating factor

(G-CSF) in improving innate immune function and enhancing Aβ clearance in aged APP/PS1 mice. SCF and G-CSF was subcutaneously injected for 12 days in 25-month-old male APP/PS1 mice. Five weeks after treatment, mice were sacrificed for pathological examinations using immunohistochemistry in brain sections. We observed that SCF in combined with G-CSF (SCF+G-CSF) treatment significantly reduced the area, number, and size of Aβ plaques in both the cortex and hippocampus as compared to the vehicle control APP/PS1 mice. In addition, both the $Iba1^+$microglia and $CD45^+$microglia/macrophages were significantly increased by SCF+G-CSF treatment. The association of $Iba1^+$microglial cells with Aβ plaques was also significantly increased by SCF+G-CSF. Increased uptake of Aβ by$CD45^+$microglia/macrophages was seen in SCF+G-CSF-treatedAPP/PS1 mice. Moreover, SCF+G-CSF treatment led to increased IL-4 expressing cells and decreased nitric oxide synthase 2-positive cells. These findings suggest that SCF+G-CSF treatment in oldmice with cerebral amyloidosis enhances Aβ clearance, increases the recruitment of microglia/macrophages, and modulates innate immune activation. This study reveals potential therapeutic benefits of SCF+G-CSF treatment for restricting AD pathology in older adults.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 737.09/G8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Altered inflammatory signalling in cerebrospinal fluid of mild cognitive impairment versus Alzheimer’s disease: Analysis of cytokines/chemokines, amyloid-beta and tau

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**Abstract:** Mild cognitive impairment (MCI) is a syndrome wherein a person experiences greater cognitive decline than is normal for their age and often progresses to dementias, including Alzheimer’s disease (AD). Inflammation has been proposed as a pathogenic factor for both MCI and AD, but available data on cytokine/chemokine expression in cerebrospinal fluid (CSF) in MCI or AD are inconsistent. Here, we analysed a panel of cytokines/chemokines as inflammatory markers (IL-1β, IL-6, TNF-α, IFN-γ, IL-10, IL-12p70, IL-13, IL-2, IL-8, and IL-4) in CSF from MCI, AD and healthy control donors. Validated biomarkers of disease progression, namely Amyloid-Beta ($Aβ_{1-42}$) and TAU were also analysed to validate our diseased population. CSF from donors diagnosed with MCI, AD and aged matched controls (n=15 per group) were obtained from a biobank. Expression of cytokines/chemokines, amyloid-beta ($Aβ_{1-42}$), Total-TAU (T-TAU) and Phospho-TAU at Thr181 (P-TAU) were assessed using MesoScale

Diagnostics assays. Donors also supplied a complete history and completed the mini-mental state examination (MMSE) and Alzheimer's disease assessment scale (ADAS).
A significant deficit in MMSE performance was observed in the MCI and AD groups compared to healthy controls and ADAS score was significantly higher in the AD group compared to MCI. CSF $A\beta_{1-42}$ concentration was significantly lower in both MCI and AD compared to control, while T-TAU was significantly increased with a significantly higher concentration in AD. P-TAU was increased in AD only. TNF-α concentration was significantly higher in both MCI and AD compared to healthy controls while IL-6 was increased in the AD group. IL-8 and IL-10 were significantly elevated in the AD group compared to MCI and healthy controls.
This is one of few studies directly comparing MCI and AD individuals using optimised multiplex assays to assess cytokine, $A\beta_{1-42}$ and TAU concentration in CSF. In line with the literature, T-TAU and $A\beta_{1-42}$ were increased and decreased in MCI and AD, respectively. TNF-α has been previously reported to be upregulated in CSF of AD patients. We report a significant TNF-α increase in MCI and AD which may indicate a role for TNF-α in MCI to AD progression. Moreover, an increase in IL-8 and IL-10 specifically in AD suggests a disease-specific CSF cytokine/chemokine profile. These results demonstrate that neurodegenerative changes in MCI and AD are associated with alterations in cytokine signalling and immune system function. Thus, inflammatory signalling could represent an innovative therapeutic target in MCI/AD as well as a potential biomarker to indicate disease progression.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 737.10/G9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

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**Title:** Neutrophil adhesion in brain capillaries contributes to cortical blood flow decreases and impaired memory function in a mouse model of Alzheimer's disease

**Authors: *O. BRACKO**[1], J. C. CRUZ HERNÁNDEZ[1], C. J. KERSBERGEN[1], V. MUSE[1], M. HAFT-JAVAHERIAN[1], M. BERG[2], L. PARK[3], L. K. VINARCSIK[1], I. IVASYK[1], Y. KANG[1], M. CORTES-CANTELI[4,5], M. PEYROUNETTE[2], V. DOYEUX[2], A. SMITH[2], J. ZHOU[1], G. OTTE[1], E. DAVENPORT[1], Y. DAVIT[2], S. STRICKLAND[5], C. IADECOLA[3], S. LORTHOIS[2,1], N. NISHIMURA[1], C. B. SCHAFFER[1]

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**Abstract:** The presence of decreased brain blood flow in both human patients and animal models (APP/PS1) of Alzheimer's disease has been long known but no physiological explanation of this phenomenon has emerged. Using high-resolution *in vivo*imaging of blood flow in mouse models of Alzheimer's disease, we have identified transiently stalled capillary segments as the major cellular mechanism causing this blood flow decrease. In AD mice, about 2% of capillaries have stalled blood flow due to a leukocyte stuck in the lumen, while wild type (wt) mice have ~4 times fewer stalled capillaries (Fig. 1a and b). We determined that the majority of the capillary stalls are caused by neutrophils firmly adhered to the interior of the vessel wall. Administration of antibodies against Ly6G, a neutrophil-specific receptor, led to a ~60% reduction in the number of stalled capillaries and a ~30% increase in blood flow in cortical penetrating arterioles (Fig 1c and d). Administration of isotype control antibodies produced no changes in the number of stalls or blood flow. A single treatment with anti-Ly6G in AD mice led to significantly improved cognitive performance within 3-6 hr in tests of short-term and working memory. This acute improvement in cognitive performance was evident in mice with relatively advanced AD pathology (17 month old APP/PS1 mice, which show first cognitive impacts at 8 months) (Fig 1e and f). In summary, we have shown that neutrophils plug blood flow in a small fraction of brain capillaries in AD mouse models and that blocking this adhesion substantially increases brain blood flow and rapidly improves cognition. These data suggest that brain hypoperfusion likely contributes to cognitive deficits in mouse models of AD.

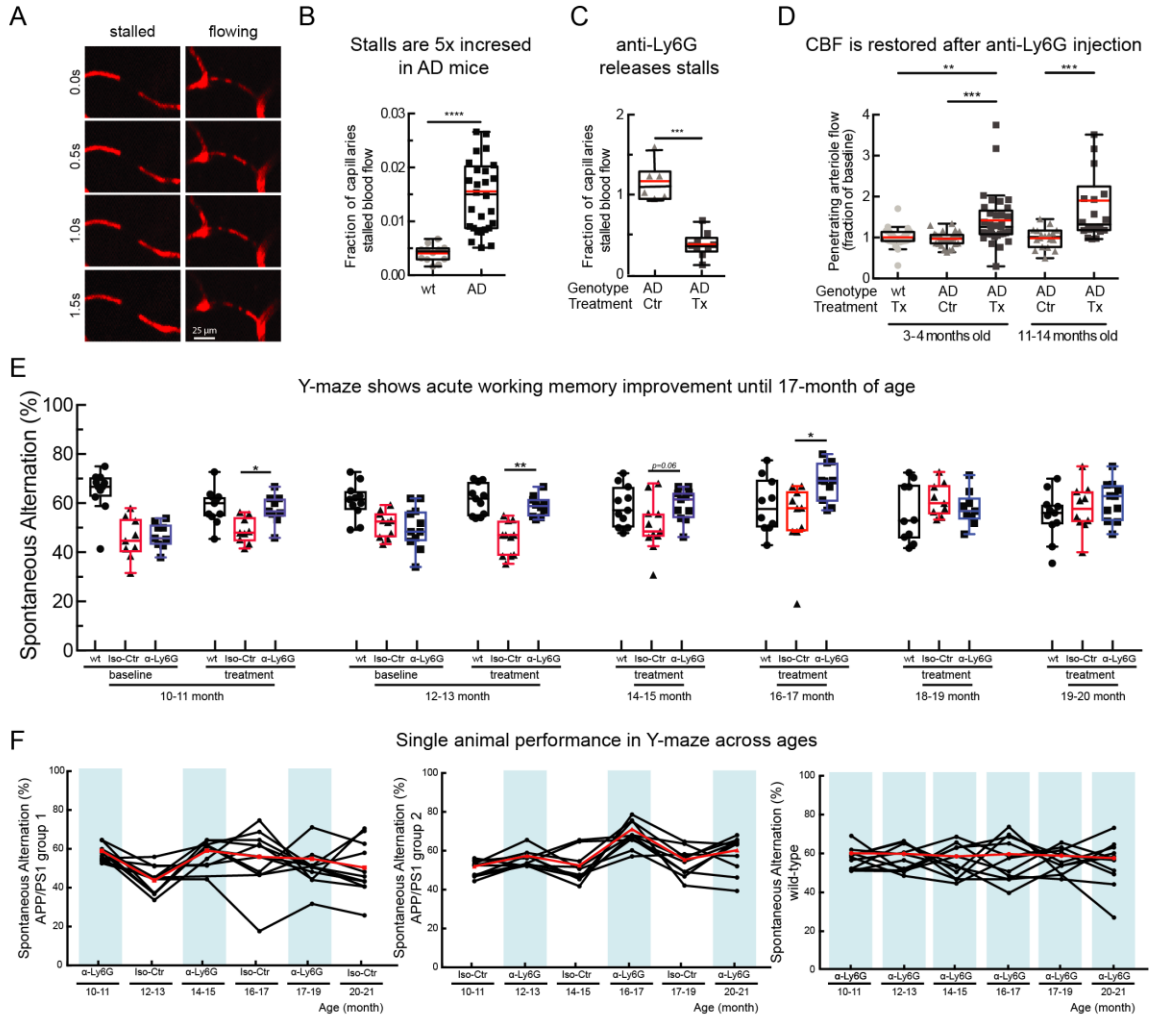


Figure 1: Stalling is a novel mechanism that leads to reduced blood flow and impaired cognitive function in AD. (A) Representative images showing a stalled vessel (stalled on left and flowing on right) red: Blood plasma. (B) Capillary stalls are 5x elevated in AD mice (C) anti-Ly6G treatment reduced the number of stalls by about 90%. (D) Blood flow is restored after single anti-Ly6G treatment. (E) Spontaneous alternation in the Y-maze task, bi-monthly measured staring at 10-11 month old APP/PS1 and wt mice at baseline and at 3-6 hr after a single administration of α-Ly6G or Iso-Ctr antibodies, (F) Single animals across age; left: group1, middle: group2 and right wt animals. Red line shows the median of each group.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 737.11/G10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH/NIA, R21AG054890
Cure Alzheimer's Fund

**Title:** Microglial ABCA7 contributes to the regulation of brain immune system

**Authors: *T. AIKAWA**[1], Y. REN[2], Y. YAMAZAKI[1], Y. A. MARTENS[1], M.-L. HOLM[1], C. T. ANDERSON[1], Y. W. ASMANN[2], G. BU[1], T. KANEKIYO[1]
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**Abstract:** The *ABCA7* gene encoding ATP-binding cassette transporter A7 is ranked as one of the top susceptibility loci for late-onset Alzheimer's disease (AD). Importantly, loss-of-function variants in *ABCA7* have been shown to increase the risk for AD. ABCA7 belongs to the ABC transporter family and likely regulates the distribution of phospholipids and cholesterol which associates with the phagocytic pathway. Although the accumulation and deposition of amyloid-β (Aβ) peptides in the brain are central events in AD, increasing evidence indicates that the brains immune system plays a critical role in disease development and progression. While we found that lipopolysaccharide (LPS)-induced mRNA expressions of pro-inflammatory cytokines were suppressed in the primary microglia and brains from heterozygous *Abca7* deficient (*Abca7*$^{+/-}$) mice compared to control wild-type mice, contributions of ABCA7 to the brains immune system are not fully understood. Thus, to identify the molecular pathway, we performed RNA-seq in the cortex from control and *Abca7*$^{+/-}$ mice with or without LPS administration. When network analysis was performed in the top-ranked module, identified through weighted gene co-expression network analysis (WGCNA), *Cd14* was identified an intramodular hub-gene inducing the differences in transcript profiles. We also confirmed that ABCA7 deficiency diminished the LPS-induced upregulation of CD14 in isolated microglia from those mice. These results indicate that CD14-mediated pathway in microglial ABCA7 could be involved in regulating the brain immune system. ABCA7 loss-of-function possibly compromises normal immune responses in the brain, which may contribute to AD pathogenesis.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 737.12/G11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant RF1 AG051495
IADC - Sarah Roush Memorial Fellowship in Alzheimer's disease research

**Title:** Fractalkine signaling drives distinct TREM2-dependant and TREM2-independant microglial responses to early amyloid pathology

**Authors: *S. PUNTAMBEKAR**[1], A. OBLAK[2], G. E. LANDRETH[3], B. T. LAMB[4]
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**Abstract:** The phagocytic and immune activity of CNS microglia in the homeostatic brain is restricted by inhibitory check-points such as the CX3CL1-CX3CR1/Fractalkine signaling pathway. While these negative signaling mechanisms are critical to limit by-stander damage within the immune-privileged brain, they prove to be detrimental under neurodegenerative conditions. In Alzheimer's disease (AD), characterized by accumulation of extracellular Aβ plaques and intra-neuronal NFTs due to hyperphosphorylation of tau, down-regulation of CX3CR1 has been implicated in shifting microglia towards a protective, disease associated (DAM) phenotype with a heightened phagocytic capacity. This protective phenotype is associated with increased expression of Triggering Receptor Expressed on Myeloid Cells-2 (TREM2). Consistent with these single-cell transcriptomics data, our studies using mouse models of AD have shown a reduction in fibrillar (ThioS$^{bright}$) Aβ plaque abundance in the CNS of APPPS1 CX3CR1$^{-/-}$ mice in early stages of pathology. Increased phagocytosis of injected Aβ by microglia in C57Bl/6 CX3CR1$^{-/-}$ mice suggests that the loss of CX3CR1 in the APPPS1 mouse model drives microglia towards a neuroprotective phenotype. By contrast, we see an increased proportion of ThioS$^{dim}$ plaques with a filamentous morphology in the APPPS1 CX3CR1$^{-/-}$ mice. These highly neurotoxic, filamentous plaques are associated with larger foci of dystrophic neurites in the cortex and hippocampus. Interestingly, this defect in plaque compaction is accompanied by reduced TREM2$^{+}$ microglia/macrophages around diffuse but not compact plaques. Furthermore, Iba1$^{+}$ cells surrounding diffuse plaques fail to polarize TREM2 to their plaque-interacting processes. To assess whether attenuated TREM2 responses and increased neurotoxicty correlate to defects in the microglial capacity to phagocytose/clear extracellular debris, we performed ex-vivo phagocytosis assays. Microglia from APPPS1 CX3CR1$^{-/-}$ mice show a significantly increased capacity to phagocytose and process internalized particles.

Consistent with our ex-vivo data, we see an increased proportion of plaque-associated Iba1$^{+}$ cells that internalize dystrophic neurites. Increased microglial phagocytosis is accompanied by region-specific changes in expression of phagocytic receptors (MerTK, Axl, TLR4) and pro-inflammatory mediators (iNos, TNF etc) in the cortex vs. hippocampus. Our data suggests that the loss of CX3CR1 during early pathology drives microglial activation that is primed to phagocytose/clear pathological structures (TREM2-independent) but is unable efficiently compact Aβ plaques (TREM2-dependant).

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 737.13/G12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Neuroprotective effects of digoxin on Alzheimer’s dementia model in rats

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**Abstract: Aims:** Alzheimer’s disease (AD) is the most common age-related neurodegenerative disorder, which causes progressive development of cognitive deficits with severe learning and memory loss, behavioral changes and eventually to morbidity and death. A complex mechanism for pathogenesis of AD has been recently proposed that involves an increase in inflammation. TNF-α is the major cytokine synthesized by activated microglia and neurons and initiating the inflammatory cascade. Examinations of postmortem AD brains has revealed that increased TNF-α co-localizes with Aβ plaques. IL-17 and TNF-α are also known to interplay and drive common molecular pathways. Although IL-17 can induce pro-inflammatory cytokines by itself, its effects are vastly increased when cooperating with TNF-α. Because Digoxin has some anti-inflammatory features due to inhibitory effects on IL-17/TNF-α in previous animal studies, we investigated the effects of Digoxin in an intracerebroventricular (ICV)-streptozotocin (STZ) animal model of sporadic-AD. **Methods:** A total of 18 Sprague-Dawley adult rats were divided into 3 groups of control (n=6), ICV-STZ+saline (n=6) and ICV-STZ+Digoxin (n=6). Twelve rats with AD, induced by STZ injection (3 mg/kg) into both lateral ventricles using a stereotaxic frame, were divided into 2 groups 5 days after the STZ injection: one treated with Digoxin (0.1 mg/kg/day, i.p.) and the other with 0.9% NaCl (1 ml/kg/day, i.p.) for 3 weeks. No surgery/treatment was given to the controls. After treatment, a passive avoidance learning (PAL) test was used followed by removal of the brain tissue in all animals. Brain TNF-α and ChAT

levels were determined, and neurons in the hippocampal CA1 and CA3 regions were counted by Cresyl violet staining. **Results:** ICV-STZ was found to significantly shorten the latency time on the PAL, increase brain TNF-α level, decrease brain ChAT activity and neuron counts in the hippocampus. On the other hand, Digoxin significantly attenuated all these detrimental effects induced by STZ. **Conclusions:** Digoxin significantly prevented the ICV-STZ-induced memory deficit by attenuating the hippocampal neuronal loss, neuroinflammation and cholinergic deficit in rats. These findings suggest that Digoxin may be beneficial for treating AD.

Results

| | Normal Group | ICV-STZ and Saline Group | ICV-STZ and Digoxin Group |
|---|---|---|---|
| Brain TNF-alfa level (ng/mg protein) | 0.31 ± 0.04 | 2.58 ± 0.45 * | 1.60 ± 0.18 # |
| ChAT (choline acetyl transferase) (U/g protein) | 115.2 ± 10.6 | 59.3 ± 6.9 * | 140.75 ± 16.9 ## |
| CA1 neurons counts | 56.3 ± 4.5 | 43.5 ± 3.1 * | 53.3 ± 4.2 # |
| CA3 neurons counts | 55.3 ± 5.02 | 29.1 ± 2.6 * | 43.5 ± 2.1 # |
| Latency time (sec) | 245.5 ± 40.6 | 48.5 ± 7.1 * | 283.2 ± 16.8 ## |

* $p<0.0001$, Saline Group compared with Normal Group, ## $p<0.0001$, Digoxin Group compared with Saline Group, # $p<0.05$, Digoxin Group compared with Saline Group

**Disclosures: M.A. Erdogan:** None. **G. Yigitturk:** None. **O. Erbas:** None.

**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 737.14/H1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant NS073670
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VA Merit Award I01BX002477

**Title:** Expression of TREM2 and its association with glia maturation factor in human Alzheimer’s disease brain

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**Abstract:** Alzheimer's disease (AD) is the most common form of neurodegenerative disease with cognitive impairment in the elderly people. The classic neuropathological hallmarks are the formation and accumulation of extracellular amyloid plaques (APs) and intracellular hyperphosphorylated tau containing neurofibrillary tangles (NFTs). In addition, neuroinflammation plays an important role in the pathogenesis of AD. We have previously demonstrated the increased expression of glia maturation factor (GMF), a brain predominant neuroinflammatory protein in AD specific brain regions. Triggering receptor expressed in myeloid cells 2 (TREM2) is implicated in AD pathogenesis. Here, we studied the expression of TREM2 and GMF and their association with APs and NFTs in the temporal cortex of AD brains. Immunohistochmemical analysis revealed an increased expression of GMF and TREM2 in AD brains as compared to age matched non-AD brains. Furthermore, we used double immunohistochemical and immunofluorescence labeling to analyze the co-localization of TREM2 and GMF with APs as well as NFTs in AD brains. TREM2 is upregulated and associated with GMF within the vicinity of APs in AD brains. Expression of TREM2 was also increased at the vicinity of NFTs in AD brains. Additionally, an increased TREM2 immunoreactivity was found to correlate with strong immunolabeling of ionized calcium-binding adopter molecule-1 (Iba-1), an activated microglial marker, as well as 6E10 labeled APs and phosphorylated tau stained NFTs. Brain regions with increased APs were associated with TREM2-immunoreactive microglia as well as GMF immunoreactivity in AD brains. These findings suggest that expression of GMF and TREM2 exacerbates neuroinflammation, neurodegeneration and other pathological changes associated with AD.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 737.15/H2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** AG034214

**Title:** Trem2 regulatory region activity in human cell lines

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**Abstract:** Triggering receptor expressed on myeloid cells 2 (TREM2) genetic variation is associated with Alzheimer's disease (AD) risk and neuroinflammation. ADAM10 cleavage produces a soluble form of TREM2 (sTREM2) which is increased in MCI and AD. Since ADAM10 is not elevated in AD it is still unclear how sTREM2 levels increase in AD. In the human brain, TREM2 mRNA is expressed in regions known to be affected in AD. However, given that TREM2 plays a role in neuroinflammation in AD mouse models, it is important to understand the underlying mechanisms driving changes in TREM2 expression for potential neuroinflammation and therapeutic intervention strategies. In this investigation, it was hypothesized that trans-acting factors present in certain cell types, such as glial cells, modulate TREM2 regulatory element activity. The aims of this study were to: 1) Demonstrate that the activity of the TREM2 promoter is cell type specific. 2) Demonstrate that genetic variation in the specific regions of the promoter alter activity according to cell type. 3) Demonstrate that the 3'UTR influences promoter activity according to cell type. Information from this study will reveal which cell lines have TREM2 active trans-acting factors that influence the TREM2 gene regulation. The TREM2 promoter region was PCR amplified from human genomic DNA and cloned into a pGL4.10 luciferase reporter vector. Genomic DNA was genotyped for selected promoter SNPs. Three variant combinations (TREM2 promoter haplotypes) were identified and cloned into a pGL4.10 luciferase reporter vector alone and with the TREM2 3'UTR. This produced six TREM2 regulatory region haplotype constructs that were transiently transfected into eight human cell lines, including neuronal, glial and a hepatocyte cell line. The results show that TREM2 regulatory element luciferase reporter constructs have different activity level that depends on cell type and promoter haplotype. These results suggest that TREM2 expression is specific to certain cell types and implicates the presence of critical cell type specific trans-acting factors that act upon the TREM2 specific regions of the promoter. Understanding TREM2 regulation provides insight into potential targets for activation or inhibition of TREM2. Further research is warranted to characterize the trans-acting factors that contribute to TREM2 gene regulation.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 737.16/H3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** AG034214
DOD AZ160058
AG022304
Jane and Lee Seidman Fund

**Title:** Soluble TREM2 and inflammatory biomarkers in Alzheimer's disease

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**Abstract:** Alzheimer's disease (AD) has been genetically and pathologically associated with neuroinflammation. Triggering receptor expressed on myeloid cells 2 (TREM2) is a microglial receptor involved in neuroinflammation that is genetically linked to AD risk. However, little is known about the relationship between soluble TREM2 (sTREM2) levels and other inflammatory biomarkers in both central and peripheral compartments in AD.Given that sTREM2 levels have been described as elevated in AD, it was hypothesized that we would also observe an elevation of sTREM2 levels in CSF in our AD cohort. Secondarily, and that there is a relationship between sTREM2 levels and blood brain barrier (BBB) integrity and other measures of central and peripheral inflammation. Cognitively normal controls, mild cognitive impairment (MCI) and AD donated cerebrospinal fluid (CSF) and plasma to the Cleveland Clinic Lou Ruvo Center for Brain Health Biobank. Inflammatory and BBB biomarkers were measured using a Luminex, Millipore system and clinical core services. We confirmed previous findings of elevated sTREM2 in the CSF of MCI and AD. Peripheral inflammatory markers were, for the most part, not associated with CSF or plasma sTREM2 levels. Interestingy, there were significantly positive correlations between CSF sTREM2 and plasma sTREM2 and between CSF sTREM2 and a marker for blood brain barrier integrity. A consistent association of peripheral or central markers of inflammation and CSF sTREM2 levels was not found, suggesting a limited impact of general inflammation on sTREM2 levels. An association between peripheral sTREM2 levels and CSF sTREM2, as well as an association between CSF sTREM2 and a marker of blood brain barrier integrity, was observed in AD, suggesting a potential role of peripheral TREM2 in central TREM2 biology.

**Disclosures: J.B. Leverenz:** 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.; Avid, Biogen, Sanofi/Genzyme, GE Healthcare,. F. Consulting Fees (e.g., advisory boards); Axovant, GE Healthcare. **M. Khrestian:** None. **Y. Shao:** None. **L. Bekris:** None.

**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

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**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant RO1AG057754-01

**Title:** An anti-TREM2 antibody agonizes TREM2 and promotes microglial clustering around amyloid plaques in the 5XFAD mouse model of amyloid deposition

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**Abstract:** Mutations in the triggering receptor expressed on myeloid cells 2 (TREM2) gene have been associated with a significantly increased risk of Alzheimer's disease (AD). We have been characterizing a TREM2-agonizing antibody called A-002a, developed by Alector, Inc. This antibody activates the TREM2 receptor and induces DAP12 signaling in vitro. We hypothesized that agonizing TREM2 would ameliorate amyloid pathology via the engagement of microglia. To assess this, we performed intracranial and systemic administration of the A-002a antibody to 5XFAD mice. We examined brain tissue 3 days following a single intracranial injection and following 16 weekly intraperitoneal injections. In both instances we found that beta-amyloid deposition was decreased and cognition was improved in the systemic administration study. To assess the microglial response to A-002a we examined Iba1 immunohistochemically stained tissue sections that were counterstained with Congo red to localize the compact amyloid plaques. We determined that both intracranial and systemic administration of A-002a significantly increased the staining density for Iba1. In the intracranial study, we found a 100% increase in the Iba1 immunoreactivity in the hippocampus and frontal cortex. In the systemic administration study we found an 80% increase in the Iba1 immunoreactivity in the frontal cortex and a 200% increase in the hippocampus. We developed an analysis workflow that allowed us to count the number of Iba1-positive microglial cell bodies in a fixed area immediately surrounding the Congophilic amyloid plaques. We found that the numbers of microglia associated with amyloid plaques following intracranial administration of A-002a was increased from 3 microglial cells per plaque to an average of 8 microglial cells per plaque in both the frontal cortex and hippocampus. Also, a similar increase was seen following systemic administration of A-002a, where we found that there was a significant increase from an average of 2 microglial cells per plaque to an average of over 5 microglial cells per plaque. The size of the plaques was controlled for, where only plaques of a given size were selected for analysis. In conclusion, an anti-TREM2 antibody, A-002a, that has been shown to agonize TREM2 activates microglia and increases the numbers of microglial cells associated with amyloid plaques, while significantly reducing amyloid deposition in the 5XFAD mouse model.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 737.18/H5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** National Institutes of Health Grant AG048205
VA Merit Review Award I01BX002477

**Title:** Glia maturation factor (gmf) promotes alteration of mitochondrial dynamics and oxidative stress mediated apoptosis in sh-sy5y cells

**Authors: *M. E. AHMED**[1,2], S. GOVINDHASAMY PUSHPAVATHI1[1,2], R. THANGAVEL[1,2], K. DURAISAMY[1,2], S. RAIKWAR[1,2], D. IULLIA[1], S. ZAHEER[1], S. IYER[1,2], A. ZAHEER[1,2]
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**Abstract:** Beta amyloid (Aβ) peptide is shown to be toxic to the mitochondria and implicates these organelles in the progression and pathogenesis of Alzheimer's disease (AD). Glia maturation factor (GMF), a neuroinflammatory protein isolated and cloned in our laboratory plays an important role in the pathogenesis of AD. Mitochondria are constantly altering their size and shape while traversing through neurons; from the cell bodies to nerve terminals and synapses of neurons, the sites of high-energy demand. Mitochondrial fission and fusion proteins are equally balanced in healthy neuronal cells. Mitochondrial fragmentation is generally observed in the effected brain regions in (AD). We hypothesized that Glia maturation factor (GMF) a brain-localized inflammatory protein perturbs mitochondrial dynamics by altering fission and fusion protein levels and through oxidative stress- induced apoptosis as evident in Aβ (1-42) treated human neuroblastoma (SH-SY5Y) cell lines in an *in vitro* model of AD. We, report that cells incubated with GMF and Aβ (1-42) promotes mitochondrial fragmentation, disturbs mitochondrial dynamics by shift in the mitochondrial fission and fusion protein balance. This in turn leads to increased oxidative stress, oxidative DNA damage and shifts the Bax/Bcl2 expression resulting in release of cytochrome-c, and increased activation of effector caspases expression and eventual apoptosis. We report that GMF significantly upregulates fission protein Drp1 and Fis1 but downregulates fusion proteins OPA1, Mfn1 and Mfn2 levels. This study shows that GMF, an important neuroinflammatory mediator alters mitochondrial dynamics through oxidative stress mediated apoptosis. We conclude that upregulated GMF could be a risk factor for AD and suppression of GMF should represent a new and promising therapeutic strategy for combating AD

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 737.19/H6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH 5R21NS097945
NIH 5R01AG054533

**Title:** Locus coeruleus noradrenergic system and beta-adrenergic receptor modulation of neuroinflammation in mouse models of Alzheimer’s disease

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**Abstract:** Locus Coeruleus (LC) noradrenergic (NA) neurons degenerate early in Alzheimer’s disease (AD). Loss of NA tone likely contributes to AD pathophysiology and its progression. We have previously demonstrated that beta-adrenergic activation leads to modulation of chronic neuroinflammation in mouse models of AD. The current study was designed to examine mechanisms of adrenergic modulation of neuroinflammation in mouse models of AD using selective deletion of beta-adrenergic receptor (adrb1 and adrb2) subtypes on myeloid-lineage cells (e.g. microglia and macrophages). Transgenic mice over-expressing human amyloid precursor protein (APP) were crossed with adrb1- or adrb2-floxed mice expressing cx3cr1-creER to generate a myeloid-specific tamoxifen-inducible deletion of adrb1 or adrb2. Adrenergic modulation of inflammation was also examined in adrb1- or adrb2-flox/cx3cr1-creER mice in a model of LPS-induced neuroinflammation. Specificity of adrenergic effects on inflammation following LPS were also examined with selective beta-adrenergic pharmacology. At termination of each study, mice were anesthetized, blood was collected for plasma by cardiac puncture, and mice were transcardially perfused with cold phosphate buffered saline. Brain was removed and one hemisphere was fixed and the other flash frozen. Plasma was frozen on dry ice. All tissues were stored at -80 C. Amyloid beta and plasma cytokine concentrations were quantified by ELISA. RNA was isolated from brain homogenate and cytokine gene expression was quantified by real-time polymerase chain reaction. We report modulation of cytokine gene expression following knockout of adrb1- or adrb2- in myeloid-lineage cells. Deletion of beta-adrenergic receptors exacerbated the inflammatory response to LPS. Effects of LPS on cytokine responses were inhibited by beta-adrenergic agonism. These data support the hypothesis that beta-

adrenergic receptors modulate systemic and central inflammation with implications for modulation of disease progression in AD.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 737.20/H7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Alzheimer’s Association Research Grant Program (USA) in partnership with Brain Canada AARG501466

**Title:** A meta-analysis of complement proteins in Alzheimer's disease

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**Abstract:** Purpose: Genome-wide association studies implicate complement pathway activity as a cause of Alzheimer’s disease (AD), and the hallmark AD biomarker amyloid-β has been shown to activate the complement cascade; however reports of complement proteins measured in peripheral blood and cerebrospinal fluid (CSF) have conflicted. This meta-analysis seeks to quantitatively combine data from clinical studies of complement pathway data, in peripheral blood and CSF studies. Methods: Literature was searched using Medline, PubMed, Embase, PsycInfo, Cochrane Controlled Trials Register, and Cochrane Database of Systematic Reviews. Original peer-reviewed studies measuring complement and complement regulator protein concentrations in AD and healthy elderly control (NC) subjects were included. Mean (± standard deviation) concentrations for AD and NC were extracted and combined in random effects models. Results: From 3596 records, 73 studies measuring relevant CSF or peripheral blood protein concentrations have been included thus far. Preliminary results show increased CSF concentrations of complement component 1q (C1q; $N_{AD}/N_{NC}$=151/117, Z=2.46, p=0.01; $I^2$=54%) in AD compared to NC. Concerning complement pathway regulators, clusterin concentrations were increased in both CSF ($N_{AD}/N_{NC}$=371/437, Z=4.18, p<0.0001; $I^2$=31%) and plasma ($N_{AD}/N_{NC}$=1269/1651, Z=2.06, p=0.04; $I^2$=97%) in AD compared to NC, and amyloid P (AP) concentrations were increased ($N_{AD}/N_{NC}$=283/109, Z=2.94, p=0.003; $I^2$=0%) in CSF. Conclusions and Implications: The CSF results support involvement of the complement pathway in AD; elevated C1q and AP levels might promote activity earlier in the classical complement cascade, while elevated clusterin could inhibit formation of the membrane attack complex (MAC) in the final stages of the cascade. These changes would be consistent with increased

opsonization and inflammatory activity, while limiting MAC-induced cell lysis. Increased peripheral blood clusterin concentrations in AD might imply communication/coordination of immunoregulatory activities between the brain and periphery.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 737.21/H8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Supplement to NIH/NIA P30 AG010124 to S.P (PI: John Q. Trojanowski)
NanoString Technologies

**Title:** Comprehensive analysis of microglia across neuropathological stages of Alzheimer's disease (AD)

**Authors: *K. R. MILLER**[1], S. PROKOP[2], S. R. LABRA[2], R. M. PITKIN[2], E. B. LEE[2], V. M. LEE[2], J. Q. TROJANOWSKI[2]
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**Abstract:** The pathognomonic protein deposits in AD elicit an activation of microglia, but role of this innate immune activation in the course of AD is controversial, in part because mouse models of AD pathology do not fully capture the complex human disease condition. To tackle this problem, we undertook a comprehensive analysis of microglia in different stages in human AD brains to lay the groundwork for mapping the innate immune response towards extracellular and intracellular pathologies in human neurodegenerative disease. Morphologic characterization of microglia in different stages of AD using immunohistochemical (IHC) markers revealed increased microglial activation with advancement of AD neuropathological changes and an increase in dystrophic microglia in late disease stages. Our immunohistochemical findings were corroborated with cell type and pathway specific gene expression profiling using the human Neuropathology gene expression panel on the Nanonstring nCounter system, which demonstrated an increase in microglial activation with progression of AD neuropathological changes. This analysis also revealed distinct differences in gene expression profiles derived from patient samples carrying an AD associated risk variant of the microglia receptor Trem2. We further homed in on these differences by using the nCounter human Neuroinflammation panel to elucidate differentially regulated pathways in AD patients carrying Trem2 risk variants in comparison to disease stage matched patients with a normal variant of Trem2.
Our studies demonstrate that combining morphologic characterization of microglia cells with

novel cell type and pathway specific gene expression analysis in human post mortem brain specimens allows for interrogation of the innate immune system in the complex environment of a coexisting multitude of different protein pathologies in AD and provides novel insight into the role of the immune system in AD pathogenesis and progression.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 737.22/H9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant RF1AG054156
NIH Grant R56AG057768

**Title:** Associations between inflammatory profiles and human neuropathology are altered based on apolipoprotein E4 genotype

**Authors: N. AYTAN**[1], J. FRIEDBERG[2], J. D. CHERRY[3], W. XIA[4], *T. D. STEIN[5]
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**Abstract:** Alzheimer disease (AD) is a chronic neurodegenerative disease with a multitude of contributing genetic factors, many of which are related to inflammation. The *apolipoprotein E (APOE) allele E4* is the most common genetic risk factor for AD; *APOE E4* is related to a pro-inflammatory state independent of beta-amyloid deposition in mice, but its association with inflammatory profiles and the development of AD pathology in human brain tissue is largely unknown. To test the hypothesis that microglia and AD-implicated cytokines were differentially associated with AD pathology based on the presence of E4, we examined post-mortem brain tissue from participants with and without the *APOE E4* allele within a community based aging cohort ($n$ = 211). Cellular density of Iba1, a marker of microglia, was positively associated with tau pathology density as measured by AT8 immunostaining in E4 positive participants ($p$ = 0.045), but not in E4 negative participants. Analysis of cytokines implicated in AD, i.e. IL-10, IL-13, IL-4, IL-1α, revealed a significant negative association with AT8, independent of beta-amyloid$_{1-42}$ levels, in E4 negative, but not E4 positive participants. Overall, the association of mostly anti-inflammatory cytokines with less tau pathology suggests a protective effect in E4

negative participants. These associations are largely absent in the presence of E4 where tau pathology is significantly associated with increased microglial cell density. Taken together, these results suggest that *APOE E4* mediates an altered inflammatory response and increased tau pathology independent of beta-amyloid pathology.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 737.23/H10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH R01AG048993

**Title:** Effects of colonic inflammation induced by dextran sulfate sodium on the brain pathology of an Alzheimer's disease mouse model

**Authors: *M. SOHRABI**, J. WIESER, C. K. COMBS
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**Abstract:** Alzheimer’s disease (AD) is a progressive age-related neurodegenerative disorder and the most common form of dementia. The disease is characterized by the accumulation of extracellular Aβ plaque deposition, intracellular neurofibrillary tangles, and neuro-inflammation. These pathophysiological features spread throughout brain regions as the disease progresses and result in neuronal death, synaptic loss, and learning and memory decline. Aging is also associated with inflammaging which leads to increased permeability of the gut epithelial monolayer and blood-brain barrier. Besides AD, inflammatory bowel disease (IBD) is another chronic inflammatory condition with increased incidence among elderly. In spite of the fact that it is known that the brain communicates with the gastrointestinal tract via the well-established gut-brain axis, the influence exerted by chronic intestinal inflammation on the brain phenotype in AD is not fully understood. We hypothesized that increased gut inflammation would alter the brain pathology of a mouse model of AD. To test this idea, 2% dextran sulfate sodium (DSS) dissolved in the drinking water and fed *ad libitum* to male C57BL/6 wild type and $APP^{NL-G-F}$ mice (AD mouse model) at 6-10 months of age for two cycles of three days each. DSS is a negatively charged sulfated polysaccharide which results in bloody diarrhea and weight loss, pathology similar to human IBD. Both wild type and $APP^{NL-G-F}$ mice developed an IBD-like condition with an attenuated disease activity index in the AD mice. Brain histologic and biochemical assessments demonstrated increased insoluble/soluble $A\beta_{1-42}$ and soluble $A\beta_{1-40}$

levels along with the increased microglial immunoreactiviy in DSS treated $APP^{NL-G-F}$ mice compared to wild type and vehicle treated $APP^{NL-G-F}$ mice. These data demonstrate that gut inflammation is capable of altering plaque deposition and immune cell behavior in the brain. This study increases our knowledge of the impact of peripheral inflammation on Aβ deposition and neuroinflammatory aspects of AD via an IBD-like model system.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 737.24/H11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** FONDECYT 1151297

**Title:** Il-6 correlates with spatial navigation dysfunction in amnestic mild cognitive impairment

**Authors: *N. ROGERS**[1], C. SANMARTIN[2], D. PONCE[3], J. VALDES[1], M. BEHRENS[1]
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**Abstract:** The hippocampus plays an essential role in the consolidation of declarative and spatial memory; early dysfunction characterized by disturbances in evocation of recently acquired memories and spatial navigation can be seen in Amnestic Mild Cognitive Impairment (aMCI), widely recognized as a prodromal stage of Alzheimer's disease (AD). This structure is also particularly vulnerable to systemic inflammation, which in turn has been associated with pathological aging, consistent with the hypothesis that inflammatory and immune mechanisms are involved in the pathogenesis of AD. Epidemiological studies have shown an association of elevated plasma levels of IL1-B and IL-6 in AD. IL-1B plays a role in innate immunity as a mediator of the inflammatory response; it also mediates the secretion of other inflammatory interleukins such as IL-6. We aimed to determine if spatial navigation impairment in these patients, assessed by a virtual Morris Water Maze (vMWM), correlates with IL-1B and IL-6 plasma levels and gene expression in peripheral blood mononuclear cells (PBMC). We recruited 38 patients (20 healthy controls and 18 aMCI patients (Alberts et al 2011). Montreal Cognitive Assessment (MoCA) and Clinical Dementia Rating (CDR) were used as tools for diagnosis. No significant epidemiological differences were found between groups (age, sex, comorbidities, educational level). Spatial navigation was tested through a three-staged version of Virtual Morris Water Maze (vMWM) of increasing difficulty. IL-1B and IL-6 plasma levels and mRNA were measured in plasma and PBMC from aMCI patients and controls, by ultra-sensitive ELISA and qPCR respectively. aMCI patients showed a higher expression of IL-6 compared to controls

(1.28 versus 0.24 fold-changes, $p<0.05$, Mann-Whitney's U-test). Then Spearman correlations between interleukins measures and vMWM variables were conducted and we observed: positive correlation between IL-6 expression and success ratio ($r = - 0.35$, $p = 0.04$); negative correlations with the amount quadrant crossings ($r = 0.52$, $p = 0.047$), and latency to target ($r = 0.58$, $p = 0.025$) in the aMCI group; and a positive correlation between plasma IL-6 levels and distance ratio ($r = 0.57$, $p = 0.005$), a measure of path efficiency. No significant results were observed for IL-1B and behavioral variables. As a conclusion, aMCI patients's performance in the vMWM correlated proportionally to higher expression of IL-6 in PBMC. These results suggest an association between a pro-inflammatory systemic milieu and markers of hippocampal dysfunction that should be explored in future research.

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**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 737.25/H12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** KHIDI-HI17C1260

**Title:** Mir-146a regulates neutrophil extracellular trap formation that precedes Alzheimer's diseases with oligomeric Aβ deposits

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**Abstract:** Alzheimer's disease (AD) is a complex brain disease and the most common form of neurodegenerative dementia. Several genetic, environmental, and physiological factors, including inflammations and metabolic influences, are involved in the pathogenesis of AD. Inflammations are composed of complicated networks of many chemokines and cytokines with diverse cells. Inflammatory molecules are needed for the protection against pathogens, and maintaining their balances is important for normal physiological function. Recently, our studies found that miR-146a, a negative regulator of inflammation, precedes netosis in AD-Tg mice with oligomeric Aβ (oAβ) deposits. The relationship between neutrophil extracellular traps and AD has not been understood yet. Thus, our aim was to determine the role of neutrophil extracellular trap compounds as prognostic biomarkers of oAβ in AD and to study whether miR-146a affects Netosis.
In this work, we investigated the molecular role of miR-146a in the pathogenesis of oAβ in AD Tg mice using Confocal microscope and CLARITY technique. The microRNAs are mainly in

immune cells, which are one of the main protagonists of Netosis. Thus, the infiltration of activated monocyte/neutrophils in brain mediates an overactivation of the immune system. In addition, findings show that neutrophils shed neutrophil extracellular traps (NETs), which consist of cell-free DNA (cfDNA), histones, NE (neutrophil elastase), and cathepsin G that trigger the coagulation and inflammation underlying vascular complications. NE activity can provide new NET prognostic information in AD-Tg mice. These findings provide evidence of a crucial role of miR-146a in neutrophil extracellular trap generation and 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) high risk in pathogenesis of AD.

**Disclosures: S. Kim:** None.

**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 737.26/H13

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** MoE Tier 2: R-143-000-589-112 (YLL)
MoE Tier 1: R-184-000-272-114 (C-ML)
NMRC-1222-2009 (SK and C-ML)

**Title:** Arachidonic acid analogues and curcumin targeting cytosolic phospholipase A2 as anti-neuroinflammatory agents

**Authors: *C.-M. LOW**[1,2], C.-Y. NG[3], S. KANNAN[5], Y.-J. CHEN[4], F. C.-K. TAN[2], Y.-H. ONN[1], X.-H. LEE[1], W.-Y. ONG[3], M.-L. GO[4], C. S. VERMA[5], S. KESAVAPANY[6], M. ADMED[7], Y. L. LAM[3]
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**Abstract:** Cytosolic Phospholipase A2 (cPLA2) are enzymes catalyzing the sn-2 position of membrane phospholipids to release fatty acids (eg. arachidonic acid) and lysophospholipids (eg. lysophosphatidylcholine). In the central nervous system, cPLA2 activation is implicated in the pathogenesis of various neurodegenerative diseases that involves neuroinflammation, thus making it an important pharmacological target. We present a new class of arachidonic acid analogues (33 compounds), together with curcumin, and their ability to inhibit cPLA2. Several compounds inhibit cPLA2 more strongly than arachidonyl trifluoromethyl ketone (AACOCF3;

IC50 16.5+- 3.0uM), an inhibitor that is commonly used in the study of cPLA2-related neurodegenerative diseases. One of the inhibitors (2i) with IC50 2.9+-0.2uM was found to be cPLA2-selective, non-toxic, cell and brain penetrant and capable of reducing reactive oxygen species (ROS) and nitric oxide (NO) production in stimulated microglial cells. Computational studies shed insights on how 2i interacts with cPLA2. We also showed curcumin directly inhibits cPLA2, reduces ROS and NO production in stimulated microglial cells.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 737.27/H14

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** The role of immune cells in Alzheimer’s disease analyzed by crossing 5xFAD mice with $CX3CR1^{+/GFP}$ and $CCR2^{+/RFP}$ mice

**Authors: *H. CYNIS**, Y. YOLUC, V. NYKIEL, S. GEISSLER, S. BARENDRECHT
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**Abstract:** Alzheimer’s disease (AD) is a neurodegenerative disorder, characterized by an abnormally fast cognitive decline. In recent years, the role of CNS resident microglia in AD came into focus. Microglia cells normally ensure the immune surveillance of the brain. In addition, it became evident, that also peripheral monocytes might enter the brain under certain disease conditions and thereby could contribute to pathology. The aim of our project is to determine the contribution of both microglia and infiltrating peripheral macrophages to AD-like pathology in mice. Therefore, we have crossed the well-characterized 5xFAD mouse model of AD with two different reporter mice: $CX3CR1^{+/GFP}$ and $CCR2^{+/RFP}$ knock-in mice. These mice express green, respectively red, fluorescent protein instead of one allele of these receptors. These allow us to easily distinguish between resident CNS immune cells (microglia - green) and infiltrating cells (monocytes/macrophages - red) based on the fluorescent color. In addition, the function of the different immune cells is also expected to be altered by a 50% reduction of gene expression of the targeted receptors. We performed immunohistochemistry, as well as biochemical analysis of the brains to compare regular 5xFAD mice with 5xFAD mice combined with $CX3CR1^{+/GFP}$ and $CCR2^{+/RFP}$, respectively. Here, we will present data on the analysis of brains from 6 months, as well as 12 months old mice, from both sexes. We expect that a partial knock-out of each receptor results in an aggravation of pathology. The next step in our project is to investigate the behavioral consequences of the partial knock-out, as well as the complete

knock-out ($CX3CR1^{GFP/GFP}$ or $CCR2^{RFP/RFP}$), of these receptors on the neuropathology of 5xFAD mice using a battery of phenotyping tests. Subsequently, the brains of these mice will also be investigated using immunohistochemistry and biochemical methods, again at the ages of 6 and 12 months, and in both sexes. This project will help to elicit the role of different immune cells in the pathology of AD, increasing the understanding of this disease, and in future possibly leading to new targets for the development of therapies.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 737.28/H15

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** 5T32 NS077889

**Title:** An emerging role for Hsp27 in vascular cognitive impairment and dementia

**Authors: *B. R. PRICE**[1], T. L. SUDDUTH[2], C. A. DICKEY[3], D. M. WILCOCK[2]
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**Abstract: Background:**
Hyperhomocysteinemia (HHcy) is a risk factor for vascular cognitive impairment and dementia (VCID), as well as Alzheimer's disease. The mechanism by which HHcy promotes VCID or AD remains unknown. 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 this sequelae of 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 cancers and neurodegenerative diseases. Given that Hsp27 is shown to be involved in cerebrovascular dysfunction in stroke models, and is known to signal through the p38 MAPK signaling pathway, a critical driver of the proinflammatory response, we hypothesized Hsp27 is an early mediator of HHcy-induced neuroinflammation, and therefore, the downstream events that occur as a result.
**Methods:**
Wildtype and $Hsp27^{-/-}$ mice were subject to a HHcy-inducing diet for 14 weeks. 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. Western blot and MSD were used to confirm some of the identified proteins.

**Results:**

Our wildtype-HHcy model displayed significant pro-inflammatory responses and astrocytic end-foot disruptions, as well as significant microhemorrhage induction. Significantly, we found that there was no induction of the pro-inflammatory phenotype in the $Hsp27^{-/-}$ mice subjected to the HHcy-inducing diet for 14 weeks. We also found a reduction in the microhemorrhage incidence in the $Hsp27^{-/-}$ mice, as well as improved survival of the mice, indicating that they were resistant to the HHcy diet.

**Conclusions:**

Hsp27 appears to be an early essential mediator of HHcy-induced pathology. Deletion of Hsp27 provides protection from diet-induced attrition, neuroinflammation, and cerebrovascular events. This suggests that Hsp27 may be an attractive therapeutic target for the treatment of VCID.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 737.29/H16

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIA AG043522

**Title:** Microglial ablation and repopulation with a CSF1-R inhibitor alters amyloid pathology in a mouse model of Alzheimer's disease

**Authors: *B. CASALI**[1], 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 homeostasis, 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. Accordingly, 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. Although withdrawal of inhibitor leads to rapid repopulation and restoration of normal function of microglia, it is unknown how a disease context would influence the functions of repopulated microglia. In the 5xFAD mouse model of AD, we show that treatment with the highly selective CSF1-R inhibitor PLX5662 effectively ablates microglia from the brain, curtails inflammation, and reduces plaque burden in the brain. Following withdrawal of PLX5662, microglia repopulated to similar levels as control-treated animals. Interestingly, we observed regional differences in repopulated microglia's ability to alter plaque burden. This suggests that newly repopulated microglia in certain brain regions may be endowed with enhanced disease-modifying effects which could inform future studies with CSF1-R inhibitors.

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**Poster**

**737. Alzheimer's Disease and Other Dementias: Neuroinflammation and Immune Actions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 737.30/H17

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Modulation of microglia polarization by sphingolipid

**Authors: *G. WANG**[1], L. ZHONG[2], H. QIN[2], Z. ZHU[2], A. ELSHERBINI[2], E. BIEBERICH[2]
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**Abstract:** Microglia activation and neuroinflammation plays key roles in neurodegenerative diseases. We present evident here that the sphinster homolog 2 (Spns2), a S1P transporter, regulates microglia states in vitro and in vivo. Spns2 deficiency in primarily cultured microglial cells significantly reduced the production of inflammatory cytokines, while increased anti-inflammatory cytokines, induced by lipopolysaccharide (LPS) and amyloid beta peptide1-42 (Aβ42) oligomers. This regulation is accompanied by altered Toll-like receptor 4/nuclear factor kappa B (TLR-4/NFκB) signaling, shown by reduced levels of phosphorylated P65 (pP65). To study the in vivo effect of Spns2KO on microglia activation, we stereotactically administered Aβ42 oligomers into mouse brains. After 6 weeks, Spns2 deficient brains showed significantly reduced microglia activation labeled by IBA1. More interestingly, Spns2 deficiency ameliorated working memory deficit that was caused by Aβ42. These results show that Spns2/S1P signaling mediates the polarization states of microglia during neuroinflammation, and plays a potentially

crucial role in AD pathology. (Supported by a Scientist Development Grant from American Heart Association National Center and a Biomedical Research Grant from American Lung Association to GW and NIH R01 5R01AG034389 to EB).

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**Poster**

**738. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 738.01/H18

**Topic:** C.02. Alzheimer's Disease and Other Dementias

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**Title:** 27-Hydroxycholesterol as a molecular link between hypercholesterolemia and synapsis dysfunction

**Authors: *P. MERINO-SERRAIS**[1], R. LOERA-VALENCIA[1], P. RODRIGUEZ-RODRIGUEZ[1], C. PARRADO-FERNANDEZ[1], M. ISMAIL[1], S. MAIOLI[1], E. JIMENEZ-MATEOS[3], I. BJORKHEM[2], J. DEFELIPE[4], A. CEDAZO-MINGUEZ[1]
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**Abstract: Background:** Hypercholesterolemia in middle age is considered a risk factor for the development of Alzheimer’s disease (AD) and dementia (Kivipelto et al., 2001). Given the fact that cholesterol itself does not pass the blood-brain barrier (BBB), is still unclear how high levels of cholesterol in the circulation could have an impact on cognition. Accumulating evidence shows that high levels of the BBB permeable cholesterol metabolite, 27-OH, are able to induce neurodegenerative processes leading to cognitive decline (Liu et al., 2016). Moreover, higher levels of 27-OH were found in brains and cerebrospinal fluid (CSF) from AD patients (Heverin et al., 2004). In the present study, we explored the possibility that high levels of 27-OH could impact neuronal morphology and PSD95 synthesis. **Materials and Methods:** Hippocampal rat primary neurons; Cyp27Tg: transgenic mice overexpressing Cyp27A1 (sterol 27-hydroxylase enzyme, converts cholesterol to 27-OH). **Results:** *In vivo*, we analysed the dendritic spine

density in Cyp27Tg. A 3D morphological analysis of CA1 LY-injected neurons showed a significant reduction in dendritic spine density. Using a series of molecular biology tests we found decreased PSD95 levels and a dysregulation of the REST-miR124a-PTBP1-PSD95 axis in Cyp27Tg. *In vitro*, we entirely reconstructed the dendritic arbour from 70 hippocampal primary neurons using the somatodendritic marker MAP2. A 3D analysis showed in neurons treated with 27-OH a significant reduction in the complexity of the dendritic tree. We found in neurons treated with 27-OH an extreme lack of dendritic spines and PSD95 levels. Moreover, after 27-OH treatment, the neurons showed a dysregulation in the REST-miR124a-PTBP1-PSD95 axis. **Discussion**: These data further suggest that high levels of 27-OH impair dendritic spine density, complexity of the dendritic tree and the REST-miR124a-PTBP1-PSD95 axis. Our results reveal a possible molecular link between hypercholesterolemia and neurodegenerative diseases. **Conclusions**: We propose reduction of 27-OH levels as a useful strategy for preventing memory and cognitive decline in these disorders.

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**Poster**

**738. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 738.02/I1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

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**Title:** Soluble Amyloid beta42 act as allosteric activator of the core cholinergic enzyme, choline acetyltransferase

**Authors: *A. KUMAR**[1,2], E. LANA[2], R. KUMAR[2], C. LITHNER[2], T. DARREH-SHORI[2]
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**Abstract:** Cholinergic neurons, defined by the expression of enzyme choline acetyltransferase (ChAT), mainly responsible for the synthesis of the neurotransmitter acetylcholine (ACh), are the primary target in Alzheimer’s disease (AD). Another hallmark of AD pathology is the

presence of aggregated amyloid-β (Aβ) proteins, believed to play a crucial role in AD-associated cholinergic dysfunction and neurodegeneration. Despite the high vulnerability of cholinergic neurons to Aβ, the exact underlying mechanism how Aβ interacts with cholinergic neurons in the AD is still lacking. To shed light on the pathophysiological role of Aβ in early cholinergic dysfunction, we previously showed that Aβ acts as an allosteric modulator of the cholinergic signaling by forming soluble ultra-reactive ACh-degrading complexes termed BAβACs, together with apolipoprotein-E and butyrylcholinesterase (Kumar et al., *Brain, 2016*). **Aim:** In this study, we further investigated whether Aβ peptides interact with ChAT protein and whether such interaction alters the activity of this core-cholinergic enzyme. **Method:** We performed both *in silico* and *in vitro* analyses to study the direct interaction effect of Aβ peptides on recombinant ChAT activity and catalytic efficiency using a newly designed High-Throughput fluorometric assay and *in silico* molecular docking studies. **Result:** Detailed *in vitro* enzyme kinetic analysis indicated that both soluble Aβ40 and Aβ42 increase ChAT activity by ~ 21% and 26%, respectively. Interestingly, Aβ42 was more efficient in activating ChAT and showed a ~ 10 fold less $EC_{50}$ value as compared to Aβ40. Most importantly, the significant increase in ChAT activity was observed at the Aβ40:Aβ42 concentrations of 1.28:0.12 ng/ml, corresponding to Aβ peptides physiological concentration ranges in CSF. Advanced *in silico* molecular docking analysis confirmed the above findings, and further provided the possible binding sites for Aβ peptides on ChAT protein. **Conclusions:** We report for the first time that Aβ42 peptides act as allosteric enhancer of ACh-biosynthesizing enzyme, ChAT. Together with two previous observations, this point at a complex molecular cross-talk between Aβ and the enzymatic machinery involved in maintaining cellular, synaptic and extra-synaptic ACh homeostasis, warranting further investigation.

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**Poster**

**738. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

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**Program #/Poster #:** 738.03/I2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

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**Title:** The effect of glycemic changes on brain metabolism and sleep/wake *in vivo* using biosensor technology

**Authors: *C. M. CARROLL**[1], M. STANLEY[3], M. PAIT[4], C. HOLLINGSWORTH[4], D. M. HOLTZMAN[5], S. L. MACAULEY[2]
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**Abstract:** Type 2 diabetes increases the risk for developing Alzheimer's disease by 2-4-fold; however, it remains unclear how alterations in peripheral and brain metabolism affect normal brain functioning. The goal of this study, therefore, was to elucidate how the brain regulates metabolism in euglycemic conditions, as well as when challenged with hyper- and hypoglycemic conditions. ISF lactate, glutamate, and glucose all have well-established patterns across the sleep/wake cycle. To replicate these metabolic patterns, we implanted biosensors bilaterally into the mouse hippocampus and paired cortical EEG and EMG recordings to measure arousal state. ISF glucose was used as a reference to contrast changes in ISF glutamate and ISF lactate across manipulations to glycemic state as a function of arousal. During euglycemia, ISF lactate increased progressively in both waking and REM sleep and decreased across NREM sleep. ISF glutamate increased across waking bouts, while ISF glucose showed an initial dip followed by an increase. ISF glucose also increased across NREM sleep, but decreased across REM sleep. We then wanted to explore the effect of hyper- and hypo-glycemia on the brain's metabolic profile as a function of sleep/wake state. The mice were challenged with a 2mg/kg IP injection of glucose resulting in a hyperglycemic challenge, as well as a hypoglycemic challenge with 1mg/kg injection of glibenclamide, a KATP antagonist. As expected, ISF glucose increased following glucose injection and decreased following glibenclamide injection. ISF lactate increased in response to both injections, indicating a decoupling of the typical glucose and lactate relationship as a function of these glycemic challenges. When we compared these metabolic changes to alterations in arousal state, we found that waking increased in response to both injections, while NREM sleep decreased after both injections. These data led us to conclude that not only do spontaneous changes in arousal state affect levels of ISF lactate, glucose, and glutamate, but acute changes in glycemic condition can lead to changes in both arousal state and metabolic profile. Metabolic and sleep dysfunction are known markers of Alzheimer's Disease, so understanding the interactions between these factors may help to clarify the mechanism behind the increased AD risk seen in Type 2 Diabetes.

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**Poster**

**738. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 738.04/I3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Maintained LTP and memory are lost by amyloid-$\beta_{1-42}$-induced $Zn^{2+}$ influx into dentate granule cells

**Authors: *Y. SATO**, T. MURAKAMI, H. FUJII, H. TAMANO, A. TAKEDA
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**Abstract:** Amyloid-β (Aβ) accumulation, the hallmark pathology of Alzheimer's disease (AD), is believed to play an upstream role in AD pathogenesis. Through mechanisms that are uncertain, Aβ oligomers can induce synapse dysfunction that contributes to cognitive decline in the pre-dementia stage of AD. The soluble forms of $A\beta_{1-42}$ are the most toxic species that cause neuronal damage in the brains. On the other hand, $Zn^{2+}$ has been implicated in AD pathogenesis by inducing Aβ oligomerization. We have reported that $A\beta_{1-42}$ takes $Zn^{2+}$ as a cargo into the dentate granule cells in the normal brain and transiently affects memory acquisition via impairment of LTP induction in the normal brain; the formation of Zn-$A\beta_{1-42}$ in the extracellular compartment rapidly increases both intracellular $Zn^{2+}$ and $A\beta_{1-42}$ in dentate granule cells of normal young rats, followed by $A\beta_{1-42}$-induced cognitive decline that is due to increase in intracellular $Zn^{2+}$ released from $A\beta_{1-42}$. On the other hand, the mechanism of memory retention is poorly understood and memory is lost by not only neuronal death but also abolishment of plastic synapse changes. Involvement of Aβ-induced abolishment of plastic synapse changes in memory loss remains to be clarified. Here we tested whether $A\beta_{1-42}$-induced $Zn^{2+}$ influx affects memory via impairment of maintained LTP in the normal brain of freely moving rats. Both three-day-maintained LTP at perforant path-dentate granule cell synapses and 3-day-old space memory were impaired by local injection of 250 μM $ZnCl_2$ (2 μl) into the dentate gyrus. Three-day-maintained LTP was also impaired by local injection of either $A\beta_{1-40}$ or $A\beta_{1-42}$ (25 μM, 2 μl) into the dentate gyrus. $A\beta_{1-40}$-induced impairment of maintained LTP was rescued by co-injection of CaEDTA, an extracellular $Zn^{2+}$ chelator, but not by co-injection of ZnAF-2DA, an intracellular $Zn^{2+}$ chelator. In contrast, $A\beta_{1-42}$-induced impairments of maintained LTP and space memory were rescued by co-injection of either CaEDTA or ZnAF-2DA. Intracellular $Zn^{2+}$ in dentate granule cells was locally increased by $A\beta_{1-42}$ injection into the dentate gyrus, but not by $A\beta_{1-40}$ injection into the dentate gyrus. The present study indicates that maintained LTP and memory are lost by $A\beta_{1-42}$-induced $Zn^{2+}$ influx into dentate granule cells, which more readily occurs than free $Zn^{2+}$-induced $Zn^{2+}$ influx. In contrast, it is likely that maintained LTP is lost by $A\beta_{1-40}$ via a different mechanism that may involve extracellular $Zn^{2+}$.

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**Poster**

**738. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

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**Title:** Postsynaptic protein Shank3 deficiency: Potential effects on cognitive performance and Shank3 interactome in a murine model of Alzheimer's disease

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**Abstract:** Besides amyloid and tau pathologies, Alzheimer's disease (AD) is characterized by synaptic loss and a reduction in brain synaptic proteins. However, it remains elusive to what extent the decrease of a synaptic protein is translated into phenotypically and clinically significant effects. Shank3, a postsynaptic protein located in postsynaptic densities (PSD), may be an exception. The loss of a single allele of the SHANK3 gene is sufficient to cause profound cognitive symptoms, indicating that its expression in the brain must be tightly regulated. It is also the main candidate gene for 22q13.3 deletion syndrome, which is characterized by severe cognitive defects. These facts led us to hypothesize that a Shank3 deficiency could contribute to the apparition or aggravation of cognitive symptoms and neuropathology in AD. We first confirmed a 30-50% *postmortem* loss of Shank3 in brains of AD patients (Braak stage 4-5) and a significant correlation between Shank3 concentrations and *antemortem* cognitive scores in these individuals. A more marked decrease was also found in AD synaptosomes. To further probe the role of Shank3 in AD, we developed a new model by crossing mice with or without Shank3 deficiency with the 3xTg-AD model of AD neuropathology. We validated our new model using *in situ* hybridization on sections and Western Blot on PSD extracts from parietotemporal cortex. The results confirmed that Shank3 protein and mRNA expression were significantly reduced by 30-50% in Shank3-deficient mice compared to non-deficient animals, which is similar to our finding in the brains of AD patients. The novel object recognition behavioral test (NOR) showed that a synergy occurred between Shank3 disruption and APP/tau transgenes at 9 months as only 3xTg-AD-Shank3 mice failed the NOR test at this age. All groups with Shank3 defects failed the NOR at 12 months. Anxiety and locomotion parameters have also been evaluated by dark-light

emergence and openfield tests. No difference has been found between groups. Levels of other synaptic proteins, such as PSD-95, Cortactin and Septin3 were analysed using Western blot on PSD extracts from the parietotemporal cortex but not significant variation was found between groups or ages. Further investigations of the effect of Shank3-deficiency on the neuropathological markers of AD (amyloid-β and tau protein) by ELISA and Western Blot analysis are ongoing. Taken together, these results suggest that Shank3 deficiency could play a role in the apparition of cognitive impairment in AD, but the exact mechanism remains to be unveiled.

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**Poster**

**738. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 738.06/I5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

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**Title:** Dendritic spines provide cognitive resilience against Alzheimer’s disease

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**Abstract:** Neuroimaging and other biomarker assays suggest that the pathological processes of Alzheimer’s disease (AD) initiate years prior to clinical dementia onset. However some 30%-50% of older individuals that harbor AD pathology do not become symptomatic in their lifetime. It is hypothesized that such individuals exhibit cognitive resilience that protects against AD dementia. We hypothesized that in cases with AD pathology structural changes in dendritic spines would distinguish individuals that had or did not have clinical dementia. We compared dendritic spines within layers II and III pyramidal neuron dendrites in Brodmann Area 46 dorsolateral prefrontal cortex using the Golgi-Cox technique in 12 age-matched pathology-free controls, 8 controls with AD pathology (CAD), and 21 AD cases. We used highly optimized methods to trace impregnated dendrites from brightfield microscopy images which enabled accurate three-dimensional digital reconstruction of dendritic structure for morphologic analyses. Spine density was similar among control and CAD cases but reduced significantly in AD. Thin

and mushroom spines were reduced significantly in AD compared to CAD brains, whereas stubby spine density was decreased significantly in CAD and AD compared to controls. Increased spine extent distinguished CAD cases from controls and AD. Linear regression analysis of all cases indicated that spine density was not associated with neuritic plaque score but did display negative correlation with Braak staging. These observations provide cellular evidence to support the hypothesis that dendritic spine plasticity is a mechanism of cognitive resilience that protects older individuals with AD pathology from developing dementia.

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**Poster**

**738. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 738.07/I6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Beta-amyloid increases neuronal $Ca^{2+}$activity in hippocampal neurons via reduction of nicotinic acetylcholine receptor-mediated inhibitory inputs

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**Abstract:** Beta-amyloid (Aβ) peptide accumulation has long been implicated in the pathogenesis of Alzheimer’s disease (AD). However, a well-defined mechanism that is generally agreed upon about how Aβ causes AD pathogenesis has not yet been established. Imaging intracellular $Ca^{2+}$ dynamics using a genetically encoded $Ca^{2+}$ indicator, GCaMP, shows that acute 250nM Aβ42 treatment is sufficient to increase calcium activity in cultured mouse hippocampal excitatory neurons. Furthermore, this Aβ42-induced calcium increase is dependent on glutamate NMDA receptors as indicated by a decrease in activity when the receptor antagonist (50μM DL-APV) is applied. Importantly, Aβ42 inhibits nicotinic acetylcholine receptor (nAChR) function, causing neuronal dysfunction. Notably, applying Aβ42 coupled with inhibition of nAChRs via 20μM curare further increases $Ca^{2+}$ activity. As nAChRs are highly expressed in hippocampal GABAergic interneurons, we hypothesized that Aβ42 reduces GABAergic neuronal activity via blocking nAChRs, leading to an increase in hippocampal excitatory neuron activity. Indeed, Aβ42-induced $Ca^{2+}$ hyperactivity is significantly reduced when Aβ42 is applied with 25nM muscimol, a $GABA_A$ agonist. Taken together, Aβ42 blocks nAChRs in GABAergic neurons, reducing inhibitory activity ultimately making excitatory neurons more excitable. Given that neuronal hyperexcitability in the pre-symptomatic stages of AD may play an important role in the disease progression, knowledge of Aβ42’s interaction with GABAergic inhibitory neurons via nAChRs may yield potential receptor targets for therapeutics for patients with AD.

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**Poster**

**738. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

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**Program #/Poster #:** 738.08/I7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

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**Title:** An innovative tool to modulate ADAM10 synaptic localization and activity in a mouse model of Alzheimer's disease

**Authors: S. THERIN**[1], S. MUSARDO[1,4], F. SEIBT[5], A. RIBEIRO[1], D. DI MARINO[6], C. BALDUCCI[7], G. FORLONI[7], V. GRIECO[2], C. GIUDICE[2], F. GARDONI[1], J. PITA-ALMENAR[5], M. DI LUCA[1], *E. MARCELLO[3,1]
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**Abstract:** Alzheimer's disease (AD) is characterized by the aggregation of amyloid beta peptide (Aβ) that is derived from the amyloid precursor protein (APP), which can undergo two mutually exclusive pathways. The amyloidogenic pathway involves BACE and γ-secretase activities and leads to Aβ formation. In contrast, the non-amyloidogenic pathway involves ADAM10, a disintegrin and metalloproteinase 10, which cleaves APP in the domain corresponding to Aβ, thus precluding Aβ production. Recently, we have identified a new binding affinity between the cytoplasmic tail of ADAM10 and AP2. This interaction leads to the clathrin mediated endocytosis of ADAM10, and therefore its activity towards its substrates at the cellular surface is affected. Interestingly, ADAM10/AP2 interaction was observed to be significantly increased in AD patients' brain compared to healthy control subjects, suggesting a role of ADAM10/AP2 in AD pathogenesis. In this framework, we have recently developed a cell permeable peptide (CPP) capable of interfering with ADAM10/AP2 association and, thereby, with ADAM10 endocytosis. The intraperitoneal (IP) administration of this CPP to wild-type mice for two weeks is safe and effective for both impairing ADAM10 endocytosis and increasing ADAM10 synaptic localization. As a result, the relative activity of ADAM10 towards APP is increased, leading to greater levels of sAPPα. The 14-days IP administration of the CPP to a mouse model of AD;

APP/PS1 mice at a full-blown pathology stage (9 months old), suggests that the treatment reverts both the decrease in ADAM10 synaptic localization and the reduction in the synaptic levels of the GluN2A subunit of NMDA that was observed in APP/PS1 mice. A significant decrease of sAβ levels was also observed in the cortex of those treated APPPS1 mice suggesting an effect on the amyloid cascade. Furthermore, results obtained in a Y-maze test suggest a rescue of the cognitive impairment in APP/PS1 mice at early stages of Aβ induced pathology (6 months old) after CPP administration. These positive results point to ADAM10 internalization as a potential target mechanism for the development of an effective AD therapy acting on the neuronal activity. In order to investigate the functional impact of this approach, ongoing electrophysiology assays are being performed to provide insight on molecular changes observed at the synapses and their effect on synaptic transmission.

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**Poster**

**738. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

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Progetto di Ricerca di Interesse Nazionale (PRIN2015N4FKJ4)
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**Title:** A synapse to nucleus signalling pathway in Alzheimer's disease

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**Abstract:** We have recently identified the RING Finger Protein 10 (RNF10) as a novel synapse-to-nucleus protein messenger, enriched at the excitatory synapses and associated with the GluN2A subunit of NMDA receptors. RNF10 translocates from synapses to the nucleus, upon the activation of synaptic GluN2A-containing NMDA receptors, inducing the expression of specific target genes that have a role in Alzheimer's disease (AD) pathogenesis or that are

associated with the regulation of dendritic spine morphology.Our objective is to characterize RNF10 in Aβ signalling, by using RNF10 knockout (KO) mice and by studying RNF10 trafficking in neuronal cultures. RNF10 expression is reduced in AD patients' hippocampi at the earlier stages of the disease and Aβ oligomers trigger RNF10 translocation from the synapse to the nucleus. RNF10 KO mice present reduced body weight with an increase in food intake. In behavioural characterization at 6 months, in novel object recognition test, these animals do not present any difference when compared with wild-type animals, but at older ages, in the Y-Maze test, homozygous RNF10 KO animals spend more time in the novel arm. The molecular characterization shows downregulation of the amyloid cascade players in the hippocampus, and a consequent decrease in amyloid levels. Concerning spine morphology, RNF10 KO animals show a significant decrease in mushroom-type spines, without changes in the length or in the width. Overall, these data suggest an involvement of RNF10 in AD pathogenesis, pointing towards a possible protective role for RNF10 in cognitive dysfunction along aging.

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**Poster**

**738. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

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**Topic:** C.02. Alzheimer's Disease and Other Dementias

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**Title:** Excitation:inhibition imbalance associates with increased pathology in Alzheimer's disease

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**Abstract:** Epileptic seizures occur in at least 20% of Alzheimer’s disease (AD) patients. In parallel, patients with chronic epilepsy may exhibit AD-like neuropathology, such as amyloid-β42 ($A\beta_{42}$) and tau pathology. These data suggest an interaction between epilepsy and AD. Network hyperexcitability and epileptogenesis have been associated with a number of molecular abnormalities leading to an excitation: inhibition (E:I) imbalance, including the downregulation of the GABAergic signaling via decreased expression of $GABA_A$ receptors ($GABA_AR$) and dysregulation of calcium ($Cl^-$) co-transporters NKCC1 and KCC2. We hypothesize that similar epilepsy-associated alterations will be observed in brain tissue from AD patients, and to a greater extent in tissue from AD patients with seizure history. We further hypothesize that seizures in AD patients may promote neurodegeneration.Postmortem temporal cortex tissue from AD cases

(n=18), with (AD+Sz) or without (AD-Sz) known seizure history, and control samples (n=7) were used for Western blot and ELISA analysis. Tissue samples were obtained from the Center for Neurodegenerative Disease Research (CNDR) of the University of Pennsylvania (Philadelphia, PA) with the local IRB approval.We found that the expression of NKCC1 was significantly upregulated in AD (159% of controls, $p<0.05$), with no change in KCC2. However, we found a significant decrease in KCC2 levels in AD+Sz compared to AD-Sz (56.5% of AD-Sz, $p<0.05$), suggesting an increase in depolarizing $GABA_AR$s in the AD cohort with seizure history. Similarly, levels of α1 subunit of $GABA_AR$ were significantly decreased in AD+Sz compared to AD-Sz (65% of AD-Sz, $p<0.05$), although there was no difference when comparing all AD cases with controls. We also found a significant increase of phosphorylated tau Thr212/Ser214 in all AD compared to controls (2828% of controls, $p<0.0001$), and a further significant increase in the AD+Sz group compared to the AD-Sz cohort (164% of AD-Sz, $p<0.05$). In addition, we found a significant increase in the duration of cognitive impairment prior to death in the AD+Sz group compared to AD-Sz (+8 years, $p<0.001$), suggesting that seizures may induce cognitive impairment earlier in AD patients.These results demonstrate that the hyperexcitability phenotype in AD is associated with markers consistent with impaired GABAergic inhibition and suggest that seizures may worsen AD pathology, exacerbating tau hyperphosphorylation and cognitive impairment. These findings indicate a bidirectional relationship between epileptogenic changes and AD related neuropathologic changes in human brain tissue.

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**Poster**

**738. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

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**Topic:** C.02. Alzheimer's Disease and Other Dementias

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**Title:** Impaired LTP-like synaptic plasticity in amnestic mild cognitive impairment

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**Abstract: Background.** Mild cognitive impairment (MCI) can represent a transition state between healthy cognitive aging and dementia. Amnestic MCI (aMCI) is the earliest and most common clinical manifestation of Alzheimer's disease (AD). Models of AD implicate beta-amyloid in declines of long-term potentiation (LTP) plasticity. Transcranial magnetic stimulation (TMS) offers the potential to directly assess the efficacy of neuroplastic mechanisms in humans. While TMS measures of LTP-like plasticity are impaired in patients with dementia due to AD, it is not yet known if aMCI shows a similar pattern.
**Objective.** To compare measures of LTP-like plasticity in patients with aMCI and demographically similar controls.
**Methods.** In 17 aMCI (Mean ± SD, age: 69 ± 9 years, gender: 41 percent female) and 24 controls (Mean ± SD, age: 66 ± 8 years, gender: 58 percent female), motor evoked potentials (MEPs) were elicited by single-pulse TMS to the motor cortex before and after intermittent theta burst stimulation (iTBS). LTP-like plasticity was assessed in terms of the change in MEP amplitude 5, 10, 20, and 30-min post-iTBS.
**Results.** There were no significant differences in age, gender, or baseline MEP amplitude between the two groups. Compared to controls, aMCI participants showed almost no facilitation in MEP amplitude after iTBS. The difference was significant between groups at 5-min post-iTBS (p=.017).
**Conclusion.** The mechanisms of LTP-like plasticity are impaired in aMCI compared to controls. TMS plasticity measures may be a valuable tool for measuring the efficacy of the mechanisms of neural plasticity in early AD pathogenesis, and is a promising tool to investigate targets for future therapies in AD.

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**Poster**

**738. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

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**Topic:** C.02. Alzheimer's Disease and Other Dementias

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**Title:** GABAergic postsynaptic mechanism involved in hippocampal hyperactivity in a mouse model of Alzheimer's disease

**Authors: *Y. LI**[1], N. LI[2], K. ZHU[2], L. LI[2], X. XIAO[2], L. LI[2], Y. ZHENG[2], X. WANG[2]
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**Abstract:** Alzheimer's disease (AD) is the most common neurodegenerative disease in the elderly. Although hippocampal synaptic dysfunction has been found in early stage of AD, the mechanism involved in the synaptic dysfunction is still unknown. In the present study, field potential recording and biochemical experiments showed that long-term potentiation (LTP) declined with intraneuronal Aβ accumulation in hippocampal CA1 of 5XFAD mice at 2-3 months old. Further, we used whole-cell patch-clamp to determine the action potential (AP) of hippocampal CA1 pyramidal neuron by current-clamp configuration in acute brain slices of 5XFAD mice at 2.5 months old. We found that the frequency of spontaneous APs of CA1 pyramidal neuron in 5XFAD mice increased dramatically, while the amplitude of APs, the resting membrane potential and the frequency of spontaneous burst firing did not change compared to WT mice. Moreover, the initial frequency of APs, the input resistance, as well as rheobase of CA1 pyramidal neuron in response to evoked protocols were not changed in 5XFAD mice compared to their littermates. These findings indicated that the intrinsic excitability of CA1 pyramidal neuron was not altered by the transgenic background in early stage of AD-like pathology. Next, in the voltage-clamp, we found that the amplitude of miniature inhibitory postsynaptic current (mIPSC) of CA1 pyramidal neuron decreased and the frequency of mIPSC increased in 5XFAD mice, while the miniature excitatory postsynaptic current (mEPSC) did not change. Concurrently, there was no difference in dendritic spine density of CA1 neurons in 5XFAD mice compared to WT mice. Furthermore, the firing rate of CA1 pyramidal neurons in WT mice was successfully suppressed by γ-aminobutyric acid A ($GABA_A$) receptor agonist, Gaboxadol (GBX), but the CA1 pyramidal neuron in 5XFAD mouse exhibited lower sensitivity to GBX, indicating a desensitization of $GABA_A$ receptor on postsynaptic membrane. We also detected synaptic subcellular distribution of $GABA_A$ receptor alpha1 subunit ($GABA_A$ Rα1) in hippocampus from 2.5-month-old 5XFAD mouse, we found the expression of $GABA_A$ Rα1 in synaptosome decreased obviously while the total amount of $GABA_A$ Rα1 was not altered compared to WT mouse. In conclusion, in early stage of AD-like pathophysiological process, the inhibitory input efficiency decline due to $GABA_A$ receptor desensitization on postsynaptic membrane of CA1 neuron in hippocampus may contribute to the hippocampal network aberrance.

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**Poster**

**738. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

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**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Princess Nourah bint Abdulrahman University

**Title:** Trisomic vs. disomic synaptic proteins: Their interaction with Alzheimer's disease pathology in Down's syndrome

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**Abstract: Introduction:** Down's syndrome (DS), or trisomy21, is the most common genetic condition that results in intellectual disabilities. The incidence of DS is around 1 in 800 live births; it is almost caused by inheritance of a whole extra copy of chromosome 21 (chr21). People with DS have a high risk of developing Alzheimer's disease (AD) pathology at an earlier age in contrast to the typical population, around the age of 40. Synaptic dysfunction is one of the ultimate neuropathological alterations preceding neuronal death in the brain of subjects with AD, however, it is poorly understood. Intersectin-1 (ITSN1) and synaptojanin1 (SYNJ1) are presynaptic proteins with genes located on chr21 that are involved in synaptic vesicles recycling. The triplication of these genes may cause synapse disruption and contribute to symptoms and to AD pathological mechanism in the brains of DS. In this study we investigate the interaction of disomic and trisomic synaptic proteins with AD pathology. **Methods:** Post-mortem tissue was available from 15 DS, 10 AD and 12 control subjects. Concentrations of 5 synaptic proteins, ITSN1, SYNJ1, β-tubulin, synaptophysin (SYN38) and PSD95 were assessed in the frontal and temporal cortices by semi-quantitative western blotting. AD pathological hallmarks, amyloid beta $(A\beta)_{1\text{-}40\ \&\ 1\text{-}42}$, total tau (tTau) and phosphorylated tau (pTau), have been detected using MILLIPLEX® MAP assay and semi-quantitative immunohistochemistry (IHC) where possible. **Results:** SYNJ1 levels were significantly lower in AD compared to DS and control in the frontal and temporal cortices. There was a significant decrease in the levels of SYN38 in the temporal region of DS compared to control. The levels of insoluble $A\beta_{1\text{-}40}$, $A\beta_{1\text{-}42}$ and pTau/tTau were significantly higher in DS and AD than control in the frontal cortex and only in DS in comparison to controls in the temporal cortex (Kruskal-Wallis test and Dunn's pairwise tests with Bonferroni correction $p<0.005$). There was a significant inverse correlation between SYN38 and insoluble pTau/tTau ratio in the temporal cortex ($rs=-.503$, $n=36$, $p=0.002$). IHC did not show interaction between AD pathology and synaptic proteins. **Conclusions:** These studies

revealed that the extra copy of the genes encoding two of the 5 synaptic proteins studied in DS results in different trends in their levels against diagnostic category. Further investigation is required to understand how SYNJ1, where levels were similar to control despite the presence of severe AD pathology, may take part in disease pathogenesis.

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**Poster**

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2017M3C7A1028949

**Title:** Repositioning of udenafil, a PDE5 inhibitor approved for male erecetile dysfunction, as an Ab and phospho-tau clearing drug in Alzheimers disease

**Authors: *H. KIM**[1], Y. YOON[2], J.-Y. KOH[3]
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**Abstract:** Alzheimer’s disease (AD) is the most common cause of dementia. AD is characterized by brain atrophy, extracellular deposition of beta-amyloid (Ab) peptide, intra-neuronal accumulation of phosphorylated tau, neuronal and synaptic loss, and inflammation. Recent studies suggest that lysosomal dysfunction may contribute to the accumulation of pathogenic proteins in AD as well as in other neurodegenerative diseases. While precise mechanisms leading to lysosomal dysfunction in these conditions are yet to be determined, some studies have demonstrated that cAMP may have a beneficial effect on lysosomal function by correcting its pH. Consistently, we have previously showed that PDE inhibitors such as cilostazol are able to normalize lysosomal function by increasing cAMP levels. Udenafil (Zydena; Dong-A ST Co, Seoul, South Korea) is a clinically approved PDE5 inhibitor, which has been used to treat male erectile dysfunction. While it is supposed to act selectively on PDE5, our screening assay revealed that it also inhibited PDE1, and substantially increased cAMP levels in cultured cortical neurons and astrocytes. We tested this in a cell model of arrested autophagy. Astrocytes were exposed to chloroquine (CQ), which inhibited acidification of lysosomes and fusion between

cargoes and lysosomes. Addition of Udenafil (1 uM) re-acidified lysosomes in CQ-treated astrocytes, and promoted the fusion between cargoes and lysosomes. As a result, Udenafil treatment restored autophagy flux in CQ-treated astrocytes. In synthetic Ab1-40 exposed astrocytes, Udenafil also reduced the intracellular accumulation of Ab. Indicating that these effects were mediated by cAMP, dibutryl cAMP (db-cAMP) mimicked, and protein kinase A inhibitor blocked the effects of Udenafil. Since Undenafil has been safely used in human patients, provided its efficacy is proven in future studies, drug repositioning of Udenafil, or other PDE inhibitors, seems a highly cost-effective route to developing new drugs targeting lysosomal dysfunction in AD.

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**Poster**

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**Title:** Sigma-1 receptor interactions with lipid rafts

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**Abstract:** Sigma-1 Receptor (S1R) is a single-transmembrane intracellular receptor, primarily residing in the endoplasmic reticulum (ER) membrane. Pharmacological activation of the receptor has been shown to be neuroprotective in a number of brain disorders including Alzheimer’s, Huntington’s diseases, Amyotrophic lateral sclerosis. It has been proposed that S1R functions as an auxiliary regulatory subunit for various ion channels and receptors, modulating their activity and gating properties. However, the molecular mechanism underlying S1R function in the cell remains unknown. In our study we explored S1R-lipid interactions using a combination of biophysical and biochemical approaches. First, we confirmed that S1R localizes at the specific ER compartment - mitochondria-associated membranes (MAM). Then, we showed that wild-type S1R binds to major raft components such as cholesterol and sphingomyelins. We identified protein motifs responsible for S1R-cholesterol interactions. Intact cholesterol-binding sequence was essential for proper S1R targeting to the MAM regions.

Finally, we purified and then reconstructed recombinant S1R in artificial lipid bilayers (supported lipid bilayers and giant unilamellar vesicles). Bilayers of different lipid composition were used to study S1R protein-lipid interactions. We propose that on the molecular level S1R may function as a lipid raft-stabilizing protein of the ER.

**Disclosures: V. Zhemkov:** None. **M. Kim:** None. **I. Bezprozvanny:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; TEVA.

**Poster**

**738. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 738.16/I15

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** A novel mechanism of neurotoxicity in Alzheimer's disease: Astrocyte-derived extracellular vesicles

**Authors: *C. J. NOGUERAS-ORTIZ**[1], E. J. GOETZL[2], V. MACHAIRAKI[3], D. KAPOGIANNIS[4]
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**Abstract:** Background: Alzheimer’s disease (AD) is the most common neurodegenerative disease and is neuropathologically characterized by deposition of amyloid-β (Aβ) peptides extracellularly and hyperphosphorylated tau intracellularly. A plethora of molecular mechanisms have been shown to mediate progressive synaptic loss and neurodegeneration in AD, with recent research documenting the transneuronal propagation and seeding of pathogenic Aβ and tau. However, the mechanisms underlying the propagation of neurodegeneration in AD remain largely elusive.
Extracellular vesicles (EVs), nanovesicles secreted from all cells including neurons and astrocytes, may be important vehicles for the spread of Aβ, tau and other pathogenic molecules in AD. In our Lab, we have pioneered a technique for isolating neuronal- and astrocyte-derived EVs (NDEVs and ADEVs, respectively) from plasma and have found that, in AD patients, these EVs contain high levels of pathogenic Aβ and tau as well as potentially toxic complement. Based on these observations we hypothesized that ADEVs and/or NDEVs from plasma of AD patients are neurotoxic.
Methods/Results: We isolated plasma ADEVs and NDEVs from 4 patients with sporadic AD and 4 age-matched controls and used them to incubate cultures of rat cortical neurons and human iPSC-derived neurons. Neurons incubated with ADEVs from AD patients exhibited significantly

decreased neurite density by Tuj-1 immunoreactivity, decreased cell viability by MTT assay, and increased necrotic cell death by EthD-1 assay, compared to neurons treated with patient NDEVs or control ADEVs or NDEVs.
Conclusions: This is the first demonstration that blood-borne ADEVs from AD patients are neurotoxic, as hypothesized based on their cargo, which points to a novel mechanism in AD.
Future experiments: Results obtained with plasma-derived EVs will be validated using brain- and CSF-derived EVs from AD patients as well as ADEVs and NDEVs from AD-hIPSC-derived cultures. Additionally, we will seek to clarify the mechanisms of ADEV-mediated neurotoxicity and evaluate whether it is dependent on EV internalization by neurons and Aβ, tau and complement transmission.

**Disclosures: E.J. Goetzl:** None. **V. Machairaki:** None. **D. Kapogiannis:** None.

**Poster**

**738. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 738.17/I16

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** R01NS075487
T32NS095775
Alzheimer's Association

**Title:** The Alzheimer’s disease risk gene BIN1 regulates network hyperexcitability

**Authors: *Y. VOSKOBIYNYK**, J. COCHRAN, T. RUSH, J. ROTH, M. WAQAS, E. D. ROBERSON
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**Abstract:** Alzheimer’s Disease (AD) affects about five million Americans, who receive only a very modest benefit from current treatment options. Multiple treatment trials have failed in the past, raising interest in identifying new targets to treat AD. GWAS have identified bridging integrator 1 (*BIN1*) as one of the leading genetic risk factors in AD. Neurons express unique BIN1 isoforms, and a growing body of evidence indicates loss of neuronal BIN1 in AD. However, the function of neuronal BIN1 remains unclear and its contribution to AD is critical to investigate. We generated brain-specific BIN1 knockout (KO) mice and discovered that the loss of BIN1 in the brain leads to network hyperexcitability, with increased seizure susceptibility. Network hyperexcitability is observed in AD: patients with mild cognitive impairment or dementia due to AD have epileptiform activity. Such aberrant activity is recapitulated in multiple rodent models of AD. Multiple lines of evidence suggest that increased network hyperexcitability results from inhibitory neuron dysfunction in AD patients. Network synchrony

is tightly regulated by the activity of inhibitory GABAergic interneurons that coordinate synchronous excitatory neuron firing required for proper brain oscillatory activity. Therefore, interneuron impairment may play an important role in AD pathogenesis. To investigate the mechanisms by which brain-specific BIN1 loss induces network hyperexcitability, we generated mice lacking BIN1 in inhibitory or excitatory neurons. Assessing pharmacologically-induced seizures, behavior, and acute slice electrophysiology, we investigated the mechanisms by which BIN1 loss in inhibitory or excitatory neurons regulates network hyperexcitability. We found that loss of BIN1 in inhibitory neurons increased seizure susceptibility, phenocopying BIN1 loss in the whole brain, while BIN1 loss in excitatory neurons decreased seizure susceptibility. Mice lacking BIN1 in inhibitory neurons had age-dependent behavioral deficits and decreased survival. In addition, initial electrophysiological studies provide evidence that loss of neuronal BIN1 decreases neuronal activity. These data generate fundamental insights about the mechanistic role BIN1 plays in AD to provide promising therapeutic strategies for targeting inhibitory neuron dysfunction and network hyperexcitability in AD.

**Disclosures: Y. Voskobiynyk:** None. **J. Cochran:** None. **T. Rush:** None. **J. Roth:** None. **M. Waqas:** None. **E.D. Roberson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. Roberson owns intellectual property related to tau..

**Poster**

**738. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 738.18/I17

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Alberta Innovates (Alberta Prion Research Institute)
The Alzheimer Society of Alberta and NWT

**Title:** Genetic depletion of amylin receptors improves hippocampal synaptic transmission and plasticity in a transgenic mouse model of Alzheimer’s disease

**Authors: *R. KIMURA**[1], W. FU[2], D. WESTAWAY[2,3], J. H. JHAMANDAS[2]
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**Abstract:** Alzheimer's disease (AD) is characterized by accumulation of amyloid-β peptide (Aβ) in the brain regions that subserve memory and cognition. We have previously demonstrated that effects of soluble oligomeric $A\beta_{1-42}$ and human amylin on hippocampal long-term potentiation (LTP) are mediated by the amylin receptor, comprised of dimers of calcitonin receptor (CTR) and receptor activity membrane proteins. In this study, we first examined $A\beta_{1-42}$ and human

amylin-evoked depression of LTP at Schaeffer collateral-CA1 hippocampal synapses in heterozygous CTR (hetCTR) mice, that demonstrate half the complement of amylin receptors as their wild-type (WT) littermates. In mouse hippocampal brain slices, field excitatory postsynaptic potentials (fEPSPs) were recorded from the stratum radiatum layer of the CA1 area in response to electrical stimulation of Schaeffer collateral afferents. In WT mice, $A\beta_{1-42}$ (50 nM) and human amylin (50 nM) depressed LTP evoked using 3-theta burst stimulation (TBS) protocols. HetCTR mice did not demonstrate abnormalities in basal synaptic transmission or LTP. However, in hetCTR mice, Aβ- and human amylin-induced reduction of LTP was approximately half that observed in WT mice. We also investigated effects of HetCTR depletion on hippocampal LTP in TgCRND8 AD mice at 8-12 months of age. Basal synaptic transmission as measured by the average slope of input/output (I/O) curves was significantly impaired in TgCRND8 mice compared to age-matched WT and HetCTR mice. HetCTR+TgCRND8 mice demonstrated improved LTP compared to TgCRND8 mice, which show low basal levels of LTP. Application of AC253 (250 nM), an amylin receptor antagonist, further improved LTP in HetCTR+TgCRND mice to levels comparable to those observed in age-matched WT littermates. These results show 1) that the degree of hippocampal LTP reduction evoked by Aβ and human amylin in hetCTR mice is blunted in proportion to the CTR (and hence amylin receptor) knockdown 2) genetic depletion of amylin receptors in TgCRND8 AD mice results in an improvement in LTP. These studies provide further evidence for consideration of the amylin receptor as a therapeutic target in AD.

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**Poster**

**738. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 738.19/J1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** SyDAD Marie Sklodowska-Curie grant agreement No 676144

**Title:** Linking actin-dependent dendritic spine remodelling and ADAM10 activity in AD: The role of CAP2

**Authors: *L. L. VANDERMEULEN**[1], S. C. PELUCCHI[1], M. B. RUST[2], S. FRYKMAN[3], M. DI LUCA[1], E. MARCELLO[1]
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**Abstract:** Alzheimer’s disease (AD) is pathologically characterized by amyloid beta (Aβ) depositions and by hyperphosphorylated tau. A disintegrin and metalloproteinase 10 (ADAM10), is responsible for the α-secretase cleavage of Amyloid Precursor Protein (APP), that prevents Aβ generation. The synaptic localization and its activity towards APP are modulated by protein partners, that interact with the cytoplasmic tail of ADAM10. Considering the importance of the ADAM10 cytoplasmic domain in the regulation of ADAM10 activity, we performed a two-hybrid screening that has recently identified cyclase-associated protein 2 (CAP2) as a novel protein binding partner of ADAM10. CAP2 is an actin-binding protein implicated in actin cytoskeleton remodelling and vesicle trafficking of non-neuronal cells.
The aim of the project is the evaluation of the role of the ADAM10/CAP2/actin complex in the amyloid cascade and in AD-related synaptic dysfunction, in order to rescue early synaptic defects in AD. Preliminary data show that CAP2 is self-aggregating and interacts with both actin and ADAM10. Remarkably, in the hippocampus of CAP2 knockout mice the postsynaptic levels of ADAM10 and the NMDA receptor subunit 2A (GluN2A) are significantly reduced, suggesting that the lack of CAP2 affects their localization. In particular, the binding of CAP2 to actin is essential for ADAM10 synaptic localization. In CAP2 knockout mice brain sections, we also measured an altered spine morphology and density in hippocampal neurons. These data indicate the relevance of CAP2 in synaptic function, and in particular, in structural plasticity. With regards to AD, a significant reduction in CAP2 protein levels and in its postsynaptic localization is detected in the hippocampi of AD patients when compared to age-matched healthy control subjects. Where, in AD patient hippocampi an increased association of CAP2 to actin is observed. In addition, we found that in primary hippocampal cultured neurons treated with Aβ oligomers, the postsynaptic levels of CAP2 are reduced, suggesting that CAP2 localization is a target of Aβ oligomers. Moreover, a decreased interaction between CAP2 and ADAM10 upon Aβ oligomer treatment is found. Overall these data indicate a potential role of CAP2 in AD pathogenesis.

**Disclosures: S.C. Pelucchi:** None. **M.B. Rust:** None. **S. Frykman:** None. **M. Di Luca:** None. **E. Marcello:** None.

**Poster**

**738. Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 738.20/J2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** KAKENHI 18K14817
KAKENHI 17H05697
Naito Foundation
Uehara Memorial Foundation

Takeda Science Foundation

**Title:** Subunit-specific effects on AMPA-type glutamate receptors caused by amyloid beta oligomers during hippocampal long-term potentiation

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**Abstract:** Alzheimer's disease (AD) is the most common cause of dementia. Recent studies have suggested that amyloid beta (Aβ) oligomers are toxic entities especially at an early stage of AD, and that they impair the ability of learning and memory by blocking induction of synaptic plasticity such as long-term potentiation (LTP) in the hippocampus. However, the pathological effects at synapses remain to be clarified at a molecular level. To address this issue, we have tried to visualize effects of Aβ oligomers on changes of AMPA-type glutamate receptors (AMPA receptors) during hippocampal LTP. First, we coated cover glass with a presynaptic adhesion molecule Neurexin, and cultured rat hippocampal neurons on it. The coated Neurexin bound to a postsynaptic adhesion molecule Neuroligin and induced the formation of postsynaptic-like membrane (PSLM) on the glass surface. Then, we performed live-cell imaging of AMPA receptor subunit GluA1 or GluA2 labeled with super-ecliptic pHluorin (SEP), a pH-sensitive form of GFP, using total internal reflection fluorescence microscopy. This method enables us to observe GluA1- or GluA2-SEP signals around PSLM with a high signal-to-noise ratio by reducing the background fluorescence. LTP-inducing stimulation increased the GluA1- and GluA2-SEP signals in both PSLM and non-PSLM. We also recorded individual exocytosis of GluA1- and GluA2-SEP, whose frequencies increased after LTP induction by electrical field stimulation. The increase of GluA1-SEP signals and the frequency of GluA1-SEP exocytosis were suppressed by Aβ oligomers, whereas the effects on GluA2-SEP were limited. These results suggest that Aβ oligomers primarily inhibit the increase in number of GluA1 containing AMPA receptors and suppress the hippocampal LTP expression.

**Disclosures: H. Tanaka:** None. **D. Sakaguchi:** None. **T. Hirano:** None.

**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.01/J3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Arizona Alzheimer's Consortium
NIH Grant 2RF1AG037637-07

**Title:** Characterization of necroptosis machinery across Braak stages in Alzheimer's disease

**Authors: *E. C. TURNER**, A. CACCAMO, C. BRANCA, E. FERREIRA, S. ODDO
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**Abstract:** Alzheimer's disease (AD) is characterized by severe neuronal loss, and exposing the mechanisms underlying this loss in AD is critical to the development of new therapeutic approaches. Previously, we have shown that necroptosis, a programmed form of necrosis, is activated in AD. Necroptosis is activated by formation of a necrosome, a multiprotein complex which consists of protein kinases RIPK1 and RIPK3 and pseudokinase MLKL. Here, we analyzed the absolute levels of RIPK1, RIPK3, and MLKL by immunofluorescence and western blot in multiple human brain regions and across all Braak stages. In addition, we assessed necrosome formation, which is an indirect indication of necroptosis activation. Consistent with our previous findings, we show that there is a correlation between necroptosis markers and Braak stage. The changes we report in MLKL levels are the most notable, as the phosphorylation and translocation of MLKL represents the final step before membrane rupture and cell death. Altogether, these data provide strong evidence for targeting necroptosis as a valid therapeutic approach for AD.

**Disclosures: E.C. Turner:** None. **A. Caccamo:** None. **C. Branca:** None. **E. Ferreira:** None. **S. Oddo:** None.

**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.02/J4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** R01 AG037637
Arizona Alzheimer's Consortium

**Title:** Necroptosis contributes to tau induced neuronal loss

**Authors: *R. VARTAK**[1], C. BRANCA[1], I. S. PIRAS[2], A. CACCAMO[1], S. ODDO[1]
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**Abstract:** Recently, we have shown that necroptosis is activated in and contributes to neuronal loss in Alzheimer's disease (AD). Necroptosis is a caspase-independent cell death pathway activated by the formation of the necrosome, which consists of kinases RIPK1 and RIPK3 and the pseudokinase MLKL. Tau plays a crucial role in the neuronal loss in AD and other tauopathies; however, the mechanisms underlying Tau-induced neuronal loss remain elusive.

Our data in human AD brains suggest a possible interaction between tau and necroptosis activation. To this end, we found that Braak stage strongly correlates with necroptosis activation as indicated by levels of necroptosis markers RIPK1 and MLKL. We also show that phosphorylated Tau co-localizes with the necrosome. We provide biochemical and molecular evidence to show that necroptosis contributes to tau induced neuronal loss in AD and other tauopathies.

**Disclosures: R. Vartak:** None. **C. Branca:** None. **I.S. Piras:** None. **A. Caccamo:** None. **S. Oddo:** None.

**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.03/J5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** R01 AG037637
Alzheimer's Association International Research Grant

**Title:** Pim1 inhibition as a novel therapeutic strategy for Alzheimer's disease

**Authors: *S. KNOWLES**[1], R. VELAZQUEZ[3], A. CACCAMO[3], S. ODDO[3,2]
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**Abstract:** Accumulation of amyloid-β (Aβ) and neurofibrillary tangles are the prominent neuropathologies in patients with Alzheimer's disease (AD). Strong evidence indicates that an imbalance between production and degradation of key proteins contributes to the pathogenesis of AD. The mammalian target of rapamycin (mTOR) plays a key role in maintaining protein homeostasis as it regulates both protein synthesis and degradation. A key regulator of mTOR activity is the proline-rich AKT substrate 40 kDa (PRAS40), which directly binds to mTOR and reduces its activity. Notably, AD patients have elevated levels of phosphorylated PRAS40 (pPRAS40), which correlate with Aβ and tau levels as well as cognitive deficits. Physiologically, pPRAS40 is regulated by Pim1, a protein kinases of the protoconcogene family. We have identified a Pim1 inhibitor (Pim1i) that crosses the blood brain barrier and reduces pPRAS40. Here, we tested the effects of a selective Pim1i, on spatial reference and working memory and AD-like pathology in 3xTg-AD mice. Pim1i-treated 3xTg-AD mice performed significantly better than their vehicle treated counterparts and as well as non-transgenic mice in a spatial reference memory task after 4 weeks on treatment. Additionally, 3xTg-AD Pim1i-treated mice showed a reduction in soluble and insoluble Aβ40 and Aβ42 levels, as well as a 45.2% reduction

in Aβ42 plaques within the hippocampus. Furthermore, phosphorylated tau immunoreactivity was reduced in the hippocampus of Pim1i-treated 3xTg-AD mice by 38%. Mechanistically, these changes were linked to a significant increase in proteasome activity. These data strongly suggest that Pim1i might be a valid therapeutic target for AD. Notably, there were peripheral side effects with the Pim1i, evident by splenomegaly at autopsy. In light of these side effects, we next proposed a series of experiments in order to reduce peripheral side effects and extend our findings. We are currently developing a strategy to increase the amount of Pim1i absorbed by the brain while reducing the concentration in the periphery. Additionally, we plan to examine the Pim1i effects on neuronal cell loss in the 5xFAD mouse model of AD. Completion of the proposed work may springboard the use of the Pim1i for AD to clinical trials.

**Disclosures: S. Knowles:** None. **R. Velazquez:** None. **A. Caccamo:** None. **S. Oddo:** None.

**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.04/J6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant R01 AG037637

**Title:** Role of S6K1 signaling pathway in AD brains

**Authors: *R. BELFIORE**[1,2], E. FERREIRA[1], A. CACCAMO[1], S. ODDO[1,3]
[1]Arizona State Univ. Biodesign Inst., Tempe, AZ; [2]BIOMETEC, Univ. of Catania, Catania, Italy; [3]Sch. of Life Sciences, Arizona State University, Tempe, Arizona, 85281, USA, Tempe, AZ

**Abstract:** Aging is the most prominent risk factor for Alzheimer’s disease (AD), The ribosomal protein S6 kinase 1 (S6K1), a ubiquitously expressed enzyme, plays a key role in aging and it regulates protein translation and cell homeostatic systems. For example, deletion of the S6K1 gene in mice increases lifespan and decrease the incidence of age-dependent motor deficits, insulin resistance, and obesity. The goal of this study was to assess the role of S6K1 in AD pathogenesis**.**
We used postmortem human AD brains to probe for a link between S6K1 and AD pathogenesis. We also bred 3xTg-AD mice with S6K1 knockout mice to reduce the expression of S6K1. Using a multidisciplinary approach, we have collected data from aged NonTg, 3xTg-AD, and 3xTg-AD/S6K1$^{+/-}$ mice brains. Our findings show that higher S6K1 activity correlates with increased Aβ levels and decreased Mini Mental State Examination (MMSE) scores in AD patients. We found that reducing S6K1 levels also reduces Aβ and Tau pathology in 3xTg-AD/S6K1$^{+/-}$ mice, improves spatial learning and memory deficits as well as rescues synaptic deficits. Moreover, our

preliminary data show that cognitive improvements in 3xTg-AD/S6K1$^{+/-}$ mice are linked to a decreased phosphorylation of his downstream targets, rpS6 and eEF2K proteins. Our results are extremely exciting as implicate S6K1 dysregulation as a previously unidentified molecular mechanism underlying synaptic and cognitive deficits in AD.

**Disclosures: R. Belfiore:** None. **E. Ferreira:** None. **A. Caccamo:** None. **S. Oddo:** None.

**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.05/J7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** R01 AG037637

**Title:** Genetic reduction of Nrf2 exacerbates cognitive deficits in a mouse model of Alzheimer's disease

**Authors: *A. RODIN**, C. BRANCA, E. FERREIRA, A. CACCAMO, S. ODDO
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**Abstract:** Aging is the major risk factor for several neurodegenerative diseases, including Alzheimer's disease (AD). However, the mechanisms by which aging contributes to neurodegeneration remain elusive. The nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is a transcription factor that regulates expression of a vast number of genes by binding to the antioxidant response element. Nrf2 levels decrease as a function of age, and reduced Nrf2 levels have been reported in postmortem human brains and animal models of AD. Nevertheless, it is still unknown whether Nrf2 plays a role in the cognitive deficits associated with AD. To address this question, we used a genetic approach to remove the Nrf2 gene from APP/PS1 mice, a widely used animal model of AD. We found that the lack of Nrf2 significantly exacerbates cognitive deficits in APP/PS1, without altering gross motor function. Specifically, we found an exacerbation of deficits in spatial learning and memory, as well as in working and associative memory. Different brain regions control these behavioral tests, indicating that the lack of Nrf2 has a global effect on brain function. The changes in cognition were linked to an increase in Aβ and interferon-gamma (IFNγ) levels, and microgliosis. The changes in IFNγ levels are noteworthy as previously published evidence indicates that IFNγ can increase microglia activation and induce Aβ production. Our data suggest a clear link between Nrf2 and AD-mediated cognitive decline and further strengthen the connection between Nrf2 and AD.

**Disclosures: A. Rodin:** None. **C. Branca:** None. **E. Ferreira:** None. **A. Caccamo:** None. **S. Oddo:** None.

**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.06/J8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Arizona Alzheimer's Consortium
NIH R01 AG037637

**Title:** RIPK1 regulatory activity in Alzheimer's disease

**Authors: *L. M. BUSTOS**[1,2], A. CACCAMO[2], C. BRANCA[2], I. S. PIRAS[3], E. FERREIRA[2], M. J. HUENTELMAN[3], W. S. LIANG[3], B. READHEAD[2], S. ODDO[2]
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**Abstract:** Severe neuronal loss is a key characteristic of the Alzheimer's disease (AD) brain, and is a focal point for AD research. Necroptosis is a programmed form of necrosis, which involves the formation of the necrosome, a multiprotein complex containing receptor-interactive protein kinases (RIPK) 1 and 3, which activates the mixed lineage kinase domain-like (MLKL) protein. We found that necroptosis is activated in human AD brains. Specifically, we found that RIPK1 and MLKL positively correlated with Braak stages, and inversely correlated with cognitive scores. Furthermore, we generated a causal gene regulatory network modeling RIPK1 interaction in AD-relevant tissues. The network was inferred from DNA and transcriptomic data generated from post-mortem samples across two brain regions, which were used to build RIPK1 networks in the anterior prefrontal cortex and the entorhinal cortex. Across both regions, we identified 819 genes whose expression covariate with *RIPK1* expression. These genes significantly overlapped with multiple, independent AD gene expression profiles, comprising non-demented AD (which are characterized by moderate neuropathology, without cognitive impairment) and clinical AD. There was uniform consistency between the signed relationship linking *RIPK1* expression with its downstream neighbors, and the direction of differential expression in the clinical AD profiles; specifically, genes negatively regulated by *RIPK1* overlapped with genes down regulated in AD. This large, concordant overlap between genes regulated by *RIPK1* and genes differentially expressed across multiple AD severity and regional contexts suggests that RIPK1 activity could explain a significant portion of transcriptomic changes in AD.

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**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.07/J9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NSFC YQS No. 81271226

**Title:** Mlkl loss-of-function variant increases alzheimer's disease risk through enhancing gamma-secretase activity

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**Abstract:** Alzheimer’s disease (AD) is an age-related neurodegenerative disorder of the central nervous system, which causes the most common form of dementia in the elderly. More than 95% AD cases were found in people aged over 65 years, termed as late onset AD (LOAD). In recent years, many AD risk variants have been identified through next generation sequencing (NGS), in which apolipoprotein E ε4 (ApoE ε4) is believed to be the major and most well-known genetic risk factor for LOAD. To identify novel genetic factors other than ApoE ε4 that contribute to LOAD development, we conducted a whole-exome analysis of 246 ApoE ε4-negative LOAD cases and 172 matched controls in Hong Kong Chinese population. We identified a rare stop-gain variant (p.Q48X) in **m**ixed **l**ineage **k**inase domain **l**ike pseudokinase (*MLKL*) gene. The rare variant (*MLKL: p.Q48X*) introduces a premature termination codon (PTC) TAA at the 48th codon of MLKL mRNA. As the PTC occurs close to the beginning of *MLKL* transcription, nonsense-mediated mRNA decay would probably be induced. The qRT-PCR showed that the *MLKL* mRNA level of *MLKL: p.Q48X* carrier is significantly lower than subjects with wild-type (WT) *MLKL*. In addition, Sanger sequencing analysis of *MLKL* cDNA indicated that the variant carrier lost the heterozygosity of *MLKL* at the cDNA level. These results demonstrated that *MLKL* mRNA decay was induced by the *MLKL:p.Q48X* variant. To verify the impact of this variant on AD pathogenesis, *MLKL* was knock down (KD) in HEK293 cells expressing human *APP695* with Swedish mutation. Aβ42 and Aβ40 were detected using ELISA. The results demonstrated that the Aβ42/Aβ40 ratio was significantly elevated at the absence of *MLKL*. We then detected the expression of APP, α-, β-, and γ-secretase after *MLKL* KD through qRT-PCR and western blot. The data showed no significant changes of these target genes at both mRNA

and protein levels, suggesting that *MLKL* modulate Aβ generation through regulating γ-secretase activity. To evaluate γ-secretase activity, *MLKL* was knock down in N2a cell expressing NotchΔE or APP695 Swedish mutant. The production of NICD and AICD (the γ-cleavage product of Notch and APP) was significantly elevated in *MLKL* KD cells through western blot analysis. The γ-secretase fluorogenic substrate assay further confirmed that γ-secretase activity was enhanced at the absence of *MLKL*. Taken together, our study identified a rare *MLKL* loss-of-function variant in a Hong Kong Chinese ApoE ε4-negative LOAD cohort. This variant confers susceptibility to AD through enhancing γ-secretase activity.

**Disclosures: Z. Zhang:** None. **S. Bao:** None. **B. Wang:** None. **X. Ma:** None. **L. Chu:** None. **Y. Song:** None.

**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.08/J10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH/NIA 5R01AG042890
NIH/NIA R56AG058281
Kleberg Foundation

**Title:** Specific miRNAs enriched in neural stem cell-derived exosomes reduce vulnerability of hippocampal synapses to the dysfunctional impact of amyloid beta and tau oligomers

**Authors: *M.-A. MICCI**[1], O. ZOLOCHEVSKA[2], B. KRISHNAN[3], R. KAYED[3], W.-R. ZHANG[3], E. BISHOP[1], C. ANACKER[4], G. TAGLIALATELA[3]
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**Abstract:** Alzheimer’s disease (AD) is the most common and severe age-associated neurodegenerative dementia. While aging is the most significant risk factor for AD, disruption of synapses by oligomers of both amyloid beta (Aβ) and tau, via converging synergistic mechanisms, is one of the earliest events leading to memory dysfunctions. Interesting, AD pathology can occur years before symptoms become manifest, suggesting that aging renders synapses more vulnerable to the detrimental action of oligomers. Although there is ample consensus that an effective treatment should target the synaptic damaging impact of oligomers of both Aβ and tau, a strategy to achieve this goal remains unresolved. We previously found that exosomes specifically secreted by hippocampal neural stem cells (NSC-exo) render synapses resistant to the dysfunctional impact of amyloid oligomers. We have further shown that doses of

oligomers of Aβ and tau (alone or in combination) that are ineffective in reducing long-term potentiation (LTP) in the hippocampus of young wild type mice (2 months), significantly reduces LTP in the hippocampus of old mice (18 months), suggesting an age-dependent synapse vulnerability. Here we set up to determine whether increasing NSC in the hippocampus of aged mice can reduce synaptic sensitivity to amyloid toxicity in an exosomes-dependent fashion. We further set to determine whether specific miRNA cargos in NSC-exo could mediate their protective effect on the synapses.
We found that age-dependent synaptic vulnerability was rescued by delivering NSC-exo in the intracerebroventricular space (icv) into aged (18 months old) mice. We further found that increasing the number of NSC in the aged hippocampus (using 18 months old transgenic iBax$^{nes}$ mice induced with tamoxifen) significantly reduced synaptic vulnerability to low doses of oligomers. Using Deep sequencing, we found that NSC-exo possess a unique set of miRNAs (miR-485, miR-322,miR-17), as compared to exosomes secreted from mature neurons, and showed that icv injection of their mimics (alone or in combination) into male and female wild type mice significantly reduced synaptic binding of amyloid oligomers and prevented Aβ and tau oligomer-driven reduction of LTP in hippocampal slices. These results further points to NSC-exo as modulators of synaptic susceptibility to the dysfunctional impact of both Aβ and tau oligomers and unmask a novel therapeutic target for AD based on the delivery of NSC-exo or their bioactive cargoes.

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**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.09/J11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH 1R01AG042890 (GT)
NIH F31AG057217 (OZ)

**Title:** Epigenetic modulation of synaptic resilience to amyloid beta oligomers in Alzheimer’s disease

**Authors: *O. ZOLOCHEVSKA**, G. TAGLIALATELA
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**Abstract:** Alzheimer’s Disease (AD), the sixth leading cause of death in the US and the most common form of age associated dementia, is accompanied by synaptic loss, at early stages, and

neuronal death, at late stages of the disease. Amyloid beta (Aβ) and tau oligomeric aggregates, the most toxic species of the two hallmark proteins in AD, are capable of targeting and disrupting synapses thus driving cognitive decay. Certain individuals (here referred to as Non-Demented with Alzheimer's Neuropathology – NDAN) are capable of withstanding Aβ and tau toxicity, and thus remain cognitively intact despite the presence of AD neuropathology. Understanding the involved mechanism(s) would therefore lead to the development of novel and effective therapeutic strategies aimed at promoting synaptic resilience to amyloid toxicity. Proteomic studies of postsynaptic density fractions of hippocampi prepared from post-mortem brains of AD, NDAN and healthy control individuals revealed 31 unique proteins that are significantly different in AD vs. NDAN. Potential drivers of these changes, microRNA-485, -4723 and -149, were predicted by Ingenuity Pathway Analysis and experimentally confirmed to be differentially expressed in AD vs. control and NDAN brains. We hypothesized that changes in these microRNAs (miRNAs) levels play an important role in either promoting synaptic resistance or sensitization to Aβ oligomers binding. To test our hypothesis, we used an *in vivo* model to determine if modulation of these miRNAs can affect the ability of Aβ oligomers to associate with synaptic elements. Synaptosomes were prepared from hippocampi of wild-type mice (male and females) 24 hours after intracerebroventricular injection of mimics or inhibitors of the identified miRNAs, and Aβ binding was evaluated using flow cytometry. We found that *in vivo* modulation of microRNA-4723, -485 and -149 levels significantly decreased Aβ binding to the synapses in both male and female mice. Taken together, our findings suggest that miRNA regulation and homeostasis are crucial for Aβ interaction with synaptic terminals, and strongly suggests that, in NDAN individuals, a unique epigenetic profile could be driving synaptic resistance to Aβ toxicity, thus contributing to preserved cognitive abilities.

**Disclosures: G. Taglialatela:** None.

**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.10/J12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Tata Trusts Grant

**Title:** Early hippocampal deficits in a mouse model of Alzheimer'sdisease

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**Abstract:** Memory dysfunction in the early stages of Alzheimer's Disease (AD) has been attributed to deficits in hippocampal-entorhinal circuit. To understand whether hippocampal neuronal deficits substantially precede the overt appearance of clinical AD including the formation of extracellular amyloid plaques, we carried out dendritic spine analysis of hippocampal CA1 pyramidal neurons at 1 month of age in $APP_{Swe}$/PS1ΔE9 (APP/PS1) mouse model of AD. We noticed a selective reduction of mushroom spines as against the percent contributions of thin and stubby spine density in the tertiary apical dendrites of CA1 pyramidal neurons. However, dendritic spine density was unaltered in secondary apical dendrites. We further hypothesized that the molecular basis of decrease in spine density in the hippocampus could have its roots in impaired activity dependent protein translation, which is critical for synaptic plasticity. We observed that in 1m old APP/PS1 mouse hippocampus, all the signaling proteins involved in the Akt-mTOR cascade, such as Akt, mTOR, GSK, p70-s6k, 4E-BP and S6 regulating the activity dependent protein translation were repressed. Since the number of dendritic spines, spine plasticity, and morphology are basic to memory consolidation and storage, we further investigated memory impairment in 2 month old APP/PS1 mouse using explicit and implicit memory tests. Explicit memory was assessed with episodic- like memory tasks and implicit memory with contextual Fear conditioning and Morris Water Maze (MWM) task. 2m old APP/PS1 mice showed specific impairment in 'where/which'-episodic-like - memory tasks. However, the "what" component of the episodic-like-memory was intact. In contextual fear conditioning, the mice exhibited a significant long-term fear memory deficit compared to wild-type littermates, while in MWM learning, 2m old APP/PS1 mice showed normal spatial learning capabilities. Therefore, we conclude that there are early signs of molecular and structural deficits in the hippocampus that culminates in selective learning impairments during the prodromal stage of AD in APP/PS1 mice.

**Disclosures: R.D. Gowaikar:** None. **S. Kumar:** None. **K. Singh:** None. **S. Karunakaran:** None. **V. Ravindranath:** None.

**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.11/J13

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Tata Trusts Grant
Ramalingaswami Fellow of the Department of Biotechnology (BT/RLF/Re-entry/50/2014)

**Title:** Aβ mediated F-actin loss and cognitive deficits are ameliorated by overexpression of glutaredoxin1 in Alzheimer's disease mouse model

**Authors: *R. KOMMADDI**[1], S. KARUNAKARAN[2], D. TOMAR[1], A. RAY[1], V. RAVINDRANATH[1,2]
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**Abstract:** Synaptic dysfunction, considered to occur early in AD is often seen as loss of dendritic spines. Fibrillar actin (F-actin) is highly enriched in dendritic spines and defines spine structure. We recently reported that synaptosomal F-actin levels were significantly decreased in APPswe/PS1ΔE9 (APP/PS1) mice as early as one month of age. APP/PS1 mice showed recall deficit upon contextual fear conditioning (cFC) at two months, which was reversed by F-actin stabilizing agent, jasplakinolide. Reactive oxygen species (ROS) generated by β-amyloid (Aβ) has been implicated in Alzheimer's disease (AD) pathogenesis. However, it is unclear whether ROS contributes to F-actin loss in synaptosomes, in vivo, in mice. Therefore, we investigated whether altered redox signaling could contribute to F-actin loss and behavioral deficits seen early in AD. We used age matched WT and APP/PS1 mice for our experiments. Highly enriched F-Actin and G-Actin fractions were isolated from synaptosomes prepared from cortices of WT and APP/PS1 mice. We also used AMS-derivatization approach to determine reduced form of F-actin. AAV-glutaredoxin1 viral particles were delivered into hippocampus of mouse brain using stereotaxic injections. Reduced form of F-actin was significantly decreased while reduced form of G-actin was unaffected in synaptosomes of APP/PS1 mice as early as one month and this loss was sustained until nine months, when overt symptoms are observed. S-glutathionylation of synaptosomal actin, which is known to hinder F-actin stabilization was significantly increased in one month APP/PS1 mice in comparison to WT mice. Further, to determine the role of Aβ mediated endogenous ROS levels on F-actin loss and behavioural deficits in APP/PS1 mice AAV-glutaredoxin1 viral particles were transduced into the hippocampus of the mouse brain. Remarkably, we found that cFC behavioral deficits seen in APP/PS1 mice and loss of synaptosomal F-actin levels were restored by over expression of glutaredoxin1 in AD mice. We conclude that Aβ induced ROS-mediated glutathionylation of actin as one of the mechanisms hindering F-actin stabilization in synaptic compartments leading to behavioral deficits in APP/PS1 mice, which can be reversed by over expression of glutaredoxin1. Our novel findings provide evidence that F-actin loss through oxidative modification at the synapse plays a critical role in synaptic dysfunction in AD pathogenesis.

**Disclosures: R. Kommaddi:** None. **S. Karunakaran:** None. **D. Tomar:** None. **A. Ray:** None. **V. Ravindranath:** None.

**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.12/J14

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Tata Trusts Grant (JTTO0001)

**Title:** Model of vascular dementia using endothelin induced stroke in mice

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**Abstract:** Vascular Dementia may begin as mild cognitive changes due to blockade of blood vessels that worsen gradually as a result of multiple minor strokes, leading to cumulative damage. Patients with multiple micro infarcts as well as repeated occurrence of micro infarcts have high risk of developing dementia. Therapies to delay progression of cognitive impairments are required to minimize deficits associated with dementia. Most common animal model used to study vascular dementia is cerebral artery occlusion, which produces clear major infarct in brain depending on side of occlusion. Since we wanted to create micro infarcts rather than a severe insult we opted for bilateral intracerebroventricular injection of endothelin-1 (ET-1), which is a vasoconstrictor peptide into 4$^{th}$ventricle. We observed decreased CD31 expression which is a marker for endothelial cells in ET-1 injected animals probably due to constriction in micro vessels after 3 days of endothelin treatment. Further, there was transient associative memory deficit and down regulation of Akt-mTOR pathways in hippocampal tissue of mice injected with endothelin at 7 days indicating the effect of blockade in blood flow. The reduction in Akt1-mTOR signaling resulted in consequent decrease in GSK α/β signaling in hippocampus after 7 days of endothelin injection implying that activity dependent protein translation could potentially be affected. However, there was recovery in learning and memory deficits and Akt-mTOR signaling after 30 days of endothelin treatment. Micro infarcts caused by ET-1 injection leading to impairment of Akt1-mTOR signaling indicate a possible molecular mechanism impacting synaptic plasticity during vasoconstriction. The present study provides insights in understanding vascular pathology leading to behavior dysfunction during multiple small insults in the large disease spectrum of vascular dementia.

**Disclosures: V. Ravindranath:** None. **L. Diwakar:** None. **K. Chithanathan:** None. **D.S. Tomar:** None.

**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.13/K1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Tata Program Grant
Department of Biotechnology, India

**Title:** Localization and regulation of nanoscale machinery involved in the amyloidogenic pathway at an excitatory synapse

**Authors: *D. KUMARAN NAIR**[1], S. KEDIA[1], P. RAMAKRISHNA[2], S. NADKARNI[2]
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**Abstract:** Despite an intuitive understanding of biochemical pathways leading to differential proteolysis of Amyloid Precursor Protein, there is a little understanding of how these molecules are distributed at the synapses. The alteration in number and lateral organization of these transmembrane molecules in synapse is considered as a crucial factor in health and diseases like Alzheimer's Disease (AD). Despite several years of AD research there is indeed a limited knowledge on the factors that control the expression and activity of these molecules at the synaptic membrane. Here we try to combine high density single particle tracking and super resolution imaging techniques like Photo Activation Localization Microscopy (sptPALM), Direct Stochastic Optical Reconstruction Microscopy (dSTORM) and Stimulated Emission Depletion Microscopy (STED) to understand the localization of APP and different secretases (BACE and Presenilin) involved in the processing of APP. Additionally, we illustrate trafficking of wild type APP (APPwt) through diffusional behaviour from thousands of spatially discrete single molecule trajectories from live neuronal cells. We incorporate the experimentally observed spatio-temporal details of APP and BACE in a computational model. We simulate reaction-diffusion dynamics of these molecules on synaptic membranes and endocytic vesicles. These *Insilico* experiments reveal multiple alterations on subsynaptic organization of APP and secretases which alters the proteolytic processing of APP by amyloidogenic pathway. A combination of state of the art microscopy and biophysically realistic model allows us to appreciate finer organization and recycling of APP and secretase molecules at an excitatory synapse.

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**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.14/K2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** University of Catania intramural funds

**Title:** A combination of sub-efficacious doses of phosphodiesterase 4 and 5 inhibitors rescued spatial, recognition and fear memory in a mouse model of Alzheimer's disease

**Authors: *D. PUZZO**[1], W. GULISANO[1], M. TROPEA[1], O. ARANCIO[2], A. PALMERI[1]
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**Abstract:** Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are second messengers regulating signal transduction that cooperate to ensure memory acquisition and consolidation. Increasing their levels by phosphodiesterase inhibitors (PDE-Is) has been demonstrated to enhance cognitive functions and rescue memory loss in animal models of aging and Alzheimer's disease (AD). However, their increase in non-targeted areas and side effects due to the high doses used, have limited their application to the treatment of erectile dysfunction, pulmonary hypertension and chronic obstructive pulmonary disease. Recently, we have demonstrated that a combination of sub-efficacious doses of cAMP- and cGMP-specific PDE-Is exerted an additive effect to improve synaptic plasticity and memory in physiological conditions. Based on these findings, here we aimed to study whether this treatment was effective to rescue the AD phenotype in the APPswe mouse model. We found that a 3-week chronic treatment with a combination of sub-efficacious doses (not affecting memory per se) of the cAMP-specific PDE4-I roflumilast (0.01 mg/kg) and the cGMP-specific PDE5-I vardenafil (0.1 mg/kg) improved recognition, spatial and contextual fear memory. Interestingly, the cognitive enhancement persisted for 2 months beyond therapy suspension. Conversely, acute administration of PDE-Is did not affect memory in APPswe mice. In conclusion, we have shown that combining sub-efficacious doses of roflumilast and vardenafil, drugs already approved for other clinical applications in the elderly, reverse the AD phenotype. This treatment might have several advantages compared to single PDE-Is administration at high doses, such as a possible long-standing human use and a perspective of a better compliance due to the possibility to minimize side effects. More importantly, the persistence of the effect beyond the administration suggests a potential as disease-modifying therapy.

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**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.15/K3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Critical role of Nup153 in adult neural stem cells in a mouse model of Alzheimer's disease

**Authors: *C. COLUSSI**[1], L. LEONE[2], K. GIRONI[2], V. LONGO[2], S. FUSCO[2], M. D'ASCENZO[2], C. GRASSI[2]
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**Abstract:** Impairment of adult hippocampal neurogenesis is an early critical event in animal models of Alzheimer’s disease (AD), contributing to progressive memory loss and cognitive decline. Compelling evidence suggests that dysregulation of the balance between neural stem cell (NSC) proliferation and differentiation may contribute to AD phenotype, although the underlying molecular mechanisms are still unclear. Recently, the nuclear pore complex protein, nucleoporin Nup153, in addition to its role in nucleus-cytoplasm transport, has been described as a key regulator of adult NSC plasticity through the interaction with the transcription factor Sox2. Here we investigated the role of Nup153 in NSC dysregulation in a mouse model of AD. Our results revealed that NSCs residing in the hippocampal dentate gyrus of 2-month-old 3×Tg AD mice display reduced levels of Nup153 compared to wild-type (WT) mice. A similar decrease of Nup153 expression, at both mRNA (-36%±3) and protein levels, was also found in cultured hippocampal NSCs obtained from newborn 3×Tg mice (AD-NSCs). Moreover, Co-IP experiments revealed that Nup153 association with Sox2 was significantly reduced in AD-NSCs compared to WT-NSCs. Vector-mediated Nup153 overexpression was used to assess its role in AD-NSC function in comparison to empty-vector expressing control cells. Of note, overexpression of Nup153 increased AD-NSC proliferation, assessed by BrdU incorporation (%: AD-NSCs 33.8±1.1; AD-NSC-Nup153 69±4.5), neurosphere assay (n° of neurosferes: AD-NSCs 43.6±4.2; AD-NSC-Nup153 82.2±0.5) and phosphorylation of serine 10 on histone H3 (2-fold increase). Scratch assay revealed that Nup153 overexpression was sufficient to recover AD-NSC migration to WT-NSC level (% of remaining gap: WT-NSCs 38.3±3.1; AD-NSCs 58±3.8; AD-NSC-Nup153 31±2.2). Interestingly, this effect was paralleled by increased expression of PSA-NCAM. Inhibition of nitric oxide synthase by LNAME (5mM), antioxidant treatment (ascorbic acid, 1mM) or gamma-secretase inhibition (1μM) all increased Nup153 levels in AD-NSCs (2-fold increase), whereas treatment of WT-NSCs with amyloid-β oligomers (200 nM) led to Nup153 down-regulation (1.7 fold decrease). Collectively, these findings suggest that increased nitro/oxidative stress, which characterizes many neurodegenerative diseases including AD, may

induce Nup153 downregulation through the accumulation of Aβ42. In conclusion, our data uncover a novel role for Nup153 in AD and a potential new target to ameliorate AD-NSC function.

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**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.16/K4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Tata Trusts Grant
Ramalingaswami Fellow of the Department of Biotechnology (BT/RLF/Re-entry/50/2014)

**Title:** Gender differences in synaptosomal F-actin levels and cognitive functions in Alzheimer's disease mouse model

**Authors: R. KOMMADDI**[1], *S. KARUNAKARAN[2], K. CHITHANATHAN[1], V. RAVINDRANATH[1,3]
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**Abstract:** Incidence of Alzheimer's disease (AD) is higher in women as compared to men. Although neuroprotective effect of estrogen is well recognized, the underlying pathogenic mechanisms explaining the higher burden of AD in women are unclear, taking into account the longer lifespan in women. Several studies have demonstrated that synaptic dysfunction is considered to occur prior to the appearance of the pathophysiological and behavioural symptoms of AD. Fibrillar actin (F-actin) is one of the major cytoskeleton proteins present in dendrites and is very important for defining dendritic spine structure. Here, we measured F-actin and G-actin levels, in synaptosomes derived from the cortices of WT and APP/PS1 mice at different ages from both male and female mice. We found significant decrease in synaptosomal F-actin levels in male, but not in female, APP/PS1 mice at 4 months of age. Intriguingly, synaptosomal F-actin levels started decreasing in female APP/PS1 mice at the age of 8 months and this was sustained until 1 year of age. Furthermore, male APP/PS1 mice, but not female mice showed deficient recall upon contextual fear conditioning at the age of 4 months. However, female APP/PS1 mice started showing deficient recall upon contextual fear conditioning at the age of 8 months and cognitive deficits were sustained until 1 year as examined in both male and female mice. The

appearance of cognitive deficits and loss of synaptosomal F-actin 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.

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**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.17/K5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** University of Catania intramural funding
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**Title:** Unraveling the role of monomeric and oligomeric amyloid-β 1-40 and 1-42 at high and low concentrations in hippocampal synaptic plasticity and memory

**Authors: *W. GULISANO**[1], M. MELONE[2,3], D. D. LI PUMA[4], M. TROPEA[1], A. PALMERI[1], O. ARANCIO[5], C. GRASSI[4,6], F. CONTI[2,3,7], D. PUZZO[1]
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**Abstract:** The increase of oligomeric amyloid-beta (oAβ) has been related to synaptic dysfunction, thought to be the earliest event in Alzheimer’s disease (AD) pathophysiology. However, low physiological concentrations of Aβ have neurotrophic and neuroprotective properties and exert a positive modulatory function on synaptic plasticity and memory. Moreover, Aβ deletion in the healthy brain results in a dramatic impairment of synaptic plasticity and memory, suggesting that the peptide is needed to ensure these functions. Here, we have investigated whether different species, aggregation forms and concentrations of Aβ might differently influence synaptic function. In particular, we have tested the individual contribution

of monomeric or oligomeric Aβ40 and Aβ42 at 200 nM and 200 pM concentrations on hippocampal CA3-CA1 long-term potentiation (LTP) and spatial memory. When at 200 nM, oAβ40, oAβ42 and monomeric Aβ42 impaired LTP and memory, whereas only 200 pM oAβ42 exerted a positive effect at the synapse. Remarkably, 200 pM oAβ42 was able to rescue the detrimental effect due to depletion of endogenous Aβ. Quantification of monomer-like and oligomer-like species carried out by transmission electron microscopy revealed an increase of the monomer/oligomer ratio in the oAβ42 200 pM versus 200 nM preparation, suggesting that the content of monomers and oligomers depends upon the final concentration of the solution. Taken together, these findings suggest that the Aβ biphasic effect is influenced by different isoforms or aggregation status of the peptide. Moreover, our data suggest that, when at high concentrations, both monomers and oligomers exert a neurotoxic action. Conversely, when at low concentration, the presence of oligomers is needed for LTP and memory. Such observations should be taken into consideration when studying the role of the peptide in physiological or pathological conditions, and when developing Aβ-tailored therapies especially aimed at clearing oligomers but sparing monomers.

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**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.18/K6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Tata Trusts Grant

**Title:** Comparative transcriptional profiling in Alzheimer's disease using RNA-seq

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**Abstract:** Alzheimer’s disease (AD) is a debilitating, progressive neurodegenerative disease that is characterized by cognitive deficit. Existing therapies for AD provide symptomatic relief but treatments that can modify the progression of neurodegeneration are not available. While cognitive deficits in AD are manifested only late in life, early detection of AD is essential for developing treatment strategies that can alter the course of AD. This study aimed to explore the global changes in gene expression at early pre-symptomatic stages in APPswe/PS1ΔE9

(APP/PS1) transgenic mice in entorhinal cortex (EC) and hippocampus (HP). Thereafter, global gene expression changes in AD transgenic mouse model were compared to transcriptome data from human autopsy tissue.
Total RNA isolated from EC and HP from 4 male APP/PS1 transgenic (Tg) and wild type (WT) control mice each at 1 month and 3 months of age was processed for depletion of ribosomal RNA, cDNA library preparation followed by Illumina paired end sequencing. The raw reads were quality controlled and aligned to mouse genome and read counts were generated and normalized using DESeq2. Further, pathway analysis was performed on the significantly differentially expressed genes. Reads aligned to human reference genome were downloaded from AMP-AD Knowledge Portal. Read counts were generated from aligned reads which were normalized using DESeq2 for differential gene expression analysis. The group that corresponded to human controls had 201 samples, MCI had 159 samples and AD had 221 samples each.
App and Prnp were found to be upregulated in both EC and HP at 1 month and 3 months of age in APP/PS1 mice, which served as a positive control for the integrity of the data. In summary, expression of 309 genes was significantly altered at 1 month; and 208 genes at 3 months in EC. However, only 17 genes were significantly altered at 1 month; and 79 at 3 months in HP. Analysis of the data obtained from the AMP-AD RNA-seq study revealed that 2971 genes were significantly altered in the AD group compared to controls. However, only 117 genes were significantly altered in AD compared to MCI.
This study shows extensive gene expression perturbations as early as one month of age in APP/PS1 transgenic mice and also in human AD autopsy tissue. Greater changes in differential gene expression were observed in EC than HP at both time points. Moreover, genes involved in chemical synaptic transmission were perturbed in both 1-month EC from Tg mice and in human AD. Our data presents an interesting comparison of gene expression changes across two ages and two brain regions in APP/PS1 mice and between human MCI and AD.

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**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.19/K7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Development of a new two-photon absorbing probe for β-amyloid plaques with a negligible background signal in tissue imaging

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**Abstract:** The deposition of β-amyloid(Aβ) plaques in the specific brain regions is one of the key pathological hallmark of Alzheimer's disease(AD). Imaging and following of AD pathology is important to understand and manage the disease. Among many approaches to detect Aβ plaques, two-photon microscopy(TPM) is an attractive tool for observing biological system. Several TP probes based on dipolar structure have been developed so far, which show a substantial level of fluorescence by nature and an enhanced level of signal via intercalating into Aβ plaques. It is critical issue to remove residual signals to get much clearer and specific image data. To overcome this problem, here we propose a new folding/unfolding based TP excitable probe. A new probe has a structure of two aromatic fluorophores which prefer to exist in folded, self-quenched, form. In contrast, upon insertion into β-sheet structure of Aβ aggregates, folded structure become stretch out accompanying significant fluorescence signals. The probe enables ex vivo and in vivo tissue imaging of Aβ plaques in disease-model mouse, with a remarkably suppressed background noise. These results demonstrate that new dye will be useful in bioimaging and biomedical application with less background signal.

**Disclosures: H. Choi:** None. **S. Cho:** None. **S. Baik:** None. **K. Ahn:** None. **I. Mook-Jung:** None.

**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.20/K8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Tauopathy induced deradation of Per2 leads to circadian rhythm disruption in Alzheimer's disease

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**Abstract:** Alzheimer's disease(AD) is the most common type of dementia. Pathologies of Alzheimer's disease are represented by amyloid plaque, neuro-fibrillary tangle(NFT) and gliosis. NFT, majorly consist of Tau protein, is highly correlated with cognitive impairment in AD. Recently, sleep deprivation and circadian rhythm disruption show high correlation with AD

pathology. Previously, molecular mechanism of circadian rhythm disruption by amyloid beta(Aβ) was revealed. Focus of this study is molecular mechanism of circadian rhythm disruption in AD especially with tauopathy. AD pathology model mice($ADLP^{Tau}$) were used in this study. $ADLP^{Tau}$ has hTau P301L and showing tauopathy, not amyloid pathology. $ADLP^{Tau}$ shows tauopathy and circadian rhythm disruption. Specifically, phase delay and body temperature of $ADLP^{Tau}$ mice was altered from wildtype. In mRNA level, several clock gene oscillation was disrupted. In protein level, Per2 core clock protein was decreased in entire time point. From this results, degradation of Per2 induced by tauopathy was investigated and we suggest this for major underlying mechanism of circadian rhythm disruption in AD and tauopathy.

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**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.21/K9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Amyloid-β and tau pathology is mediated by plexin in Alzheimer’s disease pathogenesis

**Authors: *S. CHUNG**[1], J. YANG[2], H. KIM[3], W. LEE[4], A. KIM[5], K. SUH[6], H. CHOI[6], I. MOOK-JUNG[7]
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**Abstract:** Synergistic effect between Amyloid-β (Aβ) and hyper-phosphorylated tau is a predominant event in Alzheimer’s Disease (AD) pathogenesis. However, identifying a molecular mediator between Aβ and Tau is still on progress. Here, we report the novel role of Plexin, the plasma membrane protein which serves as an axon guidance and repulsion signaling molecule as a receptor for Aβ and accelerates tau hyper-phosphorylation.
Aβ oligomer treatment altered the surface expression pattern of Plexin and induced tau hyper-phosphorylation. Plexin increased the total tau level in a dose dependent manner and likewise, knockdown of the Plexin in hippocampal neuron reduced the total amount and hyper-phosphorylation of tau even in the presence of Aβ.
In the AD mouse model which manifest both Aβ and tau pathology, Plexin is colocalized with

Aβ plaque and knockdown of the Plexin in hippocampus alleviated Aβ-induced tau pathology and rescued cognitive impairment.
In conclusion, these observations indicate that Plexin can functions as a receptor for Aβ which triggers toxic tau hyper-phosphorylation in AD pathogenesis. Our finding strengthens the Aβ - tau axis hypothesis and may provide a new therapeutic target against AD.

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**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.22/K10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** CNPQ
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**Title:** mTORC1 signaling in Aβ-oligomer-based and transgenic murine models of Alzheimer's disease

**Authors: *D. C. FERREIRA**[1], F. C. RIBEIRO[3], A. AGUILAR-VALLES[4], F. G. DE FELICE[5], N. SONENBERG[4], S. T. FERREIRA[2]
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**Abstract:** The mammalian target of rapamycin (mTOR) plays a fundamental role in cell proliferation, survival and autophagy. In particular, mTOR complex 1 (mTORC1) has a key role in the regulation of protein synthesis activated by stimuli such as amino acids, insulin and growth factors. Both insulin signaling and protein synthesis are impaired in Alzheimer's disease (AD), the most common cause of elderly dementia. Because of this, the mTORC1 signaling pathway has received much attention in recent AD research. However, results from such studies remain controversial. While most groups have shown an upregulation of the mTORC1 pathway in experimental models of AD, others have reported an opposite effect. We are currently studying the mTORC1 pathway in two different models of AD: wild-type Swiss mice receiving intracerebroventricular (icv) infusions of amyloid-β oligomers (AβO), toxins that build up in the

AD brain and are thought to cause synapse failure and memory loss, and transgenic APPswe/PS1ΔE9 mice. Our results show that mTORC1 signaling is significantly reduced in the mouse hippocampus 7 days after icv infusion of AβOs. Surprisingly, we do not find any changes in mTORC1 signaling in the hippocampi of APPswe/PS1ΔE9 mice, a transgenic model engineered to overproduce the amyloid-β peptide, at either 4 or 8 months of age, when AD-related neuropathology and memory impairment are detected. Results may point to potentially critical differences between acute and chronic models of AD, and to disease stage-dependent regulation of mTORC1 signaling. Further, results may be connected to recently reported differences in mTORC1 subcellular localization (plasma membrane versus lysosomes), a possibility we are currently exploring. Resolving these apparently conflicting results may be an important step towards proper understanding of mTORC1 signaling in AD, and to the development of therapies focused on reestablishing proteostasis.

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**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.23/K11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Abeta accelerates tau propagation in the neuronal cell line

**Authors: *K. SUH**, D. KIM, I. MOOK-JUNG
Seoul Natl. Univ., Seoul, Korea, Republic of

**Abstract:** Presence of amyloid plaques and neurofibrillary tangles are major characteristics of Alzheimer's disease (AD). Both pathological proteins, amyloid beta (Aβ) and tau, are known to have highly conserved spatial pattern in accumulation among the patients that it can be the criteria for the degree of pathology. Especially, tau propagates in prion-like manner along the neuronal circuit, and as this propagation occurs in prior to cognitive decline, the spreading phenomena would play an important role for inducing the clinical symptoms of AD. In addition, accumulation of Aβ always precedes the formation and propagation of tau, which implies the effect of pre-existing Aβ in the progression of tauopathy, although the clear relationship between Aβ and tau propagation is poorly understood. First, we constructed a novel mouse model for AD, $ADLP^{APT}$ mice, which expresses both Aβ and human tau. We observed the accelerated tauopathy affected by Aβ in $ADLP^{APT}$ mice. However, Aβ pathology is not affected by the presence of tau, indicating that Aβ can work as an accelerant for the propagation of tau but not vice versa. Then, to demonstrate the process of the phenomena observed *in vivo,* we first examined whether

neurons uptake extracellular tau with the help of Aβ. Using neuronal cell line, we found that neuronal uptake of tau is accelerated in Aβ dependent manner. Taken together, we show that Aβ facilitates the propagation of tau by increasing neuronal uptake of extracellular tau, and the internalized tau induces formation of neurofibrillary tangles and cytotoxicity in receptor neurons, thereby promoting neuronal cell death.

**Disclosures: K. Suh:** None. **D. Kim:** None. **I. Mook-Jung:** None.

**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.24/K12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Effects of broad-spectrum antibiotics induced gut microbiota manipulation on tau pathology in Alzheimer's disease model mouse

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**Abstract:** The gut-brain axis (GBA) is the bidirectional communication between the gastrointestinal tract and the brain. The gut microbiota has recognized as a key regulator of this axis and there is increasing evidences that changes in the gut microbial diversity and composition can influence various neurological disease and neurodegenerative disease. The most prevalent neurodegenerative disease, Alzheimer’s disease (AD) is characterized by accumulation of amyloid beta (Aβ) peptides and neurofibrillary tangles (NFTs) comprised of hyper-phosphorylated tau proteins in the brain, resulting in the cognitive impairment. In this study, using $ADLP^{APT}$ transgenic AD mouse model, we determined whether the pathological features of AD are affected by the alterations in brain signaling from the AD-associated gut microbiota in the early stage of the disease. So we examined Aβ plaque load and NFTs formation after the altered gut microbiota in AD model mouse through its manipulation by broad-spectrum antibiotics (ABX) treatment. We found that levels of aggregated tau and hyper-phosphorylated tau significantly decreased in the ABX-treated $ADLP^{APT}$ mouse compared to the DW-treated $ADLP^{APT}$ mouse, but did not observed the reduction of Aβ plaques. These findings suggested that the altered gut microbiota might contributed to the interactions between the gut and brain that impact tau-related pathology in the early stage of AD.

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**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.25/K13

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Human mesenchymal stem cell-derived extracellular vesicles: A feasible therapeutic approach in Alzheimer's disease?

**Authors: *M. LOSURDO**[1], M. PEDRAZZOLI[3], C. D'AGOSTINO[1], E. LONATI[1], L. RIZZI[1], L. MOLTENI[1], C. ELIA[4], E. DANDER[5,2], G. D'AMICO[5], A. TORSELLO[1], M. MATTEOLI[4,6], A. BULBARELLI[1], M. R. BUFFELLI[3], S. COCO[1]
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**Abstract:** AIM: Human mesenchymal stem cells (hMSCs) possess potent immunosuppressive capacity that mainly depends on paracrine mechanisms. With the aim to develop a cell-free system to target inflammatory processes in AD, we are investigating the immunomodulatory potential of preconditioned MSC-derived extracellular vesicles (pMSC EVs) on microglia polarization in 3xTg AD model.
METHODS
Cytokine preconditioning with IFNγ and TNFα was selected as leading ex vivo strategy to prompt hMSC immunosuppressive phenotype. pMSC EVs were isolated from MSC culture medium by ultracentrifugation and tested *in vitro* on primary microglia - extracted from cortices and hippocampi of postnatal 1-2 day old mice - 2 h after inflammatory challenge. EV immunoregulatory effects were assessed after 48 h by evaluating the modulation of cytokine release (ELISA) and M1 and M2 marker expression (Western Blot). 7-month-old 3xTg mice, used in *in vivo* experiments, were intranasally injected with 15 $x10^9$ EVs and sacrificed after 3 weeks for the analysis of cortical and hippocampal microglial phenotype. Golgi Cox was used for the staining of neuronal dendritic branching.
RESULTS
hMSCs, underwent to inflammatory preconditioning, showed an increased expression of immunomodulatory markers (COX2, IDO) and preserved the expression of stemness markers (CD90, CD73) as well as the ability to differentiate into mesodermic lineage. pMSC-EVs foster microglia M2 phenotype, as evidenced by the significant reduction in the release of pro-inflammatory cytokine IL-6 and the increase of the anti-inflammatory cytokine IL-10. EVs

significantly reduced microglial density and IBA1/CD68 co-localization in the hippocampal CA1 region of EV-treated 3xTg mice compared to the controls. In the same area, EV-treated mice showed an increase of dendritic spine density compared to control animals.
CONCLUSION
Cytokine preconditioning represents a feasible method for improving MSC immunoregulatory potential without altering cell stemness properties. Preconditioned-MSC EVs might represent a therapeutic tool able to improve synaptic plasticity. This positive effect may be attributable to the ability of EVs to dampen neuroinflammation by influencing microglia behaviour.

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**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 739.26/K14

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Tau alters neural circuits in the early tauopathy

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**Abstract:** The entorhinal cortex (EC) is one of the most vulnerable brain region that is attacked during the early stage of Alzheimer’s disease. Accumulation of abnormally hyperphosphorylated tau in the EC is the earliest pathological hallmarks in AD patients and neurofibrillary tangles are known to spread in a hierarchical pattern during disease progression. However, the neuronal function of tau is still unknown despite its probable influence on specific neural circuits in the early Alzheimer’s disease. In the present study, we found that accumulation of pathological tau begins in the lateral entorhinal cortex (LEC), followed by the hippocampal CA1 region of 2- to 3-month-old tau mice. In these ages, spontaneous excitatory and inhibitory postsynaptic currents (sEPSC) are changed in hippocampal CA1. Taken together, our findings suggest the possibility that tau alters specific neural circuits by modulating synaptic transmission in the early tauopathy.

**Disclosures: E. Jung:** None. **S. Choi:** None. **S. Choi:** None. **I. Mook-Jung:** None.

**Poster**

**739. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

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**Topic:** C.02. Alzheimer's Disease and Other Dementias

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**Title:** Blood acetylcholinesterase level is a potential biomarker for the early detection of cerebral amyloid deposition in cognitively normal individuals

**Authors: D. LEE**[1], *J. PARK[2], S.-H. HAN[2], M. BYUN[3], D. YI[3], J. LEE[4], I. MOOK-JUNG[5]
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**Abstract:** Cerebral β-amyloid (cAβ) deposition and cholinergic dysfunction have been considered as major pathological and functional hallmarks of Alzheimer’s disease (AD). Acetylcholinesterase (AChE) is the one of the major cholinergic enzymes and there is no report to show the relationship between cAβ accumulation and peripheral AChE alteration in early stage of AD pathogenesis. Recent studies demonstrate that cAβ starts to deposit 15 to 20 years ahead of symptomatic appearance and this preclinical AD is important for early diagnosis of disease. In this study, we investigated the link between cAβ deposition and the peripheral AChE in cognitively normal (CN) individuals. A total of 407 individuals underwent Pittsburgh compound B (PiB)-positron emission tomography were participated in our study. Lower levels of plasma AChE and its enzymatic activity were detected in CN individuals with cAβ deposition than in those without cAβ. Plasma AChE levels and enzymatic activity were negatively correlated with the degree of cAβ deposition. Our results suggest that blood AChE can be used as a potential blood biomarker for the prediction of cAβ deposition in CN individuals.

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**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 740.01/K16

**Topic:** C.02. Alzheimer's Disease and Other Dementias

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**Title:** Metabolic and bioenergetic pathogenic changes in amyloid-a challenged neurons

**Authors: *A. A. ROSTAGNO**, K. SOTOLONGO, J. GHISO
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**Abstract:** Mitochondria play essential roles in maintaining the high levels of brain energy demands required to maintain physiological ion gradients across membranes critical for the generation of action potentials and to sustain transport systems at endothelial barriers. About 90% of the energy requirement is produced through glucose oxidation, a tightly controlled mitochondrial process leading to ATP production. As the major consumers of oxygen, mitochondria are also the most important generators of reactive oxygen species (ROS) as by-products of the electron transport chain. Thus, it is not surprising that mitochondrial dysfunction is emerging as a major contributor to the pathobiology of age-associated neurodegenerative disorders and is being considered a crucial player in the pathophysiology of AD. Indeed mitochondrial alterations, oxidative stress, reduced ATP production, low levels of central components of the oxidative phosphorylation path, and overall glucose hypometabolism coexisting with synaptic alterations have been reported in AD and recapitulated in different transgenic models. In spite of numerous studies, the mechanistic links among ROS homeostasis, cellular metabolic alterations, and changes in cell bioenergetics, particularly at the level of synapsis and in relation to oligomeric forms of amyloid-β (oligAβ), still remain elusive. Through a combination of classic biochemical and immunocytochemical approaches together with the evaluation of real-time changes in global energy metabolism, our studies provide insights into the detrimental role of oligAβ in neuronal cells. Our findings demonstrate that oligAβ induces detrimental changes in mitochondrial function with loss of mitochondrial membrane potential, release of cytochrome C, and enhanced ROS generation. Assessment of global energy metabolism in the Seahorse metabolic analyzer after sequential addition of different inhibitors of the mitochondrial metabolic pathways, demonstrate an oligAβ-mediated reduction in oxygen consumption affecting basal and maximal respiration capacity and causing decreased ATP production. Pharmacologic targeting of Aβ-challenged neurons with compounds of known

antioxidant activity such as melatonin and the vitamin E-analog trolox, restored mitochondrial integrity/function, rescuing metabolic and bioenergetic changes induced by oligAβ. Overall, our studies provide insights into the complex molecular mechanisms triggered by oligAβ which profoundly affect mitochondrial performance and highlight the potential of antioxidant pharmacologic targeting to ameliorate metabolic/bioenergetics alterations.

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**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 740.02/K17

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Carlson College of Veterinary Medicine, Oregon State University

**Title:** Early changes in NMDA receptor synaptic activity in the 5XFAD Alzheimer's disease mouse model

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**Abstract:** Alzheimer’s disease (AD) is an incurable dementia disorder that affects 10% of the population over the age of 65. The key to prevention of AD lies in understanding the early changes that occur in the brain prior to behavioral symptoms. Presenilin mutant mice show enhanced LTP and NMDA receptor (NMDAR) activity prior to showing deficits. The present study was designed to determine whether a more complex mouse model (5XFAD), which expresses 2 presenillin and 3 amyloid precursor protein (APP) mutations and develops plaques, also shows early transient hyperexcitability.
Heterozygous 5XFAD and wildtype littermates of both sexes (combined data) were raised to 1, 2, 3, or 4 months of age and euthanized by exposure to isoflurane. Hippocampal slices were prepared in low-$Ca^{++}$ (0 added) artificial cerebrospinal fluid (aCSF; all in mM: 124 NaCl, 2 KCl, 1.25 $KH_2PO_4$, 26 $NaHCO_3$, 10 glucose, 2 $MgSO_4$) and Schaffer collateral to CA1 synapses were studied with a Med64 multielectrode array. Slice recovery and early long-term potentiation (LTP; single 100Hz tetanus) was performed in 2mM calcium aCSF. For drug studies, input/output curves were obtained for total field excitatory post-synaptic potentials (fEPSP), slices were then changed to .5mM Mg aCSF, 30µM DNQX & 10µM picrotoxin solution, followed by adding 4µM Ro-25-6981 (GluN2B antagonist), and 50µM AP5 (NMDAR antagonist). Drug studies were inadvertently done in low-$Ca^{++}$ aCSF. Input/output curves

analyzed using a stimulus-response variable 4-parameter fit. Experimenters and analyzers were blinded to genotype information. Sample sizes were 3-6.
There was no effect of genotype on the total fEPSP on curve fit at any age (p = .7-.97). There were significant differences in curve fits for the NMDAR and NMDAR GluN2B subunit at 1 month of age, with greater amplitude fEPSPs per stimulus level in the heterozygotes. Non-GluN2B NMDAR responses were increased at 2 months of age. By 4 months of age, the 5XFAD heterozygotes showed significantly decreased amplitude responses for NMDAR, and GluN2B and non-GluN2B NMDARs than wildtype. There was no significant effect of genotype or age on early LTP, measured 45-50 minutes following a single tetanic stimulation.
These results suggest that there was a transient period of enhanced NMDAR responses at 1-2 months of age in 5XFAD mice that became hyporesponsive by 4 months of age. The enhanced NMDAR responses, involving the GluN2B subunit, were at 1 month of age, prior to reported appearances of amyloid plaques. This early NMDAR hyperactivity in the 5XFAD model did not appear to alter LTP, induced by high-frequency stimulation, but could lead to NMDAR excitotoxicity prior to the onset of AD symptoms.

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**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 740.03/K18

**Topic:** C.02. Alzheimer's Disease and Other Dementias

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**Title:** Aberrant EphA4 signaling mediates synaptic fatigue in Alzheimer’s disease

**Authors: *K. HUNG**[1,2,3], Y. SHEN[1,2,3], B. ZHOU[1,2,3], W.-Y. FU[1,2,3], A.-Y. FU[1,2,3], N. Y. IP[1,2,3]
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**Abstract:** People who suffer from Alzheimer’s disease (AD) exhibit memory loss and other mental dysfunctions, which are believed to be due to hippocampal synapse dysfunctions. Soluble

oligomeric amyloid-beta (Aβ) peptides are suggested to be an important factor in mediating these hippocampal synaptic deficits. We previously reported that Aβ triggers aberrant activation of EphA4 and that blockade of EphA4 activity alleviates the hippocampal synaptic plasticity deficits in AD (APP/PS1) transgenic mice. While Aβ causes aberrant accumulation of extracellular glutamate due to ineffective clearance by astrocytes, EphA4/ephrinA3 signaling regulates glutamate transporter expression in astrocytes, which is responsible for glutamate clearance. In this study, we investigated the molecular basis underlying the EphA4-dependent synaptic deficits in AD. Repetitive stimulation of postsynaptic cornu ammonis 1 (CA1) neurons in the hippocampus of normal mice reduced synaptic response, as evidenced by decreased field excitatory postsynaptic potential (fEPSP) slope, which is termed “synaptic fatigue” and impacts neurotransmission efficacy. We found that synaptic fatigue is enhanced in the hippocampus of APP/PS1 mice, which can be rescued by the inhibition of EphA4 signaling. Collectively, our findings raise the intriguing possibility that EphA4 signaling mediates synaptic fatigue in AD.

**Disclosures: K. Hung:** None. **Y. Shen:** None. **B. Zhou:** None. **W. Fu:** None. **A. Fu:** None. **N.Y. Ip:** None.

**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 740.04/L1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NRF-2016R1D1A1B03935267

**Title:** miRNA-mediated cognitive function improvement in Alzheimer's model mice

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**Abstract:** Hippocampal synaptic function and plasticity deteriorate with age, often resulting in learning and memory deficits. As microRNAs (miRNAs) are important regulators of neuronal protein expression, we examined whether miRNAs may contribute to this age-associated decline in hippocampal function. We found that age-upregulated miR-204 contributes to a decline in cognitive functions by repressing EphB2, a key synaptic regulator in hippocampus in part through regulation of the surface expression of the NMDA receptor NR1 subunit. As EphB2 is known to be targeted and degraded by amyloid beta in some patients of Alzheimer’s disease, we tested whether down-regulation of miR-204 could rescue deficits in synaptic plasticity and cognitive function in Alzheimer model mice. Adeno-associated virus (AAV) mediated, down-regulation of miR-204 through stereotaxic injection into dentate gyrus of hippocampus increased

surface expression of NR1 subunit of NMDA receptor, allowing improved NMDA signaling pathway. In turn, this synaptic change led to induced long term potentiation in hippocampus and enhanced spatial memory and recognition abilities in 5X FAD Alzheimer model mice. More importantly, this AAV mediated down-regulation of miR-204 significantly reduced amyloid beta plaque formation in the mice compared to control group that received AAV control, providing a novel therapeutic potential for recovery of cognitive functions in Alzheimer patients.

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**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 740.05/L2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** This work was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI-HI17C0212). the Brain Research Program (NRF-2015M3C7A1028790) through the National Research Foundation (NRF) of Korea funded by the Ministry of Science, ICT and Future Planning

**Title:** A<β>$_{1-42}$ impairs mGluR5-mediated enhancement of depolarization-induced suppression of inhibition and eCB mobilizations in the hippocampus

**Authors: *J. LEE**, J. KWAG
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**Abstract:** Accumulation of amyloid beta (Aβ) in the hippocampus impairs endocannabinoid (eCB) signaling, leading to synaptic dysfunction in Alzheimer's disease (AD). In hippocampal CA1 pyramidal cells (PCs), postsynaptic depolarization mobilizes eCB and causes short-term depression of inhibitory postsynaptic current (IPSC), called depolarization-induced suppression of inhibition (DSI). Especially, eCB mobilization and DSI are known to be synergistically enhanced by the activation of metabotropic glutamate receptor 5 (mGluR5) but how $A\beta_{1-42}$ impairs the mGluR5-mediated enhancement of DSI and eCB mobilization is not clear. Hippocampal slices were treated either with 200 nM $A\beta_{1-42}$ or 0.02% DMSO (vehicle). We performed whole-cell voltage-clamp recordings on hippocampal CA1 PCs *in vitro* and stimulating electrode was placed at the Schaffer collateral to evoke IPSC (eIPSC). Postsynaptic depolarization was induced by giving voltage steps to 40 mV 200 times at 1 Hz to mimic postsynaptic spikes and DSI was measured by taking the mean amplitude of 10 consecutive eIPSC following the postsynaptic spikes. mGluR5 was activated by applying group I mGluR

agonist (DHPG, 50 μM) and mGluR1a antagonist (LY367385, 100 μM) and 3 μM AM251 was used to block cannabinoid receptor type 1. 20 μM CNQX and 50 μM D-AP5 were used to block AMPA and NMDA currents in all experiments. All data were statistically analyzed with unpaired Student's *t*-test. In the vehicle-treated hippocampal slices, postsynaptic spikes alone had no effect on eIPSC amplitude thus no DSI was induced while mGluR5 activation alone induced eIPSC suppression (postsynaptic spike alone: 120 ± 10%; n = 4, mGluR5 alone: 76 ± 11%; n = 6, $p < 0.05$). However, mGluR5 activation during postsynaptic spikes induced DSI and the eIPSC suppression was greater than that with mGluR5 activation alone (postsynaptic spike + mGluR5: 45 ± 7%; n = 5, mGluR5 alone: 76 ± 11%; n = 6, $p < 0.05$), indicating that *in vivo*-like postsynaptic spikes with the concomitant activation of mGluR5 is required to induce DSI. Application of AM251 completely blocked the DSI (postsynaptic spike + mGluR5 with AM251: 118 ± 20%; n = 4, postsynaptic spike + mGluR5: 45 ± 7%; n = 5, $p < 0.01$), indicating that our DSI depends on eCB mobilization. Interestingly, in the $A\beta_{1\text{-}42}$-treated slices, activation of mGluR5 during postsynaptic spikes failed to induce DSI induced by postsynaptic spikes and mGluR5 (Aβ: 71 ± 5%; n = 8, vehicle: 45 ± 7%; n = 5, $p < 0.05$), suggesting that $A\beta_{1\text{-}42}$ may have blocked DSI by interrupting the eCB mobilization. Together, our results suggest that the modulation of eCB mobilization could have a potential as a therapeutic target for recovering synaptic function in AD.

**Disclosures: J. Lee:** None. **J. Kwag:** None.

**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 740.06/L3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

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**Title:** Optogenetic activation of hippocampal SST-positive interneurons recovers impaired theta oscillation in Alzheimer's disease model *in vivo*

**Authors: *H. CHUNG**[1], J. KWAG[2]
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**Abstract:** Excessive accumulation of amyloid β oligomers (Aβo) in the hippocampus disrupts hippocampal theta (3-12 Hz) and gamma (30-90 Hz) oscillation leading to learning and memory impairment in Alzheimer's disease (AD). Hippocampal somatostatin-positive ($SST^+$) interneurons are known to be involved in the generation of hippocampal oscillation and they have been reported to structurally disintegrate in AD. Thus, modulation of $SST^+$ interneurons may have a potential for recovering impaired hippocampal oscillation in AD. To directly investigate such hypothesis, we recorded spontaneous local field potential (LFP) at hippocampal CA1 region of anesthetized mice *in vivo* and $SST^+$ interneurons were selectively activated with optogenetic technique. To optically modulate $SST^+$ interneurons, light-sensitive channel (channelrhodopsin-2) virus was injected into the hippocampus of SST-Cre mice. AD mice model was created by intrahippocampal injection of 10 μM Aβo and was incubated for 3 weeks. Hippocampal oscillation was quantified by analyzing the power spectrum density (PSD) of LFP before and after light stimulation from which peak frequency and power of theta and gamma oscillation were calculated. Single unit activity was detected and sorted to analyze inter-spike interval distribution (ISId) of $SST^+$ interneurons.
We found no difference in peak frequency of theta and gamma oscillation in control mice and AD mice model. However, peak power of theta and gamma oscillation both decreased in AD mice model, similar to other studies in AD. When $SST^+$ interneurons were selectively activated with light in the AD mice model, surprisingly, the decreased peak power of theta oscillation was recovered to the level similar to that of control mice while peak power of gamma oscillation was unaffected by light stimulation. These results suggest that impaired theta oscillation can be recovered by selective activation of $SST^+$ interneurons. To further investigate how $SST^+$ interneuron spike activity was affected in AD, we analyzed ISId of $SST^+$ interneurons. ISId of $SST^+$ interneurons of AD mice model was exponentially decayed from peak at 4 ms, however, light stimulation recovered ISId similar to that of control mice, showing bell curve with peak at 50 ms, indicating that temporal spiking pattern of $SST^+$ interneurons affected by Aβo can also be recovered by light stimulation of $SST^+$ interneurons. Our results demonstrate that theta oscillation impairment in AD mice model could arise from altered spiking activity of $SST^+$ interneurons, suggesting that modulating $SST^+$ interneuron activity could have a potential for therapeutic target for recovering hippocampal oscillation in AD.

**Disclosures: H. Chung:** None. **J. Kwag:** None.

**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 740.07/L4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Fondecyt 1161078
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**Title:** P2X2R overexpression induced by chronic SOAβ treatment, produces changes in the subcellular distribution of fe65 and potentiates the amyloidogenic processing of APP

**Authors: D. MENNICKENT**[1], T. SILVA-GRECCHI[1], P. A. GODOY[1], O. RAMIREZ-MOLINA[1], A. CASTRO[2], J. GAVILAN[1], J. PANES-FERNANDEZ[1], G. MORAGA-CID[1], *J. FUENTEALBA[3]
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**Abstract:** Soluble oligomers of amyloid beta peptide (SOAβ) have been considered as central factors in Alzheimer's disease (AD). Aβ peptide is generated through the sequential cleavage of the amyloid precursor protein (APP), a process that requires the previous endocytosis of APP and that can be modulated by the multidomain adaptor protein Fe65. This protein is able to regulate the transcription of key genes directly related to AD pathogenesis, encoding proteins like APP and BACE 1. On the other hand, we have described that chronic SOAβ treatment induces an increase in the expression of the P2X2 purinergic receptor in PC12 cells and rat hippocampal neurons. Additionally, it has been described that the P2X2a isoform has an intracellular domain that can interact with Fe65, a segment which is absent on the P2X2b isoform. Using mice hippocampal neurons chronically treated with SOAβ (0.5 μM), and patch clamp experiments (voltage clamp), we found that SOAβ treated cells displayed an increase in evoked ATP currents (C: 100 ± 50%; SOAβ: 231 ± 70%; n=9). Additionally, immunocytochemistry (ICC) experiments demonstrated that these cells exhibited an increase in their P2X2R immunoreactivity (C: 100 ± 1 %; SOAβ: 149 ± 15%; n=5). Moreover, cells treated chronically with SOAβ showed a reduction in the Fe65 nuclear-cytoplasmic (N-C) ratio (C: 100 ± 6%; SOAβ: 80 ± 4%; n=5). A similar behavior was observed in PC12 cells transfected to express the P2X2a isoform, but not in those transfected with P2X2b (C: 100 ± 5%; P2X2a: 70 ± 6%; P2X2b: 95 ± 6%; n=3). Colocalization analyses demonstrated that SOAβ decreased the colocalization of Fe65 with APP (C: 100 ± 17%; SOAβ: 47 ± 12%; n=5); results that correlate with the increase observed in the colocalization of APP with clathrin (C: 100 ± 8%; SOAβ: 127 ± 8%; n=4) and Rab5 (C: 100 ± 6%; SOAβ: 132 ± 16%; n=5). In conclusion, these results suggest that chronic SOAβ treatment promotes the endocytosis of APP, potentiating its amyloidogenic processing. Additionally, we propose that P2X2R overexpression promotes Aβ generation by inducing changes in the interaction between Fe65 and APP, resulting in the potentiation of SOAβ chronic toxic effects.

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**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 740.08/L5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIA044

**Title:** Lack of Lrp4 in astrocyte enhances beta-amyloid deposition in 5XFAD mice

**Authors: *H. ZHANG**[1], W. CHEN[2,1], S. SHU[1], Z. DONG[1], W. CUI[1], K. ZHAO[3,1], L. ZHANG[1], W. XIONG[1], L. MEI[1]
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**Abstract:** Alzheimer’s disease (AD) is a progressive neurodegenerative disorder that is caused by the accumulation of amyloid plaques. Formation of amyloid plaques depends on beta-amyloid (Aβ) production and clearance; impaired Aβ clearance has been implicated in late-onset AD. However, underlying mechanisms are not fully understood. Here, we found that Aβ deposition was increased in 5xFAD mice lacking low-density lipoprotein receptor-related protein 4 (Lrp4), a member of the LDL receptor family. Neuronal inflammation, synaptic dysfunction, and cognitive deficits in 5XFAD mice were exacerbated by Lrp4 deficiency. However, Lrp4 mutation did not affect Aβ production or blood-brain barrier (BBB) integrity. Lrp4 was mainly expressed in astrocytes in the brain and could interact with Aβ and ApoE. Lrp4 mutant astrocytes were impaired in Aβ uptake and degradation. Together, our findings reveal a critical role for astrocytic Lrp4 in Aβ metabolism and a potential pathological mechanism of AD development.

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**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 740.09/L6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** ARUK PG2015-24
ARUK PhD2013-13

**Title:** Organotypic hippocampal slice cultures as tools to investigate mechanisms of presynaptic disruption in sporadic and familial Alzheimer's disease models

**Authors: *C. DURRANT**, O. SHEPPARD, M. P. COLEMAN
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**Abstract:** Loss of presynaptic proteins in the hippocampus is an early and clinically-relevant alteration in the brains of patients with Alzheimer's disease (AD). Long term organotypic hippocampal slice cultures (OHSCs) from neonatal amyloid mice provide an excellent platform to examine mechanisms of synaptic disruption, largely retaining the cellular composition and neuronal architecture of the *in vivo* hippocampus, but with *in vitro* advantages of accessibility to live imaging, sampling and intervention.
OHSCs were made from P6-P9 wild-type, TgCRND8 or APP NL-G-F knockin mice and maintained in culture for up to 2 months. Transgenic cultures were monitored for spontaneous pathology development and the mechanisms behind presynaptic disruption were probed via pharmacological manipulation of Aβ production and genetic knockdown of tau. Wild-type cultures were treated with a battery of environmental factors associated with risk of sporadic AD, such as pro-inflammatory compounds, and assessed for AD-related pathological changes.
In both TgCRND8 and APP-knockin OHSCs there is a progressive accumulation of intra-axonal Aβ. In TgCRND8 cultures, this correlates with a decline in presynaptic proteins and alterations in mRNA levels for synaptic proteins. Beta-secretase inhibitor abolished accumulation of $A\beta_{1\text{-}42}$ but surprisingly did not rescue synaptophysin levels. This raises the question of whether BACE1-independent APP products, or APP overexpression as in Down syndrome and APP duplication patients, underlie some synaptic defects. Elucidation of any synaptic changes in the APP-knockin model is ongoing, providing an effective experimental system to test this hypothesis. LPS or IL1β treatment of wild-type slices resulted in a significant loss of synaptophysin protein, similar to that seen in the TgCRND8 model.
OHSCs represent an important new system for understanding mechanisms of presynaptic disruption in AD. Comparison between genetic and sporadic models of AD may help identify common pathways to target for therapeutic intervention. Future work will examine mechanisms resulting in synaptophysin depletion, particularly in relation to the involvement of tau, relative contribution of APP overexpression and mutations, as well as alternative APP processing products.

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**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

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**Topic:** C.02. Alzheimer's Disease and Other Dementias

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FONDECYT Project 1170252
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**Title:** $Ca^{2+}$ dyshomeostasis induced by P2X2R overexpression contributes to altering the activation of CAMKIIa, modifying the neurites formation and arborization pattern of the neuronal hippocampal network

**Authors: *T. B. SILVA-GRECCHI**, P. A. GODOY, D. MENNICKENT, J. PANES, J. GAVILÁN, O. RAMIREZ-MOLINA, L. GUZMÁN, P. A. CASTRO, G. E. YÉVENES, C. MUÑOZ-MONTESINO, J. FUENTEALBA
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**Abstract:** It is widely known that the toxic effects of the beta-amyloid soluble oligomers (SO-Aβ) are central on the pathogenesis of the Alzheimer Disease (AD). In our group, it has been demonstrated that SO-Aβ have the capability to form pores in the cell membranes, allowing the flux of cations (such as calcium) and big molecules, for example ATP. We have shown that the formation of the amyloid pore causes a leakage of ATP on rat hippocampal neurons and cell lines. ATP is able to activate a family of receptors known as the P2X receptors (P2XR). We have demonstrated that after chronic treatment with SO-Aβ, the P2X2 receptor increases its functional expression. On the other hand, Calmoduline/Kinase II α (CAMKIIα) is a serine/threonine kinase, which, upon activation, phosphorylates itself on the T286 residue, granting it with autonomous activity that allows it to participate in the synthesis and liberation of neurotransmitters, microtubule assembly dynamics, ionic channels modulation, synaptic plasticity, amongst others. In neurodegenerative processes such as AD, there is a decrease in the active form of CAMKIIα (pCAMKIIα), and also a redistribution from the synaptic zone to the perinuclear area, which accompanies the impairment of the neuronal network. The aim of this work is to evaluate the impact of the calcium dyshomeostasis/overload induced by P2X2R overexpression on the activation and localization of CAMKIIα, in the context of AD. Using molecular biology techniques, we observed that after chronic SO-Aβ treatments, mice hippocampal neurons showed an increase on the levels of P2X2R compared to the control cells (C: 100.0 ± 6.4%; SOAβ: 130.1

± 10.7%, n=5). This was correlated with increased $Ca^{2+}$ signal evoked by ATP (C: 100.0 ± 12%, SOAβ: 194 ± 24%, n=4). Immunocytochemistry approaches on mice hippocampal neurons, showed that the overexpression of P2X2R induced changes on the immunorreactivity pattern of pCAMKIIα (in soma and neurites), which induced alterations on the cells morphology, and electrophysiological recordings assessed by Sholl Analysis and Patch Clamp, respectively. These results suggest that P2X2R overexpression can potentiate the toxicity of SO-Aβ, due to the chronic $Ca^{2+}$ overload and inactivation of CAMKIIα, and thus, altering the mechanisms of neuronal plasticity, the basis of the pathophysiological mechanism of AD.

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**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 740.11/L8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** COLCIENCIAS,project cod: 122265840550, CT-160-2015

**Title:** Beta-Amyloid effects on synaptic and oscillatory activity in the CA3-CA1 circuit of the hippocampus

**Authors: *C. E. GAUTHIER**[1], M. O. NAVA[2,3,6], J. M. MUÑOZ[4], M. A. VALEDERRAMA[6], F. A. MÚNERA[5]
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**Abstract:** Recent evidence suggests that, in early stages of Alzheimer´s Disease (AD), soluble Aβ induces an imbalance between glutamatergic and GABAergic neurotransmission systems resulting in the functional impairment of neural networks. Such alterations are particularly important in the hippocampus where learning and memory processes take place depending on accurate oscillatory activity tuned via the fimbria/fornix complex.
**Aim**: to evaluate the effects of soluble Aβ variants (25-35 and 1-40) on excitability, synaptic plasticity and oscillatory activity in the hippocampal CA3-CA1 synapse.
**Method**: the acute effects of Aβ were studied in anesthetized rats after intrahipocampal injection. A microelectrode with injection cannula was placed for field excitatory postsynaptic potentials (fEPSP) recording in CA1. A stimulating electrode was placed in CA3. Once stablished the input-output (I/O) relationship of the preparation, stimulus intensity necessary for evoking ~50%

(I50) of the maximal response was selected for evaluating short- and long-term plasticity.
**Results**: it was found excitability reduction after Aβ injection compared with controls (inverse Aβ 35-25). After HFS (100-μs, I50 intensity, 100-Hz, 600 pulses) LTP impairment was found in Aβ-injected subjects. Spectral variations (theta and gamma band) during the processing of synaptic stimuli were characterized, finding that the observed phase modulation reversal after LTP induction was reduced after Aβ administration.
**Conclusion**: Aβ-induced synaptic plasticity and excitability impairment in the hippocampus is associated with lack of phase modulation reversal triggered by HFS. Therefore, we confirm that soluble Aβ impairs neural network activity. This new analysis approach is a useful model for understanding the physiopathology of early AD.

**Disclosures: C.E. Gauthier:** None. **M.O. Nava:** None. **J.M. Muñoz:** None. **M.A. Valederrama:** None. **F.A. Múnera:** None.

**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 740.12/L9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** R01 NS069689
CH Foundation

**Title:** Region- and circuit-specific changes in somatostatin and parvalbumin interneuron networks in novel Alzheimer’s disease mouse models: Insights into seizure-induced circuit remodeling

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**Abstract:** Dysfunction of GABAergic inhibitory interneuron circuits is implicated in early stages of Alzheimer’s Disease (AD) pathogenesis. Two major classes of inhibitory interneuron classes, parvalbumin (PV)-positive and somatostatin (SOM)-positive classes, exhibit differences in function and connectivity, yet their contributions to hippocampal-dependent memory impairment in AD are poorly understood. In addition, both PV and SOM subtypes contribute to the maintenance of excitation-inhibition balance, yet it is not clear how impairment of PV and SOM circuits in AD disrupts excitation-inhibition balance and contributes to seizure susceptibility. Knowledge of which specific hippocampal PV and SOM interneuron subtypes are

most vulnerable to during AD remains poorly understood. In this study, we investigated the differential contributions of specific PV and SOM circuits to the etiology of AD using the J20 mouse transgenic model that overexpresses a mutant form of human amyloid precursor protein (hAPP). To enable PV or SOM circuits to be visualized during AD pathogenesis, we created homozygous PV-CRE;tdTomato and SOM-CRE;tdTomato mouse lines in which the red fluorescent protein tdTomato is driven by the PV or SOM promoter, and subsequently crossed them into heterozygous J20 AD mice. We then investigated alterations in the number, laminar distribution, and axonal connectivity of distinct PV- or SOM- interneuron subtypes in heterozygous J20 mice by comparing quantitative changes in tdTomato intensity to their age-matched wild-type (WT) sibling littermates. In preliminary experiments, we found a 2-5 fold reduction in PV-CRE/;tdTomato expression in all layers of the hippocampus of 7-month-old J20 AD mice. However, this reduction was both region- and layer-specific; the loss of tdTomato fluorescence was more profound in CA3 stratum radiatum and CA1 stratum pyramidale layers, specifically implicating dysfunction of dendritically targeting PV subtypes in CA3 and PV basket cells in CA1. In contrast, tdTomato intensity was generally increased in the hippocampus of SOM-CRE;tdTomato;J20 mice. The most striking difference was a 22-fold increase of tdTomato intensity concentrated in the inner molecular layer of the dentate gyrus (DG). This observation is consistent with compensatory SOM/NPY circuit remodeling accompanying the epileptic phenotype of the J20 mouse. Our study provides novel insights into differential alterations of PV and SOM circuitry during AD pathogenesis. This work will advance knowledge that will lead to new treatment strategies for GABAergic subtype-specific vulnerabilities in AD.

**Disclosures: J.J. Lawrence:** None. **R. Wang:** None. **B. Hoang:** None.

**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 740.13/L10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** IWT/VLAIO Grant 141698 to AS

**Title:** Is synaptic plasticity in the ventral dentate gyrus more sensitive to Alzheimer's pathology than in the dorsal?

**Authors: *A. SCHREURS**, D. BALSCHUN
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**Abstract:** Alzheimer's disease (AD) is the most common neurodegenerative disorder, but a cure is still lacking. Since many clinical trials that targeted late pathological phases have failed and a preventive strategy would be of most therapeutic interest, the field is increasingly focusing on early AD stages. These preclinical phases are linked with synaptic deficits and can be modelled in transgenic mice expressing Alzheimer-associated mutated human genes. An integral part of synaptic function and fundamental process underlying learning and memory formation, is synaptic plasticity. It is commonly studied using sensitive electrophysiological readouts, such as long-term potentiation (LTP) induced by high-frequency stimulation. Here, we examined LTP in hippocampal slices from bigenic APP(V717I) x Tau(P301L) mice that mimic both amyloid and tau pathology, the main hallmarks of AD. This model displays a rather late onset pathology, with amyloid plaques abundantly present from 10 months and tau tangles from 13 months of age in AD-relevant brain regions (Terwel et al., 2008). We have previously found LTP deficits in the medial prefrontal cortex and dorsal hippocampal CA1 region of APPxTau mice at 3-5 months of age, well before the appearance of plaques and tangles, and likely caused by oligomeric forms of amyloid-beta and/or tau. In contrast, no deficits were observed in the dorsal dentate gyrus (DG) at this age. However, the DG is important for various types of learning and memory and also affected in AD patients. In the current study, we therefore hypothesized that DG-LTP would get impaired in APPxTau mice at more advanced ages. To investigate this, we used male mice at two age groups: 6-8 months (i.e. before onset of plaques and tangles) and 14-16 months (at the final stage of full-blown pathology). Furthermore, we compared LTP from dorsal versus ventral DG slices, since we have previously reported that the ventral DG expresses much higher levels of LTP than its dorsal or intermediate counterparts, but that this dorsoventral gradient was less pronounced in aged mice (Schreurs et al., 2017). In line with this apparently higher sensitivity of the ventral DG to age-related processes, we found in the current study that LTP was impaired in the ventral, but not dorsal DG of 6-8 months old APPxTau mice. Yet surprisingly, the ventral DG-LTP deficit seemed to be completely restored again in the oldest age group (14-16 months). Our findings add a new facet to the increasing evidence for dorsal-ventral differences in hippocampal function, but the complex mechanisms underlying the region- and age-dependent differences in DG-LTP remain to be elucidated.

**Disclosures: A. Schreurs:** None. **D. Balschun:** None.

**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 740.14/L11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant R01NS104349

**Title:** Amyloid-beta oligomers inhibit the expression and function of acid-sensing ion channel 1a

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**Abstract:** Alzheimer's disease (AD) is a common neurodegenerative disease characterized clinically by progressive impairments in learning/memory and neuronal loss. Although the exact mechanism underlying the generation of AD remains to be determined, accumulation of the amyloid-β (Aβ) peptide 1-42 and the formation of extensive plaques have been suggested to be the primary event leading to the progress of the disease. Lines of evidence also suggest that the memory deficit can be caused by diffusible oligomeric assemblies of Aβ1-42. However, how exactly diffusible Aβ1-42 causes synaptic dysfunction and memory loss remains elusive. Acid sensing ion channels (ASICs) are proton-gated cation channels, which are abundantly distributed throughout the nervous system. There has been experimental evidence suggesting that activation of ASIC1a contributes to the synaptic plasticity and learning and memory. Thus, a reduced function of these channels may contribute to the impairment of leaning/memory of AD patients. In this regard, we tested the effect of Aβ1-42 on ASIC1a expression and acid-activated current in primary cultured mouse cortical neurons. Our results show that incubation with 100 nM Aβ1-42 oligomers for 3 to 7 days significantly decreased ASIC1 protein expression. In addition, the density of ASIC current was decreased dramatically. Ongoing studies will determine whether the decreased function of ASIC1a by Aβ1-42 oligomers contributes to impaired learning and memory at the early stage of AD.

**Disclosures: T. Leng:** None. **R. zhou:** None. **Z. Xiong:** None.

**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 740.15/L12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH/NIA grant RF1AG056976

**Title:** Two protein prenylation pathways differentially affect synaptic plasticity and cognitive function

**Authors: *D. A. HOTTMAN**[1], W. QU[2], W. LIU[1], L. YUAN[3], L. LI[1]
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**Abstract:** Prenylation is a post-translational modification that adds hydrophobic prenyl molecules to proteins and facilitates trafficking of proteins to membranes. Protein prenylation includes two processes, farnesylation and geranylgeranylation, catalyzed by farnesyltransferase (FT) and geranylgeranyltransferase-1 (GGT) or GGT-2, respectively. Prenylated proteins are involved in regulating synaptic morphology and neuronal functions. Previously we have shown that genetic manipulation of FT and GGT differently affects the pathogenesis of Alzheimer's disease (AD). Heterozygous deletion of FT ameliorated amyloid-β (Aβ) pathology, neuroinflammation, and cognitive impairment in a mouse model of AD, whereas heterozygous deletion of GGT reduced Aβ and neuroinflammation but failed to rescue cognitive deficits. Recently, we have shown that systemic GGT haplodeficient mice and forebrain neuron-specific GGT knockout out mice exhibit severe impairment in hippocampal long-term potentiation (LTP), loss of synaptic spines, and deficit in memory function. In contrast, our preliminary studies demonstrated that FT haplodeficient mice showed a similar magnitude of LTP in acute hippocampal slices comparing to their wild-type (WT) littermates. Consistent with the electrophysiology data, haplodeficient FT mice showed similar learning and memory capability and comparable anxiety levels as WT mice. These findings indicate that the two prenylation pathways mediated by GGT and FT differentially affect synaptic plasticity and cognitive function. To further assess the cellular mechanisms underlying the differences, analyses are underway for the prenylation level of FT/GGT downstream targets and the cell-type specific FT/GGT functions employing the Cre-loxP system. Results from this study will shed lights on the roles of prenylation pathways in shaping neuronal functions and provide novel insights into the pathogenesis of AD.

**Disclosures: D.A. Hottman:** None. **W. Qu:** None. **W. Liu:** None. **L. Yuan:** None. **L. Li:** None.

**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 740.16/L13

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Increased PSD-95 may explain why old memories are protected against Alzheimer's disease

**Authors: *K. B. DORE**, R. MALINOW
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**Abstract:** Accumulation of the amyloid-beta (Aβ) peptide has been strongly implicated in Alzheimer's (AD) but the molecular mechanisms by which it destroys synapses are poorly understood. Interestingly, the effects of Aβ on synapses can be prevented by NMDA receptor

(NMDAR) blockade. PSD-95, a major scaffolding protein at the synapse, binds directly to NMDARs and studies have shown it is significantly depleted in brain tissue of AD patients as well as in neural tissue exposed to Aβ. Given these properties of PSD-95 and the fact that its overexpression potentiates synapses, we reasoned that increased amounts of this protein might interfere with the synaptic depression produced by Aβ. Using paired patch recordings in organotypic hippocampal slices; we show that PSD-95 overexpression can potentiate synapses even in the presence of Aβ. Interestingly, in tissue from GluA1 knockout animals, PSD-95 overexpression produced no significant potentiation but still blocked Aβ induced depression. Therefore, PSD-95 overexpression prevents Aβ-induced depression independently of its ability to potentiate synaptic transmission. Because of its direct interaction with the NMDA receptor c-terminal domain (NMDAR CTD), PSD-95 could block the signaling mediated by conformational movements in the NMDAR CTD, which are required for synaptic depression (Aow, Dore and Malinow, PNAS, 2015). To test this, we measured the effect of Aβ with or without PSD-95 overexpression on the NMDAR CTD conformation with FRET-FLIM. We observed that Aβ significantly reduced the FRET efficiency between GluN1-GFP and GluN1-mCherry, indicating that the NMDAR CTD adopted a conformation that was similar to the one measured during LTD induction. PSD-95 overexpression blocked this effect suggesting that interactions between PSD-95 and the NMDAR CTD block Aβ-induced conformational movement of the NMDAR CTD, and thereby block the signaling associated with such movement that produces synaptic depression. Importantly, we find that large spines, containing increased amounts of endogenous PSD-95 are not affected by Aβ. Big spines have a similar NMDAR CTD conformation as spines not exposed to Aβ. Moreover, PSD-95 content was specifically reduced in small spines exposed to Aβ; larger spines being unaffected. In neurons from the thalamus, which is less affected in AD, we observed that PSD-95 content was not affected by Aβ. Overall, our data suggests that increased amounts of PSD-95 are protective against AD. If older memories are encoded by synapses with more PSD-95, our results may explain why such memories are protected in AD.

**Disclosures: K.B. Dore:** None. **R. Malinow:** None.

**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 740.17/L14

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Private swedish foundations
KI grants

**Title:** Cyp46A1 overexpression induces sex-specific changes in synaptic functions in aged mice

**Authors: *S. MAIOLI**[1], P. RODRIGUEZ-RODRIGUEZ[2], M. LATORRE LEAL[1], L. FRANCHINI[3], I. BJÖRKHEM[1], P. MERINO SERRAIS[1], A. CEDAZO MINGUEZ[1]
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**Abstract:** Emerging evidence have shown that up-regulation of Cyp46A1 reduces levels of amyloid beta plaques, rescues cognitive decline and promotes neuroprotection in several mouse models of neurodegenerative diseases, such as Alzheimer's disease (AD). In our lab we have performed extensive studies in vivo showing a key role of 24 (S)-hydroxycholesterol (24OHC) and 27 hydroxycholesterol (27OHC) in cognitive functions.
We have analyzed the behavior of males and females Cyp46A1 overexpressing (Cyp46 Tg) mice, with high levels of 24OHC in brain and plasma. Cyp46 Tg old females showed cognitive enhancement and increased levels of synaptic proteins in hippocampus, when compared to control mice (Maioli S, 2013). Noteworthy, these results were not found in old males, where Cyp46A1 overexpression led to impairment of spatial memory and increase of anxiety like-behavior. These results were further confirmed by sex-specific differences in the morphology of dendritic spines in CA1 neurons: while Cyp46 Tg females show a significant increase in area and length of the dendritic spines, Cyp46 Tg males show significant reduction of dendritic spine density when compared to control animals.
Studies in vitro suggest that 24OHC is able to activate neurosteroid signaling and biosynthesis in neurons: these novel mechanisms proposed for 24OHC may underlie the sex-specific changes observed in vivo.
In summary, we show sex-specific effects of overexpression of Cyp46A1 in synaptic functions in vivo, where the neuroprotective effects promoted by upregulation of Cyp46A1 seems to be activated only in female mice. These findings can have great clinical impact and help to define new targets for treatment of AD and new preventive interventions specifically addressed to women.

**Disclosures: S. Maioli:** None. **P. Rodriguez-Rodriguez:** None. **M. Latorre Leal:** None. **L. Franchini:** None. **I. Björkhem:** None. **P. Merino Serrais:** None. **A. Cedazo Minguez:** None.

**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 740.18/L15

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Elucidating an Alzheimer's disease role for SORLA-mediated neuroprotection through synaptic enhancement

**Authors: *J. STUPACK**, H. XU, T. HUANG
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**Abstract:** Cognitive impairment is invariably associated with Alzheimer's Disease (AD) onset, and with the lack of effective therapies currently available, understanding mechanisms underlying AD-associated synaptic dysfunction is essential. SORLA is a genetic AD risk factor that plays a role attenuating Aβ generation through trafficking of Amyloid Precursor Protein (APP). It is currently unknown whether SORLA may have additional roles in conferring neuroprotective effects in addition to limiting amyloidogenic APP processing. Interestingly, transgenic SORLA overexpression in mice results in resistance to Aβ-dependent LTP impairment, indicating a further role for SORLA in enhancing synaptic function. This suggests that SORLA has additional roles in promoting neuronal protection. Evidence from freshwater hydrozoa (*Hydra* spp.) indicates that SORLA promotes head and limb regeneration after injury; whether SORLA confer similar effects in enhancing regeneration and outgrowth in neuronal dendrites is not known. Our results indicate that SORLA overexpression can promote neurite outgrowth and regeneration with injury in cultured neurons. Further, SORLA overexpression can enhance dendritic arbor and complexity in the hippocampus in transgenic SORLA animals. These results implicate a new role for SORLA in neuronal morphogenesis and repair. We are currently working to determine mechanisms underlying SORLA-dependent neurite outgrowth, repair, and synaptic enhancement. Given that SORLA is an AD risk factor, we will determine whether SORLA-dependent enhancement mechanisms can confer resistance to synaptic dystrophy and cognitive impairment with Aβ proteotoxicity. As SORLA likely has effects in both attenuating Aβ accumulation and mediating neuroprotective effects in neurite regeneration and synaptic function, enhancing SORLA-associated mechanisms may prove to have good efficacy in future therapeutic strategies in AD.

**Disclosures: H. Xu:** None. **T. Huang:** None.

**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 740.19/L16

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** FIS/IMSS/PROT/G15/1397

**Title:** Changes in microvessels in a murine model (3xTg-AD) for Alzheimer's disease

**Authors: *A. ISLAS**[1], M. A. DELI[2], P. CAMPOS-BEDOLLA[3], P. GARCIA-DELATORRE[4]
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**Abstract:** The normal microvasculature of the brain preserves its integrity; in Alzheimer's disease (AD), Notch's cut, which is dependent on presenilin, is diminished, which prevents angiogenesis, thus affecting the normal function of the vasculature and the integrity of the brain. In this regard, it has been suggested that this pathological angiogenesis leads to the aggregation of plaques and the secretion of a neurotoxic peptide that kills cortical neurons. Angiogenesis in AD can be seen as neurovascularization, increase in capillary density, formation of vascular loops and glomeruloid structures as well as the expression of angiogenic factors. The triple transgenic murine model (3xTg-AD) develops aggregates of both Aβ and Tau, a characteristic described in the development of AD in humans. This allowed us to evaluate the effect of mutations in APP (amyloid precursor protein), Tau and presenilin (PSEN1 and PSEN2) as well as the effects of Aβ and tau accumulation in the microvasculature of these mice. Murine models for AD with mutations in APP have already described differences in microvessels such as aggregates of Aβ, hindered microcirculation, etc. In fact, some studies have used the 3xTg-AD model in which they describe a decrease in cerebrovascular volume and an increase in collagen I and IV.In this study we aimed to determine if there were changes in the microvessels at different stages of AD progression (9 and 13 months) in a triple transgenic murine model (3xTg-AD) by means of western blot analysis. We analysed the protein components of the tight junctions in the vascular system of the brain and observed the structure of the microvessels by means of photonic microscopy. We found differences between 3xTg-AD and controls in the protein composition of the microvessels as well as a decreased amount of Zo1 and occludin proteins from the tight junctions. Morphological differences were also observed in the microvessels of the animals 3xTg-AD in comparison with the WT and between the animals of 9 and 13 months, with morphological damage being more evident in the older animals.

**Disclosures: A. Islas:** None. **M.A. Deli:** None. **P. Campos-Bedolla:** None. **P. Garcia-delaTorre:** None.

**Poster**

**740. Alzheimer's Disease and Other Dementias: Mechanisms of Synaptic Dysfunction in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 740.20/L17

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH R01 AG030205

**Title:** V-ATPase dysfunctions contribute to lysosome-autophagosome mediated proteinopathy and synaptic pathophysiology in early stages of Alzheimer's disease pathogenesis

**Authors: *S. H. MUSTALY**, N. KAPECKI, K. D. BEAMAN, A. GILMAN-SACHS, J. MCDAID, S. SCHRANK, R. A. MARR, G. E. STUTZTMANN
Rosalind Franklin Univ., North Chicago, IL

**Abstract:** Alzheimer's disease (AD) is a neurodegenerative disorder characterized by abnormal protein aggregates and synaptic deficits. The organelles that regulate these processes, such as lysosomes for protein handling, and synaptic vesicles for neurotransmission, require highly acidic microenvironments in order to function. This is maintained by a vacuolar H+-ATPase (V-ATPase) which pumps in $H^+$ ions against a concentration gradient. In lysosomes, this process is essential for autophagy, a catabolic pathway to degrade abnormal proteins; in synaptic vesicles the acidic environment is necessary for neurotransmitter uptake and synthesis. In AD, V-ATPase disruption can lead to abnormal β-amyloid and tau accumulation, and deficient synaptic vesicle stores. A concurrent mechanism with V-ATPase defects is intracellular $Ca^{2+}$ dyshomeostasis, which alters ion exchange and thus pH within these organelles. We hypothesize that altered $Ca^{2+}$ signaling disrupts V-ATPase ion exchange and instigates AD pathology. We used immunoassays and live cell imagin in model cells, induced human neurons (iN) transformed from AD patient, and AD mouse models to explore this hypothesis. Immunohistochemistry in fixed hippocampal slices from 3-month old 3xTg-AD mice revealed diminished expression of V-ATPase subunits (V1B2, V0a1), lysosomes (Lamp1), pre-synaptic vesicles (synaptophysin), and increased expression of mature autophagosomes (LC3B) relative to non-transgenic (NTg) controls. These phenotypes in 3xTg-AD were restored to NTg levels with a 30-day Ryanodex treatment (NAM of ryanodine receptor (RyR); 10mg/kg). The decreased V-ATPase expression and increased autophagosomes in 3xTg-AD mice reflects impaired lysosomal and synaptic vesicle functionality, which is mediated through upstream RyR-$Ca^{2+}$ dyshomeostasis. Live cell imaging of iN and RyR-overexpressing HEK293 cells using a lysosomal-pH indicator (LysosensorDND-160) revealed lysosomal alkalization with RyR stimulation (caffeine 10mM), suggesting that aberrant RyR-$Ca^{2+}$ signaling disrupts autophagosome-lysosome mediated protein degradation. Protein aggregates, such as β-amyloid and hyperphosphorylated tau, were increased in iN treated with 500nM bafilomycin (V-ATPase inhibitor). Expression of these protein aggregates was resolved with Ryanodex treatment. Therefore, increased RyR-mediated $Ca^{2+}$ release alkalizes lysosome pH resulting in abnormal protein aggregation. Prior to overt histopathology or cognitive deficits, abnormal $Ca^{2+}$ signaling in AD disrupts intracellular organelle function leading to altered autophagic-mediated protein clearance and synaptic pathophysiology.

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**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.01/L18

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Hitachi, Ltd.

**Title:** Classification among clinical data of normal control subjects, mild cognitive impairment, and Alzheimer’s disease patients by applying machine learning methods to the Japanese Alzheimer’s disease neuroimaging initiative (J-ADNI) database

**Authors: *T. FUNANE**, M. KIGUCHI, J. ADNI
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**Abstract: Introduction:** It is necessary to have indicators to assess the stage of disease in order to develop disease-modifying therapy for Alzheimer’s disease (AD). In this study, to develop a system for risk assessment or early diagnosis of AD, the classification among data of normal control (NL) subjects, mild cognitive impairment (MCI) patients, and AD patients was conducted by applying machine learning methods to the Japanese Alzheimer’s Disease Neuroimaging Initiative (J-ADNI) database (accession no.: JGAS00000000051). **Method:** Machine learning methods using deep neural networks (i.e., deep learning) and support vector machines (SVMs) have been applied to the classification of clinical data with the features extracted from the J-ADNI database (number of included subjects: NL 149, MCI 231, and AD 149). Alzheimer's disease assessment scale-cognitive subscale: ADAS-cog, the clinical dementia rating: CDR, mini-mental state examination: MMSE, the global deterioration scale: GDS, and the analytical parameters from the structural MRI were used as features for the machine learning methods. The classification performance was assessed by a 10-fold cross validation. **Results:** Classification among NL subjects, MCI, and AD patients, and classification between NL and AD, were successfully classified at 93.6 ± 4.0% (n = 529, SVM) and 98.7 ± 1.7% (n = 290, deep learning) accuracy, respectively, by using four kinds of clinical and psychological tests. The NL-AD classification task was conducted at 84.2 ± 4.1% (n = 290, SVM) accuracy using only FreeSurfer analysis data from structural MRI data. **Discussion:** Almost all of the features were included in the analysis for the structural MRI data. If only the relevant features could be selected, the classification accuracy would be improved. In the future, a convolutional neural network (CNN) will be applied and an MCI conversion prediction will be investigated. **Conclusion:** Machine learning methods were successfully applied to the J-ADNI database and performance could be improved when relevant features were selected in the analysis.
**Acknowledgments:** We thank the authors of the J-ADNI project. We are also grateful for the

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**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.02/M1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** GE-Healthcare
FWO Grant G0F8516N Odysseus
IWT 135043

**Title:** [$^{18}$F]flutemetamol PET predicts the neuropathological phase of amyloid β-protein deposition by SUVR-based thresholds

**Authors: *D. R. THAL**[1,2], T. G. BEACH[3], M. ZANETTE[4], J. LILJA[5], K. HEURLING[6], A. CHAKRABARTY[7], A. ISMAIL[7], G. FARRAR[8], C. BUCKLEY[8], A. P. L. SMITH[8]
[1]Dept. of Neurosci., KU-Leuven, Leuven, Belgium; [2]Pathology, UZ Leuven, Leuven, Belgium; [3]Banner Sun Hlth. Res. Inst., Sun City, AZ; [4]3E Healthcare Life Sci., Marlborough, MA; [5]Hermes Med. Solutions AB, Stockholm, Sweden; [6]Wallenberg Ctr. for Mol. and Translational Medicine, Dept. of Psychiatry and Neurochemistry, Univ. of Gothenburg, Gothenburg, Sweden; [7]Pathology and Tumour Biology, Leeds Inst. of Mol. Medicine, St. James Hosp., Leeds, United Kingdom; [8]GE-Healthcare Life Sci., Amersham, United Kingdom

**Abstract:** The deposition of the amyloid β-protein (Aβ) in senile plaques is one of the histopathological hallmarks of Alzheimer's disease (AD). Aβ-plaques arise first in neocortical areas and, then, expand into further brain regions in a process described by 5 phases. Since it is possible to identify amyloid pathology with radioactive-labelled tracers by positron emission tomography (PET) the question arises whether it is possible to distinguish these Aβ phases with amyloid PET imaging. To address this question we reassessed the end-of-life study cohort of the phase 3 [$^{18}$F]flutemetamol trial (93 autopsy cases covering all neuropathological phases of Aβ deposition) by combining the standardized uptake value ratios (SUVRs) with pons as reference region for neocortical and caudate nucleus-related [$^{18}$F]flutemetamol-retention and tested them for their prediction of the neuropathological pattern found at autopsy. By defining threshold levels for neocortical and caudate nucleus SUVRs we were able to distinguish four different levels of [$^{18}$F]flutemetamol uptake termed PET-Aβ phase estimates. When comparing these PET-

Aβ phase estimates with the Aβ phases as determined neuropathologically we found that PET-Aβ phase estimate 0 corresponded with Aβ phases 0-1(2), 1 with Aβ phases (2)-3, 2 with Aβ phase 4 and 3 with Aβ phase 5. Thus, we provide a novel method to convert SUVR levels into PET-Aβ phase estimates that correspond to the neuropathological phases of Aβ deposition. This method opens a unique chance to study amyloid pathology in living individuals with direct conclusions about the pathological correlatives and its progression and is more sensitive than visual assessment strategies. (ClinicalTrials.gov identifier NCT01165554)

**Disclosures: D.R. Thal:** 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.; Collaboration with Janssen Pharmaceutical Companies. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Collaborations with Novartis Pharma and Probiodrug. F. Consulting Fees (e.g., advisory boards); GE-Healthcare, Covance Laboratories. **T.G. Beach:** F. Consulting Fees (e.g., advisory boards); GE-Healthcare. **M. Zanette:** A. Employment/Salary (full or part-time):; GE-Healthcare. **J. Lilja:** A. Employment/Salary (full or part-time):; GE-Healthcare. **K. Heurling:** A. Employment/Salary (full or part-time):; GE-Healthcare. **A. Chakrabarty:** F. Consulting Fees (e.g., advisory boards); GE-Healtcare via University of Leeds. **A. Ismail:** F. Consulting Fees (e.g., advisory boards); GE-Healthcare via Univerity of Leeds. **G. Farrar:** A. Employment/Salary (full or part-time):; GE-Healthcare. **C. Buckley:** A. Employment/Salary (full or part-time):; GE-Healthcare. **A.P.L. Smith:** A. Employment/Salary (full or part-time):; GE-Healthcare.

**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.03/M2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Chinese Academy of ScienYouth Innovation Promotion Association 2016084
National Basic Research Program 2015CB351702

**Title:** Local to remote cortical functional connectivity in Alzheimer's disease

**Authors: *H. LI**[1], Y. ZHANG[2]
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**Abstract:** Previous studies reported alterations in both local and remote functional connectivity in Alzheimer’s disease (AD) patients, however, few studies investigated the local and remote

alterations in the same group of patients. In the present study, we aimed to explore whether AD patients would show abnormal local-to-remote functional connectivity in functional homogeneity. Fourteen AD patients (age: 72.21 ± 7.79, 5 males) and 23 healthy older adults (age: 74.47 ± 4.52, 11 males) were included in the current study. The data were obtained from the Alzheimer's disease Neuroimaging Initiative database (http://adni.loni.usc.edu). All of them completed structural and resting-state fMRI scanning and a standardized clinical interview and comprehensive neuropsychological assessments, which were used to provide standard measurement of participants' cognitive ability. We employed resting-state functional magnetic resonance imaging (rfMRI) connectome index, regional functional homogeneity on the 2-dimensional cortical surface, to detect full-cortex vertex-wise changes of the local rfMRI connectivity. When the changes of local functional connectivity were found, the regions were taken as seed regions to explore the remote functional connectivity in AD patients. We further investigated the correlations between alterations in local and remote connectivity and neuropsychological scores in AD patients. We found that AD patients presented decreased left posterior cingulate cortex in comparison with healthy controls. The results revealed significantly decreased remote functional connectivity between left posterior cingulate cortex and right middle cingulate cortex in AD patients. Both the local and remote functional connectivity in AD patients were negatively correlated with immediate Auditory Verbal Learning Test and immediate Wechsler Memory Scale Logical Memory score.
The remote functional connectivity in AD patients was also negatively correlated with delayed Auditory Verbal Learning Test score. The current study suggested that AD patients showed decreased local and remote functional connectivity with the surface-based regional functional homogeneity method. Both alterations in local and remote connectivity in AD patients fell in default mode network. The distance-related connectivity profiles show that the dysfunctional pattern of the decreased cortical connectivity may be a potential biomarker of patients with neurodegenerative disease.

**Disclosures: H. Li:** None. **Y. Zhang:** None.

**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.04/M3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant U01 AG024904
DOD Grant W81XWH-12-2-0012

**Title:** Brain pathology and cognitive reserve are associated with executive functioning performance, but not memory, in healthy older adults in an ADNI dataset

**Authors: *C. BAUER**, T. HAMMOND, C. BROWN, B. T. GOLD
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**Abstract: Background**: Alzheimer's Disease (AD) is a debilitating condition in which potential protective mechanisms are not well understood. Here, we sought to examine brain pathology and cognitive reserve and how they are associated with memory and executive function (EF) in both healthy aging and diseased states. More specifically, for AD pathology, we focused on structural connectivity of major brain networks, as well as biochemical analysis of the CSF, as an independent predictor. We hypothesized that AD pathology would be negatively correlated with memory and EF, particularly in impaired individuals, while the opposite effect would be observed with cognitive reserve. **Method:** Using the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, we selected all 203 participants with available DTI scans at the time of this study. Participants were divided into healthy (no MCI or AD) and impaired (MCI or AD) groups. An AD pathology composite consisting of FA values of major white matter tracts, volumetric measures, and Tau over Abeta was calculated using backwards elimination of variables in SPSS to include only statistically relevant variables. Similarly, a cognitive reserve composite was calculated using this same approach, ultimately including both education and ANART scores. Dependent variables memory performance and EF were estimated from composites of neurocognitive outcome measures. The association between AD pathology/cognitive reserve and memory/EF performance was tested using the general linear model. **Results:** The AD pathology composite was negatively correlated with memory composite scores in impaired individuals ($p < 0.001$), but not in healthy older adults. AD pathology was negatively correlated with EF in both groups ($p < 0.001$, $p < 0.040$). Likewise, cognitive reserve was positively correlated with memory only in impaired individuals ($p < 0.032$), but not healthy older adults. Cognitive reserve was positively correlated with EF in both groups ($p< 0.013$, $p < 0.001$). **Conclusion:** We provide pilot data suggesting that both a brain pathology and cognitive reserve composite can separately predict memory and EF performance in impaired individuals, and EF performance in healthy older adults. These results imply that EF may be affected by clinically silent disease burden even before any diagnosis, and that cognitive reserve could be useful during this phase to reduce disease-related decline. Further work is necessary to see if cognitive reserve truly moderates this association. The preservation of networks in prodromal AD through prophylactic interventions remains critical.

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**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.05/M4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Differences in scalp - recorded EEG based brain functional connectivity network between Alzheimer`s disease and elderly controls

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**Abstract:** Alzheimer’s disease (AD) is a progressive neurodegenerative disease which symptom is a disturbance of memory and cognitive functions. Recently, many findings have been reported that both of EEG and fMRI could be useful to find differences between AD and elderly controls. In this study, resting - state EEGs were recorded for 6 patients with AD and 6 elderly controls, and BFCNs (brain functional connectivity networks) were constructed, where connectivity between any pair of electrodes was quantified by synchronization likelihood (SL). We constructed BFCN of AD patients with control SL value of 1, for six frequency bands (Fig.1). When AD average SL value of AD for each node pair, was lower than that of the control, the color of the edge was defined to be blue, while, if AD SL value is higher, red was assigned. The AD-BFCN connections, comparing with those of elderly controls, were strong on frontal (Fp1-Fp2) and parieto-occipital (P3-Pz-O1-O2) in lower α, upper α,β,θ and γfrequency bands. Thus, AD might be characterized by disconnection between frontal and parieto-occipital networks.

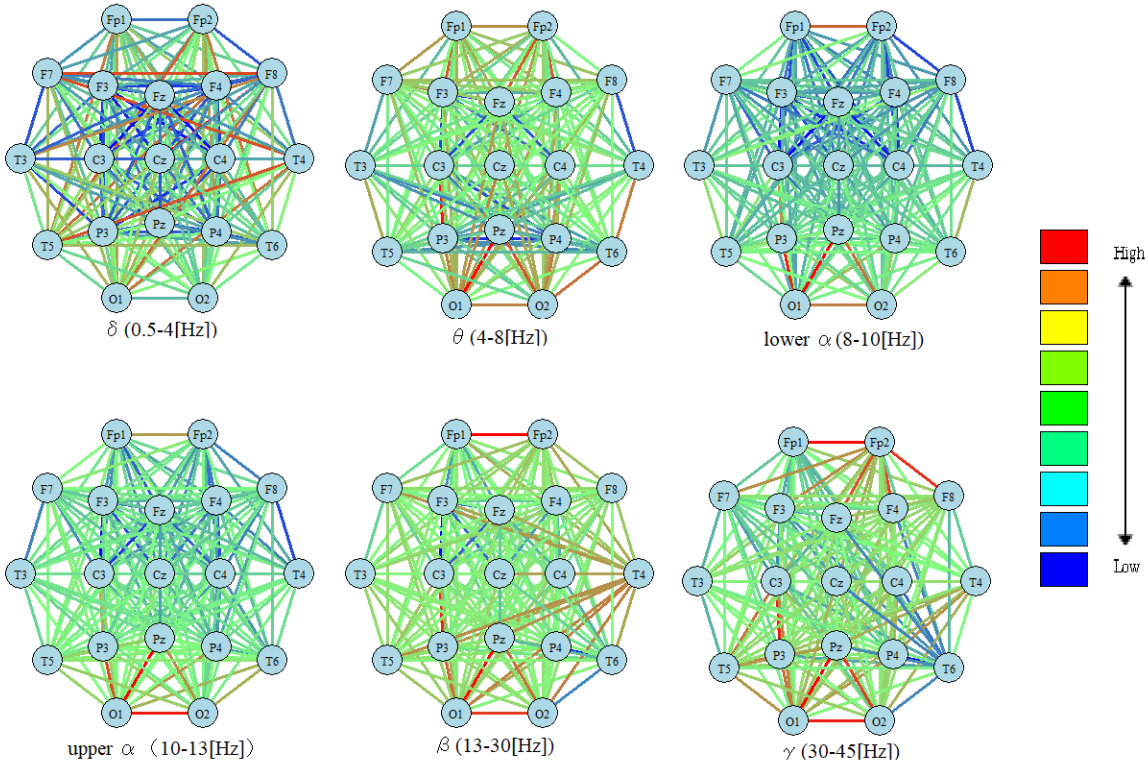



Fig.1 BFCNs for AD patients

**Disclosures: Y. Kuroiwa:** None. **T. Hirai:** None. **T. Yamazaki:** None.

**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.06/M5

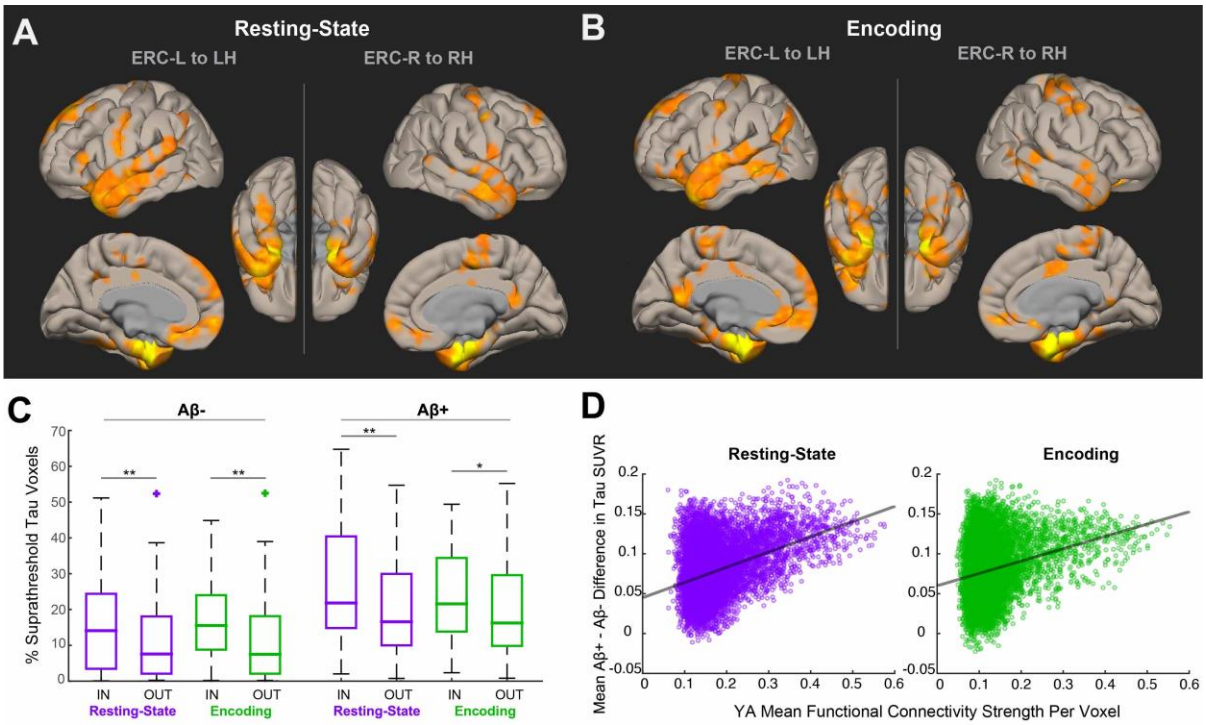
**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH R01-AG034570

**Title:** Functional connectivity of the entorhinal cortex in young adults predicts spatial distribution of tau in cognitively normal older adults

**Authors: *J. N. ADAMS**[1], A. MAASS[1,2], T. M. HARRISON[1], W. J. JAGUST[1,3]
[1]UC Berkeley, Berkeley, CA; [2]German Ctr. for Neurodegenerative Dis., Magdeburg, Germany; [3]Lawrence Berkeley Natl. Lab., Berkeley, CA

**Abstract: Background:** Because the entorhinal cortex (ERC) is the initial site of tau deposition in aging and Alzheimer's disease, its connectivity may drive the location of tau deposition. We therefore examined patterns of functional connectivity with the ERC in young adult (YA) subjects to predict the spatial distribution of tau deposition in cognitively normal older adults (OA).
**Methods:** fMRI was performed on 24 YA (27±4 yrs, 10 females) during both resting-state and an encoding task. Using an ROI of the ERC, seed-to-voxel correlations were performed separately for resting-state and encoding (correct trials) within each hemisphere. Regions of significant connectivity for each condition ($p$<0.001 uncorrected) were used to create masks for subsequent analyses. In 112 OA (76±6 yrs, 67 females), we quantified tau with [18F] AV-1451 PET and amyloid-β (Aβ) with [11C] PiB. Suprathreshold tau voxels (SUVR >1.31) were defined as 2 SDs above a group mean cortical value. OA subjects were divided into Aβ- ($n$=65) and Aβ+ ($n$=46) groups based on global PiB uptake.
**Results:** ERC functional connectivity patterns derived from YA were similar during resting-state and encoding (Fig 1A,B; Dice coefficient = 0.49), and included temporal, retrosplenial, and medial frontal regions. The proportion of suprathreshold tau voxels was significantly higher within versus outside the ERC connectivity masks for both Aβ- and Aβ+ OA (Fig 1C; $p$<0.001). Within the masks, mean YA functional connectivity strength in a voxel was positively associated with the mean difference in tau SUVR between the Aβ+ and Aβ- groups for resting-state ($r$=0.39) and encoding ($r$=0.25, $p$s<0.001; Fig 1D).
**Conclusions:** Within regions of significant functional connectivity with ERC in YA, tau SUVR values were more likely to be high in OA, with a stronger effect in Aβ+ OA. Connectivity strength also predicted the spatial pattern of differences in tau deposition between Aβ- and Aβ+ OA. These results indicate that ERC functional connectivity patterns in YA are associated with tau deposition in OA, and this relationship may further be related to the presence of Aβ.




**Disclosures: J.N. Adams:** None. **A. Maass:** None. **T.M. Harrison:** None. **W.J. Jagust:** None.

**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.07/M6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** 2018 DIJF Research Grant
Joint Research Program of Joint Usage/Research Center at the Institute of Development, Aging and Cancer, Tohoku University
Starter Research Fellowship FY2017

**Title:** Vitamin D deficiency and temporal lobe morphology associated to visual memory in healthy young people

**Authors: *K. KUNITOKI**[1], H. TAKEUCHI[2], R. KAWASHIMA[3], Y. TAKI[4]
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**Abstract:** - Introduction: Vitamin D deficiency is reported to increase the risk of Alzheimer's disease. Various effect of Vitamin D on central nervous system assumed (ex. immunomodulation calcium homeostasis and antioxidant). Though underlying mechanisms have been still unclear, previous studies showed cognitive decline and executive dysfunction in those who with vitamin D deficiency, and visual memory were reported to be lower among memory task. Therefore, this study aimed to reveal neural basis of the relationship between cognitive decline and lower vitamin D status. - Method: We used 3T brain MRI and blood data from 294 healthy Japanese participants aged 19 to 27. We obtained informed consent from all the subject, and obtained approval from our local ethical committee. Plasma vitamin D level was measured using ELISA method (25(OH)-Vitamin D direct day ELISA, Immundaignostik AG). 48 participants were in vitamin D sufficiency (more than 50 nmol/l) and 160 in deficiency(less than 30 nmol/l). Then, we picked these 208 participants and compared regional gray matter volume (left and right fusiform gyrus) of these two groups. There were no significant difference in age, sex, BMI and total brain volume between the two groups. T1-weighted MR images were analyzed using the Statistical Parametric Mapping 12 (SPM12), and voxel-based morphometry (VBM) analysis was conducted using the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) procedures with 8-mm smoothing. MarsBar was used in ROI analysis with AAL brain atlas. - Results: There were no significant difference in the sufficient and the deficient group in whole brain analysis. In region-of-interest analysis, The right fusiform gyrus were significantly smaller in the deficient group than the sufficient group (corrected P=0.049). Left fusiform gyrus were not significantly different, however, there are tendency to smaller volume in the deficient group than the sufficient group (corrected P=0.081). - Conclusion: We revealed the smaller bilateral fusiform gyrus in the vitamin D deficiency group compared to the vitamin D sufficiency group. The fusiform gyrus is known as center of visual recognition. Therefore, lesser volume in this region may be a neural basis in lower visual memory in vitamin D deficient people. This result would be helpful to further analysis on the relationship between vitamin D and Alzheimer's disease.

**Disclosures: K. Kunitoki:** 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.; Nisshin Oillio Group, Danone. **H. Takeuchi:** None. **R. Kawashima:** None. **Y. Taki:** 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.; Nisshin Oilio group.

**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.08/M7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** SNF 124111, 125378
MINZ, ZNZ, CRPP

**Title:** Low subicular volume as a surrogate marker of beta-amyloid associated low episodic memory performance at high age: A combined PET-7 Tesla MR study

**Authors: *P. G. UNSCHULD**[1], C. SCHROEDER[2], J. VAN BERGEN[2], S. J. SCHREINER[3], L. VIONNET[4], V. TREYER[5,2], A. BUCK[5], P. KAUFMANN[5], R. M. NITSCH[1,2], K. P. PRUESSMANN[4], C. HOCK[1,2]
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**Abstract: Background:** Alzheimer's disease (AD) includes a decade long preclinical phase during which beta-amyloid (Aβ) progressively accumulates. This study investigated old-aged, non-demented adults for a relationship between hippocampal substructure-volumes, cortical Aβ burden and episodic-memory (EM) performance within the normal range. **Methods:** 61 nondemented old-aged adults (mean age: 70.23(SD 6.52) years) were administered a T1-weighted MP2RAGE sequence (TR/TE = 4.8 ms/2.1 ms, voxel size = 0.6mm$^3$) on a Philips 7-Tesla Achieva whole-body scanner (32-channel receive coil). 11C-PiB-PET and 18F-Flutemetamol-PET were used for dichotomization of the study population ("high-" versus "low-Aβ ") by standard SUVR positivity-cutoff. The Verbal Learning and Memory Test (VLMT), was used for dichotomization of the study group in high- versus low EM. FreeSurfer (V6.0) was used for assessing volumes of hippocampal subfields. Alpha was adjusted by FDR. **Results:** When performing a multiple Analysis of Variance (MANOVA), Mahalanobis distances indicated most distinguished effects on variation of hippocampal subfield volumes for coexistent criteria "high-Aβ" and "low EM" ($\lambda$=0.34, $p$=0.039). Secondary analysis indicated a significant interactive effect between Aβ and EM for the subiculum (F(1, 57) = 5.90, $p$=0.018). Volume of the subiculum was significantly lower in subjects with high- Aβ" and low EM compared to the rest of the study popualtion (F(1, 59) = 16.8, $p$=0.002). **Discussion:** Our findings are consistent with earlier reports that aging-related hippocampal pathology may manifest first by atrophy of the

subiculum. In addition, our data suggest that subicular volume might represent a surrogate marker for Aβ-burden related variation in episodic memory at high age.

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**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.09/M8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Conseil québécois pour le développement des médicaments (CQDM)
Brain Canada Institute
Ontario Brain Institute

**Title:** Validation of a hyperspectral retinal imaging method to predict cerebral amyloid PET status

**Authors: *J.-P. SOUCY**[1], C. CHEVREFILS[2], J.-P. SYLVESTRE[2], S. BEAULIEU[3], T. A. PASCOAL[5], S. M. SHARAFI[6], J.-D. ARBOUR[7], M.-A. RHÉAUME[7], A. ROBILLARD[4], C. CHAYER[4], P. ROSA-NETO[5], S. S. MATHOTAARACHCHI[5], Z. S. NASREDDINE[8], S. GAUTHIER[5], F. LESAGE[6]
[1]Montreal Neurolog. Inst., Montreal, QC, Canada; [2]Optina Diagnostics, Montreal, QC, Canada; [3]Nuclear Med., [4]Neurol., Hôpital Maisoneuve-Rosemont, Montreal, QC, Canada; [5]McGill Ctr. for Studies in Aging, McGill Univ., Montreal, QC, Canada; [6]Génie électrique, École Polytechnique de Montréal, Montreal, QC, Canada; [7]Clinique ophtalmologique 2121, Montreal, QC, Canada; [8]MoCA Clin. and Inst., Greenfield Park, QC, Canada

**Abstract: Background:** A simple, accessible and inexpensive approach to identify amyloid positive subjects at or before the earliest stages of cognitive impairment could dramatically transform the design and execution of clinical trials evaluating new therapies for Alzheimer’s disease (AD) by greatly reducing cerebral PET amyloid imaging-related expenses, and could also be clinically useful for screening purposes. In this study, a non-invasive retina (an extension of the central nervous system) imaging approach with the Metabolic Hyperspectral Retinal Camera requiring no amyloid-labeling agent is evaluated as a mean to identify biomarkers correlating with the cerebral load of amyloid plaques determined with PET.**Methods:** The cohort (n=45) included probable AD cases (n=16) and age-matched controls (53 to 85 years) with no retinal diseases nor significant ocular media opacity. Hyperspectral retinal measurements were

obtained at 450-900 nm. Image texture analysis of the spatial/spectral dimensions in segmented retinal vascular areas allowed extraction of 16 different statistical measures. A classifier was trained using 112 datasets (1-3 per subject) to establish the predictive value of those texture features, based on the cerebral amyloid status determined from binary reads by a panel of 3 expert raters on $^{18}$F-Florbetaben PET studies. A leave-one-out approach determined the sensitivity and specificity values of the method. Other vascular metrics such as vessel tortuosity and diameter were also evaluated in the retinal images for possible correlation with the cerebral amyloid status.**Results:** Consistent with literature reports, 2/16 clinically probable AD cases were amyloid negative, while 5/29 cognitively normal subjects were amyloid positive. Excellent retinal scanning correspondence with PET amyloid status was achieved, independently of cognition, when texture features extracted from the principal retinal vessels were used, with sensitivity and specificity values of 84% and 86% respectively. The arteriolar diameter and the arteriovenous ratio were found to be statistically different between the amyloid negative and positive subjects, but not between AD and control cases. **Conclusions:** The developed machine learning approach, based on a non-invasive hyperspectral retinal imaging technique which does not require amyloid labeling, shows promise in predicting cerebral amyloid PET status and could serve as a screening tool to identify subjects in the early stages of the AD continuum, for instance in a drug development context. We are currently testing this approach and other retinal measures in additional subjects.

**Disclosures: J. Soucy:** None. **C. Chevrefils:** A. Employment/Salary (full or part-time):; Optina Diagnostics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Optina Diagnostics. **J. Sylvestre:** A. Employment/Salary (full or part-time):; Optina Diagnostics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Optina Diagnostics. **S. Beaulieu:** None. **T.A. Pascoal:** None. **S.M. Sharafi:** None. **J. Arbour:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Optina Diagnostics. **M. Rhéaume:** None. **A. Robillard:** None. **C. Chayer:** None. **P. Rosa-Neto:** None. **S.S. Mathotaarachchi:** None. **Z.S. Nasreddine:** None. **S. Gauthier:** None. **F. Lesage:** None.

**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.10/M9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** P41EB015896
1R01EB023281

R01EB006758
R21EB018907
R01EB019956
5R01AG008122
R01AG016495

**Title:** A histologic and quantitative analysis of cortical layer thickness in the human temporal neocortices

**Authors: K. A. NESTOR**, *J. C. AUGUSTINACK, C. MAGNAIN, R. WANG, M. FOGARTY, B. FISCHL
Radiology, Massachusetts Gen. Hosp., Charlestown, MA

**Abstract:** Cortical thinning in the temporal neocortex (TNC) has been linked to decreases in cognitive ability both in preclinical and clinical Alzheimer's disease (AD), and may be an early biomarker for cognitive vulnerability (1,4). While the TNC has a notoriously similar cytoarchitecture, few studies have evaluated the TNC histologically to establish more precise markers for neuroimaging tools. We aimed to establish the relative layer thickness histologically in Brodmann areas (BA) 36, 20, 21, and 22 in n=4 post mortem brain samples. The samples ranged in age from 45-82 years, 3 male/1 female and all were cognitive controls at death. Each TNC block was sectioned coronally at 50 μm and stained for Nissl. For each brain sample, data collection was based on three histological slices approximately 250 μm apart, which were then digitized using a Nikon microscope and Stereo Investigator software (MBF Bioscience). The stained and digitized TNC images were loaded into Freeview (Freesurfer) and the layers were labeled using the point set tool (pial surface to gray white matter boundary). The Laplace equation was applied using the line profile tool, and layer thickness measurements (mm) were computed (3). All BA measurements were restricted to the crown of each gyrus (no sulci were sampled) for consistency. The absolute measures were averaged, and all data are presented as a relative cortical thickness, as a percentage of the whole cortical thickness (2) to avoid tangential bias of each section. An ANOVA was performed using JMP (SAS Institute) with the relative thickness as the dependent variable and the case ID, BA and layer as the independent variables. The results showed that the thickness of the lamina differed significantly from one another but the thicknesses did not differ across BA 36, 20, 21, and 22 or among cases. The averages for the relative thickness for the layers were layer I (8%), layer II (8.4%), layer III (27%), layer IV (10%), layer V (24%) and layer VI (22%). Layer IV showed the least variability in cortical thickness and the pyramidal layer III was the thickest layer. The cytoarchitectural differences among these BAs were subtle: dark chromophilic neurons in layer II and closely apposed layers V and IV in area 36, chromophilic layer IIIb in area 20, layers II and IV appear band-like within area 21, and columnar organization dominates area 22. Using ground truth histology as the basis, these results about laminar differences within the TNC may ultimately create more specific measures for cortical thickness in neuroimaging tools to disambiguate the heterogeneity of AD.

**Disclosures: K.A. Nestor:** None. **J.C. Augustinack:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CorticoMetrics (Bruce Fischl). **C. Magnain:** None. **R. Wang:** None. **M. Fogarty:** None.

**B. Fischl:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Corticometrics (Bruce Fischl).

**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.11/M10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NSF Grant DGE 1418060
NIH Grant R21 AG055034
NIH Grant P50 AG005142
NIH Grant P01 AG052350

**Title:** Brainstem structural integrity in the progression of Alzheimer's disease

**Authors: *S. DUTT**, Y. LI, D. A. NATION
Psychology, USC, Los Angeles, CA

**Abstract:** Prior research has established specific nuclei of the brainstem, namely the locus coeruleus and the dorsal raphe nucleus, as the earliest sites of tau pathology in Alzheimer's disease (AD). However, few studies have examined the utility of brainstem structural magnetic resonance imaging (MRI) in predicting dementia risk, nor have they related brainstem volumes to AD biomarkers or cognitive outcomes. The present study compared brainstem, midbrain, and pons volumes across the spectrum of neurocognitive decline and AD biomarker abnormality, examined neuropsychological profiles linked to these regional brainstem volumes, and investigated their predictive value for future dementia. Alzheimer's Disease Neuroimaging Initiative (ADNI) participants (N = 1677) classified as cognitively normal (CN), mild cognitive impairment (MCI), or AD underwent baseline MRI scanning, cerebrospinal fluid (CSF) lumbar puncture, and neuropsychological testing with clinical follow-up (6-120 months). T1-weighted structural images were segmented to obtain volumes of the whole brainstem, midbrain, and pons. Two neuropsychological tests from each of three domains of cognition (memory, attention/executive function, language) were examined. Levels of CSF $A\beta_{1-42}$ and phospho-tau classified individuals as biomarker-positive or biomarker-negative. One-way analyses of covariance, with age, sex, and education as covariates, tested group differences in neuropsychological and neuroimaging variables, and proportional hazards survival analyses via Cox regressions assessed risk for progression to dementia. We observed significantly smaller brainstem and midbrain volumes in AD and MCI patients relative to CN, with no difference in pons volumes. Among CN individuals, those who never progressed to dementia exhibited larger baseline brainstem and midbrain volumes, and larger baseline midbrain volume conveyed

decreased risk of progression to AD. CN older adults who were AD biomarker-positive also showed larger brainstem, midbrain, and pons volumes relative to those who were biomarker-negative. Among MCI patients, larger brainstem volumes correlated with better neuropsychological performance. Findings demonstrate reduced brainstem volume in MCI and AD compared to CN, and implicate whole brainstem and midbrain volume in risk for future dementia in preclinical populations. These volumetric differences early in the AD process are consistent with neuropathological findings of AD-related pathology first appearing in specific brainstem nuclei. Brainstem volumes may thus be an independent biomarker for identifying preclinical individuals at risk for dementia.

**Disclosures: S. Dutt:** None. **Y. Li:** None. **D.A. Nation:** None.

**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.12/M11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Neural basis for preservation of musical memory and effects on functional intra network connectivity in early Alzheimer’s disease and mild cognitive impairment

**Authors: *M. H. THAUT**[1], T. A. SCHWEIZER[2], M. LEGGIERI[3], N. CHURCHILL[2], L. FORNAZZARI[2], C. FISCHER[2]
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**Abstract:** OBJECTIVE AND RATIONALE. Recently emerging clinical behavioral research offers evidence that musical memories and associated autobiographical responses are preserved longer than other memories in Alzheimer’s Disease (AD). However, there is little research on the potential of music based interventions (MI) to therapeutically enhance cognitive functions in AD. There are also no studies examining the neural mechanisms underlying preserved musical memories or the potential impact of MI on brain function in AD. Therefore, the study aims were (A) to identify differences in musical memory networks (MMN) processing long-term familiar music (LTM, +20 years) vs . briefly familiar music (BFM, first listening 60 min before fMRI) for potential sparing mechanisms for MMN during the disease process, and (B) to examine if 3 weeks of structured daily listening can modify resting state functional connectivity with the MMN and cognitive measures.
METHODS. Twenty persons (10 musicians M+, 10 non-musicians M-, aged 65+) with early AD or MCI underwent brain scanning (fMRI) alternately listening to LTM vs. BFM. After a 3 week

daily listening protocol a post test scan was given to analyze functional intra network connectivity during resting state. Prior to first scan and second scan cognitive tests were administered (MOCA).
RESULTS. A MMN common for both conditions was found in left cerebellum, bilateral temporal lobes, left IFG, right basal ganglia, and bilateral superior marginal gyrus (voxel strength $p < .005$ during music listening for inclusion in MMN). LTM showed statistically significant additional bilateral and extensive activations including bilateral cerebellum, putamen, posterior cingulate, IFG, precentral gyrus, and SMA. The M+ group showed higher functional intra network connectivity at first scan, whereas the M- group showed greater average increases during resting state at post test. Cognitive measures improved but nonsignificantly.
CONCLUSION. LTM activates potential sparing mechanisms for MMNs and associated memory functions in an extensive bilateral network of prefrontal, emotional, motor, auditory as well as subcortical regions (cerebellum , putamen, limbic structures). The activation of extensive additional bilaterally distributed neural tissue, and engagement of subcortical regions may offer structural and functional cues why long-term MMNs may at least initially 'survive' biomarker development in AD and MCI. Furthermore, a short MI can alter functional brain connectivity in AD with a particular advantage for M- which may be relevant for therapeutic considerations of helping sustain or boost cognitive functions in AD and MCI.

**Disclosures: M.H. Thaut:** None. **T.A. Schweizer:** None. **M. Leggieri:** None. **N. Churchill:** None. **L. Fornazzari:** None. **C. Fischer:** None.

**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.13/M12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant 5R01NS034467
Leducq Foundation 16 CVD

**Title:** Development of a user interface software for quantification of microbleeds in rodents

**Authors: *K. SHAH**[1], J. PRINCE[1], S. BARNES[2], M. T. HUUSKONEN[1], J. RATELADE[3], R. E. JACOBS[1], A. JOUTEL[3], A. MONTAGNE[1], B. V. ZLOKOVIC[1]
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**Abstract:** Cerebral microbleeds (CMB) are small foci of blood products, best seen using magnetic resonance imaging (MRI) techniques sensitive to iron deposits (*i.e.*, gradient-echo

(GRE) T2*-weighted and susceptibility-weighted imaging), frequently encountered in small vessel disease (SVD) and also in other central nervous system disorders including Alzheimer's disease (AD). Among available pulse sequences, T2*-weighted (GRE) MRI lacking the 180° refocusing pulse characteristic of spin-echo (SE) or fast-spin echo techniques is highly sensitive to the susceptibility effect. Notably, the areas of low intensity that appear on T2*-GRE images are larger than the corresponding hemosiderin deposits, representing the so-called "blooming" effect. It is important to note that because extent of blooming varies with MRI parameters, the size of the measured signal void will depend on factors beyond the size of the corresponding histopathological CMB. The MRI factors of greatest influence on CMB detection are pulse sequence, sequence parameters, spatial resolution, magnetic field strength and post-processing. The potential effect of these factors on microbleed conspicuity and detection is important to take into consideration. Here, we developed a high-resolution 3D-T2*-GRE sequence for both *in vivo* and *ex vivo* rodent brain imaging at 7 and 11.7T to detect microbleeds in mouse models of AD (*5xFAD*) and SVD ($Col4a1^{+/G498V}$). We also developed a user interface module allowing regional CMB quantification (*i.e.*, number and size per brain region). We first validated our software by cross-comparison MRI-histology (*i.e.*, Prussian Blue staining) in 1-month-old $Col4a1^{+/G498V}$ mice developing hundreds of microbleeds throughout the pons, thalamus, cerebellum and olfactory bulb. It is of note that we found an averaged 75% microbleed-size overestimation due to "blooming" effect. This proposed MATLAB gui works by thresholding 3D-MR datasets and creating a binary mask disguising voxels that are considered iron-containing voxels from those that are not. A breadth first search algorithm is then implemented on this binary mask, counting not only the number of microbleeding events, but also the size and shape of each bleed. Finally, we are currently optimizing our software by adding sublevels of quantification (including susceptibility-shape analysis) to distinguish between microbleeds and other superparamagnetic signals potentially coming from amyloid brain depositions, vessel calcifications and atherosclerotic plaques.

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**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.14/M13

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Lowell R. Lamb Research Fund for Alzheimer's disease ATS11393

**Title:** Can cognitive and neural alterations be detected among healthy participants with a genetic predisposition for Alzheimer's disease?

**Authors: *R. PAZ**[1,2], E. BERGMANN[1], T. FALIK-ZACCAI[3], J. AHARON-PERETZ[2], I. KAHN[1]
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**Abstract:** In recent years significant research is directed to finding novel methods to detect subtle alterations among genetically at risk population for developing Alzheimer's Disease (AD), in presymptomatic stages. Understanding whether there are measurable alterations that can be used as early markers will open a time window for intervention and prevention. The current study aims to identify potential cognitive and neural alterations among healthy participants with near certainty to develop Alzheimer's disease. Here, we studied a group of participants with a unique duplication of the amyloid precursor protein (APP) gene, which causes familial Alzheimer's disease with autosomal dominant inheritance and early onset of disease with near certainty (98% penetrance). In this rare population, we sought to characterize the relation between genetic predisposition, cognitive performance as well as functional and structural brain organization which were estimated using MRI. Ten presymptomatic APP carriers and ten age-matched controls from the same family were recruited for this study. Participants underwent a 45-minute-long MRI scanning followed by an hour and a half of neurocognitive assessment, psychological screening and neurological examination. Preliminary behavioral results from a task assessing visual short-term memory for objects' identity and location (Oxford's `What Was Where` task), provide evidence for impaired performance in general item localization precision and in association generation between objects and their locations among carriers. Structural imaging data suggest a trend for reduced hippocampal volume. Functional connectivity analyses will take advantage of data-driven approaches such as the classical multidimensional scaling (MDS). This approach allows to explore different dimensions of the data and later quantify their effect on the variance using PCA, as was recently shown. Standard data-informed fMRI approaches will be used as well.
The combination of this unique cohort and the extensive data, collected across multiple levels per individual, may allow to more finely estimate the changes that occur in presymptomatic AD, and perhaps identify potential markers of the presymptomatic stage in non-familial forms of AD.

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**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.15/M14

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Canadian Institutes of Health Research foundation grant,

**Title:** The preclinical phase of autosomal dominant genetic form of Alzheimer's disease is characterized by accelerated brain aging that is independent from amyloid pathology

**Authors: *E. VACHON-PRESSEAU**[1], A. T. BARIA[2], A. PICHET BINETTE[3], T. BENZINGER[5], J. C. MORRIS[6], R. J. BATEMAN[7], J. C. BREITNER[4], J. POIRIER[3], J. GONNEAUD[3], S. VILLENEUVE[3]
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**Abstract: Background** Overlaps exist between the neural systems vulnerable to brain aging and Alzheimer's disease (AD). It is a matter of debate if ageing and AD progression are independent phenomenon.

**Objective**

We used the topological properties of the brain to predict age from brain functions. We then used the difference between the predicted age and the chronological age to tested if cognitively normal individuals in the preclinical phase of autosomal dominant Alzheimer's disease (ADAD) have premature ageing (DIAN cohort). We then tested if the amyloid status (positive (Aβ+) or negative (Aβ-)) contributed to the discrepancy between the estimated age from brain functions and the chronological age. We repeated these analyses in cognitively normal individuals at risk of sporadic AD while comparing *APOE4* carriers to non-carriers (PREVENT-AD cohort).

**Methods**

We used resting sate functional connectivity (rsfMRI) collected in 1,187 cognitively normal participants provided by the DIAN, the PREVENT-AD, the CAM-Can, the ADNI, and the ICBM to build the brain age predictive model. For each subject, BOLD activity time series from 238 regions were used to construct a 238x238 Pearson correlation matrix from which we extracted 26 graph metrics quantifying network topological properties. We used training data (n = 773) to generate a neural net model predicting age based on the graph metrics and assessed its accuracy using a validation set (n = 47) to assess potential bias and/or overfitting. The model was then tested in 367 left-out participants.

**Results**

The results show that age can be predicted from topological properties of graph constructed from rsfMRI in a large number of participants selected across multi-site cohorts. Our model explained above 60% of the variance between estimated age and chronological age in training, validation, and test sets. Importantly, our model estimated that DIAN mutation carriers (+) were older (mean = 42.36 years old; std = 14.10 y.o.) than their actual chronological age (mean = 34.27 years old; std = 9.56 y.o.) ($t_{(127)} = 5.17$; $p < 0.0001$). This discrepancy between the estimated and chronological age was greater in the mutation carrier compared to the non-carrier ($F_{(1,156)} = 7.69$; $p = 0.006$). The amyloid status however had no impact on discrepancy between the predicted and actual age ($F_{(1,126)} = 0.621$; $p = 0.54$). *APOE*4 carriers and amyloid status were not related to an over estimation of age in the PREVENT-AD individuals.

**Conclusions**

The preclinical phase of ADAD is characterized by accelerated functional brain aging. This phenomenon is independent from, and might therefore preceded, amyloid accumulation.

**Disclosures: E. Vachon-Presseau:** None. **A.T. Baria:** None. **A. Pichet Binette:** None. **T. Benzinger:** None. **J.C. Morris:** None. **R.J. Bateman:** None. **J.C. Breitner:** None. **J. Poirier:** None. **J. Gonneaud:** None. **S. Villeneuve:** None.

**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.16/M15

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIA R01 AG054671

**Title:** Medial temporal lobe activation during memory encoding is related to AD pathology in autosomal dominant AD

**Authors: *E. PARDILLA-DELGADO**[1], F. D'OLEIRE UQUILLAS[1], E. GUZMAN-VELEZ[1], J. T. FULLER[1], A. ARTOLA[1], A. BAENA[3], J. GATCHEL[1], L. RAMIRES-GOMEZ[2], Y. BOCANEGRA[3], F. LOPERA[3], Y. QUIROZ[1]
[1]Psychiatry, [2]Neurol., MGH/Harvard Med. Sch., Boston, MA; [3]Grupo de Neurociencias, Univ. de Antioquia, Medellin, Colombia

**Abstract:** Intro: Autosomal dominant Alzheimer’s disease (ADAD) provides an ideal model to study AD-related brain changes in the preclinical stages (i.e., before clinical symptoms occur), given that individuals are virtually certain to develop dementia in their 40s and do not have age-related comorbidities (e.g., cardiovascular disease). We previously showed that cognitively-unimpaired carriers of ADAD have abnormal hippocampal activation during associative memory

paradigms, several years before onset of clinical symptoms. Here, we examine whether task-related hippocampal activation is associated with amyloid-beta and tau accumulation in cognitively-unimpaired individuals who belong to the large Colombian kindred with ADAD due to E280A presenilin-1 (PSEN1) mutation. Method: 9 mutation carriers (age M=35, SD=5) and 17 age, sex, and education matched non-carrier family members (age M=37, SD=6) participated in the study. Participants completed cognitive testing, amyloid PiB PET, flortaucipir (FTP) tau PET, and a face-name associative memory task inside a 3.0T fMRI scanner. fMRI analysis focused on the hippocampal activation contrasting novel face-name pairs vs. repeated pairs. Regional FTP SUVRs were measured in entorhinal and inferior temporal cortices. PiB DVRs were measured in a neocortical aggregate region (FLR). Spearman's rank correlations were performed to characterize the associations among task-related hippocampal activation, cortical amyloid, regional tau, and cognition. Results: Compared to non-carriers, carriers had less activation in hippocampus (non-carriers: M=0.02, SD=0.26; carriers: M= -0.51, SD=0.37, Mann-Whitney U-test p=0.001). Among carriers, less hippocampal activity was associated with increased cortical PiB burden (r= -0.92, p=0.001), and higher entorhinal tau (r= -0.89, p=0.002), but not with inferior temporal (r= -0.50, p=0.17). Further, less hippocampal activation was associated with worse memory performance (r=0.70, p=0.03). Discussion: Our results confirm previous findings of abnormalities in hippocampal activation in preclinical stages of ADAD (approx. 9 years prior to symptom onset in our sample). Importantly, these abnormalities seem to be related to markers of AD pathology, providing further evidence for the use of memory-related functional activity as a possible biomarker of preclinical AD. This study is limited by its small sample size; therefore, these findings need to be validated with larger samples.

**Disclosures: E. Pardilla-Delgado:** None. **F. D'Oleire Uquillas:** None. **E. Guzman-Velez:** None. **J.T. Fuller:** None. **A. Artola:** None. **A. Baena:** None. **J. Gatchel:** None. **L. Ramires-Gomez:** None. **Y. Bocanegra:** None. **F. Lopera:** None. **Y. Quiroz:** None.

**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.17/M16

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** a grant from Canadian Institute of Health Research (CIHR) awarded to Professor Alan C. Evans (286404)

**Title:** Integrating multimodal data in biomarker identification for Alzheimer's disease with sparse model

**Authors: *K. KWAK**[1], J.-M. LEE[2], A. C. EVANS[1]
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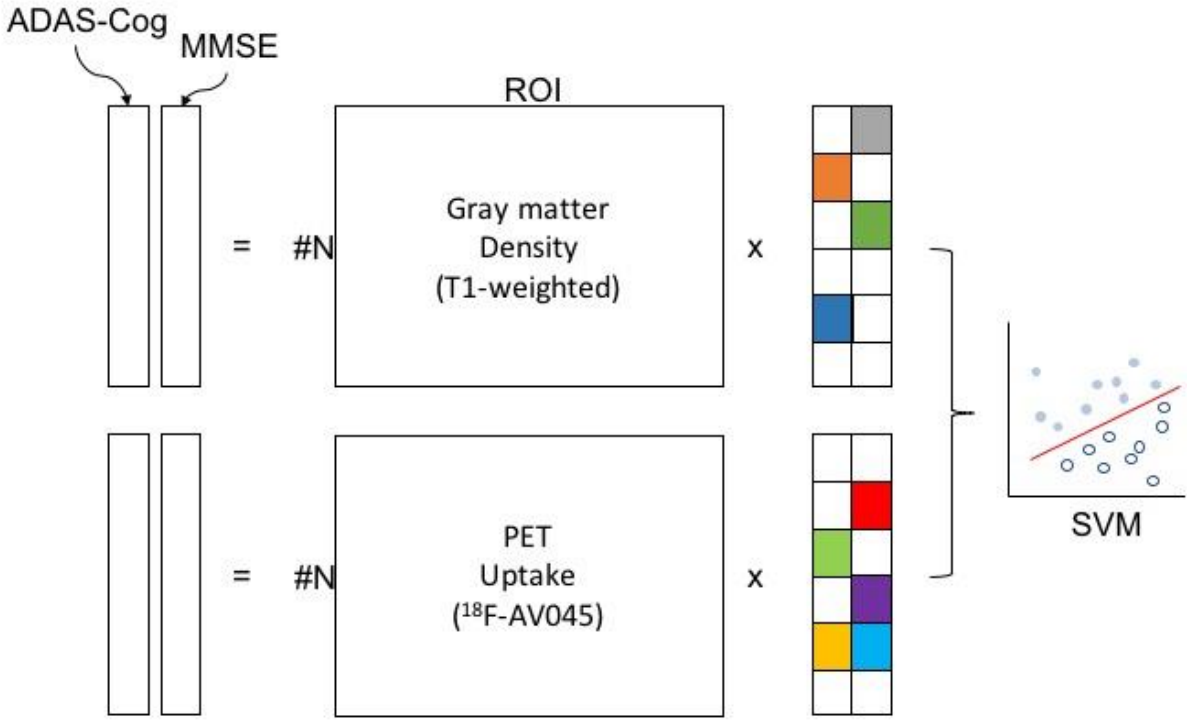
**Abstract:** Many neuroimaging biomarkers based on magnetic resonance imaging (MRI) and/or 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) have been suggested for Alzheimer's Disease (AD)/mild cognitive impairment (MCI) detection, which can be roughly categorized into two types according to the brain structure or function. First, structural neuroimaging biomarker based on T1-weighted MRI include cortical thickness, tissue density and regional volume. Second, functional neuroimaging biomarkers based on FDG-PET include regional cerebral glucose metabolic rate changes. This study aims to investigate prediction model for Alzheimer's Disease and Mild Cognitive Impairment using a sparse model to jointly explain multiple variables from structural T1-weighted MRI and FDG-PET. Specifically, our method contains two subsequent steps: (1) clinical scores are determined by the same underlying abnormal regions from multi-modal images. (2) a support vector machine which predicts groups of subjects based on the measure of extracted region. The figure 1 demonstrates the proposed classification framework.




To validate our method, we performed 10-fold cross validation on the ADNI dataset with MRI and FDG-PET images from 71 AD subjects, 163 MCI subjects and 85 healthy control subjects (HCs). We extracted abnormal regions from multi-modal images and found this method to be discriminative and robust for AD and MCI prediction. Also, the extracting inter-related regions in T1 and FDG-PET is expected to promote prediction performance from the relationship between brain structural and functional information. The proposed classification framework has

excellent discriminatory power for AD and MCI compared to HCs. Furthermore, thanks to the availability of various imaging modalities, it would be beneficiary to combine their complementary biomarker for classification problem. But further studies are needed, as this may not apply in all situations, for example, distinguishing the AD from fronto-temporal dementia.

**Disclosures: K. Kwak:** None. **J. Lee:** None. **A.C. Evans:** None.

**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.18/M17

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant R01AG033036
NIH Grant R01AG055449
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NIH Grant P01AG030128
NIH Grant TL1TR001997

**Title:** Component diffusivities within default-mode network white matter that are associated with Alzheimer's disease pathology, but not age, predict longitudinal change in executive function in cognitively normal older adults

**Authors: *C. BROWN**, B. T. GOLD
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**Abstract: Introduction:** Alterations in microstructure of white matter (WM) pathways connecting the default mode network (DMN) mediate age- and Alzheimer’s disease (AD) pathology-related changes in DMN function, which in turn contribute to poorer executive function (EF). Previous work has focused on the summary measure of fractional anisotropy, but it is unclear whether alterations in specific component diffusivity measures are impacted by age and AD pathology. Further, it is unclear how these different component diffusivity measures may predict decline in EF over time. **Methods:** Thirty-two cognitively normal (CN) older adults with available diffusion tensor imaging (DTI), cerebrospinal fluid (CSF) levels of tau and β-amyloid (Aβ), and annual neuropsychological testing were included in the present study. DTI measures of DR and DA were measured within a previously developed template of DMN WM pathways. AD pathology was quantified using the CSF tau/Aβ ratio. An EF composite measure was created by averaging the standardized residuals of Trails-B and Digit Symbol tests after regressing out Trails-A as a measure of processing speed. Annual change in EF composite was calculated for each year and then averaged to calculate a single measure of average annual

change in EF over the three-year follow-up period. Bivariate correlations were performed to examine relationships between DTI metrics, AD pathology, and age. Further partial correlations were performed to examine the relationship between DTI metrics and average annual change in EF after controlling for baseline EF. **Results**: Bivariate correlations revealed that higher CSF tau/Aβ ratios were associated with increased DR ($r$ = 0.37, $p$ = .040) but not DA ($p$ = .369), while increasing age was associated with increased DA ($r$ = 0.37, $p$ = .040) but not DR ($p$ = .396). Three participants were identified as outliers in annual change in EF (>3 SD from mean) and were excluded from longitudinal analyses. Annual change in EF was associated with DR ($r$ = -0.48, $df$ = 26, $p$ = .009) but not with DA ($r$ = -0.26, $df$ = 26, $p$ = .188). **Conclusion:** These findings suggest different mechanisms underlying age- and AD pathology-related changes in WM microstructure. Further, it appears that longitudinal change in EF is associated with AD pathology-related changes in WM microstructure but not age-related changes in this CN cohort. These findings suggest that AD-related WM change plays an important role in future cognitive performance and may be an important target for studies aiming to slow or prevent cognitive decline.

**Disclosures: C. Brown:** None. **B.T. Gold:** None.

**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.19/M18

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Anatomical and behavioral effects of high sucrose consumption on APOE animals

**Authors: *S. GRANT**
Northeastern Univ., Boston, MA

**Abstract:** Alzheimer’s disease is the most common form of age-related dementia. The estimated direct costs of Alzheimer’s disease and other related dementias on American society is $277 billion. Late-onset AD is correlated with a mutation on the apolipoprotein E (APOE) locus, and the APOEε4 allele is linked to substantial increases in AD risk. Alzheimer’s disease has been linked to the “Western diet”, which is characterized by high levels of refined sugars and saturated fats. In this study we characterized the anatomical and behavioral effects of a diet containing 68% sucrose (by energy) on female Sprague-Dawley rats with the APOEε4 allele. fMRI and diffusion weighted imaging (DWI) allowed for assessment of brain volumes, functional connectivity, and white matter architecture. Behavioral assays measured memory differences and cognitive impairment. Female APOEε4 rats on a high sucrose diet showed global decreases in functional connectivity, worsened behavioral memory and cognitive abilities, and

DWI differences in the hippocampus and frontal cortex. The data suggests that the presence of a "Western" high sugar diet is a detrimental environmental factor in the progression of Alzheimer's disease in at-risk patients.

**Disclosures: S. Grant:** 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.; Horizon Discovery.

**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.20/N1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Wellcome Trust
BRACE
Alzheimer's Research UK

**Title:** Long term memory consolidation and hippocampal changes in preclinical Alzheimer's disease

**Authors: *A. WEARN**[1], V. NURDAL[1], M. J. KNIGHT[1], R. A. KAUPPINEN[1], E. J. COULTHARD[2]
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**Abstract:** Episodic memory impairment is a predominant early symptom of Alzheimer's disease (AD). This is thought to be due to damage to areas within the hippocampus and medial temporal lobe cortical regions. Here we explore how episodic memory tests could be made more sensitive to early stage incipient AD. Behavioural data suggest that accelerated long-term forgetting (ALF) could be a very early sign of cognitive decline. Current neuropsychological protocols rarely test memory over longer than 30 minutes and therefore do not probe long term memory. We test the hypotheses that: 1) Hippocampal subfields subiculum and CA1 affected first in AD and are critical for long term memory performance. 2) ALF might be an early predictor of incipient AD. Our current dataset includes 22 healthy older controls, 21 individuals with subjective cognitive decline (SCD) and 9 mild cognitive impairment (MCI) patients who have undergone extensive cognitive testing, including 3 distinct tests of long term memory consolidation (story, word-list, complex figure). Immediate, 30-minute, and 4-week recall were tested. Furthermore, we explore the neuroanatomical structures that are critical for long term

memory using volumetric MRI and automated hippocampal subfield segmentation. We show here that healthy controls cannot be distinguished from individuals with SCD on the immediate or 30-minute recall timepoints of any test. However, after 4 weeks, those with SCD perform significantly worse than controls on the word-list, and indeed become statistically indistinguishable from the MCI patient group. Preliminary imaging data show a strong correlation of all hippocampal subfields with immediate recall on the word list, with a stepwise decrease in correlation strength as delay time increases. Only subiculum and CA1 subfields maintain statistically significant correlation with 4-week recall on the word-list. This preliminary analysis confirms previous literature suggesting that ALF may be a useful, pragmatic routine screening procedure for AD. Ongoing work will further examine the relationship between ALF and hippocampal subfield volumes in this cohort, as well as assessing the predictive power of ALF for future cognitive decline over subsequent years.

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**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.21/N2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant AG14449
NIH Grant AG025204

**Title:** Pittsburgh Compound-B binding and pyroglutamate amyloid-beta concentration in the precuneus cortex across clinical stages of Alzheimer's disease

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**Abstract:** Positron emission tomography (PET) imaging demonstrates high [C-11] Pittsburgh compound-B (PiB) retention in the default mode network (DMN), including precuneus cortex (PreC, BA7), which reflects accumulation of fibrillar amyloid-beta (Abeta) in Alzheimer’s disease (AD). N-truncated and pyroglutamate-modified Abeta forms [e.g., Abeta(pE3-42)], are particularly fibrillogenic. We hypothesized that Abeta(pE3-42) concentration corresponds to regional PiB retention in the PreC cortex. To test this hypothesis, we quantified [H-3]PiB binding and formic acid-extracted Abeta(pE3-42) and full-length Abeta1-42 concentrations in

PreC cortex, from cases with a premortem clinical diagnosis of no cognitive impairment (NCI, n=11), mild cognitive impairment (MCI, n=14), or mild AD (mAD, n=15). Analysis revealed that [H-3]PiB binding was significantly different across the clinical diagnostic groups, with greater levels in mAD compared to both NCI and MCI. Abeta(pE3-42) concentration was also higher in mAD cases compared to both NCI and MCI, while Abeta1-42 was higher in mAD relative to NCI but not MCI. Overall, higher PreC [H-3]PiB binding correlated strongly with greater Abeta(pE3-42) levels (r2=0.82) and greater Abeta1-42 (r2=0.81). Worse antemortem MMSE scores correlated with greater levels of both Abeta(pE3-42) and Abeta1-42 forms (r2=0.23 and r2=0.18, respectively). The strong associations of PreC PiB binding with Abeta(pE3-42) and Abeta1-42 suggests that increases in both Abeta forms contribute to PiB binding in this brain region. Weak associations of both Abeta forms with MMSE indicate that other pathological molecules (e.g., tau) are more relevant to global cognitive decline in AD. Characterization of pyroglutamate-modified and full-length Abeta forms in other DMN regions will further clarify their relation to pathogenesis and cognitive decline in AD, as well as to regional [C-11]PiB PET retention.

**Disclosures: V.N. Pivtoraiko:** None. **J. Shin:** None. **E.E. Abrahamson:** None. **W. Paljug:** None. **M. Debnath:** None. **W. Klunk:** None. **E.J. Mufson:** None. **M.D. Ikonomovic:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; GE Healthcare.

**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.22/N3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** ADNI (U01 AG024904)
(U54 EB020403)

**Title:** Brain aging assessed with longitudinal magnetic resonance imaging (MRI): Effects of changes in scanner types

**Authors: *C. P. BOYLE**[1], C. R. CHING[2], S. I. THOMOPOULOS[2], A. ZAVALIANGOS-PETROPULU[2], A. MEZHER[4], P. M. THOMPSON[3]
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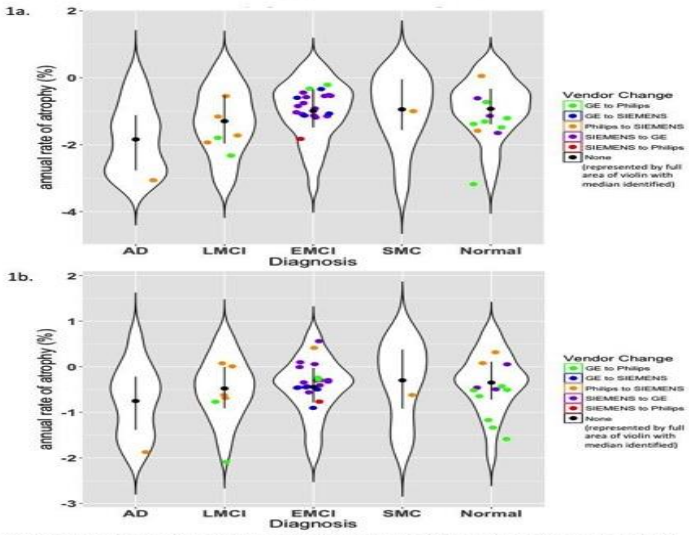
**Abstract: Objective and Rationale:**
Reliable measurement of brain atrophy in longitudinal studies depends on stable MRI acquisition. In the Alzheimer's Disease Neuroimaging Initiative (ADNI) participating sites were encouraged to use the most current scanner technology, so some participants were scanned on different machines over time. Here we calculated the annual rate of brain tissue loss, expressed as a percentage, in different diagnostic (Dx) groups. We tested if the estimated mean rate of atrophy per Dx group differed between subgroups of subjects with and without a scanner vendor change.
**Methods:**
We used unbiased tensor-based morphometry (TBM) to analyze n = 2,358 scans, from 811 ADNI-GO/2 participants scanned with accelerated T1-weighted MRI at 3T.
The study cohort of 811 subjects included 183 healthy normal controls (age at screening visit: 73.1 ± 8.3 years, 94F/89M), 57 with significant memory complaint (SMC; age: 71.8 ± 5.4 years, 34F/23M), 292 with early mild cognitive impairment (EMCI; 71.3 ± 8.4 years, 130F/162M), 158 with late mild cognitive impairment (LMCI; 72.1 ± 7.8 years, 74F/84M), and 121 with Alzheimer's Disease (AD; 74.5 ± 8.1 years, 47F/74M) patients, scanned at 0, 3, 6, 12, 24 and 36 months. We identified subject visits involving a scanner change during serial scanning (n = 41 visits).
Numerical summaries were obtained from Jacobian (tissue loss rate) maps using two different region-of-interest (ROI) methods (Fig. 1). Numerical summaries were converted to atrophy or expansion rates, normalized for the interscan interval.
**Results and Conclusion:**
Plots were created (using R) showing atrophy rates using each ROI method (Fig. 1).
In the EMCI group - but not for other Dx groups - we found a significant difference between vendor change and no vendor change in the estimated atrophy rates (*p=.011;statistical ROI, p=.003;anatomical ROI; t-test)*. Continued analysis of later ADNI scans will offer more insight into effects of vendor change on atrophy rate estimates.

Figure 1: TBM-Derived Brain Atrophy and Vendor Change across ADNI-GO/2




Atrophy rates are defined as the numerical summary of the 3D Jacobian map within a statistically (Fig. 1a) or anatomically (Fig. 1b) defined ROI from the temporal lobes[1]. Violin plots show the probability density of the data at different values and include a marker for the median of the data. In each plot we visualize the data points with no vendor change with violins and scatter the relatively sparse data points with vendor change, for visual comparison. Visually, the data points with vendor change are consistent with the bulk of the data involving no change in vendor.

1. X Hua, CRK Ching, A Mezher, BA Gutman, DP Hibar, P Bhatt, AD Leow, CR Jack Jr, M Bernstein, MW Weiner, PM Thompson and the Alzheimer's Disease Neuroimaging Initiative. MRI-based brain atrophy rates in ADNI phase 2: Acceleration and enrichment considerations for clinical trials. Neurobiology of aging. 2016;37:26-37. doi:10.1016/j.neurobiolaging.2015.09.018.

**Disclosures: C.P. Boyle:** None. **C.R. Ching:** None. **S.I. Thomopoulos:** None. **A. Zavaliangos-Petropulu:** None. **A. Mezher:** None. **P.M. Thompson:** None.

**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.23/N4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Big Data in Medicine Project University of Louisville 21st Century Initiative

**Title:** A significant regional based diagnosis framework of Alzheimer's disease using $^{11}$C PIB-PET scans

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[1]Bioengineering, [2]Neurol., Univ. of Louisville, Louisville, KY; [3]Information Technol., Mansoura Univ., Mansoura, Egypt; [4]Univ. of Louisville Sch. of Med., Louisville, KY

**Abstract:** Alzheimer's disease (AD) is one of the most neurodegenerative disorders that target the central nervous system. Brain biomarkers are one of the AD's tests that significantly help the

diagnosis. Our main aim is to use the carbon-11 labeled Pittsburgh compound B based positron emission tomography ($^{11}$C PiB-PET) scans to present a precise regional computer-aided diagnosis system to serve the personalized diagnosis of AD. A dataset of 103 $^{11}$C PiB-PET scans (19 normal control (NC), 65 mild cognitive impairment (MCI), and 19 AD) from Alzheimer's Disease Neuroimaging Initiative (ADNI) database is used to evaluate the system that in turn goes into five stages: (1) preprocessing to prepare the scans for the anatomical labeling and to de-noise them, (2) Labeling into 70 brain regions using Brodmann Areas (BAs) atlas, (3) Feature extraction, from each region, using Laplacian of Gaussian with automatic scale selection method, (4) Statistical analysis two-sample t-test, assisted by Bonferroni method to determine the significant BAs rather than working with the 70 region and to offer a precise diagnosis, and (5) Two diagnosis layers, regional then global diagnosis. The regional diagnosis, using probabilistic support vector machine (pSVM), shows the disease's severity in each significant region. The global diagnosis, using standard SVM, presents a final subject's diagnosis using the first layer's results. Due to the nature of the used methods, the statistical analysis and the diagnosis are done in two levels, level 1 between NC and abnormal groups (MCI+AD) and level 2 between MCI and AD groups separately. The found significant regions are 27 in level 1 and 33 regions in level 2 where these results are confirmed by the literature. For the classification performance, leave-one-subject-out method (LOSO) is applied for (1) the evlauation of different SVM kernels, the linear, radial basis function, and polynomial kernels, (2) the comparison with state-of-the-art classifiers and other related work that uses the same database. The linear pSVM/SVM shows better results than the other kernels with an overall accuracy of 98.05% and average accuracy, specificity, and sensitivity of 99.02%, 99.09%, and 96.48%, respectively. These results exceed the state-of-the-art classifiers' results of average accuracy, specificity, and sensitivity 94.72%, 72.62%, and 94.07% for the decision tree, ensemble classifier, and k-nearest neighbor, respectively. Also, our results exceed those of the related work that has a maximum overall accuracy of 87.50%. These results encourage evaluating the system on a larger dataset and analyzing other modalities in the future.

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**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.24/N5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant NS082870

Sidney R. Baer Jr. Foundation
Khorana Scholars Program
KVPY Fellowship

**Title:** Noninvasive brain stimulation marker for cognitive decline in Alzheimer's disease

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**Abstract:** Background
Alzheimer's Disease (AD) is the most common cause of dementia. Markers for early diagnosis and accurate progression are vital to manage the growing burden of AD. Transcranial magnetic stimulation (TMS) has shown AD is associated with cortical hyperexcitability, as reflected by a lower TMS-measured resting motor threshold (RMT) compared to cognitively intact healthy people. However, it is unknown how this hyperexcitability relates to the severity of cognitive dysfunction in AD.
Aim
The purpose of this study was to assess the relationship of RMT with cognitive dysfunction in AD.
Methods
A retrospective test-validation-evaluation analysis was conducted. First, the relationship was tested in a well-characterized test cohort, consisting of 20 AD subjects and 27 cognitively intact controls. Second, the relationship was validated in an independent cohort of 128 AD patients acquired from a multi-center clinical trial sponsored by Neuronix Ltd. (ClinicalTrials.gov Identifier: NCT01825330). RMT was defined as the intensity (as % of maximum stimulator output) required to elicit MEPs $\geq 50\mu V$ in at least 5 out of 10 trials. The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) was used to capture the severity of dementia symptoms. Third, a meta-analysis of 7 published studies with total 152 AD subjects was conducted to evaluate the relationship between the inverse Mini-Mental Status Examination (MMSE) score and RMT. Across cohorts, clinical diagnosis of mild-to-moderate AD was determined by the study clinician based on DSM-IV/NINCDS-ADRDA.
Results
In the test cohort, simple linear regression (SLR) revealed a significant correlation between ADAS-Cog and RMT for the AD group ($n = 20$, $\beta = -0.62$, $p = 0.004$) but not for the control group ($n = 27$, $\beta = -0.13$, $p = 0.511$). Multiple regression and mediation-moderation analysis showed that scalp-to-cortex distance is a moderator, cortical thickness is an independent covariate, electric field intensity is the latent variable and excitation-inhibition balance is an RMT determinant. The validation cohort confirmed this result, with SLR showing a significant relationship between ADAS-Cog and RMT ($n = 128$, $\beta = -0.29$, $p = 0.001$). The meta-analysis found a medium effect with moderate heterogeneity by Hunter Schmidt estimation using a random-effects model ($r' = -0.23$, 95% CI: [-0.46, -0.09], $p = 0.049$ , $I^2 = 52.37\%$).
Conclusion
The present study found that in independent AD cohorts across assessments, RMT was related to

global cognition. As a reliable, inexpensive, noninvasive, and objective measure of cortical hyperexcitability, RMT may be a useful marker of disease progression in AD in future clinical trials.

**Disclosures: S. Zadey:** None. **S. Buss:** A. Employment/Salary (full or part-time):; Beth Isreal Deaconess Medical Center. **K. McDonald:** A. Employment/Salary (full or part-time):; Beth Isreal Deaconess Medical Center. **P.J. Fried:** A. Employment/Salary (full or part-time):; Beth Isreal Deaconess Medical Center. **A. Pascual-Leone:** A. Employment/Salary (full or part-time):; Beth Isreal Deaconess Medical Center. F. Consulting Fees (e.g., advisory boards); Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Cognito, Constant Therapy, and Neosync.

**Poster**

**741. Alzheimer's Disease and Other Dementias: Clinical and Pre-Clinical Imaging Studies in Alzheimer's Disease**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 741.25/N6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** R01 NR015452

**Title:** Longitudinal structural connectome mapping in supernormals

**Authors: *Q. CHEN**[1], Z. ZHANG[2], T. BARAN[3], F. LIN[4]
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**Abstract:** Cognitive decline is common in normal aging and AD. Yet some older adults, known as Supernormals (SN), maintain cognitive superiority and resist to AD pathophysiology. Characterizing neural profile of SN may help identify therapeutic targets for cognitive decline and neurodegeneration. Our recent studies (Wang et al., *Cere Cortex*, 2017; Lin et al., *Cortex*, 2016) suggest that the function of a unique set of brain regions in SN is aging and AD-resistant. However, the white matter fiber pathways underlying the functional integrity, a critical aspect supporting information transport across brain regions, remain unexplored. Here we conducted a longitudinal study using a cutting-edge population-based structural connectome framework (Zhang et al., *Neuroimage*, 2018). We used the cohort from ADNI, including a group of SN identified by us (Lin et al., *JAD* 2017). We hypothesized that SN maintain a unique set of structural connectomes that are immune to AD pathophysiology, supporting longitudinal cognitive success.

**Disclosures: Q. Chen:** None. **Z. Zhang:** None. **T. Baran:** None. **F. Lin:** None.

**Poster**

**742. Alzheimer's Disease and Other Dementias: APP and Metabolites: Function and Processing**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 742.01/N7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Insulin reduces amyloid-b production by regulating the processing of its precursor

**Authors: *O. KWON**, Y. CHO, S. CHUNG
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**Abstract:** Alzheimer’s disease (AD) is caused by the accumulation of neurotoxic amyloid-β (Aβ) peptides. Aβ is derived from amyloid-β precursor protein (APP). In non-amyloidogenic pathway, APP is cleaved by α-secretase and γ-secretase at the plasma membrane excluding Aβ production. Alternatively, APP in the plasma membrane is internalized through clathrin-dependent endocytosis, and delivered to early endosomes and lysosomes, where it is cleaved by β-secretase and γ-secretase. Recently, some studies have shown that insulin in the periphery crosses the blood-brain barrier and plays important roles in brain. Furthermore, impaired insulin signaling has been linked to the progression of AD, and intranasal insulin administration improves memory impairments and cognition. However, the underlying molecular mechanisms of insulin treatment are remained largely unknown. To investigate the effects of insulin on APP processing, we tested the effects of insulin on neuroblastoma cell line (SH-SY5Y) overexpressing APP, and cultured rat cortical neurons. We found that insulin increased the level of cell surface APP, decreasing the endocytosis rate of APP. Insulin reduced Aβ generation through up-regulation of APP O-GlcNAcylation via Akt insulin signaling. Our present data suggest that insulin affects Aβ production by regulating APP processing through APP O-GlcNAcylation. These results provide a mechanistic insight into the beneficial effects of insulin and possible link between insulin deficient diabetes and cerebral amyloidosis in the pathogenesis of AD.

**Disclosures: O. Kwon:** None. **Y. Cho:** None. **S. Chung:** None.

**Poster**

**742. Alzheimer's Disease and Other Dementias: APP and Metabolites: Function and Processing**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 742.02/N8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** BK21 PLUS
NRF-2016R1C1B2010206

**Title:** The roles of PEN2 in maintaining the integrity of γ-secretase structure which is essential for intracellular autophagic clearance

**Authors: *H. HEO**[1], J. KANG[1], J. CHANG[1,2]
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**Abstract:** Accumulation of various types of abnormal/unwanted intracellular substances has been thought to one of the main causes of the development of neurodegenerative diseases including Alzheimer's disease (AD). Autophagy-lysosome degradation system is responsible for the clearance of these materials. Thus, efforts have been made to identify the underlying cellular pathogenesis of AD by determination of the relationships between AD-related genetic alterations and autophagy. The series of these studies begins with the study on an important familial AD gene, *PSEN1*, which encodes a subunit of γ-secretase regulating the processing of beta-amyloid (Aβ) from amyloid precursor protein (APP). PSEN1 has been shown to be required for the maintenance of the acidic lysosome environment by regulating the lysosomal targeting of a V-ATPase subunit, V0a1. It has also been reported that genetic alterations in *PEN2/PSENEN* gene encoding PEN2, another subunit of γ-secretase, cause the onset of the familial AD. Therefore, to further investigate the pathogenesis of familial AD by γ-secretase abnormalities, we generated cell lines lacking PEN2 using a CRISPR/Cas9-mediated knockout (KO) system and analyzed the phenotypes associated with autophagy. We have found that the deficiency of PEN2 severely inhibits the assembly of the γ-secretase complex and simultaneously destabilizes PSEN1 and PSEN2 proteins. The autophagic activity of the PEN2-KO cell lines was weakened as compared with that of the normal cells as in the case of previously described PSEN1-KO cell lines. By further analysis of phenotypes induced by the re-expression of PEN2-D90N, a familial AD form of PEN2, we showed that PEN2 is a core component for maintaining the integrity of γ-secretase structure which is indispensable for proper autophagic process. From the above results, here we propose a novel cellular pathogenesis of AD associated with autophagy.

**Disclosures: H. Heo:** None. **J. Kang:** None. **J. Chang:** None.

**Poster**

**742. Alzheimer's Disease and Other Dementias: APP and Metabolites: Function and Processing**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 742.03/N9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** DFG PI 379

**Title:** N-terminal truncated A beta peptides starting at p2 are generated by meprin beta

**Authors: *C. U. PIETRZIK**[1], A. MAZURA[1], A. OHLER[1], S. STORCK[1], L. MARENGO[1], S. WEGGEN[3], U. SCHMITT[2], C. BECKER-PAULY[4]
[1]Inst. for Pathobiochemistry, [2]Dept. of Psychiatry and Psychotherapy, Univ. Med. Ctr. of the Johannes Gutenber, Mainz, Germany; [3]Heinrich-Heine-University, Duesseldorf, Germany; [4]Inst. of Biochem., Univ. of Kiel, Kiel, Germany

**Abstract:** One of the major hallmarks of Alzheimer´s Disease (AD) is the accumulation of soluble and aggregated amyloid β (Aβ) peptides in the brains of AD patients. Aβ peptides are generated from the amyloid precursor protein (APP). Most prominent, BACE 1 (β-site APP cleaving enzyme 1) cleaves APP at the β-secretase cleavage site and generates the N-terminus of Aβ. Second, the γ-secretase complex cleaves the remaining 99 amino acids long C-terminal fragment (CTF/C99) and releases the C-terminus of Aβ. As both secretases are not restricted to a single site, Aβ peptides vary in length. BACE 1 can only generate Aβ peptides starting in position p1 or p11 (Aβ1 x/11 x) whereas γ-secretase complex has several cleavage sites and can generate varying C-termini of Aβ. In the last years, it became evident that N-terminally truncated Aβ variants, such as Aβ2-42, are increased in AD brains. This is in line with results showing decreased levels of Aβ2-42 in CSF of AD patients. Since BACE-1 is not capable in directly generating this peptide, a suggested model for the emergence of N-terminal truncation is the existence of alternative enzymes. We have previously demonstrated that the metalloprotease meprin β cleaves APP as a β-secretase reminiscent of BACE 1, however, predominantly generating N-terminally truncated Aβ2-x variants. We observed that meprin β derived N-terminally truncated Aβ2-40/42 peptides display increased aggregation compared to non-truncated Aβ peptides and demonstrate increased staining of meprin β in brains of sporadic Alzheimer disease patients compared to non-demented control subjects. Surprisingly familiar AD mutations located at the N-terminal region of the Aβ-sequence dramatically influence the catalytic activity of meprin β. The APP Swedish (swe) mutation at position 672 results in reduced generation of N-terminally truncated Aβ. The recently described APP mutation A673T that has been shown to protect against AD and BACE 1 cleavage, also protects from meprin β derived N-terminally truncated Aβ2-40/42 peptides. This offers an interesting possibility, that

meprin β only generates Aβ peptides from APP in sporadic AD cases or AD cases harboring mutations close to the γ-secretase cleavage site. To address this possibility we crossed APP London mice with meprin β knock-out mice and analyzed histopathological hallmarks and behavioral phenotypes in these animals. In a reverse setup we used an overexpression system by injecting meprin β expressing AAV into the hippocampus of APP London mice and demonstrate its effect on APP processing in vivo. We propose that meprin β may be involved in the generation of N-terminally truncated Aβ2-x peptides of APP in vivo.

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**Poster**

**742. Alzheimer's Disease and Other Dementias: APP and Metabolites: Function and Processing**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 742.04/N10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant AG15379
NIH Grant AG44486

**Title:** C99 RFP-GFP: FRET biosensor for visualizing Aβ production

**Authors: *M. MAESAKO**, N. SEKULA, L. ANDERSON, M. CALVO RODRIGUEZ, S. DUJARDIN, O. BEREZOVSKA
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**Abstract:** Presenilin (PS)/γ-secretase is responsible for the generation of β-amyloid (Aβ) by cleaving the β-site processed APP (APP C99/CTFβ). Accumulation of Aβ, so called senile plaques, in the brains is a hallmark of Alzheimer's disease (AD). The successful development of specific antibodies and/or fluorescently or radioactively labeled compounds against Aβ allowed clear detection of the Aβ plaques not only in post-mortem AD brain but also in the brain of living patients. However, it has never been fully elucidated *when, which cells, and where within the cell* Aβ is generated. To tackle these crucial questions, we have successfully developed and validated a novel Förster resonance energy transfer (FRET) biosensor - C99 RFP-GFP (C99 R-G) probe to report the activity of endogenous PS/γ-secretase. C99 R-G is an ideal chimeric molecular probe that includes APP C99 (the precursor substrate of PS/γ-secretase) and two fluorescent proteins - EGFP (donor) and RFP (acceptor) in the 1:1 ratio. The cleavage of the APP C99 in the C99 R-G probe by endogenous PS/γ-secretase would result in the change of the proximity between EGFP and RFP, i.e., change in the FRET efficiency, and thus would simultaneously report the production of the Aβ peptides. Therefore, by monitoring changes in the FRET efficiency

between EGFP and RFP in the C99 R-G probe we would be able to “visualize” the APP C99 cleavage by PS/γ-secretase. The extensive validation of the probe in cultured primary neurons, CHO, MEF and HEK cell lines supports plausibility of using the C99 R-G probe to report PS/γ-secretase activity and “visualize” Aβ production on a cell-by-cell basis with high subcellular resolution. The probe can be easily modified to detect processing of other PS/γ-secretase, e.g. Notch1, suggesting that C99 R-G would be a prototype of assays to further investigate the roles of PS/γ-secretase in other diseases.

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**Poster**

**742. Alzheimer's Disease and Other Dementias: APP and Metabolites: Function and Processing**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 742.05/N11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** R56AG056507-01

**Title:** Age-related increases in intracellular amyloid aggregates cleared by gamma-secretase inhibitor/modulator or metabolic/redox boost

**Authors: C. G. GLABE**[1], R. A. HERRERA[1], R. E. TANZI[3], S. L. WAGNER[4], *G. J. BREWER[2]
[2]MIND Inst. and Biomed. Engin., [1]UC Irvine, Irvine, CA; [3]Massachusetts Gen Hosp, Harvard Med. Sch., Charlestown, MA; [4]UC San Diego, La Jolla, CA

**Abstract:** How aging influences the processing of APP into Aβ is unknown. We propose an age-related accumulation of misfolded and aggregated long Aß peptides and APP-CTFs inside neurons that leads to either a) metabolic impairment and neuronal death or vice versa b) metabolic impairment of aging alters processing of APP causing aggregated long intracellular Aß peptides (iAβ). This is the opposite of the conventional amyloid hypothesis that Aß is first secreted from neurons as a soluble peptide, aggregates outside the cell to exert neurotoxicity. Our ability to culture neurons from any age animal allows investigation of age as a dependent variable, removed from an aging vasculature, hormones and immune system. We first demonstrated that gamma secretase inhibitors or modulators decreased intracellular accumulation of Aβ in neurons from the 3xTg-AD mouse, indicating that iAß contains Aβ processed by gamma secretase. Further, the kinetics of iAß decline was faster than inhibition of extracellular release. Punctate staining of Aβ aggregates with anti-Aß-aggregate or anti-C-terminal Aβ45 co-localized with the endosome marker rab7 as well as with mitochondria and

lysosomes. iAβ increased exponentially with age of neurons grown from young, middle age or old mice. The age-dependent increases in iAβ along with Alz-50 tau staining were exacerbated by glutamate. Inhibition of autophagy with bafilomycin lowered iAß as well as the NAD/NADH precursor nicotinamide, or either of two Nrf2-inducers for redox control. These results suggest that age-related metabolic impairment contributes to the generation of intracellular Aβ, possibly overwhelming clearance by autophagy unless neurons receive a metabolic boost.

**Disclosures: C.G. Glabe:** 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.; R56AG056507-01. **R.A. Herrera:** None. **R.E. Tanzi:** 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.; Cure Alzheimers Fund. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); equity in Neurogenetic Pharmaceuticals.. **S.L. Wagner:** None. **G.J. Brewer:** None.

**Poster**

**742. Alzheimer's Disease and Other Dementias: APP and Metabolites: Function and Processing**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 742.06/N12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** KAKENHI 15H02492
JSPS Research Fellowship for Young Scientists

**Title:** Identification of the genetic regulators for Aβ production by CRISPR/Cas9

**Authors: *Y. CHIU**, I. EBINUMA, Y. HORI, T. TOMITA
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**Abstract:** Alzheimer disease (AD) is a progressive neurodegenerative disorder pathologically characterized by deposition of amyloid β peptide (Aβ) as senile plaques. Aβ is generated through the sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretases. γ-Secretase is a 4-protein complex composed of Aph1, Nicastrin (Nct), Pen-2 and the catalytic subunit Presenilin 1 (PS1) or PS2. APP is cleaved by the γ-secretase at multiple positions, thereby causing the heterogeneity in the C-terminal length of Aβ, such as Aβ40 and Aβ42. Although Aβ42 consists 5-10% of total Aβ, Aβ42 is highly toxic and prone to aggregate. To date, various evidence indicates that the aberrant Aβ production is associated with the pathogenesis of AD.

However, the precise regulatory mechanism of Aβ generation remains unknown.
To identify the genetic regulators of Aβ production, we have established murine neuroblastoma Neuro2a cell pool whose genome was edited by CRISPR/Cas9 system with the genome-wide lentiviral gRNA library. Among this cell pool, we chose 3 monoclonal cell lines with altered levels of secreted Aβ. We isolated the gRNAs from these cell lines using next generation sequencer and analyzed the molecular functions of their targets in the Aβ production pathway. Through this study, we identified *Cib1* targeting gRNA from Neuro2a cells with increased Aβ production. CIB1 is a small myristoylated calcium-binding protein with 4 EF-hand domains. Notably, CIB1 was identified previously as PS2 binding protein by yeast 2-hybrid screening, while its role in Aβ production remained unclear. Disruption of *Cib1* increased the Aβ40 and Aβ42 production without affecting the expression level of APP, β- nor γ-secretase. In contrast, overexpression of mouse CIB1 in *Cib1* disrupted cell rescued the upregulated Aβ secretion, supporting our notion that CIB1 is a genetic regulator for Aβ production. Thus, our results suggest that *Cib1* is a suppressive factor in the AD pathogenesis by altering Aβ production. Further molecular and cellular studies would clarify the mechanistic role of CIB1 in APP processing and the etiology of AD.

**Disclosures: Y. Chiu:** None. **I. Ebinuma:** None. **Y. Hori:** None. **T. Tomita:** None.

**Poster**

**742. Alzheimer's Disease and Other Dementias: APP and Metabolites: Function and Processing**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 742.07/O1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** R21AG052718-02

**Title:** Cathepsin D regulates cerebral Aß42/40 ratios via markedly differential degradation of Aß42 versus Aß40

**Authors: *C. N. SUIRE**[1], S. LANE[2], M. A. LEISSRING[2]
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**Abstract:** Mutations in presenilin/γ-secretase are known to cause early-onset Alzheimer's disease (AD) by increasing cerebral Aß42/40 ratios, but it is unknown whether this critical parameter is regulated by other factors that might be disturbed in sporadic AD. We report here that Aß42/40 ratios are regulated via markedly differential catabolism of Aß42 and Aß40 by cathepsin D (CatD), which we also show to be the principal Aß-degrading protease regulating lysosomal Aß levels *in vivo*. Genetic deletion of CatD results in several remarkable effects,

including: increases in insoluble Aß exceeding those present in mice lacking insulin-degrading enzyme, neprilysin or both; intralysosomal deposits of endogenous Aß42 by 3 weeks of age; and elevated cerebral Aß42/40 ratios comparable to those induced by *presenilin* mutations. Mechanistically, we show that the alteration in Aß42/40 ratios is driven by pronounced differences in the kinetics of Aß42 *versus* Aß40 degradation by CatD. Relative to Aß40, Aß42 exhibits a remarkably stronger, sub- to low-nanomolar affinity ($K_m$) for CatD and a nearly 200-fold slower turnover rate ($k_{cat}$), which together render Aß42 a highly potent competitive inhibitor of CatD. Notably, similar differences are observed for the processing of murine Aß42 and Aß40 by CatD, as well as the corresponding alpha-secretase-derived P3 fragments, reinforcing the conclusion that these effects are attributable to aggregation-independent factors. Collectively, our findings uncover a previously unrecognized interplay between Aß42 and CatD with strong relevance to AD pathogenesis.

**Disclosures: C.N. Suire:** None. **S. Lane:** None. **M.A. Leissring:** None.

**Poster**

**742. Alzheimer's Disease and Other Dementias: APP and Metabolites: Function and Processing**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 742.08/O2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Traumatic brain injury induces amyloid precursor protein increase in adult mice

**Authors: *Y. XIE**[1], S. WANG[2], K. D. RYNEARSON[3], P. NGUYEN[3], B. P. HEAD[4], C. WU[3], S. L. WAGNER[3]
[1]Yunan Univ. of Traditional Chinese Med., Yunnan, China; [2]VA Healthcare System, UCSD, San Diego, CA; [3]Neurosciences, UCSD Sch. of Med., San Diego, CA; [4]Anesthesiol., VA Med. Ctr., San Diego, CA

**Abstract:** Traumatic brain injury (TBI) is considered a risk factor for the development of Alzheimer's disease (AD). Post-TBI consequences include increase expression of amyloid precursor protein (APP) and amyloid-β(Aβ) generation. Experimental studies of TBI-induced Aβ accumulation as a risk of AD pathology are usually performed using transgenic mouse models of amyloidosis. These transgenic mice continually over-express APP, producing supra-physiologic concentrations of APP and Aβ in the brain. Thus it is difficult to find out the direct relationship between TBI and AD under physiological conditions. To avoid confounds associated with transgene-driven APP overexpression, we would use wild type mouse to determine whether TBI causes acute increase in APP and amyloid β peptides ($Aβ_{40/42}$) in the brain and plasma. Male C57BL/6 mice of 6 months of age were divided into sham and TBI model groups. TBI were performed by controlled cortical impact (CCI) of the right parietal cortex. After one day

exposure to experimental TBI, Aβ levels in the ipsilateral, contralateral of the brain as well as in the plasma were quantified using a MSD-based sandwich enzyme-linked immunosorbent assay (ELISA).Protein levels of full-length APP in the mouse brain were measured by Western blotting.We found that TBI caused a significant increase in APP protein level in the injured hemisphere at Day 1 after TBI. This is consistent with other studies showing that TBI altered APP processing in transgenic mouse brains and in human brains.The increased processing of full-length APP caused increased production of $A\beta_{40}$ and $A\beta_{42}$ in mouse brain. We found that injury caused a increase in levels of $A\beta_{40}$ and $A\beta_{42}$ compared to sham both in the ipsilateral and contralateral brain at Day 1 postinjury. However, $A\beta_{40}$ and $A\beta_{42}$ in plasma were significantly decreased in injured animals compared with injured animals($P = 0.0022$ and $P = 0.0267$, respectively).Notably, TBI increased levels of full-length APP in ipsilateral brains. Similar to our Western blot data, levels of $A\beta_{40}$ and $A\beta_{42}$ in TBI mice brains increased too. Others have previously demonstrated that TBI increases levels of Aβ in the brain using human APP Tg mice. Here, we found that rapid generation of Aβ after injury also occurs in WT mice. Interestingly, in contrast to brain tissues, the levels of Aβ in mouse plasma was obviously decreased after TBI. Though there is a lot of evidence indicating that plasma levels of $A\beta_{40}$ and $A\beta_{42}$ robustly correlate to brain in AD patients and in APP Tg mouse, our results may indicate a faster clearance or a utilization for wound healing of Aβ in plasma.

**Disclosures: Y. Xie:** None. **S. Wang:** None. **K.D. Rynearson:** None. **P. Nguyen:** None. **B.P. Head:** None. **C. Wu:** None. **S.L. Wagner:** None.

**Poster**

**742. Alzheimer's Disease and Other Dementias: APP and Metabolites: Function and Processing**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 742.09/O3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant AG039668
NSF IOS-1347090
New Jersey Health Foundation Grants
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**Title:** The amyloid-β precursor protein is a ubiquitous, permanent resident of a specialized tubular endoplasmic reticulum compartment

**Authors: *V. MURESAN**, Z. LADESCU MURESAN
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**Abstract:** The function of the Amyloid-β Precursor Protein (APP), one of the most studied disease-relevant proteins, is poorly understood. APP is a type I transmembrane protein that undergoes extensive proteolytic cleavage into smaller polypeptides, which have been implicated in the neuronal pathology of Alzheimer's disease (AD). In neurons, the cleavage of APP generates N- and C-terminal fragments (NTFs and CTFs), and - subsequently - internal fragments. After cleavage by β-secretase, the NTFs, comprising the ectodomain of APP, distribute as soluble polypeptides in the lumen of intracellular membrane-bounded compartments, while the CTFs remain attached to the membrane via their transmembrane domain. Here we show that, in the brainstem derived neuronal cells, CAD, APP is cleaved to a large extent in a juxtanuclear compartment of the tubular endoplasmic reticulum (ER) that is associated with neurofilaments. While the CTFs exit the ER along the secretory route, and are transported into the neurites by TGN-derived vesicles, the NTFs - released in the ER lumen - never exit the ER, and are carried to the growth cones within specialized ER tubules that lack machineries for protein and lipid synthesis. Throughout the neuron, the NTFs colocalize with Reticulon 4B (Rtn4B), a structural protein of the tubular ER, but not with the longer isoform, Rtn4A (NogoA). The subcellular fractionation of rat brain homogenates reveals a fraction that contains Rtn4B and several forms of NTFs, but lacks the translocon-associated protein, TRAPα, Rtn4A, and full-length APP. The NTFs and Rtn4B redistribute identically under experimental conditions that disrupt the structural integrity of the compartments where they reside. The treatment of cells with Brefeldin A, an agent that blocks the anterograde vesicle transport along the traditional secretory route, does not affect the accumulation of NTFs and Rtn4 at the growth cone. Also, the induction of neurite retraction causes a coordinated retraction of the NTFs and Rtn4B, at a faster pace than the retraction of neurites. Thus, the NTFs and Rtn4B reside in the same compartment, both in the soma and in neurites; in neurites, this compartment represents a specialized, dynamic, biochemically distinct subcompartment of the tubular ER. The NTFs are trafficked in and out of neurites within the extending or retracting ER tubules. The ER localization of the NTFs is also detected in the neurites of cortical, hippocampal, and DRG neurons, and in advancing protrusions of HEK293 cells, and endothelial and epithelial cells (HUVEC, BAEC, MDCK). Together, these results indicate that the NTFs are ubiquitous residents of the tubular ER, with yet to be determined functions.

**Disclosures: V. Muresan:** None. **Z. Ladescu Muresan:** None.

**Poster**

**742. Alzheimer's Disease and Other Dementias: APP and Metabolites: Function and Processing**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 742.10/O4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH AG051266
Alzheimer Association ZEN-14-283969
Bright Focus Foundation A2015275S
NIH NS050276

**Title:** N-terminal truncated Aâ4-x proteoforms and their relevance for Alzheimer pathophysiology

**Authors: *J. GHISO**, E. CABRERA, T. NEUBERT, A. ROSTAGNO
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**Abstract:** Impaired brain clearance and abnormal Aβ degradation are considered key events for the formation and progressive accumulation of soluble neurotoxic oligomers and the development of synaptic pathology, one of the strongest correlates to cognitive impairment in AD. Clearance studies, mostly centered in monomeric Aβ40, have provided a basic assessment of the participating mechanisms, but the complex molecular and structural heterogeneity of the brain Aβ peptidome -going far beyond the classic Aβ40/Aβ42 dichotomy- has been largely overlooked. The most common heterogeneity resides in the multiple N- and C-terminal truncated fragments that consistently populate the Aβ peptidome and of which little is known in regards to their homeostatic regulation and potential contribution to disease pathogenesis. Our studies indicate that while C-terminal truncations increase solubility and abrogate oligomerization/fibrillogenesis, features clearly associated with clearance mechanisms, N-terminal truncations, particularly abundant components of parenchymal deposits in AD, non-human primates, and multiple APP transgenic models drive enhanced pro-amyloidogenic properties. Notably, the poorly studied Aβ4-x fragments -truncated at position 4 but bearing an intact C-terminus, ending at Val40 or Ala42 as their respective full-length counterparts- provided further insights into the potential role of these truncated forms in AD pathogenesis. *In vivo* clearance experiments using oligomeric radiolabeled homologues validated their poor brain removal characteristics when compared with their monomeric counterparts or to the full-length oligomeric parent molecules. In addition, proteomic studies of tissue deposits in conjunction with the use of novel antibodies specific for the free N-terminus of Aβ4-x revealed their primarily topographic association with fibrillar plaque cores. Remarkably these antibodies, highly specific for the free N-terminus of Aβ4 and blind for any other Aβ derivatives including full-length Aβ40 and Aβ42, were able to abrogate oligomerization, fibrillization and neurotoxicity of the highly amyloidogenic Aβ4-42 *in vitro.* Overall, our findings highlight the potential contribution of N-terminal truncations for the disease pathogenesis and identify fragments truncated at Phe4 as novel, not previously recognized targets for therapeutic intervention.

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**Poster**

**742. Alzheimer's Disease and Other Dementias: APP and Metabolites: Function and Processing**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 742.11/O5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Identification of a novel cleavage site associated with pathogenesis risk of familial Alzheimer’s disease on amyloid precursor protein

**Authors: *Y. CHEN**, X. NIU, X. HOU, Y. GENG
IRCBC, SIOC, Chinese Acad. of Sci., Shanghai City, China

**Abstract:** Point mutations of Amyloid Precursor Protein (APP) could increase Abeta production and cause early onset Alzheimer’s disease. Whereas APP Iceland mutation reduces Abeta production and decrease AD risk. These evidence strongly support Abeta hypothesis for AD. However, some mutations on gamma secretase reduce Abeta production but still cause familial AD. There are also studies that suggest these AD causing Presenilin 1 mutations are loss of function mutations. Given the recent difficulties on the development of Abeta targeting therapies, doubts have been casted on the original hypothesis. One possibility is that Abeta is not the sole disease-causing production of APP. We studied metabolism of APP and identified a novel cleavage that is more dominant in disease-causing APP mutants. This suggests that product of this novel cleavage might contribute to the pathogenesis of familial APP mutations. Further studies have been done to identify the interacting proteases that might be responsible for this cleavage with a novel biochemical approach. This could provide new mechanism and drug target for AD.

**Disclosures: X. Niu:** None. **X. Hou:** None. **Y. Geng:** None.

**Poster**

**742. Alzheimer's Disease and Other Dementias: APP and Metabolites: Function and Processing**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 742.12/O6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NMRC STaR 0009 2012

**Title:** Enhanced cleavage of amyloid precursor protein (APP) by overexpression of beta-secretase (Bace1) alters the normal distribution of APP in neurons

**Authors: *T.-R. HUANG**[1], J. AOW[3,2], E. H. KOO[4,5]
[1]Grad. Sch. for Integrative Sci. and Engineering, Natl. Univ. of Singapore, [2]Natl. Univ. of Singapore, Singapore, Singapore; [3]Genome Inst. of Singapore, Agency for Science, Technol. and Res. (A*STAR), Singapore, Singapore; [4]Dept Neurosciences, UCSD, La Jolla, CA; [5]Yong Loo Lin Sch. of Medicine, Natl. Univ. of Singapore, Singapore, Singapore

**Abstract:** The amyloid-β-peptide (Aβ) is centrally implicated in the pathogenesis of Alzheimer's disease (AD). Cleavage of the amyloid precursor protein (APP) by β-secretase (Bace1) yields the secreted sAPPβ fragment and the β-CTF fragment that is then cleaved by γ-secretase to generate Aβ. Bace1 exhibits cleavage activity at the trans-Golgi-network (TGN), the endosomal network, and the plasma membrane. As APP processing by Bace1 represents the initial step in Aβ production, much research has focused on determining the intracellular location(s) and regulatory pathways of the APP/Bace1 interaction. Recent studies on APP and Bace1 trafficking in primary neurons or non-neural cell lines have relied on co-transfection of APP and Bace1 constructs tagged at the C-terminus with fluorescent proteins, followed by imaging assays that quantify colocalization or Förster resonance energy transfer (FRET) between the fluorescent proteins. We set out to examine a previously reported neuronal activity-dependent APP-GFP/Bace1-mCherry interaction. Unexpectedly, co-transfection of these tagged APP and Bace1 constructs in primary hippocampal neurons resulted in a loss of surface APP levels without corresponding reduction in signal from the C-terminal fluorescent protein tag, indicating a significant decrease in full-length APP (APP-FL) levels. The decrease was blocked by a Bace1 inhibitor, confirming the role of Bace1 mediated cleavage. In addition, dual labeling of APP N- and C-termini in permeabilized APP/Bace1 co-transfected neurons revealed an anterograde distance-dependent drop in the N-/C-termini signal ratio, suggesting that the increased APP cleavage occurs at the neuronal soma. Transfection with a Bace1-uncleavable APP mutant restored the loss in cell surface APP signal. Finally, biochemical experiments showed an increase in the β-CTF/APP-FL ratio in APP/Bace1 co-transfected cells, consistent with enhanced β-secretase cleavage of APP. Taken together, our results suggest that the majority of the fluorescent protein signal distal to the neuronal soma may not arise from tagged APP-FL, but rather from tagged β-CTF cleaved earlier in the secretory pathway. Thus, care is needed in interpretating results in situations where APP is detected only with a C-terminal tag in the presence of Bace1 overexpression. In this context, it is essential to monitor the presence of accelerated APP cleavage by BaceI. In light of these observations, previous findings may need to be reinterpreted if it is unclear whether APP is present as an intact molecule or as β-secretase cleaved CTF.

**Disclosures: T. Huang:** None. **J. Aow:** None. **E.H. Koo:** None.

**Poster**

**742. Alzheimer's Disease and Other Dementias: APP and Metabolites: Function and Processing**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 742.13/O7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant NS094738
the Brain Institute of Florida Atlantic University

**Title:** The effect of APP mutations on its surface distribution and synaptic membrane cholesterol homeostasis

**Authors: *Q. ZHANG**[1,2]
[1]Pharmacol., Vanderbilt Univ., Nashville, TN; [2]Brain Inst. of Florida Atlantic Univ., Jupiter, FL

**Abstract:** Amyloid precursor protein (APP) is a type I transmembrane protein with a close tie to Alzheimer's disease (AD). Its proteolytic products, β-amyloid peptides (Aβs), are the major constituents of amyloid plaque, the hallmark of AD. Importantly, various point mutations of APP have been found in familial AD (FAD), and transgenic mice carrying those mutations exhibit some pathologies similar to AD. Most cell-based analyses FAD mutations had focused on the changes in Aβ production and aggregation, especially the more toxic Aβ42. However, more and more evidence has suggested that amyloid plaques or Aβ aggregation are not the cause of AD. So far, almost all therapeutic attempts targeting Aβ, β- or γ-secretases had failed, further questioning the amyloid cascade hypothesis. On the other hand, studies about APP's intrinsic function had led to a plethora of hypotheses. Importantly, those proposed functionalities often require APP to be in specific membrane sections such as cell surface or intracellular organelles. Moreover, α- or β-secretases and the associated nonamyloidogenic or amyloidogenic proteolysis are also sequestered in neuronal surface or intracellular membranes, testifying the significance of APP membrane distribution. Recently, we discovered an intriguing link between the plasma membrane cholesterol and APP distribution using live-cell fluorescence imaging and a dual-fluorescence APP reporter, which led us to test if and how different APP mutations affect its membrane trafficking and processing. We found that point mutations in the newly identified cholesterol-binding motif alters APP distribution in the manner similar to the reduction of surface membrane cholesterol. Furthermore, moderate decrease of surface membrane cholesterol was observed in neurons expressing such mutations. We have extended our investigation to major FAD mutations to test their impacts on the neuronal membrane cholesterol as well as APP trafficking. Together, our studies demonstrate the significance of APP transportation in addition to proteolytic processing and APP's association with the homeostatic regulation of neuronal membrane cholesterol, which can play an important role in AD etiology.

**Disclosures: Q. Zhang:** None.

**Poster**

**742. Alzheimer's Disease and Other Dementias: APP and Metabolites: Function and Processing**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 742.14/O8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Swedish Research Council
Knut and Alice Wallenberg Foundation
Alzheimerfonden

**Title:** Characterization of amyloid precursor protein-b zebrafish mutants with defects during early development and adulthood

**Authors: *R. BANOTE**[1], M. EDLING[2], T. ŞATıR[2], J. CHEBLI[2], A. ABRAMSSON[2], H. ZETTERBERG[2,3]
[1]Dept. of Psychiatry and Neuroschemistry, Univ. of Gothenburg, Goeteborg, Sweden; [2]Dept. of Psychiatry and Neurochemistry, Inst. of Neurosci. and Physiology,, Gothenburg, Sweden; [3]Dept. of Mol. Neurosci., UCL Inst. of Neurol., Queen Square, London, United Kingdom

**Abstract:** The amyloid precursor protein (APP) plays a central role in the pathophysiology of Alzheimer's disease due to its sequential proteolytic cleavages that result in the generation of β-amyloid peptide (Aβ). Although APP is expressed widely in the central nervous system, its physiological function in the development and maintenance of the central nervous system remains elusive. From our previous work, we found that the APP homologue in zebrafish, Appb, is strongly expressed in the brain and spinal cord and the partial knockdown of Appb affected motor neuron guidance and Mauthner cell development. In this study, we characterized zebrafish with a homozygous *appb* mutation generated with CRISPR/Cas9 technology. We report that the mutation in *appb* displayed perturbed cell adhesion phenotypes at blastula stage, show smaller size at early stages but appear reasonably normal at later developmental stages. Furthermore, the larvae of zebrafish at 5 dpf showed behavioral deficits and adult mutants show anxiolytic behavior in novel tank diving test. While investigating the reason, we found the altered expression of other family members *appb* mutants. All together, these results indicate that the loss of appb results in early aberrations in the development, but phenotypes are likely compensated by the altered expression of other App family members.

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**Poster**

**742. Alzheimer's Disease and Other Dementias: APP and Metabolites: Function and Processing**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 742.15/O9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** R01AG051086
R41AG053117
IADC P30 AG010133

**Title:** Role of the repressor element 1 silencing transcription factor in Alzheimer's disease

**Authors: *R. WANG**, B. MALONEY, D. LAHIRI
Indiana Univ., Indianapolis, IN

**Abstract:** Background:
Alzheimer's disease is one of leading world-wide causes of dementia. Its global prevalence constantly increases due to an aging population. Nevertheless, the underlying pathogenesis of AD is still poorly understood. Genetic, epigenetic, and environmental factors play important roles in AD etiology (Maloney and Lahiri, *Lancet Neurol*-2016). We hypothesize that AD results from misregulation of key biochemical pathways and their regulatory molecules, including transcription factors and non-coding RNAs. Misregulation of one such factor, Repressor Element Silencing Transcription Factor (REST) could lead to AD.
Methods:
Human neuroblastoma (SK-N-SH) and HeLa cell lines were transfected with siRNA against REST, as well as other siRNAs. Neuroblastoma differentiation was induced by all-*trans* retinoic acid (ATRA) treatment. Western blotting and qRT-PCR followed to determine protein, and mRNA expression levels respectively, of key gene products, REST, APP, BACE1, Neprilysin, and MAPT. In addition, RES levels were assessed in human tissue specimens from AD patients and non-AD-matched control subjects.
Results:
At least four REST bands were found by western blotting, 120kDa, 140kDa, 160kDa and above 250kDa. The latter two were positively correlated with AD progression. The specificity of REST bands were determined by REST siRNA transfection and at least two anti-REST antibodies recognizing different epitopes. The transfection of REST siRNA in differentiated neuroblastoma cell line altered brain derived neurotropic factor (BDNF) level.
Conclusion:
Our initial data indicates that REST have many post-translational modifications. Some isoforms of REST protein remains relatively stable even REST mRNA level drops significantly. While

there are two REST bands reduce with REST siRNA transfection, the knockdown of which leads to changes of BDNF precursor proteins. This might help to explain why REST level is correlated with AD progression.

**Disclosures: R. Wang:** None. **B. Maloney:** None. **D. Lahiri:** None.

**Poster**

**742. Alzheimer's Disease and Other Dementias: APP and Metabolites: Function and Processing**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 742.16/O10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant R15NS091934

**Title:** Amylin and pramlintide modulate γ-secretase activity and APP processing in lipid rafts by increasing gangliosides synthesis in TgSwDI mice

**Authors: *Y. MOUSA**[1], A. KADDOUMI[2]
[2]Drug Discovery and Develop., [1]Auburn Univ., Auburn, AL

**Abstract:** One of the major characteristics of Alzheimer's disease (AD) is the accumulation of misfolded amyloid beta (Aβ) protein. Several studies linked AD with diabetes mellitus through reported similarities between Aβ and human amylin. Accordingly, amylin and its analogue pramlintide were proposed as possible therapeutic molecules against AD; however, their effect on AD pathology is still controversial. The objectives of this study were to explore the effect of amylin and pramlintide on AD pathology and the predisposing molecular mechanisms behind the observed effects in TgSwDI mouse model. The CAA/AD mouse model TgSwDI (male, 4 months old) was used for these experiments. Mice were divided to 3 groups (n = 8/group), the control group received intraperitoneal injection of PBS as vehicle, and the amylin and pramlintide groups received 200 µg/kg/day each for 30 days. At end of treatments, behavioral studies were performed followed by brains collection. Brain homogenates and isolated lipid rafts were used to evaluate effect of treatments on Aβ-related biomarkers. Compared to control, amylin and pramlintide treatments did not improve cognitive function in TgSwDI. In addition, both peptides significantly increased soluble and insoluble Aβ in brain homogenates and reduced expression of post-synaptic marker PSD-95. Furthermore, in brain homogenates, amylin and pramlintide did not change the levels of APP, BACE1, presenilin-1, presenilin-2, and nicastrin, however, pramlintide significantly increased sAPP-β and both human peptides reduced sAPP-α levels. To explain these results, alteration in APP, BACE1, presenilin-1, presenilin-2 and nicastrin in lipid rafts was evaluated. Findings demonstrated that pramlintide and amylin significantly increased presenilin-2 and nicastrin levels, and only pramlinitide increased APP and

presenilin-1 levels in lipid rafts. Such effect was associated with increased expression of B4GALNT1, the enzyme responsible for gangliosides synthesis, and GM1. In conclusion, amylin and pramlintide increased Aβ brain levels by stimulating APP processing in the lipid rafts through activating gangliosides synthesis. Thus, these results suggest that amylin and pramlintide exacerbate AD pathology in TgSwDI mice.

**Disclosures: Y. Mousa:** None. **A. Kaddoumi:** None.

**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.01/O11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** IDPH 73282022E

**Title:** Increased miR-21 levels prevented beta-amyloid-induced tau toxicity in cultured hippocampal neurons

**Authors: *A. B. FERREIRA**, C. PARKER
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**Abstract:** MicroRNAs (miRNAs) are ~21-nucleotide-long, non-coding RNAs involved in the regulation of gene expression in a sequence-specific manner. An overall loss of miRNAs has been detected in aging brains. Furthermore, the levels of several miRNAs are significantly lower in brain samples obtained from Alzheimer's disease (AD) subjects when compared to age-matched controls. In the present study, we assessed the involvement of miR-21 in the regulation of genes associated with tau pathology in the context of AD. To analyze the effects of this miRNA on neuronal degeneration and tau-mediated toxicity induced by beta-amyloid (Aβ), we overexpressed miR-21 using a lentiviral vector in cultured hippocampal neurons obtained from embryonic day 18 (E18) pregnant rats. Neurons cultured for 3 weeks were transfected with GFP-miR-21 24 hours prior to their incubation with aggregated Aβ. Untreated cultures, GFP-miR-21 expressing neurons, and neurons cultured in the presence of Aβalone were used as controls. Neuronal survival was analyzed one day after the addition of the peptide. Post-translational tau modifications (i.e. phosphorylation and cleavage) known to induce neurodegeneration in the presence of Aβwere also analyzed. These experiments were performed by means of LIVE/DEAD Cell assays, quantitative Western blot analysis, and immunocytochemistry using specific tau antibodies in samples obtained from at least 5 independent culture preparations per experimental condition. Our results showed that increased levels of miR-21 prevented cell death in Aβ-treated cultured hippocampal neurons in a dose-dependent manner. This enhanced neuronal survival was accompanied by a significant decrease in calpain activation and, hence, in

the generation of the $tau_{45-230}$fragment. We have previously shown that this tau fragment has neurotoxic effects including neurite degeneration, synapse loss, and cell death in hippocampal neurons that develop in situ or in culture. Together, these results suggest that age-dependent downregulation of miR-21 could result in an increased susceptibility of hippocampal neurons to Aβ-induced neurodegeneration. In addition, they suggest that increased levels of miR-21 could attenuate Aβ-induced neuronal death, at least in part, by preventing calpain-mediated tau fragmentation into the $tau_{45-230}$neurotoxic fragment.

**Disclosures: A.B. Ferreira:** None. **C. Parker:** None.

**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.02/O12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Canadian Institutes of Health Research

**Title:** A role for astrocyte-derived amyloid β peptides in the degeneration of neurons in an animal model of Temporal Lobe Epilepsy

**Authors: *S. KAR**, A. KODAM, D. OURDEV, M. MAULIK, J. HARIHARAKRISHNAN, M. BANERJEE, Y. WANG
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**Abstract:** Kainic acid, an analogue of the neurotransmitter glutamate, can trigger seizures and neuronal loss in the hippocampus/limbic structures in a manner that mirrors the neuropathology of human temporal lobe epilepsy (TLE). However, mechanisms behind this neurodegeneration remain unclear. Since amyloid-β (Aβ) peptides, which are critical to the development of Alzheimer's disease, can mediate toxicity by activating glutamatergic NMDA receptors, it is likely that enhanced glutamatergic transmission that renders hippocampal neurons vulnerable to kainic acid may involve Aβ peptides. Thus, we seek to establish what role Aβ plays in kainic acid-induced toxicity. Our results show that kainic acid injection leads to loss of hippocampal neurons accompanied by increased levels/processing of amyloid precursor protein (APP), resulting in the enhanced production of Aβ-related peptides. These changes were evident in activated astrocytes, implying a role for astrocytic Aβ in the degeneration of neurons. Accordingly, we showed that treating cultured astrocytes with kainic acid leads to increased Aβ production/secretion. Additionally, we revealed that kainic acid induces neuronal loss more in neuronal/astrocyte co-cultures than pure neuronal culture, and this is attenuated by precluding Aβ production. Collectively, these results suggest a role for APP/Aβ peptides derived from activated astrocytes in the degeneration of neurons associated with TLE.

**Disclosures: S. Kar:** None. **A. Kodam:** None. **D. Ourdev:** None. **M. Maulik:** None. **J. Hariharakrishnan:** None. **M. Banerjee:** None. **Y. Wang:** None.

**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.03/O13

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** BrightFocus Foundation A2017180S
Alzheimer’s Association AARG-17-528817

**Title:** Novel role of death-associated protein kinase 1 in neuronal cell death and alzheimer's disease

**Authors: *N. KIM**[1,2], T. LEE[1,2]
[1]Beth Israel Deaconess Med. Ctr., Boston, MA; [2]Harvard Med. Sch., Boston, MA

**Abstract: Background**
While the role of apoptosis in cellular and animal models of neurodegeneration has been largely documented, its occurrence and role in human Alzheimer’s disease (AD) brain is still controversial and not fully understood. Death-associated protein kinase 1 (DAPK1) is a Ser/Thr kinase and functions as a positive mediator of apoptosis and is genetically linked to AD. We previously showed that DAPK1 expression is markedly increased in 75% of human AD brains. Moreover, we showed that DAPK1 ablation in mice decreases tau phosphorylation at multiple AD-related sites. Furthermore, we demonstrated that the levels of insoluble Aβ are significantly reduced in APP-Tg/DAPK1-KO mice brain. However, little is known about the molecular mechanisms of DAPK1 involved in neuronal cell death and pathogenesis of AD because direct DAPK1 substrates have not been identified.
**Methods**
We conducted an unbiased peptide library screening and identified novel DAPK1 substrates that are involved in neuronal cell death and AD including N-myc downstream-regulated gene 2 (NDRG2). We investigated the role of DAPK1 in regulating NDRG2-mediated neuronal cell death in AD by Aβ treatment using comprehensive approaches including gene knockout, knockdown in cell culture models and mouse, and human patient tissues. The results are presented as means ± standard error of the three independent experiments. Statistical significances were calculated by one-way analysis of variance followed by Dunnett’s multiple comparison post-hoc test.
**Results**
We demonstrated that DAPK1 interacts with NDRG2 and directly phosphorylates the Ser350 residue. Moreover, DAPK1 overexpression increases neuronal cell death through NDRG2

phosphorylation after Aβ treatment. In contrast, inhibition of DAPK1 by overexpression of a DAPK1 kinase-deficient mutant and shRNA, or by treatment with a DAPK1 inhibitor significantly decreases neuronal cell death, and abolishes NDRG2 phosphorylation in cell culture and in primary neurons. Furthermore, NDRG2-mediated cell death by DAPK1 is required for a caspase-dependent PARP cleavage. In addition, DAPK1 ablation suppresses Aβ-induced cell death in mouse brain and neuronal cell death in APP overexpression mice. Finally, levels of phosphorylated NDRG2 Ser350 and DAPK1 are significantly increased in human AD brain samples.

**Conclusions**

Our results indicate that DAPK1 is a critical regulator of NDRG2 both in neuronal cell death and during the progression of AD. Our studies also suggest that DAPK1 represents a potential novel therapeutic approach for treating AD.

**Disclosures: N. Kim:** None. **T. Lee:** None.

**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.04/O14

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** VIEP-BUAP DIFA-NAT17I
VIEP-BUAP MAMG-NAT17-I
VIEP-BUAP TRMS-NAT17-I
PRODEP (511-6/17-8017, PTC 550)
PRODEP (511-6/17-8017, PTC 552)
PAPIIT-UNAM (IN214117)

**Title:** Metabolic syndrome exacerbates the recognition memory impairment and oxidative-inflammatory response in rats with an intrahippocampal injection of amyloid beta 1-42

**Authors: *A. D. DIAZ**[1], S. TREVIÑO[2], C. MORAN[3], J. GUEVARA[4], B. VENEGAS MENESES[5], M. MUNOZ ARENAS[6]
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**Abstract:** An important worldwide health problem as the result of current lifestyle is metabolic syndrome (MS). It has been shown that MS induced by a high caloric diet (HCD) in rats, produces cognitive deterioration in the recognition of novel objects test (NORT) and decreases

synaptic connections and dendritic order in the hippocampus. However, it is unknown whether MS induced by an HCD participates in the cognitive process observed with the injection of $A\beta_{1-42}$ into hippocampus of rats as a model of Alzheimer disease (AD). The induction of MS in rats produces a deterioration in NORT, however, rats with MS injected with $A\beta_{1-42}$, show a major deterioration in the cognitive process. This event could be explained by the increment in the oxidative stress in both cases studied (MS and $A\beta_{1-42}$): in together, the hippocampus and temporal cortex produce an enhancer effect. In the same way, we observed an increment in interleukin 1B, TNFa and GFAP, indicative of an exacerbated inflammatory processes by the combination of MS and $A\beta_{1-42}$. We can conclude that MS might play a key role in the apparition and developed of cognitive disorders, including AD. We propose that metabolic theory is important to explain the apparition of cognitive diseases.

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**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.05/O15

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant 1R01AG042890 to GT

**Title:** Modulation of neurotoxic amyloid beta oligomers: A role for hsp60

**Authors: *C. MARINO**[1], F. CAPPELLO[2], G. TAGLIALATELA[1]
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**Abstract:** Alzheimer’s disease (AD) is the most common form of dementia worldwide, affecting more than 40 million individuals. Being clinically and histologically well characterized, the design of disease-modifying therapies has been unsuccessful due to the number of factors leading to AD pathology. Among all the hypotheses suggesting possible mechanisms involved in AD pathology, the pro-amyloidogenic processing of amyloid precursor protein (APP), upstream of the amyloid beta peptide (Aβ) formation and subsequent neurotoxic oligomerization (Aβo), remains one of the most supported theories. Further, the impairment of the protein quality control machinery due to aging and aberrant accumulation of misfolded proteins during AD progression is another alteration characterizing the disease. Particularly, evidence suggests that the age-related impairments of chaperones, a class of modulatory proteins involved in the protein quality control of the cell, contributes to the neurotoxicity induced by Aβo, but the underlying mechanism remains unresolved. In the present work, we characterized the effect of the

mitochondrial chaperone Hsp60 in protecting against toxic Aβo conformations using both cell free, *in vitro and ex vivo* approaches. Specifically, the Chinese Hamster Ovary (CHO) cell line overexpressing human APP751 variant of APP (7PA2 cell line), a model of human Aβo production, was used along with immunocytochemistry, ELISA and western blotting techniques to investigate the effect of Hsp60 overexpression on Aβ production and release in the extracellular compartment. Further, we investigated changes in toxicity of toxic Aβo both *in vitro* by testing changes in cytotoxicity on neuroblastoma cell line and *ex vivo* by testing changes in long term potentiation on hippocampal brain slices. Finally, we used a cell free approach to characterize the effect on Hsp60 on toxic Aβ conformations by testing changes in the biophysical properties of treated oligomers using immunoprecipitation, proteinase K assay, western blotting and spectroscopy techniques. Our data suggest that Hsp60 has a direct effect on toxicity of Aβo resulting in a reduction of cytotoxicity and a rescue of synaptic plasticity, thus proposing Hsp60 as a potential candidate for future therapies targeting Aβo neurotoxicity.

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**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.06/O16

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** DFG Grant RA68993

**Title:** The gaseous anaesthetic xenon, a weak NMDA receptor antagonist, shows neuroprotective properties on ß-amyloid-mediated synaptotoxic effects

**Authors: *C. KNOLL**[1], K. HADIAN[2], K. SCHORPP[2], M. BÜRGE[3], G. RAMMES[4]
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**Abstract:** Volatile and intravenous anaesthetics are routinely used for general anaesthesia in humans including patients suffering from Alzheimer's disease (AD). Several studies suggest that commonly used volatile anaesthetics such as isoflurane and sevoflurane may induce changes consistent with AD neuropathogenesis, e.g., increased amyloid beta protein (Aß) aggregation resulting in an increased synaptotoxicity. In contrast to that, the gaseous anaesthetic xenon has frequently been reported to be neuroprotective against cerebral damage. In our study, we investigated the interaction of equipotent concentrations of xenon, isoflurane and sevoflurane with different Aß-isoforms regarding Aß aggregation, synaptic activity and autophagy. Time-resolved fluorescence resonance energy transfer (TR-FRET) and silver staining revealed that

isoflurane and sevoflurane did not interfere with Aß aggregation whereas xenon even decreased the propensity for Aß to aggregate. Xenon partially restored $A\beta_{1-42}$-induced synaptotoxic effects measured by LTP. In the presence of $A\beta_{1-42}$ and $A\beta_{1-40}$, anaesthetic-induced reduction of neuronal activity propagation in the tri-synaptic hippocampal circuit, monitored by voltage-sensitive dye imaging (VSDI), completely recovered after xenon, but not isoflurane and sevoflurane removal. Autophagy, a catabolic process to maintain cellular homeostasis, which might be closely associated with the pathophysiology of AD, was not affected by either single drug or the combined application of anaesthetics with Aß. Our presented results show that commonly used anaesthetics may interfere with Aß-dependent pathophysiology of AD. Interestingly, in contrast to other volatile anaesthetics, xenon showed beneficial effects on Aß aggregation and on synaptic activity when experimental conditions resemble the clinical situation with patients suffering from AD and requiring anaesthesia for surgery. Our results point to neuroprotective properties of xenon, which might be a meaningful alternative for anaesthesia in AD patients.

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**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.07/P1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH R01 AG044263
Fund for Medical Discovery (FMD) from Massachusetts General Hospital

**Title:** Mitochondrial calcium dysregulation *in vivo* in a mouse model of Alzheimer's disease

**Authors: *M. CALVO RODRIGUEZ**[1], S. HOU[1], E. HUDRY[1], A. SNYDER[1], Z. FAN[1], M. GARCIA ALLOZA[2], A. SERRANO-POZO[1], B. J. BACSKAI[1]
[1]Dept. of Neurol. Alzheimer Res. Unit, Mass. Gen. Hosp. and Harvard Med. Sch., Boston, MA; [2]Div. of Physiology, Sch. of Med., Cadiz, Spain

**Abstract:** Alzheimer’s disease (AD) is the most common neurodegenerative disorder and cause of dementia. Pathologically, AD is characterized by the deposition of the amyloid beta (Aβ) peptide in extracellular senile plaques, and the microtubule-associated protein tau in intraneuronal neurofibrillary tangles. However, how these pathological hallmarks relate to the neuronal dysfunction and death underlying cognitive decline remains unclear. Aβ oligomers (Aβo) surrounding plaques, rather than amyloid plaques themselves, are thought to be the neurotoxic species of Aβ and to be upstream of tau aggregation. Among the downstream

neurotoxic effects of Aβo, calcium dyshomeostasis resulting in $Ca^{2+}$ overload in the cytosol of neurons and neurites, and mitochondrial dysfunction resulting in oxidative stress have been proposed as early pathogenic events according to the amyloid cascade hypothesis. Mitochondria buffer cytosolic $Ca^{2+}$ rises in physiological conditions, but whether there are alterations in mitochondrial $Ca^{2+}$ contributing to a more general cytosolic $Ca^{2+}$ dyshomeostasis in AD remains unknown. We hypothesized that soluble Aβ oligomers may lead to mitochondrial $Ca^{2+}$ overload in neurons.
To test this hypothesis, we developed and validated in vitro and in vivo a FRET-based ratiometric $Ca^{2+}$ indicator Yellow Cameleon 3.6 targeted to neuronal mitochondria (hsyn.2mtYC3.6). Using this tool and intravital multiphoton imaging, we measured $Ca^{2+}$ levels in neuronal mitochondria in the AD transgenic mouse model APP/PS1, which develops amyloid plaques similar to human AD as early as 4 month of age. Quantitative $Ca^{2+}$ imaging revealed an increase in the mitochondrial $Ca^{2+}$ concentration in APP/PS1 mice, compared to wild-type mice. Moreover, direct topical application of Aβo-enriched transgenic conditioned media (TgCM, obtained from 14 DIV neurons prepared from Tg2576 mouse embryos) to the brain of wild-type C57Bl/6 mice increased the $Ca^{2+}$ concentration in individual mitochondria, whereas conditioned media obtained from the wild-type littermates neurons (WtCM) or Aβo-depleted conditioned media had no effect on mitochondrial $Ca^{2+}$ levels. Taken together, these data support the idea that there is a mitochondrial $Ca^{2+}$ dyshomeostasis with $Ca^{2+}$overload in AD, and that it is, at least partially, due to soluble Aβo.

**Disclosures: M. Calvo Rodriguez:** None. **S. Hou:** None. **E. Hudry:** None. **A. Snyder:** None. **Z. Fan:** None. **M. Garcia Alloza:** None. **A. Serrano-Pozo:** None. **B.J. Bacskai:** None.

**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.08/P2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant RO1AG048993
NIH Grant RO1AG042819
NIH Grant P20GM103442

**Title:** Comparing salivary AB and oral microbiome in alzheimer's disease mouse models

**Authors: *A. M. FLODEN**, M. SOHRABI, S. NOOKALA, G. D. MANOCHA, C. K. COMBS
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**Abstract:** Beta amyloid (Aβ) peptide containing plaque aggregations in the brain are a hallmark of Alzheimer’s Disease (AD). However, Aβ is produced by cell types outside of the brain

suggesting that the peptide may serve a broad physiologic purpose. It has been reported that elevated levels of Aβ can be found in the saliva of AD patients but the source and function of this salivary Aβ is not fully understood. Based upon our prior work documenting expression of amyloid precursor protein (APP) in intestinal epithelium we hypothesized that salivary epithelium might also express APP and be a source of Aβ. To begin testing this idea, we compared C57BL/6 wild type mice to two mouse models of AD, littermate control APP/PS1 mice and the APP (NL-G-F) mouse line. At 12-15 months of age, salivary secretion was stimulated from all three lines and compared to salivary gland, serum, and brain Aβ levels to determine whether a specific relationship existed between saliva, blood, and brain in either line. As expected, both APP/PS1 and APP (NL-G-F) lines demonstrated robust brain increases in Aβ 1-40/42 with lower levels of Aβ 1-40 in APP (NL-G-F). Both APP/PS1 and APP (NL-G-F) mice also showed an increase in Aβ 1-42 levels in serum with higher Aβ 1-40 levels in APP/PS1 compared to APP (NL-G-F) mice. On the other hand, significantly increased levels of Aβ 1-42 were quantified from saliva of only APP (NL-G-F) mice. No significant differences in total volume or flow rate were observed. To assess potential effects of salivary composition on oral microbiome, saliva was plated from all three strains compared to APP knockout mice. Total CFUs were not different between males across all strains although APP knockout male mice had increased numbers of tooth lesions. Female APP knockout mice had significantly lower CFUs compared to wild type female mice with no significant increase in tooth lesions, however. These data support the idea that a ratiometric relationship exists between saliva, blood, and brain Aβ levels and salivary composition may differ during disease state. In addition, APP expression or its metabolites may influence oral microbiome as well as tooth decay. AD mouse models may be useful for exploring the diagnostic potential of this relationship as well as the source and function of salivary Aβ.

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**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.09/P3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Galectin-3 haploinsufficiency reduces amyloid-beta oligomerization and amyloid plaque in APP/PS1 mice

**Authors: *E. H. LEE**[1], C.-C. TAO[1], K.-M. CHENG[2], Y.-L. MA[1]
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**Abstract:** Amyloid-β (Aβ) oligomers are believed as the major component that contributes to synaptic deficits, cognitive impairment and initiates the cascade for the pathology of Alzheimer's disease (AD). Galectin-3 (Gal-3) is a member of the galectin protein family that promotes inflammatory responses. It also enhances cancer cell homotypic aggregation. Here we examined the role and mechanism of Gal-3 in Aβ oligomerization and amyloid plaque formation. Galectin-3 knockout (KO) mice, various genotypes of APP/PS1;Gal-3 mice and brain tissues from AD patients were used. Results show that Aβ oligomerization is reduced in Gal-3 KO mice injected with Aβ whereas overexpression of Gal-3 enhances Aβ oligomerization in the hippocampus of Aβ-injected mice. There is an age-dependent increase in Gal-3 expression that parallels with the amount of endogenous Aβ oligomerization in APP/PS1 mice. Moreover, Aβ oligomerization and amyloid plaque are reduced in APP/PS1;Gal-$3^{+/-}$ mice compared with APP/PS1;WT mice and the cognitive performance of APP/PS1;Gal-$3^{+/-}$ mice is also better. Galectin-3 is primarily expressed in microglia cells and Gal-3 is preferentially associated with Aβ monomers. Immunohistochemical result show that Gal-3 distribution overlaps with endogenous Aβ and amyloid plaque to some extent in APP/PS1 mice. Further, β-secretase activity is decreased but neprilysin expression is increased in Gal-3 KO mice. These explain why Aβ oligomerization is reduced in Gal-3 KO mice injected with Aβ. Consistent with the observation in mice, Gal-3 expression is increased in the frontal lobe of AD patients and it parallels with Aβ oligomerization. Because Gal-3 expression is dramatically increased as early as 3 months of age in APP/PS1 mice and anti-Aβ oligomerization is believed to protect against Aβ toxicity, Gal-3 could be considered as a novel therapeutic target against AD.

**Disclosures: E.H. Lee:** None. **C. Tao:** None. **K. Cheng:** None. **Y. Ma:** None.

**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.10/P4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Oligodendrocyte and myelin alterations in Alzheimer's disease

**Authors: *S. DWYER**, J. Y. K. LEUNG, M. KIRKCALDIE, J. C. VICKERS, A. E. KING
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**Abstract:** Previous and current Alzheimer's disease research has a strong focus on the role of neurons and amyloid-beta peptides in the progression of Alzheimer's disease. Recent research has implicated a role for oligodendrocytes in the progression of the disease, demonstrated by focal demyelination at plaque sites and alterations to oligodendrocyte populations in animal models of early Alzheimer's disease. The main aim of this study is to understand the effect of amyloid-beta on oligodendrocyte development or health, which may have downstream effects on

myelin and contribute to the degeneration of neurons. To help us understand this, we have examined the effect of extracellular amyloid-beta on oligodendrocyte development *in-vitro.* Pure oligodendrocyte precursor cell (OPC) cultures were derived from mixed glial cultures from Sprague Dawley neonatal rats at postnatal day 1-3. OPCs were induced to mature into myelin-forming oligodendrocytes over 5 days *in-vitro* in the presence or absence of amyloid-beta. Tracing of oligodendrocyte morphology demonstrated significantly reduced branching, suggesting that oligodendrocytes exposed to 5uM amyloid-beta 1-40 and 1-42 are less mature when compared to controls. However, immunocytochemical and trace analysis demonstrated that 1uM amyloid-beta 1-40 as there was a statistically significant increase in the number of MBP-positive oligodendrocytes and branches (n=3 separate cultures per treatment, p<0.05). This suggests that low concentrations of amyloid-beta *in*-vitro plays a role in inducing OPC differentiation indicated by an increased number of mature oligodendrocytes. To complement *in-vitro* findings, we are currently investigating the effect of amyloid-beta on myelination during a learning task as well as the effect on OPC maturation in an animal model of Alzheimer's disease. By studying a model of induced myelination, we hope to correlate the amyloid-beta present in these animals and observe differences in their myelination profiles and oligodendrocyte populations to further support our hypothesis that oligodendrocytes have a key role in Alzheimer's disease progression.

**Disclosures: S. Dwyer:** None. **J.Y.K. Leung:** None. **M. Kirkcaldie:** None. **J.C. Vickers:** None. **A.E. King:** None.

**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.11/P5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Alzheimer's Association SAGA Award
Knight ADRC at Washington University

**Title:** Effects of inhibiting glucocorticoid receptor dimerization on beta amyloid in male and female mice

**Authors: *C. M. YUEDE**[1], C. E. WALLACE[2], H. M. EDWARDS[2], H. L. RIDENBARK[2], T. A. DAVIS[2], J. R. CIRRITO[2]
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**Abstract:** Results from both human and animal studies over the last decade have identified a clear increase in the rate of Alzheimer's disease (AD) in women. Sex differences in the

prevalence or severity of many diseases are well recognized. A common underlying feature of disorders more prevalent in females is an association with stress, such as in anxiety and depression. Stress increases glucocorticoids (GC) in the brain, and the link between GCs and AD has been confirmed by several studies. We previously found that acute stress rapidly increases levels of Aβ in the mouse brain (Kang et al., 2007). GCs function through a nuclear GC receptor (GR) that acts as a dimer to facilitate transactivation or as a monomer to repress transcription (transrepression). The sex-related differences in transactivation versus transrepression remain unclear and the influence of either pathway on AD pathology has not been defined. Using microdialysis, Aβ levels in the interstitial fluid (ISF) of the hippocampus were measured in male and female APP/PS1 mice (3-4 months old). Samples were collected every hour for a baseline period, 3-hour restraint stress, and 12-hour post stress period. To evaluate the effects of blocking the transactivation arm of GR signaling through GR dimerization, we crossed APP/PS1 mice with the glucocorticoid receptor dimerization deficient mouse model (GRdim), to create GRdim APP mice. We also studied the effects of pharmacologically blocking GR dimerization using Compound A, administered via reverse microdialysis before restraint stress. We observed a significant difference between male and female mice in the percent increase in ISF Aβ during acute stress, with female mice having a much greater and sustained increase in ISF Aβ compared to males. ISF Aβ levels in female GRdim APP mice did not rise dramatically during acute stress, and stayed near baseline during the post stress period. Compound A completely blocked the increase in ISF Aβ induced by restraint stress in female mice. These results suggest that females are more sensitive to stress-induced increases in Aβ, and that acute stress increases Aβ in female mice through a GR dimerization dependent mechanism.

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**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

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**Topic:** C.02. Alzheimer's Disease and Other Dementias

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**Title:** BDNF receptor cleavage in Alzheimer’s disease: Quantification in human brain samples and molecular consequences

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**Abstract:** Alzheimer's disease (AD) is the most common form of dementia worldwide and the accumulation of amyloid-β (Aβ) peptide in the brain is considered the main hallmark of this disease. In AD, Brain-derived neurotrophic factor (BDNF) signalling is seriously impaired, compromising neuronal survival, differentiation and plasticity. Actually, in AD brain patients there are decreased levels of both BDNF and its receptor (TrkB-FL) and upregulated levels of TrkB truncated isoforms (negative modulators of BDNF signalling). Recently, we described that Aβ peptide accumulation leads to calpain overactivation and subsequent TrkB-FL cleavage, decreasing its levels and forming a membrane-bound truncated receptor (TrkB-T') and an intracellular fragment (TrkB-ICD).In this work we studied TrkB-ICD dynamics in neuronal cultures and we evaluated TrkB-FL cleavage in *post-mortem* human brain samples with varying degree of AD-related neurofibrillary pathology. The use of human brain samples for this study was approved by the Ethics Committee of Kuopio University Hospital, Finnish National Supervisory Authority, University of Eastern Finland and Finnish Ministry of Social Affairs and Health. Subjects' consent was obtained according to Declaration of Helsinki. Our data show that, in transfected primary neurons and in a neuroglioma cell line, TrkB-ICD I) is a stable fragment (half-life time: 8h), II) is translocated to nucleus overtime and III) promotes the phosphorylation of somal, axonal and nuclear proteins. In human brain samples, through proteomic analysis, we detected calpains activation, a decrease of TrkB-FL levels and an increase of TrkB-ICD levels in relation to increasing AD-related neurofibrillary pathology. Importantly, TrkB-FL transcript levels are not changed over AD progression, supporting the hypothesis that TrkB-FL decreased levels could be directly attributed to calpain activation. Taken together, these results shed light on the mechanism underlying the AD neuronal vulnerability due to impairment on the major endogenous neuroprotective pathway, BDNF/TrkB-FL system.

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**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.13/P7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** National Natural Science Foundation of China(Grant No.81171206)

**Title:** Presenilin1 and Presenilin1 mutants alter the distribution and activity of BACE1 through acting on transport process

**Authors: N. LI**, Y. QIU, *H. QING
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**Abstract:** Alzheimer's disease (AD) is a progressive cognitive disorder and the mainly characterized by the degeneration of central nervous system. One of the hallmarks of AD is excessive production of Amyloid β-peptide (Aβ). Aβ is derived from the β-amyloid precursor protein (APP) through sequential cleavages by β-(BACE1) and γ-secretase. BACE1 is the key to the pathogenic process of AD. Presenilin1(PS1) is the active center of the γ-secretase, participating in the APP hydrolysis process. Previous studies show that PS1 can co-localize with the BACE1. The deficiency of the PS1 can not only inhibit the activity of the BACE1, but also decreases the expression of C-terminal products. To investigate how the PS1 affect the activity of BACE1, we studied the transport process of BACE1with PS1. We used sucrose density gradient centrifugation to separate organelles and tested the distribution of BACE1 in different organelles. We found that the transfection of PS1 results in an increased BACE1 level in endoplasmic reticulum (ER), which indicates that PS1 can affect the transportation of BACE 1. So, it proved that PS1 can change the distribution of BACE1 in subcellular structure through extension of the dwelling time in ER. Through immunofluorescene and Time-lapse results its was found that BACE1 distributed evenly in cytoplasm, co-localizing with ER, Golgi, and early endosome slightly without transfecting PS1. On the contrary, when transfecting PS1, BACE1 migrated to periphery of nucleus distinctly, co-localizing with Calnexin in high amount, indicating that PS1 can force BACE1 to migrate to ER. In the meantime, the transfection of PS1 increases co-localization of BACE1 with Syn-6 and EEA1, which shows PS1 improved the maturity of BACE1 in Golgi. Because BACE1 interacts with APP in early endosome, the transfection of PS1 promoted BACE1 binding with APP to perform the functions. The results above manifest that PS1 can extend the dwelling time of BACE1 in ER and improve the distribution of the BACE1 in ER and Golgi. We also tested the effect of PS1 mutations on BACE1 transportion. Results indicated that D257A mutant has no effect on BACE1 transportation; and S170F mutant facilitates the transfer and the maturity of BACE1 from ER to golgi as compared to PS1 wildtype. In conclusion, PS1 affects the distribution and activity of BACE1 through acting as the synthesis and maturity of BACE1 precursor.

**Disclosures: N. Li:** None. **Y. Qiu:** None. **H. Qing:** None.

**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.14/P8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** FONDEF PFB/2007
CONICYT pre-doctoral fellowship N°21151116

**Title:** $A\beta_{42}$ oligomers deregulate AMPA receptor membrane trafficking

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**Abstract:** Aβ oligomers are the main components of senile plaques in the brain of Alzheimer's disease patients. Interestingly, a great body of evidence suggests that Aβ oligomer accumulation and not the amount or size of senile plaques, have a direct positive correlation with the onset of Alzheimer's disease. Moreover, it has been found that Aβ oligomers cause different deleterious effects over synaptic architecture, like loss of dendritic spines and decrease in CaMKII clusters. Overall, Aβ oligomers affect excitatory synapses causing failures in physiological synaptic plasticity (i.e., long-term potentiation), which is consistent with a malfunction in AMPA receptor dynamics. Using super resolution microscopy on living hippocampal neurons, we aimed to understand the dynamic of endogenous GluA2-containing AMPA receptors in response to $A\beta_{42}$ oligomers. We discovered that short-term (15-30 min) treatment with 1 μM $A\beta_{42}$ oligomers does not affect notably the dynamics of plasma membrane AMPA receptors. Higher concentration of 5 μM $A\beta_{42}$ oligomers, known to cause endocytosis of AMPA receptors, increase the fraction of immobile AMPA receptors at synaptic sites as fast as 15 min after treatment, without affecting those receptors localized in extrasynaptic sites. Finally, we wanted to test a low but longer application, using 0.5 μM $A\beta_{42}$ oligomers for a period of 2 hours. Interestingly, we observed an opposite effect, GluA2-containing AMPA receptors located at the plasma membrane became more mobile. Altogether, these data suggests a two-step process in which $A\beta_{42}$ oligomers trigger first, unbinding of AMPA receptors from synaptic sites followed by endocytosis of mobile receptors, thus overall decreasing the fraction of mobile receptors.

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**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.15/P9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Metallothionein induction prevents cognitive decline caused by $Zn^{2+}$ released from amyloid-$\beta_{1-42}$ in dentate granule cells

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**Abstract:** The basal levels of extracellular $Zn^{2+}$ are in the range of low nanomolar concentrations (~10 nM) in the hippocampus and probably increased age-dependently. In the dentate gyrus, non-zincergic perforant pathway innervates dentate granule cells. Nonetheless, the rapid excess influx of extracellular $Zn^{2+}$ into dentate granule cells, which more readily occurs in aged rats, is a cause of aged-related cognitive decline. Amyloid-β (Aβ) is a causative candidate for the pathogenesis of Alzheimer's disease (AD). The formation of Zn-$A\beta_{1-42}$ in the extracellular compartment rapidly increases both intracellular $Zn^{2+}$ and $A\beta_{1-42}$ in dentate granule cells of normal young rats, followed by $A\beta_{1-42}$-induced cognitive decline that is due to increase in intracellular $Zn^{2+}$ released from $A\beta_{1-42}$. Metallothioneins (MTs) are small, cysteine-rich proteins and bind zinc and copper. They function as metal ion regulation and detoxification. The basal level of intracellular $Zn^{2+}$ is estimated to be ~0.1 nM in hippocampal neurons. MTs have $Zn^{2+}$-binding sites in hippocampal neurons and can capture $Zn^{2+}$ released from $A\beta_{1-42}$. MTs bind four $Zn^{2+}$ with high affinity (Kd, ~1 pM) and bind another two $Zn^{2+}$ with lower affinity. MTs bind the seventh $Zn^{2+}$ with nanomolar affinity (Kd, ~1 nM). Here we report that hippocampal MT induction defends cognitive decline, which was induced by $A\beta_{1-42}$-mediated excess $Zn^{2+}$ in dentate granule cells. Excess increase in intracellular $Zn^{2+}$, which was induced by local injection of $A\beta_{1-42}$ into the dentate granule cell layer, attenuated in vivo LTP at perforant pathway-dentate granule cell synapses, while the attenuation was rescued by preinjection of MT inducers, i.e., zinc, cadmium, and corticosterone, into the same region. Intraperitoneal injection of dexamethasone, which increased hippocampal MT proteins and blocked $A\beta_{1-42}$-mediated $Zn^{2+}$ uptake, but not $A\beta_{1-42}$ uptake, into dentate granule cells, also rescued $A\beta_{1-42}$-induced impairment of memory via attenuated LTP. The present study indicates that hippocampal MT induction blocks rapid excess increase in intracellular $Zn^{2+}$ in dentate granule cells, which originates in $Zn^{2+}$ released from $A\beta_{1-42}$, followed by rescuing $A\beta_{1-42}$-induced cognitive decline. Furthermore, LTP was vulnerable to $A\beta_{1-42}$ in the aged dentate gyrus, consistent with enhanced $A\beta_{1-42}$-mediated $Zn^{2+}$ uptake into aged dentate granule cells, suggesting that $A\beta_{1-42}$-induced cognitive decline, which is caused by excess intracellular $Zn^{2+}$, can more frequently occur along with

aging. Hippocampal MT induction is an attractive defense strategy against $A\beta_{1-42}$-induced cognitive decline.

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**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.16/P10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant P50 AG005681
NIH Grant P01 NS074969

**Title:** Rapid, real-time and sensitive measurement of *in vivo* amyloid-beta levels and half-life using novel micro-immunoelectrode technology

**Authors: *H. EDWARDS**, C. YUEDE, J. CIRRITO
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**Abstract:** Alzheimer’s disease (AD) is a neurodegenerative disease that is hallmarked by the accumulation of amyloid-beta (Aβ) peptide into oligomers and plaques. Soluble oligomers, particularly within the brain extracellular, or interstitial, fluid (ISF), are thought to be one of the highly toxic species of the peptide. We have developed a novel electrochemical technique to detect and measure these oligomers using a carbon fiber micro-immunoelectrode (MIE). The MIE uses amperometry to oxidize tyrosines within the protein of interest. Specificity for a protein target is provided by covalently attaching an antibody to the surface of the carbon fiber. The oxidation of tyrosine releases an electron which the carbon fiber detects as current; the amount of current detected is proportional to the amount of tyrosine present. The tip of the carbon fiber MIE is coated with an oligomer-selective antibody (A11), which provides specificity to oligomeric forms over monomeric Aβ. Additionally, we bathe the MIE in a 1% BSA solution to block all space not occupied by antibody. The electrodes are sensitive to detect Aβ oligomers (AβO) down to 0.2 fg/ml. We have validated the species of Aβ detected in vitro using size excluded human brain homogenates and can detect concentrations of AβO in human cerebral spinal fluid (CSF) samples. Additionally, we have used the MIE to monitor the minute to minute changes in oligomer kinetics in the brains of living mice. Using the AβO MIE in the APP/PS1 transgenic mouse model of AD, we measure rapid increases in AβO levels following injection of picrotoxin, a GABA-A receptor antagonist. The kinetics of AβO increases are distinct from Aβ40 monomer. Additionally, we detect decreased AβO levels following

administration of a γ-secretase inhibitor, which enables us to calculate the in vivo elimination half-life of AβO from the brain ISF in a living mouse.

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**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.17/P11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Amyloid β induces oxidative neuronal deaths in mouse cortical cultures in a concentration-dependent manner via NADPH oxidase- and/or mitochondria-dependent ROS production

**Authors: *J.-K. KIM**[1], S. HWANG[2]
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**Abstract:** Amyloid β peptide (Aβ) is a main component of senile plaques in Alzheimer's disease and is known as a major pathogenic factor of the disease. Oxidative stress by the generation of reactive oxygen species (ROS) is known as one of the mechanisms of Aβ-induced neuronal death. Currently, NADPH oxidase (NOX) and mitochondria are considered as primary sources of ROS induced by Aβ. However the contribution of NOX and mitochondria to Aβ-induced ROS generation has not been well defined. Present study was performed to delineate the relative involvement of NOX and mitochondria to Aβ-induced oxidative neuronal death in mouse mixed cortical cultures. Intracellular and mitochondrial ROS were monitored employing dihydroethidium (DHE) and dihydrorhodamine 123 (DHR) respectively. Cell death was assessed by measuring lactate dehydrogenase efflux to bathing media 24 hr after exposure to $A\beta_{25\text{-}35}$, a fragment of Aβ with an equivalent neurotoxic effect. Treatment with 10-20 μM $A\beta_{25\text{-}35}$ induced significant DHE fluorescent signals but failed to induce any DHR fluorescent signals. Treatment with 20 μM $A\beta_{25\text{-}35}$ produced about 25% neuronal death. Furthermore, treatment with apocynin, a NOX inhibitor, markedly attenuated both the 20μM $A\beta_{25\text{-}35}$-induced DHE fluorescent signals and neuronal death, but mitotempo, a mitochondria-targeted antioxidant, did not affect both the DHE fluorescent signals and the neuronal death. While increasing the concentration of $A\beta_{25\text{-}35}$ to 40 μM induced significant fluorescent signals of both DHE and DHR, treatment with 40 μM $A\beta_{25\text{-}35}$ produced about 40% neuronal death. Treatment with mitotempo markedly attenuated both the DHR fluorescent signals and the neuronal death. The findings indicate that the concentration of $A\beta_{25\text{-}35}$ has an influence on the involvement of mitochondria for ROS production in Aβ neurotoxicity.

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**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.18/P12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Characterization of molecular interaction between exosomal ceramide and beta amyloid, revealing a role of ceramide in Abeta aggregation and toxicity

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**Abstract:** Alzheimer’s Disease (AD) is characterized by progressive neuronal death, accumulation of neurotoxic and gliotoxic beta-amyloid peptides (Abeta), amyloid plaques, and neurofibrillary tau tangles. The exact mechanism of amyloid aggregation is still unclear. We have shown that astrocyte-derived exosomes contribute to AD progression by seeding amyloid plaques, although the exact mechanism of exosome-induced Abeta aggregation is unknown. We have also shown that these exosomes contain PAR-4, a protein sensitizing cells to ceramide-induced apoptosis. Proximity Ligation Assay showed that ceramide in the exosomal membrane forms a complex with Abeta. Treatment of neuronal cultures with Abeta42-associated exosomes (Abeta/Exos) showed increased neuronal structural damage and death as compared to Abeta42 oligomers or exosomes alone. Using immunocytochemistry, we detected intracellular labeling for ceramide and PAR-4 in neurons exposed to Abeta42/Exos suggesting transfer of pro-apoptotic ceramide and PAR-4 into neurons. To understand interaction of Abeta with ceramide and neuronal uptake of Abeta42/Exos we visualize binding to and uptake of these complexes using super-resolution fluorescence microscopy. Using an antibody developed in our laboratory, ceramides were labeled by immunocytochemistry to visualize their distribution on the plasma membrane of different cells with virtually molecular resolution by direct stochastic optical reconstruction microscopy (dSTORM). Super-resolution images showed that 50-60 % of all membrane ceramides are located in ceramide-rich platforms (CRPs) with a size of about 75 nm that contained at least 20 ceramide molecules. CRPs in exosomes are hypothesized to mediate binding to Abeta to initiate formation of Abeta/Exos and potentially, uptake into neurons. Exploiting super-resolution microscopy might give more insight into the precise molecular interaction between exosomes and Aβ and reveal the role of ceramide in Aβ aggregation and subsequently neuronal degeneration.

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**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.19/P13

**Topic:** C.02. Alzheimer's Disease and Other Dementias

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**Title:** Metabolic syndrome plus injection of amyloid-β 25-35 peptide into hippocampus not impairs spatial memory and decreased microgliosis in cholinergic regions

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**Abstract:** Metabolic syndrome (MetS) can lead neuroinflammation and cognitive impairment. The injection of Amyloid-$\beta_{25-35}$ peptide ($A\beta_{25-35}$) into cognitive regions induces oxidative stress, neuroinflammation, neuronal death and impairs spatial memory. Particularly, cholinergic nucleus in basal forebrain trigger a neuroinflammatory response in presence of $A\beta_{25-35}$, but we do not know how basal forebrain response in presence of MetS+$A\beta_{25-35}$ when $A\beta_{25-35}$ is injected in an innervated cholinergic region as hippocampus (Hp). The aim of our study was evaluated the spatial memory, microglia and astrocyte response in cholinergic nucleus of MetS plus $A\beta_{25-35}$ hippocampal injured rats. MetS group was obtained by consumption of 20% sucrose in drinking water meanwhile control group (C) received tap water. At eight weeks of treatment, MetS model was evaluated. After, all rats were yield to stereotaxic surgery to the injection of vehicle or $A\beta_{25-35}$ [100µM] into CA1 subfield of Hp, (coordinates; AP: -4.0, L: ±2.3, P: -2.6). The experimental groups were C+Vehicle, MetS+Vehicle, C+$A\beta_{25-35}$ and MetS+$A\beta_{25-35}$. At 15th day post-surgery, experimental groups were tested for spatial learning in the Morris water maze (MWM) and 5 days later, were memory tested. We obtained the brains to assess the immunoreactivity of glial fibrillar acid protein (GFAP) and the ionized calcium binding adaptor molecule 1 (Iba-1) in medial septal nucleus (MS), the vertical nucleus of diagonal band (VDB) and the horizontal limb of diagonal band (HDB). We found that MetS+$A\beta_{25-35}$ not modified spatial learning and memory in the MWM compared to the C+Vehicle. Regarding to microglia and astrocyte immunoreactivity, C+$A\beta_{25-35}$ exhibited increases of Iba-1 stained area in MS (16%), HDB (45%) and VDB (30%) meanwhile GFAP immunoreactivity did not modify in the same subfields

compared to the C+Vehicle. MetS+$A\beta_{25-35}$ reduced Iba-1 stained area in MS (20%), VDB (27%) and HDB (31%) and GFAP staned area did not modify in the same subfields compared to the C+$A\beta_{25-35}$. We found that the injection of $A\beta_{25-35}$ [100µM] into CA1subfield of Hp in MetS model, not impair spatial learning and memory tested in MWM, decrease the microglia reactivity in cholinergic nucleus and astrocyte reactivity differs in MetS model with or without neurotoxic lesion.

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**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.20/P14

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Pfizer-FRQS Grant 31273

**Title:** The deleterious effects of soluble amyloid-beta oligomers on memory acquisition and sleep in an animal model of early Alzheimer's disease

**Authors: *D. CASTONGUAY**[1,3], L. ST-CYR[4], A. DEGRAEVE[1,3], C. PROVOST[3], N. LEMMETTI[2], V. MONGRAIN[5,2,3], J. BROUILLETTE[1,3]
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**Abstract:** Alzheimer’s disease (AD) primarily impairs the acquisition of hippocampal-dependent explicit memory (memory for facts and events) in association with chronic sleep loss. Recent studies have shown that accumulation of toxic soluble amyloid-beta oligomers (Aβo) give rise to cell death and memory deficits in early AD. However, one seminal question remains unanswered: How Aβo and sleep loss influence each other to induce neurodegeneration and cognitive impairments at the onset of AD? The main objective of this research project is to uncover the deleterious effect of soluble Aβo on memory acquisition and sleep hallmarks affected at the onset of AD. To achieve our goal, we took advantage of our AD animal model which mimics the synaptic and neuronal loss observed in early AD in the hippocampal CA1 region. Repeated hippocampal injections of soluble Aβo (once a day for 6 days; 0.2 µg/µL; 2 µL) induced gradual neuronal loss in the CA1area in Long-Evans rats. We observed by immunofluorescence a lower level of NMDA receptors in association with a higher level of the phosphatase STEP, which is implicated in the internalization of the glutamatergic NMDA and AMPA receptors. An increased level of reactive astrocyte marked with GFAP was also found

after Aβo injections. Aßo induced memory deficits in the spatial object recognition task, a hippocampal-dependent memory task, but not in the novel object recognition test, which rely mainly on the prefrontal cortex instead of the hippocampus. Aßo altered wakefulness and non rapid eye movement (NREM) duration during the dark period. Taken together, these results indicate that the neurotoxicity induced by Aßo in the hippocampal CA1 region decreased the acquisition of hippocampal-dependent memory and altered sleep architecture. The identification of the specific signature of Aβo on the different EEG features when Aβo begins to induce neurotoxicity in the CA1 area might serve as a non-invasive biomarker of early AD. A better understanding of the molecules affected by soluble Aβo when memory acquisition deficits start to appear will bring valuable information to develop new disease modifying targets efficient at the onset of the illness.

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**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.21/P15

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** PI15/00473
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**Title:** Amyloid-beta promotes Cdk5 activation leading to p53 stabilization and neurotoxicity

**Authors: *A. ALMEIDA**[1], R. LAPRESA[1], J. AGULLA[2], I. SANCHEZ-MORAN[1], J. P. BOLANOS[3]
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**Abstract:** Neurodegeneration in selective areas of brain underlies the pathology of Alzheimer's disease (AD). The p53 tumor suppressor protein functions as a key regulator of cell apoptosis and has been described to accumulate in affected brain areas from AD patients. However, the role of p53 in AD is controversial. Here, we evaluated the role of p53 on amyloid beta (Abeta)-induced neuronal apoptosis and the underlying mechanism. We found that whereas p53 mRNA levels remained unchanged, exposure of neurons to the amyloidogenic fragment 25-35 of the Abeta peptide (Abeta 25-35) promoted p53 phosphorylation and stabilization, which triggered mitochondrial dysfunction and neuronal apoptosis in vitro. Abeta activated the p53

phosphorylating kinase Cdk5 (cyclin dependent kinase 5) and treatment with the Cdk inhibitor, roscovitine, prevented p53 accumulation. Abeta-induced mitochondrial depolarization and neuronal apoptosis were prevented by both genetic and pharmacological inhibition of p53 (pifithrin-alpha, PFT-alpha) and Cdk5, (roscovitine). Furthermore, p53 accumulated in degenerating neurons upon Abeta exposure in vivo. Abeta-caused dendrite disruption and neurotoxicity were prevented by genetic deletion or inhibition (PFT-alpha) of p53 in vivo. Our results reveal that Abeta triggers Cdk5 activation, which induces p53 phosphorylation and stabilization, leading to neurodegeneration. Then, inhibition of the Cdk5-p53 pathway may provide a novel neuroprotective therapy against Abeta-induced neuronal loss. This work was funded by The Instituto de Salud Carlos III (PI15/00473; RD16/0019/0018); European Regional Development Fund (FEDER); European Union's Horizon 2020 Research and Innovation Programme (Grant Agreement 686009); and Junta de Castilla y León (IES007P17).

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**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 743.22/Q1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** VIEP-BUAP 2018

**Title:** Activation of the CB1 receptor into hippocampus improves memory and decreases the neurotoxicity induced by amyloid-β 25-35 peptide in rats

**Authors: *A. PATRICIO**[1,2], R. SÁNCHEZ-ZAVALETA[1,4], I. MARTÍNEZ-GARCÍA[3], I. D. LIMÓN[1]
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**Abstract:** The pro-inflammatory response mediated by astrocytes and microglia in response to peptide $A\beta_{25-35}$ induces the expression of inducible nitric oxide synthase (iNOS), an enzyme responsible for increasing levels of nitric oxide (NO). It has been observed that the increase in NO concentrations triggers biochemical pathways that contribute to neuronal death and cognitive damage. Cannabinoids have been shown to be neuroprotective agents because of their anti-inflammatory properties and to reduce excitotoxic processes. These properties have been proposed to cannabinoids as drugs for the treatment of various neurodegenerative diseases. The aim of this study was to evaluate the activation of the CB1 receptor plus $A\beta_{25-35}$ peptide

administration on the spatial memory, NO levels, iNOS expression and neurodegeneration into CA1 subfields of the hippocampus (Hp). Male Wistar rats were used. ACEA was used as a agonist for the CB1 receptor and AM-251 as a CB1 antagonist. Seven experimental groups were formed: 1) vehicle + PBS, 2) PBS + ACEA, 3) PBS + AM-251, 4) vehicle + $A\beta_{25-35}$, 5) ACEA + $A\beta_{25-35}$, 6) AM-251 + $A\beta_{25-35}$ y 7) AM-251 + ACEA + $A\beta_{25-35}$. Each treatments were administered bilaterally by stereotactic surgery into CA1 subfields of the Hp (AP: -3.8, L: ± 3.0, P: -2.0). The learning assessment was made in the eight-arm radial maze at 20 days after injection. The memory test was done eight days after the learning assessment. Twenty nine days post-lesion were euthanasia performed on animals to extract the brains. The results show that administration of the $A\beta_{25-35}$ peptide decreases the learning and spatial memory processes. However, the administration of ACEA + $A\beta_{25-35}$ improves the learning and memory processes respect to the $A\beta_{25-35}$ group. The PBS + ACEA and PBS + AM-251 groups did not modify the learning and memory process. On the other hand, we found that $A\beta_{25-35}$ group increase the NO levels in Hp compared to the vehicle + PBS group. In contrast, the ACEA + $A\beta_{25-35}$ treated group decreased the NO levels compared with the $A\beta_{25-35}$ group. Moreover, treatment with PBS + ACEA and PBS + AM-251 groups did not changes NO levels compared the vehicle group. Nevertheless, when evaluating iNOS expression in CA1 subfields of the Hp in each experimental group, the $A\beta_{25-35}$ group showed an increase in iNOS expression respect to the intact group. On the other hand, the ACEA + $A\beta_{25-35}$ decreases the iNOS expression respect to the group $A\beta_{25-35}$. Finally, we found that the group treated with ACEA + $A\beta_{25-35}$ decrease neuronal degeneration compared with the $A\beta_{25-35}$ group. These results suggest that activation of the CB1 receptor by ACEA decreases neurotoxicity induced by $A\beta_{25-35}$ peptide and improves memory process.

**Disclosures: A. Patricio:** None. **R. Sánchez-Zavaleta:** None. **I. Martínez-García:** None. **I.D. Limón:** None.

**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.23/Q2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Function and mechanism of RIN3 in neurodegeneration in Alzheimer's disease

**Authors: *Y. GU**[1], R. SHEN[2], X. ZHAO[3], L. HE[2], R. A. RISSMAN[4], J. DING[2], C. WU[5]
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**Abstract:** Although β-amyloid plaques (derived from amyloid precursor protein, APP) and Tau-containing neurofibrillary tangles are the two most prominent features of Alzheimer's disease (AD), the disease is a multi-faceted disorder that likely involves many known and unknown genetic factors. Recent genome-wide association studies (GWAS) have uncovered >20 new susceptibility loci associated with sporadic, late onset AD (LOAD). Among which, the Ras and Rab interactor 3 (RIN3), a guanine exchange factor for Rab5 has been implicated in regulating endocytosis and intracellular trafficking of APP, hence production and clearance of Aβ. More recently, a missense mutation in the SH2 domain of $RIN3^{W63C}$ has been identified as a prominent risk factor for AD. Virtually nothing is known about the role(s) of RIN3 in AD pathogenesis. These findings warrant careful examination of RIN3 in AD pathogenesis at the cellular and molecular level.
Our hypothesis is that increased expression or activity of RIN3 activates and stabilizes Rab5 in its activated form to disrupt axonal function leading to neuronal degeneration. We focus on investigating the potential cellular mechanisms by which intraneuronal accumulation of APP/βCTF acts through RIN3 to impair axonal function, a likely mechanism that contributes to early AD pathogenesis. We found RIN3 was upregulated in APP/PS1 AD mouse model at as early as 3 month of age. This was accompanied with an increase in activated Rab5. Furthermore, both $RIN3^{WT}$ and $RIN3^{W63C}$ induced hyperactivation of Rab5 in vitro, and siRNA-mediated knockdown of RIN3 mitigated Rab5 activation. We are actively pursuing studies of knocking down expression of RIN3 in APP/PS1 AD mouse model. We would like to test if these measures rescue or prevent AD-related behavioral and neuropathological deficits. These studies will provide exciting opportunities in establishing RIN3 as a novel drug target for AD therapies.

**Disclosures: Y. Gu:** None. **R. Shen:** None. **X. Zhao:** None. **L. He:** None. **R.A. Rissman:** None. **J. Ding:** None. **C. Wu:** None.

**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.24/Q3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH R01ES026057
NIH R01ES026067-S2
NIH P30ES005022

**Title:** DDT exposure increases amyloid precursor protein levels and amyloid-beta pathology: Mechanistic links to Alzheimer's disease risk

**Authors: *D. C. GERMAN**[1], J. R. RICHARDSON[3], A. EID[3], B. BUCKLEY[4], C. L. WHITE[2]
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**Abstract:** The interaction of senescent-related, genetic, and environmental factors significantly contributes to the etiology of late-onset, sporadic Alzheimer's disease (AD). We previously reported that serum levels of *p,p*'DDE, a long-lasting metabolite of the organochlorine pesticide DDT, was significantly higher in patients with AD and associated with risk of AD diagnosis. Further, brain levels of DDE were similar to levels found in blood in 10 matched samples (Richardson et al., 2014). Here we report that in 20 post-mortem AD brains, detectable levels of DDE were present in every brain (14.5 - 43.7 ng/g), and that levels in the temporal lobe were similar to those in the cerebellum, indicating that DDE levels are uniform throughout the brain. However, the mechanisms by which DDT may contribute to AD pathogenesis is unknown. Here, we demonstrate that DDT exposure significantly increased the mRNA levels of *APP*, *PSEN1* and *APOE* in differentiated SHSY5Y cells as well as *App* mRNA and protein levels in mouse primary hippocampal neurons. The increase in APP protein levels was accompanied by increased Aβ secretion in SHSY5Y cells exposed to DDT, and was abolished by the sodium channel antagonist tetrodotoxin. In male wild-type mice treated with 3 mg/kg DDT every 3 days for 30 days, significant increases in APP mRNA and protein levels (~25%), along with increases in mRNA expression of *Nep* (77%) and *ApoE* (150%) in the hippocampus, were observed. We also observed increased $A\beta_{42}$ levels in the hippocampus, and $A\beta_{40}$ and $A\beta_{42}$ in the cortex of female 3xTG mice at 12 months of age following exposure to 3 mg/kg DDT for 3 months. This was accompanied by enhanced plaque pathology in the female 3xTG mice exposed to DDT. Collectively, these data, combined with our previous epidemiological findings, identify a potential mechanism by which DDT exposure may contribute to increased risk of AD. Supported in part by NIH R01ES026057, R01ES026067-S2 and P30ES005022.

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**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.25/Q4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Mentor Start-up account

**Title:** Dysregulation of NSUN2 in Alzheimer's disease

**Authors: *Y. A. KIM**, I. SANTA-MARIA
Columbia Univ., New York, NY

**Abstract:** Accumulation of extracellular amyloid beta (Aβ) deposits, intracellular neuronal tangles composed of hyperphosphorylated tau and synaptic loss are the main hallmarks of Alzheimer's disease (AD), the most prevalent form of dementia. Currently, the molecular basis of AD is unclear. However, several studies support that altered microRNA (miRNA) expression and/or function plays an important role in AD pathogenesis. However, the mechanisms governing how miRNAs are regulated in the brain are poorly understood. RNA methylation is a prevalent posttranscriptional modification that regulates accuracy of translation initiation, RNA stability, biogenesis and processing of RNA. Historically, it has been shown that methylation occurs on transfer RNA, ribosomal RNA and messenger RNA. Recently, methylation of miRNAs has also been found. However, methyltransferases involved in this process are still under investigation. NSUN2 is one the few known brain-enriched methyltransferases in higher eukaryotes that is able to mediate methylation of miRNAs. Moreover, the loss of NSUN2 in *Drosophila* and mouse models causes memory and learning deficits, indicating a potential role of NSUN2 in cognitive function. Furthermore, in humans, mutations in the NSUN2 gene cause intellectual disability. Interestingly, the role of microRNA methylation in AD pathogenesis has not been reported. Here, our data supports dysregulation of NSUN2 in post-mortem brain tissue from AD patients when compared to healthy controls. In addition, we found that oligomeric Aβ induces both dysregulation of NSUN2 and changes in tau proteostasis in primary neuronal cultures. Furthermore, bioinformatic analysis shows predicted methylation sites in miRNAs that have been implicated in AD, supporting a possible link between NSUN2 dysfunction, microRNAs and AD pathogenesis.

**Disclosures: Y.A. Kim:** None. **I. Santa-Maria:** None.

**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.26/Q5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** CIHR Grant

**Title:** The role of ATF4 in neuronal death under Alzheimer's disease conditions

**Authors: *G. PETROFF**[1], S. P. CREGAN[2]
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**Abstract:** Alzheimer's Disease (AD), the most common cause of dementia, is pathologically characterized by amyloid plaques and neurofibrillary tangles. In addition to these pathological hallmarks, increased markers of neuronal stress have been reported. Amyloid β can aggregate into amyloid plaques, however it is thought that soluble oligomeric forms of the peptide are more toxic and induce greater neuronal stress. To try and mitigate stressors that they encounter, cells can enter into the Integrated Stress Response (ISR) pathway. Activation of the ISR leads to translational upregulation of activating transcription factor 4 (ATF4), which can then modulate its downstream target genes. Previously, it has been found that ISR members upstream from ATF4 are elevated in AD patients' brains. It is believed that acute activation of the ISR is pro-survival and that prolonged activation in response to chronic stressors can lead to the activation of pro-apoptotic pathways. This chronic activation can potentially result in the neurodegeneration seen in diseases such as Alzheimer's. Therefore, we aimed to determine if amyloid β-induced neuronal death occurs through ATF4-dependent upregulation of pro-apoptotic genes. Mouse CD1 primary cortical neurons, harvested on embryonic day 14.5, were treated with 1μM amyloid β. Using a Hoechst stain assay, amyloid β-treated neurons showed higher apoptotic cell death compared to controls. Additionally, following amyloid β treatment, immunoblotting showed a sustained increase in ATF4 protein levels and quantitative RT-PCR results demonstrated significant increases in the expression of pro-apoptotic transcripts, such as CHOP, Trib3, and Gadd45α ($p > 0.05$). In ATF4-null neurons ($ATF4^{-/-}$) treated with amyloid β, pro-apoptotic transcript levels and apoptotic cell death were both attenuated compared to $ATF4^{+/+}$ neurons. Therefore, ATF4 plays a necessary role in amyloid β-induced neuronal death. To conclude, these results suggest that targeting the ISR or ATF4 may be a potential therapeutic target for the treatment of Alzheimer's disease.

**Disclosures: G. Petroff:** None. **S.P. Cregan:** None.

**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.27/Q6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Edmondson/Crump Professorship, LA Tech Univ. (TAM)

**Title:** Beta amyloid oligomer internalization via recently discovered nicotinic receptors may contribute to cholinergic cell death in Alzheimer's disease

**Authors: *G. WILLIAMS**[1], T. A. MURRAY[2]
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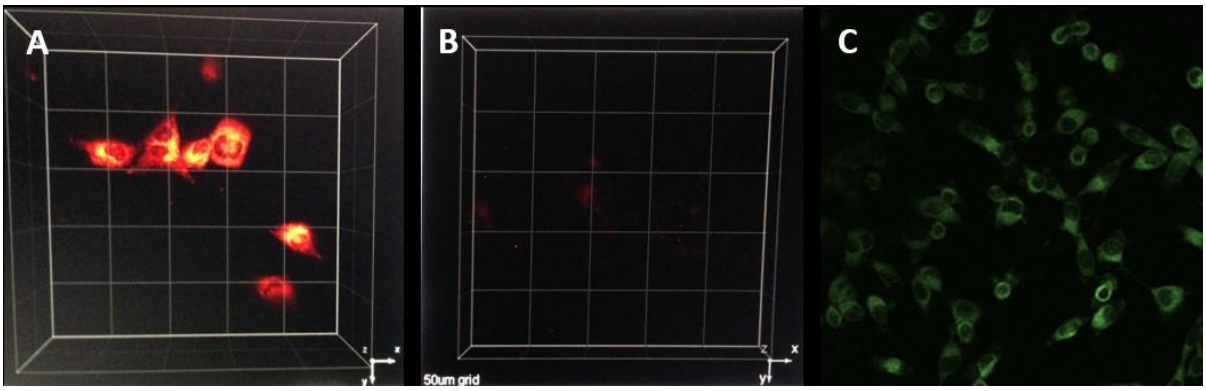
**Abstract:** Central cholinergic neuron death and accumulation of beta-amyloid plaques are pathogenic features of Alzheimer's disease (AD). Despite scientific advances, the etiology of AD is not fully understood. The α7β2 nicotinic acetylcholine receptor (nAChR), a recently discovered neurotransmitter receptor subtype, is expressed in the septum and hippocampus of the brain regions of cell death early in AD. Research has shown that α7-nicotinic acetylcholine receptors (α7-nAChR) mediate β-amyloid peptide (Aβ) internalization and contribute to neuronal death. Studies have not yet focused on α7β2 nAChR mediated internalization of $A\beta_{1\text{-}42}$. Based on previous research, α7β2 is suspected to have a higher affinity for Aβ.Our study focused on comparing α7β2- to α7-nAChR mediated internalization of Aβ. SH-EP1 human neuroepithelial cell lines stably expressing α7-nAChRs (Fig 1A) or α7β2-nAChRs (Fig 1B), and wild type cells were incubated with oligomeric $A\beta_{1\text{-}42}$ or scrambled peptide (Fig 1C) followed by incubation with Amylo-Glo® dye (Biosensis). Aβ internalization was analyzed through a comparison of fluorescence intensity. Cell death assays were also performed.

Higher rates of Aβ internalization were displayed in cells expressing α7-nAChRs versus cells with α7β2-nAChRs, however both were markedly higher than cells incubated with scrambled $A\beta_{1\text{-}42}$ and wild type cells. Notably, cells expressing α7β2-nAChRs had a high rate of cell death. This suggests that internalization by α7β2-nAChRs could contribute to loss of function and cell death in AD.

These results provide new insights into mechanisms of intracellular Aβ accumulation and cytotoxicity. The α7β2 receptor is expressed in the septum and hippocampus where cholinergic cell death is observed in AD pathology. Because Aβ aggregation is a hallmark of AD pathology that contributes to neurodegeneration, further understanding the role of nicotinic acetylcholine receptors, particularly α7β2-nAChR, on β-amyloid is crucial to working towards treatment options and preventative measures.




**Disclosures: G. Williams:** None. **T.A. Murray:** None.

**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.28/Q7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NHRI grant NPPP03-014 and NHRI and Central Government S & T grant, Taiwan (106-1901-01-10-02)

**Title:** A novel thiourea possessing anti-inflammatory property rescues Aβ-induced bioenergetic dysfunction in microglia

**Authors: *Y.-S. SUN**[1,3], F.-S. SHIE[2], M.-H. CHAN[3], Y.-T. HSU[2]
[1]Ctr. For Neuropsychiatric Res., Natl. Hlth. Res. Inst., Zhunan town, Taiwan; [2]Ctr. for Neuropsychiatric Res., Natl. Hlth. Res. Inst., Zhunan Town, Taiwan; [3]Inst. of Neuroscience, Natl. Chengchi Univ., Taipei, Taiwan

**Abstract:** Alzheimer's disease (AD), a neurodegenerative disease, is characterized by the progressive neuronal loss and overactive microglia. Besides, amyloid-β (Aβ) is recognized as the biomarker in AD, which plays a crucial role in the pathogenesis of this disease. The imbalance between Aβ production and clearance leads to the accumulation of Aβ in extracellular and intracellular compartments. Growing evidence suggests that excessive amyloid-β (Aβ) accumulation instigates early deficits in mitochondrial function and causes a self-propelling cycle of microglial overactivation, eventually leading to neuronal damages. However, how Aβ affects mitochondrial function in microglia is still illusive. Here, we used the Seahorse XF$^e$24 Extracellular Flux Analyzer and the Seahorse XF Cell Mito Stress Test Kit to measure the oxygen consumption rate (OCR) as an indicator of mitochondrial functionality in microglia. The assay equipped with automatic drug delivery system targeting components of the electron transport chain (ETC) in the mitochondria provides us the key parameters of metabolic function, including ATP production, maximal respiration, and non-mitochondrial respiration. Our data show that Aβ induced a decline of the OCR in microglia as evidenced by significantly reduced maximal respiration and spare capacity. Intriguingly, the treatment of a novel thiourea rescued the abnormal OCR in microglia and improved the mitochondrial function. Our data further indicate that the rescuing effects of the novel compound on the aberrant bioenergetics elicited by Aβ are involved in the modulation of ERK activity that is highly associated with mitochondrial damages under the circumstances of Aβ toxicity. Taken together, our findings support the notion that Aβ undermines the mitochondrial bioenergetics in microglia. The beneficial effects of our novel thiourea on improving the mitochondrial function might aid the development of future treatments for AD.

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**Poster**

**743. Alzheimer's Disease and Other Dementias: Abeta Mechanisms of Toxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 743.29/Q8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Department of Science and Technology, Govt. Of India

**Title:** Neuroprotective effect of minocycline on mitochondrial mediated toxicity in Abeta-42 induced Alzheimer's disease using *Drosophila melanogaster* as an alternate model

**Authors: *R. KHATOON**
Jamia Hamdard, New Delhi, India

**Abstract:** Mitochondrial dysfunction is the foremost perpetrator of neurodegeneration in Alzheimer’s disease (AD). Studies suggest that minocycline have potential to reduce mitochondria mediated neurotoxity in AD but the exact underlying mechanism is not well explored. We investigated the protective effect of minocycline on Abeta-42 induced mitochondrial mediated neuronal dysfunction in *Drosophila melanogaster* at the organismal level by climbing, survival assay as well as cellular level through estimation of mitochondrial stress markers and apoptosis markers. Overexpression of Abeta-42 in the brain induced behavioral deficits in Drosophila *melanogaster* fruit fly. Deficits at a organisamal level were assessed by the using climbing, and survival behavior paradigms that is revealed by the Minocycline. Minocycline reduced the mitochondrial ROS and increases mitochondrial membrane potential determined by the Flow cytometer. Minocycline has also potential to decrease the denstometric ratio of Bax, Cleaved caspase 3 and cuts protein and increase in Bcl2 done by the western blotting. Moreover, our study suggests that minocycline shows a neuroprotective effect in Abeta-42 induced neuronal toxicity in AD.
**Key words:** Alzheimer‘s Disease, Abeta-42, Mitochondria, neurological dysfunction
**Funding:** The work was supported by a DST-SERB Program awarded to SP. RK was supported by a DST-JRF.

**Disclosures:**

**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.01/Q9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Alzheimer's Research UK grant ARUK-IRG2014-10

**Title:** Investigating the temporal progression of neurovascular, neuropathological, and cognitive changes in the hAPP-J20 Alzheimer's mouse model

**Authors: *K. E. AMEEN-ALI**, P. S. SHARP, L. W. BOORMAN, J. E. SIMPSON, P. HEATH, S. B. WHARTON, J. BERWICK
Univ. of Sheffield, Sheffield, United Kingdom

**Abstract:** Neural activity is closely followed by a localised change in cerebral blood flow, a process termed neurovascular coupling. Impaired neurovascular coupling may be an early pathogenic factor in Alzheimer's disease (AD), which could also serve as a perfusion-based imaging biomarker of cerebral pathology. However, few studies have examined neurovascular dysfunction in AD mouse models, potentially due to the challenges of controlling physiological parameters in mice and profound effects of anaesthetics on vascular physiology. In the present study, we adapted an anaesthetic regime producing hemodynamic responses comparable to those in the awake mouse for use as a chronic anaesthetised preparation, to determine the onset and evolution of neurovascular alterations in the hAPP-J20 mouse model of AD and wild-type (WT) control animals. In addition, neuropathology was characterised relative to cognitive assessments in a separate cohort of animals. Animals were between 9 and 12 months of age at the start of the chronic imaging experiment. Optical imaging spectroscopy (OIS) produced functional maps of changes in tissue oxygenation and cerebral blood volume in response to whisker stimulation and vascular reactivity challenges. Following implantation of the imaging chamber, mice spent 7 days recovering before 3 chronic imaging sessions performed 30 days apart. A concurrent multi-depth electrophysiology and OIS acute experiment was performed to measure both neural activity and the hemodynamic responses. The hemodynamic response was largely preserved in the AD and WT groups, in contrast with previous reports. However, in the final acute experiments there was a distinct difference between these groups, similar to previous reports using acute preparations. This suggests that hAPP-J20 mice may be more susceptible to an acute CNS challenge, such as insertion of an electrode, compared to WT animals. The method of investigation may be a critical aspect in assessing neurovascular breakdown in mouse models of disease. Short-term recognition memory was preserved up to 12 months of age, but long-term recognition memory was impaired from 3 months of age. Aβ plaques were present from 6

months, with reactive microglia and astrocyte activation in the hippocampus significantly greater in the AD mice at 9 months, compared to WT. Preserved short-term but impaired long-term recognition memory therefore preceded Aβ deposition and glial activation. Defining early neurovascular, neuropathological, and cognitive changes could provide insight into new therapeutic targets early in the disease process, when intervention is most likely to effectively slow disease progression.

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**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.02/Q10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH AG054562

**Title:** Potential therapeutic properties of dietary sialic acid in the 5xFAD model of Alzheimer's disease

**Authors: *L. L. SOMERVILLE**[1], D. F. DELOTTERIE[3], J. T. KILLMAR[2], Y. XUE[2], M. P. MCDONALD[4]
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**Abstract:** Funding: NIH-NIA (AG054562)
Reduction of amyloid β (Aβ) is a key goal in the treatment of Alzheimer's disease. Sialic acid binds to Aβ with high affinity and exogenously-administered sialic acid improves cognition and attenuates neurotoxicity in several animal models. In this and our previous study, we used glycomacropeptide (GMP) from bovine milk to elevate levels of sialic acid and brain gangliosides.
In our previous study, administration of GMP in mouse chow had a positive effect on memory performance tasks and reduced both soluble and aggregated Aβ. The activated microglia and reactive astrocytes normally observed in cortical and hippocampal regions in 5xFAD transgenics were also significantly reduced in mice eating GMP.
Our current study uses male and female 5xFAD mice, which harbor human transgenes containing two PSEN1 and three APP mutations. Mice were given whey protein isolate either without (WPI group) or with GMP (WPI+GMP) in their drinking water, or water alone. In the first study, experimental diets were administered from 4 to 9 months of age and cognitive testing

was conducted before sacrifice at 9 months. The second study used a similar design, but with older mice starting experimental diets at 9 months and behavioral assessments at 14 months. The first cohort of younger mice treated with WPI+GMP demonstrated a modest improvement in cognitive and motor function compared to controls. Although preliminary, these results taken with our initial study suggest that dietary GMP may provide therapeutic benefit against Alzheimer's-related cognitive and neural impairments.

**Disclosures: D.F. Delotterie:** A. Employment/Salary (full or part-time):; UTHSC. **J.T. Killmar:** A. Employment/Salary (full or part-time):; UTHSC. **Y. Xue:** A. Employment/Salary (full or part-time):; UTHSC. **M.P. McDonald:** A. Employment/Salary (full or part-time):; UTHSC.

**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.03/Q11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant MH101634
NIH Grant MH113924
NIH Grant GM7536

**Title:** High density awake recording of CA1 neurons in APP/PS1 mouse model of Alzheimer's disease

**Authors: *U. CHOCKANATHAN**, E. WARNER, L. TURPIN, M. O'BANION, K. PADMANABHAN
Univ. of Rochester, Rochester, NY

**Abstract:** Alzheimer's disease (AD) affects five million Americans and is the sixth leading cause of death in the United States. Individuals with AD often experience a loss of independence and decrease in quality of life stemming from the range of cognitive and behavioral symptoms caused by the disease. Despite substantial progress toward uncovering molecular and cellular hallmarks of AD and considerable work examining the behavioral consequences of that neuropathology, the alterations of neural activity patterns in the context of AD remain relatively unexplored and constitute a major gap in the understanding of the disease. Thus, interrogating changes in neural circuits is essential for linking the cellular pathology with behavioral changes and identifying potential loci for intervention. Using high density silicone array recordings in awake head-fixed animals, we recorded large populations of single neurons in the CA1 region of the hippocampus in the APP/PS1 transgenic mouse model of AD and in aged controls.

Extracellular recordings were made using 128-channel probes targeted to the dorsal CA1 (dCA1) region while the mice ran on a one-dimensional running wheel. 4 control and 4 APP/PS1 mice, all 11-12 months of age, were head-fixed and trained to run on a wheel for an hour per day for a 7-day period, after which the recordings were made. We analyzed first and second order statistics of neural activity and then linked the observed patterns to behavior. First, mean firing rates and inter-spike intervals were not significantly different between the two groups. However, our data showed that in the APP/PS1 mice, units were less correlated with each other, on average, than in control animals. Moreover, units from APP/PS1 mice were more correlated with running behavior than those from control mice. Additionally, population spike-train entropy, a measure of network disorder, was significantly higher in the APP/PS1 mice. These data show that dCA1 neuronal circuit activity is less structured in APP/PS1 mice; consequently, we have identified a potential link between the previously reported alterations in dendritic structure, synaptic connectivity, and neuronal excitability and network activity. Such a connection may provide insight into how the behavioral deficits that are a hallmark of the disease may arise from changes in the activity patterns of neural networks.

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**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.04/Q12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Study funded by Camara de la Industria de la Cerveza y la Malta, S.A. de C.V. CONACYT-Mexico.

**Title:** Lycopene protects against mitochondrial alteration and synaptic loss, while improving cognition in APPPS1 mice

**Authors: C. LOZANO-VILLALOBOS**[1], D. CUERVO ZANATTA[1], A. CRUZ-SANTOYO[1], B. TRIGUEROS- GARCÍA[1], A. GÓMEZ-MENDOZA[1], A. BAUTISTA-AVELINO[1], B. PEREZ-GRIJALVA[1], V. SANCHEZ-VALLE[1], E. MARTINEZ-ROJAS[2], *C. PEREZ-CRUZ[1]
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**Abstract:** Alzheimer’s disease (AD) is the most common form of dementia that involves neurodegenerative processes affecting synaptic function and memory formation. Mitochondrial dysfunction is widely related to the pathogenesis of AD, causing an increase in

cellular oxidative stress and, consequently, neuronal death. Several reports indicate that antioxidant supplementation has beneficial effects in animal models of AD. Lycopene is a potent antioxidant able to recover mitochondrial function in *in vitro* models, as well as in animals administered with the peptide Abeta1-42. However, the effect of lycopene in a transgenic model of AD has not been demonstrated. It should be noted that commercial lycopene is mainly extracted from tomatoes, which makes this product very expensive and not very accessible to the population. Therefore, in this project it is proposed to evaluate the therapeutic effect of lycopene obtained through a sustainable and economic process utilizing waste products from the process of beer production. **Objective:** To elucidate the mechanism by which lycopene improves cognition, synaptic density and mitochondrial morphology in APPPS1 mice. **Methods:** Lycopene (4 mg/kg, Sigma) or organic compound (4mg/kg) were given by oral cannulation to 4 month-old male APPPS1 (n=6) and WT mice (n=6), during 4 weeks. Vehicle (tween 5%) treated mice were included as controls (n=6). Cognitive performance was assessed 3 days before finalizing treatments. Animals were sacrificed and brain was immediately collected. Coronal hippocampal sections were used to assess amyloid pathology by BAM10 immunoreactivity, and spine density was evaluated after biolistic labelling. Mitochondria hippocampal morphology was evaluated by Transmission Electronic Microscopy (TEM). OPA1, DRP1 and PGC1-alpha proteins were measured in cortex samples. **Results:** We observed a significant improvement in short-term memory in APPPS1 mice treated with Lycopene (Sigma), while no recovery was observed with the organic compound. This behavioral recovery was accompanied by decreased Abeta load, increased spine density in hippocampus, recovery of mitochondria morphology, and OPA1, DRP1 and PGC1-alpha protein increases compared to APPPS1. **Conclusion**: Lycopene protects from cognitive alterations in APPPS1 by restoration of mitochondrial functioning, resulting in increased synaptic density. Hence we conclude that a nutritional supplementation with antioxidant compounds can be used as a therapeutic strategy against degenerative diseases, and may modulate the course of Alzheimer´s disease. *Study funded by Camara de la Industria de la Cerveza y la Malta, S.A. de C.V., and CONACYT-Mexico.*

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**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.05/Q13

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Canadian Institutes of Health Research Grant
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**Title:** Evaluating the benefits of angiotensin-converting enzyme inhibition in *Drosophila* models of Alzheimer's disease

**Authors: *S. LEE**, S. GOMES[1], G. BOULIANNE[2,1]
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**Abstract:** Alzheimer's disease (AD) is the most common cause of dementia in the aging population for which there is no cure. Through genetic studies of familial AD, mutations were identified in Presenilins (PS), which encode the catalytic component of the γ-secretase complex, which cleaves the amyloid precursor protein C-terminal fragment (APP-CTF) to produce amyloid peptides. Mutant forms of presenilin result in aberrant cleavage of APP-CTF to produce longer, more toxic forms of amyloid (Aβ42) that have been suggested as a major cause for AD-related neurodegeneration. Although several PS-targeting drugs have been developed, controversy remains as to whether this is an effective strategy as PS can also affect processing of many other proteins. One alternative strategy would be to target the interaction of PS with specific proteins such as APP-CTF.
Our lab used a genetic approach in *Drosophila* to identify proteins that specifically modulate the interaction between PS and APP-CTF. One such candidate is Angiotensin-converting enzyme (ACE), a metalloprotease of the renin-angiotensin system known to regulate blood pressure in humans. Interestingly, several recent studies have also shown that ACE inhibition can reduce the risk of AD, although the precise mechanisms are unknown. To determine whether ACE inhibitors are beneficial in AD and to identify the mechanism of action we utilized *Drosophila* lines that express three different AD-related human transgenes (APP/C99$^{WT}$; APP/C99$^{V717I}$; Aβ42) under the control of either an eye (GMR-GAL4), or CNS (ELAV-GAL4) specific promoter. We then examined whether Captopril, an ACE inhibitor or Losartan, an Angiotensin receptor blocker, had any effect on age-dependent, neurodegenerative phenotypes generated by expression of each AD transgene.
To date, we observed beneficial effects associated with inhibition of ACE in flies expressing APP/C99$^{V717I}$ including a reduction in cell death and an increase in lifespan. In contrast, ACE inhibition had no effect in flies expressing APP/C99$^{WT}$ or Aβ42. Moreover, neither Captopril or Losartan had any effect on Notch, a known target of γ-secretase, suggesting that these drugs are specific to AD related pathways. To determine the mechanism of action of Captopril and Losartan, we used western blots and ELISA assays to examine the effect of the drugs on the levels of C99 and amyloid peptides. We observed changes in the levels of C99 and the production of β-amyloid peptides only in APP/C99$^{V717I}$ expressing flies suggesting that ACE inhibition may affect the cleavage of APP-CTF by PS/γ-secretase. Future studies will focus on determining how ACE inhibition affects this interaction.

**Disclosures: S. Gomes:** None. **G. Boulianne:** None.

**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.06/Q14

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** L.I.F.E. Foundation
Albert J. Ryan Foundation
NIH T32 DK059803-15

**Title:** Hypothalamic-pituitary-adrenal axis hyperactivity precedes cognitive impairments in female mice genetically vulnerable to Alzheimer’s disease

**Authors: *E. T. NGUYEN**[1,2], N. J. BALMER[1], A. N. GREENE[1,2], R. L. MORANO[1], A. FRANCO-VILLANUEVA[1], C. M. ESTRADA[3], M. B. SOLOMON[1,2]
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**Abstract:** Stress, likely due to hypothalamic-pituitary-adrenal (HPA) axis hyperactivity and excessive glucocorticoid secretion, is linked to the pathophysiology of Alzheimer’s disease (AD). For example, glucocorticoids worsen AD neuropathology (i.e., brain Aβ formation and tau accumulation) and cognitive impairment. Previous work from our laboratory indicate sex differences in glucocorticoid signaling in rats and mice in response to acute and chronic stress exposure. Notably, relative to men, women are twice as likely to suffer from stress-related disorders (e.g., depression) and AD. The goal of the present study was to investigate whether chronic variable stress (CVS) exacerbates and accelerates AD-related endpoints in a sex-dependent manner in young mice. This was accomplished using the triple transgenic mouse model of AD (3xTg), and their corresponding background strain (B6129SF2/J) as controls. Prior to CVS, 3xTg females, but not 3xTg males, showed a heightened corticosterone response to a restraint challenge. Observed at 4 months, this suggests that HPA-axis dysfunction may precede the onset of some AD-related endpoints in genetically vulnerable females. However, CVS exposure induced a persistent (6 weeks) elevation in basal corticosterone concentrations only in males, regardless of genotype. Together, these findings suggest sex differences in HPA-axis function prior to and following CVS exposure. Throughout the study, 3xTg mice of both sexes exhibited coat state deterioration, a depression-like phenotype. This finding supports the documented link between depression and AD. Cognitive deficits in AD encompass spatial, object, and social memory. Here, we evaluated social memory using the 3-chambered social preference and recognition test. At 6 months, male 3xTg mice did not display any observed cognitive deficits. However, female 3xTg mice displayed deficits in social memory, independent

of CVS history. This suggests a sex difference in amygdala-related memory vulnerabilities in the 3xTg mice. Based on these findings, CVS does not appear to negatively impact behavioral (i.e., cognition and depression-like) or endocrine (i.e., basal corticosterone) phenotypes in 3xTg mice at the observed age. However, given sex differences in HPA-axis responsivity and social memory, we will determine if CVS accelerates and exacerbates AD-related cellular anomalies (e.g., Aβ, phosphorylated tau) in a sex-dependent fashion. These data may further our understanding of how stress impacts neuroendocrine, behavioral, and cellular anomalies associated with AD in both sexes; thereby, shedding more light into the pathophysiology of this debilitating disease.

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**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.07/R1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant NS085171
NIH Grant NS086965

**Title:** ΔFosB regulates expression of genes that control neuronal excitability in the dentate gyrus of a transgenic mouse model of Alzheimer’s disease

**Authors: *G. S. STEPHENS**[1], J. PARK[1], Y. ZHENG[1], C.-H. FU[1], Y. LIU[2], J. CHIN[1]
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**Abstract:** Alzheimer’s disease (AD) is characterized by cognitive decline, the severity and rate of which are modulated by seizure activity. Although seizures are often infrequent, they contribute importantly to cognitive deficits in both AD patients and transgenic mice expressing human amyloid precursor protein (APP), and treatment with the antiepileptic drug levetiracetam improves cognition. We reported that even infrequent seizures in APP mice produce hippocampal accumulation of the transcription factor ΔFosB, which epigenetically alters expression of plasticity-related genes and drives persistent cognitive deficits. ChIP-sequencing and network profiling of genes bound by ΔFosB in APP and nontransgenic (NTG) mice demonstrated that the gene regulatory programs controlled by ΔFosB in the hippocampus undergo functional diversification in APP mice, revealing novel target genes involved in the regulation of neuronal excitability, glutamatergic signaling, and calcium homeostasis. In new

studies, we have focused on ΔFosB target genes that regulate excitability, aiming to investigate endogenous mechanisms by which neurons control excitability in conditions of recurrent seizures. We identified a number of novel, excitability-related ΔFosB targets that are suppressed in the hippocampus of APP mice, including a calcium-activated chloride channel that was not bound by ΔFosB in NTG mice, consistent with diversification of target genes in APP mice relative to NTG mice. AAV-mediated restoration of expression of the calcium-activated chloride channel revealed a worsening of neuronal alterations that are known to reflect the frequency and magnitude of seizure activity. These results and others suggest that ΔFosB-induced suppression of specific target genes may act to limit excitability in conditions accompanied by recurrent seizures, such as Alzheimer's disease and epilepsy.

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**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.08/R2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant R15 AG05194001A1

**Title:** An histological analyses of Alzheimer's disease (AD) markers and immunological response in a primate model of aging and AD

**Authors: *J. J. NEIWORTH**, C. KWON
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**Abstract:** Histological analysis of cotton top tamarin brain tissue showed that Alzheimer's Disease (AD) markers were present and increase with age of monkey. Labeling techniques using DAB staining and 6E10 antibody for beta amyloid, AT8 for neurofibrillary tangles, and GFAP for astrocytes were used, along with a light thionine stain for background tissue and to note cell volume and degradation. A separate lab was used with blind identification of age of monkey to corroborate findings. It was evident that there were beta amyloid plaques in monkeys around age 12-14, with levels increasing and pushing into vasculature with age. An abundance of neurofibrillary tangles were labeled in the oldest monkey post-mortem, who died at age 24. Less and/or rare levels of neurofibrillary tangles were present in tissue from younger monkeys. Double-labeling was used to study the relationship between astrocyte health, atrophy, hypertrophy, and adjacency to beta amyloid plaques. We discuss an interaction between levels of AD markers and immunological response based on age, and will correlate with cognitive

dysfunction to build a cognitive and neural description of aging, dysfunction, and AD-like symptoms in tamarins.

**Disclosures: J.J. Neiworth:** None. **C. Kwon:** None.

**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 744.09/R3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** CIHR Grant

**Title:** The effects of extracellular serum concentration on APP processing in NPC1-deficient APP-overexpressing N2a cells

**Authors: *G. PHUKAN**[1], M. MAULIK[4], D. VERGOTE[2], J. CHUNG[3], G. THINAKARAN[5], S. KAR[6]
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**Abstract:** Amyloid precursor protein (APP) is cleaved by a set of proteases including α-/β-/γ- and recently identified η-secretases, generating C-terminal fragments (CTFs) of varying lengths and amyloid β (Aβ) peptides, which are considered to play a pivotal role in Alzheimer's disease (AD) pathogenesis. Cellular cholesterol content/distribution can regulate the production/clearance of APP metabolites and hence modify AD pathology. To determine the functional relation between endosomal-lysosomal (EL) cholesterol sequestration and APP metabolism, we used our recently developed mouse N2a-ANPC cells that overexpress Swedish mutant human APP in the absence of cholesterol-trafficking Niemann-Pick type C1 (Npc1) protein. Here, we report that neither increased levels nor EL cholesterol sequestration altered APP holoprotein levels but caused the intracellular accumulation of APP α-/β-/η-CTFs and Aβ1-40/42 peptides. The levels of APP-cleaved products increased as a function of extracellular serum concentration in N2a-ANPC cells, which are more vulnerable to death than the control cells. Additionally, we show that pH of the lysosomal vesicles in N2a-ANPC cells shifted to a less acidic range with increasing serum concentrations, thus making them less efficient functionally. Interestingly, the addition of cholesterol to the culture media not only increased the levels of cellular cholesterol and APP-cleaved products but also rendered the cells more vulnerable to toxicity. Collectively, our results suggest that extracellular cholesterol

concentration in serum under conditions of Npc1 deficiency can influence intracellular cholesterol content/distribution and lysosomal efficacy, triggering the accumulation of toxic APP-cleaved products, eventually leading to cell death.

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**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.10/R4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Early detection of abnormal sensory-evoked eeg responses in mice over-expressing amyloid beta

**Authors: B. D. HARVEY**[1], *R. KOMOROWSKI[1], F. PONTARELLI[2], A. W. DUNAH[2], M. HAJOS[1]
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**Abstract:** While the role of β-amyloid (Aβ) in the loss of synapses and neurons contributing to Alzheimer's disease has been well-established, interventions that suppress Aβ have, to date, failed at translating into successful medicines. One contributing factor to these failures is the lack of an objective clinical biomarker that can detect the impact of early synaptic pathology on neuronal circuits, as these circuits give rise to proper encoding of sensory information leading ultimately to cognition and memory. In these sets of experiments, we recorded steady-state sensory EEG responses in wild-type and TG2576 mice which express high concentrations of the mutant Aβ due to a transgene coding for the isoform of Aβ precursor protein. These TG2576 mice exhibited abnormal sensory-evoked EEG activity which correlated with age and increasing Aβ-related pathology. Such low-level sensory-evoked responses may provide early insights into cortical pathologies that could be translated into patients as both an early measure of Aβ-driven synaptic dysfunction and as an objective measure of treatment response.

**Disclosures: B.D. Harvey:** 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. Komorowski:** 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. **F. Pontarelli:** A. Employment/Salary (full or part-time):; Biogen. **A.W. Dunah:** A. Employment/Salary (full or part-time):; Biogen. **M. Hajos:** A. Employment/Salary (full or part-time):; Biogen. E. Ownership

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**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.11/R5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** HI14C1913
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2017M3C7A1028949

**Title:** Presenilin1 and 2 regulates zinc homeostasis and zinc dysregulation affects lysosomal dysfunction

**Authors: *H. LEE**[1], *Y. YOON[2], J.-Y. KOH[1]
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**Abstract:** Several mutations in presenilin 1 and 2 (PS1/2) genes cause familial Alzheimer's disease (FAD). While earlier studies focused on their role in Aβ-generating γ-secretase activity as a possible pathogenic mechanism, recent studies have reported that normal functions of PS1/2 include the regulation of the autophagy-lysosomal pathway, and the loss of PS1/2 function by their mutations hence causes defective autophagy-lysosomal degradation, a possible contributing mechanism in AD. Since zinc homeostasis is also likely involved in the regulation of autophagy lysosomal pathway, we examined the possible interaction between PS1/2, zinc homeostasis, and autophagy lysosomal degradation. In PS1/2 double knockout (DKO) mouse embryonic fibroblast (MEF) cells, levels of several autophagy-lysosomal proteins were increased, yet no further increases were induced by the addition of bafilomycin A1, an inhibitor of lysosomal acidification, indicating that lysosomal function was abnormal in PS1/2 DKO cells. Furthermore, when incubated with Aβ1-42, levels of accumulated Aβ in PS1/2 DKO cells were substantially greater than those in WT cells. Next intracellular free zinc levels were assessed with a zinc-specific fluorescent dye, FluoZin3-AM. Compared with intracellular free zinc levels in WT MEF cells, those in PS1/2 DKO MEF cells were significantly higher at the resting state. Furthermore, exposure to 100 uM zinc for 30 min, increased zinc levels more so in PS1/2 DKO cells than in WT cells. In contrast, lysosomal free zinc levels appeared lowered in PS1/2 DKO cells than in WT cells at resting state. However, exposure to zinc clioquinol increased lysosomal free zinc levels in PS1/2 DKO cells, which ameliorated lysosomal dysfunction and reduced levels of Ab in

these cells. Interestingly, while cytosolic zinc levels increased to a greater level in DKO cells, DKO cells were less sensitive to zinc toxicity than were WT cells. Consistent with this, with identical zinc exposure, zinc-induced lysosomal membrane permeabilization (LMP) was less pronounced in DKO cells than in WT cells. Present results support the idea that PS1/2 may regulate autophagy lysosomal pathway, likely by maintaining lysosomal acidification. At the same time, PS1/2 may contribute to cytosolic and lysosomal zinc homeostasis. The absence of PS1/2 may increase cytosolic zinc levels but decrease lysosomal zinc levels, which changes may contribute not only to autophagy lysosomal dysfunction in PS1/2 DKO MEF cells, but also to their diminished vulnerability to zinc-induced LMP and cell death.

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**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.12/R6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** The effects of insulin receptor substrate-2 deficiency on amyloid β dynamics in a mouse model of Alzheimer's disease

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**Abstract:** One of the major neuropathological hallmarks of Alzheimer’s disease (AD) is the extracellular deposition of amyloid β (Aβ) peptides as senile plaques. Many epidemiological and experimental studies have indicated that type 2 diabetes mellitus (T2DM) is a risk factor of AD. Some reports showed signs of insulin resistance in postmortem brains of patients with AD. Thus, insulin resistance has been considered as a common molecular pathological feature shared by AD and T2DM. In the mouse models of AD, however, Aβ deposition has been shown to be attenuated by knockout (KO) of *Irs2* encoding insulin receptor substrate-2 (IRS-2), a major signaling molecule that mediates the insulin effects. To gain insights into the molecular mechanism of the inhibitory effect of *Irs2* disruption on Aβ pathology, we examined *Irs2* deficient APP transgenic mice (A7 line). *Irs2* KO A7 mice exhibited hyperglycemia and systemic insulin resistance. The Aβ levels in the cortical homogenates of A7 mice measured by ELISA were not altered by *Irs2* deficiency by 6 months of age, whereas the levels of soluble and insoluble Aβ were both reduced at 9 months of age. Immunohistochemical staining of cortices of 15-month-old A7 mice revealed that *Irs2* deletion remarkably mitigated Aβ deposition.

However, the levels of APP fragments or APP processing enzymes in the cortical homogenates of 9-month-old *Irs2* KO A7 mice were similar to those in A7 mice, indicating that deletion in *Irs2* does not affect Aβ production. Furthermore, *in vivo* microdialysis showed that the Aβ levels of the interstitial fluid (ISF) of hippocampus as well as the half-life of Aβ42 (as determined by administration of a γ-secretase inhibitor Compound E) were not significantly different between genotypes in 9-month-old mice, suggesting that *Irs2* deletion does not modify Aβ clearance. Taken together, these results suggested that *Irs2* knockout does not affect production or clearance of Aβ; alteration in other aspects of Aβ dynamics, e.g., aggregation of Aβ, may be the cause of Aβ reduction in *Irs2* KO mice.

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**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.13/R7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** 5R01AG048993

**Title:** Defining the temporal progression of Alzheimer’s disease in the brain vs. intestine using APP/PS1 and APP (NL-G-F) mouse models

**Authors: *G. D. MANOCHA**[1], A. M. FLODEN[1], N. M. MILLER[1], A. SMITH[1], K. NAGAMOTO-COMBS[2], T. SAITO[3], T. C. SAIDO[4], C. K. COMBS[5]
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**Abstract:** The amyloid precursor protein (APP) is highly expressed by neurons compared to other cell types in the brain. APP is metabolized to numerous fragments including the amyloid beta (Aβ) peptides which are known to fibrillize and likely stimulate the degenerative and inflammatory changes characteristic of Alzheimer’s disease (AD) brains. Based upon the fact that enteric neurons also express APP and elderly are often afflicted with intestinal dysfunction such as constipation and fecal incontinence we hypothesized that the enteric nervous system may also produce Aβ production leading to an intestinal component of disease that may be temporally unique from the brain. To test this idea, we compared C57BL/6 wild type male and female mice to two models of AD, littermate control APP/PS1 mice and the newly characterized APP (NL-G-F) mice at 3, 6, and 12 months of age. Brain Aβ plaque deposition, microgliosis, astrogliosis, and

oligomeric and fibrillar Aβ deposition in APP (NL-G-F) and APP/PS1 mice were increased in an age-dependent manner. The increase in both male and female APP (NL-G-F) mice preceded that observed in the APP/PS1 mice, observable by 3 months of age. APP (NL-G-F) also demonstrated reduced Aβ 1-40 levels compared to the APP/PS1 mice at 3 months of age correlating with the Iberian mutation to promote a higher Aβ 1-42/1-40 ratio. Interestingly, female but not male APP/PS1 and APP (NL-G-F) mice demonstrated memory dysfunction at 3 months of age. In addition, 3 month old female APP (NL-G-F) mice also presented decreased intestinal motility as compared to the wild type and APP/PS1 mice. However, 3 month old female APP/PS1 mice demonstrated significantly increased intestinal permeability compared to wild type and APP (NL-G-F) mice. In addition, both APP/PS1 and APP (NL-G-F) males had increased mRNA expression of proinflammatory cytokines and the inflammation marker, Lipocalin-2, at 3 and 6 months of age while females had increased Lipocalin-2 at 3 months of age. These data demonstrate that both AD mouse models have cognitive and intestinal dysfunction by 3 and 6 months of age correlating with Aβ production and both mouse models present significant gender differences in their brain and intestinal inflammatory phenotype. The unique nature of Aβ production and deposition as well as intestinal changes across the two mouse models suggests that further study is required to better characterize the brain and peripheral disease progression for ultimate comparison to human disease.

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**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.14/R8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Learning and memory deficits of two transgenic Alzheimer’s disease mouse models in the Barnes maze test

**Authors: *E. AUER**, S. KURAT, R. RABL, I. HERNANDEZ, S. FLUNKERT, V. NIEDERKOFLER, B. HUTTER-PAIER
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**Abstract:** Introduction: Alzheimer’s disease (AD) is a progressive neurodegenerative disease that manifests as memory loss, learning dysfunction and dementia. Spatial learning and memory of AD rodent models is often assessed via navigational cues in mazes, most popular are the Morris water maze and the dry-land Barnes maze. Improved performance over sessions or trials is thought to reflect learning and memory.

Method: The Barnes maze is considered less stressful compared to water mazes and also useful for rodent models with minor motor deficits. The Barnes maze is a circular platform top with several holes equally spaced around the perimeter edge. Animals of $APP_{SL}$ and 5xFAD transgenic AD mouse models in a symptomatic age were analyzed in the Barnes maze test using a hippocampal learning protocol.
Results: Barnes maze results were analyzed for escape latency, speed, distance traversed, number of target entries, and the abidance in the target quadrant during the probe trial. Data of the two animal models were compared.
Conclusion/Summary: Our data show that the dry-land behavioral test apparatus of the Barnes maze is a valuable tool to analyze learning and memory deficits of different rodent AD models. This method might be an effective alternative to the Morris water maze while causing less stress to the animals.

**Disclosures: S. Kurat:** None. **R. Rabl:** None. **I. Hernandez:** None. **S. Flunkert:** None. **V. Niederkofler:** None. **B. Hutter-Paier:** None.

**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.15/R9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Department of Pharmacology, Toxicology, and Neuroscience LSU Health Sciences Center - Shreveport

**Title:** Gene transfer induced hypercholesterolemia in amyloid mice

**Authors: *M. S. GRAMES**[1], R. D. DAYTON[1], M. D. WOOLARD[2], R. L. KLEIN[1]
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**Abstract:** This study used a gene transfer approach to investigate the cardiovascular disease (CVD)-Alzheimer’s disease (AD) inter-relationship. A risk factor for the development of CVD, hypercholesterolemia, was induced in AD transgenic mice via gene transfer for mutant PCSK9 using a recombinant adeno-associated virus (AAV) vector in combination with a high fat diet. Cholesterol levels were dramatically elevated by 5-6-fold in the amyloid mice from 3 to 13 weeks after PCSK9 gene transfer compared to the control group of amyloid mice receiving a green fluorescent protein vector. We tested whether the robust hypercholesterolemia would exacerbate the deposition of amyloid-ß (Aß) plaques in the hippocampus and cortex at 7 months of age. Plaque burden was increased in the hippocampus of PCSK9 treated mice compared to the

control group though the increase was only modest compared to the large elevation in cholesterol. Studying the consequences of elevated cholesterol via gene transfer could be valuable in AD models as well as a variety of disease models involving the heart, the brain, and other tissues, as compared to making crosses with current germ-line transgenic mouse models of CVD.
Keywords: Alzheimer's disease; amyloid-ß plaques; cardiovascular disease; hypercholesterolemia; adeno-associated virus; PCSK9; gene transfer

**Disclosures: M.S. Grames:** None. **R.D. Dayton:** None. **M.D. Woolard:** None. **R.L. Klein:** None.

**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.16/R10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** PhD fellowship of the Boehringer Ingelheim Fonds

**Title:** iSPECS: a proteomic method identifies the secretome of brain cells and novel substrates of the Alzheimer beta-secretase BACE1

**Authors: *J. TÜSHAUS**[1], S. A. MÜLLER[2], S. F. LICHTENTHALER[2]
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**Abstract:** Proteins secreted or proteolytically released from cells constitute the secretome and have a major function in the cell-cell communication in the nervous system, for example between neurons and glial cells or microglia. One of the contributing proteases is the beta-secretase BACE1 which cleaves the amyloid precursor protein (APP) and is a major drug target for Alzheimer's disease. However, BACE1 also cleaves numerous other substrates besides APP. A detailed understanding of the substrate repertoire as well as the function of the released ectodomains is necessary to predict potential side effects.
In a first step, we developed the 'improved secretome protein enrichment with click sugars' (iSPECS) method, which uses metabolic glycoprotein labelling and click chemistry and determines the secretome of (primary) cells, even in the presence of serum or serum-like culture supplements. To demonstrate the power of the method, we determined the secretome of the major brain cell types (neurons, astrocytes, microglia or oligodendrocytes) freshly isolated from mouse brain. This is a valuable resource for studying cell-cell communication in neuroscience. Next, we used iSPECS and determined BACE1 substrates in primary neurons in a brain region-

specific manner, such as from hippocampus and cortex. Several identified substrates were validated by immunoblots and are being functionally validated.
Taken together, we introduce iSPECS, a novel proteomic method used for secretome determination of the major brain cell types. Additionally, the identification of new BACE1 substrates has to potential to advance our fundamental knowledge of the function of BACE1 in the brain and to predict consequences of its inhibition when treating Alzheimer's disease.

**Disclosures: J. Tüshaus:** None. **S.A. Müller:** None. **S.F. Lichtenthaler:** None.

**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.17/R11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH grant AG046200
Alzheimer Association IIRG-10-173180

**Title:** Dietary Methionine Restriction improves behavior, reduces amyloid and alters gut microbiota in APP/PS1 mice

**Authors: *K. SAMBAMURTI**[1], N. H. GREIG[3], M. A. PAPPOLLA[4], D. K. LAHIRI[5], N. R. BHAT[6], C. SABIN[1], V. CHENTHAMARAKSHAN[2], V. PADMARAJU[1]
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**Abstract:** Alzheimer Disease (AD) is defined by the pathological lesions of senile plaques (SP) and neurofibrillary tangles (NFT) containing amyloid beta protein (Abeta) and microtubule-associated protein Tau (MAPT), respectively. Transgenic mouse models expressing familial AD (FAD) mutant *APP* and *PSEN1* cDNAs have provided a number of insights into genetic and environmental factors that drive Abeta aggregation and deposition of SP in AD and these changes correlate with human clinical AD. Our hypothesis was that overnutrition coupled with failure of homeostasis might drive conditions that favor SP formation. Reduced food or calorie intake is already known to benefit AD model mice. Restriction of Met, an essential amino acid, is known to increase longevity, without calorie restriction. We treated APP/PS1 transgenic mice with a 75% Met restricted (MR) diet and compared it with a isocaloric isonitrogenous complete diet (CD) for 12 months. Our data show that the treatment significantly drops brain soluble Abeta at 3 and 6 months. Older animals continue to show trends towards reduction of Abeta, but

the levels are not significantly different. Nevertheless, older mice show significant improvement in behavior in a novel object recognition task. In addition, MR diets significantly alter gut microbiota composition. As expected, the bacteria that metabolize Met and Cys are reduced significantly. Furthermore, several major species of bacteria were reduced significantly and the overall diversity of microbiota appears to be increased. This lack of concentration of some species may reduce inflammation. Thus, such diets may play an important role in strategies to prevent AD.

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**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.18/R12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** SyNergy
DFG (FOR2290)
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**Title:** Physiological substrates of BACE1: Safety issues or biomarkers?

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**Abstract:** The beta-secretase BACE1 is the enzyme responsible for amyloid beta generation and is a major drug target in Alzheimer’s disease. However, therapeutic BACE1 inhibition may cause unwanted side effects due to the loss of cleavage of additional BACE1 substrates besides APP. Different proteomic studies have identified more than 40 membrane proteins as potential BACE1 substrate candidates, but most of them have not yet been validated nor functionally characterized.

Here, we validate seizure protein 6 (SEZ6) as an exclusive BACE1 substrate both in primary neurons and in the brain of BACE1-deficient mice. In order to investigate the function of SEZ6 and the consequences of loss of SEZ6 cleavage by BACE1, we developed a novel proteomic technique to determine the surface proteome of primary neurons. Using this method, we found that SEZ6 specifically controls neuronal surface levels of a subgroup of glutamate receptors with key functions in neurotransmission. Mechanistic analyses suggest that SEZ6 is required for glutamate receptor transport along the secretory pathway and may influence synaptic transmission. Additionally, we demonstrate that the BACE1-generated soluble ectodomain of SEZ6 (sSEZ6) is strongly reduced in the CSF of BACE1-deficient mice. Importantly, sSEZ6 is reduced also in the CSF of BACE-inhibited monkeys in a dose dependent manner.
Taken together our results prove that SEZ6 is a major substrate of BACE1, both *in vitro* and *in vivo*. Moreover, we discover a novel function of SEZ6 as glutamate receptor regulator and we investigate the possibility to use sSEZ6 as a potential companion diagnostic to monitor BACE1 activity in patients treated with BACE inhibitors.

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**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.19/R13

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Illinois Department of Public Health 63282003D
Center for Alzheimer’s disease and Related Disorders at SIU School of Medicine
Kenneth Stark Endowment
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SIU School of Medicine Foundation

**Title:** Glutamate neurotransmission, cognition, and risk factors in Alzheimer’s disease

**Authors: *E. R. HASCUP**[1,2], J. BRITZ[2], M. K. RUSSELL[3], S. TISCHKAU[2], H. A. BOGER[3], K. N. HASCUP[1]
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**Abstract:** Alzheimer’s disease (AD) is characterized by β-amyloid $(A\beta)_{42}$ plaques and neurofibril tangles. Evidence supports soluble $A\beta_{42}$ as the neurotoxic isoform precipitating AD

pathology and levels increase during AD progression in humans and mouse models of AD, including transgenic AβPP/PS1 and knock-in $APP^{NL-F/NL-F}$ mice. The abundance of soluble $A\beta_{42}$ strongly correlates with synaptic dysfunction and neurodegeneration supporting that AD lies on a continuum with dynamic neurobiological markers that are constantly in flux based upon genetic and modifiable lifestyle factors. For example, we have demonstrated that soluble $A\beta_{42}$ interacts with presynaptic neurons to elicit glutamate (Glu) release. As soluble $A\beta_{42}$ accumulation increases during AD progression, Glu dysregulation becomes more pronounced and eventually cascades into dementia associated with AD. To support this hypothesis, we present data from AβPP/PS1 and $APP^{NL-F/NL-F}$ mice that details the relationship between genetic and modifiable life style factors as it relates to Glu neurotransmission in AD. We observed an inverse relationship between basal and evoked Glu release in AβPP/PS1 mice compared to age-matched C57BL/6 controls. Evoked release was elevated prior to cognitive decline and plaque accumulation, but was similar during cognitive deficits and plaque formation. However, in these same mice, basal Glu was unchanged early on, but significantly elevated when pronounced AD pathology was present. Furthermore, we examined the relationship between obesity-induced insulin resistance and cognitive impairment. C57BL/6 mice fed a high fat diet (HFD) had impaired memory recall, whereas AβPP/PS1 HFD displayed deficiencies in both learning and memory, as determined by Morris water maze. Additionally, Glu neurotransmission, as well as VGLUT1 and GFAP density, were significantly elevated in the hippocampus of AβPP/PS1 low fat diet (LFD) compared to age-matched C57BL/6 LFD mice. HFD further elevated these levels compared to genotype matched controls. Finally, prodromal treatment with Riluzole, but not LY379268, in AβPP/PS1 mice prevented cognitive decline and restored hippocampal Glu neurotransmission with long-lasting effects, potentially demonstrating a viable treatment option in early AD. Initial examination of $APP^{NL-F/NL-F}$ mice are in agreement with studies in AβPP/PS1, further supporting the role of $A\beta_{42}$ in altered Glu neurotransmission and cognition associated with AD. The data presented here support Glu neurotransmission as a potential early biomarker and therapeutic target to alter disease outcome. 8-14 male mice/group were used for all data presented.

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**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.20/R14

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Reversion of the Alzheimer's disease phenotype by reducing mitochondrial oxidative stress, restoring mitochondria respiration and decreasing tau accumulation and amyloid-beta fibrillation with polyprenols treatment

**Authors: G. DELL'ACQUA**[1], T. MC FADDEN[1], B. BLANC[2], R. LASSEUR[2], *N. COMPAGNONE[2]
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**Abstract:** The relationship between brain aging and Alzheimer's disease (AD) is contentious, yet extensive literature exists supporting a role for mitochondrial dysfunction and oxidative damage in the pathogenesis of AD. Using a patient-derived fibroblast model of AD, we investigated the activity of polyprenols studying the mitochondrial phenotype associated with AD. Polyprenols are the plant analogues and precursors of the transport lipid dolichol that play a crucial role in maintaining and protecting cell function. Dolichols are involved in protein glycosylation, controlling the regulation of protein synthesis and function. Found in the phospholipid bilayer, they modify the fluidity and permeability of membranes. We sought to determine how 3 escalading doses of polyprenols impacted mitochondrial functions associated with AD. We studied bioenergetics, redox status, mtDNA content, protein synthesis and ER stress through quantification of mitochondrial associated membranes (MAMs). We also quantified Tau, pTau expression level and amyloid beta fibrillation, hallmarks of the disease. In all experiments, polyprenols were able to dose-dependently restore a normal phenotype. In AD fibroblasts, induction of oxidative stress induced a higher oxidative response than in healthy cells. Polyprenols decreased $H_2O_2$-induced mtROS production, thus showing anti-oxidant properties at the two highest doses tested. This effect conveyed a 75-78% anti-oxidant rescue compared to a 43% generated by resveratrol. In AD fibroblasts, bioenergetics was impaired. Polyprenols normalized AD fibroblasts bioenergetics by improving: i) oxygen consumption; ii) ATP production; iii) lactate production and iv) the NAD+/ NADH ratio. Polyprenols also normalized mtDNA mass dose-dependently without affecting mtDNA content. Amyloid-beta fibrillation was increased in AD-fibroblasts compared to healthy cells. Polyprenols reduced amyloid fibril deposition in the extracellular space, in a dose dependent manner. They reduced Tau expression and the hyperphosphylorated form of Tau by 0.51-fold. Finally, in the AD fibroblasts there was an increase in MAMs, consistent with increased ER stress, and by using PLA we demonstrated that polyprenols normalized these interactions. In this work we confirmed the association between mitochondria dysfunction and AD. We also showed that polyprenols play an important role in reversing both mitochondria dysfunctions and pathological hallmarks of the disease, confirming their disease modifying capabilities. *The authors are grateful to Prenolica Ltd. for providing Bioeffective® R ("Ropren®), a concentrated extract of polyprenols.*

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**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.21/R15

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** 1DP3DK094292
1R24082842
Program for neurology research and discovery

**Title:** Saturated free fatty acids increase amyloid precursor protein levels in exosomes: A novel mechanism for the increased risk of Alzheimer’s disease in metabolic syndrome

**Authors: *B. KIM**, F. E. MENDELSON, C. FIGUEROA-ROMERO, E. L. FELDMAN
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**Abstract:** The prevalence of metabolic syndrome (MetS), including obesity and diabetes, among US adults aged 18 years or older has risen by more than 35% in last 20 years. In 2015, 30.3 million Americans had diabetes and more than 2 in 3 adults were considered overweight or obese. Multiple studies report that patients with MetS have an increased risk of developing Alzheimer’s disease (AD) compared to age- and gender-matched controls. An increase in free fatty acids (FFAs), especially saturated FFAs (sFFAs) such as palmitate, is one of the main characteristics found in obese people. Furthermore, higher levels of sFFAs in plasma is inversely correlated with cognitive function and are a significant risk factor for developing AD.
Exosomes are extracellular vesicles secreted by virtually all mammalian cells, including neurons, and they can be taken up by other cells. This exosome transfer allows intercellular communication but can also spread pathological proteins involved in neurodegenerative diseases such as AD, Parkinson’s disease, and prion diseases. Amyloid precursor protein (APP), β- & γ-secretases, and tau drive the progression of AD and are found in exosomes derived from AD neurons and microglia. These proteins accumulate in plaques in AD brains, and inhibition of exosome secretion reduces the plaque load in mouse models of AD. These findings indicate that exosomes not only deposit amyloid beta (Aβ), but also spread the ability to initiate plaques between cells.
Studies demonstrate that exosome production is increased in diabetes and obesity. In the current study we examined exosomes and their role in spreading APP pathology via FFAs. Treatment with the sFFAs, palmitate or stearate, increased APP levels in exosomes isolated from the cell culture supernatant of the HK-532 human cortical stem cell line or rat primary embryonic cortical neurons. APP levels in the cell lysates were not affected by sFFA treatment. In contrast, treatment with the unsaturated FFA, oleate, did not increase APP levels in exosomes and slightly

decreased the levels in the cell lysates. Metformin is an anti-diabetic medicine that modulates AMP-activated protein kinase (AMPK). We found that activation of AMPK by metformin or AICAR reduced APP levels in the lysates as well as in exosomes of basal and palmitate-treated neurons.
Overall, increased levels of APP in exosome following sFFA treatment suggest a possible explanation for the increased risk of AD in MetS.
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**Poster**

**744. Alzheimer's Disease and Other Dementias: APP/Abeta: Animal and Cellular Models III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 744.22/R16

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH AG051946
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UCLA, Department of neurology grant

**Title:** Targeting the DK-switch of nSMase2 to suppress tau propagation

**Authors: T. BILOUSOVA**[1], C. ELIAS[1], E. E. MIYOSHI[2], J. CAMPAGNA[1], K. VADIVEL[1], B. JAGODZINSKA[1], C. ZHU[1], M. ALAM[1], A. HATAMI[1], B. SIMMONS[3], N. GARG[3], *K. GYLYS[2], V. JOHN[1]
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**Abstract:** A number of tauopathies, including the most prevalent form of dementia – Alzheimer's disease (AD), have been described, but there are no approved therapies targeting tauopathies that are currently available. The common feature of this group of neurodegenerative disorders is accumulation of tau protein aggregates in neurons and/or glial cells. Notably, onset and severity of clinical symptoms in AD and some other tauopathies have been shown to correlate with the degree/stage of tau pathology, making modulation of tau propagation pathways an approach for therapeutic development.
Our screening efforts for tau propagation inhibitors led us to the identification of a brain permeable small molecule – cambinol – that is a known inhibitor of the neutral sphingomyelinase 2 (nSMase2). nSMase2 is a known gatekeeping enzyme involved in ceramide-

mediated exosome production. According to our data, cambinol inhibits cell-to-cell spread of tau oligomers derived from AD brain synaptosomes (P2) in tau biosensor-based D+R assay ($EC_{50}$ = 14 μM) and in the EV-mediated secondary assay. Interestingly, P2-seeded biosensor cells released 3.5 times more extracellular vesicles (EVs) compared to cells treated with empty liposomes. Biochemical examination of known exosome markers CD63, CD9 and syntenin-1 in the EV fractions by immunoblotting suggests that tau aggregation may interfere with some but not other exosome biogenesis pathways. An initial *in vivo* study shows that cambinol can reduce the level of the nSMase2 activity in the brain after oral administration at a dose of 100mg/kg. These data suggest that cambinol can engage the target, nSMase2, in the brain and is therefore a promising molecular probe to further evaluate this mechanism in tauopathy models. Our molecular docking and simulation analysis reveal that cambinol can target the DK-switch in the nSMase2 active site, and modulate the interaction between Asp430 (D430) and Lys435 (K435) involved in nSMase2 enzyme activity. Discovery of this novel molecular mechanism of the interaction between cambinol and nSMase2 has implications in the rational design and synthesis of novel nSMase2 inhibitors with superior drug-like properties that could inhibit propagation of pathologic forms of tau.

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**Poster**

**745. Alzheimer's Disease and Other Dementias: Abeta as a Therapeutic Target**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 745.01/R17

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Aβ aggregation modulator MRZ-99030 reverses synaptotoxic effects of $Aβ_{1-42}$ on LTP even following serial dilution to 1000:1 stoichiometric excess of $Aß_{1-42}$, suggesting a beneficial prion-like seeding mechanism

**Authors: *G. RAMMES**[1], H. RUSS[2], A. PEARLMAN[3], C. G. PARSONS[4]
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**Abstract:** Recent evidence indicates that soluble oligomers of β-$amyloid_{1-42}$ ($Aβ_{1-42}$) rather than plaques are the major cause of early synaptic dysfunction and neurodegeneration in Alzheimer's disease (AD). This has furthermore been hypothesised to progress by the self-replication and spreading of toxic Aβ oligomers through a prion-like mechanism. Recently we identified MRZ-99030, as a small molecule that promotes the formation of off-pathway, non-toxic aggregates

thereby reducing the amount of intermediate toxic soluble oligomeric Aβ species. When applied at a 10:1 stoichiometric excess to Aβ, MRZ-99030 clearly reversed the synaptotoxic effects of $A\beta_{1-42}$ oligomers on synaptic plasticity and cognitive performance (Parsons et al., 2015; Rammes et al., 2015). Based on long lasting beneficial "trigger" effects observed in *in vivo* models, we hypothesised that MRZ-99030 might be able to seed a beneficial self-replication of non-toxic Aβ aggregates. To test this hypothesis, we prepared a serial dilution of MRZ-99030 starting with a 10:1 stoichiometric excess to $Aß_{1-42}$ (100nM). After incubating the $Aß_{1-42}$/MRZ-99030 mixture for 20 mins 10% (5mL) was transferred to a freshly prepared solution with Aβ (100nM). This dilution step was repeated 5 times finally resulting in a 1000:1 stoichiometric excess of $Aß_{1-42}$ over MRZ-99030. The final solution was then tested for its ability to impair long-term potentiation (LTP) in CA1 neurons. In this study we show that serial dilution of MRZ-99030 applied for 90 mins to acute murine hippocampal slices at room temperature reversed the synaptotoxic effect of $Aß_{1-42}$ on CA1-LTP after tetanic stimulation (100Hz/1s) of the Schaffer collaterals (LTP control=154±4%, n=24; with 100nM $Aß_{1-42}$=117±2%, n=7; in the presence of (1000:1) $Aß_{1-42}$/MRZ-99030=139±6%, n=13). Since the rate of $Aß_{1-42}$ oligomer formation has a steep linear temperature dependence we performed the same experiments also under physiological temperature (37°C). Under these conditions control LTP reached 151±6% (n=8) of baseline which was reduced by 100nM $Aß_{1-42}$ to 15±2% (n=5). When slices were incubated with (1000:1) $Aß_{1-42}$/MRZ-99030, the detrimental effects of $Aß_{1-42}$ on LTP reversed to 44±11% (n=6). In summary, the present results demonstrate that MRZ-99030, when serially diluted, even at very low concentrations neutralizes the synaptotoxic effects of Aβ oligomers on hippocampal LTP. We hypothesise that MRZ-99030 acts via a "beneficial prion-like" mechanism which promotes non-toxic structural variants of Aβ aggregates that propagate their conformations through template-directed folding of naïve Aβ peptides, thereby reducing synaptotoxic effects.

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**Poster**

**745. Alzheimer's Disease and Other Dementias: Abeta as a Therapeutic Target**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 745.02/R18

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Investigating the effect of a small molecular compound YS620 in the treatment of Alzheimer's disease

**Authors: *R. LIU**[1], J. YUE[2], S. YANG[3], W. WU[1,4]
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**Abstract:** The autophagy-lysosome system is one of the major intracellular protein degradation systems. Dysregulation of autophagy contributes to neuronal cell death in Alzheimer's Disease (AD). β-site amyloid precursor protein cleaving enzyme 1 (BACE1) is the β-secretase that initiates generation of beta amyloid (Aβ), a major toxic species in AD. Recent studies illustrated that BACE1 can be recruited to autophagic vacuoles(AVs) for further degradation in lysosomes via the autophagy-lysosome pathway. However, whether modulating autophagy would delay or prevent the progression of AD via regulating BACE1 remains to be determined. We used a recently developed small molecular compound, YS620, to regulate autophagy flux in vitro and found this regulation occurs in an autophagy-related protein 5(Atg5)-dependent manner. This novel autophagy inducer remarkably reduces the level of BACE1 expression and decreases Aβ generation in N2aAPPswe cells, an AD cellular model. We further verified the effect of YS620 using an in vivo transgenic (Tg) animal model of AD. After daily treatment with YS620 from 8-weeks until 5-months of age, the learning and memory impairment of female TgCRND8 mice, were improved compared to vehicle-treated female Tg mice, as measured by Morris Water Maze. [WW1] The YS620-treated Tg mice also had a reduction in hippocampal amyloid burden at 5 months old.Taken together, these results illustrate that YS620 can prevent cognitive malfunction in a transgenic mouse model of Alzheimer's Disease and that at a cellular level, this process involves the autophagy-mediated regulation of BACE1. Thus, YS620, a novel autophagy inducer, may be a potentially effective therapeutic agent for the treatment of AD.

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**Poster**

**745. Alzheimer's Disease and Other Dementias: Abeta as a Therapeutic Target**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 745.03/S1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Uighur Medicine Foundation of Xinjiang Uygur Autonomous Region No.2015KL005
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**Title:** Total flavonoid extract from dracoephalum moldavicaL. attenuates β-amyloid-induced toxicity through anti-amyloidogenesic and neurotrophic pathways

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**Abstract: Aims:** Alzheimer's disease (AD) is an incurable neurodegenerative disorder characterized by global cognitive impairment with accumulation of amyloid-beta peptides (Aβ) in the brain. Herbal approaches can be used as alternative medicines to slow the progression of AD. This study aimed to determine the beneficial effects and potential mechanisms of total flavonoid extract from *Dracoephalum moldavica* L. (TFDM) for attenuating Alzheimer-related deficits induced by Aβ.
**Main methods:** We used the amyloid precursor protein (APP) and presenilin 1 (PS1) double transgenic mouse and copper-injured APP Swedish mutation overexpressing SH-SY5Y cells to demonstrate the beneficial effects of TFDM. Further, the mechanisms were conducted on anti-amyloidogenic and neurotrophic transductions both *in vitro* and *in vivo*.
**Key findings:** Our results indicated that TFDM treatment ameliorated cognitive impairments and neurodegeneration and improved antioxidant defense system in APP/PS1 mice. TFDM also reduced Aβ burden by relieving Aβ deposition, decreasing insoluble Aβ levels and inhibiting β-amyloidogenic processing pathway involving downregulation of β-secretase and β-C-terminal fragment in the brain. In the AD cell model, TFDM protected injured cells, combined with the beneficial effects of decreasing APP levels, lowering $A\beta_{1-42}$ and regulating the redox imbalance. Moreover, TFDM preserved the extracellular signal-regulated kinase/cAMP response element-binding protein/brain-derived neurotrophic factor pathway both *in vitro* and *in vivo*.
**Significance:** In conclusion, TFDM clearly demonstrated neuroprotective effects by restoring the anti-amyloidogenic and neurotrophic transductions in the context of AD-associated deficits. These findings raise the possibility of using herb-based substances as supplement or potential alternative supplement for attenuating progression of AD.

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**Poster**

**745. Alzheimer's Disease and Other Dementias: Abeta as a Therapeutic Target**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 745.04/S2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH/NINDS U01 NS 074501 Wagner (PI)
Cure Alzheimer's Fund (CAF) Wagner (PI) Tanzi (PI)
4T32AG000216-25

**Title:** γ-secretase modulator and BACE1 inhibitor combination therapy for Alzheimer's disease

**Authors: *O. PRIKHODKO**[1], P. D. NGUYEN[2], E. M. ROCKENSTEIN[2], J. B. FLORIO[2], M. MANTE[2], T. SEKHON[3], R. E. TANZI[4], R. A. RISSMAN[2,5], S. L. WAGNER[2,5]
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**Abstract:** Alzheimer's disease (AD) is the most prevalent form of dementia in the elderly, which affects about 5.4 million individuals in the US. Current AD treatments are limited to temporary and mild alleviation of cognitive and behavioral symptoms in a subset of patients; there is no cure, effective prevention therapy or treatment which alters the course of AD. The pathological features of AD include β-amyloid (Aβ) plaques and neurofibrillary tangles in the cerebral cortex and hippocampus. Aβ peptides are the product of the amyloid precursor protein (APP) proteolysis by BACE1 (β-site APP cleaving enzyme 1) to produce the membrane-bound C-terminal fragment C99, which is further processed by γ-secretase to generate a number of distinct Aβ species. Aβ40 is the most abundant secreted Aβ peptide; however, the more fibrillogenic Aβ42 is the primary constituent of Aβ plaques. Our group developed and tested a series of small molecule γ-secretase modulators (GSMs), with BPN15606 emerging as the leading candidate for clinical development. BPN15606 demonstrates excellent in vivo PK/PD properties, highly significant dose-dependent biochemical efficacy and dose proportional exposures. At higher doses, this compound can almost completely eliminate Aβ42 levels in both brain and in CSF. In the current study, we evaluated the benefit of a combinational therapy using BPN15606 and a BACE1 inhibitor, LY2886721, in multiple *in vitro* assays and in an animal study. We present the biochemical, behavioral and pathological results of the treatments in two age groups, pre- and post-plaque formation PSAPP mice.

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**Poster**

**745. Alzheimer's Disease and Other Dementias: Abeta as a Therapeutic Target**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 745.05/S3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** JST and MEXT

**Title:** Photooxygenation by biocompatible catalyst reduces the Aβ level in the brains of Alzheimer's disease model mice

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**Abstract:** Several lines of evidence suggest that the aggregation and deposition of amyloid-β peptide (Aβ) are associated with the pathogenesis in Alzheimer disease (AD). Therefore, the inhibition of Aβ aggregation and clearance of deposited Aβ have been focused as the therapeutic strategy for AD. We previously found that the photooxygenation of synthetic Aβ by small compound catalysts, which are activated by irradiation of light, reduced the aggregation potency and neurotoxicity of Aβ *in vitro* (Taniguchi et al., Nat Chem 2016; Ni et al., Chem 2018). To verify the effects of oxygenation of Aβ *in vivo*, we carried out the photooxygenation experiment using APP knock-in (NL-G-F; Saito et al., Nat Neurosci 2014) mice, and analyzed the brain Aβ amyloid by biochemical methods.
First, we analyzed the effect of photooxygenation on the aggregated synthetic Aβ *in vitro*. One to four oxygen adducts in Aβ were detected by MALDI-TOF-MS. Notably, the mobility of Aβ was shifted to 10 kDa on SDS-PAGE/immunoblot analysis, suggesting that the photooxygenation changed the conformation and/or biochemical character of Aβ. Next we performed the photooxygenation reaction using brain lysate obtained from 7-months old AD model mouse. Upon irradiation, 10 kDa Aβ was appeared in a similar manner to that observed in the experiment using synthetic Aβ, indicating that Aβ amyloid was successfully oxygenated in the brain. Finally, to photooxygenate the deposited Aβ in living mice, we injected the catalyst into hemi-hippocampus of 7-months old mice followed by irradiation by LED fiber. After 7 times of reactions, we collected the hippocampus and analyzed by immnoblotting. We found that 10 kDa Aβ was also detected under the reaction, indicating that oxygenation reaction occurred in the brains of living mice. In addition, this photooxygenation reaction decreased the total amount of Aβ in the brain.
These results indicate that the catalyst could photooxygenate not only synthetic Aβ but also Aβ deposited in the AD model mice brain. Moreover, the photooxygenation in living AD model mice significantly decreased the Aβ level, suggesting that photooxygenated Aβ was metabolized faster than naive Aβ. Thus, artificial photooxygenation by the catalyst would be a novel strategy for AD prevention and treatment.

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**Poster**

**745. Alzheimer's Disease and Other Dementias: Abeta as a Therapeutic Target**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 745.06/S4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NHRI Grant NPPP03-014
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**Title:** A novel antibody against Abeta as a theranostic drug for Alzheimer's disease

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**Abstract:** Pathological insults instigating self-propelling neuro-inflammation in the brain might occur many years before the presence of clinical manifestations in Alzheimer’s disease (AD). The severely compromised functioning of the brain due to such chronic insults makes AD treatment more difficult. Thus, intervention using a multi-functional treatment at the early stage of the disease is emerging as a promising therapeutic paradigm. However, preclinical diagnosis and effective cure for AD are not available so far. Recently, we have newly developed an antibody in both mouse and fully humanized versions, which recognizes various Aβ species and N-terminally modified pyro-glutamate Aβ. We found that this novel antibody can be used for early detection of cerebral Aβ levels and exerts multifaceted functionality in alleviating the AD-like pathology in APP/PS1 mice. This antibody exerts an ability of Aβ plaques engagement across blood-brain barrier through intraperitoneal injection and is able to transform over-activated microglia into ramified microglia with a healthy morphology, while enhancing microglial Aβ phagocytosis. Our data further indicate that treatment of this novel antibody appears to improve neuronal functions in APP/PS1 mice. For early detection of cerebral Aβ, intraperitoneal injection of this antibody triggered a robust efflux of cerebral Aβ into the bloodstream. The escalating Aβ levels in the serum were positively correlated with the cerebral Aβ levels in both Aβ plaques-laden and non-Aβ plaques-bearing APP/PS1 mice, which can be used to predict Aβ levels in the brain by monitoring the antibody-induced Aβ in the circulation. Data suggest that this novel antibody might exert theranostic potential for AD.

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**Poster**

**745. Alzheimer's Disease and Other Dementias: Abeta as a Therapeutic Target**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 745.07/S5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Genetic and pharmacological inhibition of calcium-sensing receptor (CaSR) prevents amyloid pathologies and neuronal degeneration and restores cognitive deficits in mouse models of familial Alzheimer's disease

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**Abstract: Background and objective:** Alzheimer's disease (AD) is a growing nerurodegenerative disease that causes cognitive dysfunction in aging populations. The extracellular calcium sensing receptor (CaSR) was originally found in parathyroid cells where it senses minute changes in extracellular [Ca(2+)] by raising intracellular Ca(2+) concentrations to control secretion of parathyroid hormone and mineral metabolism. We reported previously that increased CaSR expression in hippocampus neuron underlies neuronal apoptosis and degeneration in ischemic condition. The current study tested the role of CaSR in the pathogenesis of AD, as soluable Amyloid-beta was reported to activate this receptor directly, by examining the impact of pharmacological or genetic inhibition of CaSR activity in 5XFAD mice, an animal model with accelerated development of AD pathology. **Materials and Methods:** The 5XFAD mice were daily injected with a CaSRantagonist (NPS2143, 1mg/kg) from 3-6 months of age or bred with mice with targeted Casr gene KO (CaSR-/-) in hippocampal neurons by expressing CamKIIa-Cre transgene and homozygous floxed-CaSR alleles. Cognitive functions were assessed monthly by Y-maze test and novel objective recognition tests and brain histology was performed at 6-month age. **Results:** While significant worsening of cognitive functions ($p<0.01$) and loss of hippocampal neurons ($p<0.01$) were observed in the 5XFAD mice from 3 to 6 months of age, daily NPS2143 injections ($p<0.01$) and CaSR KO ($p<0.01$) completely prevented these adverse effects. In line with this, neuronal apoptosis assessed by caspase 3 staining were significantly increased ($p<0.05$) in 5XFAD mice, but suppressed by NPS2143 injections ($p<0.05$) and CaSR KO ($p<0.05$) in the latter mice. Furthermore, accelerated amyloid-β deposition assessed by immunohistochemistry in the 5XFAD mice was significantly reduced by NPS2143 injections ($p<0.05$) and CaSR KO ($p<0.05$). **Conclusion:** Suppression of CaSR expression and/or activity preserves cognitive function and prevents neuronal degeneration in the AD mouse model potentially by preventing a feed-forward 'amyloid cascade' that may cause neuronal hyperactivity and subsequent cell death. Because CaSR antagonist, calcilytics, has been used clinically for treatments of mineral diseases, this receptor represents a highly translatable therapeutic target for prevention and/or treatment of AD.

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**Poster**

**745. Alzheimer's Disease and Other Dementias: Abeta as a Therapeutic Target**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 745.08/S6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** CONACYT Grant CB-2013-220006
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**Title:** Structural characterization and *in vitro* effects of amyloid beta variants on citotoxicity, apoptosis and autophagy

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**Abstract:** Structural characterization and in vitro effects of amyloid beta variants on citotoxicity, apoptosis and autophagy.
Alzheimer´s Disease (AD) is the most common type of senile dementia that affects human health. Deposition of Amyloid beta (Aβ) peptide in the brain is one of the most important events in AD progression. Soluble oligomers are now considered as primary toxic agents in amyloid diseases. Preventing formation of these soluble oligomers could stop amyloid β-sheet self-assembly. For that reason, formation of Aβ oligomers is being considered a target for therapeutic strategies for AD. Aβ peptide amino acid sequence is essential for its aggregation properties, oligomer formation, leading to the amyloid plaque and ultimately causing cell death. In this work, we used three variants of Aβ peptide: One containing amino acids 1-42 which is the whole sequence of Aβ, another one with amino acid 1-40 and other restricted to amino acids 25-35 known as it's hydrophobic core. We inserted point mutations at positions: A30W, K28A and M35C to assess the effect of the amino acids in these positions in Aβ-peptide oligomer formation and their in vitro effects on citotoxicity, apoptosis and autophagy. We used AFM and Western blot to determine in vitro formation of oligomers. AFM results show that A30W, K28A and M35C variants of Aβ (25-35), Aβ (1-42) and Aβ (1-40) A30W generated oligomers with different structure comparing with WT peptide. Aβ (1-40)-K28A and Aβ (1-40) M35C generated more fibrils. Western blot showed that oligomers of WT and the variants were capable of cell

internalization. We tested the effects of the mutant peptides on citotoxicity, apoptosis and autophagy using the rat C6 glioma cell line. Aβ (25-35) mutants did not change in vitro effects of citotoxicity, apoptosis and autophagy comparing with WT peptide. But Aβ (1-40) and Aβ (1-42) mutants produced less cell death comparing with WT peptides. Our results demonstrate that point mutations are capable to change oligomer structural characteristics, cytotoxicity, apoptosis and the effect on autophagy compared to the Aβ WT peptide. The strategy of introducing these point mutations could be used to modulate or prevent cell death in Alzheimer's disease.

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**Poster**

**745. Alzheimer's Disease and Other Dementias: Abeta as a Therapeutic Target**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 745.09/S7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH P30 NS47466

**Title:** Double D-peptide injections interfere with uptake of corresponding D-peptide in Tg AD model mice

**Authors: *T. VAN GROEN**[1], N. JIANG[2], I. KADISH[1], D. WILLBOLD[2]
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**Abstract:** Our transgenic mouse lines express one gene with AD mutations, i.e., APPswe/dutch/iowa. They develop plaques at about four months of age, and we have described that two types of deposits are present, plaques, and diffuse deposits around blood vessels. Both plaques and blood vessel deposits are surrounded by activated glial cells. We have treated these mice with both D3 and RD2, anti Aβ42 oligomer targeted D-peptides, and improved cognitive deficits. We studied labeling of these deposits following single and double intracerebral (hippocampus) D3 and/or RD2 fluorescently labeled injections in these mice. We sacrificed and transcardially perfused the mice at two days following the injections. The brains were cut and immunohistochemically stained for Aβ species, and GFAP and Iba-1. Following the two day survival time the AD mice displayed a clear labeling of Aβ in the overlying cortex and hippocampus. No change was present between the labeling pattern following either D3 or RD2 injections. Labeled Aβ is present in lysosomes in neurons near the injection site, but surprisingly no labeled Aβ is present in astrocytes or microglia. Following double injections of both D3 and RD2 there are different labeling patterns, however, these are caused by the attached fluorophore,

not the different peptides. Furthermore, combined injections of unlabeled D-peptide and labeled D-peptide show that D3 limits uptake of labeled D3 but not RD2, and vice versa. Thus, likely the uptake of the D-peptides is through slightly different mechanisms, and, the choice of fluorophore significantly changes the properties of the combination. Finally it is likely that the two D-peptides target slightly distinct oligomers, suggesting a combination therapy.

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**Poster**

**745. Alzheimer's Disease and Other Dementias: Abeta as a Therapeutic Target**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 745.10/S8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIA Postdoctoral Training Grant (T32 AG00096)

**Title:** Probing the structures of beta-amyloid oligomers with antibodies generated against conformationally and structurally defined oligomers

**Authors: *A. KREUTZER**[1], R. MALONIS[2], M. DIAB[1], J. QUIROZ[2], S. YOO[1], G. GUAGLIANONE[1], J. LAI[2], J. NOWICK[1]
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**Abstract:** This talk introduces a new class of antibodies generated against structurally defined homogenous oligomers derived from the β-amyloid peptide Aβ. Polyclonal and monoclonal Aβ antibodies have been important tools for probing the structures of the toxic Aβ oligomers that are central to the pathogenesis of Alzheimer’s disease. Although the structures of Aβ oligomers remain unknown, “conformation dependent” antibodies have allowed researchers to probe oligomeric and fibrillar Aβ structures *in vitro* as well as in mouse and human brain tissues and fluids. Conformation dependent antibodies for Aβ oligomers are most commonly generated against Aβ oligomers and Aβ fibrils prepared *in vitro* from recombinantly expressed or chemically synthesized Aβ that are then used to immunize rabbits or mice. The antigenic Aβ oligomers in these preparations are heterogeneous in structure and stoichiometry and contain a vast diversity of conformational epitopes with inherently undefined structure, making it challenging to identify the exact epitopes that these conformation dependent antibodies recognize. These challenges demonstrate the need for more homogeneous and structurally defined Aβ oligomers for use in generating conformation dependent antibodies and in identifying and characterizing molecular targets for Alzheimer’s disease.
Our laboratory has elucidated the X-ray crystallographic structures of trimers, hexamers, and dodecamers composed of peptides derived from Aβ. These oligomers are the first ones derived

from Aβ in which the three-dimensional structures are known at high resolution, and are stable and homogeneous in solution. These oligomers are antigenic and contain conformationally distinct epitopes that have thus far been unexplored in Aβ structural biology. This talk will focus on monoclonal and polyclonal antibodies that specifically recognize these oligomers and how we have used these antibodies to correlate the high-resolution structures of our Aβ-derived oligomers with disease-relevant assemblies of the Aβ peptide. Western blotting and immunofluorescence studies in transgenic mouse and human brain tissue demonstrate that these antibodies recognize low-molecular-weight soluble Aβ oligomers, such as trimers, hexamers, and dodecamers and do not recognize the insoluble fibrils or plaques. These studies provide insights into the structures of soluble low-molecular-weight Aβ oligomers and pave the way for designing new therapies and diagnostics for Alzheimer's disease.

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**Poster**

**745. Alzheimer's Disease and Other Dementias: Abeta as a Therapeutic Target**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 745.11/S9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Supported by Fondecyt 1180752.

**Title:** Anti degenerative effectiveness by blocking multiple steps in the amyloid beta toxicity cascade

**Authors: *L. G. AGUAYO**[1], C. PETERS[2], F. BURGOS[2], D. BASCUÑAN[2]
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**Abstract:** The main neurotoxic agent of Alzheimer´s disease corresponds to diffusible oligomers of the β amyloid peptide (Aβ) released to the extracellular compartment and that subsequently associate to the neuronal membrane forming "pore-like" structures. These early membrane perforations can cause delayed alterations in calcium homeostasis leading to synaptic failure and death. Current therapies are not effective at curing or deterring disease progression, thus new approaches are needed. The importance of the C terminal region of Aβ in the association and perforation of the neuronal membrane was previously demonstrated. Using a pentapeptide derived from the primary sequence of Aβ, we were able to block multiple toxic steps of Aβ such as aggregation, association, membrane insertion, intracellular calcium increase and synaptotoxicity.
We are now examining a library of synthetic compounds in order to find small molecular weight peptidomimetic molecules that have similar neuroprotective effects, but with higher

pharmacological potential. A group of molecules having high *in silico* interaction with Aβ were selected and analyzed for their effects on Aβ aggregation, association, mitochondrial function and membrane perforation in PC12 cells and/or rat hippocampal neurons.
One of the new compounds examined, at low micromolar concentrations, was able to inhibit Aβ aggregation, membrane association, and intracellular calcium increase without producing an intrinsic toxic effect. It also blocked the synaptotoxicity and mitochondrial toxicity induced by Aβ. Experiments with Aβ injected in the hippocampus showed that the compound also blocked in vivo toxicity.
In conclusion, the present results indicate that it is feasible to develop peptidomimetic molecules that exert protective actions against Aβ at multiple steps similar to those reported with the G33LMVG37 pentapeptide.

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**Poster**

**745. Alzheimer's Disease and Other Dementias: Abeta as a Therapeutic Target**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 745.12/S10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** The neuroprotective effects of an active core sequence of amyloid beta on amyloid beta-induced synaptic deficits

**Authors: *K. FOREST**[1,2], K. ARORA[2], R. TAKETA[2], R. A. NICHOLS[3]
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**Abstract:** Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by progressive memory decline and loss of cognitive functions. AD is histologically characterized by the pathological aggregation of beta amyloid (Aβ) and tau neurofibrillary tangles. Monomeric soluble Aβ can switch from helicoidal to β-sheet conformation, promoting its assembly into toxic oligomers. These oligomers have been reported to induce neuronal death and synaptic transmission impairments. However, there is now considerable evidence that in normal healthy brains, soluble oligomeric Aβ functions as a neuromodulator. Our laboratory has shown that at low concentrations (pM-nM) a naturally produced N-terminal Aβ fragment (N-Aβ fragment) is nearly twice as effective as full-length Aβ as a neuromodulator, stimulating receptor-linked increases in $Ca^{2+}$, enhancing long-term potentiation (LTP) and enhancing contextual fear conditioning. In addition, we have recently shown that N-Aβ fragment protects against $Aβ_{42}$-induced neurotoxicity. We further identified a hexapeptide core sequence within the N-Aβ fragment, YEVHHQ (N-Aβcore), which is found to be equally as effective in $Ca^{2+}$ signaling and was shown to also be neuroprotective against $Aβ_{42}$-induced oxidative stress and neuronal death.

Here, we investigated the neuroprotective role of the N-Aβcore on synaptic plasticity in rodent hippocampal slice LTP and LTD. Additionally, we utilized inhibitors of kinases and phosphatases implicated in LTP and LTD, respectively, to understand the neuroprotective action of the N-Aβcore. We examined changes on various kinases in the MAPK pathway and proteins that have been linked with $A\beta_{42}$-induced toxicity and implicated in learning and memory upon NMDAR activation. Lastly, we compared the differential gene expression induced by N-Aβcore to that by full-length Aβ, in order to gain insights into the underlying mechanisms of neuroprotection by N-Aβcore over beta amyloid-induced neurotoxicity. The differentially modulated genes included, most notably, Rcan3, Parp1, Apba3, Rab11 and Kif1c. Elucidating the molecular pathway of the N-Aβcore provides a better understanding of its neuroprotective mechanism and its role at the synapses in the context of accumulating Aβ in AD. The neuroprotective action of the N-Aβcore suggests the possibility of using this core sequence as a scaffold for optimization of a potential biologic for protection against Aβ -induced toxicity.
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**Poster**

**745. Alzheimer's Disease and Other Dementias: Abeta as a Therapeutic Target**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 745.13/S11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant AG027924
NIH Grant AG046205

**Title:** Intranasal delivery of human iPSC-derived neural stem cells as a novel strategy for AD therapy

**Authors: *Y. FU**, J. ZHAO, M. DAVIS, Y. CHEN, C.-C. LIU, G. BU
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**Abstract:** Alzheimer’s disease (AD) is the most common cause of dementia, characterized by deposition of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain, accompanied by synaptic dysfunction and neuronal loss. Stem cell-based therapy has recently been explored as a promising treatment option for AD as it offers the potentials to provide a trophic environment for neuronal survival and cell replacement. The human induced pluripotent stem cells (iPSCs) reprogrammed from somatic cells offer versatility for stem cell-based therapy. However, optimizing cell delivery method to the central nervous system remains a challenge. Accumulating evidence has suggested that direct intranasal delivery of drugs, peptides, and nanoparticles to the central nervous system can bypass the blood-brain barrier and thus has

emerged as a non-invasive alternative to oral and parenteral routes. Here we investigated the feasibility of intranasal administration of iPSC-derived neural stem cells (NSCs) to mouse brain. Following intranasal delivery of GFP-labeled NSCs, we found that they effectively integrated into mouse brain as differentiated neurons and astrocytes. We thus plan to extend these studies to addressing therapeutic potentials of human iPSC-derived NSCs in AD model mice. As apolipoprotein E (*APOE*) ε4 allele is the strongest genetic risk factor for late-onset AD, we plan to test the effects of delivering NSCs with different *APOE* genotypes into the brains of 5xFAD amyloid model mice. We hypothesize that intranasal delivered human iPSC-derived NSCs will reduce amyloid pathology, rescue the neuronal loss, and slow down cognitive decline in 5xFAD mice in an *APOE* genotype-dependent manner. Behaviors and AD-related pathology will be evaluated at different time points after intranasal delivery of different dosages of cells. The successful completion of this project will not only address promises and limitations of stem cell-based therapy but also provide guidelines for the design of human clinical trials to treat AD.

**Disclosures: Y. Fu:** None. **J. Zhao:** None. **M. Davis:** None. **Y. Chen:** None. **C. Liu:** None. **G. Bu:** None.

**Poster**

**745. Alzheimer's Disease and Other Dementias: Abeta as a Therapeutic Target**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 745.14/S12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** 5 T32 AG 50061-2
UCD STAIR Award JVSTAR2 (To John Voss)

**Title:** The role a small, bi-functional molecule plays in reducing oxidative stress induced by intracellular amyloid-β in neuronal cell cultures

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**Abstract:** Alzheimer’s Disease (AD) is the most common cause of memory loss and associated dementia symptoms for which an effective treatment is still unavailable. The greater the understanding of the neurodegenerative processes of the AD brains, the more emphasis has been placed on the role of intracellular amyloid beta (Aβ) in the resulting pathological entities such as increased amyloid burden and neurofibrillary tau tangles leading to neurodegeneration. A most recent focus on the pathological interdependence of cellular toxicity events related to AD

pathology reveals the pathological trio of intraneuronal Aβ, oxidative stress and mitochondrial dysfunction as main causes of cognitive decline in AD. It is therefore imperative to explore avenues to disrupt the correlation between the factors leading to progression of disease. Here we explore the ability of a bi-functional small molecule to reduce aggregation of intracellular Aβ and attenuate oxidative stress in cultured neurons. Structurally, this small molecule is comprised of a nitroxide spin label linked to an amyloidophilicfluorene and is known as spin-labeled fluorene (SLF). The effect of the SLF on intracellular Aβ accumulation and oxidative stress was measured in MC65 cells, a human neuronal line with inducible expression of the Aβ precursor protein APP. Super-resolution microscopy imaging showed SLF decreases accumulation of intracellular Aβ. Confocal microscopy imaging of MC65 cells treated with a reactive oxygen species (ROS)-sensitive dye demonstrated SLF significantly reduced the intracellular Aβ-induced ROS signal. In order to determine the contributions of the separate SLF moieties to these protective activities, experiments were also carried out on cells with nitroxides lacking the Aβ targeting domain or fluorene derivatives lacking the nitroxide functionality. These findings support a synergistic effect of SLF in counteracting both the conformational toxicity of Aβ and its promotion of ROS.

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**Poster**

**745. Alzheimer's Disease and Other Dementias: Abeta as a Therapeutic Target**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 745.15/S13

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant NS094137
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**Title:** Molecular characteristics of amyloid-associated vascular dysfunction using single-cell RNAseq

**Authors: *A. WOJTAS**[1,2], J. P. SENS[1,2], K. E. BAKER[2], J. D. FRYER[1,2]
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**Abstract:** Alzheimer's disease (AD) is the most common form of age-related dementia and is pathologically characterized by amyloid-β (Aβ) peptide deposition in brain parenchyma as plaques and in cerebral blood vessels as cerebral amyloid angiopathy (CAA). We have previously investigated the effect of clusterin (CLU), a genetic risk factor for AD, on amyloid pathology using the APP/PS1 mouse model of AD amyloidosis on a Clu wild-type (*$Clu^{+/+}$*) and Clu knock-out (*$Clu^{-/-}$*) background. We have found that loss of CLU led to abundant CAA with the simultaneous reduction of parenchymal amyloid deposits. Surprisingly, despite the several-fold increase in CAA, mice lacking CLU had significantly less hemorrhage and inflammation. Although, our previous study suggests that CLU is a key player in regulating the balance between Aβ deposition and clearance in the brain, additional mechanisms underlying the pathogenesis of AD and CAA are still poorly understood. Here, we performed a single-cell transcriptomic study to characterize the brain vascular cell types and states using a transgenic mouse model of amyloidosis with differential CLU expression. We uncovered novel genes and cell-type specific pathways involved in CLU-dependent and/or amyloid-dependent vascular changes. Additional bioinformatics analyses and validation that aim to identify functionally different cell subpopulations based on their transcriptional profiles and CLU expression are currently being explored. This study significantly improves our ability to define the complex mechanisms of amyloid deposition in brain cerebrovasculature and its consequences.

**Disclosures: A. Wojtas:** None. **J.P. Sens:** None. **K.E. Baker:** None. **J.D. Fryer:** None.

**Poster**

**746. Alzheimer's Disease and Other Dementias: ApoE and Associated Pathways**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 746.01/S14

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIA grant #AG004085-26

**Title:** The effect of depressive symptoms on neuronal reward processing in apolipoprotein E4carriers

**Authors: *E. A. KAPOULEA**[1,2], C. MURPHY[3,1]
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**Abstract: Background:** Apolipoprotein (APOE) E4 is a well-established genetic risk factor for Alzheimer's Disease (AD), a devastating neurological disease that afflicts 46.8 million people globally. AD is characterized by a decline in memory, language, problem-solving, and other cognitive skills. Previous studies have reported synergistic interactions between depressive symptoms and APOE E4 on risk of AD. To our knowledge, this phenomenon has not yet been

evaluated in relation to processing taste stimuli. The objective of this study was to use functional magnetic resonance imaging (fMRI) to investigate the effects of depressive systems on neural reward processing in E4+ and E4- individuals when responding to taste stimuli. **Methods:** Blood-oxygenation-level-dependent (BOLD) activations (N=35) were measured during an fMRI scan. Participants were divided into one of two groups: E4- (n =22) and E4+ individuals (n = 12), based on results from genomic testing. Participants were orally and randomly administered three different aqueous solutions of caffeine, saccharine, and sucrose and asked to rate the intensity and pleasantness of each tastant using a general Labeled Magnitude Scale (gLMS). Participants were also asked to answer questions on the Beck Depression Inventory-II (BDI-II) to measure levels of depressive symptoms. The imaging data were processed using AFNI software. Beta coefficients were extracted from a priori regions of interest (ROIs) implicated in taste and reward processing. For each stimulus, partial correlation analyses, controlling for age, were performed between a priori ROIs and BDI scores. **Results:** A one-way ANOVA showed no significant differences between the groups in age, odor threshold, taste threshold, BDI scores, and hedonic ratings of caffeine pre and post scan. In the E4+ group, during the hedonic evaluation of caffeine, BDI scores positively correlated ($r(12) = .789$, $p = .004$) with activation in the anterior cingulate cortex (ACC). In the E4- group, during the hedonic evaluation of caffeine, BDI scores negatively correlated with ACC activation($r(22) = -.547$ , $p = .010$). **Conclusions:** Results suggest differences in neuronal activation in response to taste stimuli between E4+and E4- individuals. As BDI scores increased, those in the E4+ group had increased activation in the ACC, while those in the E4- group had decreased activation as BDI scores increased. The ACC has been associated with reward processing by encoding general task values and received rewards. Results suggest that E4+ individuals with higher depressive symptoms may need to rely on a greater neural network to process reward stimuli in comparison to E4- individuals.

**Disclosures: E.A. Kapoulea:** None. **C. Murphy:** None.

**Poster**

**746. Alzheimer's Disease and Other Dementias: ApoE and Associated Pathways**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 746.02/S15

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Neuropathological characterization of neuronal Apolipoprotein E in normal aged controls and AD brains

**Authors: *I. KAWAKAMI**, A. S. POZO, E. HUDRY, B. T. HYMAN
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**Abstract:** ***Introduction*** *APOEε4* is well known to be the genetic factor for late onset Alzheimer disease (AD). Previous studies have suggested that *APOEε4* increases amyloid beta

accumulation in human brains, but the correlation between the APOE status and tau pathology remains uncertain. ***Methods*** In the present study, we used a stereological approach to investigate the distribution of intraneuronal apoE in the hippocampus and temporal/occipital neocortex of normal aged controls in comparison with pathologically confirmed AD cases, stratifying the results by *APOE* genotypes. In addition, we examined whether there was a correlation between the presence of apoE in neurons and the presence of neurofibrillary tangles (NFTs). ***Results*** In control cases, we observed consistent and widespread intraneuronal apoE immunoreactivity in the hippocampus, especially within the CA1 region (less so in cortices). By contrast, AD brains displayed milder immunoreactivity in hippocampus but also in the cortices. ApoE positive neurons could occasionally be identified as pre-tangle and ghost tangle neurons, while most did not show any immunoreactivity for pathological tau. *APOEε4* carriers had lower neuronal apoE as compared with other genotypes, which resulted in a lower apoE/NFTs ratio. ***Conclusions*** Our findings suggest that the presence of apoE in neurons may be neuroprotective, and that the presence of *APOEε4* is negatively correlated with neuronal apoE in AD brains with a high burden of NFTs.

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**Poster**

**746. Alzheimer's Disease and Other Dementias: ApoE and Associated Pathways**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 746.03/S16

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH grant R01-NS100447

**Title:** The apolipoprotein E4 allele renders corpus callosum microcirculation and cognitive function more susceptible to cerebral hypoperfusion

**Authors: *S. AHN**[1,2], Y. HATTORI[1], L. PARK[1], C. B. SCHAFFER[2,1], C. IADECOLA[1]
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**Abstract:** The apolipoprotein E4 (ApoE4) allele is an emerging risk factor for the subcortical white matter (WM) injury underlying vascular cognitive impairment. Supplied by terminal arterioles in overlapping arterial territories, the subcortical WM is particularly vulnerable to vascular dysfunction and reduced cerebral perfusion. However, little is known about the microcirculation of the deep cortical WM and the impact that cerebral hypoperfusion exerts on WM microvascular flow and cognition. We sought to determine if the ApoE4 genotype is associated with alterations in WM microcirculation that may render the WM more susceptible to injury and produce more severe cognitive deficits. We used isoflurane-anesthetized human ApoE

targeted replacement mice (ApoE4-TR and ApoE3-TR) (Sullivan et al., JBC, 272:17972, 1997) (males; age 3-4 months; n=4-5/group). Bilateral carotid stenosis (BCAS) was induced by placing 0.18 mm microcoils around the common carotid arteries. Red blood cell (RBC) speed and vessel diameter were evaluated in the CC microcirculation at baseline and 4 weeks after BCAS in the same mice by three-photon excited fluorescence microscopy (3PEFM), which enables deeper penetration into the WM of the corpus callosum (CC) (≥1mm below the pial surface). At baseline, microvascular diameter in CC did not differ between ApoE4-TR (4.6±0.1 μm) and ApoE3-TR mice (5.0±0.1 μm; $p>0.05$), but RBC speed was slower in ApoE4-TR mice (ApoE4, 1.5±0.1; ApoE3, 1.9±0.1 mm/sec; $p<0.05$). Following BCAS, RBC speed decreased in both strains of mice, but the flow reduction was more severe in ApoE4-TR than in ApoE3-TR mice (ApoE4-TR, -48±8%; ApoE3-TR, -30±13%; $p<0.05$). However, microvascular diameter remained unchanged (ApoE4-TR, 4.9±0.1 μm; ApoE3-TR, 4.7±0.1 μm; $p>0.05$). Next, to assess the impact of the greater CC flow reduction in ApoE4-TR mice, we investigated the WM damage produced by BCAS and the attendant cognitive deficits. BCAS resulted in more marked CC demyelination in ApoE4-TR than in ApoE3-TR mice ($p<0.05$). BCAS also impaired cognition more severely in ApoE4-TR mice, examined with Y maze arm alternation and novel object recognition ($p<0.05$). These data suggest that the ApoE4 genotype is associated with more severe alterations in CC flow and cognitive function in the setting of cerebral hypoperfusion. Such alterations may play a role in the increased susceptibility to subcortical WM damage observed in individuals carrying the ApoE4 allele.

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**Poster**

**746. Alzheimer's Disease and Other Dementias: ApoE and Associated Pathways**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 746.04/S17

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Alzheimer's disease associated APOE4 regulates gene expression in the genomic vicinity of apolipoprotein E

**Authors: *R. URFER**, A. URFER-BUCHWALDER
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**Abstract:** Alzheimer’s disease (AD) affects millions of people worldwide. AD is caused by a combination of a subject’s genes, lifestyle and medical condition, as well as environmental factors. The single most important genetic contributor to AD is APOE4, a variant of the apolipoprotein E gene. We previously showed that the single nucleotide polymorphism rs429358 that defines APOE4 creates a recognition motif for the transcription factor nuclear respiratory

factor 1 (NRF1 ; UniProt Q16656). We hypothesized that this recognition motif acts as a transcriptional enhancer and thereby affects the expression of genes in the genomic vicinity of APOE4. In order to test this hypothesis, we performed a gene expression analysis in genetically defined human neurons. To this end, we built a custom gene array to probe genes located within 2 Mb of APOE on human chromosome 19 by quantitative polymerase chain reaction (qPCR). We measured differential gene expression in iPSC-derived human neurons homozygous for either the APOE4 (E4E4 ; AD-patient derived), APOE3 (E3E3 ; healthy control subject) or APOE2 (E2E2 ; healthy control subject) variants. qPCR analysis identified genes that are specifically regulated in E4E4 neurons but were unregulated between E3E3 and E2E2 neurons. Most of the E4E4-regulated genes were downregulated compared to the levels measured in E3E3 or E2E2 neurons. This finding is in line with known effects of enhancers that can both stimulate and inhibit gene expression. In conclusion, our data suggests that genes located in the genomic vicinity of APOE4 are regulated by this genetic variant in human AD neurons and may represent AD-causing genes.

**Disclosures: R. Urfer:** A. Employment/Salary (full or part-time):; Selonterra, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Selonterra, Inc. **A. Urfer-Buchwalder:** A. Employment/Salary (full or part-time):; Selonterra, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Selonterra, Inc..

**Poster**

**746. Alzheimer's Disease and Other Dementias: ApoE and Associated Pathways**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 746.05/S18

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** American Heart Association 15SDG22460003

**Title:** Deletion of LRP1 in vascular mural cells causes cognitive impairment depending on apoE isoforms

**Authors: *H. OUE**, Y. YAMAZAKI, I.-E. MOSNEAG, T. AIKAWA, M.-L. HOLM, G. BU, T. KANEKIYO
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**Abstract:** Since cerebral blood vessels play a critical role in maintaining brain homeostasis, cerebrovascular dysregulation leads to neuronal damage and diffuse white matter lesions, resulting in vascular cognitive impairment and dementia (VCID). VCID and Alzheimer's disease (AD) are the major causes of dementia in the aged population, while they often co-exist.

Accumulating evidence has shown that the ε4 allele of the apolipoprotein E (*APOE4*) gene increases the risk for VCID as well as AD, where *APOE4* disturbs cerebrovascular function and cerebrovascular endothelial integrity. In addition, a major apoE receptor, low density lipoprotein receptor-related protein 1 (LRP1), abundantly expressed in vascular mural cells including pericytes and smooth muscle cells. Thus, we investigated how the deletion of LRP1 in vascular mural cells, and apoE isoforms, affect the cerebrovascular system and cognitive performances using vascular mural cell specific LRP1 knockout mice (*smLrp1*$^{-/-}$) with *APOE3* or *APOE4* background. These mice were generated by breeding *Lrp1* floxed mice, sm22α-driven Cre recombinase mice and *APOE3*- or *APOE4*-targeted replacement (TR) mice. Morris Water Maze test revealed that spatial learning and memory ability was significantly impaired in *smLrp1*$^{-/-}$ mice compared to control mice with *APOE4* background, but not with *APOE3* background. We also found that the density of collagen IV, which is a main component of the vascular basement membrane, was lower in the brains of *APOE4; smLrp1*$^{-/-}$ mice than those of *APOE4* control mice when analyzed by immunohistochemistry. However there was no difference between *APOE3; smLrp1*$^{-/-}$ and *APOE3* control mice. The coverage of pericyte, tight junction proteins and astrocyte end-feet on cerebrovascular endothelial cells did not differ among the four groups. Taken together, our results suggest that LRP1 dysfunction in vascular mural cells contributes to cerebrovasculature dysregulation and related cognitive impairment in an apoE isoform-dependent manner.

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**Poster**

**746. Alzheimer's Disease and Other Dementias: ApoE and Associated Pathways**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 746.06/T1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIA Grant P01 AG26572
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**Title:** Effects of diet induced obesity and APOE genotype on Alzheimer-related pathology in female EFAD mice

**Authors: *A. CHRISTENSEN**[1], C. J. PIKE[2]
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**Abstract:** Alzheimer’s disease (AD) risk is significantly influenced by genetic and environmental risk factors. The greatest genetic risk factor for late onset AD is APOE genotype, with E4 carriers being at a greater risk than E2 or E3 carriers. This increased risk in APOE4

carriers is exacerbated in females. Further, obesity in midlife has been shown to significantly increase AD risk in late life. To investigate whether APOE genotype and obesity interact to affect AD pathogenesis in females, we studied the effects of diet-induced obesity in the EFAD mouse model of AD. EFAD mice have knock-in of human APOE3 (E3FAD) or APOE4 (E4FAD) in the presence of 5xFAD genes. Female EFAD mice were maintained on either Western diet (WD; 45% fat, 21% sugar) or a control diet (10% fat, 7% sugar) for 12 weeks. E3FAD mice showed greater metabolic impairments after WD including increased glucose dysfunction and increased circulating leptin. E4FAD mice did not show impairments after WD, but had poorer metabolic function at baseline than E3FAD mice. E3FAD mice on WD were impaired on cognitive tasks and showed increased beta-amyloid pathology. E4FAD mice were more impaired on the behavior tests and had greater beta-amyloid neuropathology in comparison to E3FAD mice, but showed no further impairment by WD. Microglia are believed to play an important role in the progression of AD neuropathology and are implicated in the effects of both APOE4 and obesity. We assessed the activation of microglia in the hippocampus. As with beta-amyloid pathology, E3FAD mice showed increased microglial activation after WD. E4FAD mice had more activated microglia than E3FAD mice, but no further impairment after WD. Overall, these findings demonstrate significant gene-environment interactions between APOE and obesity in female EFAD mice.

**Disclosures: A. Christensen:** None. **C.J. Pike:** None.

**Poster**

**746. Alzheimer's Disease and Other Dementias: ApoE and Associated Pathways**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 746.07/T2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** K01 AG044490 (NFF)
RF1 AG056371 (IL)
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R01 AG037919 (IL)
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**Title:** Apoe isoform specific effects on amyloid-β induced changes in microglial response

**Authors: *N. F. FITZ**, F. LETRONNE, B. E. PLAYSO, C. WOLFE, K. NAM, I. M. LEFTEROV, R. KOLDAMOVA
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**Abstract:** Although inheritance of APOE4 allele is a major genetic risk factor for late-onset Alzheimer’s disease (AD), the mechanisms underlying this association remain elusive. APOE

can differentially modulate amyloid β (Aβ) aggregation and clearance through blood brain barrier, or by astrocytic and microglial degradation. Microglia involvement in response to neurodegenerative processes and maintaining brain homeostasis is achieved through their ability to rapidly interact to changes in the brain microenvironment, enabling adequate phenotypic transformations. We hypothesize that APOE interacts with Aβ in an isoform-dependent manner, differentially impacting neuroinflammatory processes, particularly microglial response, influencing the progression of AD pathology. To test the hypothesis we infused co-incubations of Aβ with APOE3 or APOE4 native particles into the brains of WT mice to determine changes in microglial phenotypes. Utilizing magnetic-activated cell sorting we isolated microglia and neurons followed by RNA-seq to determine the impact of APOE isoform in the presence of Aβ on the transcriptomics of the two cellular populations. Utilizing FACS sorting we isolated the microglial into population which contain or lack infused fluorescently tagged Aβ and performed RNA-seq to determine changes in microglial response. Furthermore, using flow cytometry we determined the number of microglia containing Aβ for the Aβ+APOE3 and Aβ+APOE4 groups. Lastly, we utilized immunohistochemistry to confirm the RNA-seq results and further classify the microglial phenotypes of the two groups. We first show that microglial gene expression is more significantly impacted by the native APOE lipid particles when compared to neurons. Microglia in the Aβ+APOE3 group display significantly increased complexity and projections oriented toward the infusion site when compared to the Aβ+APOE4 group. Furthermore, microglia from the Aβ+APOE3 group show increased markers for chemotaxis. Microglia that contain Aβ in the APOE4 group display a unique transcriptome while displaying decreased phagocytic capacity. Infusion of Aβ+APOE3 or Aβ+APOE4 into $Trem2^{ko}$ mice further illustrate the importance of Trem2 in the microglial response to Aβ, Trem2 dependent mechanisms and differential impact of the APOE isoform even in microglia lacking Trem2. This study increases our understanding of the isoform-dependent effect of APOE on the microglial response to Aβ. Moreover, it provides a mechanism by which APOE isoform impacts the progression of AD and associated neuroinflammation.

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**Poster**

**746. Alzheimer's Disease and Other Dementias: ApoE and Associated Pathways**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 746.08/T3

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH/NIA R03AG0449288
NIH/NIA R25AG0478433
NIH/NIMH MH-091460

The DANA Foundation Clinical Neuroscience Grant

**Title:** The mechanism of olfactory dysfunction in APOE-associated dementia: Olfactory study in human APOE4 carriers and APOE mice

**Authors: *M. M. MISIAK**[1], J. N. O'NEIL[1], R. RAYHAN[1], M. HIPOLITO[2], N. RAI[2], C. K. MCLEAN[2], K. F. MANAYE[1], E. A. NWULIA[2]
[1]Dept. of Physiol. and Biophysics, Howard University, Col. of Med., Washington, DC; [2]Dept. of Psychiatry, Howard Univ. Hosp., Washington, DC

**Abstract:** As the number of older Americans grow rapidly, there is a dire need to identify and validate early pre-clinical markers for Alzheimer's disease (AD). Recent studies have shown that abnormalities in olfactory structure and function may precede overt symptomatic development of AD by more than a decade. However, the molecular mechanisms of olfactory neural dysfunctions in AD are poorly understood. In our recent review article we presented preclinical research revealing persuasive evidence that Apolipoprotein E (APOE) impacts olfactory neuronal structure and function and AD pathogenesis. However, this finding has not yet been demonstrated in living human subjects. In this preliminary analysis, we examine olfactory pathways in transgenic murine models of AD and APOE mice and APOE4 human carriers. We used 6-9 month old knock in (APOE3 and APOE4) and 5X-FAD mice and collected both Olfactory Bulb (OB) and Olfactory Mucosa (OM) for microarray and protein analysis. Gene, sex, and phenotype interactions were correlated with pathology of OM and OB. Initial findings show APOE4 variant had significant effects on the level of oxidative stress, mitochondrial dysfunction, Tau and collapsin response mediator protein 2 (CRMP2) phosphorylation in the olfactory tissues of AD mice. In our human study, we used our platform of human derived olfactory tissue to explore differences in molecular signatures comparing olfactory neuronal isoforms derived from APOE4 carriers (n =2) and isoforms derived from non-carriers of APOE4. More specifically, we were interested in exploring protein expression of CRMP2 (n=2), a microtubule-associated protein that is specifically hyperphosphorylated in AD. We have optimized the protocol and trouble shooting strategy in the study of protein and molecular signatures in human olfactory neuronal isoforms of APOE4 and non-APOE4 carriers. We found that both total and phosphorylated CRMP2 levels were increased in olfactory neurons from APOE4 carriers compared to non-carriers of APOE4. Our findings illustrate the utility of olfactory epithelial and neuronal platform as a model to study preclinical development of AD in those at high clinical risk. We anticipate extending this platform for detailed morphologic, molecular and proteomic studies that would define mechanisms of AD development and progression in preclinical populations. Although further validation is warranted, results indicate that analysis of olfactory structure in relation to pre-clinical markers may have important translational potential in the near future.

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**Poster**

**746. Alzheimer's Disease and Other Dementias: ApoE and Associated Pathways**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 746.09/T4

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** National Institutes of Health

**Title:** ApoE isoform-dependent microglial functions in response to demyelination

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**Abstract:** Emerging genetic, pathological, and mechanistic studies have provided strong evidence supporting a critical role of microglia in the pathogenesis of Alzheimer's disease (AD). Although known as the primary immune defense system in the brain, microglia and the inflammatory responses can play beneficial and/or detrimental roles upon neuronal injury and during disease progression. The ε4 allele of the apolipoprotein E (*APOE*) gene is the strongest genetic risk factor for late-onset AD, whereas *APOE* ε2 is protective compared to ε3 allele. Although apoE isoforms have been implicated in microglial functions, a direct comparison of how the three apoE isoforms impact microglial responses to neuronal injury is lacking. Here, we demonstrated dramatic differences of apoE isoforms in the activation and function of microglia upon cuprizone-induced demyelination. In particular, microglia in human apoE2-targeted replacement (apoE2-TR) mice are more efficient, whereas those in apoE4-TR mice are less efficient in the clearance of myelin debris compared to apoE3-TR mice. Deficiency of microglia in apoE4-TR mice was also evident morphologically as they exhibited a dystrophic phenotype. Importantly, several key molecules known to mediate microglial activation, migration, phagocytosis, and lipid catabolism were upregulated in the corpus callosum of cuprizone-treated mice in an apoE isoform-dependent manner. Our findings indicate that differential effects of apoE isoforms in microglia might contribute to their distinct ability to limit neuronal damages and/or facilitate repairs upon injuries, providing a novel pathway by which apoE2 reduces and apoE4 increases the risk of neurological diseases such as AD.

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**Poster**

**746. Alzheimer's Disease and Other Dementias: ApoE and Associated Pathways**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 746.10/T5

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH/NIAR03AG0449288
and NIH/NIAR25AG0478433

**Title:** Spatial learning and memory in murine models: Examination of gender, genotype and their interaction in 5xFAD and APOE transgenic mice

**Authors: *J. N. O'NEIL**, R. RAYHAN, M. M. MISIAK, K. F. MANAYE
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**Abstract:** Alzheimer's disease (AD) is the most common cause of elderly dementia with women having a higher incidence than men do. Genome-wide association studies have shown that the apolipoprotein Ɛ4 (APOE 4) allele is the strongest genetic risk factor for developing late-onset AD along with age and sex. Individuals with APOE Ɛ4 allele are predisposed to develop an accelerated decline in cognition compared to non-carriers, due to underlying changes in brain structure. Using APOE knock-in mice (APOE 3 and APOE 4) and 5xFAD transgenic mice that overexpress mutant human APP(695) with the Swedish (K670N, M671L), Florida (I716V) and London (V717) familial mutations, we investigated the impact of human APOE alleles (Ɛ3, Ɛ4) and human Alzheimer's mutations (5xFAD) on cognitive performance. Mice aged (6-9 months) were trained on the Barnes maze apparatus for 4 days followed by a 72-hour probe to assess long–term spatial memory. In this preliminary study, we determined whether significant differences due to gender, genotype, and their interactions effected spatial cognition and long-term memory throughout the protocol. During training day 1 there was no significant difference in latency times, however, from training day 2- 3 both wild type and APOE 3 found the target hole at a faster and more significant rate than 5xFAD and APOE 4 mice. On training day 4, APOE 4 mice found the target hole at a similar rate as APOE 3 and WT. In contrast, 5xFAD did not show any learning and was significantly different from all three groups. On the 72-hr probe assessing long-term spatial memory these differences persisted. All behavior data will be further correlated with pathology studies, Understanding the cognitive performance in this model will be important in developing treatment strategies for AD in the near future.

**Disclosures: R. Rayhan:** None. **M.M. Misiak:** None. **K.F. Manaye:** None.

**Poster**

**746. Alzheimer's Disease and Other Dementias: ApoE and Associated Pathways**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 746.11/T6

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH T32 DA007097
NIH R01 AG058081
NIH R21 AG056025
College of Pharmacy, Center on Aging, Academic Health Center of the University of Minnesota

**Title:** A clinically tested HDL mimetic peptide mitigates apoE4 associated lipidation and memory deficits

**Authors: *D. S. CHERNICK**[1], S. ORTIZ-VALLE[1], A. GRAM[2], L. LI[2]
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**Abstract:** The apoE ε4 allele is the primary genetic risk factor for late-onset Alzheimer's disease (AD), while apoE ε2 is protective, and apoE ε3 is neutral in this context. ApoE found in the brain is primarily produced and secreted by astrocytes, whereupon it binds lipids to form high-density lipoprotein (HDL)-like particles in the interstitial and cerebrospinal fluid. While the mechanisms by which apoE4 affects the development of AD are not completely understood, compelling evidence indicates that the pathogenic effects of apoE4 are mediated by lipid-related pathways. ApoE4 is known to be deficient in lipidation and formation of HDL in the brain, when compared to apoE3, while apoE2 is lipidated most effectively. ApoE directly interacts with amyloid-β (Aβ), and the level and lipidation state of apoE affects Aβ aggregation and clearance pathways. Our previous studies showed that a clinically tested 18-aa HDL mimetic peptide, 4F, increases the secretion and lipidation of apoE from wild-type primary murine astrocytes and mitigates Aβ-induced lipidation deficiency. Current results using primary murine astrocytes expressing the human apoE variants, as well as primary human astrocytes, confirm the relevance of our earlier work to human physiology. 4F restores apoE4 lipidation to a level similar to that of apoE2. Further, our studies indicate that apoE4 may be uniquely susceptible to the detrimental lipidation-inhibitory effect of Aβ, while apoE2 is protected against this insult. Our ongoing efforts seek to determine whether treatment with 4F can reverse the lipidation deficiency of apoE4 and improve memory and cognition *in vivo*. Aged mice expressing human apoE2, apoE3, or apoE4, were administered a once-daily I.P. injection of 2.5mg/kg D-4F for 3 weeks. 4F treatment was found to mitigate apoE4-associated memory deficits in this pilot study. Biochemical analyses of these animals are underway. Future studies will investigate the role of

4F in mitigating amyloid pathology in the context of the human apoE variants using mouse models of AD.

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**Poster**

**747. Alzheimer's Disease and Other Dementias: Other Dementias**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 747.01/T7

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Pilot study to detect Dementia based on vocal analysis

**Authors: *Y. OMIYA**[1], T. TAKANO[1], T. URAGUCHI[1], M. NAKAMURA[2], S. SHINOHARA[3], M. HIGUCHI[2], S. MITSUYOSHI[3], S. TOKUNO[4]
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**Abstract:** The prevalence of dementia tends to increase with the aging society. To deal with this problem, early detection and treatment of dementia is important. For diagnostic support and screening, intelligence test, biomarkers and image diagnosis such as CT, MRI, PET are used as the conventional method. However, these methods have problems such as high inspection cost, invasiveness, requirement for dedicated equipment.
Our relevant research was to estimate health conditions, such as depression and stress state using voice. Analysis using voice is advantageous in terms of providing diagnostic support for physicians, it is non-invasive, it can be performed remotely and it doesn't require special equipment. In this paper we examined pilot study to detect dementia based on vocal analysis.
In the experiment, we collected voice (96kHz, 24bit, wav file) using an IC recorder and a pin microphone from healthy subjects (n=18) and patients with Dementia (n=39) in a hospital's consulting room. The voices were collected when the subjects read 13 fixed phrases. Informed consent was obtained from the subjects.
In the evaluation, extracted 600 acoustic features from each phrase's speech using the openSMILE software. Then, to develop an algorithm using the J48 decision tree-induction algorithm (Weka implementation of C4.5) with 10-fold cross validation for classifying healthy subjects and patients with Dementia. As a result, the classification performance of the algorithm relative to healthy subjects, patients with a dementia is 79.6% with recall of 0.679 and 0.847, respectively, and precision of 0.659 and 0.858, respectively.
Consequently, the algorithm performed well in classifying healthy subjects and patients with dementia, which suggest the utility of the classification algorithm in estimating disease

conditions based on speech. Future studies will subdivide dementia into Alzheimer's type, Lewy body type, etc., verify with voice collected at other hospitals, and improving its accuracy.

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**Poster**

**747. Alzheimer's Disease and Other Dementias: Other Dementias**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 747.02/T8

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** Internal call for projects of the University Hospital of Strasbourg, Alsace Alzheimer 67 Association and Fondation Université de Strasbourg
Inter-regional hospital research grant (IDRCB 2012-A00992-41)
Ministerial PhD scholarship

**Title:** Functional connectivity profile during inter-task resting state in dementia with Lewy bodies

**Authors: *E. CHABRAN**[1], D. ROQUET[2], D. GOUNOT[2], F. BLANC[2,3]
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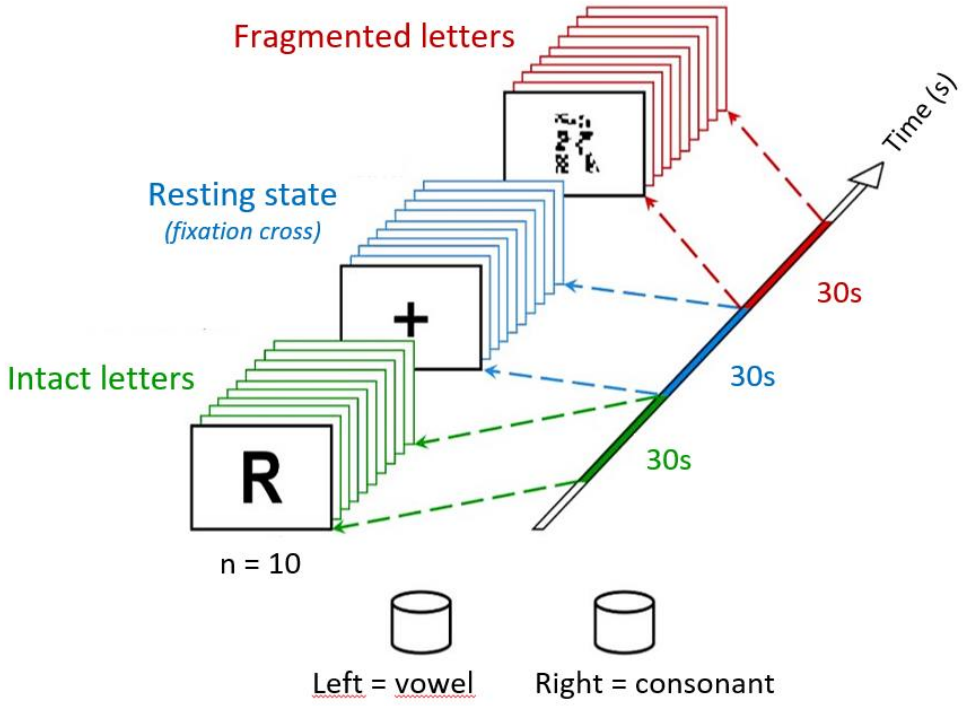
**Abstract: *Aims*:** Limited research has been done on the functional connectivity in visuoperceptual regions in dementia with Lewy bodies (DLB) patients. This study aimed to investigate the functional connectivity differences between a task condition and an inter-task resting-state condition within a visuoperceptual paradigm, in DLB patients compared with Alzheimer’s disease (AD) patients and healthy elderly control subjects.
***Methods*:** 26 DLB, 29 AD and 22 healthy subjects underwent a detailed clinical and neuropsychological examination along with a functional MRI during the different conditions of a visuoperceptual paradigm. Functional images were analyzed using group-level spatial independent component analysis and seed-based connectivity analyses.

***Results*:** While the DLB patients scored well and did not differ from controls and AD groups in terms of functional activity and connectivity during the task conditions, they showed decreased functional connectivity in visuoperceptual regions during the resting-state condition, along with a temporal impairment of the default-mode network activity. Functional connectivity disturbances were also found within two attentional-executive networks, and between these networks and visuoperceptual regions.
***Conclusion*:** We found a specific functional profile in the switching between task and resting-state conditions in DLB patients. This result could help better characterize functional impairments in DLB and their contribution to several core symptoms of this pathology such as visual hallucinations and cognitive fluctuations.

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**Poster**

**747. Alzheimer's Disease and Other Dementias: Other Dementias**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 747.03/T9

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** The Jerome Lejeune Foundation Grant #1483

**Title:** Chronic suppression of monoacylglycerol lipase improves adult neurogenesis in septal but not temporal part of DG in a mouse model of Down syndrome

**Authors: D. FOZOONMAYEH**[1], J. YU[1], M. SANKARAN[1], M. WALSH[1], M. SAWA[1], A. TYRTYSHNAIA[1,2], M. KHOTIMCHENKO[2], *A. M. KLESCHEVNIKOV[1]
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**Abstract:** Chronic treatment with the selective monoacylglycerol lipase (MAGL) inhibitor JZL184 restores hippocampal long-term potentiation and improves cognition of aged Ts65Dn mice, a genetic model of Down syndrome (DS) (Lysenko et al, 2014). To assess possible mechanisms responsible for these improvements, here we examined the effects of JZL184 treatment on adult neurogenesis in the Ts65Dn dentate gyrus (DG). JZL184 (8 µg/kg, i.p.) or vehicle were injected in 9 months old trisomic and control euploid (2N) mice once a day during 20 days. BrdU was injected on days 11-14 of the JZL184 treatment. Total number and density of BrdU-positive cells were significantly reduced in the vehicle-treated Ts65Dn mice indicating reduced adult neurogenesis. JZL184 treatment increased the rate of adult neurogenesis in Ts65Dn but not in 2N mice. Analysis of DG subregions showed that the changes were mostly similar in the septal, middle, and temporal portions of Ts65Dn *vs*. 2N DG. However, the effects of the JZL184 treatment in Ts65Dn mice were mostly confined to the septal part of the dentate gyrus. Thus, in the septal portion of DG, the BrdU+ cell density was reduced in Ts65Dn Veh group to 41.7 ± 11.9% ($p = 0.03$) and restored in Ts65Dn JZL group to 99.5 ± 34.7% ($p = 0.78$) of the corresponding values in the vehicle-treated 2N control mice. In the temporal portion of DG, the BrdU+ cell density was also reduced in Ts65Dn Veh group to 58.4 ± 6.7% ($p = 0.03$) but remained reduced in Ts65Dn JZL group at 57.9 ± 3.6% ($p = 0.03$) of the 2N Veh controls. Selective restoration of adult neurogenesis in the septal but not temporal DG may explain previous observations that JZL184 treatment improved cognition but had no effect on anxiety related behavior in Ts65Dn mice. Thus, chronic treatment of aged Ts65Dn mice with the selective MAGL inhibitor JZL184 selectively improved adult neurogenesis in the septal portion of Ts65Dn DG. Together with previous data, these results indicate that JZL184 treatment have several beneficial effects in the Ts65Dn model of DS and, therefore, can be regarded as a prospective approach for pharmacotherapy of cognitive impairment in DS.

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**Poster**

**747. Alzheimer's Disease and Other Dementias: Other Dementias**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 747.04/T10

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Increased kynurenic acid in cerebrospinal fluid of patients with hydrocephalus

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**Abstract: Background** Symptomatic normal pressure hydrocephalus is a potentially reversible neurodegenerative disease commonly characterized by gait and urinary disturbance and occurrences of dementia. There is also hydrocephalus e-vacuo characterized by occurrence of dementia but without gait and/or urinary disturbance and no cerebrospinal fluid (CSF) pressure elevation. Since kynurenic acid (KYNA) is suggested to be involved in dementia present study aimed to investigate KYNA levels in the CSF of patients with hydrocephalus.
**Material and Methods** Clinical parameters in the CSF and serum of hydrocephalus patients (N=9) and of control subjects (CO, N=30), obtained from Neurological Department General Hospital Amstetten, Austria were evaluated. In addition by using HPLC method we measured KYNA levels in the CSF. Study was carried out according to ethical rules of the Lower Austrian Government.
**Results** We found significant increase of protein in CSF of patients with normal pressure hydrocephalus (207.2 % of CO; $p<0.01$) but not with hydrocephalus e-vacuo, comparing to control subjects. Furthermore, also albumin in CSF, IgG CSF, ratio CSF:serum IgG and ration CSF:serum albumin were significantly increased in the patients with normal pressure hydrocephalus (217, 290, 270 and 230 % of CO; $p<0.01$, respectively) but not in patients with hydrocephalus e-vacuo. KYNA levels in CSF of patients with normal pressure hydrocephalus were moderately but significantly increased (141 % of CO, $p<0.05$) and in patients with hydrocephalus e-vacuo significant increase of KYNA levels in CSF was found (225 % of CO, $p<0.01$), comparing to control subjects.
**Conclusion** KYNA levels are moderately but significantly increased in CSF of patients with normal pressure hydrocephalus and in hydrocephalus e-vacuo the increase was markedly higher. Measurement of KYNA levels in CSF might be interesting additional approach distinguishing patients between normal pressure hydrocephalus and hydrocephalus e-vacuo. We suggest that an enhancement of KYNA in CSF found in patient with normal pressure hydrocephalus and e-vacuo might play a role for the occurrence of dementia. All authors have no conflict of interest.
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**Poster**

**747. Alzheimer's Disease and Other Dementias: Other Dementias**

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**Program #/Poster #:** 747.05/T11

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** MOP-FDN 148418

**Title:** Altered pupil dynamics in patients with neurodegenerative diseases

**Authors: *J. HUANG**[1], B. C. COE[1], M. SMORENBURG[1], D. BRIEN[1], S. E. BLACK[2], E. FINGER[3], M. FREEDMAN[4], A. E. LANG[5], M. J. STRONG[6], R. H. SWARTZ[7], M. CARMELA TARTAGLIA[5], L. ZINMAN[5], .. ONDRI INVESTIGATORS[1], D. P. MUNOZ[1]
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**Abstract:** The progressive loss of brain matter in neurodegenerative diseases leads to impairments in numerous autonomic, motor, and cognitive functions. An easy-to-measure method that is increasingly used in clinical investigations to assess cognitive function is pupillometry. In addition to global luminance and arousal, pupil size is also modulated by converging bottom-up sensory and top-down cognitive signals. Furthermore, the circuitry for pupil control is suggested to be linked to the saccade generation system. We hypothesize that disruptions in neural circuitry due to neurodegeneration or brain injury can affect pupil control and its relationship to the saccade system. Here, we examined pupil dynamics in patients diagnosed with one of 6 neurodegenerative diseases (Alzheimer’s disease, mild cognitive impairment, Parkinson’s disease, amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), vascular cognitive impairment) during an interleaved pro-/anti-saccade task, and hypothesized that specific components of the pupil response should be altered due to neurodegeneration. Pupil size and eye position were recorded while subjects performed the task. The pupil response following the presentation of the fixation cue consisted of an initial constriction component, which was mainly driven by the change of luminance level from fixation cue onset, followed by a dilation component that has been previously linked to saccade suppression and voluntary saccade preparation. Analysis revealed distinct differences between patient groups and age-matched controls in pupil dynamics. Pupil constriction was reduced in the patient groups compared to controls as was pupil dilation, suggesting changes in the light reflex pathway and the top-down preparation signals, respectively. Furthermore, there were differences in pupil measurements among the patient groups that may reflect disease differences in

neurological deficits. Reduction in pupil dilation was smallest in ALS and greatest in FTD, which was in line with anti-saccade performance where FTD showed the highest error rate among patient groups. The results demonstrated changes in pupil dynamics linked to neurodegeneration, showing that pupil measurements in visuomotor tasks have the potential to provide relevant early behavioural biomarker for diagnosis of neurodegenerative diseases and tracking disease progression.

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**Poster**

**747. Alzheimer's Disease and Other Dementias: Other Dementias**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 747.06/T12

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIH Grant RO1 MH111265
PET Program project, grant P50 AG005133

**Title:** Co-registration of mri-defined white matter lesions with ex-vivo registration

**Authors: *S. MCKEON**[1], A. RANGARAJAN[2], M. WU[3], N. FARHAT[2], T. SANTINI[2], S. WOOD[2], T. IBRAHIM[2], M. IKONOMOVIC[4], J. KOFLER[5], O. LOPEZ[6], B. KLUNK[3], H. AIZENSTEIN[3]
[2]Bioengineering, [3]Psychiatry, [4]Neurol., [5]Pathology, [6]Radiology, [1]Univ. of Pittsburgh, Pittsburgh, PA

**Abstract:** In older adults hyperintense signal is often found in the cerebral white matter on T2-weighted magnetic resonance imaging. These white matter lesions are found to be clinically associated with a cognitive, mood, and functional disturbances. These lesions are believed to have heterogenous origin, including both inflammatory and ischemic components. However, histopathologic correlations are limited since the WMLs are only seen on in-vivo scans and not on the postmortem ex-vivo MRI. Thus, alignment from in-vivo to ex-vivo MRIs is essential for improved understanding of the histopathology of WMLs. In the current study we address this challenge by developing an automated alignment method to register the in-vivo MRI to ex-vivo histopathology. Further WMH histological characterization is a long term goal that this method would facilitate. We scanned subjects (N=3, age during in-vivo scan= 87 (SD 1), age at death = 91(SD 1)) in-vivo and at postmortem (left hemisphere (LH)) to obtain T1-weighted, T2-weighted fluid attenuated inversion recovery (FLAIR) 7T MRIs. The ex-vivo tissues were cut into slabs of

1cm thickness and photographs were obtained. The ex-vivo MRI LH was reoriented into the same orientation as the in-vivo LH using FSL linear affine registration (flirt). The ex-vivo LH was mirrored to also create a full-brain ex-vivo image. Both ex-vivo and in-vivo whole brains were run through the SPM segmentation feature to acquire their forward and inverse deformation fields into MNI template. Spatial normalization within SPM12 was then used to apply the deformation fields to the original images. The forward deformation fields were applied to their corresponding MRIs to normalize them to the MNI template, while the ex-vivo inverse deformation field was applied to both the in-vivo and ex-vivo MRI. This method was applied to both the FLAIR MRI and the corresponding white matter segmentations. This produced a registration across the in-vivo, ex-vivo, FLAIR and white matter hyper intensities. The alignment allows us to view the WMLs on both the ex-vivo MRI and the postmortem histology.

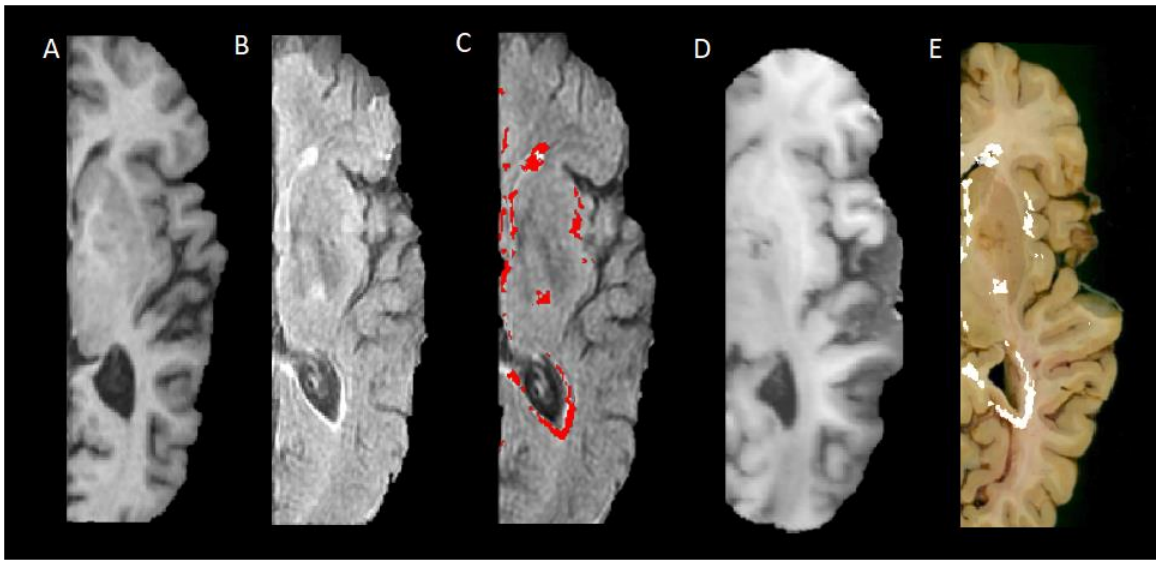


**Figure 1: Left hemisphere of A. T1-weighted in-vivo MRI B. T2-weighted (FLAIR) in-vivo MRI C. Segmented white matter hyper-intensities (red) overlaid on T2-weighted in-vivo D. T1-weighted ex-vivo MRI E. Segmented white matter hyper-intensities (white) overlaid on ex-vivo slab (1cm thickness) photograph**

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**Poster**

**747. Alzheimer's Disease and Other Dementias: Other Dementias**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 747.07/T13

**Topic:** C.02. Alzheimer's Disease and Other Dementias

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**Title:** Identification of disease-specific features of electroencephalograms of REM sleep behavior disorder patients with deep neural network

**Authors: *D. YEO**[1], S. HER[1], K. CHA[1], P. SEO[1], H. KIM[1], S. CHOI[1], K.-Y. JUNG[2], K. KIM[1]
[1]Yonsei Univ., Wonju / Gangwon-Do, Korea, Republic of; [2]Seoul Natl. Univ. Med. Ctr., Seoul, Korea, Republic of

**Abstract: Introduction:** Rapid eye movement sleep disorder (RBD) is a neurological disorder characterized by the loss of atonia during REM sleep. We investigated disease-specific features of event-related electroencephalograms (EEGs) during visuospatial attention task, and applied them to classify RBD patients from healthy controls using deep neural network. **Methods:** Nineteen healthy subjects (63.47 ± 7.37 years) and 16 drug-naïve idiopathic RBD patients (64.94 ± 6.92 years) participated in the study. Subjects performed Posner's cueing task. Valid and invalid stimuli were presented at 50:50 ratio, and the interval between cue and target was set to 200 ms and 1000 ms, respectively. Subjects were instructed to press a button when the target stimuli appeared. During the experiment, 60 channel EEG was recorded. Source localization analysis was performed. A 5-layer feedforward neural network was used as a pattern classifier. The inputs for the classifier were constructed from the time-samples of single-trial event-related current density time-series (-200 ms to 900 ms around the target onsets) . Layer-wise relevance propagation was used to find important time interval and brain area for classification from the trained neural network. **Results:** The classification accuracy was 83.29 ± 1.07%, and the sensitivity and specificity were 80.23% and 84.65%, respectively. The most important features for the classification were found to be the cortical currents within occipital and frontal regions at 200-350 ms poststimulus. **Discussion:** The temporal and spatial characteristics of the features crucial for the classification of RBD imply dysfunction of inhibitory attentional process of RBD patients. This is in accordance with the lack of the inhibition of return (IOR) associated with RBD.

**Disclosures: D. Yeo:** None. **S. Her:** None. **K. Cha:** None. **P. Seo:** None. **H. Kim:** None. **S. Choi:** None. **K. Jung:** None. **K. Kim:** None.

**Poster**

**747. Alzheimer's Disease and Other Dementias: Other Dementias**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 747.08/T14

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Sex-dependent effects of prediabetes in mouse models of Alzheimer's disease and mixed dementia

**Authors: *L. S. ROBISON**[1], O. GANNON[1], A. E. SALINERO[1], M. THOMAS[2], A. TYSON[1], K. L. ZULOAGA[1]
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**Abstract:** Alzheimer's Disease (AD) and vascular dementia are the two most common forms of dementia, and it has been estimated that 60% of individuals with AD have underlying cerebrovascular pathology/mixed dementia (MD). Diabetes increases the risk for both vascular and non-vascular dementia (including AD). Less is known about the effects of prediabetes, insulin resistance and glucose intolerance in the absence of hyperglycemia. This is a critical gap in knowledge, as prediabetes is 3x more common than diabetes and affects 38% of Americans. Prediabetes has been linked to early indicators of dementia, including hippocampal atrophy and memory deficits. Despite strikingly high prevalence and rates of comorbidity, much less is known about the effects of prediabetes on vascular and AD pathology and symptomology, particularly when these pathologies co-occur. In addition, since females have higher rates of dementia and faster rates of decline in cognition, sex differences must be explored. Therefore, the aim of the current study was to determine whether sex differences in the effects of prediabetes (modeled by chronic high fat diet) exist in mouse models of AD and MD. Male and female 3xTg-AD mice received either sham (AD model) or right unilateral common carotid artery occlusion (rUCCAO) surgery (MD model) at ~2.5 months of age; these were compared to wild-type (WT)/sham surgery (control) mice of both sexes. Mice were then placed on either low fat (LF; 10% fat) or high fat (HF; 60% fat; prediabetes model) diet for 3 months, then subjected to a glucose tolerance test (GTT), and used for either assessment of neurogenesis or behavior/cognition. Additional aspects of neuropathology (e.g. cerebral blood flow, amyloid, inflammation, cell death, and integrity of white matter, vasculature, and blood brain barrier integrity) are also being assessed. rUCCAO resulted in ~20% reduction in blood flow to the right hemisphere immediately after surgery. HF diet increased body weight gain and visceral fat mass, and impaired glucose tolerance, across groups. These metabolic deficits appear to be greater in females compared to males, and in 3xTg-AD mice regardless of surgery (AD and MD models) compared to WT mice. HF diet did not affect novel object recognition performance in WT mice; however, most AD and MD groups were impaired on this task. HF diet generally impaired spatial memory in the Morris water maze across mouse models, and MD (regardless of diet) also

hindered performance. This study will be critical for understanding sex differences in the effects of prediabetes on Alzheimer's disease and mixed dementia, and may point to pathways that could be targeted to enhance functional outcomes.

**Disclosures: L.S. Robison:** None. **O. Gannon:** None. **A.E. Salinero:** None. **M. Thomas:** None. **A. Tyson:** None. **K.L. Zuloaga:** None.

**Poster**

**747. Alzheimer's Disease and Other Dementias: Other Dementias**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 747.10/T15

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Title:** Microglia engulfment of Purkinje cell dendrites precedes neurodegeneration in the NPC1$^{nmf164}$mutant mouse

**Authors: L. KAVETSKY**[1], K. GREEN[2], *I. SOTO[1]
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**Abstract:** In Niemann Pick Type-C (NPC) disease, progressive and severe degeneration of neurons in different regions of the brain, but more severely in the cerebellum, is accompanied by neuroinflammation. Although neuroinflammation is considered a pathological hallmark of NPC, the temporal activation and its contribution to neuronal degeneration have not been elucidated. The aim of this study was to determine the sequence of neuroinflammation and its correlation with Purkinje cell (PC) loss and behavioral deficits in the NPC1$^{nmf164}$ mouse model of the disease. At early stages of NPC disease (4wk), when no signs of motor dysfunction were detected, microglia reactivity and activation were already evident in the molecular layer (ML) where PCs synaptic connections reside. Significant changes in IBA1+ cell number and morphology in the ML were remarkable even without loss of PCs at this early stage. Also, accumulation of CD68+ phagosomes in microglial cells was already evident at early stages of the disease in the mutant mice. At stages of moderate (8wk, ~50%) and severe (12wk, ~80%) degeneration of PC, the number of IBA1+ microglia/macrophages was significantly elevated and the morphology of these cells was found less ramified and more amoeboid shape. In addition, the accumulation of CD68+ phagosomes and autofluorescent material in these cells was remarkably higher when compared with younger NPC1$^{nmf164}$ mice, indicating increased phagocytic activity and lack of proper lysosomal function in these cells. For instance, more PC dendrites were found to be engulfed by microglia/macrophages in the mutant mice, suggesting that dendrite degeneration and engulfing by phagocytes precede neuronal death. We also found that the majority of these phagocytic cells were negative for the resident microglia marker TMEM119, suggesting that the majority of IBA1+ myeloid cells in the cerebellum at these stages of NPC disease are infiltrating monocytes. The increased neuroinflammation found in the late stages of

NPC was directly correlated with the loss of Purkinje cells and motor deficits in the NPC1$^{nmf164}$ mutant mouse. Our findings suggest that neuroinflammation in the cerebellum of NPC1$^{nmf164}$ mutant mice is a pathological event that precedes the death of PC and that is involved in the degeneration of PC dendrites.

**Disclosures: L. Kavetsky:** None. **K. Green:** None. **I. Soto:** None.

**Poster**

**747. Alzheimer's Disease and Other Dementias: Other Dementias**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 747.11/T16

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** 5R01NS082265-05

**Title:** Identification and characterization of frontotemporal dementia risk factor TMEM106B interacting proteins

**Authors: *R. CHARAN**[1], T. L. UNGER[2], D. AMADO[2], J. MAK[2], M. P. HERNANDEZ-CON[2], A. S. CHEN-PLOTKIN[2]
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**Abstract:** Frontotemporal lobar degeneration (FTLD) is characterized by selective degeneration of the frontal and temporal lobes of the brain, and is one of the leading causes of early-onset dementia. However, the pathological mechanisms underlying this disorder are not very well understood. Common variants at the gene encoding Transmembrane Protein 106B (*TMEM106B*) have been shown to increase genetic risk for FTLD with TAR DNA-binding Protein 43 (TDP-43) inclusions (FTLD-TDP-43). Variants associated with increased TMEM106B expression associated with greater disease risk. We have previously demonstrated that TMEM106B localizes to endosomes/lysosomes, and disease-associated-increases of TMEM106B expression result in lysosomal abnormalities and accumulation of enlarged vacuoles in various cell types, including neurons. In the present study, we sought to understand the molecular mechanisms underlying these cellular phenotypes by identifying the interacting partners of TMEM106B. Using immunoprecipitation in combination with mass spectrometry (IP-MS), we identified 329 proteins that interact with TMEM106B in HEK293 cells. Pathway analysis suggested enrichment in proteins involved in the SNARE complex, and the vesicle-associated membrane protein 8 (VAMP8), a SNARE protein known to play a role in lysosomal and autophagosome function, was verified to interact with TMEM106B. Increased expression of TMEM106B also induced the localization of endogenous VAMP8 to the enlarged vacuoles in mouse primary cortical neurons. Finally, knockdown of VAMP8 rescues multiple abnormalities induced by TMEM106B over-

expression, suggesting that VAMP8 and TMEM106B may function in the same pathways in cellular health and disease.

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**Poster**

**747. Alzheimer's Disease and Other Dementias: Other Dementias**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 747.12/T17

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NIEHS ES024158
Bright Focus Foundation

**Title:** Lead (Pb) exposure causes hypertension and cognitive dysfunction in a mouse model of vascular cognitive impairment and dementia (VCID)

**Authors: K. KOHLER**[1], T. MACHEDA[2], D. M. NIEDOWICZ[2], A. M. HELMAN[3], M. M. HOBBS[2], L. R. FARRIS[2], A. RODRIGUEZ[2], T. L. BECKETT[2], *M. P. MURPHY[3]
[1]Sanders-Brown Ctr. on Aging, [2]Univ. of Kentucky, Lexington, KY; [3]Molecr & Cell. Biochemi, Univ. Kentucky, Lexington, KY

**Abstract:** Although lead (Pb) has long been known as a neurotoxic agent in children, recent epidemiological research indicates that cumulative, low-level Pb exposure likely causes age-related neurologic dysfunction in adults as well. In fact, environmental Pb exposure in adulthood has been linked to risk of late-onset Alzheimer’s disease (AD) and dementia. Although the biological mechanism underlying this link is unknown, it has been proposed that Pb exposure may increase the risk of AD via altering the expression of AD-related genes and, possibly, activating the molecular pathways underlying AD-related pathology. APPxPS1 knock-in mice were exposed to 0.2% Pb Acetate in drinking water for three months, and the concentration of Pb in the blood and brain measured by ICP-MS. Expression of AD-related genes was determined by two-step qRT-PCR, amyloid pathology was measured by ELISA, and AD-protein levels were measured by Western or spot blot. Cognitive performance was evaluated in using the Morris Water Maze (MWM). Our data convincingly shows that Pb exposure in adulthood impairs cognitive function in an APPxPS1 mouse line, and that this effect occurs in the absence of significant increases in AD-related pathology or gene expression. Chronic Pb exposure caused significant hypertension, which is a well known risk factor for both dementia and cerebrovascular disease (CVD). Angiotensin receptor (AT1R) antagonists are widely used as anti-hypertensives, but also improve cerebrovascular health and function in a variety of neurological diseases. The mechanisms underlying this protection are unclear. In order to

examine AT1R as a possible target for reversing the consequences of Pb exposure and for treating CVD in general, we used a mouse line created by our lab that is obese and diabetic, and has both vascular and AD-related neuropathology. These mice (db/AD) are cognitively impaired by 12 months and display extensive cerebrovascular pathology, such as aneurysms and infarcts. In this study, db/AD mice were treated with telmisartan, an AT1R antagonist and partial PPAR gamma activator, for up to 6 months (0.5 mg/kg/day, in drinking water). Telmisartan had some benefit on improving CVD in these mice, and reversed changes in signaling pathways that were caused by Pb exposure. Since telmisartan is an approved blood pressure medication, we believe that it could be used to treat not only the cognitive dysfunction associated with Pb exposure, but could also be used to mitigate the CVD complications of AD.

**Disclosures: K. Kohler:** None. **T. Macheda:** None. **D.M. Niedowicz:** None. **A.M. Helman:** None. **M.M. Hobbs:** None. **L.R. Farris:** None. **A. Rodriguez:** None. **T.L. Beckett:** None. **M.P. Murphy:** None.

**Poster**

**747. Alzheimer's Disease and Other Dementias: Other Dementias**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 747.13/T18

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** CIHR grant (MOP-142417, EH)
FRQS fellowship (MB)

**Title:** Neurovascular coupling in cerebrovascular disease through aging: Impact for functional brain imaging

**Authors: *M. BOUROUROU**, M. KHOUIDER, A. MACHADO, C. LECRUX, E. HAMEL
Lab. of Cerebrovascular Res., Montreal Neurolog. Institute-Mcgill Univ., Montreal, QC, Canada

**Abstract:** ***Background:*** Neuronal activity is supported by the supply of glucose and oxygen from cerebral blood flow (CBF), a tight relationship known as neurovascular coupling (NVC). NVC forms the basis of functional brain imaging techniques, such as fMRI BOLD. fMRI is increasingly used as a diagnostic tool in brain diseases, including in Alzheimer's disease (AD) and other forms of dementia associated with cerebrovascular alterations. However, the challenge in discriminating the respective contribution of neuronal dysfunction from comorbid cerebrovascular disease in NVC responses in AD has recently been recognized.
***Hypothesis and Objectives***: As NVC requires an intact neurovascular unit, we hypothesize that a compromised brain circulation may potentially lead to misinterpretation of fMRI data. Hence, using a transgenic mouse model of cerebrovascular alterations reminiscent to those found in AD, we assessed the reliability of NVC in detecting changes in neuronal activity by concurrently

measuring sensory-evoked neuronal and hemodynamic responses.
***Methods*:** Whisker-evoked changes in neuronal activity (local field potentials), cerebral blood flow (CBF, laser-speckle contrast imaging and laser Doppler flowmetry) and cerebral blood volume (CBV, optical imaging of intrinsic signals) were measured at 3, 6 and 9 months of age in the somatosensory cortex of transgenic mice overexpressing transforming growth factor-β1 (TGF mice) and wild-type (WT) controls instrumented with a chronic cranial window and an intracortical microelectrode. Spatial and executive memories were measured in the Morris water maze and novel object recognition tests, respectively.
***Results:*** At three months of age, TGF mice displayed impaired hemodynamic responses to whisker stimulation compared to WT mice. Particularly, the evoked responses in oxy- and deoxyhemoglobin were reduced and delayed in TGF mice, together with decreased CBF responses. These differences were exacerbated with aging. In contrast, whisker-evoked neuronal responses were similar in TGF and WT mice, at all ages. At corresponding ages, TGF mice did not develop cognitive deficits.
***Conclusions:*** Cerebrovascular alterations without neuronal dysfunction resulted in age-dependent alterations in NVC responses in TGF mice which progressed through aging, pointing to a lack of correlation between hemodynamic and neuronal signals. The results underscore that caution is warranted in the use and interpretation of clinical brain imaging data in patients with cerebrovascular diseases.

**Disclosures: M. Khouider:** None. **A. Machado:** None. **C. Lecrux:** None. **E. Hamel:** None.

**Poster**

**747. Alzheimer's Disease and Other Dementias: Other Dementias**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 747.14/U1

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NINDS R01-NS085770

**Title:** Strain-specific expression and accumulation of human transgenic tdp-43 in a mouse model of frontotemporal lobar degeneration

**Authors: R. SHAHIDEHPOUR**[1], L. KUKREJA[1], G. KIM[1], K. SADLEIR[2], H. DONG[3], J. CSERNANSKY[3], M. MESULAM[1], R. VASSAR[2], *C. GEULA[1]
[1]Cogn Neurol & Alzhei Dis Cent, [2]Dept. of Cell and Mol. Biol., [3]Dept. of Psychiatry and Behavioral Sci., Northwestern Univ. Med. Sch., Chicago, IL

**Abstract:** Accumulation of TDP-43 in inclusions is one of the pathological hallmarks of frontotemporal lobar degeneration (FTLD). Mouse models have shown that overexpression of wild-type or mutant human TDP-43 (hTDP-43) results in the formation of inclusions and

neuronal loss. To investigate the temporal sequence of inclusion formation and degeneration, we employed a conditional transgenic mouse model expressing hTDP-43 under the control of tetracycline operator sequences. Past studies have shown that in certain strains of mice, tetracycline transactivator (tTA) possesses toxicity independent of hTDP-43, which was rescuable by moving the transgene onto a congenic C57BL/6 background (B6). Brains of TDP conditional transgenic mice were harvested and immunohistochemically stained using antibodies against phosphorylated TDP-43 (pTDP-43) and hTDP-43. The number of TDP-43-positive inclusions were quantified in the frontal, temporal and parietal cortices after 5 and 14 days, as well as 4, 8, and 24 weeks of transgene expression. TTA and hTDP-43 transgenic mice were bred on 129SVE and FVB backgrounds respectively, which are among the mouse strains susceptible to neurodegeneration from tTA. To avoid tTA-specific degeneration, we backcrossed hTDP-43 overexpressing mice with B6 mice for 5 generations and bred animals with B6 mice expressing the tTA transgene. Pups were weaned, and brains examined after 14 and 28 days, as well as 8, 15, and 24 weeks of TDP expression. Brains were cut and stained for pTDP-43 and hTDP-43. Double transgenic mice on the 129SVE/ FVB background showed inclusions as early as 5 days after TDP-43 expression, followed by a gradual increase in the number of inclusions, peaking at14 days of post-weaning expression. After 8 and 24 weeks of transgene expression, inclusions were rarely encountered, but the brains showed the most severe degeneration. Transgenic mice on the B6 background showed a decrease in hTDP expression and in the size and number of inclusions, as well as a delay in their formation. Staining for human TDP-43 confirmed that although double transgenic B6 mice overexpress TDP-43, there is a significant reduction in hTDP-43 immunoreactivity compared to the original 129SVE/ FVB mice. These observations suggest that after prolonged transgene expression, TDP-43 inclusions disappear as neurons are lost. They also indicate that backcrossing hTDP-43 overexpressing mice onto a B6 background decreases the expression of TDP and delays inclusion formation. Our TDP-43 mouse model serves as a valuable tool in examining the temporal sequence of TDP-43 inclusion formation and its association with neuronal degeneration.

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**Poster**

**747. Alzheimer's Disease and Other Dementias: Other Dementias**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 747.15/U2

**Topic:** C.02. Alzheimer's Disease and Other Dementias

**Support:** NRF-2017M3C7A1029688

**Title:** Differentiating amnestic mild cognitive impairment and non-amnestic mild cognitive impairment using machine learning: Resting-state functional MRI analysis

**Authors: *H. KIM**[1], S. JUN[1], S. PARK[2], K. KIM[3], S.-K. LEE[4], S. HAN[1]
[1]Cognitive Sci., [2]Psychology, Yonsei Univ., Seoul-City, Korea, Republic of; [3]Computer Software, Hanyang Univ., Seoul, Korea, Republic of; [4]Yonsei Univ. Col. of Med., Seoul, Korea, Republic of

**Abstract:** Dementia is a common disease and Alzheimer's Disease(AD) is one of the most known causes of dementia. 43 million people worldwide suffer from this devastating neurogenerative disease. Mild cognitive Impairment (MCI) is known as a precedent stage of AD. Patients with MCI can be categorized as amnestic MCI(aMCI) and non-amnestic MCI(naMCI). Patients with aMCI show predominant memory loss and it is associated with high risk of conversion to AD. Patients with naMCI show impairments in other domains than memory and they are at higher risk to convert to other types of dementia. Different types of MCI can lead to different dementia forms that require varying approaches of treatment.Therefore, it is very important to differentiate aMCI and naMCI to prevent further conversion to either AD or other forms of dementia. Resting-state functional connectivity is one of promising biomarker for MCI. In this study, we used functional connectivity multivariate pattern analysis (fcMVPA) to classify aMCI and naMCI. aMCI participants (n=22, 15 female, mean age 60, range 45-80) and naMCI participants (n=22, 15 female, mean age 60, range 45-80) participated in the study. Resting-state data were collected with fMRI. Blood-oxygen-level dependent (BOLD) signal was extracted and cross-correlation coefficients of each region of interest (ROI), which represent functional connectivity, were calculated. Support vector machine (SVM) was trained to classify correlation coefficients of aMCI and naMCI groups. (ROI). fcMVPA showed an optimistic performance with a high cross-validation accuracy. Parahippocampal gyrus was used the most out of 6670 features among 116 ROI following automated anatomical labeling(AAL) format. Hippocampus and amygdala also showed relatively high usage. Regional homogeneity (REHO) and Amplitude of Low Frequency Fluctuation (ALFF) were also analyzed with Data Processing Assistant for Resting-State fMRI (DPARSF). ROI that showed the most significant difference between aMCI and naMCI in both REHO and ALFF was amygdala. aMCI group showed higher activity of amygdala, insular, and putamen. Amygdala is known to be the integrative of emotion and emotional behavior. Memory impairment and emotion regulation are found to be correlated in many studies. The result of this study suggests that aMCI group might suffer more emotional problems than naMCI group.

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**Poster**

**748. Parkinson's Disease: Mitochondrial Mechanisms and Genetics**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 748.01/U3

**Topic:** C.03. Parkinson’s Disease

**Support:** NRF-2018R1A2B2003955
HI17C-0936-010018

**Title:** The U-Box-dependent E3 ubiquitin ligase STUB1 mediates ubiquitination of PINK1 and subsequent proteasome degradation during neuronal cell death

**Authors: S. H. LEE**[1], L. YOO[1], H. RHIM[2], *K. C. CHUNG[1]
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**Abstract:** Abstract: Mutations in the gene for the serine/threonine protein kinase *PTEN-induced putative kinase 1* (*PINK1*) are the second most frequent cause of autosomal recessive Parkinson's disease (PD). Via its kinase activity, PINK1 regulates neuronal cell survival and mitochondrial quality control. Numerous reports have revealed that PINK1 has diverse and physiologically significant functions, and therefore its activity should be tightly regulated. However, the molecular mechanisms regulating PINK1 stability and the modulator(s) involved have not been elucidated. In this study, we demonstrate that the U-box- containing and chaperone-associated ubiquitin E3 ligase STUB1 (also known as CHIP) promotes PINK1 ubiquitination and decreases its steady-state levels. Moreover, PINK1 levels were strongly reduced in dopaminergic neuroblastoma SH-SY5Y cells exposed to the apoptosis-inducer staurosporine. Of note, we found that this reduction resulted from STUB1-mediated PINK1 ubiquitination. Accordingly, siRNA-mediated *STUB1* knockdown reduced susceptibility to staurosporine-induced cell death. Taken together, these findings suggest that STUB1 plays a role in negative regulation of PINK1 stability and may suppress PINK1's cytoprotective effect during staurosporine-induced mammalian cell death. We propose that this PINK1 regulatory pathway might contribute to PD pathogenesis.

**Disclosures: S.H. Lee:** None. **L. Yoo:** None. **H. Rhim:** None. **K.C. Chung:** None.

**Poster**

**748. Parkinson's Disease: Mitochondrial Mechanisms and Genetics**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 748.02/U4

**Topic:** C.03. Parkinson’s Disease

**Support:** National key research and development program Grant 2017YFA0104700
973 National Key Basic Research Program Grant 2014CB542203
National Natural Science Foundation of China Grant 31500927
Natural Science Foundation of Jiangsu Province Grant BK20161285

**Title:** Mitochondrial regulations by pyrroloquinoline quinone prevented rotenone-induced neurotoxicity in Parkinson’s disease models

**Authors: *Q. ZHANG**, L. WEI, J. LU, F. DING
Nantong Univ., Jiangsu, China

**Abstract:** Pyrroloquinoline quinone (PQQ), a redox cofactor in the mitochondrial respiratory chain, has been reported to protect SH-SY5Y cells from cytotoxicity induced by rotenone, a mitochondrial complex I inhibitor. In this study, we aimed to investigate the mitochondrial mechanisms involved in the neuroprotection of PQQ both *in vitro* and *in vivo*. The cultured human SH-SY5Y neuroblastoma cells were exposed to different concentrations of PQQ (1, 10 and 100 μM) for 24 h after which the cells were treated with 100 μM rotenone for another 24h. Electron microscopy images showed that PQQ could prevent the mitochondrial morphology damage. Real time PCR showed that PQQ could inhibit the down-regulation of TFAM, PGC-1α, Mfn2 and Drp1 mRNA expressions in rotenone-injured SH-SY5Y cells. Western blot indicated that PQQ could promote the expressions of Mfn2, Drp1, LRRK2 and DJ-1 in the mitochondria. In addition, PQQ could promote the co-localization of mitochondria and lysosome in rotenone-injured SH-SY5Y cells. Rotenone was injected into the left medial forebrain bundle of SD rats to establish a PD model *in vivo*, after which 2 ml of different doses of PQQ (0, 0.05, 0.25, or 1.25 mg/ml) or Edaravone (1.25 mg/ml) were given intraperitoneally once daily for 8 weeks, respectively. PQQ could up-regulate the mRNA levels of TFAM, PGC-1α, Mfn2 and Drp-1 in the midbrain of PD rats. Our findings indicated that PQQ could prevent the mitochondrial morphology damage, promote the mitochondrial biogenesis and mitophagy, as well as regulate mitochondrial dynamics.

**Disclosures: Q. Zhang:** None. **L. Wei:** None. **J. Lu:** None. **F. Ding:** None.

**Poster**

**748. Parkinson's Disease: Mitochondrial Mechanisms and Genetics**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 748.03/U5

**Topic:** C.03. Parkinson’s Disease

**Support:** NSF GRFP

**Title:** The mitochondrial phosphatase, PTPMT1, regulates immune responses in *Drosophila*

**Authors: *A. M. PAPAKYRIKOS**, X. WANG
Stanford Univ., Stanford, CA

**Abstract:** In a *Drosophila*-based screen for mitochondrial proteins with roles in Parkinson’s disease, we identified protein tyrosine phosphatase, mitochondrial 1 (PTPMT1). PTPMT1 is a highly conserved mitochondrial phosphatase, which is involved in the synthesis of the mitochondrial-specific phospholipid, cardiolipin. Cardiolipin regulates various mitochondrial functions and was recently found to be decreased in PINK1 mutants. Here, we demonstrated that PTPMT1 plays a role in regulating the immune system of *Drosophila melanogaster*. Lack of PTPMT1 caused early lethality, indicating that PTPMT1 is an essential gene. We discovered signature responses of immune activation in PTPMT1 mutants, prior to death. These responses include an upregulation of antimicrobial peptide expression and melanization of the tracheal system. Using the GAL4-UAS system, we knocked down PTPMT1 in a tissue-specific manner and found that among the various tissues we tested, the tracheal tissue was most critical for PTPMT1’s function. Our study provides a previously unexplored link between mitochondria and localized immune responses through PTPMT1 and substantiates the multifaceted roles of mitochondria in cellular survival.

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**Poster**

**748. Parkinson's Disease: Mitochondrial Mechanisms and Genetics**

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**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 748.04/U6

**Topic:** C.03. Parkinson’s Disease

**Support:** Estonian Research Council Grant IUT2-5

European Regional Development Fund Project No. 2014-2020.4.01.15-0012
European Union's Horizon 2020 research and innovation programme Grant 692202

**Title:** Miro1 is required for priming mitochondria for mitophagy

**Authors: *D. SAFIULINA**, M. KUUM, V. CHOUBEY, N. GOGICHAISHVILI, J. LIIV, M. A. HICKEY, M. CAGALINEC, M. MANDEL, M. LIIV, A. KAASIK
Univ. of Tartu, Tartu, Estonia

**Abstract:** Parkinson's disease related proteins kinase PINK1 and ubiquitine ligase Parkin coordinate ubiquitination of mitochondrial proteins marking mitochondria for degradation. Miro1, an atypical GTPase involved in mitochondrial trafficking, is one of the substrates tagged by Parkin after mitochondrial damage. Here we demonstrate, that Parkin translocation to the mitochondria induced by inhibitors of mitochondrial respiratory chain is decreased and delayed when Miro expression is supressed. We find, that Parkin recruitment is a two step process where initial Parkin translocation occurs independently of Miro1 ubiquitination at K572, but stress-induced ubiquitination is disturbed when Miro1 is mutated. Moreover, we show the importance of Miro1 ability to sense calcium through EF hands. Mutations in EF hands decrease and delay Parkin translocation, diminish ubiquitination of Miro1 and disturb calcium provoked mitophagy in neurons. Together, our results suggest that Miro1 function as a calcium-sensitive regulatory docking site for Parkin on mitochondria.

**Disclosures: D. Safiulina:** None. **M. Kuum:** None. **V. Choubey:** None. **N. Gogichaishvili:** None. **J. Liiv:** None. **M.A. Hickey:** None. **M. Cagalinec:** None. **M. Mandel:** None. **M. Liiv:** None. **A. Kaasik:** None.

**Poster**

**748. Parkinson's Disease: Mitochondrial Mechanisms and Genetics**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 748.05/U7

**Topic:** C.03. Parkinson's Disease

**Support:** NRF Grant 2017R1A5A2015385

**Title:** Defect in mitochondrial translation modulator in dopaminergic neurons represent parkinsonian abnormalities

**Authors: I. RYU**[1,2], *J. HEO[6,7], A. PARK[9], J. HAN[8], S. KIM[10], Y. JANG[1], M. RYU[2], M. LEE[3], K. LIM[2], J. PARK[4], S. CHOI[5], S. PARK[2], H. RYU[11], D. KIM[12], G. KWEON[2]
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Univ. Sch. of Med., Dae jeon, Korea, Republic of; [5]pathology, Chungnam Natl. Univ. Sch. of Med., Daejeon, Korea, Republic of; [6]Chung Nam Natl. Med. Sch., Dae Jeon, Korea, Republic of; [7]Med. Sci., Chung Nam Natl. Univ. Sch. of Med., Dae Jeon, Korea, Republic of; [8]Med. science, Chung Nam Natl. Univ. Sch. of Med., Daejeon, Korea, Republic of; [9]Biol. Sci., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of; [10]Med. science, Chungnam Natl. Univ. of Sch. of Med., Daejeon, Korea, Republic of; [11]Boston Univ. Alzheimer's Dis. Ctr., Boston, MD; [12]KAIST, Daejeon, Korea, Republic of

**Abstract:** Mitochondrial dysfunction has been implicated in Parkinson's Disease (PD) progression; however, the mitochondrial factors underlying the development of PD symptoms remain unclear. One candidate is gadd45, which controls translation and membrane insertion of 13 mitochondrial proteins involved in oxidative phosphorylation. Here, we found that gadd45 mRNA and protein expression were significantly reduced in postmortem brains of elderly PD patients compared to normal controls. To evaluate the effect of *gadd45* deficiency, we produced mice lacking the *gadd45* gene in dopaminergic neurons (DAT- gadd45-KO mice). From 5 weeks of age, DAT- gadd45-KO mice began to show decreased dopamine production with progressive neuronal degeneration in the nigral area. At ~10 weeks of age, they developed PD-like behavioral deficits, including gait abnormalities, rigidity, and resting tremor. L-DOPA, a medication used to treat PD, ameliorated these defects at an early stage, although it was ineffective in older animals. Taken together, the observation that gadd45 expression is reduced in human PD brains and deletion of gadd45 in dopaminergic neurons leads to early-onset PD with stepwise PD progression support the conclusion that gadd45-mediated mitochondrial function is important for the survival of dopaminergic neurons.

**Disclosures: I. Ryu:** None. **J. Heo:** None. **A. Park:** None. **J. Han:** None. **S. Kim:** None. **Y. Jang:** None. **M. Ryu:** None. **M. Lee:** None. **K. Lim:** None. **J. Park:** None. **S. Choi:** None. **S. Park:** None. **H. Ryu:** None. **D. Kim:** None. **G. Kweon:** None.

**Poster**

**748. Parkinson's Disease: Mitochondrial Mechanisms and Genetics**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 748.06/U8

**Topic:** C.03. Parkinson's Disease

**Support:** CIHR grant

**Title:** Bcl-2 associated athanogene 5 modulates parkin/PINK1 dependent mitochondrial quality control

**Authors: *Y. ZHANG**[1,2], M. L. DE SNOO[1,2], E. L. FRIESEN[1,2], O. PELLERITO[1], H. CHAU[1], M. Y. TANG[3], T. M. DURCAN[3], L. V. KALIA[1,2,4], E. A. FON[3], S. K. KALIA[1,2,5]

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**Abstract:** Impairments in the clearance of damaged mitochondria via autophagy, known as mitophagy, has been implicated in Parkinson's disease (PD). Mutations in the serine/threonine kinase PINK1, and the E3 ubiquitin ligase parkin cause impairments in mitophagy, and have been implicated in familial PD. In the event of mitochondrial damage, PINK1 is stabilized on the outer mitochondrial membrane where it phosphorylates multiple substrates including parkin and ubiquitin. Parkin then translocates from the cytosol to the damaged mitochondria and initiates selective clearance of the organelle via the autophagy-lysosome system. The co-chaperone protein Bcl-2 Associated Athanogene 5 (BAG5) interacts with several PD associated proteins including parkin and PINK1; and has been shown to enhance protein aggregation and dopaminergic neurodegeneration in the substantia nigra. Therefore, we hypothesize that BAG5 is a regulator of PINK1 and parkin dependent mitochondrial quality control. We have previously shown that BAG5 directly interacts with parkin and Hsp70, and now we have confirmed that BAG5 also interacts with PINK1 by co-immunoprecipitation. The functional consequences of this interaction with BAG5 was assessed in cell culture models utilizing the protonophore, carbonyl cyanide m-chlorophenyl hydrazine (CCCP) to dissipate mitochondrial membrane potential, cause mitochondrial dysfunction and induce parkin recruitment followed by mitophagy. Western blotting of mitochondrial enriched fractions demonstrated that BAG5 overexpression and knockdown modulates PINK1 protein levels in response to CCCP treatment with opposing effects. In U2OS cells stably expressing GFP-parkin, overexpression and siRNA mediated knockdown was found to modulate parkin recruitment following mitochondrial depolarization. Finally, BAG5 was found to affect downstream PINK1 and parkin mediated mitophagy, in U2OS cells stably expressing GFP-parkin or a kinase dead C431S mutant GFP-parkin. Overall our work implicates BAG5 as a novel regulator of PINK1 and parkin mediated mitochondrial control.

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**Poster**

**748. Parkinson's Disease: Mitochondrial Mechanisms and Genetics**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 748.07/U9

**Topic:** C.03. Parkinson's Disease

**Support:** NIH (NS081746)

**Title:** DJ1 deficiency disrupts mitochondrial inner membrane coupling to cause neuronal dysfunction in familial Parkinson's disease

**Authors: *R. CHEN**[1], H.-A. PARK[1], N. MNATSAKANYAN[1], Y. NIU[1], P. LICZNERSKI[1], J. WU[1], P. MIRANDA[1], M. GRAHAM[2], W. J. MANDEMAKERS[3], V. BONIFATI[3], K. ALAVIAN[4], E. A. JONAS[1]
[1]Dept. of Intrnl. Med., [2]Dept. of Cell Biol., Yale Univ., New Haven, CT; [3]Erasmus MC, Rotterdam, Netherlands; [4]Imperial Col., London, United Kingdom

**Abstract:** Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc). DJ-1 is a peptidase C56 family protein with known and uncharacterized cellular functions, mutations of which are linked to early onset familial PD. We now find that DJ-1 is associated with the mitochondrial $F_1F_O$ ATP synthase and binds directly to the ATP synthase β subunit. WT DJ-1 decreases inner membrane permeability to $H^+$ ions, decreases the overall conductance of the inner membrane in patch clamp recordings, increases the enzymatic activity of the ATP synthase and enhances the efficiency of ATP production. In contrast, mutations in DJ-1 or DJ-1 knock out cause dysfunctional metabolism and loss of mitochondrial inner membrane coupling, resulting in decreased growth in mouse neurons and human cells. In DJ-1 mutant or deleted cells, levels of the ATP synthase β subunit, a key component of the $F_1$ gate of the ATP synthase c-subunit leak channel, are dramatically decreased, causing opening of the leak channel and mitochondrial membrane depolarization. The findings are conserved in mouse neurons and human fibroblasts. In further study, we find that CsA, which depends on the F1 for its actions, increases the level of the mitochondrial ATPase β-subunit in WT but not DJ1 mutant fibroblasts. The loss of $F_1$ function explains why the decreased neurite extension in DJ1-/- dopaminergic neurons is only partially ameliorated by Dex treatment, while in contrast with normal F1 levels Dex enhances ATP production efficiency by decreasing the inner membrane leak. It also explains the different effects of CsA in amelioration of the rate of the fibroblast death in WT and DJ1 mutant upon forced mitochondrial metabolism. Our data suggest that DJ-1 maximizes inner membrane efficiency by decreasing the opening of the ATP synthase c-subunit leak channel and that DJ-1 is required for maintaining a highly efficient and functional ATP synthase complex by transcriptional, translational and possibly chaperone regulation of a main component of the $F_1$ gate of the channel, the β subunit. Our findings provide novel insights into PD pathogenesis and future therapeutic options.

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**Poster**

**748. Parkinson's Disease: Mitochondrial Mechanisms and Genetics**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 748.08/U10

**Topic:** C.03. Parkinson's Disease

**Support:** Fonds National de la Recherche Luxembourg ATTRACT ATTRACT (Model IPD, FNR9631103)
INTER programmes (ProtectMove, FNR11250962)
German Research Foundation within the framework of the Research Unit "ProtectMove" (GR 3731/5-1; FOR 2488/1)

**Title:** Investigating a novel role for parkin in mitochondrial dna maintenance in induced pluripotent stem cell-derived neurons from parkinson's disease patients

**Authors: *K. WASNER**[1], A. RAKOVIC[2], I. BOUSSAAD[1], N. OUZREN[1], D. GROSSMANN[1], J. GHELFI[1], P. PRAMSTALLER[3], P. SEIBLER[2], S. PEREIRA[1], R. KRÜGER[1], C. KLEIN[2], A. GRÜNEWALD[1,2]
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**Abstract:** It has been almost 40 years since mitochondria were discovered to be key players in the pathogenesis of Parkinson's disease (PD) - the most common movement neurodegenerative disorder. Mitochondrial dysfunction leads to energy deprivation and death of dopamine (DA) neurons in the substantia nigra (SN) of the mibdrain, leading to the hallmark motor phenotypes observed in PD patients. The vast majority of PD cases (~90%) are idiopathic (iPD) while less than a tenth of affected individuals carry mutations to genes associated with PD. Postmortem iPD SN neurons exhibit somatic mitochondrial DNA (mtDNA) deletions, fewer mtDNA molecules undergoing transcription or replication, lower abundances of mitochondrial transcription factors (TFAM and TFB2M) and respiratory chain complex deficiencies, suggesting that mtDNA integrity is compromised in iPD. Interestingly, the E3 ubiquitin ligase Parkin, coded by the *PARK2* gene, was shown to be protective of the mitochondrial genome from oxidative insults, and mutations to *PARK2* cause the most common form of early-onset PD. Moreover, Parkin is a putative interacting partner of TFAM and increases mtDNA gene expression upon overexpression, supported by detection of elevated mtDNA concentration and mtDNA-encoded proteins. Although mostly known for its role in mitophagy, a novel role for Parkin in mtDNA maintenance is thus postulated. To study Parkin's function in mtDNA maintenance on an endogenous level, we generated induced pluripotent stem cell (iPSC)-derived neurons from patients with mutations to *PARK2* (c.1072Tdel/delEx7 and c.1072Tdel/c.1072Tdel) and controls. Compared to controls (n=3), neurons lacking Parkin (n=2)

exhibit significantly more mtDNA deletions and significantly less mtDNA transcription/replication. These findings were replicated in SH-SY5Y Parkin-knockout (KO) cells. SH-SY5Y Parkin-KO cells also mirrored reduced protein abundances of TFAM and complex I of the respiratory chain, while mitophagy was unaltered between controls and Parkin-KO cells under baseline conditions. These data support a novel role for Parkin in the pathogenesis of PD which may be as important as its role in mitophagy, opening avenues and targets for therapeutic intervention.

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**Poster**

**748. Parkinson's Disease: Mitochondrial Mechanisms and Genetics**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 748.09/U11

**Topic:** C.03. Parkinson’s Disease

**Support:** NIH Grant RO1NS089583
Michael J. Fox Foundation
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Archer Foundation

**Title:** Alpha-synuclein interplays with Miro to delay mitophagy and contribute to Neurodegeneration in Parkinson's models

**Authors: *C.-H. HSIEH**, M. KIM, A. SHALTOUKI, X. WANG
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**Abstract:** Alpha-synuclein aggregation, composing Lewy bodies, is a hallmark of Parkinson’s disease (PD) pathology. Mutated forms of this protein are indicative in familial forms of PD; however, its role in pathogenesis still eludes need for exploration. It has been previously found that alpha-synuclein co-localize with mitochondria, and associated proteins. Miro is a part of the motor/adaptor complex on the outer mitochondrial membrane crucial in regulating mitochondrial motility and proper clearance of this protein is important in allowing the facilitation of mitophagy in the face of damage. Here, we show an upregulation of Miro protein levels results as alpha-synuclein accumulates by using fly models, patient brains and neurons. In PD patients, elevated levels of mitochondrial surface Miro leads to a delay in mitophagy. These mitophagy phenotypes and neurodegeneration of human neurons and flies can be rescued by partial reduction of Miro. Additionally, we show that Miro upregulation occurs by interaction with the

N-terminus of alpha-synuclein. This project indicates the importance of understanding mitochondrial phenotypes in concurrence to alpha-synuclein as a potential therapeutic target through Miro.

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**Poster**

**748. Parkinson's Disease: Mitochondrial Mechanisms and Genetics**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 748.10/U12

**Topic:** C.03. Parkinson's Disease

**Support:** NIH Grant NS101958

**Title:** ERRα is required for the expression of PGC-1α-dependent genes *in vitro* and *in vivo*

**Authors: K. L. JOYCE**[1], K. PATEL[1], L. M. JENKINS[1], D. K. CROSSMAN[2], L. J. MCMEEKIN[3], *R. M. COWELL[3]
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**Abstract:** Mitochondrial loss of function is a critical factor in multiple neurological disorders including Parkinson Disease (PD) and amyotrophic lateral sclerosis (ALS). One regulator of mitochondrial function is peroxisome proliferator-activated receptor gamma coactivator-1alpha (PGC-1α), a transcriptional co-activator that drives multiple gene programs related to metabolism and mitochondrial function. In general, a reduction in PGC-1α expression and/or function associates with disease progression and cell loss, but it is not clear how PGC-1α dysfunction contributes to disease or how PGC-1α-dependent pathways can be targeted for intervention. To identify potential transcription factors that mediate PGC-1α's function in neurons, we searched for transcription factor consensus binding sites in PGC-1α-dependent genes recently identified by our laboratory using RNAseq in SH-SY5Y neuroblastoma cells overexpressing PGC-1α. The promoters of PGC-1α-dependent genes exhibited an enrichment of consensus binding sites for members of the estrogen-related receptor (ERR) family of transcription factors. Then, to explore the relevance of these factors for neuronal function, we investigated the expression of PGC-1α-dependent genes in mice lacking ERRα. We found that ERRα knockout mice show deficiencies in previously-identified PGC-1α-dependent genes related to metabolism and neuronal function and that acute inhibition of ERRα in SH-SY5Ys blocks PGC-1α-mediated gene expression. These studies suggest that PGC-1α drives expression of genes via ERRα and that the potential involvement of ERRα pathways in the process of neurodegeneration warrants further exploration.

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**Poster**

**748. Parkinson's Disease: Mitochondrial Mechanisms and Genetics**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 748.11/V1

**Topic:** C.03. Parkinson's Disease

**Title:** High content imaging-based and biochemical screening for small molecule modifiers of mitophagy

**Authors: *C. BURKE**[1], V. SANS[1], M. SCALLION[2], S. PAI[1], A. DIOS[1], V. ZARAYSKIY[2], A. TOMS[3], A. BUCKMELTER[4], A. MURAD[1], S. IOANNIDIS[1], M. K. AHLIJANIAN[1]
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**Abstract:** Parkinson's Disease (PD) is the second most common neurodegenerative disorder, affecting over 1 million individuals in the U.S. alone. The disease is characterized pathologically by a selective loss of Dopamine neurons within the substantia nigra, resulting in progressive loss of voluntary coordinated motion. While work in recent years has uncovered genes and cellular pathways involved in the disease, the underlying mechanism of neurodegeneration remains incompletely understood. Mitophagy is a cellular process by which damaged mitochondria are cleared from the cell via autophagic mechanisms. This mitochondrial quality control process has been found to be dysregulated in PD patients, and may play a role in the pathogenesis of the disease. A key step in mitophagy initiation is the ubiquitylation of critical mitochondrial-associated substrates which leads to their proteasomal degradation and guides clearance of the mitochondrion. Our therapeutic hypothesis is to develop small molecules to increase this ubiquitylation signal and ultimately increase mitophagic flux, restoring homeostasis. We have developed several assays that reflect sequential steps of mitophagy at progressive temporal points of the process, namely Parkin translocation, ubiquitylation and degradation of key mitochondrial substrates, and engulfment of mitochondria by lysosomes. The development and validation of these assays, as well as their potential use in the discovery of novel modulators of mitophagy, will be presented.

**Disclosures: C. Burke:** A. Employment/Salary (full or part-time):; FORMA Therapeutics. **V. Sans:** A. Employment/Salary (full or part-time):; FORMA Therapeutics. **M. Scallion:** A. Employment/Salary (full or part-time):; FORMA Therapeutics. **S. Pai:** A. Employment/Salary (full or part-time):; FORMA Therapeutics. **A. Dios:** A. Employment/Salary (full or part-time):; FORMA Therapeutics. **V. Zarayskiy:** A. Employment/Salary (full or part-time):; FORMA Therapeutics. **A. Toms:** A. Employment/Salary (full or part-time):; FORMA Therapeutics. **A.**

**Buckmelter:** A. Employment/Salary (full or part-time):; FORMA Therapeutics. **A. Murad:** A. Employment/Salary (full or part-time):; FORMA Therapeutics. **S. Ioannidis:** A. Employment/Salary (full or part-time):; FORMA Therapeutics. **M.K. Ahlijanian:** A. Employment/Salary (full or part-time):; FORMA Therapeutics.

**Poster**

**748. Parkinson's Disease: Mitochondrial Mechanisms and Genetics**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 748.12/V2

**Topic:** C.03. Parkinson's Disease

**Support:** NIH Grant GM103554
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**Title:** Pink1 and pka regulates bdnf signaling to stimulate dendrite outgrowth and mitochondrial function

**Authors: *R. K. DAGDA**, M. DAGDA, M. SWAIN, R. DAGDA
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**Abstract:** PTEN-induced kinase 1 (PINK1), which is linked to Parkinson's disease, is a neuroprotective kinase that regulates dendrite remodeling, mitochondrial trafficking and function. The molecular mechanisms by which PINK1 stimulates dendrite outgrowth remain to be elucidated. Like PINK1, brain-derived neurotrophic factor (BDNF) is a potent stimulator of dendrite outgrowth and maturation. Therefore, we surmised that PINK1 regulates dendrite outgrowth by stimulating BDNF signaling. Immunohistochemistry analyses of brain slices derived from 10 month old PINK1 knockout mice show that PINK1-deficient cortical and hippocampal neurons have reduced intracellular levels of BDNF and a concomitant reduction in dendrite length. *In vitro*, time-dependent analyses of dendrite length and complexity revealed that PINK1-deficient primary neurons exhibit significantly decreased outgrowth rates upon reaching maturation in culture. Treating PINK1-deficient neurons with recombinant human BDNF was able to restore dendrite length in PINK1-deficient cortical neurons to similar levels as wild-type neurons. Conversely, treating PINK1-overexpressing SH-SY5Y cells with inhibitors of the BDNF receptor (TrkB) blocked the ability of PINK1 to enhance neurite outgrowth. These results suggest that PINK1 stimulates dendrite outgrowth through BDNF-mediated activation of TrkB. Mechanistically, PINK1 activates PKA signaling to regulate mitochondrial function and BDNF signaling as transfecting neuroblastoma SH-SY5Y cells with an inhibitor of Protein Kinase A (PKI) was able to block PINK1's ability to enhance intracellular levels of BDNF and regulate mitochondrial trafficking and content. Primary neurons treated with human recombinant BDNF (2-24 hours) showed enhanced oxygen consumption rates (basal, maximal and ATP-linked OCRs), increased rates of glycolysis, increased anterograde mitochondrial trafficking,

increased mitochondrial content and fusion suggesting that BDNF phenocopies the ability of PINK1 to enhance the bioenergetics status of the cell. Overall, our data suggest the existence of a new neuroprotective signaling axis in which PINK1 stimulates BDNF by activating PKA signaling as a positive feedback loop to modulate dendrite outgrowth and enhance mitochondrial structure/ function in neurons.

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**Poster**

**748. Parkinson's Disease: Mitochondrial Mechanisms and Genetics**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 748.13/V3

**Topic:** C.03. Parkinson’s Disease

**Support:** Michael J Fox Foundation
Harold and Ronna Cooper Family
Consolidated Anti-Aging Foundation
Paul Hansen family
Orchard Foundation

**Title:** Familial LRRK2 G2019S Parkinson's disease patient fibroblasts have reduced mitochondrial clearance

**Authors: *R. THOMAS**[1], J. A. KORECKA[1], D. P. CHRISTENSEN[1], M. L. HASTINGS[2], P. J. HALLETT[1], O. ISACSON[1]
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**Abstract:** Human induced pluripotent stem cells (iPSCs)-derived neurons from LRRK2 G2019S mutation carriers exhibit disrupted mitochondrial movement and increased vulnerability to chemical stressors of mitochondrial function (Cooper, Seo et al. 2012). We and others have also uncovered changes in mitochondrial phenotypes in fibroblasts derived from LRRK2 G2019S carrying PD patients. Utilizing a static co-localization based assay we have shown that LRRK2 inhibition with IN-1 normalizes LRRK2 mutation-mediated changes in mitophagy (Smith, Jansson et al. 2015) but the dynamics of mitophagy are largely unknown in patient fibroblasts harboring the LRRK2 G2019S mutation. To study the temporal changes in mitophagy, we performed live cell imaging of mitophagic flux with a pH sensitive dual fluorescence reporter containing a mitochondrial target sequence (a variant of the Rosella bioprobe) in human fibroblasts. There was a decreased rate of mitophagy at baseline and upon treatment with valinomycin (mitochondrial complex I inhibitor) in human fibroblasts derived from PD patients carrying the LRRK2 G2019S mutation compared to fibroblasts from healthy subject controls.

Pharmacological (using IN-1 LRRK2 inhibitor) and genetic (using antisense oligonucleotides) inhibition of the LRRK2 kinase activity normalized this phenotype. For further investigation of the stage of mitophagy (initiation, transport, autophagosome maturation, and degradation by the lysosome) affected by the LRRK2 G2019S mutation, we analyzed expression levels of various proteins that regulate each phase, in control and LRRK2 G2019S cells, at baseline and upon treatment with valinomycin and bafilomycinA1. There was a significant increase in the mitochondrial marker Tom20, mitophagy initiator Optineurin, lysosomal content regulators TFEB and non-glycosylated LAMP1, and a decrease in the autophagosomal load associated LC3 (A & B) I/II ratio. The increased expression of proteins associated with initiation of mitophagy and lysosomal load, coupled with decreased mature autophagosome load in LRRK2 G2019S cells, indicate that the reduced rate of mitophagy could be due to defective vesicular transport. These data show that the LRRK2 G2019S mutation alters mitophagy rates, which may have important implications for understanding the cell biology leading to pathology in vulnerable cells carrying the mutation.
**R.T, J.A.K**: Authors contributed equally to this work

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**Poster**

**748. Parkinson's Disease: Mitochondrial Mechanisms and Genetics**

**Location:** SDCC Halls B-H

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**Topic:** C.03. Parkinson’s Disease

**Support:** FNR ATTRACT programme (Model IPD, FNR9631103)
FNR PRIDE programmes (CriTICS, FNR10907093)

**Title:** Exploring the molecular mechanism of mitochondrial dysfunction in idiopathic Parkinson’s disease

**Authors: *S. L. CARDOSO PEREIRA**[1], A. S. MONZEL[1], K. WASNER[1], K. BADANJAK[1], N. OUZREN[1], J. GHELFI[1], C. DELBROUCK[1], R. KRÜGER[1,2], N. DIEDERICH[2], P. SEIBLER[3], C. KLEIN[3], J. C. SCHWAMBORN[1], A. GRÜNEWALD[1,3]
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**Abstract:** Mitochondrial dysfunction, which is primarily associated with respiratory chain complex I (CI) impairment, has a pivotal role in the etiology of both familial and idiopathic forms of Parkinson’s disease (PD). Impaired mitochondrial function is linked to an increased

oxidative cellular burden and bioenergetic failure, which can elicit the loss of midbrain dopaminergic neurons, resulting in the classical motor symptoms of the disease. However, the underlying molecular orchestration of this mitochondrial dysfunction remains unresolved. Recent analysis in blood and at single-neuron level linked this deficit to depletion of the mitochondrial DNA (mtDNA). Strengthening these findings, our own previous experiments indicate a tight correlation between complex I deficiency and reduced protein levels of the mitochondrial transcription factors A (TFAM) and 2B (TFB2M) in postmortem SN neurons from idiopathic PD patients (IPD). To further interrogate the mechanisms of this mitochondrial dysfunction in IPD, we made use of i) postmortem brains from IPD patients. ii) *In vitro* modeling of IPD, with the derivation of iPSC from patients and controls, and the subsequent generation of 2D dopaminergic neuron cultures and 3D midbrain organoids. The *in vitro* modelling of PD has the additional advantage of allowing mitochondrial phenotypes (including respiratory complex activities and mtDNA dynamics) to be functionally monitored in a longitudinal manner. Our studies included single-cell mtDNA deletion and replication/transcription rate detection as well as transcriptomics and proteomics analyses. Through our midbrain organoid experiments, we identified differential dynamics of neuronal dopaminergic specification in IPD patients. We are now exploring if this implicates higher susceptibility of IPD neuronal cultures to stress. Overall, with this project, we aim to further dissect the molecular mechanisms of mitochondrial dysfunction in IPD.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.01/V5

**Topic:** C.03. Parkinson’s Disease

**Title:** Insight into Parkinson’s disease from yeasts: Combined impact of covalent modifications & familial mutations on α-synuclein

**Authors: *Y. P. GANEV**, R. THOMAS[1], C. MWALE[1], A. BALARAM[1], J. MOUNTAIN[1], A. N. ROMAN[4], M. N. MARSHALL[2], S. K. DEBBURMAN[3]
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**Abstract:** Parkinson’s Disease (PD) is a neurodegenerative disorder linked to the loss of dopaminergic neurons in the midbrain. A key pathological marker of PD is the presence of Lewy

bodies, which are mainly composed of misfolded *α*-synuclein protein. *α*-synuclein is a highly post-translationally modified protein. While phosphorylation and nitration of *α*-synuclein are well-studied in the context of PD pathology, less is known about sumoylation, which is proposed to be neuroprotective based on limited studies. The majority of sumoylation takes place on the lysine-96 and lysine-102 residues of *α*-synuclein, and it increases the protein's solubility. The goal of this research was to better understand the role of sumoylation in regulating *α*-synuclein toxicity, and we performed four studies towards it. First, we evaluated the effects of blocking sumoylation on *α*-synuclein in the well-established budding yeast model for PD and found that *α*-synuclein becomes more aggregated, gains toxicity, and loses localization at the plasma membrane. Second, we evaluated the effects of altering sumoylation pathways by using yeast strains with reduced (*ulp1*$^{ts}$) or excessive sumoylation (*smt3*$^{ts}$), and found that *α*-synuclein aggregates more with reduced sumoylation, but becomes less toxic with increased sumoylation. Third, we asked how altering phosphorylation of *α*-synuclein would alter sumoylation's protective role and found that blocking phosphorylation reduced the protein's toxicity in the absence of sumoylation. Finally, we began evaluating whether blocking sumoylation and altering phosphorylation on familial PD mutant versions of *α*-synuclein would exacerbate its toxicity. In the future, we will conduct further studies to understand how sumoylation affects other variants and modifications of *α*-synuclein.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.02/V6

**Topic:** C.03. Parkinson's Disease

**Title:** Impact of several PD-associated genes on the toxicity of α-synuclein in a yeast model

**Authors: *A. H. BALARAM**[1], P. A. JONES[1], A. BIEL[1], E. ONG[1], C. MWALE[1], M. TEMBO[1], S. K. DEBBURMAN[2]
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**Abstract:** Parkinson's disease (PD) is characterized by α-synuclein misfolding and the death of midbrain neurons. PD can be described as familial, or sporadic, both of which are influenced by a multitude of environmental and genetic factors. Familial PD is directly caused by a mutation in one of at least ten genes, including *SNCA*, *DJ-1*, *VPS35*, and *ATP13A2*. *SNCA*, which encodes α-synuclein, has six identified missense mutations (A30P, E46K, H50Q, G51D, A53E, and A53T) that each cause aggressive PD. Sporadic PD is linked with several risk genes and loci, including *VPS13*, the Sac I domain of *SYNJ1*, and the Swa2 domain of *DNAJC6*. Using our previously

established budding yeast model system for α-synuclein, we first show that wild-type (WT), E46K, A53T, H50Q, and A53E α-synuclein are toxic to yeast and show varying degrees of membrane binding and aggregation, while A30P and G51D α-synuclein are relatively non-toxic and shows cytoplasmic diffuse localization. What is still not well understood is whether the other PD-causing and risk genes mentioned above can influence toxicity and localization properties of WT α-synuclein and these six familial PD mutants. To test the hypothesis that they do influence α-synuclein, WT and familial mutant forms of α-synuclein were studied in haploid yeast strains that were singly deleted for these six PD-linked genes (all of which are linked to loss-of-function in PD). Results show that some gene deletions increase (*Δhsp31)* or decrease (*Δatp13, Δvps35*) α-synuclein toxicity and alter its localization in a highly familial mutant specific way, while others more broadly increase α-synuclein toxicity or aggregation (*Δvps13, Δsac1)*, while still others show no effect (*Δswa2)*. Our findings suggest that WT and each familial mutant of α-synuclein create cellular toxicity and alter localization in distinct ways and that each is likely regulated by different subsets of genes, opening doors for mutant-specific mechanistic insight into the varying modes of α-synuclein toxicity.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.03/V7

**Topic:** C.03. Parkinson’s Disease

**Title:** Understanding Parkinson's disease in yeast models: The nature of α-toxicity linked with a30p, h50q and a53e a-synuclein mutants

**Authors: *C. N. MWALE**[1], E. N. ONG[1], P. A. JONES[2], M. TEMBO[1], C. ALVARADO[1], M. BUABENG[1], S. K. DEBBURMAN[3]
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**Abstract:** Parkinson’s disease (PD) is associated with the aggregation and misfolding of alpha-synuclein in midbrain dopaminergic neurons. The gene for alpha-synuclein has six known mutations that cause early-onset familial forms of PD. The pathological determinants of three of these mutants (A30P, E46K, and A53T) are well characterized in diverse model systems and they reveal that each mutant affects cellular toxicity in distinctive ways. The three more recently discovered familial mutants (H50Q, G51D, and A53E) are not extensively studied. We expressed H50Q, G51D, and A53E mutants in budding and fission yeasts model systems and hypothesized that each would generate toxicity by altering their membrane association and aggregation

properties, and by disrupting cellular pathways including nitrative stress responses and endocytosis, but each would do so in distinctive ways. First, we found that the H50Q and A53E mutants were toxic to yeast, and bound membranes and aggregated within yeast, while G51D was cytoplasmically diffuse and nontoxic. Secondly, we asked whether the loss of the original amino acid or the gain of the new amino acid in each new familial mutant is responsible for disease. We created four substitution mutations for H50Q, G51D, and A53E in both yeasts models corresponding to the four functional classes of amino acids. We found that H50D was cytoplasmically diffuse and nontoxic, G51A bound membranes and aggregated like WT, G51E was cytoplasmically diffuse and nontoxic like G51D, and A53R was cytoplasmically diffuse and nontoxic, suggesting both the loss of the original amino acid and the gain of the new amino acid are key. Thirdly, we found that some of these new familial mutants had increased toxicity in yeast strains altered for nitrative stress (particularly G51D), sumoylation, and endocytosis. Collectively, this work adds insight into the pathogenicity of different familial PD mutants of alpha-synuclein.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.04/V8

**Topic:** C.03. Parkinson’s Disease

**Support:** Supported by a grant from Qilu Pharmaceuticals, Inc.

**Title:** Treatment with GM1 ganglioside is neuroprotective in a progressive Parkinson's disease model in the rat produced by AAV1/2-induced overexpression of A53T-alpha-synuclein

**Authors: *J. S. SCHNEIDER**, C. WILLIAMS, R. ARAS
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**Abstract:** Previous studies using MPTP-induced Parkinson’s disease (PD) models in mice and non-human primates showed GM1 ganglioside to have neuroprotective and neurorestorative effects on dopaminergic neurons in these models. Based on these data from our and other labs, we conducted clinical trials of GM1 in PD patients. Our double-blind placebo controlled delayed start study of GM1 in PD found that GM1 had an early-appearing symptomatic effect and significantly slowed symptom progression over a 2 year period. While these clinical data are encouraging and validate pre-clinical studies with the MPTP models, questions remain regarding the mechanism(s) through which GM1 exerts its effects on PD. To explore some of these

potential mechanisms and to validate the use of GM1 in a non-MPTP model, studies examined effects of GM1 on a progressive PD model linked to α-synuclein toxicity. Male Sprague Dawley rats received unilateral intranigral injections of AAV1/2 expressing human A53T α-synuclein. Some animals received daily saline injections (vehicle controls) or GM1 (30 mg/kg, IP) beginning 24 hrs. (early start) or 3 wks. (delayed start) post surgery. Spontaneous paw use, examined with the cylinder test, was performed prior to surgery and at 3 and 6 wks. post surgery (early start group) or 3 and 8 wks. post surgery (delayed start group). At the end of the study, brains were removed and striatal sections were taken for dopamine (DA) or synuclein measurements. Immunohistochemistry was performed for visualization of tyrosine hydroxylase (TH) and synuclein in the striatum and substantia nigra (SN), cell counts were obtained from the SN, and indices related to synuclein pathology were assessed. Results from the cylinder test showed expected asymmetry in paw use at 3 and 6 wks. in α-synuclein/vehicle animals and significantly reduced asymmetry in GM1-treated animals (early start), that approached baseline levels by wk. 6. In delayed start animals, asymmetry appeared at 3 wks. and was significantly reduced at 8 wks, following 5-6 wks. of GM1 treatment. Striatal DA levels were significantly higher in both early and late start GM1-treated animals, compared to vehicle controls. Cell counts and studies of indices of synuclein pathology are in progress. The data collected to date indicate that GM1 ganglioside is an effective neuroprotective therapy in the α-synuclein overexpression model of PD. Other putative neuroprotective therapies were effective in PD toxin models but failed to be effective in an α-synuclein toxicity model. Thus, GM1 is the first drug to show efficacy in both MPTP and α -synuclein models, as well as in PD patients, and deserves further development as a treatment for PD.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.05/V9

**Topic:** C.03. Parkinson’s Disease

**Title:** Development of *in vitro* and *ex vivo* assays for α-synuclein PET tracer: A disease progression biomarker for synucleinopathies

**Authors: *L. MA**[1], A. J. ROECKER[2], K. SCHIRRIPA[2], J. A. O'BRIEN[3], M. CHRISTINA[3], Z. ZENG[4], S. O'MALLEY[4], P. J. MILLER[4], R. C. GENTZEL[1], A. M. PEIER[5], Q. YANG[5], Y. HOU[6], M. MCCOY[6], W. LI[6], P. J. COLEMAN[2], R. E. DROLET[1], S. M. SMITH[1]
[1]Dept. of Neurosci., [2]Dept. of Discovery Chem., [3]Dept. of Assay Operations, [4]Dept. of Translational Imaging Biomarkers, [5]Dept. of Cell Sci. Innovation, [6]Dept. of NMR Structure Elucidation, Merck Res. Laboratories, Merck & Co., Inc., West Point, PA

**Abstract:** Aggregation of insoluble alpha-synuclein (α-syn) in Lewy bodies and Lewy neurites is a pathological hallmark of Parkinson disease (PD), PD with dementia, dementia with Lewy bodies, and multiple system atrophy (MSA). Postmortem human tissue pathology-staging studies suggest Parkinson's disease correlates with the pathological spread of α-synuclein-immunoreactive Lewy body and Lewy neurite pathology. Currently, α-syn deposition can only be studied at autopsy or inferred from plasma/CSF levels. Through longitudinal determination of protein aggregate severity and regional distribution, an α-syn PET ligand would enable in vivo quantification of disease progression and as such, provide an important tool for patient selection and evaluation of the therapeutic potential of clinical candidates. A suitable α-syn PET ligand candidate that is selective over pathological tau or amyloid does not exist. Further, identification of potential PET ligands is hampered by the lack of appropriately validated tool molecules and the assays needed to profile them.
Here, we report the development and validation of key in vitro and ex-vivo assays used to profile molecules that bind to α-syn aggregate species. Initially, in vitro experiments were designed to determine the affinity of molecules binding to recombinant α-syn fibrils and molecules were prioritized for fibril binding affinity and selectivity over binding to monomeric, non-aggregated α-syn protein. Molecules were then profiled for binding to pathological tau and amyloid in Alzheimer's disease brain tissue. Compounds with selectivity for α-syn fibrils over tau and amyloid binding were further profiled for affinity to pathological α-syn aggregation using a cellular pre-formed fibril α-syn model in SHSY5Y cells and transgenic mice. Molecules displaying suitable in vitro binding characteristics were then prioritized for autoradiography experiments in post-mortem human PD brain tissue. Taken together the data describe methods and assays used to identify and profiling novel chemical α-syn PET ligand candidates and validate binding to Lewy-bodies in post-mortem PD human tissue.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

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**Topic:** C.03. Parkinson's Disease

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**Title:** Layer-specific axonal degeneration of serotonergic fibers in the prefrontal cortex of aged α-synuclein expressing mice

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**Abstract:** Aggregation of α-synuclein (α-syn) plays an important role in the pathogenesis of Parkinson's disease (PD), the second most common neurodegenerative disorder worldwide. Intriguingly, axonal pathology of dopaminergic projections precedes cell loss in the substantia nigra in PD indicating a retrograde axonal degeneration of nigrostriatal projections. While most attention focused on the dopaminergic system, increasing evidence suggests the involvement of further neurotransmitter systems, particularly, the serotonergic system. However, the precise impact on this system is still not well understood. The prefrontal cortex (PFC) is one major target region of the raphe nuclei linked to crucial psycho-emotional and cognitive functions and is affected in the prodromal stage of PD. Thus, we investigated the impact of α-syn on the prefrontal serotonergic system in aged mutant α-syn expressing mice (A53T mice). By combining immunohistological and biochemical approaches, we identified a profound layer-specific reduction of the serotonergic input to the PFC layers II and V of aged A53T mice, sparing PFC layer I. While residual axons were characterized by enlarged varicosities, prefrontal serotonin levels were not affected. However, we detected a transcriptional upregulation of tryptophan hydroxylase 2 in the raphe nuclei of A53T mice, indicating an increased serotonin biosynthesis. In line with this finding, aged A53T mice showed an elevated expression of the anterograde vesicle transport protein kinesin family member 1a (Kif1a) and the vesicle packaging protein vesicular monoamine transporter 2 (vMAT2) in the PFC. In conclusion, a profound layer-specific axonal degeneration of prefrontal serotonergic projections in A53T mice was observed paralleled by compensatory mechanisms such as increased serotonin synthesis, vesicle packaging and transport capacity. Broadening our knowledge of axonal degeneration and compensatory mechanisms during the long-lasting prodromal phase of PD is an important prerequisite for the development of disease-modifying therapies.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

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**Topic:** C.03. Parkinson's Disease

**Support:** The University of Bordeaux and the Centre National de la Recherche Scientifique provided infrastructural support.
Marie-Laure Arotcarena is a recipient of an MESR fellowship.

**Title:** Assessment of neuroprotective effects of overexpressing TFEB in a mouse model of multiple system atrophy

**Authors: M.-L. AROTCARENA**, M. BOURDENX, S. DOVERO, P.-O. FERNAGUT, W. MEISSNER, E. BEZARD, *B. DEHAY
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**Abstract:** Synucleinopathies are neurodegenerative diseases characterized by the presence of α-synuclein-positive intracytoplasmic inclusions into the central nervous system. Increasing evidence indicates that impairment of lysosomal function may contribute to the pathogenesis of the synucleinopathies, including Parkinson's Disease and Multiple system atrophy (MSA). The transcription factor EB (TFEB) is a master gene of lysosomal biogenesis which coordinates the expression of lysosomal genes leading to an induction of autophagy. It has been demonstrated that overexpressing TFEB in a rat parkinsonian model triggers the restauration of the lysosomal machinery which leads to an enhancement in the clearance of α-synuclein, finally leading to neuroprotective effects. To investigate the efficiency of TFEB overexpression as a common therapeutic strategy for all synucleinopathies, we used a viral-based approach to overexpress TFEB under a neuronal or an oligodendroglial promoter into a transgenic mouse model of MSA, the PLP-Syn mice, which overexpresses in oligodendroglial cells the human WT-α-synuclein under the mouse myelin proteolipid protein (PLP) promoter. We here report that overexpressing TFEB under an oligodendroglial promoter leads to some neuroprotective effects regarding the dopaminergic nigro-striatal pathway. This neuroprotection is associated with an increased clearance of α-synuclein in the substantia nigra of the TFEB-injected PLP-Syn mice. Finally, we report some TFEB-mediated neurotrophic effects which can potentiate the neuroprotective effects observed in TFEB-injected mice.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

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**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.08/V12

**Topic:** C.03. Parkinson's Disease

**Title:** Behavioral and dopaminergic changes in double mutated human α-synuclein mouse model of Parkinson´s disease

**Authors: *U. JULKU**, T. KILPELÄINEN, R. SVARCBAHS, T. T. MYÖHÄNEN
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**Abstract:** Alpha-synuclein (aSyn) is the main component of the Lewy bodies, a histopathological finding of Parkinson's disease. Familial mutations in aSyn gene correlate with early onset of Parkinson´s disease. Misfolded aSyn aggregates and oligomers are believed to have toxic effects on neurons. aSyn regulates dopamine transporter function indicating that misfolded aSyn can alter synaptic dopamine recycling and be a possible cause to dopaminergic neurodegeneration in Parkinson´s disease. Richfield at al (Exp Neurol, 2002) introduced a novel double mutated human A30P*A53T aSyn transgenic mouse strain (C57BL/6J-Tg(Th-SNCA*A30P*A53T)39Eric/J) to model Parkinson´s disease. Heterozygous transgenic mice expressed human aSyn in cell bodies, axons, and terminals of the nigrostriatal system. Mice had decreased locomotor activity at age of 7-9 and 13-23 months, and lowered concentration of dopamine and its metabolites in the striatal tissue at the age of 16-18 months. Younger mice did not have significant changes in locomotor activity or in the striatal dopamine concentration.The aim of our study was to characterize behavioral and dopaminergic changes in homozygous A30P*A53T aSyn transgenic mice. We created a novel genotyping protocol to identify homozygous transgenic mice because genotyping method used in the previous studies was not able to separate heterozygous and homozygous mice. We measured 22 hour locomotor activity and amphetamine induced locomotor activity every 3 months until the age of 18 months and extracellular dopamine in 12 months and in 18 months old homozygous mice by microdialysis. Night time activity in 22 hour locomotor experiment was decreased in 6 months, 9 months and 12 months old transgenic mice compared to wild-type littermates but increased in 18 months old transgenic mice. Baseline level of extracellular dopamine was similar in transgenic and wild-type mice at the age of 12 months and 18 months. Amphetamine-induced dopamine release caused higher extracellular level of dopamine in 12 months old wild-type mice than in 12 months old transgenic mice indicating altered dopamine transporter function but there was no difference in amphetamine-induced dopamine level in 18 months old mice. In conclusion, homozygous aSyn transgenic mice have age-dependent changes in locomotor activity and in the striatal dopaminergic function that are partly different than in heterozygous mice. Altered dopaminergic function needs to be studied further but this mouse strain could be a useful animal model to study treatments for Parkinson´s disease.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

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**Topic:** C.03. Parkinson's Disease

**Support:** DAAD
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**Title:** Alpha-synuclein transmission from noradrenergic locus coeruleus neurons to the striated muscle of mouse esophagus via the nucleus ambiguus

**Authors: *B. LEE**[1], F. GEIBL[1], M. HENRICH[1], W.-H. CHIU[1], L. MATSCHKE[1], N. DECHER[1,2], J. WÖRL[2], C. CULMSEE[1], G. GANJAM[1], W. OERTEL[1]
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**Abstract:** The locus coeruleus (LC) is a small nucleus among the catecholaminergic cell groups, but it has extensively branched axons, and it innervates broad areas in the brain. According to the most widely accepted Parkinson's disease (PD) staging model of Braak, the LC is the second brain area affected by alpha-synuclein (αSyn) pathology, but the possible neurochemical changes induced by axonal αSyn-transmission from the LC have never been investigated. Therefore, we overexpressed human wild-type αSyn (WT-αSyn) or the control protein luciferase (luc) in the mouse LC via unilateral stereotactic delivery of the recombinant adeno-associated virus (rAAV), and subsequent pathological alterations were investigated in a time-dependent manner. Stereology results demonstrated that the LC neurons were not vulnerable to WT-αSyn overexpression, yet rigorous microgliosis and astrogliosis occurred as early as 3 weeks post-injection. Intriguingly, the number of anti-choline acetyltransferases (ChAT) immunoreactive (ir) neurons in the dorsal motor nucleus of the vagus (DMnX) and in the nucleus ambiguus (nAmb) significantly decreased in the αSyn group post 3 and 9 weeks. The putative axonal connectivity between the LC and the cholinergic motor nuclei and the loss of ChAT-ir were further elucidated and reproduced by microinjection of Tyrosine Hydroxylase (TH) promoter-specific viral vectors (rAAV2/5-TH-WT-αSyn) in the LC. We found robust αSyn-ir axonal varicosities around the DMnX neurons, and remarkably, intraneuronal αSyn was present in ambiguus neurons in both hemispheres as early as 3 weeks post-injection. As nucleus ambiguus compact formation controls the esophagus, we investigated the cervical, thoracic and abdominal parts of the esophagus tissues of these mice. As a result of aSyn overexpression in the LC, we observed αSyn-ir cells and varicosities in the muscle layers, and notably, some of these αSyn-ir neurons co-localized with Protein Gene Product 9.5 (PGP 9.5)-ir myenteric plexus ganglia post 3 and 9 weeks. Furthermore, we also found that, unlike the majority of the Vesicular Acetylcholine Transporter (VAChT) signals, some motor nerve endings were weak and dispersed from the motor receptors. Our data reveal that LC neurons induced the transsynaptic and transneuronal presence of αSyn in the vagal motor nuclei and suppressed cholinergic efferents terminating on motor endplates in the esophagus. It appears that αSyn can travel via the anatomically connected brain regions as proposed in the early staging model of PD, implying α-synucleinopathy in noradrenergic neurons may potentially disturb the cholinergic modulation of the upper gastrointestinal tract.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

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**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.10/V14

**Topic:** C.03. Parkinson's Disease

**Title:** Interrogating the relationship between glycolipids and alpha synuclein pathology in a preformed fibril *in vitro* model

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**Abstract:** GBA1 encodes the lysosomal enzyme glucocerebrosidase (GCase) which metabolizes the lipids, glucosylceramide (GlcCer) and glucosylsphingosine (GlcSph). Mutations in GBA reduces trafficking of GCase to the lysosome resulting in loss of enzyme activity and lipid accumulation and significantly increase the risk of PD. In several preclinical in vitro paradigms, pharmacological or genetic inhibition of the enzyme and lipid elevation is capable of exacerbating α-syn aggregation in pre-formed fibril and overexpression models of PD. However, it remains unclear whether reduction of glycolipid content is capable of ameliorating or reducing α-syn aggregation. Pharmacological inhibition of glucosylceramide synthase (GCSi's) is a promising therapeutic approach for treating PD, however, more work is required to understand the mechanism of action of these molecules and profile their therapeutic potential. In the present studies, we utilize a preformed fibril (PFF) in vitro model of α-synuclein pathology to investigate the relationship between glycolipid biology and α-syn pathology. The PFF model uses recombinant α-syn PFFs to seed recruitment of endogenous α-Syn into insoluble, phosphorylated α-syn aggregates, similar to the pathology observed in PD. Consistent with previous findings, our data show pharmacological inhibition of GBA with a selective inhibitor, conduritol B epoxide (CBE) robustly modulates glycolipid levels in SH-SY5Y cells, rodent primary cultures, and human iDopa neurons. In addition to elevating glycolipid content, CBE also markedly increases detergent-insoluble phosphorylated α-syn aggregates. Consistent with these pharmacological studies, genetic inhibition of GCase (through GBA1 mutation) similarly causes accumulation of glycolipids and elevates insoluble phosphorylated α-syn. Lastly, we demonstrate GCSi (Ibiglustat) administration effectively decreases glycolipid content in SH-SY5Y cells, rodent primary cultures, and human iDopa neurons and can reduce αSyn pathology in PFF in

vitro models. Together, our data support the hypothesis that glycolipids promote aSyn pathology, and reduction of glycolipids through GCS inhibition provides a novel therapeutic approach for treating PD.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.11/V15

**Topic:** C.03. Parkinson’s Disease

**Support:** National Taiwan University
Ministry of Science and Technology

**Title:** Establishing a rat model to study the progression of sporadic Parkinson's disease

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**Abstract:** Parkinson’s disease (PD) is the second most common neurodegenerative disease, clinically characterized by bradykinesia, resting tremor, and rigidity. The etiology of PD is attributed to the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), further decreasing the release of dopamine (DA) through the nigrostriatal pathway to the striatum, where DA binds to different types of DA receptors, producing various responses (activation/inhibition) for the fine control of locomotor activity. Losing these DA neurons in SNpc results in insufficient dopamine and thus breaks the balance of neurotransmission in the striatum. Specifically, the hallmark in both familial and sporadic PD is the presence of intra-neuronal proteinaceous inclusions, termed “Lewy Bodies”, mainly composed by aggregation of alpha-synuclein (α-syn), which can be distributed across the whole brain during PD progression. However, how α-syn aggregates propagate across brain or other systems remains unclear. Current PD animal models are either induced by toxic agents causing rapid PD onset, or made by carrying inherited pathogenic genes resembling familial PD but not sporadic PD. In this study, we aim to establish a rat model to mimick sporadic PD during adulthood. Male Sprague-Dawley rats (~250 gw) were deep anesthetized for stereotaxic surgery. The 2 μL solution containing DNA plasmids (5 μg/μL) was microinjected into SNpc to deliver genes expressing membrane-bound green fluorescence protein (GFP). Five electric pulses were delivered by homemade

platinum electrodes via ear bars, with duration of 50 msec and intervals of 950 msec, yielding the electric field strength of 133 V/cm. After 14-16 days following *in vivo* electroporation, the rats were sacrificed to verify gene expression in the SNpc by immunofluororescence staining. Double stainings for GFP and tyrosine hydroxylase (TH) showed the colocalization of both signals, demonstrating the success of *in vivo* electroporation. Therefore, this *in vivo* electroporation technique can be used as a gene delivery method to introduce the human pathogenic α-syn mutant in adult rats, serving as a sporadic PD model.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.12/V16

**Topic:** C.03. Parkinson’s Disease

**Title:** Evaluation of alpha-synuclein pathology and glycolipids in post-mortem parkinson’s disease brain samples

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**Abstract:** While the etiology and pathogenesis of Parkinson’s disease (PD) remain poorly understood, mutations in the genes that encode α-synuclein (αSyn) and glucocerebrosidase (GCase) proteins are the strongest genetic risk factors for the disease. Preclinical in vitro and in vivo experiments have depicted a biochemical relationship between αSyn and the glycolipid substrates of GCase. In some post-mortem brain experiments from PD patients, glycolipid content is altered in distinct brain regions compared to control patient samples. However, additional data is needed in this area to better characterize the role of glycolipids in PD, and further understanding of the relationship between GCase and αSyn in the disease pathogenesis. One limiting factor has been the availability of well-characterized post-mortem brain tissue that allows sampling across relevant brain regions that are vulnerable in the disease. Second, direct quantitation of a broad array of glycolipid species has been challenging and prevented direct comparison across laboratories.
To this end, the present studies utilized a validated LC-MS assay to quantitate several glycolipid species including: glucosylceramide (C16-24_1), glucosylsphingosine, and ceramide (C16-24) from several regions across the Braak neuraxis. Serial thin sections were prepared from distinct brain regions including, dorsal motor nucleus of the vagus (n=15), substantia nigra (n=30), temporal cortex (n=24) to allow for a robust characterization of αSyn pathology in adjacent sections to those evaluated for glycolipid content. αSyn pathology from adjacent sections was

determined using: histochemical staining of Lewy-bodies with H&E, immunohistochemical detection using LB509, and biochemically from detergent soluble and insoluble fractions using a validated alphalisa assay to quantify absolute amounts of αSyn phosphorylated at serine-129. Data from these studies suggest glycolipid content of certain species are altered in disease when compared to control patients. αSyn pathology, while robust in many patients, is variable across brain region and from patient to patient. Together, these studies expand on the current data available in the field, and continue to define a role for glycolipids in PD pathogenesis.

**Disclosures: R. Kesilman (korn):** None. **L. Yao:** None. **A. Ramirez:** None. **J. Schachter:** None. **N. Hatcher:** None. **R. Drolet:** None. **S. Smith:** None.

**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.13/W1

**Topic:** C.03. Parkinson’s Disease

**Support:** Physics-to-Medicine initiative (P2M), Goettingen, Germany
Cluster of Excellence Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB), Goettingen, Germany

**Title:** The influence of iron on the alpha-synuclein pathology in Parkinson's disease

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**Abstract:** Parkinson’s disease (PD) is a slowly progressing neurodegenerative disorder. The pathological characteristics of PD are the degeneration of dopaminergic neurons in the Substantia nigra pars compacta as well as neuronal protein inclusions called Lewy bodies (LBs). LBs mainly consist of misfolded and aggregated variants of the small presynaptic protein alpha-synuclein (α-syn). Aggregation processes of α-syn result in the formation of α-syn fibrils, being prone to propagate throughout the whole brain. So far, the mechanisms behind this spreading pathology of α-syn in PD are still elusive. In biophysical studies, iron was shown to bind to native α-syn, fostering its aggregation process. Therefore, iron and α-syn have become important targets to understand PD pathophysiology. The influence of iron brain load on the α-syn spreading pathology may be a key mechanism for new therapeutic approaches in the treatment of PD. In our current *in vivo* study with C57BL/6 mice, an iron intoxication paradigm combined with intra-striatal injections of pathogenic α-syn preformed fibrils (PFFs) was performed.

Increased iron accumulation in the brain was achieved by feeding mouse pups with different concentrations of carbonyl iron (60, 120 and 240 mg / kg body weight) from p10 to p17. Cognition was impaired in mice intoxicated with the highest iron dosage at 3 months post iron intoxication (N = 14 - 20). PFFs-injected mice showed also strong cognitive impairments at 90 days post α-syn PFFs injection (N = 27 - 28). Furthermore, we evaluated the effects of the different iron dosages on α-syn PFFs spreading throughout the mouse brain. Since the pathophysiology of PD cannot be entirely mimicked by the mouse model, we used postmortem midbrain tissue of PD patients and age-matched controls to investigate the distribution of iron and other elements on a subcellular level. Here, α-syn-positive LBs were analyzed using X-ray fluorescence and X-ray diffraction to identify PD-specific patterns of metal content and crystalline structures. Our results showed a high iron content and a reduction of copper in the LB, which has to be confirmed in a larger sample size. Our data from human tissue suggests a dyshomeostasis of iron and copper in α-syn-positive LBs of PD patients. Furthermore, the animal data supports a deleterious role of iron on cognition, but its influence on α-syn spreading remains to be determined in further experiments.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.14/W2

**Topic:** C.03. Parkinson’s Disease

**Title:** Human Plasma Fraction reduces the detrimental effects of alpha-synuclein overexpression in mice

**Authors: *C. TUN**, H. HACKBART, S. REGE, M. K. CAMPBELL, A. LIU, E. CZIRR, S. BRAITHWAITE, S. S. MINAMI
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**Abstract:** We have previously demonstrated that treatment of aged immunocompromised mice with young human plasma improves aging-associated memory and motor deficits and enhances neurogenesis. We have now identified a novel human plasma fraction (PF) that enhances both cognition and neurogenesis beyond the levels seen with young plasma. Importantly, this newly identified plasma fraction, with only a portion of the complexity of whole plasma, can be administered to immune-competent mice with no deleterious side effects. This allowed us to test whether PF could ameliorate the motor and cognitive deficits observed in a mouse model of Parkinson’s disease, specifically, human alpha-synuclein overexpressing mice (Line 61). We treated transgenic mice with either vehicle or PF intravenously and found significant

improvements in motor function three weeks later in wire suspension, beam walk, and the pasta gnawing test for motor function. We further assessed whether neuronal survival was affected by immunohistochemistry and found significantly more NeuN-positive cells in the hippocampus and striatum of PF-treated mice compared to vehicle-treated mice. To determine whether these changes were associated with reduction in neuroinflammation, we assessed the same brain regions for Iba1-positive microglia and CD68-positive activated microglia and found significant reductions in both. These findings suggest that treatment of alpha-synuclein transgenic mice with a human plasma fraction ameliorates multiple Parkinson's disease-related symptoms, including motor deficits, neuronal loss, and neuroinflammation, and provides strong support for clinical evaluation of this plasma fraction in Parkinson's disease.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.15/W3

**Topic:** C.03. Parkinson's Disease

**Support:** Parkinson UK

**Title:** Motor impairment due to alpha-synuclein-mediated dopaminergic neuron dysfunction in *C. elegans*

**Authors: S. K. KALIA**[1], K. MENEZES[1], N. TRAN[1], J. B. RODGERS[1], H. CHAU[1], K. FUJISAWA[1], K. CHEN[1], A. M. LOZANO[1], J. G. CULOTTI[1], S. SUO[2], W. S. RYU[1], *L. V. KALIA[1]
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**Abstract:** Parkinson's disease is a neurodegenerative movement disorder characterized by motor impairment due to death of dopaminergic neurons in the substantia nigra pars compacta. Accumulation of the protein alpha-synuclein is implicated in the initial dysfunction and eventual loss of these neurons. To date, transgenic *C. elegans* have been used to model the later stages of alpha-synuclein-mediated neurodegeneration in which neurite retraction or complete cell loss is already evident. To develop a *C. elegans* model of earlier alpha-synuclein-mediated dopaminergic neuron dysfunction, we ectopically expressed alpha-synuclein in dopaminergic neurons and identified a motor impairment using quantitative phenotyping with high-resolution worm tracking, custom imaging processing, and machine learning. This motor phenotype preceded the onset of prominent loss of dopaminergic neurites or cell bodies but was associated with impaired dopaminergic signalling as measured by a green fluorescent protein reporter. The

motor phenotype was not due to neuromuscular junction abnormalities or alterations in lifespan. We developed an unbiased, semi-automated, quantitative method for multi-worm measurements of the motor phenotype. The severity of the motor phenotype correlated with alpha-synuclein protein levels. Treatment of alpha-synuclein transgenic *C. elegans* with dopamine reduced the motor impairment whereas treatment of non-transgenic *C. elegans* with a $D_2$ dopamine receptor antagonist induced the motor impairment. Together, our findings demonstrate that alpha-synuclein causes dopaminergic neuron dysfunction associated with motor impairment in this *C. elegans* system. The motor impairment occurs in advance of severe dopaminergic neurodegeneration and thus models an earlier stage of alpha-synuclein cytotoxicity.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.16/W4

**Topic:** C.03. Parkinson’s Disease

**Support:** Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 116060 (IMPRiND)
University of Bordeaux
Centre National de la Recherche Scientifique

**Title:** Biochemical and physical characterization of -synuclein aggregates in Parkinson’s disease extracted material used for modeling synucleinopathies in viv

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**Abstract:** Synucleinopathies are neurodegenerative diseases characterized by the presence of α-synuclein-positive intracytoplasmic inclusions in the central nervous system. α-synuclein protein shares key features with prions such as i) conformational change of physiological α-synuclein into misfolded pathological forms; ii) seeding of α-synuclein pathogenic properties; iii) cell-to-cell transmission and spreading of α-synuclein protein among neuronal regions. To model *in vivo* α-synuclein seeding and spreading afferent to PD pathogenesis, we inoculated human PD-derived samples into mice and monkeys. In that extent, after tissue homogenization, the autopsy

material was fractionated on sucrose density gradients allowing a fine separation of α-synuclein aggregates: Lewy bodies (LB), containing the majority of aggregated α-synuclein, and noLB fractions composed mainly of the monomeric form of the protein and finely granular α-synuclein. In parallel to the analysis of the pathology induced by the injection of the extracted material, the aim of this study was to characterize biochemically and biophysically the nature of LB and noLB fractions. To unravel the physical properties of α-synuclein aggregates (i.e. LB vs noLB), we performed different and complementary assays. We first assessed their amyloid nature by measuring their binding of Thioflavin S labelling to the fractions, and by using the α-synuclein Cisbio detection kit to quantify the amount of aggregates through this FRET-like methodology. We also directly observed the assemblies using electron microscopy examination. Then, taking advantage of a collaboration with Synchrotron SOLEIL, we were able to resolve their secondary structure (i.e. α-helix and β-sheet composition). We then directly estimated the size and density of these assemblies by sedimentation and floatation ultracentrifugation techniques. Lastly, we determined the prion-like biochemical properties of the α-synuclein aggregates by measuring their resistance to Proteinase K digestion, and to detergent solubilisation and denaturation (SDS-Urea treatment). Overall, this study represents a crucial step in understanding the composition and nature of LB and noLB fractions in terms of α-synuclein aggregated species, allowing us to directly relate their pathogenic propensity to the quaternary structure of their α-synuclein content. More than a physical characterization, it will allow a better understanding of synucleinopathies pathogenesis, and help us moving towards the development of therapeutic approaches

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 749.17/W5

**Topic:** C.03. Parkinson’s Disease

**Title:** Neuro-inflammation is associated with T cell infiltration in an alpha-synuclein tg models of Lewy body disease

**Authors: *M. IBA**[1], C. KIM[1], A. VERMA[2], R. A. RISSMAN[3], R. SEN[4], J. SEN[2], E. MASLIAH[1]
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**Abstract:** Alpha-synuclein (α-syn) is a presynaptic protein which progressively accumulates in neuronal and non-neuronal cells in neurodegenerative diseases such as Parkinson's disease (PD), Dementia with Lewy bodies (DLB), and Multiple system atrophy. In addition to accumulation of oligomers and fibrils, the mechanisms of neurodegeneration in these synucleinopathies might involve propagation to neuronal and non-neuronal cells such as astrocytes and microglia leading to neuro-inflammation. To understand the role of immune cell involvement in PD, we evaluated 10-11 months old α-syn mouse model which overexpress human wild type α-syn (α-syn Tg: Thy1 promoter line 61) comparing its littermates non-transgenic mice (non-Tg). We collected organs including brain, spleen, liver, lymph node and thymus. Over all, α-syn Tg showed tendency of smaller body weight, as well as spleen and liver weight, hence the total cell number in these organs in the α-syn Tg decreased when compared to non-Tg mice. Flow cytometric analysis of immune cells revealed that α-syn Tg showed significant decrease of NKT cells in the spleen, liver and lymph nodes, and an increase of NKT cells in the brain in α-syn Tg mouse. Immunohistochemical analysis of brain sections revealed significant increase of CD3 and CD4 (T cells), but not CD20 (B cells) in cortex, hippocampus and striatum of α-syn Tg compare to non-Tg mouse. Macrophage marker CD68 also increased in the same brain regions in α-syn Tg mouse as well as microglia and astrocytes. These results suggest alterations in the balance between innate and adaptive immune responses play an important role in neuroinflammation and neurodegeneration in synucleinopathies and that modulating such responses might be a viable therapeutic target.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

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**Program #/Poster #:** 749.18/W6

**Topic:** C.03. Parkinson's Disease

**Support:** MULTISYN FP7 602646

**Title:** Modeling prodromal Parkinson's disease in alpha-synuclein transgenic rats: Behavioral and neurobiological insights into Parkinson's disease pathophysiology

**Authors: *A. V. POLISSIDIS**[1], M. XILOURI[1], V. KOLLIA[1], M. KORONAIOU[1], M. BOYONGO[1], S. VRETTOU[1], N. CASADEI[2], O. RIESS[2], L. STEFANIS[1,3]
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**Abstract:** Alpha-Synuclein (α-syn) is a presynaptic neuronal protein linked genetically and neuropathologically to Parkinson's disease (PD). PD is associated with severe motor symptoms, however, they are often accompanied and even preceded by debilitating non-motor symptoms (NMS) such as olfactory deficits, cognitive decline, anxiety, depression and psychosis that significantly impact the quality of life of patients. Furthermore, beyond nigrostriatal dopaminergic dysfunction, there is a widespread deregulation of other neurotransmitters. The aim of this study was to evaluate the progression of NMS in male and female α-syn BAC transgenic rats, generated by Olaf Riess, Tubingen University (Nuber et al. 2013), using a behavioral test battery [open field (locomotor activity), elevated plus maze (anxiety), buried pellet test (olfaction), prepulse inhibition (sensorimotor gating), Morris water maze (learning & memory), forced swim test and sucrose preference (depressive-related behaviors)], neurochemical analysis (catecholamines, glutamate and GABA) with HPLC and electrochemical detection and α-syn biochemistry at 3, 6, 9, 12 and 18 months. α-syn BAC males exhibit reduced food consumption and body weight, increased locomotor activity and reduced anxiety starting at 3 months. Furthermore, both females and males exhibit an early onset olfactory deficit and depressive-like phenotype at 3 months, a spatial learning deficit at 6 months and sensorimotor impairment at 12 months, with males presenting an overall worse phenotype. Neurochemical correlates indicate dopaminergic dysfunction in the striatum and glutamatergic and GABAergic dysfunction in the amygdala and hippocampus, possibly related to observed locomotor hyperactivity, reduced anxiety and cognitive impairment, respectively. In addition, phosphorylated and oligomeric α-syn species accumulate with age in relevant brain regions. Attempts to reverse specific behavioral phenotypes via 1) silencing of α-syn expression with microRNA stereotaxic injections in the ventral tegmental area and 2) pharmacologically modulating dopaminergic neurotransmission are currently underway. α-syn BAC rats provide a valuable translational tool to evaluate the role of α-syn in the pathogenesis of NMS and assess potential early therapeutic interventions for PD.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

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**Topic:** C.03. Parkinson’s Disease

**Support:** NIA Grant P01AG014930
CPT Foundation

**Title:** Deuterated fatty acid supplementation is neuroprotective against a-synuclein induced dopamine toxicity

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**Abstract:** Clinical trials of disease modifying treatments to target Parkinson's disease (PD) have thus far all failed. Evidence suggests that a key etiologic factor is membrane-associated oxidative stress. Lipid peroxidation plays a central role in oligomeric α-synuclein (α-syn) toxicity, mitochondrial dysfunction and neuronal degeneration, all key processes in the pathogenesis of PD. Poly unsaturated fatty acids (PUFAs), that make up synaptic and mitochondrial membranes, are often the first molecular targets attacked by reactive oxygen species, resulting in membrane dysfunction and generation of toxic reactive carbonyls and isoprostane-containing species. We examined a novel non-antioxidant based approach that makes PUFAs resistant to the non-enzymatic chain reaction of lipid peroxidation. The rate-limiting step of the chain reaction of ROS-initiated PUFA autoxidation involves hydrogen abstraction at bis-allylic sites. The rate of this step can be slowed down if hydrogens are replaced with deuteriums. D-PUFAs are considered safe and tolerable drugs, with no off-target activities, and are approved for human use. Here we show that overexpression of human A53T α-syn in the rat substantia nigra (SN) using an adeno-associated viral vector reproduces several of the neuropathological and biochemical features seen in PD patients, including nigrostriatal dopamine (DA) degeneration. Consistent with prior findings that dietary isotopic reinforcement with D-PUFA protects against MPTP-induced nigrostriatal damage in mice, chronic dietary supplementation with D-PUFAs improved behavioral deficits and preserved SN DA neurons and their striatal nerve terminals. D-PUFAs were also effective against axonal damage, oxidative stress, and inflammation produced by α-syn toxicity. These studies will support moving D-PUFAs forward into clinical trials to evaluate their efficacy as a neuroprotective therapy for PD.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

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**Topic:** C.03. Parkinson's Disease

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**Title:** Longitudinal characterization of motor and non-motor deficits in the “Line 61” alpha-synuclein mouse model of Parkinson’s disease

**Authors: *A. KHAN**, M. MAILE, C. WITTMER, K. TATSUKAWA, D. PRICE, M. GILL, D. BONHAUS
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**Abstract:** Accumulation of aggregates of alpha-synuclein (ASYN) in brain is linked to several neurodegenerative disorders and synucleinopathies including Parkinson’s disease (PD) and Dementia with Lewy bodies (DLB). Transgenic (Tg) mouse models with overexpression of ASYN have proved useful in characterizing the behavioral, neuropathological, and biochemical consequences of ASYN aggregation.
The mThy1-ASYN Tg mouse model (commonly referred to as Line 61), overexpresses wild-type human ASYN and develops extensive accumulation of ASYN in brain and peripheral regions relevant to PD, neurodegeneration (including loss of tyrosine hydroxylase immunoreactivity in the striatum), inflammation, and both motor and non-motor functional deficits. Neuropore Therapies Inc. has licensed and established a colony of mThy1-ASYN transgenic mice and here we report the results of efforts to confirm and extend a detailed characterization of the motor and non-motor phenotype of this PD model.
Body weight, spontaneous locomotor activity, grip strength, and hind limb clasping were measured at the ages of 1, 3, 6, 9 and 12 months in separate cohorts of age matched non-transgenic and transgenic mice (Line61 tg). A transgenic phenotype on these measures emerged between 3-6 months of age consisting of decreased body weight, increased locomotor activity, decreased grip strength and increased hind limb clasping. The changes in transgenic body weight and grip strength were stable after 6 months of age. The hyper locomotor activity resolved between 9 and 12 months of age (back to non-transgenic levels). Hind limb clasping deficits were progressive between 3 and 9 months of age and then stable from 9 months through 12 months of age.
A separate cohort of age matched animals was used to conduct repeated measurements of colonic motility and whole gastrointestinal (GI) transit starting at 3 months of age and including 6, 9, 12 and a separate cohort tested at 16 months of age. A decrease in colonic motility (utilizing bead expulsion test) was present in L61 tg mice starting at 3 months of age. A statistically significant deficit in colonic motility (increased time to expel glass bead) was also present at 6 and 12 month of age. There was no evidence for slowed GI transit (timed dye gavage) at any age tested.
Taken together, these data confirm and extend observations of motor and non-motor deficits in Line 61 tg mice as early as 3 month of age with some persistent or progressive changes through 12-16 months of age. Efforts are ongoing to characterize ASYN pathology (brain and periphery) and translatable markers in samples collected from these subjects.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.21/W9

**Topic:** C.03. Parkinson's Disease

**Support:** Innovative Medicines Initiative 2 No. 116060 (IMPRiND)

**Title:** High content analysis of α-synuclein pools in primary cultures of wild-type mouse cortical neurons challenged with extractive and recombinant assemblies

**Authors: F. DE GIORGI-ICHAS**[1], F. LAFERRIERE[1], E. FAGGIANI[1], B. DEHAY[2], *G. PORRAS[3], E. BEZARD[2], F. ICHAS[1]
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**Abstract:** We developed a High-Content Screening (HCS) assay aimed at detecting and profiling candidates (i.e. genes or drugs) capable of interfering with both the onset and the progression of *α*-synucleinopathy. In order to maximize the probability of eventually ending up with an assay meeting the minimal robustness requirements for screening, we focused on wild type mouse cortical neurons challenged with exogenous *α*-synuclein assemblies. Indeed, late embryonic cortical neurons are easily isolated in large quantities and are amenable to standardized 96-well culture, and (ii) additions of exogenous *α*-synuclein assemblies allows to control the exact amount brought to the target neurons. Setting up this assay allowed us to explore dose/response and time-dependent effects of exposure to α-synuclein assemblies, using a variety of readouts based on immunofluorescence (IF) staining, and taking into account the different phases of the *α*-synuclein-neuron interaction. We exposed neurons to low concentrations (10 nM) of *α*-synuclein and applied machine learning strategies with random forest algorithms to treat the resulting IF images: this allowed us to observe and quantify the early formation of scattered hybrid *α*-synuclein speckles at the level of the target neurons. These speckles were big (in the 100nm-1µm size range) and consisted in the apposition of exogenous human *α*-synuclein clumps with endogenous synuclein counterparts on the processes of most neurons. Later on, and only in a fraction of the neurons bearing these speckles, extensive phosphorylation of endogenous *α*-synuclein took place, showing this time a "whole cell" pattern instead of a scattered one. Investigation of the nature and of the causal relationship between hybrid speckles and extensive *α*-synuclein phosphorylation is underway *in vitro* as well as *in vivo* and an update will be presented in the poster.

**Disclosures: F. De Giorgi-Ichas:** None. **F. Laferriere:** None. **E. Faggiani:** None. **B. Dehay:** None. **G. Porras:** A. Employment/Salary (full or part-time):; Motac neuroscience. **E. Bezard:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent

holder, excluding diversified mutual funds); Motac Holding. F. Consulting Fees (e.g., advisory boards); Motac neuroscience. **F. Ichas:** None.

**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.22/W10

**Topic:** C.03. Parkinson's Disease

**Support:** UCB

**Title:** α-synuclein post-translational modifications are not only markers of pathology but are also key regulators of lewy body formation and maturation; implications for therapies targeting α-syn and pathology spreading

**Authors: *A.-L. MAHUL-MELLIER**[1], F. ALTAY MELEK[1], J.-C. COPIN[1], J. BUTSCHER[1], N. MAHARJAN[1], N. AÏT BOUZIAD[1], S. VINGILL[2], R. WADE-MARTINS[2], R. HAMELIN[1], S. DEGUIRE[1], R. BURAI[1], H. LASHUEL[1]
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**Abstract:** Parkinson's disease (PD) is the second most common neurodegenerative disorder characterized by the neuronal accumulation of misfolded alpha-synuclein (α-syn) into intracellular inclusions named Lewy bodies (LB). Despite increasing evidence indicating that α-syn plays a central role in PD pathogenesis, the molecular and cellular mechanisms that trigger the conversion of soluble α-syn to its aggregated form and regulate LB formation and the role of these processes in PD are still elusive. Recent findings have demonstrated that misfolded α-syn can be transmitted to recipient neurons, and serve as efficient seeds to initiate aggregation, thus spreading the pathology throughout the brain in a prion-like manner. Taking advantage of the seeding capacity of pre-formed fibrils (PFFs) to induce the formation of intracellular LB-like structures, we sought to decipher the role of post-translational modification in 1) the processing of α-syn PFFs; 2) α-syn seeding capacity and fibril formation**;** and 3) the formation and maturation of LB-like inclusions in primary neurons. Using an integrative imaging and proteomic approaches, including correlative light electron microscopy imaging, temporal proteomic analyses and biochemical characterization, we were able to uncover novel mechanisms that govern the initiation of α-syn misfolding in neurons and identify specific PTMs that occur during the various stages of α-syn seeding, aggregation and LB formation. First, temporal proteomic profiling of the LB-like inclusions formed in neurons revealed similarity with the proteins content related to the *bona fide* LB detected in human brain reinforcing the physiological relevance of the seeding model for studying the biogenesis of LBs. Second, our temporal proteomic studies revealed that treatment with α-syn fibrils induces the activation of specific enzymes that regulate α-syn PTMs during the initiation of the seeding process and later

during the growth and maturation of the newly formed aggregates. Third, we showed that C-terminal modifications are required for the efficient packaging of fibrils and LB maturation. Finally, our results point towards a potential failure of the protein degradation machinery to clear off these inclusions leading to the intracellular accumulation of LB as failed aggresomes-like inclusions. In conclusion, our work helped to uncover new mechanisms that possibly contribute to the origin of the LBs and the development of PD. Furthermore, this work represents the first comprehensive biochemical and structural characterization of α-syn aggregation, interactome and inclusion formation in a neuronal seeding model of PD and synucleinopahties.

**Disclosures: F. Altay Melek:** A. Employment/Salary (full or part-time):; EPFL. **J. Copin:** A. Employment/Salary (full or part-time):; EPFL. **J. Butscher:** A. Employment/Salary (full or part-time):; EPFL. **N. Maharjan:** A. Employment/Salary (full or part-time):; EPFL. **N. Aït Bouziad:** A. Employment/Salary (full or part-time):; EPFL. **S. Vingill:** A. Employment/Salary (full or part-time):; University of Oxford. **R. Wade-Martins:** A. Employment/Salary (full or part-time):; University of Oxford. **R. Hamelin:** A. Employment/Salary (full or part-time):; EPFL. **S. Deguire:** A. Employment/Salary (full or part-time):; EPFL. **R. Burai:** A. Employment/Salary (full or part-time):; EPFL. **H. Lashuel:** A. Employment/Salary (full or part-time):; EPFL.

**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.23/W11

**Topic:** C.03. Parkinson’s Disease

**Support:** Fondation pour la Recherche sur le Cerveau
Association France Parkinson
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CONICYT Becas-Chile Scholarship

**Title:** Perivascular macrophages control synucleinopathy spreading and toxicity in mouse models of Parkinson’s disease

**Authors: *S. HUNOT**, J. FUENTEALBA, E. C. HIRSCH
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**Abstract:** Parkinson’s disease (PD) is a movement disorder characterized by the loss of dopaminergic neurons (DN) in the substantia nigra (SN) and the presence of intraneuronal inclusions (Lewy bodies and neurites) enriched in alpha-synuclein (alpha-syn), a protein believed

to have prion-like propagation/aggregation properties. The mechanisms underlying the progression of neurodegeneration remain poorly understood, but probably involve both cell-autonomous and non-cell autonomous processes. Indeed, accumulating evidence suggests that pathological neuro-immune interactions could play a critical role in PD pathogenesis. In particular, microglial activation and T-cells are found in the SN of PD patients, but also in several animal models of the disease. The presence of circulating cells within the diseased brain may indicate alterations of the blood-brain barrier (BBB), as reported by several studies. The structural and functional properties of the BBB are tightly controlled by perivascular elements such as pericytes and perivascular macrophages (MPVs). The importance of MPVs in pathophysiological mechanisms of the CNS is a recent concept that has notably found echo in proteinopathies and in particular Alzheimer's disease. However, their response and pathogenic role in PD have, so far, never been investigated. Our present data suggest that PVMs may play a role in PD pathophysiology. Using a mouse model of degenerative synucleinopathy we found that the number of PVMs dynamically increases within the SN during the course of neurodegeneration. We further demonstrated that local cell proliferation accounted for this PVM recruitment with no involvement of peripheral immune cell engraftment. Importantly, similar increase in PVM density was observed in the *postmortem* brain of PD patients. The specific ablation of PVMs aggravates the demise of DN in our animal model, revealing their neuroprotective potential. This feature is very likely associated to their immunomodulatory properties and their ability to clear toxic molecules from the perivascular space. In line with this, we found that PVM depletion dramatically increases synucleinopathy spreading in mice injected with toxic α-syn assemblies. Overall, our results highlight the importance of PVMs in regulating the toxicity and spreading of synucleinopathy and suggest that immunotherapeutic approaches in PD could be oriented selectively to maintain or even boost the beneficial functions of immune cells like PVMs.

**Disclosures: S. Hunot:** None. **J. Fuentealba:** None. **E.C. Hirsch:** None.

**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.24/W12

**Topic:** C.03. Parkinson’s Disease

**Title:** Investigating the role of the ubiquitin proteasome system in a rodent model of Parkinson’s disease

**Authors: *C. MCKINNON**[1], E. GONDARD[3], M. L. DE SNOO[4], C. NEUDORFER[1], G.-S. NGANA[1], J. M. BROTCHIE[2], J. B. KOPRICH[5], A. M. LOZANO[6], L. V. KALIA[7], S. K. KALIA[8]

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**Abstract:** ***Background:*** Dysfunction of the ubiquitin-proteasome system (UPS) has been implicated in the pathogenesis of a wide range of neurodegenerative disorders, which are characterized by the accumulation of misfolded proteins in affected neurons. In the context of Parkinson's disease (PD), impairment of the catalytic activity of the 26S proteasome has been reported in post-mortem sporadic PD brain tissue, various rodent models and in cultured cells lines overexpressing mutant alpha-synuclein. It remains unclear whether proteasome inhibition is associated with functional impairment of the UPS *in vivo* and whether this could contribute to an early loss of dopaminergic neurons. ***Aim:*** To measure UPS activity at different stages of dopaminergic neurodegeneration following viral-mediated expression of A53T alpha-synuclein in rat substantia nigra ***Methods:*** Adult female rats received unilateral co-injection of adeno-associated viruses (AAVs) expressing human A53T alpha-synuclein and the $Ub^{G76V}$GFP reporter substrate into the substantia nigra. Timed-culls were performed at different stages of disease progression and *in vivo* UPS activity measured by immunofluorescence and fluorogenic peptide cleavage assays. ***Results:*** Expression of A53T alpha-synuclein was associated with accumulation of the $Ub^{G76V}$GFP reporter in both dopaminergic and non-dopaminergic cell populations in the substantia nigra. In contrast, dopaminergic neurons in the neighboring ventral tegmental area did not show evidence of UPS dysfunction, despite accumulation of misfolded A53T alpha-synuclein. ***Conclusion:*** Expression of mutant alpha-synuclein is associated with functional impairment of the UPS in a rodent model of PD. As a result, strategies to upregulate UPS activity could have therapeutic benefit in PD and related protein misfolding disorders.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.25/W13

**Topic:** C.03. Parkinson's Disease

**Support:** Van Andel Research Institute

**Title:** Parkinson's disease proteinopathy is exacerbated in the Engrailed1$^{+/-}$-mouse model

**Authors: *D. CHATTERJEE**[1], D. S. SANCHEZ[2], E. QUANSAH[3], N. L. REY[4], J. A. STEINER[3], M. L. ESCOBAR GALVIS[3], Z. MADAJ[3], J. H. KORDOWER[1,3], P. BRUNDIN[3]
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**Abstract:** Parkinson's disease (PD) is a multifactorial synucleinopathy with selective vulnerability of the nigral dopaminergic system. Current models of PD pathology fail to recapitulate the temporal sequence of disease progression or exhibit comprehensive phenotype. With this study, we aimed to generate a model to define the effects of combining two primary pathogenic factors, mitochondrial deficits and proteostatic stress, on the formation of protein aggregates and nigrostriatal intregrity. We employed the heterozygous Engrailed 1 (*En1*$^{+/-}$) mouse that features progressive loss of nigral dopamine neurons, striatal dopamine deficiency, axonal dysfunction and neuroinflammation. *En1*$^{+/-}$ mice display significant mitochondrial deficits and lysosomal deficiencies which are akin to phenomena observed in clinical PD. We tested the hypothesis that mitochondrial deficits underlying the *En1*$^{+/-}$ phenotype will enhance the effects of intrastriatal injections of pathogenic human α-synuclein (α-syn) fibrils (hPFFs). We unilaterally injected 4 week-old *En1*$^{+/-}$ and control wild-type mice with hPFFs and sacrificed animals at 3 months of age for post-mortem analysis. Using immunohistochemistry and stereology, we established the effects of *En1*$^{+/-}$ on the propagative dynamics of synucleinopathy. Following the intrastriatal PFF injection, *En1*$^{+/-}$ mice exhibited a near-threefold increase in pS129-α-syn-positive neurons in the substantia nigra when compared to wild-type mice injected with hPFFs, as assessed by unbiased stereology. To compare this exacerbation of pathology to another anatomical region with direct projections to the striatum, we counted the number of pS129-α-syn-positive neurons in the amygdala. *En1*$^{+/-}$ mice also featured a significant increase in amygdala inclusions compared to control mice, although not as dramatic as the enhanced nigrostriatal pathology. Additionally, we assigned pathology scores in regions throughout the neuraxis to assess widespread propagative potential. We observed amplified pathological aggregation in *En1*$^{+/-}$ animals along multiple bilateral cortical pathways including, but not limited to, motor cortex, perirhinal/entorhinal cortices, and somatosensory cortex. In conclusion, we found that following intrastriatal injection of hPFFs, mitochondrial dysfunction is more permissive to the aggregation of pathological α-syn, with heightened insult selectively along the nigrostriatal pathway. Here, we present our updated characterization of the *En1*$^{+/-}$-hPFF model. We anticipate that this double-hit model may be more predictive of pre-clinical therapeutic development and success for PD than existing mouse models.

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**Poster**

**749. Parkinson's Disease: Alpha-Synuclein: Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 749.26/W14

**Topic:** C.03. Parkinson's Disease

**Support:** Michael J Fox Foundation

**Title:** Optimising a rat model of Parkinson's disease based on AAV vector-mediated alpha synuclein transfer in the nigra

**Authors: *J. MUDANNAYAKE**[1], T. BJORKLUND[2], F. P. MANFREDSSON[3]
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**Abstract:** Animal models based on α-synuclein overexpression that replicate a range of disease pathology represent a more clinically relevant alternative to toxins-based Parkinson's disease (PD) models. However, the inability to faithfully reproduce the temporal and neurochemical patterns of pathology and behavior of published work on these models hinders its wide applicability in the research setting. To generate a replicable, 'standardized' adeno-associated virus (AAV) vector-mediated α-synuclein model, we aim to first comparatively analyze commonly used AAV serotypes coupled with various DNA promoter and post-transcriptional regulatory elements, prior to characterizing pathology and behavior deficits of a PD model generated with the optimal vector construct. The below expression plasmids were cloned: ssAAV-CBA-αSyn-WPRE-bGHpA, ssAAV-Syn-αSyn-WPRE-lateSV40pA, scAAV-CBh-αSyn-WPRE3-enSV40pA, scAAV-Syn-αSyn-WPRE3-enSV40pA, scAAV-CMV/Syn-αSyn-WPRE3-enSV40pA, and scAAV-PGK-αSyn-WPRE3-enSV40p. All constructs were packaged into AAV5, while scAAV-CBh-αSyn-WPRE3-enSV40pA was additionally packaged into AAV2 and 6. Titer-matched vector constructs will be unilaterally injected into the wild-type rat nigra and brains histochemically assessed four weeks post-injection to determine the vector construct generating optimal levels of protein expression. The selected vector construct, together with a control construct expressing the fluorescent tagBFP2 protein will be then tested as per above and pathology and behavior deficits assessed at 4, 8, and 12 weeks post-injection.

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**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 750.01/W15

**Topic:** C.03. Parkinson's Disease

**Support:** Lundbeck Foundation - R248-2016-2518
Aarhus University

**Title:** Regulation of a-synuclein levels by Parkinson's disease-associated kinases

**Authors: P. H. JENSEN**[1], R. H. KOFOED[1], N. FERREIRA[1], C. BETZER[1], L. REIMER[1], M. R. LARSEN[2], O. SOROKINA[3], D. ARMSTRONG[4], *P. JENSEN[1]
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**Abstract:** Background:
Parkinson's disease (PD) is the second most common neurodegenerative disease affecting approximately 1% of the population over the age of 60 years. α-Synuclein is a key molecule in the pathogenesis of PD and genetic studies have linked the level of α-synuclein with the risk of developing PD. The level of α-synuclein is therefore a possible target as a disease modifying treatment for PD.
Findings:
We have recently published that Polo-like kinase 2 is able to regulate α-synuclein protein and mRNA levels in mice, brain slices and primary neurons (Kofoed et al., 2017, Neurobiol. Dis.). Following this, we have obtained data showing the involvement of two additional PD-associated kinases in the pathway. Our data presents a novel approach for decreasing α-synuclein levels using small molecule compounds.
Perspectives:
Decreasing α-synuclein levels can decrease α-synuclein pathology and motor dysfunctions in PD animal models, however, these treatments often relies on viral injections in the brain for siRNA expression. The ability to decrease α-synuclein using small molecule compounds therefore holds the potential as disease modifying treatment for PD suitable for treatment of human patients.

**Disclosures: P.H. Jensen:** None. **R.H. Kofoed:** None. **N. Ferreira:** None. **C. Betzer:** None. **L. Reimer:** None. **M.R. Larsen:** None. **O. Sorokina:** None. **D. Armstrong:** None. **P. Jensen:** None.

**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 750.02/W16

**Topic:** C.03. Parkinson’s Disease

**Support:** AFB 170005
FONDECYT 11170212

**Title:** Andrographolide modulates the overexpression and aggregation of Alpha synuclein in an *in vitro* model of Parkinson's disease

**Authors: *S. BASTÍAS-CANDIA**, N. INESTROSA
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**Abstract:** Parkinson disease (PD) is one of the most common neurodegenerative disorders affecting up to the 0,5-1,0% of the current population and rising 1 to 3 percent among 80 years old people. PD has a multifactorial etiology, involving genetics and environmental causes, but even when its origin can be different they have a common feature, the overexpression and aggregation of the α-synuclein (SNCA) protein. SNCA correspond to a presynaptic protein involved in the dopamine release, synaptic vesicle formation, and recapture of the dopamine from the extracellular spaces. Because of its multiple functions, the overexpression and consequent aggregation of SNCA has been related with neuronal dead through oxidative stress, neuroinflammation and interference with the dopamine synthesis and exocytosis, among others. Besides the substantial information about PD pathophysiology, currently there is no effective treatment. In the last years, natural compounds with neuroprotective effects have been proved against several neurodegenerative disorders, but only a few have shown to improve o reverse the selective neuronal damage. That is the case of Andrographolide (ANDRO), a labdane diterpene isolated from the plant Andrographis paniculata, with neuroprotective properties on oxidative stress and neuroinflammation. Its mechanism of action seems to involve the activation of Nrf2/ARE and NFκB pathways, but more important, its relationship with GSK-3β indicates a possible link with the Wnt/β-catenin signaling pathway. In this regard, ANDRO have demonstrated to have neuroprotective effect through the reduction of phosphorylated tau protein and amyloid β aggregate maturation in aged Octodon degus, a natural model of Alzheimer’s disease, with a clear recovery of cognitive impairment. We hypothesize that ANDRO can modulates the overexpression of SNCA in a sporadic in vitro model of PD. Rotenone, a classic PD-like model capable to generates mitochondrial dysfunction and SNCA overexpression was used in a SH-SY5Y neuroblastoma cell line. We assess the levels of SNCA and tyrosine hydroxylase as markers of PD, and the levels of Nfr2/HO-1 and NFkB as oxidative and inflammatory markers. The modulatory ANDRO effects were evaluated by Western blotting and

Immunofluorescence techniques. Thus, in the present work we postulate that ANDRO a natural compound, with modulatory effects on the Wnt signaling, is capable to exert neuroprotective activity on a sporadic model of PD.

**Disclosures: S. Bastías-Candia:** None. **N. Inestrosa:** None.

**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 750.03/W17

**Topic:** C.03. Parkinson’s Disease

**Support:** Idex Grant Extrabrain

**Title:** Disorganization of the brain extracellular matrix through microglial activation in the Lewy body-injected mouse

**Authors: *E. BEZARD**[1], F. N. SORIA[2], B. DEHAY[1]
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**Abstract:** We wish to explore the interplay of the extracellular matrix and microglia in a murine model of Parkinson’s disease. The extracellular matrix (ECM) is an intricately arranged molecular framework comprised of secreted proteins and complex sugars that support cell function and survival. Changes in the highly-hygroscopic hyaluronan (HA) network, the structural scaffold of the ECM in the brain, can dramatically modify the extracellular space (ECS) volume. The neuropathological hallmark in Parkinson’s Disease (PD) is the presence of Lewy Bodies (LB), intraneuronal proteinaceous inclusions constituted, among other components, by alpha-synuclein (-syn). The ECS/ECM participate both in the spreading of toxic conformers of alpha-synuclein and in the regulation of inflammation, key events leading to the loss of dopaminergic neurons in the substantia nigra (SN).
Here we sought to explore the HA network in the SN of mice injected with LB fractions derived from PD patients containing a very small amount (pg) of human -syn. This inoculation induced 40% of neurodegeneration 4 months after surgery (Recasens et al., 2014). Since HA and microglia can be visualized with fluorescent probes, we analyzed its structure by confocal microscopy and quantified the extent of the HA network in the SN by image analysis.
We found a substantial alteration of the HA network in LB-injected mice compared to controls, as well as microglial invasion of the SN. No changes were detected in HA synthesis and degradation enzymes. However, we observed increased expression of inflammation markers TNF-alpha and CD68, and the glial HA receptor CD44. Interestingly, we observed engulfment of HA structures by activated microglia in LB-injected mice.

These results suggest a role of microglia in the alteration of the ECM in a context of alpha-synuclein-induced neurodegeneration. Our results provide insight on a crucial and underexplored component of the brain and adds to our understanding of the pathophysiology of PD

**Disclosures: E. Bezard:** None. **F.N. Soria:** None. **B. Dehay:** None.

**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 750.04/W18

**Topic:** C.03. Parkinson’s Disease

**Support:** MEXT 26461263
MEXT 15H01550

**Title:** Extracellular α-synuclein internalizes into cells by modulating flotillin-1-assisted endocytosis of DAT

**Authors: *T. HASEGAWA**[1], J. KOBAYASHI[3], N. SUGENO[2], S. YOSHIDA[2], M. EZURA[2], A. KIKUCHI[2], A. TAKEDA[4], M. AOKI[2]
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**Abstract: Background:** The neuropathological hallmarks of Parkinson’s disease (PD) are the appearance of alpha-synuclein (αSYN)-positive Lewy bodies and the extensive loss of catecholaminergic neurons. Although αSYN is primarily localized in neuronal cytosol, it has also been detected in extracellular fluid, suggesting that a mechanism promoting the uptake of extracellular αSYN in susceptible neurons may exist. In this study, we focused on a membrane-associated protein, flotillin-1 (FLOT1), which is highly expressed in brainstem catecholaminergic neurons and is strikingly upregulated in PD. The FLOT microdomain is known to provide endocytic platforms that are involved in the uptake of cell surface molecules including dopamine transporter (DAT). **Objective:** The main purposes of this study were to determine whether extracellular αSYN could influence on the endocytic process of FLOT1 and DAT. **Methods:** HEK 293 cells expressing GFP-DAT and induced pluripotent stem cells derived dopaminergic neuron were incubated with conditioned medium containing recombinant human αSYN monomer. Distinct endosomal structures including early endosomal autoantigen 1 (EEA1), Rab7A, and Rab11A were investigated by immunohistochemistry. Time-lapse imaging was performed to explore the spatiotemporal distribution of monomeric αSYN and DAT. Co-immunoprecipitation was adopted to demonstrate the molecular interaction between αSYN, FLOT1 and DAT. **Results:** We found that FLOT1 co-assembled with extracellular monomeric αSYN on the cell surface, thereby facilitating the endocytic uptake of monomeric αSYN.

Furthermore, extracellular monomeric αSYN triggered the internalization of DAT via FLOT1-assisted endocytosis and downregulated DAT activity. Surprisingly, αSYN was concomitantly endocytosed into cells by hijacking endocytic trafficking of DAT. **Conclusion:** (1) extracellular αSYN has a regulatory role on FLOT1-assisted DAT trafficking. (2) αSYN internalizes into cells by hijacking the endocytic process of DAT.

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**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 750.05/X1

**Topic:** C.03. Parkinson’s Disease

**Title:** Systematic analysis on the seeding activity of familial mutant forms of α-synuclein

**Authors: *N. XU**[1], G. ITO[2], A. TARUTANI[1], T. TOMITA[1,2]
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**Abstract:** Parkinson disease (PD) is one of the most common neurodegenerative diseases characterized by loss of dopaminergic neurons in the midbrain. PD is pathologically characterized by the deposition of aggregated α-synuclein proteins as Lewy bodies and Lewy neurites. Six missense mutations in the α-synuclein gene (i.e., A30P, E46K, H50Q, G51D, A53E, and A53T) have been identified in familial PD cases, implicating the pathological importance of α-synuclein. Recently, interneuronal propagation of amyloid protein has emerged as a common paradigm explaining how the pathology spreads in the patient brains of neurodegenerative diseases. However, it remains unclear how pathogenic mutations in α-synuclein alter the propagation. In this study, we examined seeding and propagation activities of α-synuclein mutants in in vitro fibrillization assays, primary cultured neurons and wild-type mouse brain. These α-synuclein mutants were produced in E. coli, and incubated at 37 ℃ with agitation for several days to induce aggregation. The formed aggregates were then sonicated and used as seeds for subsequent experiments. First, the seeded aggregation with mouse α-synuclein monomer was measured by a thioflavin assay. We found that all the mutants, but not G51D, showed a seeding activity. Next, rat cortical primary neurons were treated with the α-synuclein seeds for 7 days, and induction of phosphorylation of S129 in endogenous α-synuclein, which represents the formation of aggregated α-synuclein, was examined by an immunocytochemical analysis. All mutants were able to induce phosphorylation of endogenous α-synuclein. Finally, we tested the propagation of α-synuclein pathology in wild-type mouse brains unilaterally injected with the α-synuclein seeds into the striatum. One month after injection of wild-type α-

synuclein seeds, we confirmed the induction and spreading of phosphorylated α-synuclein. The result of systematic in vivo experiment using α-synuclein mutants will also be presented. These results will elucidate the difference between wild-type and mutant α-synuclein in terms of the seeding activity both in vitro and in vivo, which might explain the pathogenicity of the mutations.

**Disclosures: N. Xu:** None. **G. Ito:** None. **A. Tarutani:** None. **T. Tomita:** None.

**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 750.06/X2

**Topic:** C.03. Parkinson’s Disease

**Support:** KAKENHI Grant JP26117005
KAKENHI Grant JP23228004
AMED JP14533254

**Title:** Characterization and inactivation of pathogenic α-syn species

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**Abstract:** In α-synucleinopathies, such as Parkinson's disease, dementia with Lewy bodies (DLB) and multiple system atrophy (MSA), the presence of abnormal α-synuclein (α-syn) aggregates in neuronal and/or glial cells is a defining neuropathological feature. A growing body of evidence strongly suggests that these forms of α-syn have prion-like properties, and self-amplify by conversion of normal α-syn and spread throughout the brain by transmission between cells. However, it is not yet clear whether such prion-like pathogenic α-syn poses a risk of secondary infection to humans, as is the case for certain prion diseases, such as iatrogenic Creutzfeldt-Jakob disease. In this study, we investigated in detail the prion-like seeding activities of several kinds of pathogenic α-syn, including synthetic fibrils and detergent-insoluble fractions extracted from brains of patients with α-synucleinopathies. We determined the minimum amounts of these pathogenic α-syn species required for induction of seeded α-syn aggregation in SH-SY5Y cells and non-Tg mice. Exposure to synthetic α-syn fibrils at concentrations above 100 pg/mL caused seeded aggregation of α-syn in SH-SY5Y cells, and seeded aggregation was also observed in C57BL/6J mice after intracerebral inoculation of at least 0.1 μg/animal. α-Syn aggregates extracted from brains of MSA patients showed higher seeding activity than those

extracted from patients with DLB, and their potency was similar to that of synthetic α-syn fibrils. We also examined the effects of various methods that have been reported to inactivate abnormal prion proteins ($PrP^{SC}$), including autoclaving at various temperatures, exposure to sodium dodecyl sulfate (SDS), and combined treatments. The combination of autoclaving and 1% SDS substantially reduced the seeding activities of synthetic α-syn fibrils and α-syn aggregates extracted from MSA brains. However, single treatment with 1% SDS or generally used sterilization conditions proved insufficient to prevent accumulation of pathological α-syn. In conclusion, α-syn aggregates derived from MSA patients showed a potent prion-like seeding activity, which could be efficiently reduced by combined use of SDS and autoclaving.

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**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 750.07/X3

**Topic:** C.03. Parkinson’s Disease

**Support:** Innovation Fund Denmark (7039-00049B)

**Title:** Proteomics screen in search for regulators of formation and clearance of neuropathological a-synuclein and tau aggregates

**Authors: *M. LUBAS**[1,2], M. AMBJØRN[1], K. THIRSTRUP[1], J. ANDERSEN[2], K. FOG[1]
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**Abstract:** Aggregated forms of the proteins alpha-synuclein (a-syn) and tau constitute the pathological hallmarks in the brain of patients with Parkinson’s and Alzheimer’s disease. Although discovered at least 20 years ago, we still lack an understanding of the cellular mechanisms that contribute to the complex and dynamic protein aggregation process, heavily restricting our possibilities to rationally target either the aggregation process itself or the cellular ability to degrade these aggregates. The hypothesis that aggregated forms of either a-syn or tau are not only affecting neuronal function and survival, but also actively contributing to spreading of the disease in the brain was a breakthrough for modelling disease pathology.
With current model systems, it is possible to initiate the intracellular aggregation by adding pre-aggregated forms of a-syn and tau to the media. Taking advantage of seeding model systems and recent advances in quantitative proteomics, we set out to conduct an in-depth analysis of a-syn and tau aggregate-associated proteins at their distinct aggregation stages. In addition, our analysis incorporates information on the posttranslational modification (PTM) status of the aggregate proteins focusing on ubiquitylation and phosphorylation. We believe that by dissecting

aggregate interactomes and PTM signatures throughout aggregation stages across experimental models, we will increase our understanding on how intracellular inclusion formation and clearance (degradation or release) are regulated and can be modulated.

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**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 750.08/X4

**Topic:** C.03. Parkinson’s Disease

**Title:** Robust synapse loss in striatal spiny projection neurons from transgenic mice overexpressing human wild-type alpha synuclein

**Authors: J. SANCHEZ-PADILLA**, G. TOMBAUGH, S. GELMAN, K. KRETSCHMANNOVA, H. FERNANDES, A. GHAVAMI, J. BELTRAN, K. CIRILLO, *S. RAMBOZ
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**Abstract:** Alpha-synuclein is a central component of Lewy bodies present in Parkinson’s disease (PD) patients. The consequences of synucleopathy in neuronal function remains unclear and preclinical therapy testing targeting alpha-synuclein are needed. To help identify biomarkers, we utilized whole-cell patch clamp in brain slices to evaluate alterations in synaptic properties in the dorsal striatum from Line 61 transgenic mice overexpressing human wild-type alpha synuclein. Brain slices were prepared from Line 61 mice at ages where they display significant impaired motor behavior and synuclein pathology. Analysis of striatal spiny projection neurons (SPNs) showed a robust decrease in the frequency of miniature excitatory synaptic events in Line 61 compared to wild-type littermates. This phenotype was the same between 2-month and 6-month old Line 61 mice, suggesting a stable readout throughout aging. Analysis of paired-pulse ratio in 6-month old Line 61 corticostriatal synapses revealed no changes in the probability of release, indicating a decrease in excitatory drive in Line 61 is related to synapse loss. The reduction in the frequency of synaptic events was accompanied by a significant increase in the amplitude of synaptic events. This suggests that striatal SPNs from Line 61 underwent synaptic scaling to compensate for the loss of synapses. To further support the synapse loss and scaling phenotype in Line 61, alterations in levels of different synaptic protein markers in the striatum from Line 61 mice will be analyzed using western blotting. Altogether, we have a stable and robust synaptic deficit in the Line 61 model that we can offer for preclinical testing, supporting and translatable to the loss of dendritic spines reported in PD patients and rodent models.

**Disclosures:** **J. Sanchez-Padilla:** A. Employment/Salary (full or part-time):; PsychoGenics. **G. Tombaugh:** A. Employment/Salary (full or part-time):; PsychoGenics. **S. Gelman:** A. Employment/Salary (full or part-time):; PsychoGenics. **K. Kretschmannova:** A. Employment/Salary (full or part-time):; PsychoGenics. **H. Fernandes:** A. Employment/Salary (full or part-time):; PsychoGenics. **A. Ghavami:** A. Employment/Salary (full or part-time):; PsychoGenics. **J. Beltran:** A. Employment/Salary (full or part-time):; PsychoGenics. **K. Cirillo:** A. Employment/Salary (full or part-time):; PsychoGenics. **S. Ramboz:** A. Employment/Salary (full or part-time):; PsychoGenics.

**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 750.09/X5

**Topic:** C.03. Parkinson's Disease

**Support:** NIH Diversity Supplement PA-16-288

**Title:** Developing novel FRET-based biosensors that monitor α-synuclein assembly for use in high-throughput screening

**Authors: *M. YOUNG**[1], A. R. BRAUN[1], D. THOMAS[2], J. SACHS[1]
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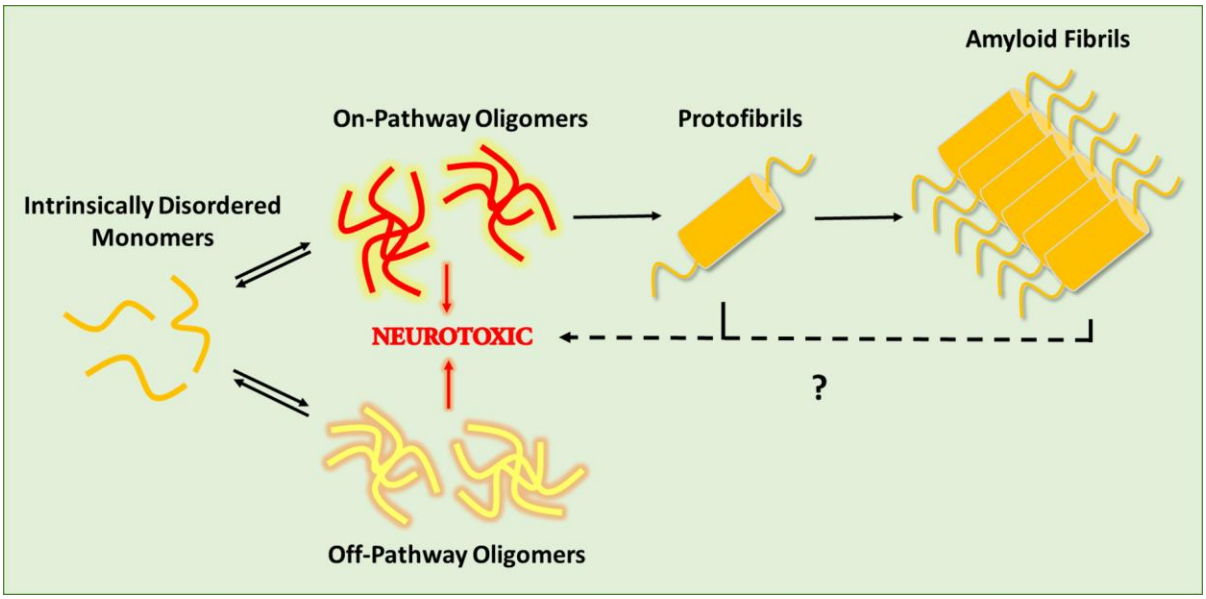
**Abstract:** Parkinson's disease (PD) is characterized by the aggregation of endogenous α-synuclein into fibrillar inclusions in the brain. Although its native function remains elusive, evidence supports that α-synuclein plays an important role in neurological function under normal physiological conditions. The aggregation of α-synuclein under pathologic conditions involves misfolding of the intrinsically disordered monomer into oligomers which can aggregate to form the fibers that make up the insoluble inclusions seen in the brains of PD patients. There has been significant effort to identify small molecule inhibitors of α-synuclein fibrillization. However, recent evidence suggests the kinetically unstable oligomeric species, and not fibrils, are the source of α-synuclein cytotoxicity.
We have developed a set of cell-free FRET based biosensors that monitor monomer-monomer interactions and fibril formation through fluorescence lifetime. Using fluorescence lifetime provides a 30-fold increase in sensitivity over more traditional FRET measurements. We are currently optimizing these biosensors for use in high-throughput screening to identify inhibitors of oligomer and fibril formation. We have achieved an optimal FRET of 14.99% for WT oligomeric interactions and a seeded induced change in FRET of 15.34%. HTS hits will be validated for FRET dose response, biophysical changes in aggregation kinetics via thioflavin T assays and AFM characterization, and functional properties via cell death assays.




**Disclosures: M. Young:** None. **A.R. Braun:** None. **D. Thomas:** None. **J. Sachs:** None.

**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 750.10/X6

**Topic:** C.03. Parkinson’s Disease

**Support:** MSA Coalition grant 2017-10-007
The American Parkinson Disease Association (APDA)
The Parkinson Alliance

**Title:** α-Synuclein in neuron- and oligodendroglia-derived blood exosomes distinguishes multiple system atrophy from Parkinson’s disease

**Authors: *S. DUTTA**[1], I. D. ROSARIO[2], K. PAUL[3], J.-A. PALMA[4], S. L. PERLMAN[3], W. W. POON[5], H. KAUFMANN[4], B. FOGEL[3], J. M. BRONSTEIN[3], B. RITZ[3], G. BITAN[3]
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**Abstract:** Synucleinopathies, including Parkinson's disease (PD), Dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) are all characterized by aggregation and deposition of α-synuclein in the brain. Developing reliable biomarkers that can distinguish among the synucleinopathies is an urgent public health need. Multiple observations suggest that misfolding

and self-association of α-synuclein into oligomers and aggregates cause neural dysfunction and neurodegeneration in these diseases. Nonetheless, diagnosis of synucleinopathies is challenging due to overlapping symptoms among the synucleinopathies themselves and with other atypical parkinsonian syndromes. Exosomes are nano-vesicles shed by most cell types, which carry cell- and cell-state-specific proteins and nucleic acids and provide a rich source of biomarkers. Recently, α-synuclein was shown to transfer via exosomes between different brain cells suggesting that measuring α-synuclein in brain-derived exosomes isolated from patient blood could serve as a potential biomarker for synucleinopathies. In this study, we used antibody-coated magnetic beads to immunochemically isolate exosomes released by neurons or oligodendrocytes from serum of healthy individuals and patients with PD and MSA and measured biomarker concentration in them by a highly sensitive electrochemiluminescence ELISA. The aims of the study were: 1) To determine if measuring α-synuclein in serum exosomes from neurons and oligodendrocytes can distinguish between healthy controls and patients with PD or MSA, 2) To test whether analyzing α-synuclein in neuronal and oligodendroglial exosomes can distinguish between PD and MSA. Neuronal and oligodendroglial exosomes were isolated from serum of 50 controls, 50 patients with PD, and 30 patients with MSA. Significantly higher concentrations of α-synuclein were found in both neuronal and oligodendroglial exosomes from patients than in controls. α-Synuclein in oligodendroglial exosomes distinguished patients with MSA from healthy controls with 100.0% sensitivity and 96% specificity. The absolute values of α-synuclein in neuronal and oligodendroglial exosomes provided moderate separation between the PD and MSA groups, yet the ratio between the two cell types allowed separating the two disease groups with 90.0% sensitivity and 90.0% specificity. Thus, α-Synuclein in brain-derived blood exosomes provides a sensitive biomarker for distinguishing patients with MSA from healthy controls and from patients with PD using a blood test and suggest that the method can be expanded further for other neurodegenerative diseases.

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**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 750.11/X7

**Topic:** C.03. Parkinson’s Disease

**Title:** Defining cellular identity and cell-specific expression changes in the pre-formed fibril model of Parkinson's disease

**Authors: *S. FOX**[1,3], L. VOLPICELLI-DALEY[2], R. COWELL[3,4]
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**Abstract:** Parkinson Disease (PD) is a neurodegenerative movement disorder that is characterized by post-mortem observation of two pathological hallmarks including loss of dopaminergic (DAergic) neurons of the substantia nigra (SN) and alpha-synuclein aggregates (Lewy bodies and Lewy neurites). Current therapies for PD focus on managing symptoms after substantial loss of DAergic neurons with no current method of prevention of neurodegeneration. Elucidation of the underlying causes of neuronal cell dysfunction has the potential to provide new therapeutic targets to prevent loss of DAergic neurons. Post-translationally modified alpha-synuclein is the major component of filamentous inclusions in neurons throughout the brain in PD. It is not known how DAergic neurons respond to inclusion formation; defining their transcriptional profile during the cell death process could identify pathways for preventing cell death. To understand how levels of gene transcription change in neurons with Lewy pathology, we use the fibril model. According to this model, addition of alpha-synuclein preformed fibrils *in vivo* or in culture leads to corruption of endogenous alpha-synuclein over time, resulting in inclusions, defects in neuronal function, and cell death. To enable quantification of transcripts in cells containing alpha-synuclein aggregates, we optimized a new technique combining RNAscope fluorescent *in situ* hybridization with immunofluorescence for phosphorylated alpha-synuclein. With this protocol, we demonstrate that neurons with inclusions always express mRNA for alpha-synuclein, consistent with the model that inclusion formation requires cell-autonomous endogenous alpha-synuclein expression. Interestingly, inclusions were only observed in glutamatergic neurons and were not observed in GABAergic neurons, which express very low levels of alpha-synuclein mRNA. In the future, we will use this method to track transcriptional changes in a cell-specific manner during the process of inclusion formation and cell death.

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**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 750.12/X8

**Topic:** C.03. Parkinson’s Disease

**Support:** NIH/NINDS 1R01NS092667-01
Harold and Ronna Cooper Family
Consolidated Anti-Aging Foundation

Paul Hansen family
Orchard Foundation

**Title:** Alpha-synuclein and tau abnormalities caused by lipids in neurodegenerative aging

**Authors: *O. R. BREKK**, O. ISACSON, P. J. HALLETT
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**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). The connections between aging and disease-associated gene products, for example GBA1, alpha-synuclein (aSYN), or Tau, are not fully understood. We have previously observed age-dependent reductions in glucocerebrosidase (GCase) activity (encoded by GBA1) in normal aging in the human (Rocha et al., 2015, Ann. Clin. Trans. Neurol.) and mouse (Hallett & Huebecker et al., 2018, Neurobiol. Aging) brain, with concurrent accumulation of a variety of glycosphingolipids (GSLs) including glucosylceramide and glucosylsphingosine. As glucosylceramide has recently been shown to induce aSYN aggregation and attenuate neurotoxicity *in vitro* (Zunke et al., 2018, Neuron), we wish to investigate the impact of age-related lipid impairments on disease-associated proteins aSYN and Tau. In wildtype (WT) mice aged 2-24 months of age, presenting with elevated GSL content, we investigated lipid modifications of aSYN and Tau through biochemical lipid-extraction assays of whole-brain homogenates and assessed how these modifications affect protein structure and posttranslational state. Using fluorescent labeling and automated colocalization analysis, we determined the localization of these proteins within the neuronal lipid membrane compartment with known lipid membrane markers including vesicular membranes, to identify likely binding partners. Lastly, we will assess any correlation between GCase function and lipid homeostasis on aSYN burden in human sporadic PD. As an alternative to the classic view of proteinopathy, these findings illuminate the interplay between age-associated changes in lipid homeostasis and the risk for neurodegenerative disease.

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**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 750.13/X9

**Topic:** C.03. Parkinson's Disease

**Title:** The role of biological membranes in the alpha-synuclein/Nedd4-1 interaction

**Authors: *R. V. STAHELIN**, J.-C. ROCHET
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**Abstract:** Neuropathological and genetic evidence strongly suggests that aggregation of the presynaptic protein alpha-synuclein (aSyn) plays a central role in Parkinson's Disease (PD) pathogenesis. In healthy neurons, aSyn exists in an equilibrium state between a natively unfolded, non-membrane-bound form and a form physically associated with synaptic vesicles that adopts an amphipathic alpha-helical structure upon lipid binding. Although both forms can produce aggregates, the rate of aSyn aggregation is accelerated ~1,000-fold in the presence of vesicles. Additionally, it has found that familial aSyn mutants (e.g. A30P, G51D) with a high propensity to adopt a membrane-bound conformation with a short, lipid-bound N-terminal segment and unbound central and C-terminal segments (referred to here as an 'exposed' conformation) and an enhanced ability to undergo membrane-induced aggregation elicit greater neurotoxicity. These findings support a model in which the aggregation of exposed membrane-bound aSyn conformers is a key target in PD. Accordingly, cellular perturbations that stimulate the degradation of membrane-bound aSyn could alleviate aSyn neurotoxicity in the brains of PD patients.
The E3 ligase Nedd4-1 catalyzes the Lys-63-linked ubiquitylation of intracellular aSyn and degradation by the endolysosomal pathway. Nedd4-1 harbors an N-terminal lipid binding C2 domain that regulates its interactions with membranes in a calcium dependent manner. The current study will present the mechanism by which aSyn and Nedd4-1 interact on membrans to favor aSyn ubiquitylation and degradation. Additionally, the interaction mechanism with Nedd4-1 will also be presented for familial PD aSyn mutations (A30P and G51D).

**Disclosures: R.V. Stahelin:** None. **J. Rochet:** None.

**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 750.14/X10

**Topic:** C.03. Parkinson's Disease

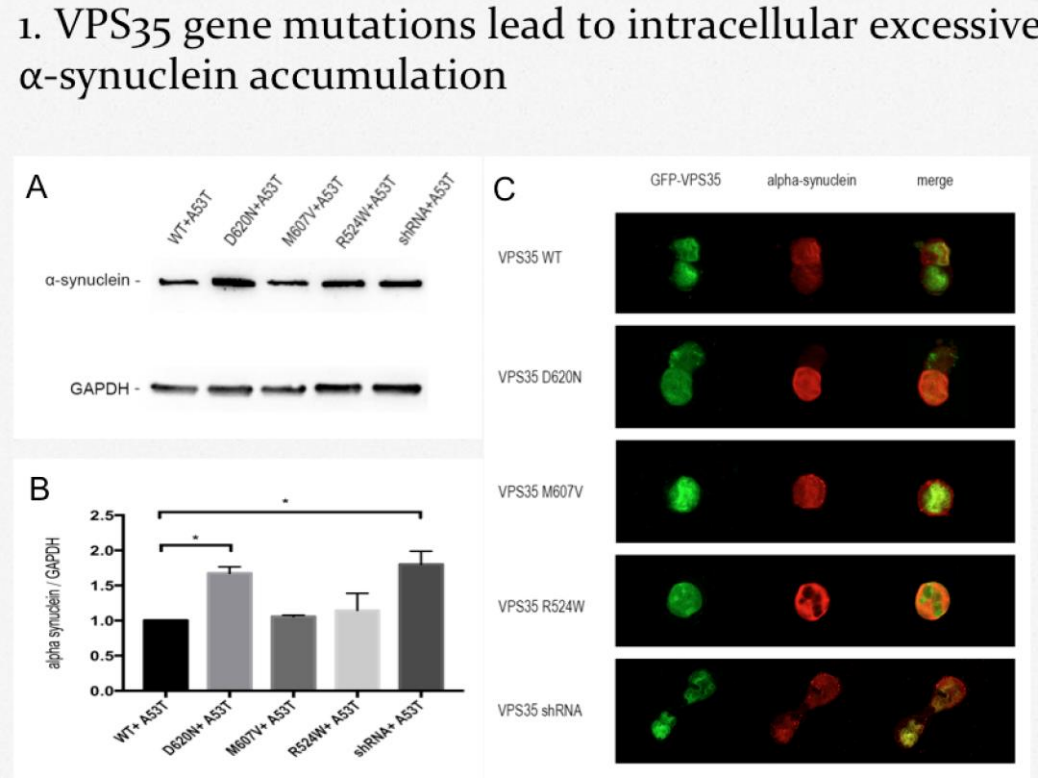
**Support:** NSFC 81771372

**Title:** VPS35 D620N impairs the endosomal trafficking pathway thus leads to excessive alpha synuclein accumulation

**Authors: *S. LUO**[1], F. LUO[2], Y. SUN[3], F. LIU[3], Y. LI[2], C. CHEN[3], W. WANG[2], J. WANG[3]
[1]Inst. of Neurol. Dept. of Neurol. Hua, Shanghai City, China; [2]Interdisciplinary Res. Ctr. on Biol. and Chem., Shanghai, China; [3]Dept. of Neurology, Huashan Hospital, Fudan Univ., Shanghai, China

**Abstract:** Vacuolar protein sorting 35 (*VPS35*) has been reported as a pathogenic gene for late-onset autosomal dominant Parkinson's disease (PD). To date, several *VPS35* variants (D620N,

M607V, R524W, et al) have been demonstrated to be prevalent in PD patients, but the mechanisms underlying how endosomal pathway defect leads to impaired protein trafficking and degradation is still not clear. In this study, we discovered that *VPS35* c.1858G>A D620N variant leads to excessive cytoplasmic alpha synuclein accumulation in comparison with other variants. In stable expressed *VPS35* D620N SH-SY 5Y cell lines, punctate aggregation of Golgi complex in the peri-nuclear region was demonstrated and aggravated after alpha synuclein pre-formed fibrils (PFF) incubation. One of the crucial lysosomal enzyme for alpha synuclein degradation, cathepsin-D was demonstrated to be trapped in the Golgi complex rather than be trafficked to the lysosomes in the *VPS35* D620N variant. With PFF incubation, chaperon-mediated autophagy and exosome release increased to compensate for inadequate alpha synuclein degradation. Cation-independent Mannose-6-phophate receptor (M6PR) is the major sorting cargo of VPS35-associated retromer and functions as the carrier of lysosomal enzymes. A reduction in the membrane fraction of M6PR, as well as co-localization of cytoplasmic fraction with multi-vacuolar bodies hint in endosomal recycling defect and the detention of Cathepsin-D. The defect can be restored by a Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA) Exendin-4 through increasing M6PR expression and thus reduce cytoplasmic alpha synuclein accumulation. <!--EndFragment-->




**Disclosures: S. Luo:** None. **F. Luo:** None. **Y. Sun:** None. **F. Liu:** None. **Y. Li:** None. **C. Chen:** None. **W. Wang:** None. **J. Wang:** None.

**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 750.15/X11

**Topic:** C.03. Parkinson's Disease

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Heart and Stroke Foundation
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Canadian Foundation for Innovation
University of Saskatchewan

**Title:** Chronic stimulation of adenosine A1 receptor leads to an increase in expression of alpha-synuclein

**Authors: *E. JAKOVA**[1], J. STOCKWELL[1], A. AMAH[1], J. S. LEE[2], F. S. CAYABYAB[1]
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**Abstract:** Accumulation of alpha-Synuclein (AS) aggregates in neurons, dendrites and glial cells are the staple of many synucleinopathies. Although various therapeutic strategies are available to alleviate the motor and cognitive deficits, none of these therapies slows aggregation of the AS. We have recently demonstrated accumulation of AS in the hippocampal and nigral neurons due to chronic stimulation of adenosine A1 receptor (A1R). We hypothesize that pharmacological inhibition of A1Rs or administration of the drug, 1-aminoindan, which was previously implicated in preventing AS misfolding (Jakova et al., 2016), can prevent the neurotoxicity-enhancing effects of increased AS in hippocampal and SNc neurons. Using male postnatal 28-35-day old Sprague-Dawley rats, we administered an adenosine-mimicking compound (AMC) for 7 days by intraperitoneal injection and tested the effects of novel neuroprotective agents in hippocampal and SNc neurodegeneration. Behavioural tests were conducted after day 8. Animals were then euthanized and used for acute tissue slicing or perfused with 4% paraformaldehyde for subsequent immunohistochemical and confocal imaging with Zeiss confocal microscope. Additional biochemical and biophysical techniques, such as nanopore analysis and electrophysiology, were used to determine the binding sites of our compounds to AS, as well as to measure the effects of these compounds on synaptic transmission by fEPSP recordings. Additionally, co-immunoprecipitaion experiments were conducted to determinate if AS forms a protein-protein complex with A1R. From western blot analysis and confocal images, the two proteins appear to interact together. Using nanopore and confocal imaging analyses, we determined that the neuroprotective compounds 1-aminoindan and DPCPX exerted their effects by binding directly to AS and preventing AS interaction with A1R. These data suggest that

adenosine signalling plays a major role in synucleinopathy and that AMC agonists/antagonists may also directly regulate alpha synuclein conformation and expression.

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**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

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**Title:** Effect of microglial activation on *in vivo* aggregation, propagation, and toxicity induced by alpha-synuclein fibrils

**Authors: *M. SWANBERG**[1], I. JIMENEZ FERRER CARRILLO[1], M. JEWETT[1], A. BOZA-SERRANO[1], K. C. LUK[2], V. M. LEE[3], T. DEIERBORG[1]
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**Abstract:** Cell-to-cell transfer of αlpha-synuclein (α-syn) is thought to underlie the stereotypical progressive pattern of α-syn pathology and symptoms in Parkinson´s Disease (PD). In this process, α-syn is suggested to trigger an immune response through transfer from neurons to astrocytes and through activation of microglia leading to increased secretion of proinflammatory cytokines and chemokines. The activation of microglia depends on α-syn conformation, i.e. oligomers, but not monomers, induce microglial activation and increase the levels of MHCII expression. However, little is known about how the coexistent activation of microglia influences the propagation of α-syn pathology. We have previously shown that genetic variants regulating the expression levels of Mhc2ta, the major regulator of MHCII transcription, lead to a modified microglial activation profile in response to overexpression of human α-syn in the rat substantia nigra pars compacta (SNpc). DA.VRA4 congenic rats, with lower transcriptional activity of Mhc2ta and MHCII genes compared to DA rats, display enhanced denervation of the nigro-striatal system and significant behavioral deficits after nigral α-syn overexpression. To answer

how activation of microglia influences α-syn pathology, we used an α-syn seeding model, with low-dose of rAAV-α-syn injected into the SNpc followed by intra-striatal administration of α-syn pre-formed fibrills (PFFs) two weeks later. We found that seeding with PFFs induced widespread a-syn pathology and microglial activation compared with rAAV-α-syn only. The impact of Mhc2ta expression on α-syn-induced pathology was assessed by comparing DA.VRA4 and DA rats with regard to microglial, lymphocyte and cytokine profiles, aggregation and propagation of α-syn, dopaminergic axonal pathology and fiber density in the striatum, dopaminergic cell survival in SNpc and motor impairments.

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**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

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**Topic:** C.03. Parkinson’s Disease

**Support:** NIH Grant NS081678

**Title:** A recombinant probe for visualizing membrane-bound alpha-synuclein at presynaptic terminals in living neurons

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**Abstract:** We have generated a structure-dependent FingR (**F**ibronectin **in**trabody **g**enerated with m**R**NA display) that binds to membrane-bound α-Synuclein. In “synucleinopathies”, such as Parkinson’s disease, the overexpression or mutation of α-Synuclein leads to the formation of toxic aggregates that impair neuronal function. Although progress has been made in identifying the cellular processes that are disrupted by misfolded α-Synuclein, its physiological functions and the pathways that trigger its pathogenic state are not well understood. The binding of α-Synuclein to synaptic vesicles and its putative interactions with synaptic proteins suggest that it has roles at the synapse. However, elucidation of these functions has been problematic for several reasons: (i) Even low-level exogenous expression of α-Synuclein alters its localization and the levels of multiple presynaptic proteins; and (ii) α-Synuclein exists in at least two structure-dependent states in neurons, a membrane-bound form that is localized to the outside of synaptic vesicles and an unstructured form that is diffuse in the surrounding cytosol. Thus, there is a need for tools that enable different endogenous states of α-Synuclein to be distinguished, so that their individual roles in neurodegeneration can be studied. When expressed in neurons the α-Synuclein FingR localizes in a punctate pattern to presynaptic terminals with α-Synuclein and

the synaptic vesicle proteins Synaptophysin, Synapsin 1/2, and VGLUT1. In cell bodies the α-Synuclein FingR associates with membranous structures, suggesting that it does not recognize the unbound form of α-Synuclein in the cytosol and nucleus. Furthermore, KCl-induced excitation of neurons results in changes in the localization of the FingR that are similar to those reported for endogenous α-Synuclein, indicating that it does not impede function. In addition, the α-Synuclein FingR co-immunoprecipitates α-Synuclein from cell lysate, but not a FingR that has its binding domains randomized. Lastly, whereas fluorescently tagged Synaptophysin, a popular probe for labeling presynaptic sites, enlarges presynaptic terminals and causes toxicity, the α-Synuclein FingR can be expressed in neurons for several weeks without producing effects on presynaptic terminals. We plan to use the FingR to visualize membrane-bound α-Synuclein at synapses in culture and *in vivo*, with the aim of identifying and dissecting pathways that control its function as well as those that can lead to its aggregation and transformation into toxic protein complexes.

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**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

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**Topic:** C.03. Parkinson’s Disease

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**Title:** Altered dopamine metabolism leads to a unique impaired aSynuclein proteostasis in Parkinson's disease

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**Abstract:** Parkinson’s Disease (PD) is pathologically characterized by the progressive loss of nigrostriatal dopaminergic neurons and aberrant accumulation of the presynaptic protein αSynuclein (αS). Several factors have been proposed to trigger αS aggregation, resulting in αS-induced neurotoxicity. One of them is 3,4-dihydroxyphenylacetaldehyde (DOPAL), a toxic dopamine metabolite, which covalently modifies lysine residues of proteins. *In vitro* and cellular studies demonstrated that DOPAL triggers αS oligomerization, prevents αS association to

synaptic vesicle membranes and affects synapse physiology. Interestingly, the release of aS toxic oligomers from diseased neurons is considered a relevant pathological mechanism in the spreading of neurodegeneration in PD. Therefore, we studied DOPAL-aS oligomers secretion and propagation by extracellular vesicles and their impact on recipient neurons. aS-containing exosomes where purified from HEK293T cells and the presence of SDS non-resistant oligomers and, upon DOPAL treatment, also SDS-resistant oligomers was confirmed. To explore the effect of aS and DOPAL-aS oligomers uptake, primary mouse cortical neurons where incubated for 24 hours with aS-containing exosomes. After exosomal uptake, neurons displayed significant neurite retraction, redistribution of synaptic vesicles pools and reduced synaptic markers after incubation with DOPAL-modified aS containing exosomes. Finally, we are conducting an ultrastructural analysis by using markers for correlated light and electron microscopy to distinctly label aS oligomers. We also aimed to determine whether DOPAL-aSyn oligomers release is due to impaired proteostasis of donor neurons and altered aS clearance. Indeed, our previous LC-MS studies revealed that some lysines of αS are preferentially modified by DOPAL; most of them are also reported as ubiquitination sites. Hence, aS half-life was measured in catecholaminergic BE(2)-M17 cells, revealing an accumulation of monomeric aS after DOPAL treatment but no significant variation in degradation kinetics. In parallel, we generated stable BE(2)-M17 cell lines with an inducible and dose-dependent aS over-expression to finely assess any synergistic effect of DOPAL and aS on cytotoxicity. Concluding, our study combines different biochemical and imaging approaches to shed light on the crucial contribution of altered dopamine metabolism in αS-associated neurodegeneration in PD.

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**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

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**Topic:** C.03. Parkinson’s Disease

**Support:** APDA Grant
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**Title:** Rab27b modulates alpha-synuclein spread and toxicity

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**Abstract:** Alpha synuclein (αsyn) is the primary component of proteinaceous aggregates termed Lewy Bodies that pathologically define Parkinson’s Disease (PD). αSyn is hypothesized to

spread through the brain in a prion-like fashion by misfolded protein forming a template for aggregation of endogenous αsyn. The release and uptake of αsyn from cell to cell are essential processes for this prion-like spread. αSyn does not have a signal peptide for classical secretion and is thought to be released through non-classical secretion mechanisms regulated by a family of proteins called Rab GTPases. Rab27b is one of several GTPases essential to the endosomal-lysosomal pathway and is necessary for the proper localization of endosomal compartments. We have developed an *in vitro* doxycycline-inducible αsyn model in M17 neuroblastoma cells (termed ISYN cells). Induction of αsyn expression by doxycycline in ISYN cells causes a corresponding increase in the release of αsyn into the conditioned media (CM). When transferred to separately-cultured primary neurons, thisαsyn-enriched CM is toxic to these neurons. We found that upon αsyn induction Rab27b protein expression increased by ~2 fold in the ISYN cells. Similarly we observed a ~2 fold increase in Rab27b expression in the postmortem human brain lysates from PD patients compared to healthy controls. To examine the impact of Rab27b dependent pathways on αsyn release and toxicity, we knocked down Rab27b expression by lentiviral transfection of shRNA. shRNA knockdown of Rab27b decreased αsyn release into the CM by ~40%. Surprisingly, despite the reduction in αsyn release, CM from induced ISYN cells in which RAB27b was knocked down cells induced greater toxicity in separately cultured SH-SY5Y cells compared to control. These data indicate a potential role for Rab27b in the release and toxicity of αsyn and ultimately in PD pathogenesis.

**Disclosures: R.N. Underwood:** None.

**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

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**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 750.20/Y2

**Topic:** C.03. Parkinson’s Disease

**Title:** Alpha-synuclein toxicity domain identification and as potential biomarker for Parkinson's disease diagnosis, prognosis and target for therapy

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**Abstract:** Parkinson’s disease (PD) is the second most common age-related neurodegenerative disorders with uncertain etiology worldwide. The hallmark of PD is the endogenous protein alpha-synuclein abnormal accumulation and progressively forms Lewy bodies within oligodendroglial cells leading to neuronal death. To date, no universal diagnostic biomarker and disease-modifying treatment are available for Parkinson’s disease. In this study, we aim to reveal a new method that could measure alpha-synuclein for potential PD diagnosis and map the

toxicity domain of alpha-synuclein. The Human alpha-synuclein full length and different fragments fusion proteins produced by *Escherichia coli*. All the fusion proteins were studied for aggregation progress. Proteins were studied also tested by the MTT assay for cytotoxicity. Here we investigated that the N-terminal 1-65 domain induced the aggregation of alpha-synuclein and increase the toxicity of alpha-synuclein. Aggregated alpha-synuclein were observed been dissociated by some organic solvent. This treatment method could be used for PD diagnosis as a potential application.

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**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

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**Program #/Poster #:** 750.21/Y3

**Topic:** C.03. Parkinson’s Disease

**Title:** Mesenchymal stem cells modulate seeding with vesicle-associated á-synuclein in Parkinson's disease

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**Abstract:** Ample evidence suggests that α-synuclein (α-syn) is released from cells and propagated to others via cell-to-cell transmission. In terms of their prion-like behavior, α-syn propagation plays key roles in the pathogenesis and progression of α-synucleinopathies. We have found evidence to suggest that α-syn can form oligomers in the extracellular space that are associated with small extracellular vesicles (EVs) explaining the paradoxical clinical and research observations that α-syn can be found in grafted neurons in Parkinson’s disease (PD) patients after transplant, and broaching the possibility that α-syn-containing EVs could represent a mechanism for disease progression. Here, we isolated EVs from mid-frontal gyrus of neuropathologically confirmed Multiple system atrophy (MSA) brains or temporal gyrus of Dementia with Lewy bodies (DLB) brains and incubated EV particles with stable cells overexpressing reporters of α-syn oligomerization. EVs from DLB and MSA brain were capable of inducing α-syn aggregation and increasing phosphorylated α-syn compared to EVs from control brains.
Mesenchymal stem cells (MSCs) secrete various cytotropic factors, including neurotrophic growth factors, chemokines, cytokines, and extracellular matrix proteins which, in turn, exert neuroprotective effects on neighboring cells. Here we investigated if MSCs could exert a neuroprotective effect on cells treated with MSA or DLB brain exosomes. α-Syn stable cell lines treated with brain MSA or DLB exosomes and cocultured with MSCs for 24 hours had less α-

syn aggregation and decreased α-syn phosphorylation compared to exosome treated cells. Further investigation indicated that MSC coculture decreased uptake of EVs into cells. These data suggest that MSCs may inhibit α-syn transmission by blocking uptake of EVs containing α-syn, inducing a prosurvival effect, and halting the spread of pathology. Because MSCs exert neuroprotective properties by inhibiting α-syn transmission they may represent a potential target for disease-modifying therapies for PD.
List institutions as:
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**Disclosures: S. Oh:** None. **J. Park:** None.

**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

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Mitchell Center for Neurodegenerative Diseases

**Title:** α-Synuclein on tau aggregation in synucleinopathies

**Authors: *U. SENGUPTA**[1], J. GERSON[2], N. PUANGMALAI[2], A. ELLSWORTH[2], N. BHATT[2], S. MCALLEN[2], M. CARRETERO-MURILLO[2], D. CASTILLO-CARRANZA[2], R. KAYED[2]
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**Abstract:** Neurodegenerative diseases are age-related disorders that are characterized by specific set of clinical symptoms and pathological hallmarks. Parkinson’s disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA) are the three major synucleinopathies, which are pathologically characterized by the accumulation of α-Synuclein protein into Lewy bodies and Lewy neurites. A growing body of evidence suggests that the intermediate aggregation state, oligomers, are the acutely toxic species, disrupting multiple cellular functions. Studies also suggest that soluble oligomers of pathogenic proteins self-propagate in a prion-like manner, thus spreading disease pathology. Neurodegenerative disease-associated pathogenic proteins often interact with one another and modulate downstream activities that disrupt their

normal functions. The co-occurrence of α-Syn and tau in multiple diseases suggests their orchestrated method of toxicity. Our laboratory and other groups have demonstrated that α-Synuclein cross-seeds tau protein, promoting its aggregation. We have previously demonstrated that PD and DLB brain tissues contain tau oligomers and they co-localize with α-Synuclein oligomers. In this study, I am investigating the ability of α-synuclein oligomers inducing tau aggregation, resulting in the formation of a disease specific aggregate. We observed that *in vitro* α-Synuclein oligomers induce tau to a more toxic aggregate. Additionally, co-aggregates of tau and α-Synuclein derived from PD (synucleinopathy) brain tissues demonstrated more toxicity than tau aggregates derived from progressive supranuclear palsy (PSP; tauopathy) brain tissue. Furthermore, we observed that brain-derived α-Synuclein oligomers are the toxic species, but the question remains as how they exert their toxicity. Thus, interactions between α-Synuclein, Tau and other amyloid proteins may be critical for the formation of disease-specific pathogenic aggregates, indicating multiple targets for disease-modifying therapeutics.

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**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

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**Topic:** C.03. Parkinson’s Disease

**Title:** Tau and alpha-synuclein: Equal partners in neurodegeneration?

**Authors: *H. J. BROWN**, F. BASSIL, J. Q. TROJANOWSKI, B. ZHANG, D. RIDDLE, V. M. Y. LEE
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**Abstract:** Accumulation of α-synuclein (α-syn) and tau aggregates are neuropathological hallmarks of Parkinson’s disease (PD) and Alzheimer’s disease (AD), respectively. Post-mortem brain investigations have reported co-morbid AD and PD in more than 35% of PD and 50% of AD patients. Interestingly, these patients show more severe motor and cognitive phenotypes and shorter disease durations, suggesting crosstalk between α-syn and tau. In addition to their coexistence in the human brain, α-syn and tau are both partially unfolded in their native states and capable of forming toxic oligomers or hetero-oligomers under pathological conditions. Previous studies have shown that α-syn and tau promote the fibrilization of one another in-vitro and in-vivo. However, the nuances of this deleterious feed-forward loop, in particular the consequence of each protein for the other, are poorly understood.
Here, we model co-morbid AD/PD pathology in-vitro and in-vivo. While previous studies have

shown the ability of exogenously applied α-syn and tau to seed and promote spreading in-vivo, we show increased accumulation and spreading of α-syn and tau aggregates in a co-pathology induced scenario. Our data points to a synergistic effect of α-syn on tau in different models and we explore the underlying mechanism that might be implicated in potentiating α-syn effect on tau.

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**Poster**

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**Topic:** C.03. Parkinson's Disease

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**Title:** *In vivo* interactions of biogenic aldehydes with aSyn increases expression of neuroinflammatory genes and exacerbates motor deficits in triple transgenic mice

**Authors: *P. A. MARTINEZ**[1,2,3], V. MARTINEZ[2], E. FERNANDEZ[1,2,4], R. STRONG[1,2,3,4]
[1]Pharmacol., [2]Barshop Inst., [3]Ctr. for Biomed. Neurosci., Univ. of Texas Hlth. Sci. Ctr. at San Antonio, San Antonio, TX; [4]Geriatric Research, Education, and Clin. Ctr., South Texas Veterans Hlth. Care Network, San Antonio, TX

**Abstract:** Parkinson's disease (PD) is the second most common neurodegenerative disease. Central to PD is the extensive and progressive loss of dopamine (DA) neurons in the substantia nigra and the subsequent depletion of striatal DA. This loss results in the cardinal symptoms, bradykinesia, resting tremor, and rigidity that are limited to only symptomatic treatment. Evidence show remaining DA neurons stain positively for alpha-synuclein (aSyn)-rich Lewy bodies, implicating aSyn in PD. Furthermore, aSyn can undergo aggregation, particularly under conditions of oxidative stress, forming neurotoxic oligomers. Data from our lab, and others, suggest toxic biogenic aldehydes may also play a pivotal role in PD. Mice deficient in aldehyde dehydrogenases, Aldh1a1 and Aldh2, result in an aldehyde load with elevated levels of the dopamine aldehyde, 3,4-dihydroxyphenylacetaldehyde (DOPAL), and the lipid peroxidation end product, 4-hydroxynonenal (4HNE). As a result, these mice display degeneration of tyrosine hydroxylase-immunoreactive neurons and deficits in motor performance. Importantly, *in vitro* studies suggest both DOPAL and 4HNE are capable of stabilizing toxic αSyn oligomers. However, the interaction of biogenic aldehydes with aSyn *in vivo* is lacking. The selective generation of DOPAL in dopamine neurons and the ability of DOPAL and 4HNE to stabilize

neurotoxic αSyn oligomers, led us to hypothesize that, αSyn is mechanistically related to the neurochemical and behavioral manifestations of PD that result from elevated biogenic aldehydes. To test this hypothesis, we generated mice deficient in Aldh1a1 and Aldh2 crossed them to mice that overexpress the human wildtype αSyn. We found that overexpression of αSyn in the presence of elevated levels of DOPAL was associated with increased expression of neuroinflammatory markers and exacerbation of deficits in motor performance. The results of neurochemical assays and treatments will be discussed.

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**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

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**Program #/Poster #:** 750.25/Y7

**Topic:** C.03. Parkinson’s Disease

**Title:** Regulation of α-synuclein expression in Parkinson′s disease by locus-specific epigenetic remodeling of SNCA

**Authors: *S. GUHATHAKURTA**, E. ADLER, S. BASU, G. JE, L. ADAMS, Y.-S. KIM
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**Abstract:** Histone post-translational modifications (PTMs) are the major epigenetic regulators of gene expression in the cell. Perturbation in epigenetic regulation of α-synuclein encoding gene (*SNCA*) plays significant role in pathogenesis of Parkinson′s disease (PD). Enhanced transcription of *SNCA* leading to production of higher amount of protein, has been linked with severity and early onset of the disease. Epigenetic deregulation also relates to generation of higher transcript and has been shown to be associated with PD.
Two important histone marks that regulate transcriptional activation or repression of gene are histone H3 lysine 4 trimethylation (H3K4me3) and H3 lysine 27 trimethylation (H3K27me3). In the NIH Roadmap epigenomics data from adult human substantia nigra (SN), it was shown that H3K4me3 is heavily enriched at transcriptionally important regions of *SNCA* along with a relatively less enrichment of H3K27me3 at the same region. In spite of its significant implication in regulation of *SNCA*, nothing has been studied so far to demonstrate their role. Remarkably, we found that normal balance between H3K4me3 and H3K27me3 is disrupted in PD brain samples with significantly higher occupancy of H3K4me3 at regulatory areas of *SNCA*. Moreover, the higher level of α-synuclein in the patients is positively correlated with this higher enrichment of permissive H3K4me3. This finding has also been replicated in PD patient-derived iPSCs. Modulation of this histone mark by overexpressing their specific histone lysine demethylase, JARID1A led to significant alteration in α- synuclein in the cell. Based on these strong scientific

premises, our objective is understand whether deregulated expression of α-synuclein in PD is mainly contributed by perturbation in the occupancies of H3K4me3 at *SNCA*. Recent advancement in CRISPR technologies has made it possible to alter gene-specific epigenetic environment without disturbing entire cellular epigenome. Using SunTag system, multiple molecules of JARID1A was recruited at the promoter of *SNCA* to effectively reduce the H3K4me3 from there. Removal of H3K4me3 reduced α-synuclein expression in the cell. Additionally, H3K4me3 was enriched more at *SNCA* promoter under oxidative stress in neuronal cells, which also supported higher expression of α-synuclein. The locus-specific removal of H3K4me3 under oxidative stress was able to control α-synuclein expression at basal level. This study has identified a novel epigenetic mechanism towards deregulated expression of *SNCA* in PD. It also paved a new strategy for locus-specific regulation of gene expression by employing novel epigenetic modulation.

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**Title:** Alpha-synuclein deregulates the expression of COL4A2 and impairs ER-Golgi function

**Authors: *T. F. OUTEIRO**[1], I. PAIVA[2]
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**Abstract:** Alpha-synuclein (aSyn) is the major protein component of Lewy bodies and Lewy neurites, the typical pathological hallmarks in Parkinson’s disease (PD) and Dementia with Lewy bodies. aSyn is capable of inducing transcriptional deregulation, but the precise effect of specific aSyn mutants associated with familial forms of PD, remains unclear. Here, we used transgenic mice overexpressing human wild-type (WT) or A30P aSyn to compare the transcriptional profiles of the two animal models. We found that A30P aSyn promotes strong transcriptional deregulation and increases DNA binding. Interestingly, COL4A2, a major component of basement membranes, was found to be upregulated in both A30P aSyn transgenic mice and in dopaminergic neurons expressing A30P aSyn, suggesting a crucial role for collagen related genes in aSyn-induced toxicity. Finally, we observed that A30P aSyn alters Golgi morphology

and increases the susceptibility to endoplasmic reticulum (ER) stress in dopaminergic cells. In total, our findings provide novel insight into the putative role of aSyn on transcription and on the molecular mechanisms involved, thereby opening novel avenues for future therapeutic interventions in PD and other synucleinopathies.

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**Topic:** C.03. Parkinson’s Disease

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**Title:** Alpha-synuclein aggregates induce c-Abl activation by disruption of cell redox state

**Authors: *S. GHOSH**[1], S. J. WON[2], J. SANCHEZ[1], A. HUYNH[1], C. WONG[1], J. ZHAO[1], R. BISHOP[2], R. A. SWANSON[1]
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**Abstract:** c-Abl is a nonreceptor tyrosine kinase that is activated in human Parkinson’s disease (PD) brain and in α-synuclein mouse models of PD. c-Abl phosphorylates α-synuclein and inhibits Parkin’s ubiquitin ligase activity, both of which promote α-synuclein aggregation. Disruption of cell redox state - e.g. by exogenous toxins, mitochondrial dysfunction, or impaired oxidant scavenging - is also known to drive pathogenesis in PD. Here we show that α-synuclein aggregates induce c-Abl activation by a mechanism involving disruption of cell redox state. Studies in primary cortical neurons were performed to evaluate the role of α-synuclein mediated stress in c-Abl activation. Incubation with human alpha synuclein fibrils (hu-synPFF) induced both oxidative stress and c-Abl activation in these cultures as measured by western blotting and immunocytochemistry. Co-treatment with N-acetyl cysteine, which promotes glutathione formation, suppressed both oxidative stress and c-Abl activation. Effects of glutathione depletion were evaluated in the $EAAT3^{-/-}$ mouse, which has reduced glutathione levels selectively in neurons. Neurons in these mice showed increased level of c-Abl activation, which was reduced back to normal by addition of N-acetyl cysteine to drinking water. These results suggest that oxidative stress induces c-Abl activation in PD brain, that α-synuclein aggregates contribute to the oxidative stress, and that treatment with thiol repletion agents such as N-acetyl cysteine can effectively prevent c-Abl activation. NAC may thus be a viable alternative to direct c-Abl inhibitors as a therapeutic agent, as NAC can cross the human BBB and does not have the toxicities associated with direct c-Abl inhibitors.

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**Poster**

**750. Parkinson's Disease: Alpha-Synuclein: Mechanisms and Transmission**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 750.28/Y10

**Topic:** C.03. Parkinson's Disease

**Support:** EU-FP7 MC-ITN IN-SENS #607616
FOKO #977265

**Title:** Molecular linking of influenza infection to cellular pathology of protein misassembly: The case of alpha-synuclein

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**Abstract:** **Appeal:** There have been repeated reports [1] describing that viral infection of the brain may be linked to triggering neurodegenerative diseases. The influenza pandemic 1916-1926 led to a significant number of cases of post-encephalitic Parkinsonism and individuals born during that time had an increased risk of developing Parkinson's disease (PD). Our main hypothesis is that influenza infection leads to impairments of cellular proteostasis affecting aggregation of alpha-synuclein (α-Syn) underlying PD. **Background:** Neurodegenerative diseases are associated with disrupted proteostasis and hallmarked by deposits of disease-specific proteins such as Lewy-bodies consisting of α-Syn in PD, extracellular beta-amyloid plaques and intraneuronal tangles of hyperphosphorylated tau in Alzheimer's disease, or TDP-43 aggregates in amyotrophic lateral sclerosis. During acute phases of infections with neurotropic viruses, neurological symptoms can occur, however the long-term effects can persist after the main infection is over. Previous studies with human post-mortem brains and rodent models suggested an association of influenza infection with molecular hallmarks of PD [1,2]. In the present study, Human dopaminergic neurons were used as an *in vitro* model to study the disturbances in the cell proteostasis that leads to α-Syn aggregation after influenza infection. **Methods:** Differentiated Lund Human MESencephalic cells were infected with the WSN33 influenza (H1N1 strain). The effect of viral infection was investigated by immunocytochemistry, biochemical and functional assays. Immunohistochemistry in a Rag-/- mice infected for 28 days with WSN33 influenza was performed. **Results:** Influenza infection of dopaminergic neurons triggered α-Syn aggregation, which was not the case for control proteins like TDP-43. Appearance of α-Syn aggregates was dependent on the viral infections titer. Functional consequences of influenza-induced α-Syn misassembly will be reported, as well as our investigations on which cellular pathways are

targeted by influenza infection that lead to α-Syn aggregation. In infected mice with Influenza virus, increased α-Syn expression and deposition was visualized in the brain regions where virus was present. **Conclusions:** We conclude that influenza virus assembly by host factors interfers in a direct way with cellular pathways that regulate α-Syn proteostasis and thus demonstrate a novel molecular mechanism of how viral infection may trigger neurodegenerative disease.
[1] R. Marreiros et al., Virus Res (2015) 207:155-64 [2] T. Rohn et al., PLoS ONE (2011) 6(5):e20495 [3] H. Jang et al., PNAS (2009) 106(33):14063-8

**Disclosures: C. Korth:** A. Employment/Salary (full or part-time):; co-authors from the company Prosetta. **R.M. Marreiros:** None.

**Poster**

**751. Parkinson's Disease: Circuit Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 751.01/Y11

**Topic:** C.03. Parkinson’s Disease

**Support:** NIH Grant R01NS078100

**Title:** Prefrontal d1 dopamine-receptor neurons and delta resonance in interval timing

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**Abstract:** Prefrontal neurons expressing D1-type dopamine receptors (D1DRs) are critical for cognitive processes such as working memory, flexibility, and timing, leading to the hypothesis that these neurons directly encode cognitive processing. During timing tasks, one form this cognitive processing might take is time-dependent ramping activity — monotonic changes in firing rate over time. Thus, we hypothesized the prefrontal D1DR+ neurons would strongly exhibit time-dependent ramping during interval timing. We tested this idea using an interval-timing task in which we used optogenetics to tag D1DR+ neurons in the mouse medial frontal cortex (MFC). While 23% of MFC D1DR+ neurons exhibited ramping, this was significantly less than untagged MFC neurons. By contrast, MFC D1DR+ neurons had strong delta-frequency (1-4 Hz) coherence with other MFC ramping neurons. This coherence was phase-locked to cue onset and was strongest early in the interval. To test the significance of these interactions, we optogenetically stimulated MFC D1DR+ neurons early vs. late in the interval. We found that 2-Hz stimulation early in the interval was particularly effective in rescuing timing-related behavioral performance deficits in dopamine-depleted animals. These findings provide insight into MFC networks and have relevance for disorders such as Parkinson’s disease and schizophrenia.

**Disclosures: Y. Kim:** None. **N.S. Narayanan:** None.

**Poster**

**751. Parkinson's Disease: Circuit Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 751.02/Y12

**Topic:** C.03. Parkinson’s Disease

**Support:** Iowa Neuroscience Institute
R01 NS100849-01A1

**Title:** Phase-locked adaptive TMS: A novel method to improve motor performance

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**Abstract:** Non-invasive neuromodulation techniques such as transcranial magnetic stimulation (TMS) is important tools in cognitive and motor neuroscience because this method is able to reveal the relevance of certain neuronal activity patterns for a given brain function. It is feasible to combine TMS with electrophysiological techniques (electroencephalography; EEG). Scalp EEG recordings can guide TMS neuromodulation approach, providing the required information to optimize when to stimulate the target brain structure. This approach can close the loop between measuring the real-time brain activity and modulating brain signals with stimulation. Motor cortical beta band oscillations are thought to be crucial component of motor encoding. To understand the role of these oscillations in normal or movement disorders motor system, computation of instantaneous amplitude and phase are required. Phase of the identified oscillation could be a better approach to modulate its pattern. Here, we exploited the benefits of phase-locked adaptive TMS to improve motor performance. Scalp EEG recording were collected in normal subjects during key-board pressing task while TMS was delivered at GO cue in-phase (90 or 270 degree) to beta (13-30 Hz) oscillation recorded from the motor cortex. Results showed that phase-locked stimulation improved motor task performance as compared to random phase-locked or sham stimulation. We present here a proof-of concept evaluation that adaptive phase-locked stimulation could be an effective approach to modulate brain activity and to induce behavioral effects.

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**Poster**

**751. Parkinson's Disease: Circuit Mechanisms**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 751.03/Y13

**Topic:** C.03. Parkinson's Disease

**Support:** NIH F31MH110092-02
NIH R01 NS089470-01

**Title:** Targeting frontostriatal circuits to rescue prefrontal dysfunction during interval timing

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**Abstract:** Prefrontal dysfunction and cognitive impairment are common in human diseases such as schizophrenia but remain untreatable. Information processing in the prefrontal cortex and its primary subcortical target, the striatum, are central to this problem. We approach this knowledge gap by using an interval-timing task, which involves working memory and attention. Previous work from our lab has found evidence of robust temporal activity in rodent medial frontal cortex (MFC) and dorsomedial striatum (DMS) during interval-timing behavior. One possible form of temporal activity at the neuronal level is that of "time-dependent ramping" activity. Our lab has found that temporally-guided behavior and DMS ramping activity both depend on the MFC. To further probe the role of these circuits in interval timing, we asked whether optogenetic stimulation of frontostriatal circuits could compensate for impaired timing behavior. Here, we bilaterally injected a viral vector expressing ChR2 optogenetic protein in the MFC. Animals were also implanted with an optrode (integrated microwire electrode and fiberoptic cannula) in the DMS and bilateral infusion cannulae in the MFC. After waiting 4 weeks for viral expression, we optogenetically stimulated MFC to DMS projection terminals with 473-nm light during the interval-timing task. In order to model "prefrontal dysfunction" and impair timing behavior, we inactivated the MFC with muscimol (a $GABA_A$ agonist). On subsequent days, we experimented with different parameters of frontostriatal-projection stimulation while the MFC was either active or inactive. We tested three conditions of optogenetic stimulation: no stimulation, 2-Hz stimulation, and 20-Hz stimulation. As described above, MFC inactivation impaired behavior on the interval-timing task. Surprisingly, we were able to rescue this impairment with frontostriatal 20-Hz stimulation but not with 2-Hz stimulation or no stimulation. This finding suggests that frontostriatal circuits are essential to basic cognition and that information processing may occur in specific frequency domains. These data help elucidate the role of frontostriatal circuits in cognitive processing and could guide strategies to compensate for prefrontal dysfunction in human disease.

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**Poster**

**751. Parkinson's Disease: Circuit Mechanisms**

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**Topic:** C.03. Parkinson's Disease

**Support:** R01NS079518
Boettcher Foundation's Webb-Waring Biomedical Research Awards
University of Colorado School of Medicine Center for NeuroScience
University of Colorado MSTP T32

**Title:** Differential parkinsonian deficits and basal ganglia output in stimulus-guided and memory-guided movements

**Authors: *A. TEKRIWAL**[1], M. J. LINTZ[2], J. A. THOMPSON[3], G. FELSEN[4]
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**Abstract:** Parkinson's disease (PD) is a progressive neurodegenerative disorder caused by loss of dopaminergic neurons (DANs) in the basal ganglia (BG). The link between loss of DANs and onset of PD motor symptoms is well substantiated; however, the degree of impairment depends on the context of the movement (e.g., whether it is habitual). Although well documented in the clinical literature, the underlying neural mechanism leading to some movements being more impaired than others is not well understood. To investigate, we record neural activity from BG output nuclei of hemi-PD and control mice trained on a two-alternative forced choice task. We elicited unilateral DAN loss via 6-hydroxydopamine infusion into the left substantia nigra pars compacta. To acquire neural recordings, we implanted drivable tetrodes into a principal output nucleus of the BG, the substantia nigra pars reticulata (SNr), ipsilateral to DAN loss. Control mice were similarly implanted. We compared behavior and neural activity between two conditions requiring otherwise-equal orienting movements: stimulus-guided or memory-guided. Under the stimulus-guided condition, the direction of movement (left vs. right) was selected based on the identity of the stimulus. Under the memory-guided condition, the direction of movement was selected based on recent history of movements (left vs. right) and whether they were rewarded. Blocks of stimulus-guided and memory-guided trials were interleaved within the behavioral session, allowing for within-session comparisons of behavior and neural activity between the two conditions. We hypothesized that the BG differently process memory-guided and stimulus-guided movements. Consistent with this hypothesis, we found that DAN loss led to greater behavioral impairment on stimulus-guided than on memory-guided trials. We predict that this behavioral difference will be reflected in altered movement-related SNr activity between the

two conditions. In control mice, we found that SNr activity depended more strongly on movement direction (i.e., activity was more direction selective) in memory-guided than stimulus-guided trials. We are currently analyzing neural data in mice with DAN loss. We expect that, in memory-guided trials, direction selectivity of SNr activity in hemi-PD mice will resemble that recorded in control mice, while in stimulus-guided trials, direction selectivity will be weaker in hemi-PD mice than in control mice. Ultimately, these studies will contribute to elucidating how the BG control different forms of movement under normal and pathological conditions.

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**Poster**

**751. Parkinson's Disease: Circuit Mechanisms**

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**Topic:** C.03. Parkinson's Disease

**Support:** NIH R25NS079173
NIH R01NS100849

**Title:** The effect of alpha-synuclein overexpression on calcium dynamics and dendritic spines in cortical neurons

**Authors: *G. M. ALDRIDGE**[1], C. A. WARWICK[2], S. M. NATHWANI[2], Y. M. USACHEV[3], N. S. NARAYANAN[4]
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**Abstract:** Lewy Body dementias, which include Parkinson's disease dementia (PDD) and Dementia with Lewy Bodies (DLB), are characterized by intracytoplasmic protein accumulations. These "Lewy Bodies" consist mainly of alpha-synuclein, and in Lewy Body dementia are often found in cortical neurons. While overexpression of alpha-synuclein in patients with genetic multiplications is associated with these diseases and leads to Lewy body accumulation, it is not known whether overexpression of alpha-synuclein directly affects neurons in the cortex. There is also evidence that alpha-synuclein can alter calcium dynamics in neurons in culture, but it is unknown if this mechanism leads to pathologic changes in vivo. We hypothesize that overexpression of alpha-synuclein has a direct effect on calcium homeostasis, leading to altered spine turnover and abnormal calcium dynamics. To test this hypothesis, we are utilizing an AAV-6 viral vector coding for full length human alpha-synuclein to induce targeted overexpression of this protein locally in the prefrontal cortex of adult mice. Furthermore, by using a P2A linker, mCherry protein is co-expressed in neurons expressing alpha-synuclein, allowing us to examine infected and neighboring neurons in vivo during live animal imaging.

Our preliminary data in post-mortem animals 3 months after viral injection shows that overexpression of alpha-synuclein leads to alterations in dendritic spine number and morphology, with the effect modulated by cortical layer. To test the hypothesis that overexpression of alpha-synuclein leads to calcium abnormalities in vivo, we have injected viral vector into mice genetically expressing gCAMP6s in cortical neurons. We then implant a cortical window to allow live animal, awake, in vivo, 2-photon imaging of calcium dynamics in freely-walking, but head fixed mice. We are able to examine calcium dynamics both in cell bodies of layer 2/3 cortical neurons, as well as subcellular calcium dynamics of spines and boutons in layer 1. These experiments will help determine whether local overexpression of alpha-synuclein, which is causative of disease in human patients, can induce pathology through direct action at cortical neurons.

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**Poster**

**751. Parkinson's Disease: Circuit Mechanisms**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 751.06/Y16

**Topic:** C.03. Parkinson’s Disease

**Support:** ISF-Legacy heritage science initiative

**Title:** Network dynamics in the primary motor cortex of mice with experimental Parkinson's disease

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**Abstract:** Parkinson's Disease (PD) is a common neurodegenerative disease, which markedly disrupts motor performance. The basal ganglia, the main brain system affected by PD, exert their physiological effects mostly by modulating neocortical activity via the cortico-basal ganglia loop. In the cortico-basal ganglia loop data is streamed from the neocortex to the striatum, processed along several parallel pathway, to finally sent back to the neocortex to modulate the activity of the neocortical network. The primary motor cortex M1, and especially layer-5 pyramidal tract (PT) neurons, integrate data from multiple brain regions, including the cortico-basal ganglia loop, to generate motor output commends that are transmitted to the brain stem and spinal cord. Thus, although PD primarily targets the basal ganglia, the motor consequences of cortico-basal ganglia disruption leading to motor disability must be mediated by impairment of the M1 network dynamics. Based on these assumptions, in this study we took a novel M1 centric approach to study PD focusing on the primary motor cortex. After training our head fixed mice

to perform a complicated motor task, hand reaching for food pallets, we monitored the activity of multiple neurons in layers 2-3 and 5 using two photon in-vivo imaging of GCaMP6 expressing pyramidal neurons in head fixed awake behaving mice. Experimental PD was induced by injection of 6 hydroxydopamine (6OHDA) into the striatum. Our findings show that experimental PD dramatically disrupts both motor behavior and the activity dynamics of M1 neurons. Changes in the cortical dynamics in M1 were seen both at the level of individual neurons, as well as at the cortical network level. Moreover, PD resulted in disruption of the network dynamics in both layers 2-3 and layer 5 of M1. These findings shed new light on the mechanisms underlying motor disabilities in PD, and identifies novel potential therapeutic targets in PD.

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**Poster**

**751. Parkinson's Disease: Circuit Mechanisms**

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**Program #/Poster #:** 751.07/Y17

**Topic:** C.03. Parkinson’s Disease

**Support:** NINDS (R00NS087098)

**Title:** Functional imaging of striatal neurons during Parkinsonism and dyskinesia

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**Abstract:** Parkinson's disease (PD) is a severe neurodegenerative disorder characterized by progressive loss of dopaminergic neurons. Administration of the dopamine precursor levodopa helps restore dopamine levels in the striatum - the brain region targeted by dopamine neurons - and thereby ameliorates motor symptoms in PD patients. However, as the disease progresses, the efficacy of levodopa decreases and leads to uncontrolled motor side effects known as dyskinesia. While several models have been proposed to explain how loss of dopamine affects downstream striatal circuits, technical limitations have prevented direct and simultaneous observation of striatal neuron populations in vivo during disease progression. Using two-photon $Ca^{2+}$ imaging in awake behaving mice, we simultaneously monitored the activity of striatal direct and indirect pathway neurons over the course of weeks under control conditions, following 6OHDA-mediated loss of dopamine neurons and upon levodopa-induced dyskinesia. Our work sheds light on the aberrant circuit dynamics that develop in the striatum during the progression of parkinsonism and dyskinetic episodes, and forms the basis for future experiments aimed at better alleviating PD symptoms.

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**Poster**

**751. Parkinson's Disease: Circuit Mechanisms**

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**Program #/Poster #:** 751.08/Y18

**Topic:** C.03. Parkinson's Disease

**Support:** NIH Grant 1F31NS093944

**Title:** Stereotyped basal ganglia output pathophysiology across dopamine depletion models emerges prior to motor deficits

**Authors: *A. M. WILLARD**[1], T. C. WHALEN[2], B. R. ISETT[1], K. J. MASTRO[3], C. KI[4], A. H. GITTIS[1]
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**Abstract:** Parkinson's disease (PD) is characterized by the progressive loss of dopamine in the basal ganglia that drastically alters circuit physiology and motor function. Individuals with PD do not develop motor symptoms until late stages of the disease. This robustness of motor function is thought to reflect compensatory changes within the basal ganglia or dopamine system. But most studies of compensatory plasticity have focused only on the input stage of the basal ganglia, with little information about how or if compensation impacts the progression of pathophysiology in basal ganglia output. To assess how basal ganglia output pathophysiology progresses under different compensatory conditions, we recorded from basal ganglia output neurons in the substantia nigra pars reticulata (SNr) during progressive dopamine loss induced at rates of 3 days - 6 months using toxin or neurodegenerative models. Because compensatory changes within the basal ganglia can take several days to weeks to stabilize, slow dopamine depletions provide more time for compensatory mechanisms to engage than rapid depletions. In vivo recordings from SNr were performed in awake, head-restrained mice at various stages of progressive dopamine loss. Surprisingly, we found that independent of the time course or mechanism of dopamine depletion, SNr pathophysiology developed at early stages of dopamine loss, when as little as ~20-40% of dopamine had been lost. The nature and severity of these pathophysiological changes, including reduced firing rates, increased firing irregularity, bursting, and synchrony, were largely independent of the mechanism or duration of dopamine depletion, and emerged well before the onset of motor symptoms. These results challenge long-standing assumptions about the role of compensatory plasticity within the basal ganglia and suggest that circuit compensations leading to the robustness of motor function occur at sites outside of the basal ganglia.

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**Poster**

**751. Parkinson's Disease: Circuit Mechanisms**

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**Program #/Poster #:** 751.09/Z1

**Topic:** C.03. Parkinson's Disease

**Title:** Responses of the substantia nigra pars reticulata to synaptic inputs from the direct and indirect pathways: A computational modeling study

**Authors: *R. S. PHILLIPS**[1], A. H. GITTIS[2], J. RUBIN[1]
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**Abstract:** The substantia nigra pars reticulata (SNr) serves as the primary output nuclei of the rodent basal ganglia (BG). Multiple synaptic input streams are integrated within the SNr, as it is targeted by synaptic excitation from the subthalamic nucleus and synaptic inhibition from direct pathway striatal neurons and indirect pathway globus pallidus (GP) neurons. Due to the convergence of these synaptic inputs, the SNr is well position to transfer pathological BG activity to downstream targets. Consistent with this idea, the SNr develops abnormal levels of burst firing in dopamine depleted (DD) conditions that is associated with behavioral impairments. Despite these important roles, computational modeling of the SNr has been limited. In this work, we developed a conductance-based differential equation model of SNr neurons. The model was tuned to reproduce key experimental observations including increased spike rates under apamin application and enhanced irregularity under block of TRPC3 channels known to exist in mouse SNr. With this data-based calibration, the model serves as a resource that we are using to test hypotheses about possible mechanisms underlying several recent findings on SNr from the literature and from the Gittis lab. First, in a version of the model including dendritic and somatic compartments to represent different sites of synapses from striatum and GP, we consider the diversity of experimentally observed SNr responses to synaptic inputs. In particular, we test four distinct proposed mechanisms to explain the paradoxical increases in SNr activity, and generally heterogeneous responses across the SNr population, following optogenetic activation of inhibitory synapses emanating from GP neurons. Second, by including short-term depression and tracking chloride concentration and potassium-chloride pump activity in the model, we provide a possible explanation for remarkable motor rescue experiments in akinetic DD mice published by the Gittis lab, in which multiple minutes-long epochs of optogenetic stimulation targeting various GP neuronal subpopulations could, for some targets but not others, lead to hours-long motor recovery associated with diminished burstiness in SNr.

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**Poster**

**751. Parkinson's Disease: Circuit Mechanisms**

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**Topic:** C.03. Parkinson's Disease

**Support:** Department of Chemical & Materials Engineering, University of Idaho
Seed Grant, University of Idaho

**Title:** Disruption of homeostasis of the Basal Ganglia circuit in Parkinson's disease

**Authors: J. SCHMALZ**, *G. KUMAR
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**Abstract:** We developed a computational model of the basal ganglia circuit that integrates chemical-level description with the electrical-level description of the basal ganglia dynamics to investigate the dynamical transition from the healthy state to the Parkinson's Disease (PD) state as a function of the depletion of dopamine neurons. A recent hypothesis in PD suggests that the beta-oscillation in the subthalamic nucleus (STN) arises from an imbalance in the direct and indirect pathways that originate in the striatum of the BG. The disruption of the striatum homeostasis creates an imbalance in the activity of neurons in the direct and indirect pathway, which are the D1 and D2 medium spiny neurons (MSNs), respectively. Recent experimental data suggests that the asymmetric activity of the D1 and D2 medium spiny neurons (MSNs) may be due to a combination of factors, such as, a difference in the dopamine binding concentration of D1 and D2 receptors, the excess release of acetyl choline, and the different muscarinic (acetyl choline) receptors on the MSNs. Based on these experimental results, we expanded the existing multi-compartment model of basal ganglia by including detailed chemical-level descriptions of dopamine and acetyl choline dynamics in the striatum as well as the projection of dopamine neurons from the substantia nigra (SN) to the striatum. To simulate the progression of PD, neurons in the SN were sequentially removed from the BG network. A key finding of this work is the emergence of beta-oscillation in the STN upon removal of SN dopamine from the healthy BG model. Our computational model of the BG shows that the removal of dopamine neurons results in a neurochemical imbalance in the striatum that disrupts the overall homeostasis of the BG. The neurochemical imbalance leads to an asymmetric activation of the direct and indirect pathways and drives the BG network from the healthy state to the PD state.

**Disclosures: J. Schmalz:** None. **G. Kumar:** None.

**Poster**

**751. Parkinson's Disease: Circuit Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

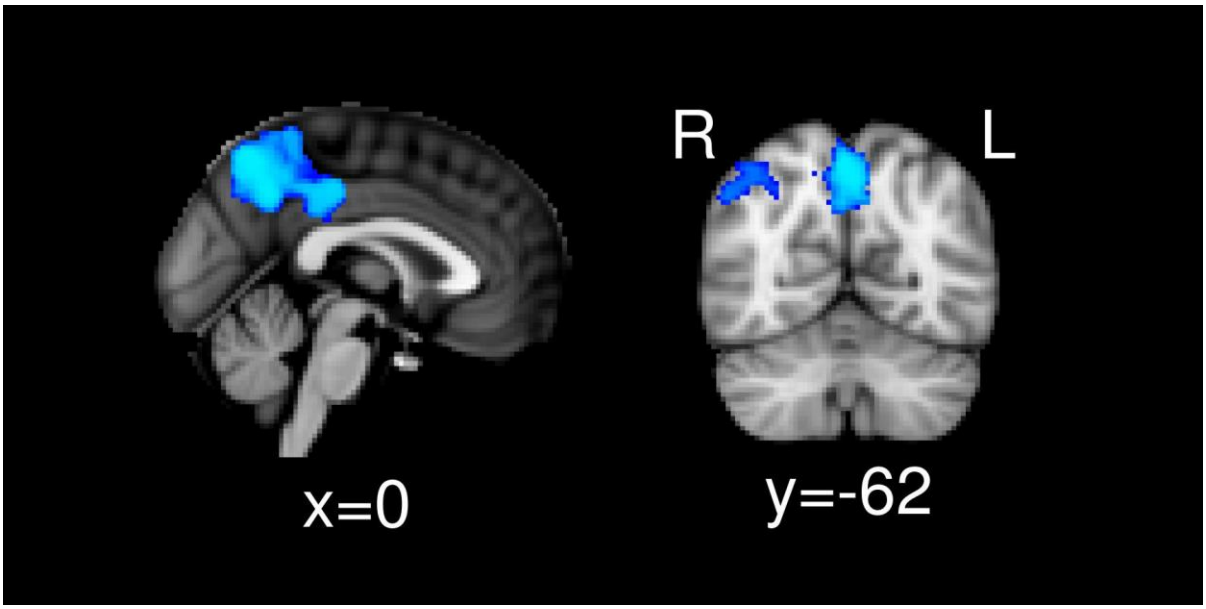
**Program #/Poster #:** 751.11/Z3

**Topic:** C.03. Parkinson’s Disease

**Title:** Reduced functional connectivity of the dorsolateral prefrontal cortex in Parkinson’s disease

**Authors: *T. IKUTA**, T. C. MYERS, M. C. INGE, A. W. COCHRAN
Communication Sci. and Disorders, Univ. of Mississippi, University, MS

**Abstract:** The dorsolateral prefrontal cortex (DLPFC) has been found to be downregulated in Parkinson’s disease (PD). Transcranial stimulation has been shown to improve balance, functional mobility, and problem solving performance in PD. The DLPFC is one of the cortical regions significantly affected by PD. However, the underlying mechanism of DLP hypofunction is not clear, especially in the context of the progression of the disease. In this study, we sought to elucidate functional connectivity reduced through the course of PD. We used resting state functional magnetic resonance imaging (rsfMRI) data from Parkinson's Progression Markers Initiative. Sixty-one patients (60.2±10.36 years old) had two sessions (15.59±5.96months apart) of rsfMRI data, and we analyzed them in a pairwise fashion to examine the longitudinal change of DLPFC functional connectivity. In a whole brain voxel-wise analysis, the right DLPFC showed significant decrease in its connectivity to the posterior cingulate cortex (PCC) and precuneus (corrected $p<0.05$). The PCC and precuneus are both a part of the default mode network. The current finding may suggest that influence of the default mode network to the DLPFC is reduced as the PD progresses. Connectivity between the DLPFC & PCC and between the DLPFC & precuneus may predict executive function, problem solving, balance, and functional mobility. Finding behavioral correlates of the functional connectivity would reveal the symptoms for which the reduced connectivity underlies.




**Disclosures: T. Ikuta:** None. **T.C. Myers:** None. **M.C. Inge:** None. **A.W. Cochran:** None.

**Poster**

**751. Parkinson's Disease: Circuit Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 751.12/Z4

**Topic:** C.03. Parkinson’s Disease

**Support:** Intramural Research Program, NINDS, NIH

**Title:** Effects of inhibitory DREADD activation in the parafascicular thalamic nucleus on nigral and cortical high beta oscillations and motor behavior in hemiparkinsonian rats

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**Abstract:** Loss of dopamine and associated excessive beta frequency synchronization in the basal ganglia (BG)-cortical motor circuits in both Parkinson's disease (PD) patients and animal models of PD are thought to contribute to parkinsonian motor dysfunction. However, the neural mechanisms and circuitry underlying these oscillations remain uncertain. Recently, we reported that synchronized activity in the substantia nigra pars reticulata (SNpr) of hemiparkinsonian rats entrains activity in the ventromedial thalamus (VM) and promotes the transmission of 25-35 Hz oscillations throughout BG-thalamocortical circuits (Brazhnik et al., 2016). The parafascicular thalamic nucleus (PF) receives inputs from the BG, cortex, and cerebellum and provides

feedback to the subthalamic nucleus (STN) and striatum (STR) and thus could be implicated in the pathophysiology of PD. Unlike the VM, however, exaggerated beta oscillations are not evident in recordings from the PF in the behaving, hemiparkinsonian rat. Instead, our latest results call attention to the potential role of PF output in tonic modulation of STR and STN activity and support the idea that reductions in PF activity may have a therapeutic effect on motor dysfunction in PD (Brazhnik et al., SFN Abst. 2015, 2017). In the present study, two groups of hemiparkinsonian rats received infusion of different inhibitory DREADD viruses into the PF: AAV2-hSyn-hM4D(Gi)-mCherry (hM4D, n=10) to inhibit PF output and AAV8-hSyn-dF-HA-KORD-IRES-nCitrine (KORD, n=3) to selectively inactivate striatal projections from the PF. Recording electrodes were implanted targeting motor cortex (MCx), STR, and SNpr. Histological analyses revealed modest DREADD virus expression in the PF with some spread to surrounding areas. Similar to previous studies, exaggerated high beta power in the MCx and SNpr and coherence between these regions were observed during treadmill walking. At 3-4 weeks post-surgery, clozapine-N-oxide (1-5 mg/kg, ip.) and salvinorin B (1-2 mg/kg, sc.), both of which activate the receptors expressed by the corresponding DREADD virus, substantially improved circular treadmill walking in the clockwise direction without modifying cortical or nigral high beta oscillations. Results suggest that selective inactivation of PF terminals in the STR reduces motor deficit in a rodent model of PD. Ongoing DREADDs experiments are further exploring the contribution of the PF to high beta oscillations in BG-cortical motor circuits as well as spiking activity in the STR, SNpr, and MCx during treadmill walking.

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**Poster**

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**Program #/Poster #:** 751.13/Z5

**Topic:** C.03. Parkinson’s Disease

**Support:** CONICET PIP 112 201301 00256
U. Cuyo SeCTyP 06/C508
ANPCyT PICT 2014-1966

**Title:** Mechanisms of cross-frequency coupling in network models of Parkinson’s disease

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**Abstract:** Recent work has shown that Cross-Frequency Coupling (CFC) is generated in several brain circuits with different architectures, and is associated with various physiological and pathological conditions. In particular, Phase-Amplitude Coupling (PAC), observed in oscillatory neuronal activity, is an important variant of the CFC phenomenon, in which the amplitude of a higher frequency band is modulated by the phase of another band with a lower frequency content. The PAC phenomenon has been reported in many frequency ranges using various techniques for recording neuronal activity and algorithms for the quantification of the CFC. In Parkinson's disease (PD), beta-gamma PAC has been observed in the local field potentials in the primary motor cortex. It has been found that it is exaggerated compared to patients without movement disorders. The reported evidence suggests that this excessive coupling is probably a manifestation of an excessive synchronization in the basal ganglia and may be related to motor dysfunction in PD. Although several works support the association of PAC with the parkinsonian state, the origin of PAC in this context has been poorly explored. In this work, we investigate the generation of PAC in models of neuronal populations whose architecture has already been proposed for the generation of pathological oscillations associated with PD. Our model is composed of three populations. They represent the motor cortex, sub thalamic nucleus (STN) and external globus pallidus (GPe). The interaction among these populations gives rise to an architecture that incorporates the hyperdirect, direct, indirect and STN-GPe loops. To describe and quantify PAC in different conditions, we have characterized, in the parameter space, the behavior of the oscillations using the Phase Locking Value (PLV), which characterizes plain PAC, and Time Locked Index (TLI), which quantifies the presence of harmonics. We have found two situations. In the first one the appearance of PAC is linked to a Hopf-Hopf bifurcation. In this case high values of PLV are associated with high values of TLI, indicating that PAC is generated by the harmonics in the non-sinusoidal shape of the waveform. In the second case PAC is associated with a secondary bifurcation by which a system that is already oscillating generates an additional frequency. In this case we obtain high values PLV and low values of TLI. This corresponds to the case of a sinusoidal waveform modulated in amplitude by a slower frequency. These results show that the proposed architecture can lead to different types of PAC. Both are linked to the dynamics of interacting populations and are informative regarding the conditions of the system.

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**Poster**

**751. Parkinson's Disease: Circuit Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 751.14/Z6

**Topic:** C.03. Parkinson’s Disease

**Support:** NINDS NS097437

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Barnes Jewish Hospital Foundation
American Parkinson Disease Association

**Title:** CSF proteins and longitudinal functional connectivity network changes in Parkinson's disease

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**Abstract: Background:** Parkinson disease progression reflects ongoing pathological proteinopathy and deficits in multiple neurotransmitter systems. Resting-state functional connectivity, as a measure of brain function, may provide a non-invasive marker of Parkinson disease progression.
**Objective:** The present study examined the relationship between baseline CSF protein levels and longitudinal changes in cortical resting-state functional connectivity networks in Parkinson disease participants compared to healthy controls.
**Methods:** Non-demented Parkinson disease (N = 64) and control (N = 27) participants completed longitudinal resting-state magnetic resonance imaging scans and clinical assessments. Participants also completed baseline lumbar punctures for CSF protein levels. Parkinson disease participants completed neuroimaging and behavioral testing after overnight withdrawal (OFF) of Parkinson disease medications.
**Results:** Functional connectivity within the sensorimotor network and the interaction between the dorsal attention network with the frontoparietal control network significantly decreased over time in Parkinson disease participants. Baseline CSF alpha-synuclein protein levels predicted decline in the sensorimotor network.
**Conclusions:** These results indicate that cortical motor and association network functional connectivity declines over time in Parkinson disease prior to dementia onset. Further, brain protein levels may contribute to longitudinal declines in functional connectivity networks.

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**Poster**

**751. Parkinson's Disease: Circuit Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 751.15/Z7

**Topic:** C.03. Parkinson’s Disease

**Title:** Origin of rest tremor in Parkinson's disease: Oscillating source in the brain or feedback induced instability in the sensorimotor loop?

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**Abstract:** Rest tremor is one of the most common and disabling symptoms of Parkinson's Disease (PD). There is good evidence that rest tremor may have a pathophysiology different from most other PD symptoms. To date, the pathophysiology of rest tremor is not clearly established. Understanding the neural origin of parkinsonian rest tremor will help us not only to optimize the existing treatment strategies such as Deep Brain Stimulation but also to develop alternative treatment strategies for rest tremor reduction. There are broadly two categories of theories that are gaining prominence to explain the origin of Parkinsonian rest tremor. The first category is the Central Oscillator Theory (COT) which proposes that the rest tremor is driven by oscillatory signals originating from the brain. These could be produced either by a nucleus with spontaneous rhythmicity or by instability in the local (central) feedback loop consisting of neuronal populations or different nuclei and their axonal connections in the brain. The second category is the Feedback-induced Instability Theory (FIT) which proposes that the rest tremor is a limit-cycle oscillation that occurs due to feedback-induced instability in the sensorimotor loop caused by increased response time (delay in the sensorimotor loop). We attempt to contrast these theories with the help of elementary simulation examples and compare the simulation trends with established clinical observed trends.

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**Poster**

**751. Parkinson's Disease: Circuit Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 751.16/Z8

**Topic:** C.03. Parkinson's Disease

**Support:** Intramural Research Program, NINDS, NIH

**Title:** Blocking GABAergic input to the subthalamic nucleus improves motor deficits and modulates beta burst activity in the motor cortex of the hemiparkinsonian rat

**Authors: *M. W. PRESTON, JR**, H. BERMUDEZ CABRERA, N. NOVIKOV, J. R. WALTERS
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**Abstract:** Parkinson's disease (PD) is characterized by the progressive loss of dopamine (DA) neurons in the basal ganglia (BG), and is associated with abnormal local field potential (LFP) synchrony in the beta frequency range (15-35Hz) coincident with motor dysfunction. Although these phenomena are well established, the link between them remains debated. Traditionally, LFP data is averaged across trials and subjects, giving the impression of continuously robust beta power during a given behavioral state. However, on a trial-by-trial basis, beta power emerges as transient bursts and the characteristic features of these bursts may provide information about underlying pathology. Unilateral injection of 6-hydroxydopamine into the rat medial forebrain bundle ablates DA neurons in the BG, resulting in both motor dysfunction and excessive beta oscillatory activity throughout the BG-thalamocortical circuit, providing a model for the study of PD. The goal of this study was to examine the characteristics of beta bursts in the motor cortex (MCx) of the hemiparkinsonian rat in conjunction with the expression of motor deficits. LFP activity was recorded from the MCx of the lesioned hemisphere of hemiparkinsonian rats, during circular treadmill walking. Results show that the distribution of beta bursts and their features periodically fluctuate as the animals walk. Specifically, bursts are less likely to occur around the time that an animal exhibits a step with the hindlimb contralateral to their lesioned hemisphere. In addition, the bursts that do occur proximal to these step times are characterized by significantly reduced amplitude. These results suggest that desynchronization of beta activity coincides with initiation of hindlimb stepping. To further investigate the relationship between MCx LFP activity and motor function, the effects of pharmacological manipulation of the subthalamic nucleus (STN) were tested. Infusion of GABA antagonist picrotoxin into the STN during treadmill walking had no significant effects on total beta power; however, results show significant modulation of beta burst features coincident with improved motor function (n=5). Additional studies with muscimol and assessment of STN LFP activity are ongoing. These results support the view that beta burst duration is an effective biomarker for parkinsonian dysfunction, and are consistent with observations in PD patients showing that adaptive deep brain stimulation of the STN both ameliorates motor dysfunction and reduces the average duration of beta bursts (Tinkhauser G, et al., 2017).

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**Poster**

**751. Parkinson's Disease: Circuit Mechanisms**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 751.17/Z9

**Topic:** C.03. Parkinson's Disease

**Support:** Intramural Research Program, NINDS, NIH

**Title:** The development of synchronized beta activity in the anterior cingulate cortex and its effects on executive function and pain processing in the hemiparkinsonian rat

**Authors: *A. R. WEISS**, Y. YANG, A. YIM, E. BRAZHNIK, N. NOVIKOV, M. W. PRESTON, Jr., A. J. MCCOY, J. R. WALTERS
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**Abstract:** The motor symptoms of Parkinson's disease (PD) have been linked to the emergence of exaggerated oscillatory activity in the 13 - 35 Hz beta range in local field potentials (LFP) recorded in the basal ganglia (BG) and motor cortex (MCx) of PD patients and parkinsonian animal models. Patients and animal models also exhibit cognitive dysfunction and increased pain sensitivity in PD, but the electrophysiological correlates of these non-motor symptoms are not well understood. As the prefrontal cortex (PFC), like the MCx, receives afferent input from the BG, prior studies have hypothesized that the PFC also develops synchronized beta in PD. These studies revealed synchronized beta activity in the PD anterior cingulate cortex (ACC) but not in the prelimbic or infralimbic cortices during a treadmill walking task (Weiss *et al.*, SFN Abst. 2016, 2017). We hypothesize that dopamine (DA) loss and the subsequent synchronization of beta activity in the ACC may be implicated in the non-motor symptoms of PD. Here, we investigate the development of synchronized low (20 - 29 Hz) and high (30 - 36 Hz) beta activity in the ACC of awake, behaving 6-OHDA-lesioned hemiparkinsonian rats in both executive function (responding to salient cues signaling the onset of expected or unexpected treadmill-induced walking) and pain processing (injection of formalin into the hind paw). Interactions between the ACC, the subthalamic nucleus (STN), and the ventral medial thalamus (VM) of the BG-thalamocortical circuit were also investigated.

Electrode bundles were implanted in the ACC, STN, and VM of rats with either unilateral DA cell lesions or saline controls. In an executive function task, LFPs and spiking activity were recorded during epochs centered on auditory stimuli and treadmill walking in DA-lesioned and non-lesioned rats, wherein beta activity was shown to be coherent between the ACC, STN, and VM of DA-lesioned rats. Further, beta spectral power, peak frequency, and coherence all increased with increasing alertness and were modified by the expectedness of treadmill walking trials. In the formalin injection test, behavioral responses, spiking, and LFP activity were recorded for 2 hours following injection. Formalin injection experiments are ongoing but initial results show that after injection, beta band spectral power is less modulated by behavior (as opposed to before injection).

Our results suggest that the transmission of synchronized oscillatory activity from the BG, through the VM, to the ACC in parkinsonian conditions may disrupt normal ACC function; and provide further insight into the significance of excessive oscillatory activity in PD, cognitive, and pain systems.

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**Poster**

**751. Parkinson's Disease: Circuit Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 751.18/Z10

**Topic:** C.03. Parkinson’s Disease

**Support:** TL1TR001428

**Title:** The role of the gut microbiota in dopaminergic neuron vulnerability

**Authors: *D. KOUTZOUMIS**[1], M. V. VERGARA[1], J. A. PINO[1], J. G. BUDDENDORFF[1,2], R. J. MANDEL[2], G. E. TORRES[1]
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**Abstract:** Parkinson's Disease (PD) is the second most common neurodegenerative disease, affecting ~1% of the individuals over the age of 65 and is characterized by the loss of dopaminergic neurons in the substantia nigra. Recent studies suggest a link between the pro-inflammatory profile associated with PD and alterations in the gut microbiota. We examined the impact of ablating the gut microbiota through antibiotic treatment in animal models of PD on motor deficits, dopaminergic integrity in the basal ganglia, and the inflammatory profile in the central nervous system and periphery. Our results demonstrate that chronic treatment with an antibiotic cocktail ameliorate the neurotoxicity of 6-hydroxydopamine in a unilateral lesion model. Motor dysfunction was reduced in antibiotic-treated groups as measured by paw-rearing measurements in the cylinder test and ipsilateral rotations observed in the amphetamine-induced rotation test. Immunohistochemistry against dopaminergic neuron marker tyrosine hydroxylase shows reduced dopaminergic neuron degeneration in antibiotic treated animals as well as a reduction in the expression of pro-inflammatory markers in the basal ganglia, but not in the periphery. These results implicate the gut microbiota as a potential source of pathology in the development of PD. However, further studies are necessary to understand the specific mechanisms involved in transducing alterations in the gut microbiota to changes in dopaminergic neuron vulnerability.

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**Poster**

**751. Parkinson's Disease: Circuit Mechanisms**

**Location:** SDCC Halls B-H

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**Topic:** C.03. Parkinson's Disease

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National Institute for Health Research (NIHR) Oxford Biomedical Research Centre
Dementias and Neurodegenerative Diseases Research Network
Wellcome Trust Clinical Research Training Fellowship to Dr Barber

**Title:** Automated measures from neuromelain MRI reveal neurodegeneration in REM sleep behaviour disorder

**Authors: *L. GRIFFANTI**[1,2], T. R. BARBER[1,2], K. M. BRADLEY[3], D. R. MCGOWAN[4], M. CRABBE[1,2], M. ROLINSKI[1,5,2], C. E. MACKAY[1,2], J. C. KLEIN[1,2], M. HU[1,2]
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**Abstract:** Patients with Rapid Eye Movement Sleep Behaviour Disorder (RBD) have a high risk of developing Parkinson's Disease (PD) or a closely related disorder and therefore represent an opportunity to study prodromal neurodegeneration. Recent studies in PD highlighted the utility of measures extracted from neuromelanin-sensitive MRI (NM-MRI) in identifying pathological changes in the substantia nigra (SN) and locus coeruleus (LC), two key sites involved early in the disease process.We sought to apply this technique in patients with RBD by firstly developing an automated method to extract measures from NM-MRI in SN and LC, and, secondly, by comparing these measures in terms of their ability to: 1) differentiate healthy controls (HC) from RBD patients; 2) differentiate RBD with normal or abnormal Dopamine transporter (DaT) SPECT/CT scan (current gold standard for assessing dopaminergic neurodegeneration); 3) correlate with clinical risk.Thirty-two patients with RBD underwent neuromelanin-sensitive MRI (NM-MRI) and DaT SPECT/CT imaging (reported as normal/abnormal by an experienced nuclear medicine radiologist). Clinical risk was calculated for each RBD patient using the Movement Disorders Society Research Criteria for Prodromal Parkinson's Disease (MDS). Twenty-five healthy controls (HC) were scanned with NM-MRI. SN and LC measures were calculated using an automated method: we defined search and reference regions of interest (ROIs) for the SN and LC on a study-specific NM template in MNI space. For each subject, the ROIs defined on the template were registered on the individual NM images to derive SN and LC volumes and other measures used in the literature (Chen et al.,2014; Sasaki et al.,2006, Schwarz et al.,2011; Isaias et al.,2016; Ohtsuka et al.,2013). NM-MRI measures were compared between

HC and RBD, between RBD with normal vs abnormal DaT SPECT/CT, and correlated with the MDS score.Compared to HC, RBDs had a significant reduction in SN volume (p=0.02) and LC volume (p=0.001). RBD patients with abnormal DaT SPECT/CT (n=17;46%) had significantly reduced peak signal intensity (p=0.002) and contrast ratio (p=0.001) within the SN compared to those with normal DaT SPECT/CT. Amongst RBDs, both SN and LC volumes correlated inversely with MDS prodromal probability scores (SN:r=-0.44, p=0.03; LC:r=-0.60, p=0.001).These results suggest that NM-MRI allows extracting quantitative measures of prodromal neurodegeneration that predict dopaminergic deficits and clinical PD risk in patients with RBD. The use of this fully automated methodology should further facilitate the replication of findings and enable the objective identification of longitudinal changes.

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**Poster**

**752. Parkinson's Disease: Neuroprotection**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 752.01/Z12

**Topic:** C.03. Parkinson’s Disease

**Support:** AA023165
AA017168
NS075097
AG047366
Michael-J-Fox foundation
Stanford CNI seed fund

**Title:** Neuroimaging of the glymphatic system in relation to motor skill in Parkinson’s disease

**Authors: *E. M. MULLER-OEHRING**[1,4], E. PETERSON[1,4], J. Y. HONG[4], K. L. POSTON[2,3], H. M. BRONTE-STEWART[2,3], T. SCHULTE[4,5]
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**Abstract:** While motor symptoms are prominent clinical and disabling features of Parkinson’s disease (PD), nonmotor symptoms such as sleep deficits start early in the course of the disease. Deterioration of basal ganglia (BG) cortical circuits affects the regulation of sleep and wakefulness. Among the multiple physiological functions of sleep, glymphatic system (GS)

activation may protect the brain from neurodegenerative decline. The GS consists of a flow of cerebrospinal and interstitial fluid through the brain parenchyma and is assumed to clean toxins and waste from the brain and spinal cord during sleep. We performed a pilot imaging study of a free-water (FW) compensated diffusion tensor imaging scan for measures of interest regarding the function of the GS and also acquired task-activated multiband fMRI to measure neurofunctional activity in relation to motor skill in nine patients with moderate PD and nine age-matched healthy control subjects (HC). In addition to experiencing clinical motor symptoms as quantified with the Unified Parkinson's Disease Rating Scale, PD patients reported more sleep problems, daytime sleepiness and dozing than HC. For GS measures, we found increased FW fraction in BG regions in PD relative to HC that was correlated with the duration of the PD diagnosis and motor symptom severity. Testing the neurofunctional correlates of motor skill using a procedural memory task, we found on average normal motor skill acquisition; both PD and HC continuously improved performance with motor skill sequence repetition, but not when performing non-repeating random sequences (control condition). Individual motor symptom severity in PD adversely affected this motor skill acquisition, in particular, bradykinesia correlated with slower learning curves. Our pilot task-activated fMRI results showed frontal hypoactivation in PD relative to HC, when performing the motor skill (learned) sequences compared to random sequences. Sleep quality and frontal FW fraction were related to the frontal activation pattern during motor performance. Together our findings provide preliminary evidence for a role of sleep and regional FW fraction measures of the GS for motor symptom severity and regional neurofunctional correlates of motor skill in PD. More and larger studies are warranted to advance our understanding on the implication of sleep and the GS for disease severity and progression. AA023165, AA017168, NS075097, AG047366, Michael-J-Fox foundation, Stanford CNI seed fund

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**Poster**

**752. Parkinson's Disease: Neuroprotection**

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**Program #/Poster #:** 752.02/Z13

**Topic:** C.03. Parkinson's Disease

**Support:** PAPIIT
UNAM
IN219617

**Title:** Co-administration of melatonin and dopaminergic agonist 7-OH-DPAT the production of BDNF as treatment in motor disorders in Parkinson's disease

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**Abstract:** Treatments for Parkinson's disease (PD) do not stop the progress of the disease.In this context,the idea has arisen that it is necessary to recover the dopaminergic system as an alternative for the treatment of PD. Recently, the importance of BDNF in the regulation of various processes of dopaminergic neurons has been reported, so maintaining their levels would produce a beneficial effect;given the background that points to melatonin (MTL) as an effective antioxidant that also increases BDNF levels and is able to increase the levels of dopamine synthesis,while the activation of the D3 receptor is able to increase BDNF levels;because it would produce a beneficial environment in which the levels of BDNF are maintained,the oxidative environment is reduced and the cell survival processes are stimulated,consequently reversing the symptoms of PD.In this study we evaluated the efficacy of co-administration of MTL and dopamine agonist(7-OH-DPAT) as inducers of BDNF production and its effect on the motor performance of pharmacologically treated animals.Sixty male Wistar rats were used;they were divided into 2 groups:the lesion group consisting of 48 rats that were injected unilaterally with 6-OHDA(8μg/μl) and fifteen days later both groups were evaluated for turning behavior with apomorphine(0.25 mg/kg) for ensuring dopaminergic loss.The lesion group was divided into three groups:the first one to which the dopamine agonist was administered, the second the melatonin and the third co-administration of both treatments.It is important to mention that the dopamine agonist was administered through a microdiffusion pump that was implanted by surgical methods subcutaneously, the pump is active for 3 months releasing 1mg/kg/day,and melatonin was administered 10mg/kg per day orally daily in the morning. The three afore mentioned groups,once the treatments were initiated, were injected with BrdU 500mg/Kg /ip(1 month daily) and they were tested for beam and stairway behavior prior to the injury and every 15 days during the treatment.Once at the end of the treatment time, the organisms were sacrificed by intracardiac perfusion for immunohistochemistry method(TH/BrdU) and Golgi technique.Preliminary behavioral results show that the effect of the co-administration of MTL/7-OH-DPAT drastically recover the motor activity,this could be happening because that treatment could be potentiating the effect of both drugs; possibly because it has been reported that melatonin recovers dopamine levels as well as increases the sensitivity of the D2 family receptor,while the D3 agonist favors the presence of BDNF,allowing a more permanent effect with treatment.

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**Poster**

**752. Parkinson's Disease: Neuroprotection**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 752.03/Z14

**Topic:** C.03. Parkinson’s Disease

**Title:** Neuroprotective potential of 1-Methyltryptophan in a mouse model of 6-OHDA induced Parkinson’s disease

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**Abstract:** Parkinson’s disease (PD) is a common neurodegenerative disorder characterized by loss of striatal dopaminergic neurons due to oxidative stress and localized neuroinflammation. Neuroinflammation results in microglial activation and release of several proinflammatory mediators. Being one of the major controllers of the immune response, the kynurenine pathway (KP) of tryptophan catabolism is also likely to be involved in the neuroinflammatory and neurotoxic cascade in Parkinson’s disease. With this background, this study is designed to evaluate the neuroprotective potential of 1-Methyltryptophan (1-MT) in 6-OHDA mouse model of Parkinson’s disease. The effect of different doses of 1-MT on oxidative stress, neuroinflammation, apoptosis, mitochondrial dysfunction, neurotransmitters levels, biochemical and behavioral alterations was assessed after induction of Parkinson’s disease by unilateral administration of 6-OHDA to the striatum. 1-MT significantly alleviates the neuromotor deficits produced by 6-OHDA in rotarod and open field test. Further, 1-MT has been found to be neuroprotective as indicated by reduced oxidative damage, neuroinflammation, mitochondrial dysfunction and neuronal apoptosis. Restoration of neurotransmitter levels and increased brain BDNF levels has been observed following treatment with 1-MT. The overall findings suggested that 1-MT, an indoleamine-2,3-dioxygenase (IDO-1) inhibitor could be an alternative in the pharmacotherapy of PD.

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**Poster**

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**Topic:** C.03. Parkinson’s Disease

**Support:** National Nature Science Fund of China (Grant 81271430)

**Title:** Cdk5 inhibitory peptide prevents loss of dopaminergic neurons and alleviates behavioral changes in a MPTP induced Parkinson's disease mouse model

**Authors: *Y. HU**[1], R. HE[2], W. HU[1], Y. HUANG[1], M. XU[1]
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**Abstract:** Parkinson's disease (PD) is one of the most affected neurodegenerative diseases in the world. Deregulation of cyclin-dependent kinase 5 (Cdk5) is believed to play an important role in neurodegenerative diseases including PD. p25 is a cleavage peptide of p35, a physiologic activator of Cdk5. p25 combines to Cdk5 and leads to the hyperactivity of Cdk5, which in turn hyperphosphorylates downstream substrates and leads to neuroinflammation and apoptosis of neurons. Previously, we have demonstrated that adeno-associated virus serotype-9 (AAV9) mediated Cdk5 inhibitory peptide (CIP) inhibits the activity of Cdk5/p25 complex and alleviates pathologic and behavioral changes in Alzheimer's disease mouse model. In this study, we evaluated whether AAV9-CIP protected dopaminergic neurons in 1-methyl-4-phe-nyl-1,2,3,6-tetrahydropyridine-probenecid (MPTP/p) induced PD mouse model. The data showed that administration of AAV9-CIP by intracerebroventricular injection one week before MPTP/p exposure protected dopamine neurons from apoptosis in substantia nigra compact of the model mice. Importantly, AAV9-CIP also alleviated the motor and anxiety-like symptoms of the disease animals. In summary, AAV9 mediated CIP might be a potential intervention for PD.

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**Poster**

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**Program #/Poster #:** 752.05/Z16

**Topic:** C.03. Parkinson’s Disease

**Title:** 7,8-Dihydroxyflavone (TrkB agonist) prevented the neuroinflammation and neurodegeneration via acting on sulfiredoxin-peroxiredoxin axis in-vitro and in-vivo MPTP model of Parkinson's disease in mice

**Authors: *M. KWATRA**, S. AHMED, B. GAWALI, V. NAIDU
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**Abstract:** Parkinson disease is (PD) a debilitating motor disorder affected million of the population worldwide. The underlying cause for the loss of substantial nigra pars compacta (SNc) neurons with several different theories have been implicated for the years but still, the actual fact is undetermined and vague. However, oxidative stress is being considered to be the most important contributing factor in neurodegeneration. With huge oxygen demand brain always remain prone to the oxidative stress. To combat this oxidative stress the body has sets of endogenous antioxidants counteracting and managed the raised oxidative stress conditions. As the intolerable limit of radical species cause redox imbalance and resulting in the pathogenesis leading neuroinflammation and neurodegeneration. Previous reports found with the involvement of sulfiredoxin-peroxiredoxin (Srx-Prx) axis role in carcinogenesis, cell proliferation, migration, and metastasis. This potential axis gets overexpressed in cancer but less express in the dopamine region of SNc and striatum. Earlier reports also suggested the peroxiredoxin (thiol-based peroxidase) isoforms if overexpress or knockout in animal or cells lead to altering the pathogenesis in PD. This peroxiredoxin with 6 isoforms serves an important function with peroxidatic activity and chaperone alike activity in hyperoxidized form (sulfonic acid; PrxSO3). The ATP and sulfiredoxin-1 (Srx-1) mediate as a key player for the restoration of reduced Prx with its peroxidatic activity in neutralizing the peroxides. For understanding the mechanistic approach we studied the effect of neurotoxins such as 6-hydroxydopamine (6-OHDA), MPP+ induced reactive oxygen species leading inflammation role in neuroblastoma and microglia cells. Moreover, we also investigated the effect of 7,8-dihydroxyflavone (7,8-DHF) on sulfiredoxin and peroxiredoxin axis. We utilized the potential Nrf2 activator (D3T; 3H-1,2-Dithiole-3-thione) we found the increased expression of sulfiredoxin-1 and with the combination of 7,8-DHF provided the add on effect that confirms the 7,8-DHF role in increasing genes and protein expressions of Srx-1 and Prx (2,3,4,6) in cells and the animal mouse model of MPTP. The tunnel assay also confirms the prevented death by 7,8-DHF in the striatum and nigral region of mice. Thus, TrkB agonist may be the future drug candidate or adjunct in treating Parkinson's disease with multiple potentials of neurogenesis and augmenting the antioxidant status.

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**Poster**

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**Title:** Is brain-derived neurotrophic factor signaling critical for mediating the benefits of vagus nerve stimulation in preclinical Parkinson's disease?

**Authors: *A. FARRAND**[1], K. HELKE[2,3], R. GREGORY[2], M. GOOZ[4], V. HINSON[5], H. BOGER[1]
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**Abstract:** We have previously shown that vagus nerve stimulation (VNS) alleviates motor impairment and neuronal degeneration in a rodent model of Parkinson's disease (PD). In addition, preliminary results from our lab demonstrated that VNS increased brain-derived neurotrophic factor (BDNF) in target regions of the locus coeruleus (LC) and substantia nigra (SN), findings similar to previous studies using a model of depression that suggest VNS exerts its beneficial effects via BDNF-TrkB signaling. Therefore, we wanted to determine if the effects of VNS in our PD model are dependent on a BDNF-TrkB signaling mechanism. To test our hypothesis, we used our double lesion rat model of PD (combining N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4)/6-hydroxydopamine (6-OHDA)) and implanted VNS cuffs and headcaps. To block the TrkB signaling pathway, rats also received a daily injection of either the potent TrkB inhibitor, ANA-12, or vehicle prior to the VNS session in which locomotor activity was recorded. We found that TrkB inhibition alone was not sufficient to prevent the beneficial locomotor effects of VNS; however, ANA-12 administration did prevent the VNS-induced increase of tyrosine hydroxylase (TH)-positive neurons in the LC and SN and the increase of TH-immunoreactivity in the striatum. In order to determine which TrkB-induced signaling pathway is involved, Western blot analysis of pAkt (Ser473), pERK, and pPLCγ was conducted. Interestingly, results showed increased phosphorylation of all three proteins following ANA-12, suggesting that TrkB inhibition alone in our model is insufficient to prevent activation of these cell-signaling proteins. Since Akt, ERK, and PLCγ can be activated through numerous pathways including inflammatory cytokine production and even crosstalk with each other, it is possible that phosphorylation of these proteins is occurring through an alternative signaling cascade. While overall our results suggest TrkB signaling does play a role in the beneficial effects of VNS, as demonstrated by ANA-12's prevention of VNS effects on TH-positive neurons, our findings suggest additional mechanisms are also involved. Therefore, current studies are ongoing to determine the cause of increased Akt, ERK, and PLCγ phosphorylation. These data will elucidate the contribution of TrkB signaling to our observed symptomatic and neuroprotective VNS effects in the PD model, thus aiding in a potential therapeutic target for PD motor dysfunction and neuropathology.

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**Poster**

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**Title:** Chronic caffeine treatment protects against α-synucleinopathy by reestablishing autophagy activity in the mouse striatum

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**Abstract:** Despite converging epidemiological evidence for the inverse relationship of regular caffeine consumption and risk of developing Parkinson's disease (PD) with animal studies demonstrating protective effect of caffeine in various neurotoxin models of PD, whether caffeine can protect against mutant α-synuclein (α-Syn) A53T-induced neurotoxicity in intact animals has not been examined. Here, we determined the effect of chronic caffeine treatment using the α-Syn fibril model of PD by intra-striatal injection of preformed A53T α-Syn fibrils. We demonstrated that chronic caffeine treatment blunted a cascade of pathological events leading to α-synucleinopathy, including pSer129 α-Syn-rich aggregates, apoptotic neuronal cell death, microglia and astroglia reactivation. Importantly, chronic caffeine treatment did not affect autophagy processes in the normal striatum, but selectively reversed α-Syn-induced defects in macroautophagy (by enhancing microtubule-associated protein 1 light chain 3, and reducing the receptor protein sequestosome 1, SQSTM1/p62) and chaperone-mediated autophagy (CMA, by enhancing LAMP2A). These findings support that caffeine—a strongly protective environment factor as suggested by epidemiological evidence—may represent a novel pharmacological therapy for PD by targeting autophagy pathway.

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**Poster**

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**Topic:** C.03. Parkinson's Disease

**Support:** NIH-COBRE 2P20GM10365306

**Title:** The neuroprotective effects of sumoylation in Parkinson's disease *in vitro* and mouse models

**Authors: *Y.-H. KIM**, D. WILLIAMS, E. CARTIER, J. VIANA
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**Abstract:** The Small Ubiquitin-like Modifier (SUMO) is a form of post-translational modification that may regulate protein function and stability. The SUMO ligase, Ubc9 conjugates SUMO to its target proteins. The role of SUMOylation in dopaminergic neurons in brain remains unclear for Parkinson's disease (PD) pathology. We hypothesize that the overexpression of Ubc9 protects dopaminergic neurons against oxidative stress. In cell viability (MTT) and cytotoxicity (LDH) assay, the Ubc9-EGFP overexpression protected N27 rat dopaminergic cells against $H_2O_2$ or MPP+ induced toxicities, compared to EGFP overexpressing control cells. We tested if the protective effects are mediated by reducing reactive oxygen species (ROS) production that is derived from oxidative stress. Using CellROX® Deep Red Reagent (Thermo, C10422) as a fluorogenic probe, we found that cellular ROS level was significantly lower in Ubc9-EGFP cells than that in EGFP cells, after the exposure of 640 μM MPP+ for 24 hrs. Hereafter, we applied the Ubc9 up- or down-regulating *in vitro* and *in vivo* models to validate SUMOylation as a potential regulatory target in PD pathological models. In MPTP-lesioned mice, we also confirmed that ROS level was lower in Ubc9 transgenic mice than that in WT siblings after chronic MPTP injection. In *in vitro* Cycloheximide-based protein stability assay, higher protein level of alpha-synuclein was identified in Ubc9-EGFP cells than in EGFP only cells. Ubc9 knock-down by RNAi in N27 parental cells showed a decrease in alpha-synuclein protein level, suggesting that SUMOylated alpha-synuclein has higher protein stability than non-SUMOylated form. Furthermore, in immunohistochemistry using confocal microscopy, we identified that dopaminergic neurons in the striatum from Ubc9 overexpressing transgenic mice are more resistant to MPTP toxicities than those from WT siblings. Our findings support that Ubc9 overexpression significantly reduces the MPTP toxicity in the striatum. Currently we are confirming the findings in Western blots quantitatively in tyrosine hydroxylase (TH) as a dopaminergic marker and in synaptophysin as a synaptic marker, using tissues from the striatum and brain stem. The most intriguing observation is that chronic MPTP injection strips off the SUMO1 from alpha-synuclein in the striatum after immuno-precipitation, which can be a

detrimental process in reducing alpha-synuclein protein stability. Our studies suggest that Ubc9 overexpression can be a regulatory target to protect dopaminergic neurons against oxidative stress, implicating that high level of SUMOylation in dopaminergic neurons can slow PD pathology.

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**Poster**

**752. Parkinson's Disease: Neuroprotection**

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**Topic:** C.03. Parkinson's Disease

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**Title:** SPG101, a novel compound with spinogenic activity, ameliorates early synaptic loss in a mouse model of Parkinson's disease

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**Abstract:** α-synuclein is a major neuronal synaptic protein implicated in Parkinson's disease (PD), dementia with Lewy bodies (DLB), Multiple System Atrophy and the lysosomal storage disorder, Gaucher's disease. Multiplication, point mutations or post-translational modification of α-synuclein can promote its abnormal aggregation and accumulation into Lewy bodies and Lewy neurites which lead to neuronal death. The primary early event associated with increased α-synuclein accumulation is dendritic synaptic loss, preceding even neuronal loss or microglial activation. Recently SPG101, has been reported to increase spinogenesis in a mouse model of Alzheimer's disease. SPG101 readily crosses the blood-brain barrier and accumulates in the brain. In order to determine if this compound would be effective to treat the early dendritic spine loss in a model of PD / DLB, SPG101 was delivered daily for 4 weeks by intra-peritoneal injection to α-synuclein-tg mice. Compared to vehicle treated animals, SPG101 treated α-synuclein-tg and non-tg mice showed an approximately 50% increase in dendritic spine density in cortical neurons after 4 weeks of treatment without any pathological complications. In addition, there was a decrease in α-synuclein accumulation in the cortex and thalamus in the α-

synuclein-tg mice treated with SPG101. Thus, SPG101 increases spinogenesis in cortical neurons and may be a potential therapeutic for neurodegenerative diseases like PD, where loss of spine density is an early pathological event.

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**Poster**

**752. Parkinson's Disease: Neuroprotection**

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**Topic:** C.03. Parkinson’s Disease

**Support:** Supported by a grant from Qilu Pharmaceuticals, Inc.

**Title:** Altered expression of genes involved in ganglioside biosynthesis in substantia nigra neurons in Parkinson’s disease brain and potential role in modulating vulnerability for neurodegeneration

**Authors: *M. VERMA**, J. SCHNEIDER
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**Abstract:** Reduced expression of GM1 and other major brain gangliosides GD1a, GD1b and GT1b have been reported in Parkinson’s disease (PD) brain. Yet, the mechanisms underlying these changes are unclear but may be related to a defect in ganglioside biosynthetic processes. The present study examined gene expression of key biosynthetic enzymes involved in synthesis of GM1 and GD1b (*B3galt4*) and GD1a and GT1b (*St3gal2*) in residual neuromelanin-containing neurons in the PD substantia nigra (SN). Since ganglioside expression is cell type-specific, interpretation of potential gene expression changes in whole SN homogenates from PD brain could be complicated due to various factors including variable loss of SN neurons, glial responses, and signals from white matter across different samples. Thus, the current study was performed using in situ hybridization histochemistry to examine *B3galt4* and *St3gal2* gene expression in neuromelanin-containing neurons in the SN of PD patients and non-PD controls. Fresh frozen human SN samples (8 normal controls, 61-92 yrs. and 7 PD subjects, 77-95 yrs.)

were obtained through the NIH NeuroBioBank and sourced from the NICHD Brain and Tissue Bank for Developmental Disorders at the University of Maryland, the Harvard Brain Tissue Resource Center, and from the Human Brain and Spinal Fluid Resource Center, VA Greater Los Angeles Healthcare System. The clinical diagnosis of Parkinson's disease was confirmed at autopsy. Tissues were sectioned at 14 µm thickness and mounted onto Superfrost Plus slides. In situ hybridization was performed using the RNAscope 2.5 HD Chromogenic Assay kit (Advanced Cell Diagnostics, Inc.) using the manufacturer's protocol, with slight modifications. For each gene, the number of dots/cell (each dot represents a single RNA molecule) was counted on coded slides, from at least 20 cells from each case that had neuromelanin clearly visible. There were significant decreases in both *B3Galt4* and *St3gal2* gene expression in residual neuromelanin-containing SN neurons in the PD brain compared to age-matched controls. In vitro studies were then performed to examine the extent to which a decrease in *B3Galt4* gene expression affects GM1 expression and potentially influences vulnerability to neurodegeneration. Exposure of differentiated SK-N-SH dopaminergic (DAergic) cells to *B3galt4* siRNA significantly decreased GM1 expression and resulted in significant cell death in response to an exposure (10µM $MPP^+$) that previously resulted in no cell loss. These results together suggest a defect in ganglioside biosynthetic processes in SN DAergic neurons in PD that may play an important role in the pathogenesis of PD.

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**Poster**

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**Topic:** C.03. Parkinson's Disease

**Support:** CIHR

**Title:** Neuroprotection and immunomodulation of progesterone in the gut in a MPTP mouse model of Parkinson's disease

**Authors: *T. P. DIPAOLO**, H. JARRAS, M. BOURQUE, M. MORISSETTE, A.-A. POIRIER, K. COULOMBE, D. SOULET
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**Abstract:** Gastro-intestinal symptoms appear in Parkinson's disease (PD) patients many years before motor symptoms suggesting the implication of dopaminergic neurons of the gut myenteric plexus (MP). Inflammation is also known to be increased in PD. Our laboratories have previously shown neuroprotective activity of progesterone in the brain as well as estrogens in the brain and gut of the mouse model lesioned with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

(MPTP). We hypothesize that progesterone also has neuroprotective activity in the gut. The objective of the present study was thus to investigate the neuroprotection and immunomodulation of progesterone in the MP of MPTP mice. A group of adult male C57BL/6 mice were administered 2 injections/day of progesterone (1µg) or vehicle for 10 days. At treatment day 5, 4 injections of MPTP (6.5 mg/kg) or a saline solution were administered. Another group of mice received first 4 injections of MPTP (6.5 mg/kg) or a saline solution. An hour after the first and last doses of MPTP and during the 5 following days, these mice received injections of progesterone (1 µg, 8 mg/kg or 16 mg/kg). Ilea were collected on day 10 of treatment and micro-dissected to isolate the MP. These tissues were processed for immunohistochemistry in order to count dopaminergic neurons and pro-inflammatory macrophages. A loss of about 60% of dopaminergic neurons, as well as an increase of about 50% of pro-inflammatory macrophages were measured in MPTP mice compared to intact controls. These changes were completely prevented in MPTP mice treated before and after MPTP injection with progesterone at a daily dose of 1 µg and normalized with a dose of progesterone of 8 mg/kg administered after MPTP. These results are similar to those that we previously reported for various dopaminergic markers in the brain of these mice, also showing neuroprotection with progesterone given before and after the MPTP lesion with a low dose of progesterone and at a higher dose given after MPTP. In conclusion, the present results showed neuroprotective and anti-inflammatory effects of progesterone in the MP of MPTP mice and extended our previous findings in the brain with this steroid. Progesterone is non-feminizing and thus could be used for both men and women in pre-symptomatic stages of the disease, as well as at disease diagnosis since we observed beneficial effects of progesterone when starting the administration before and after the lesion.

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**Title:** Preservation of astrocyte elevated gene-1 protects dopaminergic neurons *in vivo*

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**Abstract:** The role of astrocyte elevated gene-1 (AEG-1) in nigral dopaminergic (DA) neurons has not been studied. Here, we report that the expression of AEG-1 was significantly lower in DA neurons in the postmortem substantia nigra of patients with Parkinson's disease (PD) compared to age-matched controls. Similarly, decreased AEG-1 levels were found in the 6-hydroxydopamine (6-OHDA) mouse model of PD. An adeno-associated virus-induced increase in the expression of AEG-1 attenuated the 6-OHDA-triggered apoptotic death of nigral DA neurons. Moreover, the neuroprotection conferred by the AEG-1 upregulation significantly intensified the neurorestorative effects of the constitutively active ras homolog enriched in the brain [Rheb(S16H)]. Collectively, these results demonstrated that the sustained level of AEG-1 as an important anti-apoptotic factor in nigral DA neurons might potentiate the therapeutic effects of treatments, such as Rheb(S16H) administration, on the degeneration of the DA pathway that characterizes PD.

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**Topic:** C.03. Parkinson's Disease

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**Title:** Therapeutic repurposing of dutasteride as an immunomodulatory drug for the treatment of gut inflammation in a mouse model of Parkinson's disease

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**Abstract:** Motor symptoms in Parkinson's disease (PD) are often preceded by non-motor symptoms related to dysfunctions of the autonomic nervous system such as constipation, defecatory problems and delayed gastric emptying. These gastrointestinal disorders are associated with the alteration of dopaminergic (DA) neurons in the myenteric plexus (MP) of the gut. Studies in our laboratory have demonstrated the immunomodulatory effect of female sex hormones to prevent neurodegeneration in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of enteric nervous system degeneration in PD. We also showed that the 5α-reductase inhibitor dutasteride (DUT), but not finasteride (FIN), has a protective effect in the central nervous system. The objective of this project was therefore to evaluate the neuroprotective and immunomodulatory role of FIN and DUT in the MP by increasing endogenous levels of estrogen via the inhibition of 5α-reductase, thus preventing the conversion of testosterone to dihydrotestosterone. Adult C57BL/6 male mice received 1 daily injections of FIN or DUT (5 and 12.5 mg/kg) for 10 days. On day five, 4 injections of saline or MPTP (6.5 mg/kg) were administered. The brains of these mice were previously analyzed with positive results, hence supporting the chosen doses in this experiment. On day ten, mice were killed, the ileum was fixed and microdissected to isolate the MP. Immunohistochemistry with antibodies against tyrosine hydroxylase (TH) and ionized calcium-binding adapter molecule 1 (Iba-1) were performed for stereological counting of DA neurons ($TH^+$) and macrophages ($Iba\text{-}1^+$). Also, free radicals, nitric oxide and proinflammatory cytokines produced by treatment of 1-methyl-4-phenylpyridinium ($MPP^+$) were measured in human monocytic THP-1 and DA SH-SY5Y cells. We observed a loss of about 70% of $TH^+$ neurons in MPTP mice while control levels were maintained following FIN (12.5 mg/kg) and DUT (5 mg/kg) treatments. Moreover, we measured an increase of approximately 55% in the number of macrophages in MPTP mice, while control levels were maintained with DUT treatment (5 and 12.5 mg/kg), showing a significant anti-inflammatory effect of the drug in MPTP animals. In addition, DUT inhibited generation of free radicals in monocytes and DA neurons in culture treated with $MPP^+$, while FIN had no effect. Finally, $MPP^+$-induced nitric oxide and proinflammatory cytokines production were also prevented by DUT *in vitro*. Overall, the present results demonstrate that DUT treatment prevents damages to DA neurons in the MP in a MPTP mouse model of PD, mainly through anti-inflammatory effects.

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**Poster**

**752. Parkinson's Disease: Neuroprotection**

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**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 752.14/AA7

**Topic:** C.03. Parkinson's Disease

**Support:** Parkinson Canada

**Title:** Effect of the anti-depressant nefazodone on dyskinesia and psychosis in the MPTP-lesioned common marmoset

**Authors: *P. HUOT**[1], S. G. NUARA[3], D. BÉDARD[2], I. FROUNI[4], C. KWAN[1], J. C. GOURDON[3], A. HAMADJIDA[5]
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**Abstract:** The path to bring new drugs to the clinic is long and costly, with very few candidates eventually being granted approval. Drug repositioning, the process by which drugs currently on the market for a given condition, might be useful for diseases other than their primary indication, is a way to expand the therapeutic tools against certain diseases, at a faster pace and a much lower cost. Here, we hypothesised that the clinically-available anti-depressant nefazodone, which bears affinity for serotonin 1A and 2A (5-$HT_{1A}$and 5-$HT_{2A}$) receptors, would alleviate L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesia and psychosis-like behaviours (PLBs) in Parkinson's disease (PD), and assessed its benefit in the parkinsonian marmoset. Six common marmosets were rendered parkinsonian by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration. Following repeated administration of L-DOPA to elicit stable PLBs and dyskinesia, they were administered acute challenges of nefazodone (0.01, 0.1, 1 mg/kg) or vehicle, in combinaison with L-DOPA, after which motor activity was automatically detected and the severity of dyskinesia, PLBs and parkinsonian disability is being rated by a blinded observer. Analysis of motor activity reveals that nefazodone does not alter L-DOPA-induced motor activity. Full analysis of the effect of nefazodone on dyskinesia and PLBs is on-going and will be presented at the conference. However, at this stage, that nefazodone has no effect on motor activity suggests that it does not interfere with the anti-parkinsonian action of L-DOPA and that, conditional to anti-dyskinetic and/or anti-psychotic efficacy, it could be offered to alleviate symptoms of PD patients.

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**Poster**

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Fonds d'Enseignement et de Recherche de la Faculté de Pharmacie de l'Université Laval

**Title:** Neurorestorative effects of a combination of exercise and DHA intake in a mouse model of Parkinson's disease

**Authors: *O. KERDILES**[1,2,3,4], K. COULOMBE[2], C. TREMBLAY[2], V. ÉMOND[2], C. ROUXEL[2], M. SAINT-PIERRE[2], M. J. ZIGMOND[5], F. CICCHETTI[6,2], F. CALON[1,2,3,4]
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**Abstract:** Parkinson’s disease (PD) is characterized by a loss of dopamine (DA) neurons in the substantia nigra pars compacta (SNpc) and a decrease of their projections to the striatum. Previous studies in our laboratory have shown that a n-3 polyunsaturated fatty acids (n-3 PUFA) enriched diet prevents DAergic denervation in the MPTP mouse model. More recently, we found that n-3 PUFA dietary intake also exerts partial neurorestorative effects after an extensive 6-hydroxydopamine(6-OHDA)-induced lesion of the DAergic system. Since preclinical and clinical studies hint towards benefit of exercise in PD, we investigated whether the neurorestorative action of n-3 PUFA synergistically interacts with exercise to induce recovery of the nigrostriatal pathway. Male C57/BL6 mice were unilaterally lesioned by stereotactic injection of 6-OHDA, a toxic analog of dopamine, to induce a ~50% dopaminergic denervation, as confirmed with HPLC and Tyrosine hydroxylase (TH)-immunochemistry. Four (4) weeks following the lesion, animals were fed either a docosahexaenoic acid (DHA)-enriched or a control diet. At the same time, half of the mice underwent an exercise regimen (a free-access wheel). The treatments lasted 7 weeks until sacrifice. The mice performed an average number of 7823±236 wheel revolutions in 12h during the night and no significant difference was observed between lesioned and non-lesioned animals. Neither DHA or exercise altered the total travelled distance in the open field test, nor the percentage of unclockwise rotations following apomorphine administration. In the stepping test, however, an increase in the use of contro-lateral forepaw (vs. ipsilateral) was observed in lesioned animals exposed to both DHA and voluntary exercise compared to lesioned animals under either one of the treatments only. Although the combination of DHA and exercise did not improve the number of TH-positive cells in the SNpc, HPLC analysis revealed that DHA intake led to higher DA content in the striatum of 6-OHDA lesioned animals. Furthermore, the striatal rise in DOPAC/DA ratio observed in 6-OHDA-treated mice was prevented by exposition to both DHA and exercise. Our results support our previous report of partial neurorestorative effects of dietary DHA and suggest that the combination of voluntary exercise and DHA may improve additional motor behavioral components and reduce dopamine turnover.

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**Poster**

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**Topic:** C.03. Parkinson's Disease

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**Title:** Voluntary physical exercise improves subsequent motor impairments in a MitoPark mouse model of Parkinson's disease

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**Abstract: Aim:** Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease and is likely to impose an increasing social and economic burden on societies. It involves problems of movement, emotions, and cognition, affecting over 10 million people worldwide . Although a good deal is known about the pathophysiology of the disease, and information is emerging about its cause, there are no pharmacological treatments shown to have a significant, sustained capacity to prevent or attenuate the condition. Such treatments are urgently needed. Accumulating clinical evidence suggests that physical exercise is such a treatment, and studies of animal models of the DA deficiency associated with the motor symptoms of PD further support this hypothesis. Moreover, exercise is a non-pharmacological, economically practical, and sustainable intervention with little or no risk and with significant additional health benefits. In this study, we investigated the long-term effects of voluntary running wheel exercise on motor behavior as well as histology in a MitoPark mouse model of PD. **Methods:** The PD animals were separated into two groups, exercise (at the age of 6 weeks) and non-exercise, for evaluating the effects of voluntary running wheel exercise. For behavioral assessments, animals were subjected to novel object recognition test, beam walking, and rotational test. The dopamine neuron density was measured by dopamine transporter PET ([$^{18}$F]-FE-PE2I/ PET). The measurement of mitochondrial bioenergetics was performed with Seahorse XF systems. In addition, the molecular mechanisms of exercise on DA neuronal function were evaluated by immunohistochemistry and western blot analysis.
**Results:** We observed that, when compared with the non-exercise controls, four-week voluntary exercise improved the motor function, including a significantly improved beam walking speed and the latency on rotarod. However, the preference index on novel object recognition did not improved after exercise treatment. Furthermore, dopamine neuron density was higher in exercise treatment group, and the mitochondria dysfunction was also improved.

**Conclusions:** We first investigated the potential benefits after long-term exercise in the MitoPark mouse model of PD. Our findings suggest that long-term voluntary exercise reduces the progression of motor symptoms, preserves DA fibers, and elevates DA markers but does not prevent DA neuron loss in this PD mouse model.

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**Poster**

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**Topic:** C.03. Parkinson's Disease

**Support:** NSERC Discovery
Donation

**Title:** Progression of Parkinson's disease symptoms halted using dance over 3-years as assessed with MDS-UPDRS

**Authors: *J. F. DESOUZA**[1], K. A. BEARSS[2]
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**Abstract: OBJECTIVE:** To determine the overall progression of motor, non-motor, and resting state electroencephalography (rsEEG) changes of Parkinson's Disease (PD) while participating in Dance for Parkinson's classes in Toronto. Our aim is to examine and potentially construct brain-related plasticity mechanism(s) as a function of dance using multimodal neuroimaging. **RATIONALE:** PD is characterized as a chronic, progressive, degenerative disease with deteriorating motor and non-motor function as well as a loss of nigrostriatal dopaminergic neurons ultimately increasing disability while creating a deficiency of dopamine in the striatum. Data suggests a fast progression of motor dysfunction within the first 5 years, with annual rates of progression of the UPDRS III (motor) score from 5.2-8.9 points. About 40-50% of dopaminergic neurons are lost within the first decade, causing excessive inhibition of thalamo-cotical nuclei via the direct and indirect striato-pallidal pathways. Areas which have been hypothesized to be involved with alpha rhythm organization, where people with PD (PwPD) have been shown to have lower individual alpha peak frequency. **METHODS:** 16 PwPD, mild-severity ($M_{H\&Y}$= 1.25, SD= 0.86), ($M_{age}$= 68.73, $SD$= 8.41, $N_{Males}$= 11, $M_{DiseaseDuration}$= 5.54, $SD$= 4.52) were tested before and after participating in dance class (Dance for PD®) using the standardized MDS-UPDRS (I-IV), H&Y, PANAS-X, MMSE, PD-NMS and rsEEG over 3 years. **RESULTS:** rsEEG global alpha power was highest after a single dance class in comparison to before, $F(1,26) = 6.928$, $p < .025$, $\eta 2 = .210$. There is no motor impairment (UPDRS part III)

progression of PD across 3-years ($p$ = .817). In addition, non-motor aspects of daily living (UPDRS part I), motor experiences of daily living (UPDRS part II) and motor complications (UPDRS part IV) show no significant impairment ($p$ = .329), ($p$ = .540), and ($p$ = .390) after 3 years of dancing once a week, respectively. We found the annual rate of decline in the motor function scores to be zero (slope=0.000146). **CONCLUSION:** Our results indicate positive benefits of dance for motor, non-motor and neural changes in PD. Previous longitudinal studies suggest a 5.2-8.9-point annual decline in motor function whereas our cohort suggests that the annual motor impairment is drastically lower, indicating participation in dance may delay the progression of motor impairment. These findings continue to support the benefits of dance in PwPD over three years.

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**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

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**Program #/Poster #:** 753.01/AA11

**Topic:** C.03. Parkinson’s Disease

**Title:** Neurodegeneration and locomotor dysfunction in *Drosophila* scarlet mutants

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**Abstract:** Parkinson’s Disease (PD) is characterized by the loss of dopaminergic neurons, resulting in progressive locomotor dysfunction. Identification of genes required for the maintenance of these neurons should help to identify potential therapeutic targets. However, little is known regarding the factors that render dopaminergic neurons selectively vulnerable to PD. Here we show that *Drosophila melanogaster scarlet* mutants exhibit an age-dependent progressive loss of dopaminergic neurons, along with subsequent locomotor defects and a shortened lifespan. Knockdown of Scarlet specifically within dopaminergic neurons is sufficient to produce this neurodegeneration, demonstrating a unique role for Scarlet beyond its well-characterized role in eye pigmentation. Both genetic and pharmacological manipulation of the kynurenine pathway rescued loss of dopaminergic neurons by promoting synthesis of the free radical scavenger Kynurenic Acid (KYNA) and limiting the production of the free radical generator 3-hydroxykynurenine (3-HK). Finally, we show that expression of wild-type Scarlet is neuroprotective in a model of PD, suggesting that manipulating kynurenine metabolism may be a potential therapeutic option in treating PD.

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**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

**Location:** SDCC Halls B-H

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**Topic:** C.03. Parkinson's Disease

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**Title:** Pramipexole induces autophagy through a D3R-dependent D2R-independent mechanism and mTORC1 inhibition without affecting translation

**Authors: *T. GONZÁLEZ-HERNÁNDEZ**[1], F. FUMAGALLO-READING[2], D. LUIS-RAVELO[2], P. BARROSO-CHINEA[2], J. CASTRO-HERNANDEZ[2], V. MESA-INFANTE[2], D. AFONSO-ORAMAS[2], J. RODRIGUEZ-RUIZ[2], J. LOPEZ-FERNANDEZ[2], I. CRUZ-MUROS[2], P. ABREU-GONZALEZ[2], A. FEBLES-CASQUERO[2], J. SALAS-HERNANDEZ[2]
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**Abstract:** Growing evidence indicates that autophagy induction may have beneficial effects on neurodegenerative and psychiatric diseases. However, autophagy also shares signaling pathways with cell death. Therefore, prolonged use of autophagy inducers may also have serious consequences for cellular homeostasis. Recent studies indicate that dopamine D2R/D3R ligands may modulate autophagy, but mechanisms underlying the interaction between D2R and D3R and the autophagy machinery are still unknown. Here D2R and D3R overexpressing cells, and $D2R^{-/-}$, $D3R^{-/-}$ and wild-type mice were treated with pramipexole, a D2R/D3R agonist used in the treatment of Parkinson's disease and which has antidepressant effects. Assessment of autophagy markers and phosphorylation of mTOR and its downstream target p70S6K reveals that prolonged pramipexole treatment activates autophagy through mTORC1 inhibition mediated by a D3R-dependent D2R-independent mechanism. Given the differential distribution of D2R and D3R in the brain, the fact that autophagy is selectively activated by $D_3R$ directs our interest to compounds acting on specific neuronal populations through precise ligand-receptor interactions and signaling mechanisms. Interestingly, the activity of mTORC1 targets involved in translation, ribosomal protein S6 and 4E-BP1, along with cell viability, were preserved. This pattern of

mTORC1 inhibition contrasts with that of direct allosteric and catalytic mTOR inhibitors. Taken together, these findings open up new opportunities for G-protein coupled receptor ligands as autophagy inducers in the treatment of neurodegenerative and psychiatric diseases.

**Disclosures: T. González-Hernández:** None. **F. Fumagallo-Reading:** None. **D. Luis-Ravelo:** None. **P. Barroso-Chinea:** None. **J. Castro-Hernandez:** None. **V. Mesa-Infante:** None. **D. Afonso-Oramas:** None. **J. Rodriguez-Ruiz:** None. **J. Lopez-Fernandez:** None. **I. Cruz-Muros:** None. **P. Abreu-Gonzalez:** None. **A. Febles-Casquero:** None. **J. Salas-Hernandez:** None.

**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

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**Title:** A DJ-1, PD related gene, regulates the astrogliosis for repair of injured brain

**Authors: *D.-J. CHOI**[1,2], E.-H. JOE[1,2,3]
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**Abstract:** In injured brain, astrocytes become activated and contribute to repair of the injury. Here, I report that DJ-1 positively regulates repair of injured brain. MRI analyses shows delayed repair of brain damage in DJ-1-knockout (KO) mice compared with wild-type (WT) mice. Accordingly, in injured KO brain, astrocytes become less reactive and fill damaged areas more slowly, and recovery of tyrosine hydroxylase-positive neurites is delayed. However, in pure cultures, neurite outgrowth of damaged DJ-1-KO neurons is comparable to that of WT neurons. Expression levels of GDNF and BDNF are lower in astrocytes in DJ-1-KO brain and slice cultures. Expectedly, WT slice culture conditioned media (SCM) exerts stronger effects on neurite outgrowth than KO-SCM. These results suggest that DJ-1 deficiency may contribute to the development of PD by attenuating astrocyte-mediated repair of brain damage.

**Disclosures: D. Choi:** None. **E. Joe:** None.

**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

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**Topic:** C.03. Parkinson's Disease

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**Title:** Ciliary neurotrophic factor inhibits microglia-derived oxidative stress and protects dopamine neurons from $MPP^+$ neurotoxicity *in vivo*

**Authors: *J. BAEK**[1], J. JEONG[1], K. KIM[1], Y. CHUNG[2], B. JIN[2]
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**Abstract:** We previously showed that capsaicin (CAP), an agonist of transient receptor potential vanilloid subtype 1 (TRPV1), inhibits microglia activation and microglia-derived oxidative stress in the substantia nigra (SN) of $MPP^+$-lesioned rat. However, the detailed mechanisms how to regulate microglia-derived oxidative stress by CAP remain determined. Here we report that ciliary neurotrophic factor (CNTF) produced by CAP-activated TRPV1 on astrocytes, but not microglia inhibits microglia-derived oxidative stress through the CNTF receptor alpha (CNTFRα) located on microglia, which rescues dopamine neurons in the SN of $MPP^+$-lesioned rats and ameliorates amphetamine-induced rotations. Immunohistochemical analysis revealed a significant increase in levels of CNTFRα expression on microglia in the SN of tissue from humans with Parkinson's disease (PD) compared with age-matched controls, indicating that these findings may have relevance to this disease. Our results describe for the first time that CNTF endogenously produced by CAP-activated TRPV1 on astrocytes, not microglia inhibits microglia activation and microglia-derived oxidative stress *in vivo* and rescues dopamine neurons in a $MPP^+$-lesioned rat model of PD. These data suggest that TRPV1 on astrocytes may be a beneficial target in the treatment of neurodegenerative disease associated with neuroinflammation such as PD.

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**Program #/Poster #:** 753.05/BB4

**Topic:** C.03. Parkinson's Disease

**Title:** The adaptive defense mechanism associated with HFE genotype and its response to paraquat-induced toxicity

**Authors: *I. SONG**[1], A. M. SNYDER[4], B. NEELY[2], J. R. CONNOR[3]
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**Abstract:** Past research studies have identified the link between environmental toxins and mitochondrial dysfunction in Parkinson's disease. Recently, our laboratory reported protection from paraquat-induced motor impairment and cellular changes in HFE (H67D) mutant mice. The HFE protein regulates iron uptake by interacting with the transferrin receptor. Based on our previous study, we hypothesize that an antioxidant defense system is elevated in association with the HFE mutation. The candidate proteins chosen to begin to examine this hypothesis are Nrf2, cytosolic ferritins, and GSH. Because the Nrf2 pathway is preferably activated in astrocytes, we hypothesize that the HFE mutant astrocytes are responsible for the proposed neuroprotection. We performed immunostaining on primary astrocytes in cell culture that revealed an increase in both NRF2 and L-ferritin staining in the HFE mutant astrocytes compared to WT astrocytes at baseline. Paraquat treatment induced a loss of mitochondrial membrane potential as measured by TMRE assay in astrocytes of both genotypes, but the decrease in WT astrocytes (30%) was greater than that in the HFE mutant astrocytes (20%). Furthermore, paraquat exposure resulted in a greater increase in the astrocytic senescence marker B-galactosidase in the WT (300% increase) cells compared to H67D astrocytes (150% increase). To further elucidate the role of HFE mutant astrocytes in neuroprotection against paraquat-induced toxicity, we have developed a SH-SY5Y neuroblastoma model that is stably transfected with WT or H63D HFE and is further differentiated to express DAT, which is critical for paraquat uptake. Exposure to low dose (100uM) paraquat did not affect the viability of HFE mutant SH-SY5Y cells but decreased the WT SH-SY5Y cells by 20%. However, the WT and HFE mutant cells were equally affected (30% cell death) by a higher dose (200uM) of paraquat. To examine the interaction between astrocytes and neurons, astrocytes were treated with a sublethal dose of paraquat, and then the conditioned media from the paraquat-treated astrocytes was added to the neuronal cultures. A significant decrease in the viability of the WT SH-SY5Y cells was observed after treatment with WT astrocyte conditioned media (9% decrease), but there was no effect when the WT SH-SY5Y cells were treated with H67D astrocyte conditioned media. The results of our study suggest that there is a difference in vulnerability to paraquat toxicity associated with HFE genotype. The data further suggest that the difference in vulnerability is mediated by astrocytes that have adapted to the mutation by activating their antioxidant defense system.

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**Poster**

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**Title:** Increased ATP-derived extracellular adenosine is responsible for the over-activation of adenosine $A_{2A}$ receptors causing neurodegeneration in 6-OHDA-hemiparkinsonian rats

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**Abstract:** Parkinson's disease (PD) involves an initial loss of striatal dopaminergic terminals evolving into a degeneration of dopaminergic neurons in the substantia nigra (SN), which can be modeled by 6-hydroxydopamine (6-OHDA) administration. The blockade of adenosine $A_{2A}$ receptor ($A_{2A}R$) attenuates PD, but the source of the adenosine responsible for $A_{2A}R$ over-activation is unknown. Since ATP is a general danger signal, we now tested if the extracellular catabolism of adenine nucleotides into adenosine (through ecto-5'-nucleotidase or CD73) is responsible for $A_{2A}R$ over-activation in PD. In dopamine-differentiated neuroblastoma SH-SY5Y cells, 6-OHDA bolstered ATP release (from 5 minutes up to at least 6 hours) and its extracellular conversion into adenosine through an up-regulation of CD73. This CD73/$A_{2A}R$ up-regulation was a precocious event, occurring 2 hours after exposure to 6-OHDA, thus pre-dating SH-SY5Y cell dysfunction. Removing extracellular adenosine with adenosine deaminase (2 U/mL), blocking CD73 with α,β-methylene ADP (AOPCP, 100 μM) or blocking $A_{2A}R$ with SCH58261 (100 nM) were equi-effective to prevent 6-OHDA-induced dysfunction and damage of SH-SY5Y cells. *In vivo* striatal unilateral exposure to 6-OHDA increased $K^+$-evoked ATP release and the extracellular formation of adenosine from adenosine nucleotides and up-regulated CD73 and $A_{2A}R$ selectively in synapses, but not in total membranes. Intracerebroventricular administration of AOPCP (100 μM, continuous exposure) phenocopied the effect of SCH58261 (0.1 mg/kg, ip), attenuating 6-OHDA-induced: 1) increase of contralateral rotations in the apomorphine test; 2) reduction of dopamine content in striatum and SN; 3) loss of tyrosine

hydroxylase staining in striatum and SN; 4) motor dysfunction in the cylinder test; 5) short-term memory impairment in the object recognition test. This suggests that increased ATP-derived adenosine formation is responsible for $A_{2A}R$ over-activation in early PD, prompting CD73 as a new target to manage PD.

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**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 753.07/BB6

**Topic:** C.03. Parkinson’s Disease

**Support:** the National Natural Science Foundation of China81371408
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**Title:** Promoter identification and transcriptional regulation of the anti-inflammation gene cd200r1 in Parkinson's disease

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**Abstract:** Recent researches have been shown that abnormal activation of microglia plays an important role in pathogenesis of Parkinson's disease (PD). Microglia are normally inhibited in a stationary state almost by the contact inhibition between neuron and microglia. This contact inhibition recently has been found closely related to the interaction between CD200 (located in neuron) and its receptor CD200R1 (located in microglia). Normally, CD200R1 upregulates to increase CD200-CD200R1 inhibit signaling thus preventing microglia from overactivating when brain being attacked. Our previous studies showed, however, expression of CD200R1 could not increase in PD when received inflammation stimulation, which means abnormal regulation of CD200R1 expression happens in PD. However, no information about the regulatory element of the CD200R1 gene and its transcriptional regulation has been reported so far. Here we identified the CD200R1 promoter using a promoter luciferase construct that directs transcription of CD200R1. Our results show that the region from -485 to -267 (first base of CDS is +1) constitutes the core promoter and harbors motifs for the binding of NFKB1 as validated by analysis websites JARSPAR and P-MATCH. Knock down of NFKB1 dropped the promoter activity of CD200R1. Using chromatin immunoprecipitation assay and EMSA, we demonstrated the physical interaction of NFKB1 to the CD200R1 core promoter sequence. In human

peripheral blood mononuclear cell (PBMC), expression levels of NFKB1 correlated significantly to CD200R1 (P< 0.0001). Knock down of NFKB1 reduced CD200R1 expression in PBMC (P < 0.0001). Importantly, LPS stimulation led to increase expression of CD200R1 which was prevented when knock down of NFKB1 in human PBMC. Meanwhile, levels of NFKB1 showed a decrease in PD patients (P< 0.001). This is the first study identifying the CD200R1 promoter and its transcriptional regulation by NFKB1. Knowledge of the transcriptional regulation of the CD200R1 gene will implicate in enhanced understanding of its role in pathogenesis of PD.

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**Poster**

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**Location:** SDCC Halls B-H

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**Program #/Poster #:** 753.08/BB7

**Topic:** C.03. Parkinson’s Disease

**Support:** NIH Grant P30 DK063491

**Title:** Small molecule recovery of mitochondrial injury by DOPAL-treated α-synuclein

**Authors: *J. B. WATSON**, A. YACOUB, A. KUNZ, B. ARANKI, G. SEROBYAN, W. COHN, J. P. WHITELEGGE, T. A. SARAFIAN
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**Abstract:** We previously reported that overexpressed human α-synuclein can disturb mitochondrial function (Sarafian et al., 2013, PLoS One 8(5):e63557), but it was not clear which proteoform (monomer, oligomer, fibril?) was the active toxin. Since α-synuclein amyloid oligomers are likely the most neurotoxic form in Parkinson’s Disease (PD), the dopamine breakdown product, 3, 4-dihydroxyphenylacetaldehyde (DOPAL), was used to generate oligomeric α-synuclein from recombinant protein preparations [Watson et al (2017) Soc Neurosci Abstr 131.13]. DOPAL-oligomeric α-synuclein (DOS) significantly reduced by 15-30% the membrane potential in mitochondria isolated from mouse forebrain using fluorescent probes (JC-1, TMRM). Importantly, after survey of a large list (50 or more) of commercially available small molecules known to modulate mitochondrial function, multiple unrelated compounds provided complete recovery of DOS-induced mitochondrial injury. Additional HPLC/mass spectrometry studies by combined top-down/intact protein and bottom-up approaches showed that the mitochondrial inhibitory form of DOS is highly oxidized and contains multiple catechol and quinone covalent modifications. The results suggest that mitochondrial injury in brain cells, such as those in substantia nigra’s pars compacta containing dual high levels of DOPAL and α-synuclein, can be selectively rescued by cocktails of known small molecules. Experiments in progress seek to identify additional small molecules for rescue

and can provide additional clues to the mitochondrial targets of DOS injury. Overall the studies highlight DOPAL-mediated structural modification of α-synuclein as a possible mechanism underlying PD neuropathology.

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**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 753.09/BB8

**Topic:** C.03. Parkinson’s Disease

**Title:** Rapid influx of extracellular $Zn^{2+}$ into substantia nigra pars compacta via AMPA receptor causes of paraquat-induced Parkinson’s disease

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**Abstract:** Neurodegenerative disorders like Parkinson's disease (PD) are said to be caused by oxidative stress. Exposure to environmental agents such as herbicide paraquat (PQ) has been reported that acting as a reactive oxygen species (ROS) generator and been implicated in sporadic PD from epidemiological studies. Here we first report a novel mechanism of nigrostriatal dopaminergic neurodegeneration, in which rapid dysregulation of intracellular $Zn^{2+}$ via PQ-induced ROS production causes PD in Rats. We have used the microdialysis technique to perfuse PQ (3 μg/μL) in the rat's Substantia Nigra pars compacta 4h after the implantation of a microdialysis probe. During the perfusion of PQ (3 μg/μL), the extracellular glutamate and $Zn^{2+}$ levels were respectively increase and decrease in the SNpc. These changes were ameliorated by the co-perfusion with Trolox, an antioxidative agent. Accordingly, we demonstrated in vivo slice experiments. PQ (3 μg/μL) injection caused the increase of intracellular $Zn^{2+}$ and ROS levels in the SNpc. In vitro slice experiments showed that rapid PQ (3 μg/μL) exposure occurred increasing extracellular $Zn^{2+}$ influx via AMPA receptor activation. Immunohistochemical analysis showed that PQ (3 μg/μL) injection in the SNpc lost tyrosine hydroxylase (TH) and increased of turning behavior to apomorphine. These dopaminergic neurons degeneration were markedly reduced by co-injection of PQ and intracellular $Zn^{2+}$ chelator, i.e., ZnAF-2DA into the SNpc. Furthermore, surprisingly loss of nigrostriatal tyrosine hydroxylase induced with a low dose of PQ (10 ng/μL), which did not induce any behavioral abnormality, was completely blocked by co-injection of ZnAF-2DA. Increasing of Intranigral $Zn^{2+}$ levels by the low dose of PQ (10 ng/μL) was also completely blocked by extracellular $Zn^{2+}$ chelator and antioxdative agent i.e., Ca-EDTA and Trolox. Taking into account all of the results, Intracellular $Zn^{2+}$ dysregulation

in dopaminergic neurons by the PQ is the cause of PQ-induced PD in Rats and the block of intracellular $Zn^{2+}$ toxicity leads to overcoming PQ-induced pathogenesis.

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**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 753.10/BB9

**Topic:** C.03. Parkinson's Disease

**Support:** Michael J. Fox Foundation

**Title:** Brain insulin distribution in rats following intranasal application

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**Abstract:** Background: Our previous work showed that intranasal insulin is neuroprotective in a 6-hydroxydopamine-based rat model of Parkinson's Disease (PD). The aim of this study was to assess brain insulin pharmacokinetics in rats following intranasal application. Methods: Male adult rats were anesthetized with isoflurane and recombinant human insulin was administrated to both side of nostrils (20 ug each). At 15 min, 1, 2, and 6 h, rats were perfused intracardially with ice-cold PBS and brain tissue from the olfactory bulbs, striatum, thalamus, hippocampus, subtantia nigra (SN) plus ventral tegmental area (VTA), cerebellum, brainstem, and cerebral cortex were dissected for insulin measurement. Control rats were given intranasal PBS (vehicle). A total of 6 rats were included in each group. Insulin was detected by an ultrasensitive, human-specific ELISA kit, and insulin levels was expressed as pg/mg wet tissue. Data were analyzed by two-way ANOVA followed by Bonferroni post-hoc test. For microscopic study, rats were given intranasal fluorescence-tagged insulin (Ins-Alex546). Results: Insulin was detected in a wide range of brain regions, with highest levels at 15 min in all regions ($p<0.05$ vs control) except the cerebral cortex ($p>0.05$ vs control). The brainstem retained the highest levels, followed by SN-VTA, olfactory bulb, striatum, hippocampus, and thalamus. The level of Insulin decreased overtime and at 2 h, it remained significantly higher in the olfactory bulb and brainstem but not other regions. By 6 h, insulin levels declined to the control level ($p>0.05$). Consistent with ELISA data, Ins-Alex546-binding cells were found widespread in the brain 15 min following intranasal administration. The olfactory bulb and brainstem showed highest density of Ins-Alex546-binding cells, while the cerebral cortex especially the superficial layer showed very little fluorescence. Those Ins-Alex546-binding on cell membrane was confirmed by immunostaining with anti-human insulin antibody. Moreover, Ins-Alex546 binding was exclusively co-localized with NeuN immunoreactivity, indicating that insulin binds exclusively

to neurons but not glial cells. Double labeling of tyrosine hydroxylase (TH) and pAkt showed that the Akt/PI3K signaling was activated in a subset of dopaminergic neurons in the SN. Conclusion: Intranasal insulin could be rapidly distributed into brain including the SN via olfactory and trigeminal pathways.

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**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

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**Topic:** C.03. Parkinson's Disease

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**Title:** Chemically modified tetracycline (CMT) inhibits alpha-synuclein amyloid fibers formation and neuroinflammation

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**Abstract:** Parkinson's disease related death of dopaminergic neurons has been linked to pathological aggregation of alpha-synuclein protein and its transcellular traffic through the dopaminergic system. Tetracyclines, such as minocycline and doxycycline have been shown to be neuroprotective in Parkinson's disease animal models. Neuroprotective activities of minocycline have been attributed to its inhibitory effects on microglia activation. On the other hand, doxycycline has been shown to protect cells by inhibiting the formation of toxic alpha synuclein species. However, the antibiotic activity of these compounds limit their prescription for chronic treatments such as neurodegenerative disorders. Thus, chemically modified tetracyclines with diminishing or reduced antibiotic activity could represent a more adequate therapy for long-term treatments. In this regard, it was recently reported that the chemically modified tetracycline lacks antibiotic activity but retains anti-inflammatory effects. In the present study we evaluate the ability of CMT inhibit alpha-synuclein aggregation using different biophysical techniques such as fluorescence techniques, SAXS and advanced microscopies. In

addition, we evaluate the ability of CMT to modulate the inflammatory response of microglial cultures mediated by different inflammogenic compounds and we demonstrate that CMT inhibits cytokine production and Iba-1 release, as well as expression of prototypical markers of microglial activation. Considering that incyclinide has reduced antibiotic activity compared to other tetracyclines and is a well tolerated drug according to cancer-related Phase I clinical trials, we conclude that it could be a “ready to use drug”. Due to its ability to diminish toxic aggregation of alpha synuclein as well as neuroinflammatory processes, we propose CMT is poised as an promising candidate for Phase I clinical trials in neuroprotection.

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**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

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**Topic:** C.03. Parkinson’s Disease

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**Title:** A cell-specific iron suppressor exhibits neuroprotection in 6-ohda-induced pd model

**Authors: *M.-D. MU**[1,2], K.-L. RONG[1,2], X.-B. QU[1], Z.-M. QIAN[3], W.-H. YUNG[1,2], Y. KE[1,2]
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**Abstract:** Recent findings have highlighted the critical roles of iron accumulation and iron-induced oxidative stress in the pathogenesis of Parkinson's disease (PD). Removing accumulated iron and reducing oxidative stress are potential therapeutic strategies for PD. We discovered that GSK-J4, a histone demethylase inhibitor with the ability to cross blood brain barrier, is a potent iron suppressor, and may therefore exert beneficial effect on PD. We found that, in vitro, only a trace amount of GSK-J4 could significantly and selectively suppress cellular iron in the dopaminergic SH-SY5Y and MES23.5 cells but not in HEK293 and HepG2 cells. Importantly, GSK-J4 prevented 6-OHDA-induced cell death and apoptosis in PD cell model, and rescued dopamine neuronal loss and motor defects in 6-OHDA-induced PD rats and MPTP-induced PD mice. These effects were accompanied by inhibition of the increase in various reactive oxygen

species in 6-OHDA models. Consistently, GSK-J4 suppressed $H_2O_2$-induced cell death in SH-SY5Y cells. Further experiments showed that GSK-J4 rescued the abnormal changes of histone methylation (H3K27me3 and H3K4me3) and iron metabolism during 6-OHDA-treatment. The effects of GSK-J4 on iron metabolism and neuroprotection were suppressed by inhibitor of H3K4me3 but not inhibitor of H3K27me3. These results imply that upregulation of H3K4me3 caused by GSK-J4 treatment is involved in cell-specific regulation of iron metabolism and the subsequent antioxidant effect. Therefore, GSK-J4 is a potentially useful compound in suppressing PD pathogenesis.

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**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

**Location:** SDCC Halls B-H

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**Topic:** C.03. Parkinson’s Disease

**Support:** NRF-2017R1A2B4008456
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**Title:** Tubacin, an HDAC6 inhibitor, induced neuroprotective effects in MPTP mice

**Authors: *Y. PARK**, S. SONG, T. KIM, J. KIM, H. SEO
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**Abstract:** Parkinson’s disease (PD) is caused by selective vulnerability of dopaminergic neurons in substantia nigra (SN). As an external cause, MPTP [1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine] targets specifically those dopaminergic neurons involved in PD pathology. Histone deacetylase (HDAC) has critical function to unwrap DNA from histone by deacetylation and regulates specific gene expression for cell fate determination. As administration of HDAC inhibitors has been reported as potential therapeutic target in several neurodegenerative diseases. We hypothesized that inhibition of HDAC6 (class IIB HDAC) with tubacin induces neuroprotection in MPTP PD mouse model. We found that tubacin significantly improved motor balance in MPTP mice. Tubacin increased the number of tyrosine hydroxylase (TH)-positive dopaminergic neurons in the SN regions and reduced the expression of proinflammatory markers. These results suggest that tubacin could be used to study neuroprotection mechanism and future therapeutic application for PD.

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**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

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**Topic:** C.03. Parkinson's Disease

**Support:** Branfman Family Foundation
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**Title:** Neuroprotective role of the transcription factor Nfe2L1 in PD models

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**Abstract:** Parkinson's disease is a complex neurodegenerative disorder characterized by the presence of alpha-synuclein (aSyn)-positive protein aggregates called Lewy bodies and the selective death of dopaminergic neurons in the substantia nigra region of the brain. Multiple cellular pathways that are dysregulated in PD have been identified, including protein clearance systems and oxidative stress responses. Manipulation of these systems by environmental insults or genetic perturbations causes increased aggregation of aSyn, which in turn causes increased oxidative and proteasomal stress, generating a vicious cycle culminating in the death of dopaminergic neurons. Thus, strategies to enhance protein clearance and antioxidant responses have the potential to reduce aSyn aggregation and halt neurodegeneration. Nuclear factor erythroid-derived 2-related factor 1 (Nfe2L1) is an ER associated transcription factor that translocates to the nucleus under conditions of proteasomal inhibition. Once in the nucleus, NFE2L1 upregulates the expression of Antioxidant Response Elements (ARE)-regulated genes, including genes involved in glutathione biosynthesis and proteasome assembly. Nfe2L1 has been recently shown to be downregulated in the brains of PD patients, and knockdown of Nfe2L1 causes sensitization to oxidative and proteotoxic stress. We identified a SNP associated with Nfe2L1 as one of the most significant hits in a PD GWAS meta-analysis study. Based on these observations, we hypothesize that Nfe2L1 protects against neurotoxicity elicited by PD-related insults by alleviating oxidative stress and proteasomal dysfunction. Consistent with this idea, we have found that Nfe2L1 is expressed in rat midbrain dopaminergic neurons and is upregulated

upon treatment with proteasome inhibitor MG132 in rat primary midbrain cultures. Current efforts are focused on examining effects of Nfe2L1 expression on neurotoxicity in cellular models relevant to PD (e.g. primary midbrain cultures and human iPSC-derived dopaminergic neurons over-expressing aSyn or exposed to the PD-related toxin rotenone) and in the rat rAAV model. The data from these studies will yield insight into neuroprotective effects of Nfe2L1 in PD models and set the stage for developing therapies that enhance Nfe2L1 function in the brains of PD patients.

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**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

**Location:** SDCC Halls B-H

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**Topic:** C.03. Parkinson’s Disease

**Support:** NCTR protocol E751201.

**Title:** Neuroprotective effect of the acetyl-L-carnitine (ALC) in a chronic MPTP-induced Parkinson’s disease mouse model

**Authors: *S. M. LANTZ**[1], E. CUEVAS[1], J. RAYMICK[1], B. ROBINSON[1], J. HANIG[2], S. SARKAR[3]
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**Abstract:** Parkinson's disease (PD) is a progressive motor disease of unknown etiology. The clinical features of PD emerge due to selective degeneration of dopamine (DA) neurons in the substantia nigra pars compacta (SNc), which project to the caudate putamen (CPu) where they release DA. In the current in vivo mouse model study, we tested acetyl-L-carnitine (ALC) for its ability to protect against 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced damage to DA neurons. ALC is an acetylated form of L-carnitine and is found as a small water-soluble peptide located in mitochondria. It is naturally produced in vivo and is often taken as a dietary supplement. ALC has a carnitine moiety which is important for the oxidation of fatty acids and an acetyl moiety that is required for the maintenance of acetyl-CoA levels and can promote the production of the antioxidant glutathione. Studies suggest that ALC can easily cross the blood-brain barrier. In the present study, we investigated whether ALC treatment can ameliorate the pathology seen in a chronic MPTP-induced PD mouse model. There were four treatment groups: probenecid only (250mg/kg, i.p; control), MPTP (25mg/kg-10 doses)

+probenecid (250mg/kg-10doses), and MPTP (25mg/kg-10 doses) + acetyl-L-carnitine (100mg/kg-daily i.p. for 38 days) and acetyl-L-carnitine (100mg/kg-daily i.p. for 38 days). MPTP-induced losses in tyrosine hydroxylase and DA transporter immunoreactivity in the ventral midbrain SNc and CPu were significantly reduced by ALC. HPLC data suggests that decreases in CPu dopamine and other DA metabolites level produced by MPTP were also attenuated by ALC. In addition, microglial activation and astrocytic hypertrophy induced by MPTP were greatly reduced by ALC, indicating protection against neuroinflammation. ALC only treated animals did not show any change in the DA or DA metabolites. Likewise, the glucose transporter-1 that is expressed exclusively in brain endothelial cells is also protected by ALC from MPTP-induced down-regulation. This study demonstrates protection afforded by ALC against MPTP-induced damage to endothelial cells and TH loss suggesting that ALC therapy may have the potential to slow or ameliorate the progression of PD pathology.

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**Program #/Poster #:** 753.16/BB15

**Topic:** C.03. Parkinson’s Disease

**Support:** Branfman Family Foundation
Michael J Fox Foundation

**Title:** Effects of the alpha-synuclein-interacting protein endosulfine-alpha on PD-related neuropathology

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**Abstract:** Aggregation of the presynaptic protein, alpha-synuclein (aSyn), plays a major role in neurotoxicity in Parkinson’s disease (PD) and other synucleinopathy disorders. aSyn undergoes accelerated aggregation in the presence of phospholipid membranes by adopting an exposed alpha-helical structure, a state that favors membrane-induced self-assembly. In turn, aSyn aggregation at membrane surfaces may cause a disruption of dopamine vesicles, leading to preferential dopaminergic neuronal death. Endosulfine-alpha (ENSA) is a cAMP regulated

phosphoprotein that is expressed in the CNS and has been reported to interact with membrane-bound aSyn. Previously, we showed that ENSA is downregulated in the frontal cortex of patients with dementia with Lewy bodies (DLB) and shows a trend towards being downregulated in the substantia nigra (SN) region of PD brains. In primary midbrain cultures, WT ENSA, but not the S109E mutant that fails to interact with membrane-bound aSyn, alleviated aSyn-mediated dopaminergic cell death and neurite retraction. Collectively, these data provide a strong premise for the hypothesis that ENSA alleviates aSyn neurotoxicity by interfering with aSyn aggregation at the surface of phospholipid membranes. Current efforts are focused on testing this hypothesis in an *in vivo* model by determining the effects of co-expressing WT ENSA versus ENSA-S109E on aSyn neurotoxicity in the rat rAAV-aSyn model using behavioral and immunohistochemical approaches. In addition, we have developed a rat model of mild traumatic blast injury (mTBI) that shows evidence of aSyn aggregation in the SN and nigrostriatal degeneration, and this model opens new avenues for examining protective effects of ENSA against PD-related neuropathology. The results of these studies will provide new insights into the molecular underpinnings of aSyn neurotoxicity and ENSA-mediated neuroprotection and set the stage for designing therapies to slow nigrostriatal degeneration in PD or TBI patients.

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**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 753.17/BB16

**Topic:** C.03. Parkinson’s Disease

**Title:** Dynamics of development of the synaptic processes in the substantia nigra and spinal cord on rotenon model of Parkinson's disease

**Authors: *V. SARGSYAN**[1], N. BEHNAM DEHKORDI[2]
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**Abstract: Abstract Objective:** The mechanism of neurodegeneration associated Parkinson’s disease (PD) continues to be complex and in many ways still needs further investigation. At least it is important that not only the lack of dopamine neurons in Substancia Nigra (SN) is responsible for characteristic motor symptoms to be subject to symptomatic therapy. At present to assess electrophysiological, neurochemical, behavioral and cognitive manifestations of PD successfully used the rotenon model which develops within 4 weeks after the intracerebral injection of rotenone. **Methods:** On the model of PD after 2-4 weeks (w) recording of the

activity of single neurons of SN to high frequency stimulation (HFS) of Caudate-Putamen (CPu), spinal cord (SC) motoneurons (MNs) (at L4-L5 segments), as well as activity of SN neurons evoked by HFS of flexor (G) and extensor (P) hind limb nerves revealed the formation of excitatory and depressor responses in the form of tetanic depression and potentiation (TD, TP) to be combined into uni - (TD post TD , TP post TP) and multidirectional ( TD post TP , TP post TD) post-tetanic sequences **Results:** It is established, that in the SN neurons to HFS of CPu, TD going with PTD at 2nd week was close to the norm, dropping by more than half at 4th week. With the use of vipera radei venom (VR), there was tendency of reducing the TD. It is believed the advancement of deepening the depressor tetanic reactions as a carrier of protective load during neurodegeneration of different origin in the initial stage of recovery, and to facilitate the restoration of the original ratio of excitatory and depressor processes. In the present study should be evaluated the significance of tetanic depressor manifestations of SC MNs and SNs activity, best expressed in the initial stage of recovery. As is known, depressor post stimulus manifestations of activity in the form of TD and PTD mediate the inhibitory GABA or Glycine monoamines. **Conclusion:** Apparently depressor mechanism of protection mediated by, inter alia, GABA-ergic structures at different origins of neurodegeneration, contributes to the restoration the initial ratio of excitatory and inhibitory processes Keywords*: Parkinson's disease, Substantia Nigra, spinal cord motoneurons, the extensor and flexor nerve , Caudate Putamen, single spike activity.*

**Disclosures: N. Behnam Dehkordi:** None.

**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 753.18/BB17

**Topic:** C.03. Parkinson’s Disease

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2.HKRGC-AoE grant AoE/M-604/16
3.Gerald Choa Neuroscience Centre 7105306

**Title:** Amelioration of Parkinsonian motor symptoms in rat via stochastic stimulation of the motor cortex

**Authors: *X. YANG**[1,2], R.-C. PENG[1,2], Y. KE[1,2], W.-H. YUNG[1,2]
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**Abstract:** Parkinson’s disease (PD) is a neurodegenerative disease for which there is no known cure. Deep brain stimulation (DBS) is a surgical treatment that has been recognized as effective in reducing motor symptoms for PD patients. Previous work implicates DBS directly influences motor cortex through stochastic antidromic spikes. Here we developed a prototype of a multi-channel stimulating system to mimic the effects of stochastic antidromic activation on the motor cortex and assessed the efficacy in ameliorating motor symptoms in the rat PD model. The results showed that different combinations of frequency, amplitude and pulse width of electrical pulses exerted different effects on Parkinsonian rats. Among these, some stimulus patterns were able to produce transient beneficial effect on movement assessed by open-field locomotor activities. These results indicate that, in principle, cortical stimulation can achieve therapeutic outcome, and is a less invasive approach than standard DBS. More refined mode of stimulation to achieve long-lasting and more robust effect will be explored.

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**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 753.19/CC1

**Topic:** C.03. Parkinson’s Disease

**Title:** The effects of growth hormone on motor findings and neuronal morphology in Parkinson model rats

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**Abstract:** OBJECTIVE:Parkinson Disease is a neurodegenerative disease, characterized by the degeneration of dopaminergic neurons in Substantia nigra (SN). Growth hormone (GH) is a hormone that plays a role in the development of important functions in the control of brain development. There are studies showing that BH administration may be associated with recovery of neuronal functions after brain injury. Dendritic spines increases the surface area and causes the communication between all stimulating cells in the brain.There is a connection between the structural properties and functions of dendritic spines. This study aims to investigate the effect of GH therapy on motor function and neuronal morphology for 3 months.METHODS:Sprague Dawley rats; Treatment group (PD+GH) (n = 6) and Sham (PD+ Saline) (n=6) were injected with 4 µl 6-OHDA solution (Bregma AP: -2,1 mM, Lat: 2,0 mm and VL: -7,8 mm) stereotaxically. Following the injection GH and saline (0.15 mg / kg / day, s.c.) is administered daily. Rotation preferences and lesion grade are evaluated according to the rotation test. Golgi (FD Rapid Kit) and Tyrosine hydroxylase (TH) staining procedures are applied to sections of the striatum and substantia nigra (40 µm).Golgi staining was evaluated using Neurolucida

360(v2018).RESULTS:According the results of the rotation, the number of rotations in BH treatment group was significantly decreased (p = 0.0112). No significant difference was observed between the groups in SN and striatum in TH staining. Thin type dendritic spine density is significantly increased in the treatment group, which indicates restoration of neuron morphology.CONCLUSION:Long term GH administration has been shown to have positive effects on motor function and neuronal morphology.This study was supported by Marmara University Scientific Researches and Projects Committee (SAG-K-070617-0339)

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**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 753.20/CC2

**Topic:** C.03. Parkinson’s Disease

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**Title:** Formation of V-1/CP complex is required for the genetic co-regulation of adult nigrostriatal dopaminergic homeostasis via the Rho/MAL/SRF pathway *in vitro* and *in vivo*

**Authors: *I. KAWAHATA**[1], Y. LAI[1], J. MORITA[1], S. KATO[2], A. TABUCHI[3], M. TSUDA[3], C. SUMI-ICHINOSE[4], K. KONDO[4], Y. IZUMI[5], T. KUME[3], A. AKAIKE[6], K. OHASHI[1], K. MIZUNO[1], K. HASEGAWA[7], H. ICHINOSE[8], K. KOBAYASHI[2], T. YAMAKUNI[1]
[1]Tohoku Univ., Sendai, Japan; [2]Fukushima Med. Univ., Fukushima, Japan; [3]Univ. Toyama, Grad Sch. Med. Pharm Sci., Toyama, Japan; [4]Fujita Hlth. Univ., Nagoya, Japan; [5]Kobe Pharmaceut. Univ., Kobe, Japan; [6]Kyoto Univ. Fac Pharmceut Sci., Kyoto, Japan; [7]Sagamihara Natl. Hosp., Sagamihara, Japan; [8]Tokyo Inst. of Technol., Yokohama, Japan

**Abstract:** [Background] Tyrosine hydroxylase (TH), dopa decarboxylase (DDC) and nuclear receptor related 1 (Nurr1) are essential for nigrostriatal dopaminergic function. Here, we investigated an as-yet-unidentified mechanism for the coordinate expression of above three genes *in vitro* and *in vivo* to provide the first evidence for a novel regulatory system of TH/DDC/Nurr1 by a protein complex of V-1, a classical ankyrin repeat protein, and CP, an actin capping protein, the unique regulators of actin dynamics (PLoS Biol. 2010).

[Method] Lentiviral V-1 expression vectors (VSV-G/V-1) were prepared to analyze V-1/CP-regulated dopaminergic function. Wild-type (WT), mutated (D44R) or control (GFP)-conjugated VSV-G were injected into the substantia nigra of C57BL6 mice which were sacrificed 1 month after injection for the subsequent analyses. The aging-dependent failure of V-1/CP complex formation was analyzed by immunohistochemistry. Signaling pathway required for the V-1/CP function was analyzed by Rho/Rac pull-down assay and transfection of Rho, LIMK, cofilin, SRF constructs, or their mutants. A ChIP-PCR assay was employed to identify the SRF-binding site in the promoter region of TH, DDC, and Nurr1 genes. Human brains were analyzed with the approval by the ethics committee of Japan Sagamihara National Hospital.
[Results] Failure of V-1/CP complex formation by injecting mutant VSV-G/V-1(D44R, cannot bind to CP) into C57BL6 mice midbrain impaired the expression of TH/DDC/Nurr1 as well as VMAT2 and DAT in the nigrostriatum, accompanied by a reduction in dopamine levels. We also found that VSV-G/V-1(D44R) impairs RhoA/Rac1/ROCK/LIMK pathway. In cultured dopaminergic neurons, we identified that V-1/CP complex promotes RhoA/Rac1 activity, cofilin phosphorylation and facilitates actin polymerization, accompanied by enhanced MAL nuclear import to increase serum responsive factor (SRF)-mediated transcription. A ChIP-qPCR assay using an anti-SRF antibody showed the V-1/CP-regulated SRF-binding in the promoter region of TH/DDC/Nurr1 genes. Interestingly, MPP(+)-treatment impaired the association of V-1/CP, whereas VSV-G/V-1(WT) transfection to increase V-1/CP complex formation alleviated the MPP(+)-induced dopaminergic neurodegeneration by restoring the impaired TH/DDC/Nurr1/VMAT2 expression and dopamine content. Notably, we also found that the association of V-1/CP was weakened in aged C57BL6 mice and the human midbrain in Parkinson's disease (PD).
[Conclusion] We conclude that the V-1/CP complex is crucial for maintaining the adult dopaminergic system, implying that the V-1/CP complex is a novel potential target for fundamental therapy of PD.

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**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 753.21/CC3

**Topic:** C.03. Parkinson’s Disease

**Title:** Extracellular $Zn^{2+}$ influx into nigral dopaminergic neurons plays a key role for pathogenesis of 6-hydroxydopamine-induced Parkinson’s disease in rats

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**Abstract:** Glutamate excitotoxicity is the pathological process through which neurons are damaged and killed after excess activation of glutamate receptors. The influx of extracellular $Ca^{2+}$ through N-methyl-D-aspartate (NMDA) receptors plays a crucial role in glutamate excitotoxicity. Even in dopaminergic neurons where the mechanism of glutamate excitotoxicity is poorly understood, $Ca^{2+}$ influx through NMDA receptors has been believed to be a trigger for neuronal death. In contrast, it is recognizing that most of the death signaling associated with neurological conditions is mediated by not only $Ca^{2+}$ toxicity but also $Zn^{2+}$ toxicity. Dopaminergic neurons express glutamate receptors in the substantia nigra pars compacta (SNpc). It has been postulated that excess activation of glutamate receptors on dopaminergic neurons in the SNpc may be involved in pathophysiology of Parkinson's disease (PD), which is a progressive neurological disease characterized by a selective loss of nigrostriatal dopaminergic neurons. To understand PD pathogenesis, it is important to clarify the significance of cytosolic $Zn^{2+}$ toxicity and its origin in nigrostriatal dopaminergic neurodegeneration. Here we report a unique mechanism of nigrostriatal dopaminergic neurodegeneration, in which extracellular $Zn^{2+}$ influx plays a key role for PD pathogenesis induced with 6-hydroxydopamine (6-OHDA) in rats. 6-OHDA rapidly increased intracellular $Zn^{2+}$ only in the SNpc of brain slices and this increase was blocked in the presence of CaEDTA, an extracellular $Zn^{2+}$ chelator, and CNQX, an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptor antagonist, indicating that 6-OHDA rapidly increases extracellular $Zn^{2+}$ influx via AMPA receptor activation in the SNpc. Extracellular $Zn^{2+}$ concentration was decreased under in vivo SNpc perfusion with 6-OHDA and this decrease was blocked by co-perfusion with CNQX, supporting 6-OHDA-induced $Zn^{2+}$ influx via AMPA receptor activation in the SNpc. Interestingly, both 6-OHDA-induced loss of nigrostriatal dopaminergic neurons and turning behavior to apomorphine, an index of behavioral abnormality, were markedly ameliorated by co-injection of intracellular $Zn^{2+}$ chelators, i.e., ZnAF-2DA and TPEN. Co-injection of TPEN into the SNpc blocked 6-OHDA-induced increase in intracellular $Zn^{2+}$ but not that in intracellular $Ca^{2+}$. The present study suggests that the rapid influx of extracellular $Zn^{2+}$ into dopaminergic neurons via AMPA receptor activation in the SNpc causes nigrostriatal dopaminergic neurodegeneration, resulting in 6-OHDA-induced PD in rats.

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**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 753.22/CC4

**Topic:** C.03. Parkinson's Disease

**Support:** NRF-2016R1A2B3015167
NRF-2017H1A2A1046780

**Title:** Rescuing Parkinsonian motor symptoms by controlling rebound excitability

**Authors: *S. LEE**, S. CHAE, D. KIM
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**Abstract:** Parkinson's disease (PD) is a debilitating movement disorder resulting from the death of dopamine neurons. There is as of yet no stable and permanent treatment, leading to the necessity of developing new treatment method. Through optogenetic circuit dissection, we have revealed that inhibited thalamic neurons paradoxically yield rebound excitability and induce motor abnormalities associated with PD. This study focuses on the development of a new method for the cure of PD by controlling this rebound excitability. For that, we designed a method that can normalize the abnormally increased excitatory output in a desired number of neurons, and confirmed that it works properly as expected in vitro. Ultimately, we aim to find a new circuit-based therapy that can ameliorate Parkinsonian motor symptoms semi-permanently through clinical application experiments in mice and primate PD models.

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**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 753.23/CC5

**Topic:** C.03. Parkinson's Disease

**Title:** Modulation of PINK1 and PARK2 gene expression in rotenone induced Parkinson's disease model

**Authors: *Z. A. RAZZAK**[1], K. RAFI[2], G. ABBAS[3], S. SIMJEE[2]
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**Abstract: BACKGROUND**
**Objective**
Parkinson's disease (PD) is the second most leading cause of death due neurodegenerative diseases, nearly affecting 1% of population worldwide. The posture instability and shaky movements happen due to motor impairment. The hallmarks of PD occur due to death of dopaminergic neurons in substantia nigra par compacta, due to the modulation of PARK2 gene

recruited by PTEN induce putative kinase1 (PINK1). PARK2 translate the Parkin protein which participates in the degradation of misfolded protein. During oxidative stress, mitochondria concomitantly reduce the performance of electron transport chain. As a result, PINK1 activation is ceased which in series halt the recruitment of PARK2 resulting in accumulation of protein which eventually cause death of dopaminergic neuron. Available PD therapies only provides symptomatic relief, so the aim of this study is to find new leads which can halt the death of dopaminergic neurons and slow down the progression of PD.

**Methods**

In this preliminary study, *in vivo* mice model of PD was developed by intra peritoneal (IP) administration of rotenone on alternate days for 60 days. Animals were grouped into three doses (i) low dose (ii) median dose (iii) high dose. Hind limb clasping test and grip strength test were conducted to grossly evaluate the disease progression. After the appearance of maximum symptoms animals were sacrificed. Mid brain and striatum was isolated and samples were processed for RT-PCR. Neurotransmitter analysis was done by HPLC to quantify the Dopamine and DOPAC turn over in striatum of brain.

**Results and Conclusion**

Based on the initial findings, we conclude that the median dose of rotenone has the maximal potential for decreasing dopamine turn out number; this was confirmed by comparing by all respective groups. RT-PCR analysis shows decrease level of PINK1 and PARK2 expression suggesting mitochondrial dysfunction (rotenone is mitochondrial complex 1 inhibitor) which further decreases the PARK2 gene expression which resulting in the accumulation of degraded protein causing the death of neuron. In future studies, we aim to screen the novel peptides to find the possible lead compound that can be used as a potential therapeutic agent for Parkinson's disease.

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**Poster**

**753. Parkinson's Disease: Neuroprotective Mechanisms**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 753.24/CC6

**Topic:** C.03. Parkinson’s Disease

**Support:** Pfizer Inc

**Title:** Quantifying the reproducibility of an *in vivo* assay: Examination of historical amantadine effects in the macaque model of L-DOPA-induced dyskinesia

**Authors: *E. Y. PIOLI**[1], P. STANLEY[2], Q. LI[4], R. KOZAK[3], M. POPIOLEK[5], E. BEZARD[6]
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**Abstract:** This study was designed to assess the reproducibility of the amantadine anti-dyskinetic effect in the MPTP L-DOPA-Induced Dyskinesia (LID) macaque model for soundly defining the sample sizes required to test anti-dyskinetic compounds. Dyskinesia are side effects associated with chronic L-dopa treatment in Parkinson's patients that are partially alleviated by the weak NMDA antagonist amantadine. Although the current benchmark, response to amantadine is variable and effective only in a subset of patients. While recognizing that the MPTP macaque model is the gold-standard pre-clinical translational model, we provide critical information for designing and powering studies for testing of novel anti-dyskinetic strategies. We conducted the meta-Analysis of 11 studies (n ranging from 7 to 24 individuals) involving NHPs treated with vehicle and amantadine in combination with levodopa. The effect was calculated by the difference in total dyskinesia score between amantadine and vehicle. The primary objective was to quantify the reproducibility of the study responses and to understand the variability present between studies and between animals within the studies. Secondly, we determined the expected effect size and variation to ensure appropriate statistical design and power for future studies with new compounds. The mean profiles over all animals in all studies show a reasonable efficacy window between vehicle and amantadine response profiles. However, the profiles in individual studies are less consistent. The meta-analysis of the effect suggested a study-to-study heterogeneity (effect from -2.6 ± 1.45 to -15.3 ±1.03). The meta-analysis of the within-subject standard deviation suggested that the heterogeneity between-study is negligible relative to the size of the variability within-study. From the two meta-analyses, we obtained an estimate of the 'average' amantadine effect of -8.8 and an estimate of the potential size of the within-subject SD of 3.6. The number of animals required to detect 100%, 67% and 50% of the amantadine effect is 4, 6 and 12 with the corresponding power of 85%, 84% and 83% respectively. Result of this meta-analysis is of significance and confirms that the MPTP macaque model is a reliable translational model to assess the antidyskinetic ability of a novel mechanism. However, due to the intersubject variability using suitable sample size is essential to obtain consistent results.

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**Poster**

**754. Parkinson's Disease: Symptoms and Emerging Therapeutic Avenues**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 754.01/CC7

**Topic:** C.03. Parkinson's Disease

**Support:** Parkinson's Foundation Translational Research Grant
NIH Grant R01 MH107571
NIH Grant P30 NS045839

**Title:** Resting-state brain small-world network property correlates with fatigue in PD patients

**Authors: *H. RAO**, X. ZHONG, R. BHAVSAR, E. MAMIKONYAN, F. YANG, H. LEI, J. A. DETRE, D. WEINTRAUB
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**Abstract: Introduction**: Parkinson's disease (PD) is a common neurodegenerative disease affecting millions of people world-wide. Fatigue is a highly prevalent and disabling non-motor symptom in PD. However, little is known about the neural mechanisms underlying fatigue in PD, and this lack of knowledge is a significant barrier to implementing prevention and management strategies. Accumulating evidence suggests that the human brain is topologically organized as a small-world network. Our previous neuroimaging study on healthy adults suggest that disruption of the brain small-world network properties (e.g., characteristic path length λ and small-worldness σ) may underlie increased fatigue after experimental sleep deprivation. In this follow-up pilot study we used resting-state functional magnetic resonance imaging (fMRI) to examine whether these brain network properties are associated with fatigue severity in a cohort of PD patients. **Method**: We scanned 11 PD patients (6 females, mean age = 67±10 years) using a standard multi-band EPI sequence on a Siemens 3T Prisma scanner. Patients' fatigue severity was assessed by both the Fatigue Symptom Inventory (FSI) and the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF). GRETNA toolbox was used to model the resting-state fMRI data with graph theory and calculate the brain small-world network properties. **Results**: Significant negative correlations were found between network characteristic path length λ and fatigue scores from both FSI ($r$=-0.777, $p$=0.008) and MSFI-SF (for general fatigue: $r$=-0.863, $p$=0.001; for total fatigue: $r$=-0.670, $p$=0.048). However, no correlations were found between network small-worldness σ and fatigue scores in PD (all $p$>0.05). **Conclusion:** The characteristic path length λ is a measure of the average shortest paths for information transport between nodes of the brain small world network. Correlations between λ and fatigue scores suggest that fatigue in PD may also be associated with disruption of the brain small-world network property and communication efficiency.

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**Poster**

**754. Parkinson's Disease: Symptoms and Emerging Therapeutic Avenues**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 754.02/CC8

**Topic:** C.03. Parkinson's Disease

**Support:** Chinese FRFCU 2016QN81017
Chinese NSF 61673346
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**Title:** The deficits of tactile motion perception in Parkinson's disease

**Authors: *M. XIN**[1,2], Y. JIANG[1], T. SHEN[1,3], B. QU[1,2], B. ZHANG[3], H.-Y. LAI[1,2]
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**Abstract:** Parkinson's disease (PD) is a neurodegenerative disorder characterized by movement disorder. Non-motor symptoms of PD have also been paid attention to in recent years, especially the somatosensory symptoms. The tactile motion perception of somatosensory, the movement sensation between the skin and the object, has become a research focus because of its close relationship with the motor performance. The goal of the study was to characterize tactile motion perception in PD patients to explore the somatosensory symptoms in PD. To this end, we used a lab-designed ball tactile stimulator to present a series of stimulations to the center of the subject's left index fingerpad. The stimulation parameters included 8 different directions and 6 speed levels of motion. Subjects directly drew a line on the touchpad to response the tactile motion velocity (direction and speed) of stimulations. In the current study, 24 subjects were divided into three groups: seven PD patients (55-65 y), ten young-age-healthy controls ($HC_Y$, 20-30 y) and seven old-age-healthy controls ($HC_O$, 55-65 y). All Parkinson's patients were evaluated by Unified Parkinson's Disease Rating Scale (UPDRS). Our data showed that the significant difference in perception of directions ($p<0.05$) and speed ($p<0.05$) among PD, $HC_Y$ and $HC_O$ groups. The bias of direction perception in PD group was largest in three groups. The speed perception in PD subjects was shown to be less sensitive than that in $HC_Y$ ($p<0.01$) and $HC_O$ subjects ($p<0.05$). Taken together, the results indicated that the widespread deficits in tactile motion perception of PD patients.

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**Poster**

**754. Parkinson's Disease: Symptoms and Emerging Therapeutic Avenues**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 754.03/CC9

**Topic:** C.03. Parkinson's Disease

**Title:** The discovery of dopamine D1 positive allosteric modulators for the treatment of neuro-psychiatric disorders

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**Abstract:** The dopamine D1 receptor plays a critical role to maintain motor activity, reward and higher cognitive functions including working memory, attention and executive function. Increased cortical D1 activity could address critical unmet medical needs including cognitive impairment. Selective D1 agonists are active in animal models relevant to clinical applications for neuro-psychiatric disorders. However, development of D1 agonists for clinical use has not been successful due to issues with receptor desensitization, poor ADME properties, or dose limiting side effects (eg Arnsten 2016, but see Gray et al., 2018).
Objective: Test the hypothesis that a dopamine D1 positive allosteric modulator (D1PAM) could address some of these issues and offer a more physiological approach to activation of D1 receptors with temporal and spatial resolution related to endogenous dopamine release (cf. Svensson et al., 2017).
Methods: In vitro testing for potentiation of dopamine induced increase in cAMP was done using cloned human D1 cells. Mutagenesis and D1/D5 chimera studies identified the binding site for D1PAM. In vivo testing was done in human D1 receptor knock-in (hD1KI) mice due to a significant species difference in binding of D1PAM. Preclinical data will be shown for the two D1PAMs DETQ and LY3154207.
Results: DETQ shows high alpha-shift and D1 selectivity. Studies with chimeric receptors identified a novel allosteric binding site at the second intracellular loop. DETQ increased locomotor activity in hD1KI mice over a wide dose range without evidence for inverted U-shaped dose-response. DETQ reversed hypo-activity caused by pre-treatment with a low dose of the dopamine depleting agent reserpine. DETQ acted synergistically with L-DOPA to reverse the akinesia seen with a high dose of reserpine. Microdialysis studies showed that DETQ increases release of acetylcholine in the hippocampus where it had an additive effect together with rivastigmine. Testing in the novel object recognition model for cognition showed dose relate reversal of PCP induced deficits with DETQ.
Conclusions: Preclinical data support further development of D1PAMs for neuro-psychiatric

disorders. This includes LY3154207 which recently entered phase 2 studies in Parkinson's disease dementia.

**Disclosures: K.A. Svensson:** A. Employment/Salary (full or part-time):; Eli Lilly and Company. **J.P. Beck:** None. **J. Hao:** None. **J. Schaus:** None. **B. Heinz:** None. **X. Wang:** None. **S. Mitchell:** None. **K. Wafford:** None. **H.Y. Meltzer:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Eli Lilly and Company. **C.R. Yang:** None. **R.F. Bruns:** None.

**Poster**

**754. Parkinson's Disease: Symptoms and Emerging Therapeutic Avenues**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 754.04/CC10

**Topic:** C.03. Parkinson's Disease

**Support:** MOST105-2314-B-016- 001-MY3
NIH Grant NS094152

**Title:** Exercise improve spatio-temporal impairments of gait in the rat hemi-Parkinson's model via amelioration of deficits in dopamine transmission

**Authors: *Y.-H. CHEN**[1], B. J. HOFFER[2,3], C. WANG, 114[4], T.-T. KUO, 114[5]
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**Abstract:** To determine the influences of exercise on motor deficits and dopaminergic transmission in a hemiparkinson animal model, we measured the effects of exercise on the ambulatory system by estimating spatio-temporal parameters during walking, striatal dopamine (DA) release and reuptake and synaptic plasticity in the corticostriatal pathway after unilateral 6-OHDA lesions. 6-OHDA lesioned hemiparkinsonian rats were exercised on a fixed speed treadmill for 30 minutes per day. Controls received the same lesion but no exercise. Animals were subsequently analyzed for behavior including gait analysis, rotarod performance and apomorphine induced rotation. Subsequently, in vitro striatal dopamine release was analyzed by using FSCV and activity-dependent plasticity in the corticostriatal pathway was measured in each group. Our data indicated that exercise could improve motor walking speed and increase the apomorphine-induced rotation threshold. Exercise also ameliorated spatiotemporal impairments in gait in PD animals. Exercise increased the parameters of synaptic plasticity formation in the corticostriatal pathway of PD animals as well as the dynamics of dopamine transmission in PD animals. Fixed speed treadmill training 30 minutes per day could ameliorate spatial temporal gait

impairment, improve walking speed, dopamine transmission as well as corticostriatal synaptic plasticity in the unilateral 6-OHDA lesioned rat model.

**Disclosures: Y. Chen:** None. **B.J. Hoffer:** None. **C. Wang:** None. **T. Kuo:** None.

**Poster**

**754. Parkinson's Disease: Symptoms and Emerging Therapeutic Avenues**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 754.05/CC11

**Topic:** C.03. Parkinson’s Disease

**Title:** Biochemical and behavioral evidences for neuromodulatory properties of combination of ellagic acid, curcumin and mucuna pruriens against rotenone induced mice model of Parkinson's disease

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**Abstract: Aim & Objectives** The present study was designed in order to explore the possible synergistic effect of three highly naturally occurring bio-active compounds viz. Ellagic acid (EA), Curcumin (Cur) and Methanolic extract of *Mucuna Pruriens* Seeds (MPM). The neuroprotective role of combinational therapy of EA, Cur and MPM was explored in rotenone induced behavioural, oxidative and mitochondrial dysfunction in mice model of Parkinson’s disease. **Background** Ellagic acid (EA) Curcumin (Cur) and *Mucuna Pruriens*, are natural polyphenolic, powerful bioactive compounds used word wide. They exhibited numerous biological and pharmacological activities including potent antioxidant, cardiovascular disease, anticancer, anti-inflammatory effects and neurodegenerative disorders in cell cultures and animal models. **Methods** Chronic administration of rotenone (1 mg/kg i.p.) for a period of three weeks significantly impaired behavioural paradigm (Memory, learning and locomotor activity), oxidative defence (Decreased activity of superoxide dismutase, catalase and reduced glutathione level) and mitochondrial Complex-II-Succinate Dehydrogenase (SDH), Complex III- MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-H-tetrazolium bromide) enzymes activities as compared to normal control group in the brain of mice. **Results** Three weeks of EA, Curc and MPM combination (50, 100 and 200 mg/kg, p.o) treatment significantly improved behaviour parameters ($P < 0.001$) oxidative damage ($P < 0.001$) and mitochondrial enzyme complex activities ($< 0.05$, $P < 0.01$, $P < 0.001$) as compared to negative control (rotenone treated) group. We found that combination of EA, Cur and MPM restored motor deficits and enhanced the activities of antioxidant enzymes suggesting its antioxidant and neuroprotective potential in vivo. **Conclusion** Collectively, these data suggest that combination therapy of natural bioactive compounds may provide neuroprotection may be primarily attributed to the restoration effect on

antioxidant defence and mitochondrial function which lead to improved locomotor phenotype. We propose that EA, Cur and MPM combination may provide new perspectives for the development of therapeutic strategies in protecting the brain against oxidative stress-mediated neurodegenerative disorders.**Key words:** Ellagic acid, Curcumin, *Mucuna Pruriens*,; Rotenone; Neuroprotective; Parkinson's disease; Mitochondrial Dysfunction; Oxidative Stress

**Disclosures: P.K. Rane:** None. **M.B. Panchwadkar:** None.

**Poster**

**754. Parkinson's Disease: Symptoms and Emerging Therapeutic Avenues**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 754.06/CC12

**Topic:** C.03. Parkinson’s Disease

**Title:** A new combination therapy of Curcumin and Ginkgo biloba for mitochondrial biogenesis Implications for Parkinson’s disease

**Authors: *P. K. RANE**[1], M. B. PANCHWADKAR[3], D. K. KHATRI[2]
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**Abstract: Objective *** This study was designed with the objective to find out the possible synergistic effect of Curcumin (Cur) and Methanolic extract of Ginkgo biloba (EGB) Leaf in Parkinson’s disease (PD). Cur and EGB were explored for their neuroprotective effect in rotenone-induced neurodegeneration in mice model of Parkinson’s disease. **Background *** Both Cur and EGB, are natural polyphenolic, highly potent bioactive compounds. Cur has been used for centuries in traditional medicines in India. Curcumin showed several biological and pharmacological activities including potent antioxidant, cardiovascular disease, anticancer, anti-inflammatory effects and neuroprotective effect. Ginkgo biloba is one of the most widely used herbal remedies in the world to treat the symptoms of early-stage Alzheimer’s disease, vascular dementia, peripheral claudication, and tinnitus of vascular origin. **Methods *** Rotenone (1mg/kg/ i.p.) was used to induced PD in mice. Chronic rotenone administration for 21 days produced significant impairment in the behaviour pattern (learning, memory, motor coordination), decrease oxidative function (superoxide dismutase, catalase and reduced glutathione level) and mitochondrial function (Complex-I, Complex-II, Complex-III) as compared to normal control group of mice. **Results *** Simultaneous treatment with Cur and EGB combination at different dose level (50, 100 and 200 mg/kg, p.o) for 21 days significantly improved behaviour parameters ($P < 0.001$), oxidative damage ($P < 0.001$) and mitochondrial enzyme complex activities (< 0.05, $P < 0.01$, $P < 0.001$) as compared to negative control (rotenone-treated) group. The results of present study showed that the Cur and EGB combination restored the motor deficit function and

enhance oxidative and mitochondrial functions. **Conclusions *** The outcome of present investigation confirms that the treatment of mice with combination of Cur and EGB produced significant neuroprotection probably mediated through its antioxidant activity and provides a strong justification for the therapeutic potential of these compounds in management of PD. **References:** 1. Khatri D. K., Juvekar A. R, 2016. Neuroprotective effect of curcumin as evinced by abrogation of rotenone-induced motor deficits, oxidative and mitochondrial dysfunctions in mouse model of Parkinson's disease. Pharmacology, Biochemistry and Behaviour, 150-151, 39-47. 2. Kim M. S. et al., 2004. Neuroprotective effect of Ginkgo biloba L. Extract in rat model of Parkinson's disease. Phytotherapy Research, 18, 663-666. ***Keywords:*** Parkinsonism, Behavioral abnormalities, Mitochondrial dysfunction

**Disclosures: P.K. Rane:** None. **M.B. Panchwadkar:** None. **D.K. Khatri:** None.

**Poster**

**754. Parkinson's Disease: Symptoms and Emerging Therapeutic Avenues**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 754.07/CC13

**Topic:** C.03. Parkinson's Disease

**Title:** Paraquat treatment has chronic and progressive inflammatory effects in a murine model of Parkinson's disease

**Authors: *Z. DWYER**, C. RUDYK, J. ABDALI, S. BEAUCHAMP, A. DINESH, K. FARMER, P. SHAIL, A. DERKSEN, T. FORTIN, K. VENTURA, S. P. HAYLEY
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**Abstract:** The motor symptoms observed in Parkinson's disease (PD) result from the loss of dopamine producing neurons in the Substantia Nigra pars compacta (SNc). The loss of these neurons has been repeatedly linked to neuroinflammatory processes. In particular, microglial are found in a highly activated state in human PD brains, as well as in animal models of the disease. Animal models of PD have often utilized toxicants, such as the herbicide paraquat, to induce microglial activation and the release of reactive oxygen species that are toxic to dopamine neurons of the SNc. While the short-term effects of paraquat exposure are well reported the long-term effects have yet to be explored in detail. To this end, we sought to examine the long-term effects of paraquat exposure in parallel with increasing animal age. It was found that the loss of SNc dopamine neurons remained stable over the six month course of the study. Interestingly, paraquat had long-term stressor-like effects, such that corticosterone was elevated for over a month following termination of the toxicant treatment. Finally, time-dependent changes in antioxidant and inflammatory mediators were also noted and might contribute to pathology. Most importantly, many of these changes only emerged months following termination of paraquat exposure. These data suggest that paraquat might have protracted stressor effects and

highlight the importance of age and time in the manifestation of the consequences of toxicant exposure.

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**Poster**

**754. Parkinson's Disease: Symptoms and Emerging Therapeutic Avenues**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 754.08/CC14

**Topic:** C.03. Parkinson’s Disease

**Support:** CNPQ
CAPES

**Title:** Antidepressant-like effect of curcumin in a 6-OHDA rat model of Parkinson’s disease

**Authors: *M. A. VITAL**, M. M. F. MACHADO, J. C. F. VIEIRA, T. B. BASSANI
Univ. Federal Do Paraná, Curitiba, Brazil

**Abstract: Introduction:** Depression is a frequent non-motor symptom of Parkinson’s disease (PD) which impairs the patients’ quality of life. The causes of depression in PD patients may involve neurodegeneration and dysfunction of neurogenesis. Curcumin is a polyphenolic compound from *Curcuma longa* with anti-inflammatory, antioxidant and neuroprotective properties. Curcumin presents antidepressant-like effects in animal models of depression, which would be associated with an improvement in hippocampal neurogenesis. The aim of this study was to test the hypothesis that curcumin would exert an antidepressant-like effect in the 6-hydroxydopamine (6-OHDA) model of PD in Wistar rats by enhancing hippocampal neurogenesis and/or protecting substantia nigra pars compacta (SNpc) dopaminergic neurons. **Methods:** Adult male Wistar rats ($n$ = 8/group) received a bilateral intranigral injection of 6-OHDA (6 μg per injection site) or vehicle, and the curcumin treatment (60 mg/kg, gavage) was performed for 21 days, starting 1 day after surgery. The sucrose preference test (SPT) was performed before the surgery to measure basal levels, and weekly on days 7, 14 and 21 after surgery. After the behavioral tests, the animals underwent transcardial perfusion for immunohistochemical analysis of tyrosine hydroxylase immunoreactive neurons (TH-IR) in the SNpc and doublecortin (DCX)-positive cells in the dentate gyrus (DG) of the hippocampus. Group differences were analyzed using two-way analysis of variance (ANOVA) with Tukey’s multiple comparisons for the SPT and one-way ANOVA for the other tests. Significance was set at $p < 0.05$. All procedures were approved by the Ethical Committee of Animal Experiment of Federal University of Paraná (protocol 590).

**Results:** 6-OHDA-lesioned animals exhibited anhedonia-like behavior, reflected by a decrease in sucrose preference, on days 7 ($p<0.05$) and 21 ($p<0.01$) after surgery, and a marked reduction in TH-IR neurons in the SNpc, 21 days after surgery ($p<0.01$). However, there were no alterations in the number of immature neurons (DCX-positive cells) in the DG of the hippocampus. Treatment with curcumin for 21 days reversed the anhedonia-like behavior in 6-OHDA-lesioned rats, but there was no increase in TH-IR neurons within the SNpc, and no significant alterations in the number of immature neurons in the hippocampus.
**Conclusions:** These results suggest that curcumin exerted antidepressant-like effects in the 6-OHDA intranigral model of PD, which was neither associated with dopaminergic neuroprotection nor an improvement in hippocampal neurogenesis.

**Disclosures: M.A. Vital:** A. Employment/Salary (full or part-time):; Maria A. B. F. Vital, Universidade Federal do Paraná. **M.M.F. Machado:** None. **J.C.F. Vieira:** None. **T.B. Bassani:** None.

**Poster**

**754. Parkinson's Disease: Symptoms and Emerging Therapeutic Avenues**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 754.09/CC15

**Topic:** C.03. Parkinson’s Disease

**Title:** Myricetin derivatives ameliorate deficits in 6-OHDA animal model of Parkinson's disease

**Authors: D. THOMPSON**[1], S. TRUESDELL[1], M. KOPANITSA[2,6], D. MISZCZUK[2], *R. O. PUSSINEN[2], W. DURHAM[3], P. MILIANI DE MARVAL[3], T. JENSEN[3], G. FLIK[4], E. SEWARD[5], P. CRACKETT[5], P. BURY[5], D. SMALL[7], A. J. NURMI[2]
[1]GRDG Sci., Winter Haven, FL; [2]Charles River Discovery, Kuopio, Finland; [3]Charles River Discovery, Morrisville, NC; [4]Charles River Discovery, Groningen, Netherlands; [5]Charles River Discovery, Harlow, United Kingdom; [6]UK Dementia Res. Institute, Imperial Col., London, United Kingdom; [7]Charles River Labs., Wilmington, MA

**Abstract:** Flavonoids are natural polyphenols widely distributed in plants and herbs. Flavonoids, including myricetin possess anti-oxidative, anti-inflammatory, and neuroprotective properties and may therefore reduce the risk of neurodegenerative diseases. Data suggest a protective mechanism of myricetin in animal models of Parkinson Disease (PD).
An Integrated Drug Discovery program at Charles River was designed to synthesize, characterize and examine the efficacy of two novel myricetin derivatives, TA1 and TA2, in a range of therapeutic indications. Here, we present data on their pharmacokinetic (PK) properties, maximum tolerated dose (MTD), and efficacy in a rat model of Parkinson’s disease (PD). The MTD was assessed in CD1 mice over 25 days. Each compound was tested at three doses (150, 300, 600 mg/kg) QD or BID. Animals were weighed and observed for any adverse treatment

effects and clinical signs. For PK analysis, brain and plasma concentrations of TA1, TA2 and unmodified myricetin given p.o. at 100 mg/kg were assessed at 1-24 h post dose. Tissues underwent enzymatic hydrolysis to convert the conjugated metabolites into the free forms prior to bioanalysis. Finally, protective action of myricetin derivatives in prophylactic intervention against functional consequences of the degeneration of dopaminergic neurons in the substantia nigra were tested in rats that received unilateral intrastriatal infusions of 6-OHDA. In particular, effects of myricetin derivatives administered for 1 week before and 2 weeks after 6-OHDA (QD, 100 mg/kg, p.o.) on amphetamine-evoked rotations and tyrosine hydroxylase-positive cell counts (TH+) in substantia nigra were examined and compared to the effects of mesencephalic astrocyte-derived neurotrophic factor (MANF) delivered intrastriatally 24 h post 6-OHDA infusion.
Maximum plasma levels of TA1 and TA2 were detected at 1 h post dose. Both derivatives but not the unmodified myricetin crossed the blood brain barrier and were detected in the brain at 6h post dose. The brain:blood ratio was 0.02 and 0.03 for TA1 and TA2, respectively. In the MTD study, mean body weight losses for all treatment groups were acceptable and did not exceed 8%. There were no deaths or clinical signs related to treatments. In the PD model study, amphetamine-induced asymmetric rotational activity at 2, 4, and 6 weeks post 6-OHDA infusion were lower in rats treated with MANF, TA1, or TA2 than in vehicle-treated group.
In conclusion, obtained data suggest that the novel myricetin derivatives TA1 and TA2 show better PK profile then unmodified myricetin, lack pronounced side effects at high doses, and ameliorate deficits similarly to MANF in the 6-OHDA rat model of PD.

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**Poster**

**754. Parkinson's Disease: Symptoms and Emerging Therapeutic Avenues**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 754.10/CC16

**Topic:** C.03. Parkinson’s Disease

**Support:** NIH grant R01NS074303

**Title:** Myeloperoxidase exacerbates motor disabilities in the A53T-a-synuclein mouse model of Parkinson's disease and is associated with increased nitration and aggregation of a-synuclein

**Authors: *W. F. REYNOLDS**, R. A. MAKI
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**Abstract:** Oxidative damage to proteins and nucleic acids is thought to contribute to the progressive loss of dopaminergic neurons in PD. The myeloperoxidase gene (MPO) is an oxidant generating enzyme normally expressed in myeloid precursor cells, yet it can be aberrantly induced in neurons or astrocytes under stress such as that caused by accumulation of misfolded protein aggregates in PD. To investigate the potential role of MPO generated oxidants in PD, we crossed the Thy-1-A53T-a-synuclein mouse model (A53T-a-syn) to our humanized MPO mice that express a single copy of the native human -463G-MPO gene with introns and flanking regions. The human MPO promoter contains transcription factor binding sites in an upstream Alu element that can result in aberrant expression not found with the mouse MPO gene. Behavior assays were carried out to assess the effect of MPO expression in the A53T-a-syn model. As early as two months of age, the hMPO transgene resulted in significant impairment of motor abilities for the A53T-a-syn mice as shown by reduced ability to maintain balance on a rotating rod or balance beam, and reduced ability to maintain grip on an inverted wire. Survival curves further showed the huMPO-A53T-asyn mice reached end stage paralysis earlier than A53T-a-syn mice. MPO protein and mRNA was detected in subsets of neurons in cortex, hippocampus, midbrain, thalamus, and spinal base of hMPO-A53T-a-syn but not in A53T-asyn mice. MPO was similarly detected in subsets of human neurons in the human PD substantia nigra. Notably, some neurons contained multiple MPO-positive granules surrounding large aggregates of nitrated a-synuclein. Synaptosomal extracts from MPO-A53T-a-syn brain showed increased levels of a-synuclein dimers by western analysis, along with increased levels of insoluble a-synuclein aggregates detected by cellulose acetate filter trap. In summary, these findings provide evidence that the human MPO gene can be induced in neurons in human Parkinson’s disease substantia nigra and in the hMPO-A53T-a-syn mouse model. In conclusion, the hMPO transgenic mouse when crossed to the A53T-a-syn model results in exacerbation of motor impairment accompanied by increased nitration and aggregation of a-synuclein. Funding provided by NIH grant R01NS074303 to W.R.

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**Poster**

**754. Parkinson's Disease: Symptoms and Emerging Therapeutic Avenues**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 754.11/DD1

**Topic:** C.03. Parkinson’s Disease

**Title:** Physical activity optimizes circuit-specific cellular metabolism in neuroplasticity: A role for hypoxia-inducible factor-1 and its downstream targets

**Authors: *M. W. JAKOWEC**, M. R. HALLIDAY, D. ABEYDEERA, G. M. PETZINGER
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**Abstract:** Physical activity is emerging as an effective and economical approach to treat and prevent a wide range of neurological disorders, including Parkinson's disease. Studies by our research group have shown that exercise, in the form of treadmill running, mediates a type of experience-dependent neuroplasticity through the modulation of dopaminergic and glutamatergic neurotransmission, synaptogenesis, and cerebral blood flow. However, a clear understanding of the underlying molecular mechanisms driving exercise-induced physiological brain adaptation represents a major gap in our knowledge. Recently, hypoxia-inducible factor-1 (HIF-1), a member of the HIF family of proteins and master transcription factor, has attracted interest due to its ability to act as a metabolic "sensor" and relay changes in brain metabolic state to changes in homeostatic gene expression. Furthermore, the role of HIF-1 in neural tissues is not restricted to the regulation of energy metabolism and has been shown to play a critical role in regulating complex molecular events including neurogenesis, angiogenesis, and mitochondrial function (biogenesis), which are important for exercise-induced neuroplasticity and synaptogenesis. Here, we investigated the effects of aerobic exercise on the activation of the hypoxia-inducible factor-1 (HIF-1) gene program, as well as the functional transcription and translation of several candidate target genes involved in transport of energy substrates (GLUT1 and MCTs), anaerobic glycolysis (LDH), angiogenesis (VEGF). Transcript and protein levels were analyzed after one, three, five, and 10 days of exercise in the prefrontal cortex (PFC), caudate putamen (CPu), and ectorhinal cortex (ERC) using quantitative RT-PCR (qRT-PCR), Western immunoblot (WIB), and immunofluorescence (IF). Using qRT-PCR and WIB, we show evidence for an exercise dose-dependent effect on the activation of the HIF-1 gene program and downstream target genes. Additionally, our findings suggest that exercise regulates gene expression in a circuit-specific manner that primarily targets brain circuits involved in complex motor and cognitive behaviors (i.e. frontostriatal and corticostriatal circuits). Further elucidation of molecular mechanisms involving metabolic pathways will allow us to better apply exercise as a therapy for brain disorders and will aid in the search for novel therapeutic targets with the potential to enhance the benefits of exercise-induced circuit-specific neuroplasticity.

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**Poster**

**754. Parkinson's Disease: Symptoms and Emerging Therapeutic Avenues**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 754.12/DD2

**Topic:** C.03. Parkinson's Disease

**Support:** NIH NS101737
Thomas Hartman Center for Parkinson's Disease Research at Stony Brook University

**Title:** Effects of $5HT_{1A}$ receptor agonist on spontaneous inspiratory motor output in two Parkinson's disease rat models

**Authors: *I. C. SOLOMON**, R. M. WADOLOWSKI, A. BROGAN, J. J. TUCHINSKY
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**Abstract:** While Parkinson's Disease (PD) is characterized by motor symptoms, a number of different non-motor symptoms (NMS) are also observed. Amongst the NMS, respiratory abnormalities have been noted in PD patients since the first description in 1817, and multiple causes have been proposed, including impaired central respiratory control. While the loss of dopaminergic neurons is the primary pathology of PD, it is also becoming better appreciated that serotonergic (5-HT) dysfunction may also play a role in the development of motor and NMS and complications in PD. To this end, recent studies addressing the role of 5-HT in PD symptoms have revealed that activation or antagonism of specific 5-HT receptor subtypes may have therapeutic benefit. 5-HT neurotransmission is also known to play a critical role in control of breathing; thus, respiratory abnormalities in PD may be further complicated by the progressive 5-HT dysfunction in PD. Ongoing work in our laboratory has focused on characterizing the respiratory phenotype of PD in 6-hydroxydopamine (6-OHDA) neurotoxin-induced unilateral substantia nigra (SN)- and medial forebrain bundle (MFB)-lesioned rat PD models. The goal of the current study was to assess the effects of acute administration of the $5\text{-}HT_{1A}$ receptor agonist 8-OH DPAT on inspiratory motor (diaphragm EMG) activity in spontaneously breathing urethane-anesthetized adult female rats at 2-weeks after SN (n=7) or MFB (n=12) 6-OHDA injections; control rats received vehicle injections (SN, n=4; MFB, n=6). We found that in both control and SN- and MFB-lesioned rats, administration of 8-OH DPAT produced an ~50% increase in burst frequency (above baseline (BL) frequency) within ~30 s, but by 5 min post injection, this increase was attenuated to an ~18% increase in MFB-lesioned rats while SN-lesioned and control rats still exhibited an ~27-40% increase. Administration of 8-OH DPAT also produced an increase in burst amplitude albeit the magnitude of this increase was somewhat varied. Regardless of the magnitude differences, both SN- and MFB-lesioned rats exhibited a progressive increase in amplitude over BL levels while control rats showed a sustained or slightly decreased magnitude elevation compared to BL levels. While these preliminary observations suggest that (compared to control rats), SN- and MFB-lesioned rats exhibit some differences in $5\text{-}HT_{1A}$ induced amplitude alterations, differences between the 6-OHDA PD models are also noted in $5\text{-}HT_{1A}$ induced frequency effects. Additional experiments will be needed to identify specific mechanisms underlying these differences.

**Disclosures: I.C. Solomon:** None. **R.M. Wadolowski:** None. **A. Brogan:** None. **J.J. Tuchinsky:** None.

**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.01/DD3

**Topic:** C.03. Parkinson's Disease

**Support:** Weston brain

**Title:** The anti-dyskinetic effect of combined 5-$HT_{2A}$receptor blockade with $mGlu_2$receptor positive allosteric modulator activationin the 6-OHDA lesioned rat model of Parkinson's disease

**Authors: *A. HAMADJIDA**[1,2], E. BOURGEOIS-CAYER[1,2], S. BELLIVEAU[1,2], I. FROUNI[1,4], C. KWAN[1,2], D. BÉDARD[1], P. HUOT[1,2,3,5]
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**Abstract:** Dyskinesia causes significant morbidity to many of patients with advanced Parkinson's disease. Serotonin 2A (5-$HT_{2A}$) receptor blockade is a validated approach to alleviate dyskinesia, but its effectiveness appears to be of limited magnitude. Recently, we have demonstrated that activation of metabotropic glutamate 2 ($mGlu_2$) receptors with the positive allosteric modulator (PAM) LY-487,379 reduces L-3,4-dihydroxyphenylalanine (L-DOPA) induced dyskinesia in the 6-hydroxydopamine (6-OHDA)-lesioned rat. Because 5-$HT_{2A}$ and $mGlu_2$ receptors form a functional hetero-complex, we hypothesised that combining EMD-281,014, the most selective 5-$HT_{2A}$ antagonist commercially-available with LY-487,379, the most selective $mGlu_2$ PAM commercially-available, would be more effective at alleviating dyskinesia than modulating 5-$HT_{2A}$ and $mGlu_2$ receptors separately.
Female Sprague-Dawley rats were rendered hemi-parkinsonian by stereotaxic injection of 6-OHDA into the medial forebrain bundle. Following a recovery period, degree of parkinsonism was assessed through the cylinder test. Severely parkinsonian rats were then primed with chronic L-DOPA administration to induce stable axial, limbs and oro-lingual (ALO) abnormal involuntary movements (AIMs). On experimental days, rats were administered L-DOPA in combination with previously determined effective doses of each of EMD-281,014 (vehicle, 0.03 and 0.1 mg/kg s.c) and LY-487,379 (vehicle and 0.1 mg/kg s.c.). After a 3-day washout period, an acute low-dose L-DOPA challenge was administered with the combination EMD-281,014/LY-487,379, and the effect on L-DOPA anti-parkinsonian action was determined by the cylinder test.
Contrary to our hypothesis, we found that the combination EMD-281,014/LY-487,379 did not provide further anti-dyskinetic benefit compared to administration of each compound separately.

The combination of EMD-281,014 and LY-487,379 did not have any effect on L-DOPA anti-parkinsonian action.
Our results suggest that there may not be further anti-dyskinetic benefit achieved when combining 5-$HT_{2A}$ blockade and $mGlu_2$ activation in the 6-OHDA-lesioned rat model of PD. Whereas these results require confirmation in other animal models of PD, notably the parkinsonian primate, the results presented in this Abstract, coupled with these presented in the companion Abstract on EMD-281,014 and LY-354,740, suggest that there may be a maximal anti-dyskinetic benefit beyond which it may be impossible to go when modulating both halves of the 5-$HT_{2A}$/$mGlu_2$ receptor hetero-complex.

**Disclosures: A. Hamadjida:** None. **E. Bourgeois-Cayer:** None. **S. Belliveau:** None. **I. Frouni:** None. **C. Kwan:** None. **D. Bédard:** None. **P. Huot:** None.

**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.02/DD4

**Topic:** C.03. Parkinson’s Disease

**Support:** Weston Brain Institute

**Title:** Pharmacokinetic profile of the highly selective 5-$HT_{2A}$ receptor antagonist EMD-281,014 in the rat and the common marmoset

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**Abstract:** Serotonin 2A (5-$HT_{2A}$) receptor blockade represents a promising approach to alleviate symptoms of a breadth of neuro-psychiatric disorders, from schizophrenia to Parkinson’s disease. EMD-281,014 is the most selective 5-$HT_{2A}$ antagonist currently available and therefore represents the ideal compound to assess the behavioural effects of antagonising 5-$HT_{2A}$ receptors. Moreover, it has already entered clinical testing, has a documented pharmacokinetic (PK) profile in human, and well-tolerated plasma levels in clinic are known. Here, we have determined the PK profile of EMD-281,014 in the rat and the common marmoset.

In rats, blood samples were collected at more than 10 different time points, at baseline and following sub-cutaneous (sc) administration of EMD-281,014 0.01, 0.03 and 0.1 mg/kg. In marmosets, we have used a sparse sampling technique, where minimal blood volume was collected at 10 different time points, from a limited number of animals, at baseline and following sc administration of EMD-281,014 0.1 mg/kg, Additional samplings were conducted at maximal plasma concentration ($C_{max}$) time ($T_{max}$) with EMD-281,014 0.01 and 0.03 mg/kg; mathematical modelisation was employed to predict the PK profile of these two additional doses. Plasma levels of EMD-281,014 were determined by liquid chromatography and tandem mass spectrometry (LC-MS/MS). Compartmental analysis was used to determine PK parameters such as $T_{max}$, $C_{max}$ and half-life ($T_{1/2}$).
In rats, $T_{max}$ occurred 10 min after injection, regardless of the dose administered, while $T_{1/2}$ was 117, 103 and 73 min, for EMD-281,014 0.01, 0.03 and 0.1 mg/kg, respectively. In marmosets, EMD-281,014 showed a slower absorbtion and metabolism with $T_{max}$ occurring 30 min after injection, while $T_{1/2}$ was 168, 144 and 120 min, for the doses 0.01, 0.03 and 0.1 mg/kg, respectively.
To the best of our knowledge, despite that it had been tested in the clinic, the PK profile of EMD-281,014 was undisclosed in both rat and marmoset. We hope that our results will help to refine experiments where this extremely-selective compound is used in pre-clinical research, so that doses leading to plasma levels shown to be well tolerated by humans will be employed.

**Disclosures: D. Bédard:** None. **A. Hamadjida:** None. **F. Gaudette:** None. **S.G. Nuara:** None. **J.C. Gourdon:** None. **F. Beaudry:** None. **P. Huot:** None.

**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.03/DD5

**Topic:** C.03. Parkinson’s Disease

**Support:** Weston brain

**Title:** High dose of EMD-281,014, a highly selective 5-$HT_{2A}$receptor antagonist, does not lead to further reduction of dyskinesia or psychosis, in the MPTP-lesioned marmoset model of Parkinson’s disease

**Authors: *S. G. NUARA**[1], A. HAMADJIDA[4,2], I. FROUNI[4,5], C. KWAN[4,2], D. BÉDARD[4], J. C. GOURDON[1], P. HUOT[4,2,5,3,6]
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**Abstract:** L-3,4-dihydroxyphenylalanine (L-DOPA) is the most effective treatment for Parkinson's disease (PD) but, with long-term treatment, patients develop complications such as L-DOPA induced dyskinesia and, though other factors might also be at play, psychotic behaviours. Pre-clinical and clinical studies have demonstrated that antagonising serotonin 2A (5-$HT_{2A}$) receptors is effective at alleviating both dyskinesia psychosis in PD. Recently, we have demonstrated that EMD-281,014, an extremely selective 5-$HT_{2A}$ antagonist, significantly reduce dyskinesia and psychosis-like behaviours (PLBs), at doses leading to clinically-relevant plasma levels, in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned marmoset model of PD. However, whether higher doses of EMD-281,014 would lead to greater anti-dyskinetic and anti-psychotic benefit remains unknown; in other words, given its extreme selectivity, EMD-281,014 is the ideal compound to determine whether there is, or not, a ceiling to the benefit that can be achieved by blocking 5-$HT_{2A}$ receptors. Here, we sought to answer this question.
Six marmosets were rendered parkinsonian by MPTP administration. Following repeated administration of L-DOPA to elicit stable dyskinesia and PLBs, animals were administered acute challenges of EMD-281,014 (0.1, 1, 10 mg/kg) or vehicle, in combination with L-DOPA, after which the severity of dyskinesia, PLBs and parkinsonian disability was rated.
EMD-281,014 (0.1, 1 and 10 mg/kg) significantly reduced the severity of peak dose dyskinesia, by ≈ 41%, ≈ 43% and ≈ 37% (each $P < 0.05$), respectively when compared to L-DOPA/vehicle. Peak dose PLBs were also reduced by ≈ 41% and ≈ 43% (both $P < 0.05$), respectively, when EMD-281,014 (0.1 and 1 mg/kg) was added to L-DOPA, compared to L-DOPA/vehicle, while EMD-281,014 10 mg/kg reduced severity of PLBs 2-4h after treatment administration, by ≈ 50% ($P < 0.05$), when compared to L-DOPA/vehicle. The anti-dyskinetic and anti-psychotic effects of EMD-281,014 were achieved without interfering with L-DOPA anti-parkinsonian action.
Our results confirm the findings that we made in a previous experiment, *i.e*. that highly-selective blockade of 5-$HT_{2A}$ receptors is effective at alleviating psychosis and dyskinesia in PD, without interfering with L-DOPA anti-parkinsonian action. However, our results also suggest that there may be a ceiling to the potential anti-dyskinetic and anti-psychotic benefits conferred by selective 5-$HT_{2A}$ blockade.

**Disclosures: S.G. Nuara:** None. **A. Hamadjida:** None. **I. Frouni:** None. **C. Kwan:** None. **D. Bédard:** None. **J.C. Gourdon:** None. **P. Huot:** None.

**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.04/DD6

**Topic:** C.03. Parkinson's Disease

**Support:** Weston Brain Institute

**Title:** The anti-dyskinetic effect of combined 5-$HT_{2A}$ receptor blockade with $mGlu_2$ receptor orthosteric activation in the 6-OHDA lesioned rat model of Parkinson's disease

**Authors: *I. FROUNI**[1,2], É. BOURGEOIS-CAYER[2,3], S. BELLIVEAU[2,3], D. BÉDARD[2], A. HAMADJIDA[2,3], P. HUOT[2,3,1,4,5]
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**Abstract:** L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesia undermines the quality of life of patients with advanced Parkinson's disease (PD). There are numerous studies that showed that antagonising serotonin 2A (5-$HT_{2A}$) receptors may reduce L-DOPA-induced dyskinesia, but the evidence gathered to date suggests that there might be a ceiling to the effectiveness of this approach. Based on the fact that 5-$HT_{2A}$ receptors form a hetero-complex with metabotropic glutamate 2 ($mGlu_2$) receptors, we hypothesised that a synergistic effect may ensue upon simultaneous 5-$HT_{2A}$ blockade and $mGlu_2$ activation. Here, we have assessed the effect on dyskinesia of EMD-281,014, the most-selective 5-$HT_{2A}$ antagonist available, and of LY-354,740, a selective $mGlu_2$ orthosteric agonist, in the 6-hydroxydopamine (6-OHDA)-lesioned rat. Parkinsonism was induced in female rats by stereotaxic injection of 6-OHDA into the medial forebrain bundle. Following a recovery period, degree of parkinsonism was assessed using the cylinder test. Rats were primed with daily administration of L-DOPA to develop axial, limbs and oro-lingual (ALO) abnormal involuntary movements (AIMs). On experimental days, rats were administered L-DOPA in combination with previously determined effective doses of each of EMD-281,014 (vehicle, 0.03 and 0.1 mg/kg s.c) and LY-354,740 (vehicle and 0.1 mg/kg s.c.). After a 3-day washout period, an acute low-dose L-DOPA challenge was administered with the combination EMD-281,014/LY-354,740, and the effect on L-DOPA anti-parkinsonian action was determined by the cylinder test. Unlike what we had hypothesised, no synergistic effect was achieved by simultaneously administering EMD-281,014 and LY-354,740. The combination of EMD-281,014 and LY-354,740 did not have any effect on L-DOPA anti-parkinsonian action. Our results suggest that, at least in the 6-OHDA-lesioned rat model of PD, there does not seem to have any added anti-dyskinetic benefit resulting from combining 5-$HT_{2A}$ blockade and $mGlu_2$ activation. Further studies, perhaps with different compounds, or in different animal models, are required to shed light on this intriguing finding.

**Disclosures: I. Frouni:** None. **É. Bourgeois-Cayer:** None. **S. Belliveau:** None. **D. Bédard:** None. **A. Hamadjida:** None. **P. Huot:** None.

**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.05/DD7

**Topic:** C.03. Parkinson's Disease

**Support:** Weston Brain Institute

**Title:** The anti-dyskinetic effect of 5-$HT_3$ receptor blockade with ondansetron and granisetron in the 6-OHDA-lesioned rat model of Parkinson's disease

**Authors: *C. KWAN**[1,2,3], I. FROUNI[1,2], D. BÉDARD[1], A. HAMADJIDA[1,3], P. HUOT[1,2,3,4,5]
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**Abstract:** The most effective symptomatic treatment for Parkinson's disease (PD) is dopamine replacement therapy with L-3,4-dihydroxyphenylalanine (L-DOPA). However, long-term use of L-DOPA leads to the emergence of complications such as L-DOPA-induced dyskinesia in the vast majority of patients. Previous studies have demonstrated that antagonising serotonin type 3 receptor (5-$HT_3$R) reduces dopamine levels within the basal ganglia, which could therefore regulate the erratic dopamine release that occurs in dyskinesia and, consequently, alleviate L-DOPA-induced dyskinesia. We hypothesised that selective 5-$HT_3$R blockade with the clinically available and highly-selective antagonists ondansetron and granisetron would reduce the severity of dyskinesia in the 6-hydroxydopamine (6-OHDA)-lesioned rat. Female Sprague-Dawley rats were injected 6-OHDA into the medial forebrain bundle and evaluated for the degree of parkinsonism by the cylinder test. Two sets of experiments were then conducted. In the first series, rats were primed with L-DOPA to induce the expression of stable axial, limbs and oro-lingual (ALO) abnormal involuntary movements (AIMs). On experimental days, animals were administered different doses of ondansetron, granisetron or vehicle, in combination with L-DOPA, and the severity of ALO AIMs was rated. The effect of ondansetron and granisetron on L-DOPA anti-parkinsonian action was also determined by the cylinder test. In the second set, following 6-OHDA lesion, animals were administered the effective dose of ondansetron (determined in the first set) or vehicle, started concurrently with L-DOPA, once daily for 22 days, during which the severity of ALO AIMs was monitored weekly. After a 3-day washout, an acute L-DOPA challenge was administered and ALO AIMs severity was assessed. When compared to vehicle, acute challenges of ondansetron 0.0001 mg/kg significantly reduced the duration and amplitude of ALO AIMs, by 53% and 51%, respectively (both $P < 0.01$), while acute challenges of granisetron 0.01 mg/kg significantly decreased the duration and amplitude of

ALO AIMs, by 46% and 50%, respectively ($P < 0.05$ and $P < 0.01$). Ondansetron, when started concurrently with L-DOPA, attenuated the development of ALO AIMs, by 51% ($P < 0.05$), when compared to vehicle. The anti-dyskinetic efficacy of ondansetron and granisetron did not interfere with L-DOPA anti-parkinsonian action. Our results suggest that selective 5-$HT_3$R blockade with ondansetron and granisetron is a novel and effective therapeutic approach to reduce the severity and attenuate the development of L-DOPA-induced dyskinesia that is likely to be well-tolerated by PD patients.

**Disclosures: C. Kwan:** None. **I. Frouni:** None. **D. Bédard:** None. **A. Hamadjida:** None. **P. Huot:** None.

**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.06/DD8

**Topic:** C.03. Parkinson’s Disease

**Support:** NRF-2017R1A5A2014768

**Title:** MHE173 ameliorates motor deficits and dopaminergic neuronal damage induced by a specific pathobiont in mice

**Authors: *J. CHOI**, S.-M. LIM, D.-H. KIM, M. OH
Kyung Hee Univ., Seoul, Korea, Republic of

**Abstract:** Growing evidences on the pathological roles of gut microbiota have been steadily reported, but whether a specific gut pathobiont may cause Parkinson’s disease (PD) remains unexplored. In this study, we describe for the first time that a specific gut pathobiont may involve in the pathogenesis of PD. We found the remarkable increase of *Enterobacteriaceae* bacterial colonies in PD animal models and that was identified as PB-1, a specific gut pathobiont. Oral administration of PB-1 significantly induced motor deficits in parallel with dopaminergic neuronal damage and neuroinflammation in normal mice. We reveal that this phenomenon is originated from gut leakage and inflammatory responses by lipopolysaccharides produced from PB-1. In addition, we found that MHE173, a Korean herbal medicine extract, could modulate PB-1-induced behavioral and pathological abnormalities. These findings indicate the therapeutic potentials of MHE173 on PD-like pathological conditions induced by a specific pathobiont. This work was also supported by Medical Research Center Program through the National Research Foundation of Korea funded by the Ministry of Science and ICT (NRF-2017R1A5A2014768).

**Disclosures: J. Choi:** None. **S. Lim:** None. **D. Kim:** None. **M. Oh:** None.

**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.07/DD9

**Topic:** C.03. Parkinson’s Disease

**Support:** 1160441-1
S2294686

**Title:** Neuroprotective effects of MHE100 in amyloid beta-induced Alzheimer's disease models

**Authors: *N. KIM**[1], J. CHOI[1], S. PARK[2], J. LEE[1], M. OH[1]
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**Abstract:** Alzheimer’s disease (AD), an irreversible and progressive degenerative disorder of the brain, is characterized by memory impairment, loss of neuron and synapse. Although the cause of AD has not been clearly elucidated, accumulation of amyloid beta (Aβ) is considered the major pathological feature in AD. Aβ can promote neuronal cell degeneration by the increases of intracellular reactive oxygen species, which reduce anti-oxidative enzymes such as heme oxygenase-1 (HO-1) and NAD(P)H quinine dehydrogenase 1 (NQO1). Thus, the aim of this study was to explore the neuroprotective effects of Korea herbal medicine extract (MHE100) in $A\beta_{25-35}$ plaque-induced Alzheimer’s disease models. MHE100 significantly ameliorated memory impairment, neuronal cell death and synaptotoxicity via elevated expression of phosphorylated-cyclic AMP response element-binding protein (pCREB) in $A\beta_{25-35}$ plaque-injected mice. Furthermore, MHE100 inhibited intracellular ROS generation induced by $A\beta_{25-35}$ plaque via elevated expression levels of pCREB, HO-1 and NQO1, resulting in the protection of hippocampal cells. These results suggest that MHE100 may be a potential candidate to regulate the progression of AD.

**Disclosures: N. Kim:** None. **J. Choi:** None. **S. Park:** None. **J. Lee:** None. **M. Oh:** None.

**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.08/DD10

**Topic:** C.03. Parkinson’s Disease

**Support:** NIH grant 1R21NS098079-01

**Title:** Virally-mediated expression of the dopamine autoreceptor in the dorsal raphe nucleus blocks levodopa-induced dyskinesia development by inhibiting "false DA neurotransmission" from serotonin neurons

**Authors: *R. C. SELLNOW**[1,2], A. R. WEST[4], K. STEECE-COLLIER[1], N. E. CHAMBERS[5], I. M. SANDOVAL[3], M. J. BENSKEY[1], C. R. BISHOP[5], F. P. MANFREDSSON[1,6]
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**Abstract:** The current leading treatment for the motor symptoms in Parkinson's disease (PD) is levodopa (L-DOPA). Unfortunately, the majority of patients treated with L-DOPA inevitably develop debilitating and disruptive motor side-effects called L-DOPA-induced dyskinesias (LID). While the mechanisms underlying LID are multifaceted, a wealth of research suggests that the dysregulation of dopamine (DA) synthesis and release as a false neurotransmitter by striatal serotonin (5-HT) projections originating from dorsal raphe nucleus (DRN) neurons plays a pivotal role in dyskinesogenesis. While DRN 5-HT neurons can convert L-DOPA to DA, they lack the regulatory mechanisms needed for modulation of DA signaling. This is hypothesized to lead to an unregulated release of DA into the DA-depleted, hypersensitive striatum, promoting dyskinesogenesis. Preclinical studies have shown that 5-HT lesions of the DRN and 5-HT1 receptor agonists can ameliorate LID. Unfortunately, promising preclinical results have been not translated clinically. While there is an abundance of circumstantial support for the 5-HT hypothesis of LID, there is no direct evidence that dysregulated DA release from 5-HT neurons causes LID formation. In the present study, we aimed to determine if LID could be prevented by ectopically expressing DA regulatory elements—specifically the D2 autoreceptor (D2R)—in DRN neurons. Adult male rats were rendered parkinsonian with 6-hydroxydopamine, followed by delivery of rAAV2/9 expressing either D2R or GFP to the DRN. When chronically treated with L-DOPA (2-12mg/kg), animals overexpressing D2R showed a complete resistance to LID development, whereas GFP controls showed robust LID expression. *In vivo* microdialysis showed that D2R expression in raphe neurons reduced DA efflux in the striatum with no effect on 5-HT release. This study definitively confirms that abnormal DA release from 5-HT neurons in a parkinsonian model is dyskinesiogenic, and more importantly show that D2R expression in DRN neurons is sufficient to achieve and maintain proper regulation of DA release. rAAV-D2R treatment did not change anti-parkinsonian efficacy of L-DOPA shown with cylinder and stepping tests. This direct evidence of false neurotransmission and its prevention with rAAV-D2Rs gene therapy confirms the 5-HT hypothesis in LID and a modulation of 5-HT neurons as a potential therapeutic approach for patients. Ongoing work is utilizing in vivo electrophysiology to measure the impact of D2Rs expression on serotonergic neuronal activity.

**Disclosures: R.C. Sellnow:** None. **A.R. West:** None. **K. Steece-Collier:** None. **N.E. Chambers:** None. **I.M. Sandoval:** None. **M.J. Benskey:** None. **C.R. Bishop:** None. **F.P. Manfredsson:** None.

**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.09/DD11

**Topic:** C.03. Parkinson's Disease

**Support:** NS084869
NS070577

**Title:** Columnar injector for intracerebral cell therapy

**Authors: *B. SONG**[1,2], P. R. LEBLANC[1,2], M. FEITOSA[1,2], K.-S. KIM[1,2], J. S. SCHWEITZER[3]
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**Abstract:** Cell therapy for various degenerative diseases of the brain such as Parkinson's disease is an important and growing area in the therapeutic armamentarium, but surgical transplantation techniques for cellular grafts have been neither systematically investigated nor standardized. Accordingly, traumatic damage to the host tissue during transplantation and suboptimal survival and function of grafted cells are major unresolved issues for cell therapy. Here, we describe a system which we term "columnar injection technique", for precise control of injection volume and rate that makes use of the surgical entry track itself as the deposition site for the graft. This is designed to reduce pressure damage to the host tissue and results in a column of graft material with a greater surface area to volume ratio than traditional bolus injection techniques, allowing better graft uniformity and survival.

**Disclosures: B. Song:** None. **P.R. Leblanc:** None. **M. Feitosa:** None. **K. Kim:** None. **J.S. Schweitzer:** None.

**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.10/DD12

**Topic:** C.03. Parkinson's Disease

**Title:** Preclinical characterization of AN317, a novel subtype selective nicotinic α6 receptor agonist with potential in Parkinson's disease

**Authors: T. DYHRING**[1], *K. S. NIELSEN[1], D. AMRUTKAR[1], P. K. AHRING[1], J. KLEIN[1], M. VAN HOUT[2], D. PETERS[3], D. F. EMERICH[4], L. WAHLBERG[4], P. CHRISTOPHERSEN[1]
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**Abstract:** Degeneration of the dopaminergic neurons in the nigrostriatal pathway is the major cause of the motor features associated with the neurodegenerative disorder Parkinson's disease (PD), which is characterized by rigidity, tremor and bradykinesia. Apart from dopamine (DA) itself, numerous neurotransmitter systems are involved in the finetuning of DA release in the striatum, including the nicotinic cholinergic system. Indeed, there is an extensive anatomical overlap between dopaminergic and cholinergic neurons, and activation of striatal nAChRs has been shown to modulate DA release both *in vitro* and *in vivo*.
Extensive studies in parkinsonian animal models show that nicotine has a protective effect against nigrostriatal damage - findings that may explain the well-established decline in PD incidence with tobacco use. In addition, several studies have shown that nicotine reduces L-dopa-induced dyskinesias (LIDs), a debilitating complication of DA replacement therapy for PD. These combined observations suggest that nAChR stimulation may be of therapeutic benefit in relation to neuroprotection in PD and treatment of LIDs. In this respect, drugs targeting α6-containing nAChRs (α6* nAChRs) have attracted immense interest since these receptors are highly and specifically expressed in midbrain dopaminergic neurons, making this receptor subtype an attractive drug target.
Here, we present preclinical data on AN317, which is a potent agonist of α6* nAChRs with functional selectivity over other nicotinic receptor subtypes. *In vitro* studies using rat primary neurons and midbrain slices indicated that striatal DA transmission was stimulated by AN317, since both the firing rate of putative dopaminergic neurons and DA release was significantly increased by AN317. In a dopaminergic neuronal survival assay using rat primary mesencephalic cultures, AN317 afforded a significant and concentration-dependent neuroprotective effect upon treatment with the neurotoxin MPP+. Furthermore, in a LIDs model applying 6-OHDA lesioned rats, AN317 induced a significant and dose-related decrease in L-DOPA induced abnormal involuntary movements (AIMs). Altogether, these data suggest that AN317 represents an interesting drug candidate in relation to the treatment of various aspects of PD.

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**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.11/DD13

**Topic:** C.03. Parkinson’s Disease

**Support:** Gifts to the Brain Restoration Center
Tom Dupree for Parkinson's Disease Research
University of Kentucky start-up funds
National Center for Advancing Translational Sciences grant UL1TR000117

**Title:** Neuro-avatar: A reverse translational model of an ongoing cell therapy clinical trial for Parkinson's disease

**Authors: *A. S. WELLEFORD**, N. EL SEBLANI, C. G. VAN HORNE, J. E. QUNITERO, F. POMERLEAU, G. A. GERHARDT
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**Abstract:** Currently two clinical trials (NCT01833364 and NCT02369003) are underway which feature the implantation of autologous peripheral nerve grafts to the brain (targeted to the Substantia Nigra, Nucleus Basalis of Meynert, or Putamen) in combination with Deep Brain Stimulation (DBS) for the treatment of patients with Parkinson’s disease. This nerve tissue is harvested from the sural nerve, a cutaneous sensory nerve located in the lateral ankle, of patients undergoing DBS surgery. The nerve receives a conditioning injury 14 days before grafting, and samples are collected from the pre-conditioned and post-conditioned nerve. As of 5/1/18, 55 patients have received DBS plus the graft procedure.
RNA sequencing of these nerve samples shows transcriptome changes consistent with the expected pro-regenerative changes of transdifferentiated repair phenotype Schwann cells. However, the neurobiology of the graft within the brain, the regenerative activity of the pre vs post-lesioned nerve, and the survival of grafted tissue have not been examined.
In order to address these questions, this study aimed to develop an animal model of the grafting procedure using the same human tissue grafted into patients with Parkinson’s disease. Athymic nude (Hsd:RH-Foxn1$^{rnu}$) rats were stereotaxically implanted with segments of human peripheral nerve (pre-conditioned or post-conditioned) into the dorsal striatum. Each animal received a unilateral graft with a contralateral sham insertion. Two weeks or six months post-implant the brains of these animals were processed for histopathological analyses. Assessment of graft cell survival, graft morphology, and host tissue response will be reported. In summary, this study

completes the translational science cycle by using clinical trial findings and samples to answer basic science questions that will in turn guide future clinical trial design.

**Disclosures: N. El Seblani:** None. **C.G. van Horne:** None. **J.E. Qunitero:** None. **F. Pomerleau:** None. **G.A. Gerhardt:** None.

**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.12/DD14

**Topic:** C.03. Parkinson’s Disease

**Title:** Immunomodulation of mature dendritic cells in Parkinson’s disease. A novel role of intracellular toll like receptors

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**Abstract:** Parkinson's disease (PD) is a devastating clinical disorders that is characterized by progressive and selective neuronal injury and cell death. Recent studies have provided accumulating evidence for a significant role of the immune system and neuroinflammation in PD pathogenesis. In particular, neuroinflammation associated to PD is the prerequisite for the maturation of dendritic cells (DC) and their migration to the respective sites in the brain. It has become clear that Toll-like receptors (TLRs), a major family of pattern recognition receptors could mediate innate and adaptive immune response, providing an important mechanism by which microglia are able to sense both pathogen- and host derived ligands within the CNS.
The aim of our study was to evaluate the role of TLR 7,8 and 9 in DC maturation that trigger to adaptive autoimmune response related to PD.
We performed an *in vivo* model of PD, by MPTP, in single KO mice for TLR7$^{-}$, TLR8$^{-}$ and TLR9$^{-}$; and in double KO mice for TLR 7/8$^{-/-}$ and TLR7/9$^{-/-}$. All animals was compared with WT animals used as a control group.
Animals were sacrificed after 8 days and their midbrains were harvested, sectioned and processed in order to evaluate: the principal markers of PD with particular attention to TH, DAT and α-synuclein aggregate; astrocytes and microglia activation through GFAP and IBA-1; pro-inflammatory cytokine’s expression such as INF-γ and TNF-α like major product of activated microglia and astrocytes. Moreover to evaluate the formation of neuromelanin pigments in the midbrain we made the Masson-Fontana staining.
The result obtained demonstrated that the genetic absence of TLR 7,8 and 9 modified PD pathway increasing significantly the immunoreactivity for TH and DAT compared to PD groups where we found an evident reduction of these markers.

Therefore, TLRs could be considered as a possible target to develop new therapies for neurodegenerative disorders.

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**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.13/DD15

**Topic:** C.03. Parkinson’s Disease

**Support:** SAF2014-56101-R

**Title:** The effects of stem cell therapy on adult mouse neurogenesis in Parkinson's disease

**Authors: A. NELKE**, S. GARCIA-LOPEZ, A. MARTINEZ-SERRANO, *M. P. PEREIRA
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**Abstract:** Introduction: Parkinson´s disease (PD) is the second most common neurodegenerative disease in the world and the most common motor movement disorder. PD is characterized by the impairment and death of dopaminergic neurons (DAn) in the Substantia Nigra pars compacta (SNpc). Current pharmaceutical treatments do not improve the patient´s life long-term; thus, a goal of PD therapy research becomes cell replacement. Here we have tested a stem cell therapy in a PD rodent model. Methods: Adult (5 month-old) and middle-age (12 month-old) male C57BL/6 mice received a transplant of human ventral mesencephalic hVM1 clone 32 human neural stem cells, or buffer, in the left striatum after receiving 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) injections. One and four months after transplantation, mice were sacrificed. Results: DAn loss in the SNpc and tyrosine hydroxylase (TH) fiber loss in the striatum of adult mice was lessened in stem cell-transplanted compared to buffer-transplanted mice. The stem cell transplant had an effect on neuroinflammation, namely the response of astrocytes and microglia, and in addition, behavioral changes were observed via open field and paw print tests. These aforementioned changes were not observed in middle-age mice. Neurogenesis in the subventricular and subgranular zones, as shown via doublecortin (Dcx) and nestin immunostaining, was decreased in all MPTP-treated mice one and four months post-transplant; this diminution was rescued in adult mice in the subgranular zone one month post-transplant, but not in the subventricular zone.
Conclusions: Transplantation of hVM1 clone 32 human neural stem cells, which have been shown to differentiate into dopaminergic neurons in vitro, triggers behavioral amelioration and reduced dopaminergic cell loss in adult mice. However, this is not observed in middle-age mice, thus emphasizing the importance of the age of recipient and the stage of PD progression when

receiving a transplant, and stressing the fact that some preclinical studies need to be done in animals older than middle-age, more similar to the age of onset of PD.

**Disclosures: A. Nelke:** None. **S. Garcia-Lopez:** None. **A. Martinez-Serrano:** None. **M.P. Pereira:** None.

**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.14/DD16

**Topic:** C.03. Parkinson's Disease

**Support:** Michael J. Fox Foundation

**Title:** Monitoring dopamine dynamics in a G2019S LRRK2 rat model of Parkinson's disease

**Authors: *Z. SHU**[1], H. A. LAM[1], A. B. WEST[2], N. T. MAIDMENT[1]
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**Abstract:** Mutations in Leucine-rich repeat kinase 2 (LRRK2) are responsible for a large number of familial Parkinson's disease (PD) cases and variation in the LRRK2 genetic locus is a risk factor for sporadic PD. The most common mutation, G2019S, results in increased kinase activity. Consequently, LRRK2 kinase inhibitors are being aggressively developed as a potential treatment strategy, but much remains to be learned about the role of LRRK2 in neuronal function and the mechanism by which LRRK2 overactivity impacts neuronal survival. However, mounting evidence supports a role for LRRK2 in vesicle cycling and dopamine homeostasis. We are using fast scan cyclic voltammetry (FSCV) in a human G2019S LRRK2 BAC transgenic rat to probe the influence of the mutation on dopamine (DA) dynamics prior to degeneration of DA cells or terminals. FSCV coupled with carbon fiber microelectrodes implanted in the dorsal striatum of anesthetized rats revealed augmented DA responses evoked by electrical stimulation of the medial forebrain bundle, preferentially during 6-pulse ultrashort stimulations. Kinetic analysis of the DA responses showed that the G2019S mutation did not change the apparent $V_{max}$ or $K_M$ of DA uptake but rather increased DA release at the beginning of the stimulation. Pharmacological manipulation of the DA transporter (DAT) with nomifensine confirmed that impairment of DAT is not likely to account for the elevation in evoked DA signals. However, normalization of responses in the present of the D2 autoreceptor antagonist and agonist, raclopride and quinpirole, suggests an impairment in D2-mediated autoinhibition in the mutant. The enhanced DA responses in the G2019S rats are reversed by 5-day oral administration of LRRK2 inhibitor PF-360.

**Disclosures: Z. Shu:** None. **H.A. Lam:** None. **A.B. West:** None. **N.T. Maidment:** None.

**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.15/DD17

**Topic:** C.03. Parkinson's Disease

**Support:** NIEHS 1-R25-ES025494
Jerry T. and Gelnda G. Jackson Fellowsip in Parkinson's esearch to the University of Arizona

**Title:** Evaluating the effects of sub-anesthetic ketamine on microglia morphology in a pre-clinical model of L-DOPA induced dyskinesia

**Authors: *A. E. POTTENGER**[1], M. J. BARTLETT[2], T. FALK[3], H. W. MORRISON[4]
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**Abstract:** Parkinson's disease (PD) is a neurodegenerative disease caused by the death of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc), characterized by motor dysfunction. While PD symptoms are treated with levodopa (L-DOPA), continuous L-DOPA use can cause L-DOPA-induced dyskinesia (LID). We have previously demonstrated that sub-anesthetic ketamine reduced LID, measured by abnormal involuntary movements (AIMs). The literature suggests that ketamine treatment can lead to changes in dendritic spines. Microglia may play a role by phagocytosing an abundance of neuronal spines. In this exploratory study, we hypothesized that ketamine would prevent AIMs and increase microglia ramified morphology - an indicator of a microglia response. We studied the behavioral and histological outcomes with evaluators blinded to conditions. Male Sprague-Dawley rats (250 g, n = 4/group) were unilaterally lesioned with 6-hydroxydopamine (6-OHDA) to create a PD model. PD rats were then primed with daily injections of L-DOPA (6 mg/kg, *i.p.*). On days 0 and 7, rats were treated with ketamine (5x *i.p.* injections of 20 mg/kg, 2-hours apart; 5$^{th}$ injection was paired with L-DOPA) or vehicle. AIMs were scored every 3-4 days to assess changes in LID; all data were tested using ANOVA. On day 14, ketamine-treated rats showed a nearly 60% reduction in their total number of limb, axial, and oral AIMs as compared to controls ($p < 0.005$). A sub-analysis of AIMs scores in ketamine-treated animals revealed two distinct groups: those that responded to the ketamine treatment (KR) and ketamine non-responders (KNR), which showed no difference in AIMs as compared to controls. Brain tissue was collected for immunohistochemical staining in the SNpc. Microglia and DA neurons were visualized using antibodies against ionized calcium-binding adapter molecule and tyrosine hydroxylase, respectively. The SNpc on both the injured and uninjured side were imaged using confocal microscopy to obtain photomicrographs

for image analysis. All data collected from microglia analyses were normalized to the matching non-lesioned hemisphere. In the KR group, we observed a decrease in the number of microglia ($p < 0.001$ vs vehicle) and an increase in cell ramification (endpoints/cell $p < 0.0001$ and process length/cell $p < 0.001$ vs vehicle). These data are suggestive of a lingering microglia response to 6-OHDA injury in the SNpc among vehicle and KNR groups that was not present in the KR group. Future directions include microglia analysis in the motor cortex and striatum, evaluating if morphometrics and behavioral analysis correlate, and testing ketamine's effects on microglia morphologies in acute brain slices.

**Disclosures: A.E. Pottenger:** None. **M.J. Bartlett:** None. **T. Falk:** None. **H.W. Morrison:** None.

**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.16/DD18

**Topic:** C.03. Parkinson's Disease

**Support:** Fujifilm Cellular Dynamics Inc.

**Title:** Superior survival, innervation, and functional recovery by day 17 differentiated dopamine stem cells in a rat model of Parkinson's disease

**Authors: *B. M. HILLER**[1], D. J. MARMION[2], C. A. CHAVEZ[4], C. A. THOMPSON[4], N. A. ELLIOTT[4], C. W. MCMAHON[4], J. H. KORDOWER[3]
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**Abstract:** As the second most common neurodegenerative disease, Parkinson's disease (PD) presents an immense burden for the aging population. PD is a progressive neurodegenerative disease characterized by the loss of dopamine neurons in the substantia nigra subsequent to the loss of striatal dopaminergic tone. The current gold standard treatment for PD is limited to oral levodopa which eventually can lead to the development of motor fluctuation and dyskinesias. Early work with fetal and embryonic tissues suggests that a cell replacement therapy may offer relief for motor deficits associated with PD. However, these tissue sources are associated with ethical and logistical concerns.
Previously, we have shown that cryopreserved human induced pluripotent stem cells (hiPSC) reprogrammed to post-mitotic midbrain dopamine (mDA) neurons survive engraftment in the rat striatum with low levels of proliferation. Further, when striatally transplanted following a 6-hydroxydopamine lesion to the medial forebrain bundle, hiPSC-mDA neurons reverse motor asymmetry as measured by amphetamine-induced rotations (Wakeman *et al.*, 2017).

In the present study we tested the in vivo efficacy of hiPSC-mDA neurons and progenitor cells after transitioning the differentiation protocol to a cell therapy-compatible manufacturing process. $4.5x10^5$ cells were unilaterally transplanted to the 6-hydroxydopamine-lesioned striatum of athymic nude rats. Here we show that hiPSC-mDA neurons progenitors cryopreserved at day 17 (D17), D24, and D37 of the differentiation process and iCell DopaNeurons survive and project tyrosine hydroxylase-immunoreactive processes into the host parenchyma. Animals that received grafts of D17 and D24 progenitor cells showed fully reversed amphetamine-induced rotations by 6 months post-transplant, with complete reversal seen by 4 months post-grafting in animals treated with D17 progenitors. In addition, the D17 progenitors exhibited superior mDA neuron and innervation of the striatum. We found low levels of proliferating cells and no evidence of teratoma formation within the grafts as indicated by human specific Ki-67 staining and did not observe cell migration or aberrant outgrowth, demonstrating a safety profile amenable to translation to the clinic. Ongoing studies will seek to determine optimal dosing to inform future human trials.

**Disclosures: B.M. Hiller:** F. Consulting Fees (e.g., advisory boards); FCDI. **D.J. Marmion:** F. Consulting Fees (e.g., advisory boards); FCDI. **C.A. Chavez:** A. Employment/Salary (full or part-time):; FCDI. **C.A. Thompson:** A. Employment/Salary (full or part-time):; FCDI. **N.A. Elliott:** A. Employment/Salary (full or part-time):; FCDI. **C.W. McMahon:** A. Employment/Salary (full or part-time):; FCDI. **J.H. Kordower:** 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.; FCDI. F. Consulting Fees (e.g., advisory boards); FCDI.

**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.17/EE1

**Topic:** C.03. Parkinson’s Disease

**Support:** Idex grat UNI
ANR Parkington

**Title:** Controlled neural organoids grafting promotes functional recovery in experimental parkinsonism

**Authors: E. FAGGIANI**[1], M. FEYEUX[2], *A. R. CROSSMAN[3], K. ALESSANDRI[4], F. NAUDET[2], A. BENAZZOUZ[5], P. COHEN[2], P. NASSOY[4], E. BEZARD[6]
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Kingdom; [4]Inst. Optique d'Aquitaine, Bordeaux, France; [5]Univ. Bordeaux Segalen, Bordeaux, France; [6]Inst. of Neurodegenerative Dis., Bordeaux, France

**Abstract:** We propose that the striatal transplantation of 3D-neural organoids of controlled cell size and cell content, named "Controlled Neural Organoids" (CNOs), could circumvent the limitations of current cell therapy and allow functional recovery in Parkinson's disease (PD). A major impetus for research in PD is centered on cell therapy strategies that aim at replacing the dysfunctional or dying neuronal cell populations. In the past decade, pluripotent stem cells have provided unprecedented access to various human cell types, especially to central nervous system neurons. The availability of patient-specific cell lines associated with the development of highly efficient protocols to in vitro generate specific neuronal cells is an important step in overcoming the ethical and logistical challenges associated with the use of embryonic stem cells. However, mature neuronal transplantation leads to poor survival due to their detachment sensitivity and the fragility of neuritic extensions. Similarly, the transplantation of neuronal precursors does not allow in situ tight control of the neuronal identity and carries a tumor risk. CNOs were generated through cell capsules technology developed in the lab associated with differentiation protocol of dopaminergic neurons (DN) from human pluripotent stem cells. Following the neuronal transplantation in immunocompromised hemiparkinsonian rats (6-OHDA), motor functions were evaluated by stepping test, cylinder test and amphetamine-induced rotations. CNOs characterization was carried out by immunostaining. In this study, we compared the therapeutic efficacy of 3D-neural organoids versus individual neurons transplantation. From eight weeks onwards after the transplantation, CNOs allowed functional recovery associated with tyrosine hydroxylase positive neurons into the graft whereas the transplantation of dopaminergic individual neurons did not induce any effect. Our CNOs constitute more efficient and safer cell therapy products than individual neurons. Pending further validation, this innovative cell therapy approach for the treatment of PD could become a real alternative to drug-based symptomatologic treatments.

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**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 755.18/EE2

**Topic:** C.03. Parkinson’s Disease

**Support:** NRF-2017R1A2B4009963
KIOM grant K18182

**Title:** Effects of acupuncture on the levodoap-induced dykinesia in pitx3-deficient transgenic mice

**Authors: *H.-J. PARK**[1,2], Y.-K. KIM[1,3], S. AHN[4], T. HWANG[5,3]
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**Abstract:** Although L-3,4-dihydroxyphenylalanine (L-DOPA) is currently the most effective medication for treating Parkinson's disease (PD) motor symptoms, its prolonged administration causes several adverse effects, including dyskinesia. To identify the mechanisms underlying the effects of acupuncture on L-DOPA-induced dyskinesia (LID), antidyskinetic effects of acupuncture were investigated in two mouse models of PD. Acupuncture stimulation at GB34 alleviated abnormal involuntary movements (AIMs) in *Pitx3*-deficient *aphakia* mice (*ak/ak*) following L-DOPA administration and these effects were reproduced in 6-hydroxydopamine (6-OHDA)-lesioned mice with LID. A transcriptome analysis of the hypothalamus revealed pro-melanin-concentrating hormone (*Pmch*) gene was highly expressed in acupuncture-treated mouse from *ak/ak* model of LID as well as 6-OHDA model of LID. Acupuncture combined with the administration of MCH receptor antagonist did not have any beneficial effects on dyskinesia in L-DOPA-injected *ak/ak* mice, but the intranasal administration of MCH attenuated LID to the same degree as acupuncture in both *ak/ak* and 6-OHDA mice with LID. A gene expression profile with a hierarchical clustering analysis of the dyskinesia-induced *ak/ak* mouse brain revealed an association between the mechanisms underlying acupuncture and MCH. Additionally, altered striatal responses to L-DOPA injection were observed after prolonged acupuncture and MCH treatments, which suggests that these treatment modalities influenced the compensatory mechanisms of LID. In summary, present study demonstrated that acupuncture decreased LID via hypothalamic MCH using L-DOPA-administered *ak/ak* and 6-OHDA mouse models and that MCH administration resulted in novel antidyskinetic effects in these models. Thus, acupuncture and MCH might be valuable therapeutic candidates for PD patients suffering from LID.

**Disclosures: H. Park:** None. **Y. Kim:** None. **S. Ahn:** None. **T. Hwang:** None.

**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.19/EE3

**Topic:** C.03. Parkinson's Disease

**Support:** Swedish Research Counci
M.P is a New York Stem Cell Foundation Robertson Investigator

**Title:** Comparison between brain size and shape in two rat strains commonly used in xenograft studies for more precise targeting in pre-clinical validation of stem cell derived neurons

**Authors: *B. MATTSSON**, D. HOBAN, T. CARDOSO, S. GREALISH, A. ADLER, M. P. PARMAR
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**Abstract:** Stem cell derived neurons are rapidly moving towards clinical trials. An important part of their pre-clinical validation is to test their safety, functional maturation and potency in xenograft models. The most common method to circumvent the problem of graft rejection when transplanting human cells into rodents are daily administration of immune-suppressive drugs (i.e. Ciclosporine A). However, human stem cell (hESC)-derived neurons mature slowly and therefore there is often a need to study the cells for longer timepoints than is possible in immune-suppressed animals. Therefore, the use of immune-incompetent hosts such as athymic “nude” rats, that allow for at least 12 month graft survival, is increasingly used for experimental studies and pre-clinical validation. In our studies of stem cell derived dopamine neurons transplanted to rat models of PD, we have noticed that the brain size and shape is markedly different between Sprague Dawley (SD) rats and nude rats. This poses a problem when calculating co-ordinates to target specific structures for toxin, virus or cell delivery using stereotaxic surgery. To overcome this, we have collected brains from nude and SD rats of same age and weight and processed them in parallel. Brains from each strain were cut into 30 µm sections and each fourth section stained with cresyl violet were scanned and placed in 3D using Cinema 4D using “flat” skull Bregma and Lambda as anatomical landmarks for correct placement in the 3D environment. Each brain structure was illustrated as a volume making it easy to comparable the two rat strains. We found that the brain of the SD rat matches closely the commonly used Paxinos atlas, while we detected major differences in cortical volume and shape in the nude rats. This in turn illustrates that the coordinates to precisely target deep structures as Substantia Nigra and MFB are markedly different in the SD rat compared to what can be calculated using the Paxinos atlas. We have therefore started to create a 2D vector-based atlas for nude rats. This has allowed us to precisely target the dorsal and ventral midbrain, enabling us to show that hESC-derived DA neurons receive host synaptic input from different regions of the striatum depending on their placement.

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**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.20/EE4

**Topic:** C.03. Parkinson's Disease

**Title:** Chronic treatment of LRRK2 inhibitors in diet produces an effect in the lung: Comparison of the effect in rats vs. mice

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**Abstract:** Currently, there are no disease-modifying therapeutics for the treatment of Parkinson's disease (PD). Inhibition of the kinase activity of leucine-rich repeat kinase 2 (LRRK2) is one of the most promising targets for the treatment of PD and there is an abundance of ongoing studies to assess the potential efficacy of LRRK2 inhibitors in both clinical and pre-clinical studies. In addition to the efforts to understand the therapeutic potential of LRRK2 kinase inhibitors, efforts to understand the potential off target effects continue in parallel, the most studied of which in the lung. Recent data has demonstrated that pharmacological inhibition of the LRRK2 kinase increases lamellar bodies in type II pneumocytes. Here, we administered the selective LRRK2 inhibitor, PFE-360, chronically in diet to C57Bl6 and G2019S mice (1, 3, 10, 30 and 60 mg/kg/day; 42 days) and CD rats (1, 3, 10 and 30 mg/kg/day; 7 days). Following treatment, the lungs were harvested, inflated with 10% formalin, sectioned in toto and stained with H&E. For qualitative assessment, sections were evaluated by light microscopy; for quantitative assessment slides were scanned using an Aperio slide scanner and ten x40 objective field photomicrographs of parenchyma were randomly selected from each section (4 from the left lobe, 2 from each of the right cranial, right caudal, accessory and middle lung lobes). Alveolar parenchyma was assessed and type II pneumocytes were identified by their location in the alveolar walls. The numbers of vacuolated and enlarged type II pneumocytes per x40 field were counted using ImageJ software. In C57 mice, doses of 1 and 3 mg/kg/day of PF-360 were associated with minimal increases in vacuolated/enlarged type II pneumocytes in low numbers of treated animals (2/5). Similarly, low numbers of vacuolated/enlarged cells were observed in vehicle treated animals and those receiving 1 and 3 mg/kg/day of PF-360. At doses of PF-360 ≥ 10 mg/kg/day, a mild to moderate increase in the numbers of vacuolated/enlarged type II pneumocytes was observed qualitatively compared to vehicle treated animals and correlated with several fold (4.1 ± 0.9) increases in the numbers of these cells on image analysis. These findings

are more pronounced than those previously reported with LRRK2 overexpressing mice receiving the same treatment and suggest that the strain used is important in this research. Unlike the mice, rats demonstrated no meaningful change in lung endpoints. Collectively, the data reported here in mice and rats, when put into the context of previously reported data, demonstrate the importance of considering strain and species when evaluating the effect of LRRK2 inhibition on the lung.

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**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.21/EE5

**Topic:** C.03. Parkinson’s Disease

**Title:** Assessment of the anti-parkinsonian effects of the potent and selective LRRK2 kinase inhibitor PF-360 in the AAV-A53T mouse model of Parkinson’s disease

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**Abstract:** The LRRK2 kinase is one of the most studied potential disease modifying targets for the treatment of Parkinson’s disease (PD). Previous work has demonstrated that chronic administration of a LRRK2 inhibitor, PFE-475, has beneficial effects on the AAV alpha synuclein (aSyn) treated rats, which provides support for the hypothesis that LRRK2 kinase inhibitors will be effective in the treatment of PD (Daher et al., 2015). In mice, chronic in diet administration of the LRRK2 inhibitor MLI2 produces a mild lung phenotype (Fell et al., 2016). The purpose of the current work was to follow up on these findings and to create an in vivo model system to be used to assess the effect of chronically inhibiting LRRK2 pharmacologically. In addition to creating animal model platforms that can be used to assess the efficacy of novel LRRK2 kinase inhibitors, we are also working to establish the therapeutic index between efficacious doses and doses that produce measurable effects in the lung. In this study, we have assessed efficacy of another, structurally distinct LRRK2 kinase inhibitor, PF-360 in an AAV-A53T aSyn mouse model of PD. C57Bl6J and G2019S transgenic mice were unilaterally infused with either AAV-A53T or empty vector control into the substantia nigra (SNc). The treatment with a diet containing PF-360 was started 7 days prior to SNc injections, and four weeks after the

injection, the motor functions of the mice were evaluated using the fine motor kinematic analysis system. Five weeks after the infusions, the brains were processed for stereology and HPLC measurements, and the lungs were collected for histopathological evaluation. Chronic in diet treatment with PF-360 improved A53T aSyn induced motor deficits of the mice, and the motor readouts correlated with striatal dopamine concentrations (Pearson's correlation, $p < 0.001$, corr. coeff. $r = 0.80$), even though striatal dopamine levels were not significantly affected. The efficacy of PF-360 in this model was further supported by the finding that dopamine neuron loss (by TH-ir cell counting stereology) in the SNpc/VTA was spared by 41% compared to controls. Finally, drug treated animals had a significant reduction (by 81% compared to vehicle treated controls) in pS935-LRRK2 protein levels in cortex and lung indicating strong target engagement in both compartments. Taken together, these findings demonstrate the utility of the mouse AAV-A53T model as a useful tool for investigating disease-modifying strategies and that chronic in-diet administration of a LRRK2 inhibitor is effective in reducing dopaminergic related deficits mediated by AAV-A53T aSyn.

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**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 755.22/EE6

**Topic:** C.03. Parkinson's Disease

**Support:** Scottish Enterprise SMART feasibility study grant (SMART/14/042 / 14/9177)

**Title:** PR001 and PR002 modify motor phenotype in a rat model of Parkinson's disease

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**Abstract:** To date, there have been no disease-modifying therapies developed for the treatment of Parkinson's disease (PD). We have previously identified two small molecule compounds PR001 and PR002, which exhibited putative neuroprotective efficacy in *Drosophila melanogaster* with PD-relevant mutations. Here, we evaluated their efficacy in rats that received a unilateral injection into the substantia nigra of recombinant human A53T-alpha-synuclein incorporated within a recombinant AAV vector . The effects of the compounds on general

behavior, locomotor performance, as well as on tyrosine hydroxylase (TH) positive cell counts and α-synuclein staining in substantia nigra pars compacta (SNpc) were assessed. This rat PD model has been previously shown to be sensitive to neuroprotective effects of LRRK2 inhibitors, the prominent class of putative therapeutics currently tested in clinical trials as potential disease-modifying treatment for PD. AAV-A53T-alpha-synuclein treatment produced a pronounced loss of TH-positive cells in ipsilateral SNpc compared to those in rats infused with AAV-Null empty virus. Additionally, rats treated with AAV-A53T-alpha-synuclein had a fine motor skills phenotype, which was significantly attenuated by daily administrations of PR001 for 4 weeks, Treatment with PR002 also led to moderate reversal of the motor phenotype caused by the infusion of AAV-A53T-alpha-synuclein, as the value of the Fine Motor Phenotype Score in this group was intermediate between values in AAV-A53T-alpha-synuclein and AAV-Null groups and statistically different from both of them. Interestingly, administration of neither test article affected the decrease in TH-positive cells in SNpc, as TH-positive cell counts in both groups were similar to that in vehicle-treated AAV-A53T-alpha-synuclein group. This suggests that the disease-modifying effect may be occurring through a different mechanism. Additionally, neither treatment affected the number of alpha-synuclein-positive cells in SNc, which suggests that the disease-modifying benefit was not a result of lowering the levels of alpha-synuclein. Collectively, these results provide confirmation of the benefits of PR001 and PR002 as disease-modifying agents in a mammalian species. Coupled with the findings previously reported in Drosophila, they represent potential novel mechanisms that deserve further exploration. Further work to better understand the mechanism of the disease-modifying benefit is ongoing.

**Disclosures: R. Hodgson:** None. **L. Zografos:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Competing financial interests as a shareholders in businesses that exploit Drosophila for drug discovery. **D. Armstrong:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Competing financial interests as a shareholders in businesses that exploit Drosophila for drug discovery. **W. Davies:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Competing financial interests as a shareholders in businesses that exploit Drosophila for drug discovery.. **M. Kopanitsa:** None. **T. Bragge:** None. **L. Tahtivaara:** None.

**Poster**

**755. Parkinson's Disease: Preclinical Animal Studies: Cellular and Molecular II**

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**Program #/Poster #:** 755.23/EE7

**Topic:** C.03. Parkinson’s Disease

**Support:** Scottish Enterprise SMART feasibility study grant (SMART/14/042 / 14/9177)

**Title:** *Drosophila*-based phenotypic drug discovery for neurodegeneration: A case study in Parkinson's disease

**Authors: *D. ARMSTRONG**[1], L. ZOGRAFOS[2], K. STYCZYńSKA-SOCZKA[2], L. ZECHINI[2], R. W. DAVIES[3]
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**Abstract:** Parkinson's disease (PD) is a major neurodegenerative disease, economic burden and threat to an ever-ageing population. However, the discovery of a cure through disease-modifying therapeutics has been a challenge. It is therefore imperative that more effective discovery methods are developed.
Our laboratories have used transgenic *Drosophila melanogaster* as a model for phenotypic PD drug discovery for PD. In this report, we present recent findings on how these models can have impactful applications in drug repurposing, an approach that has been hailed as very promising for PD.
We used transgenic *Drosophila* lines, expressing forms of human alpha-synuclein under the control of pan-neuronal driver eval-Gal4, to screen a library of 1280 off-patent drugs, selecting the best hits and using a mammalian model of PD to pre-clinically validate them.
The library was initially screened using flies expressing wild type (wt) alpha-synuclein. We looked for compounds that reverse the well-documented climbing phenotype observed, 2 or 4 weeks post-eclosion. Of the 1280 compounds, 9 rescued the phenotype (p-value < 0.05 difference between treated and untreated groups of N = 60 flies), at both time points.
We then tested these 9 compounds in two streams, using in flies expressing either wt or A30P alpha-synuclein, looking for compounds that significantly reverse both the climbing phenotype as above but at a higher replicate number (N = 180 flies), but also the associated dopaminergic neuron death phenotypes, as quantified by measuring Tyrosine Hydroxylase immunoreactivity differences between treated and untreated whole brain samples (N = 10-15 brains, p-value < 0.05). We found 4 compounds that significantly rescued both phenotypes in both models. Of these we selected 2, PR001 and PR002, for further studies based on their assay results, combined with an analysis of their chemistry, pharmacological features and known targets.
The results of this work, in combination with the pre-clinical validation of PR001 and PR002 that followed, highlight the impact potential of *Drosophila* models in the discovery of new candidate drugs. To further strengthen this argument, it is worth noting that we followed up this work using a chemoinformatics search, which revealed
compounds free from intellectual property limitations. After compiling a library of these compounds we now have the first positive indications in preliminary experiments.

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A. Employment/Salary (full or part-time):; Brainwave-Discovery ltd. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Parkure Ltd.

**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 756.01/EE8

**Topic:** C.03. Parkinson's Disease

**Support:** NIH NINDS R01NS084975
The Grainger Foundation

**Title:** Optical Ca2+ imaging of astrocyte activity during STN DBS

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**Abstract:** The study of glia-neuron interactions is important for understanding the underlying therapeutic mechanisms of deep brain stimulation (DBS) therapies. Multiple studies using cell culture, slice, or cortical experiments have shown that activation of astrocytes by high-frequency stimulation can lead to a variety of effects including, but not limited to 1) release of gliotransmitters, 2) modulation of synaptic activity of nearby neurons, 3) modulation of neuronal activity away from the site of stimulation via propagation of calcium waves, and 4) modulation of synaptic plasticity (Fenoy 2014). However, in vivo characterization of the effects of DBS on astrocytes in intact deep brain neural circuits of awake animals remains a challenge. To address this critical need, we are using calcium imaging to directly visualize downstream effects of subthalamic nucleus (STN) DBS on astrocytes in the striatum, a brain region involved in the initiation and execution of volitional movement (Barbera, 2016, Klaus, 2017), in a Parkinsonian mice cohort.
We performed calcium imaging of striatal astrocytes in a 6-hydroxydopamine (6-OHDA) mouse model of Parkinson's disease using a miniature fluorescent microscope (Inscopix, Palo Alto, CA). To accomplish this, we transfected astrocytes within the dorsal striatum using AAV5.GfaABC1D.cytoGCaMP6f.SV40 to express GCaMP6f. Two weeks after injection, we implanted a bipolar stimulation electrode (PlasticsOne, Roanoke, VA) in the STN and a 1mm gradient index (GRIN) lens directly above the dorsal striatum. We will record changes in striatal astrocyte Ca2+ activity evoked by STN DBS under isoflurane anesthesia beginning two weeks after lens implantation, and weekly thereafter in awake freely-moving animals. Although these experiments are ongoing, we anticipate that optical imaging of astrocytic Ca2+ signaling in deep

regions of the brain in awake freely-moving animals during DBS will provide a major step toward confirming and understanding the role of glia in the therapeutic effects of DBS.

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**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

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**Program #/Poster #:** 756.02/EE9

**Topic:** C.03. Parkinson’s Disease

**Support:** NIH NINDS (R01NS084975)
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**Title:** Movement-based classification of striatal ensembles during DBS

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**Abstract: Introduction**:
The motor symptoms of disease (PD) are thought to result from maladaptive neural ensemble activity in the dorsal striatum (Jones-Parker, 2018), a brain region involved in the initiation and execution of volitional movement (Barbera, 2016, Klaus, 2017). Deep brain stimulation (DBS) is regularly used to treat the motor symptoms of PD, but its exact mechanisms of action remain elusive. Thus, there is a critical need for understanding how DBS affects striatal ensemble activity responsible for movement. The motor symptoms of PD have a non-episodic nature that is difficult to analyze, particularly in animal models that are used to study the effects of DBS. In this work, we characterized the effects of STN DBS on striatal ensemble activity during biased turning, pathological rearing, darting behavior, and at rest using a k-means clustering approach in a mouse 6-hydroxydopamine (6-OHDA) lesion model of PD. .
**Methods:**
We used the nVoke (Inscopix, Palo Alto, CA) system to collect and analyze dorsal striatal calcium imaging data in 6-OHDA hemiparkinsonian animals implanted with a DBS lead in the subthalamic nucleus. We evaluated specific behavioral traits during open field, cylinder, and parallel rod tests with or without DBS. Simultaneously, we identified movement-associated neural activity via calcium imaging. We used video tracking software (Anymaze, Stoelting, IL) to determine animal position. Similarly, we used Matlab to perform PCA dimensionality reduction and k-means clustering of the position data to classify movements.
**Results:**

We identified cCalcium activity signatures were identified for different behavioral clusters. The rate at which specific behaviors were exhibited varied with and without DBS in healthy and parkinsonian animals.

**Conclusion:**

This work sets the foundation for future studies investigating how DBS influences neural activity and its associated behaviors .

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**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 756.03/EE10

**Topic:** C.03. Parkinson’s Disease

**Support:** National Institutes of Health NINDS (R01NS084975)
The Grainger Foundation

**Title:** Mathematical characterization of dopamine release evoked by electrical stimulation in a 6-hydroxydopamine-lesioned rodent model

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**Abstract: Background**: Cognitive, mood, and movement disorders such as dementia, depression, and Parkinson’s disease (PD) are associated with degeneration of dopaminergic neurons. In an effort to understand the pathophysiology of the disease and develop new therapeutic interventions, previous studies have used fast scan cyclic voltammetry (FSCV) to measure neurotransmission in small animal models (Clark et al. 2010). Our own preliminary work has characterized the non-linear and time-varying dopamine (DA) dynamics using mathematical models of release evoked by burst stimulation of the medial forebrain bundle (MFB) in healthy anesthetized animals. However, this complex relationship has yet to be characterized in an animal model of DA degeneration. Here, we aim to characterize the nonlinear transfer function between electrical stimulation and evoked DA changes in a 6-hydroxydopamine (6-OHDA) lesioned rodent model. **Materials and Methods**: We lesioned the dopaminergic nigrostriatal pathway of male Sprague-Dawley rats with a unilateral intra-cranial injection of 6-OHDA into the dorsal MFB. After a fourteen days of toxin-exposure period, we electrically

stimulated the MFB to evoke striatal DA release under urethane anesthesia. We measured the evoked DA release using fast scan cyclic voltammetry with carbon fiber microelectrodes. Finally, we characterized the evoked DA responses using a multi-compartment parametric model. **Results**: The kinetics of MFB stimulation-evoked DA release following 6-OHDA lesioning vary with dopaminergic lesion level but the mathematical models successfully described the stimulation-evoked DA release. **Conclusions**: Characterization of burst stimulation-evoked DA release in a model of dopaminergic degeneration is an important step towards understanding neurotransmitter dynamics in the context of neurologic disease. Preliminary results demonstrate that kinetics of evoked DA release change as the DA lesion severity increases, thus suggesting that we may be able to predict the severity of DA lesion level based on the dynamics of DA responses. In the near future, we will use these kinetic responses to train machine learining strategies to predict stimulation-evoked neurochemical effects. Ultimately, this work will aid in understanding the neurochemical effects of neurodegenerative disorders and further the development of novel personalized therapeutic strategies.

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**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 756.04/EE11

**Topic:** C.03. Parkinson’s Disease

**Support:** NIH RO1 NS077657
MnDRIVE
UMN Udall Center of Excellence for Parkinson’s Disease

**Title:** Predictive encoding of motor behavior in the SMA is disrupted in parkinsonism

**Authors: *H. E. BAKER**[1], C. M. HENDRIX[1], D. L. BAUER[1], Y. YU[1], M. D. JOHNSON[2], G. F. MOLNAR[1], J. L. VITEK[1]
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**Abstract:** While the pathogenesis of parkinsonism and the role of the pre-supplementary motor area (preSMA) and SMA proper (SMAp) in normal movement initiation are well documented, the relationship between the pre-planning processes preceding movement occurring in the preSMa/SMAp and the onset of parkinsonism is not well understood. In the present study, two non-human primates (NHP) performed a visually-cued reaching task in both the naïve and

parkinsonian state, during which preSMA/SMAp local field potential (LFP) activity was recorded. This LFP activity was assessed to determine whether such activity encodes for changes in reaction time (RT) performance observed with the onset of parkinsonism. In the naïve animal, high and low-beta frequency band modulation prior to the onset of a visual go-cue were predictive of RT performance. The magnitude of high and low beta-band desynchronization and synchronization, respectively, also correlated linearly with the magnitude of RT on a trial-to-trial basis. Predictive encoding of RT in the naïve animal was also anatomically dependent and most prominent in the preSMA. In parkinsonism, predictive encoding of RT performance in the beta-band modulation of preSMA/SMAp areas was diminished, most notably in the high-beta frequency band. Additionally, the previously observed anatomical specificity of predictive encoding in the preSMA was not present in the parkinsonian state. The finding that encoding of RT was preferentially lost in high beta while remaining largely present in low beta in parkinsonism provides evidence in support of independently modulated beta rhythms, as well as beta rhythms with differing functional significance. Our findings in these areas are consistent with previous research suggesting a role for preSMA in executive functioning, and could suggest that the disruption of preSMA/SMAp predictive encoding may reflect a causal cortical mechanism underlying prolonged RT and executive function errors observed in PD.

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**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

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**Topic:** C.03. Parkinson’s Disease

**Support:** NIH NINDS P50 NS098573
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State of Minnesota MnDRIVE

**Title:** Modulating neural oscillations associated with parkinsonism using phase feedback and deep brain stimulation in-vivo

**Authors: *D. ESCOBAR SANABRIA**[1], L. A. JOHNSON[1], Y. YU[1], J. ZHANG[1], S. NEBECK[1], M. D. JOHNSON[2], G. F. MOLNAR[1], J. L. VITEK[1]
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**Abstract:** Low-frequency synchronized oscillations in the subthalamic nucleus (STN) and globus pallidus internus (GPi) are hypothesized to be involved in the development of motor signs in Parkinson's disease (PD). Approaches capable of robustly modulating these oscillations using deep brain stimulation (DBS) could help us better understand their relationship with motor signs and develop more effective DBS therapies. Based on our observations that stimulation in the GPi can evoke large potentials in the STN, we tested the hypothesis that stimulation in the GPi timed to specific phases of neural oscillations in the STN can modulate these oscillations via destructive and constructive interference. A nonhuman primate was implanted with a DBS lead in both STN and GPi and rendered parkinsonian by injections of the neurotoxin MPTP. GPi contacts selected for therapeutic isochronal DBS were chosen to deliver stimulation. STN contacts where neural oscillations at ~12 Hz exhibited elevated amplitude in the parkinsonian compared to the normal state were selected for sensing. The phase of oscillations in the 10-14 Hz band was computed in real-time and a train of 3 stimulation pulses was delivered at phases 0, 10, ⋯, 350 deg. Stimulation artifacts were removed using dynamical models of the artifacts and a blanking procedure. Mathematical models of stimulation-evoked responses and neural data were used to characterize observed modulations. We observed significant suppression and amplification of oscillations at ~12 Hz in the STN when stimulation was delivered in the GPi at two specific phases. Numerical simulations support the hypothesis that the observed modulation was due to interference between the underlying neural oscillations and potentials in STN evoked by GPi stimulation. This modulation approach will enable us to quantify in controlled experiments the relationship between measured oscillatory activity in the STN and parkinsonian motor signs and provide a rationale for the development of closed-loop DBS systems that are specific to each subject's oscillatory activity.

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**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

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**Topic:** C.03. Parkinson's Disease

**Support:** NIC Grant R01 NSO37019S
MnDrive Postdoctoral Fellowship

**Title:** Cue related LFP activity in the bi-lateral SMA and behavioral response is altered in the MPTP NHP model of PD

**Authors: *D. L. BAUER**[1], C. M. HENDRIX[1], H. E. BAKER[1], Y. YU[1], M. D. JOHNSON[2], G. F. MOLNAR[1], J. L. VITEK[1]
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**Abstract:** The paradoxical effect of external cues, particularly visual cues, is a hallmark of Parkinson Disease. Specifically, visual cues can both inhibit or disinhibit motor behavior, notably in upper limb freezing (ULF) and freezing of gait (FOG). While this influence of visual cues is prevalent on motor behavior, little is understood about the underlying pathophysiology contributing to these behavioral responses.
Visually-evoked responses in cortical local field potential (LFP) oscillations are driven by central theta rhythms originating within the medial frontal cortex (MFC). These structures are also implicated in the pathogenesis of motor disturbances found in parkinsonism. The current study examines pathophysiological changes in, and behavioral correlates of, visually-evoked LFP activity in bilateral somatic motor area (SMA) within naïve then parkinsonian non-human primates (NHPs). NHPs were trained in a controlled, visually cued center out behavioral task. Importantly, within-subject controls allow for analysis of intra-individual changes for reaction time (RT) variability, altered magnitude in visually evoked responses (ER), and inter-trial phase coherence (ITPC). Unique to this study is trial-based inference testing linking pathophysiological changes to behavioral responses on a trial-by-trial basis.
The relative change in the magnitude of the ER was greatly diminished in parkinsonism across all frequency bands (<40Hz) and animals as was the number of LFP recordings (% LFP with significant modulation). In the naïve condition, ITPC peak magnitude was centered within the theta band (5 +/- 2 Hz) and within 0.2 +/- 0.05 sec of the go-cue. In parkinsonism, peak coherence values varied considerably across frequency bands and onset relative to the go cue. Bilateral SMA frequency modulations during the reaction time were greatly diminished relative to baseline activity across 1-40 Hz frequency bands in PD and may provide a robust biomarker for PD. Disease severity and/or asymmetry may be reflected in the relative change across hemispheres. Altered theta ITPC observed in the SMA, both ipsilateral and contralateral to the working arm, likely contributes to a disruption in higher level processing related to motor behavior in PD i.e. ULF, start hesitation, etc. These findings are consistent with previous reports of structural, functional, and neurochemical declines in the frontal lobes associated with higher within-person behavior variability.

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**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 756.07/EE14

**Topic:** C.03. Parkinson's Disease

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**Title:** Bayesian adaptive dual control of deep brain stimulation in a computational model of Parkinson's disease

**Authors: *L. GRADO**[1], M. D. JOHNSON[2], T. I. NETOFF[2]
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**Abstract:** Deep brain stimulation (DBS) is an effective therapy for motor symptoms of PD. However, programming these devices is difficult and time consuming, and DBS therapy is limited by side effects and partial efficacy. Furthermore, traditional continuous DBS (cDBS) does not account for fluctuations in motor symptoms caused by factors such as sleep, attention, stress, cognitive and motor load, and current drug therapy, and as the patient's state changes, so does the need for stimulation. Current cDBS strategies are incapable of adapting to the needs of patients: once the clinician sets the parameters, they do not change until the next programming visit. In this study, we have created a Bayesian adaptive dual controller (ADC) that can respond to changes and autonomously learn to reduce pathological beta oscillations in silico.

We developed and tested the Bayesian ADC in a biophysically realistic mean-field model (MFM) of the basal ganglia-thalamocortical system, which simulates parkinsonian neural activity and responds to DBS. The Bayesian ADC is composed of two loops: an inner feedback control loop, and an outer parameter optimization loop. The inner loop is a closed-loop feedback stimulator. It delivers a stimulus to the MFM, triggered off of the phase and amplitude of the beta oscillation, thereby only delivering stimulus when the amplitude is high, and in the correct phase. The inner loop has three parameters: (a) oscillation phase threshold, (b) oscillation amplitude threshold, and (c) stimulus amplitude.

The outer loop of the ADC employs Bayesian optimization (BO) to intelligently sample the parameter space and select the optimal set of parameters in the fewest evaluations. BO is a powerful strategy for optimizing objective functions that are expensive, difficult, or time-consuming to evaluate. BO's efficiency stems from the incorporation of prior belief about the problem to balance exploration and exploitation: BO builds a model of the objective function from prior observations, and then uses the model to intelligently direct sampling. The outer loop operates on a timescale of 20s; after selecting a new parameter set, the outer loop waits 10s, and then measures the amplitude of the beta oscillation over the next 10s. It then augments the set of prior observations with the new, updates the internal model, and selects the next parameter combination.

The Bayesian ADC was able to efficiently learn the best parameters to reduce the power of a pathological oscillation in a computational model of PD. The algorithm has the potential to deliver individualized, adaptive DBS therapy that can improve the quality of life for PD patients.

**Disclosures: M.D. Johnson:** None. **T.I. Netoff:** None.

**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

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**Title:** Network-level differences in fMRI BOLD signaling for orientation-selective deep brain stimulation

**Authors: *J. SLOPSEMA**[1], L. J. LEHTO[2], Y. ERYAMAN[2], N. KOBAYASHI[3], H.-K. MIN[4], K. H. LEE[5], S. MANGIA[2], S. MICHAELI[2], M. D. JOHNSON[1]
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**Abstract:** Functional MRI (fMRI), which measures blood oxygen level dependent (BOLD) signaling, has become an important tool to probe the mechanisms of deep brain stimulation (DBS). Previous studies have shown that DBS of the ventrolateral (VL) thalamus results in notable fMRI BOLD activity changes in the sensorimotor cortex, basal ganglia, and cerebellum in a frequency and amplitude dependent manner (Paek et al., *Neuroimage*, 2015; Gibson et al., *Brain*, 2016). Here, we extend this original study by investigating the relative degree to which these brain regions can be modulated when using multi-contact, orientation-selective DBS patterns tuned to more selectively activate one or more pathways within the VL thalamus. The VL thalamus consists of a convergence of several axonal pathways, including cerebello-thalamic projections and corticothalamic / thalamocortical projections, whose main branches are oriented approximately tangential to each other. These two axonal pathways were specifically targeted with orientation-selective DBS (Lehto et al., *JNE*, 2017) in a domestic swine model . Swine underwent preoperative MRI followed by implantation of a directional DBS lead in the motor thalamus. A within-subject design was used to compare fMRI BOLD activation for each orientation-selective stimulus configuration to compare stimulation patterns predicted to modulate the cerebello-thalamic versus the corticothalamic / thalamocortical pathways more selectively. Stimulation was applied using a block design of 6 s of stimulation followed by 60 s of rest repeated 5 times for each stimulation parameter. Stimulation was preceded by 15 seconds

of blanking and an initial 60 seconds of baseline resting state. fMRI BOLD activation was measured in the motor cortex as well as the cerebellum. Preliminary results suggest that activation in the cerebellum and motor cortex was modulated when the electric field orientation was controlled using orientation-selective stimulation patterns. For example, maximal BOLD contrast in the motor cortex was found when stimulating with pulse patterns targeting fibers parallel to the DBS lead compared to pulse patterns targeting fibers perpendicular to the DBS lead, which showed reduced activation in the motor cortex. This work provides preliminary experimental evaluation of orientation-selective stimulation and motivates the need for further development of fMRI-based network analysis of orientation-selective DBS.

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**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

**Location:** SDCC Halls B-H

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**Topic:** C.03. Parkinson’s Disease

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**Title:** Features of evoked compound action potentials in non-human primate thalamic deep brain stimulation

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**Abstract:** Deep brain stimulation (DBS) is known to modulate neuronal spiking patterns and rates as well as the spectral power of local field potential activity. Additionally, DBS is known to evoke compound action potentials (ECAPs) that immediately follow each stimulus pulse with feature intensities and delays that depend on the local anatomy and physiology of the stimulation and recording targets. Previous studies have investigated ECAPs in the thalamus of cats (Kent and Grill, 2013) and in the subthalamic nucleus of human patients with Parkinson’s disease (Gmel, et al. 2015). In this study, we sought to characterize ECAPs in non-human primates through chronically implanted DBS leads in motor thalamus and subthalamic nucleus. Specifically, we investigated the changes in ECAP responses over (1) time, (2) stimulation amplitudes, and (3) spatial positioning of the recording and stimulating electrodes. Stimulation

was delivered with trains of biphasic, charge-balanced pulses that alternated in polarity such that each cathodic-anodic pulse would be followed by an anodic-cathodic pulse. The different between these two pulses resulted in a nearly instantaneous ECAP measure. The effects of stimulation amplitude were investigated using a randomized sweep of current levels to apply to the stimulus pulse train. The ECAP in motor thalamus was characterized by multiple peaks and troughs. The first two peaks (P1, P2) and troughs (N1, N2) remained stable over time, while the third peak (P3) reduced in amplitude and sharpened in time over the first 4-10 seconds of stimulation. The average P3 maximum then continued to decrease over the next 30-60 seconds without a temporal shift. As stimulus current increased, the ECAP responses increase in magnitude following a sigmoidal curve, while the artifact magnitudes increase rapidly at a perfectly linear rate. Additionally, the N1, P2, and N2 responses were observed in the average ECAP response to a cathodic pulse, but not to an anodic pulse. The unique temporal change in P3 suggests that it may reflect a different source or process than other ECAP features, and that it appears to habituate over time. Additionally, the sigmoidal curve ECAP responses to increased stimulation amplitude suggest that there is a threshold of activation that must be reached before an ECAP response can be reliably evoked, and that there is a maximum response that can be achieved. The observation that certain ECAP features appeared solely after a cathodic pulse, or at least far more visibly than after an anodic pulse, further suggests that cathodic stimulation may be more effective than anodic stimulation in evoking neural responses local to the stimulation target.

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**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

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**Topic:** C.03. Parkinson’s Disease

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**Title:** Exercise as a treatment for Parkinson's disease: The role of astrocytes in circuit-specific, exercise-induced neuroplasticity

**Authors: *A. LUNDQUIST**, M. R. HALLIDAY, G. M. PETZINGER, M. W. JAKOWEC
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**Abstract:** Aerobic exercise, in the form of motorized treadmill running, is a type of experience-dependent neuroplasticity that has been shown to be beneficial in improving motor behavior and

modifying disease progression in Parkinson's disease. Studies in our lab have shown that exercise mediates circuit-specific neuroplasticity through modulation of dendritic spine density, glutamatergic and dopaminergic neurotransmission, and regional blood flow. Astrocytes are essential for normal neuronal function and synaptic plasticity. Recently, astrocytes have begun to attract interest in exercise and neuroplasticity due to their ability to modify synapses and transport energetic substrates (including glucose and lactate) to neurons from blood vessels or through intercellular metabolic coupling, including the astrocyte-neuron lactate shuttle. While the effects of exercise on neurons are well-established, the astrocytic response to exercise is less well-known. Here, we investigated the longitudinal and regional astrocytic response to intensive treadmill training in healthy, C57BL/6 mice. Astrocyte reactivity were measured after one, two or four weeks of exercise in the prefrontal cortex (PFC), caudate putamen (CPu) and ectorhinal cortex (ERC) using immunofluorescence (IF), quantitative RT-PCR (qRT-PCR), and Western blot (WB). Astrocyte morphology was measured across regions and time points using IF, including changes in distal-proximal length, number of primary processes, length of processes, and total density of astrocytes. Using qRT-PCR and WB, relative changes in expression of GFAP (glial fibrillary acidic protein), a marker of astrocyte reactivity, were found at both the transcriptional and protein levels. Taken together, these data demonstrate that astrocytes react in a regional- and exercise-dependent fashion, further helping to explain exercise as a form of experience-dependent neuroplasticity. Such findings provide evidence that targeting specific forms of exercise to circuits within the brain may provide a means to modify motor behaviors compromised in brain disorders such as Parkinson's disease.

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**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

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**Topic:** C.03. Parkinson's Disease

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State of Minnesota MnDRIVE

**Title:** The effects of deep brain stimulation of the globus pallidus internus on reach behavior and neuronal activity in the primary motor cortex

**Authors: *M. SCHEITEL**[1], L. A. JOHNSON[2], D. ESCOBAR SANABRIA[4], S. NEBECK[5], J. ZHANG[2], M. D. JOHNSON[6], G. F. MOLNAR[4], J. L. VITEK[3]
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**Abstract:** Deep brain stimulation (DBS) of the globus pallidus internus (GPi) improves motor function in patients with Parkinson's disease (PD). Although the primary motor cortex (M1) is a key component of the basal ganglia-thalamocortical (BGTC) network and likely plays a key role in the pathogenesis of PD motor signs, little is known about the effect of GPi DBS on neuronal activity in M1. The objective of this study was to assess the impact GPi DBS has on M1 neuronal activity prior to and during movement. A rhesus monkey was chronically implanted with a DBS lead in the GPi and a microelectrode array in M1 and made parkinsonian using the neurotoxin MPTP. M1 single unit activity was recorded as the monkey performed a reach and retrieval task during DBS-OFF and DBS-ON conditions. We characterized baseline spontaneous firing rates and movement-related modulation of neuronal activity by aligning spike times to each behavioral epoch (i.e. cue, reach initiation, target touch, return initiation, reach end). Neurons were considered to have a significant modulation when a nonparametric statistical test detected a significant positive or negative change in mean discharge rate relative to spontaneous firing rates based on an alpha of 0.01 for at least 150 ms, reflecting excitatory or inhibitory effects on neuronal activity. GPi DBS significantly improved task performance, increasing the reach and return speed from 105.8 to 283.2 mm/sec and 63.4 to 180.6 mm/sec, respectively. DBS altered baseline firing rates (prior to the cue) in a subset of neurons (31%), with both significant increases (18%) and decreases (13%) observed, and was associated with more neurons showing significant changes in relation to the task in all behavioral epochs. DBS increased the number of neurons modulated in the reach epoch from 43% (6% suppressive and 37% excitatory) in the DBS-OFF to 71% (14% suppressive and 57% excitatory) in the DBS-ON condition. Of the neurons modulated, the depth of excitatory or inhibitory) modulation, defined as the magnitude of change from spontaneous firing rate to subsequent firing rate maxima or minima, was found to be greater in the DBS-ON condition. In sum, we observed that GPi DBS increased both the number of cells that were modulated during movement as well as their magnitude of modulation. These data suggest that one potential mechanism underlying the therapeutic effects of GPi DBS is via the augmentation of excitatory and inhibitory drive to selective M1 neurons leading to improved signal transmission in the BGTC network.

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**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

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**Title:** Intensity and cycle rate impact the effectiveness of subthalamic coordinated reset deep brain stimulation

**Authors: *J. WANG**[1], S. P. FERGUS[1], S. D. NEBECK[1], L. A. JOHNSON[1], D. E. SANABRIA[1], J. ZHANG[1], S. KULKARNI[3], H. BOKIL[3], M. D. JOHNSON[2], G. F. MOLNAR[1], J. L. VITEK[1]
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**Abstract:** Coordinated reset deep brain stimulation (CR DBS) is a novel approach for the treatment of patients with Parkinson's disease (PD). Rather than using high frequency isochronal pulses, CR DBS delivers low intensity pulse trains randomized through multiple electrodes. Modelling studies have suggested that variations in the parameter space can produce different effect on synchronized neuronal activity. The relative effect of these changes in parameter space, however, has not been explored systematically in vivo. In this study, we examined the impact of intensity and cycle rate on the motor signs in the MPTP non-human primate (NHP) model of PD undergoing subthalamic nucleus (STN) CR DBS.
A NHP was rendered parkinsonian through IM injections of MPTP and implanted with an 8-electrode DBS lead (NuMed) in the STN for stimulation and recording of local field potential (LFP). Both the intensity and cycle rate of STN CR DBS were varied while other parameters remained constant. Four intensities (0.05, 0.1, 0.16 and 0.24mA) and cycle rates (5, 6.95, 8 and 8.88Hz) were used. CR DBS was delivered for 4 hours daily over 5 consecutive days. Parkinsonian motor signs were assessed using a clinical rating scale and a reach/retrieval task pre, during and post stimulation. Following discontinuation of CR, motor signs were assessed each morning until the animal returned to baseline.
The effect of CR DBS was specific to intensity and cycle rate. Results demonstrated that CR at 0.16mA, 2/3 of the traditional DBS (tDBS) intensity, induced the greatest degree of acute improvement in motor signs with prolonged carryover effects following discontinuation of stimulation. Thereafter, 0.16mA was used in cycle rate tests. Cycle rate of 8.88Hz induced the most improvement in motor signs acutely with the longest carryover benefit. We observed up to 50% of improvement in the mUPDRS and an average reduction of 30% in reach, retrieval and reaction times. A high beta peak at 27Hz was seen in the power spectral density of STN LFP signals, and was close to the inter-burst rate (3 times of 8.88Hz) of the optimal cycle rate.
In summary, the therapeutic effect of STN CR DBS is dependent upon both stimulation intensity and cycle rate. Exploration of the parameter space will be critical to optimize stimulation parameters for CR DBS. Further studies will be necessary to define the relationship between the optimal cycle rate and the high beta peak frequency which could serve to facilitate optimization of cycle rate and contribute to future exploration of closed loop CR approach.

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**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

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**Topic:** C.03. Parkinson's Disease

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State of Minnesota MnDRIVE

**Title:** The effects of deep brain stimulation and L-dopa on single unit activity in primary motor cortex of an MPTP treated Rhesus macaque during a reach and retrieval task

**Authors: *S. NEBECK**[1], L. A. JOHNSON[2], J. ZHANG[2], M. D. JOHNSON[4], G. F. MOLNAR[5], J. L. VITEK[3]
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**Abstract:** Parkinson's disease (PD) is a chronic neurodegenerative disease that affects dopaminergic cells in the basal ganglia thalamocortical (BGTC) network and is characterized by cognitive and motor symptoms. L-dopa is a commonly prescribed treatment for PD patients, but over time higher doses are required and are often associated with motor fluctuations and drug induced dyskinesia. Deep brain stimulation (DBS) is increasingly being used to treat PD motor symptoms and reduce the dependence on high doses of L-dopa. Although DBS is used in combination with L-dopa, the effect of each therapy alone or in combination on the BGTC network is not well understood.
In this study a female MPTP (1-methyl-4-phenyl 1,2,3,6- tetrahydropyridine) treated Rhesus macaque was trained to perform a reach and retrieval task. While performing the task single units were recorded from the arm area of primary motor cortex during: no treatment, DBS, L-dopa and combined treatment conditions. A 96 channel Utah array was used to record single units in the primary motor cortex and an 8 channel DBS lead was implanted into the STN to deliver therapeutic DBS. Both primary motor cortex and STN were implanted contralateral to the arm used during the task. L-dopa was given orally in a dosage that alleviated motor symptoms without causing dyskinesia.
All treatment conditions (STN DBS, L-dopa only, combined STN DBS and L-dopa) improved

performance on the reach and retrieval task most notably with a reduction in reaction and return times. mUPDRS was improved between 30% and 45% with the greatest improvement occurring with combining DBS and L-dopa.
Eighty percent of M1 neurons were modulated during the task and a significant number of these were differentially affected by DBS vs L-dopa and in some cases demonstrated a combined effect that was different from either alone. By characterizing the relative effect of DBS to L-dopa on changes in primary motor cortex and motor behavior in the parkinsonian state we can gain a better understanding of the neurophysiological mechanisms underlying these therapies and how to optimally combine them.

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**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

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**Title:** Serial polarization-sensitive optical coherence tomography of the thalamus for DBS applications

**Authors: *M. YEATTS**[1], M. D. JOHNSON[1], E. M. BELLO[1], C. LUI[2], S. R. HEILBRONNER[3], T. AKKIN[2]
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**Abstract: Introduction:** Deep brain stimulation (DBS) therapy relies on precise targeting of neural pathways that are often embedded within complex networks within the brain. The thalamus, for example, has been the target of DBS for several clinical indications including essential tremor, epilepsy, minimally conscious state, and schizophrenia, among others. However, the thalamus has heterogeneous axonal tractographies that are difficult to characterize with traditional imaging techniques such as diffusion tensor imaging (DTI), limiting efforts to build predictive models of DBS therapy. In this study, we used polarization-sensitive optical coherence tomography (PS-OCT) imaging to visualize axonal pathways within non-human

primate (NHP) thalamus with 10-micron lateral resolution. **Methods:** Perfused and paraformaldehyde-fixed brain tissue was blocked about the right thalamus. PS-OCT was then used to image the thalamic tissue from the lateral sagittal face of the section. The size of the sample was such that it required imaging in tiles, each measuring 7.8 x 7.9 $mm^2$ with 5% overlap. After imaging four tiles to cover the lateral plane, a 100-micron thick slice was removed from the surface to access the deeper regions. The imaging and slicing procedure was repeated 95 times until the whole block was imaged. The reflectance, retardance, and cross polarization images were obtained from each of these tiles and then recombined based upon the designated overlap during the imaging process and correlative value assessed. The stitched images (enface images) were then aligned and stacked into a three-dimensional block to render thalamus axonal tracts. **Results:** PS-OCT enabled visualization of both afferent and efferent pathways that differed in orientation amongst thalamic nuclei are visualized. Well know tracts such as the mammillothalamic tract and stria medullaris of the thalamus were easily identified. Additionally, distinct bodies of the thalamus such as the anteriomedial and centromedian thalamic nuclei were identified. The resolution with which the myelinated fibers are seen sheds light on the intricacies of orientation. **Conclusions:** Improved understanding of axonal tractography within thalamus will be important to optimize DBS therapy for a range of existing and emerging clinical indications. This imaging approach is poised to enable rendering of axonal tracts in three dimensions and help guide future DBS lead designs and programming algorithms.

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**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

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**Topic:** C.03. Parkinson’s Disease

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**Title:** Parkinsonism alters beta burst dynamics across the basal ganglia and motor cortex

**Authors: *Y. YU**[1], L. A. JOHNSON[1], S. D. NEBECK[1], D. E. SANABRIA[1], J. ZHANG[1], J. WANG[1], M. D. JOHNSON[2], G. F. MOLNAR[1], J. L. VITEK[1]
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**Abstract:** Beta range synchronized oscillation has been hypothesized to be a biomarker of Parkinson’s disease (PD). Recently, it has been argued that the critical feature is not merely that

beta activity is increased, but rather that the duration of beta activity is prolonged. It is unclear, however, whether prolonged beta burst activity occurs across the basal ganglia-thalamocortical (BGTC) motor network. To address this, we studied beta burst dynamics across the subthalamic nucleus (STN), globus pallidus (GP), and primary motor cortex (M1) in non-human primates (NHPs) in the naïve and progressive PD states.
Local field potentials (LFPs) from the STN, GP and M1 were recorded with implanted deep brain stimulation leads and a 96 channel Utah array in the M1 arm areas at rest. Progressive parkinsonian states of NHPs were induced by sequential injections of the neurotoxin 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP). The modified Unified Parkinson's Disease Rating Scale (mUPDRS) was performed in each state to assess severity of the animal. Beta band envelope of LFPs, filtered around the peak frequency in the beta band (6 Hz bandwidth), was computed, after which beta bursts were detected using the threshold of 75 percentiles of its amplitude for naïve and PD states. The duration, average amplitude and co-occurrence of beta bursts across each structure was measured.
Results of mUPDRS scores indicated that NHP K&J reached a moderate PD state with MPTP injections. In both NHPs, more beta bursts with longer duration and higher amplitude were present in the STN and GP, and in M1 in only NHP J. The amplitude of detected beta bursts was positively correlated with the duration. Moreover, there was greater overlap in beta burst activity across M1, STN and GP in PD in both NHPs. Overlap of low beta band activity (8-20 Hz) across structures was present in the mild state and increased with severity of motor signs.
The presence and overlap of low beta band activity across multiple nodal points of the BGTC circuit that increased with severity supports the proposed role of low beta band activity in the pathogenesis of PD. We further hypothesize that this activity interferes with spatial-temporal processing of information flow and connectivity that leads to the impairment of motor function in PD.

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**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 756.16/FF9

**Topic:** C.03. Parkinson's Disease

**Support:** NIH NINDS R01 NS037019
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State of Minnesota: MnDRIVE

**Title:** Relative effects of therapeutic subthalamic and pallidal deep brain stimulation on antidromic activation of the primary motor cortex

**Authors: *L. A. JOHNSON**[1], J. WANG[1], S. NEBECK[1], D. ESCOBAR SANABRIA[1], J. ZHANG[1], M. D. JOHNSON[2], G. F. MOLNAR[1], J. L. VITEK[1]
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**Abstract:** Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or internal segment of the globus pallidus (GPi) is an effective surgical treatment for advanced Parkinson's disease (PD), though its therapeutic mechanisms remain unclear. Several studies have suggested that direct activation of the motor cortex during DBS, via antidromic activation of axonal projections from cortical neurons, may underlie its therapeutic effects on parkinsonian motor symptoms. These studies have primarily investigated motor cortical responses during STN DBS, but it has been speculated that similar effects may be elicited during GPi DBS as well. In this study we tested the hypothesis that antidromic activation of primary motor cortex neurons is a prominent feature of therapeutic STN and GPi DBS by evaluating single unit activity from high density microelectrode arrays chronically implanted in the primary motor cortex (M1) of two non-human primates made parkinsonian using the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Each animal was implanted with two scaled-down versions of human DBS leads targeting the STN and GPi, respectively, enabling within animal comparisons of M1 activity to stimulation of both nuclei. We found that STN and GPi stimulation had similar therapeutic effects based on clinical ratings of parkinsonian motor signs, however antidromic firing in M1 was only observed during STN DBS. Although the percent improvement in clinical ratings during STN and GPi DBS was similar, the proportion of cells classified as having antidromic firing differed between animals (30% vs 7%). Firing patterns of cells with antidromic firing was highly regular, with the highest interspike interval probability equaling the interstimulus interval of the DBS pulse train. Notably, over the course of four hours of continuous STN DBS, antidromic classified cells fired less robustly, whereas therapeutic benefits were maintained. These findings do not discount a potential role of antidromic M1 activation in mediating the improvement in motor signs during STN DBS, however the difference in antidromic activation between animals, the reduction of antidromic activity over time, and absence of antidromic M1 activity during GPi DBS challenge the hypothesis that antidromic activation of the motor cortex is the primary mechanism underlying therapeutic benefits during DBS.

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**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 756.17/FF10

**Topic:** C.03. Parkinson’s Disease

**Support:** PSSP

**Title:** Electrical power delivery predicts therapeutic efficacy in a mouse model of subthalamic nucleus deep brain stimulation for Parkinson's disease

**Authors: *J. SCHOR**, A. NELSON
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**Abstract:** Since the first demonstration of subthalamic nucleus deep brain stimulation (STN DBS) by Alim-Louis Benabid and Pierre Pollak, STN DBS has provided effective management of the motor symptoms of Parkinson's Disease (PD). Stimulation is traditionally delivered as rectangular pulses, which are defined by their width (pulse width), amplitude (current), and frequency. Largely due to technical limitations of early stimulators, neurosurgeons primarily varied frequency, observing greater therapeutic benefit at high frequencies compared to low frequencies. While modern stimulation devices are capable of greater ranges of stimulation, this initial observation has fueled the widely held hypothesis that frequency is the single-largest driver of effective DBS, with pulse width and current playing secondary roles. Indeed, the bulk of STN DBS research rests upon this supposition, leading to the theory that high frequency stimulation uniquely disrupts the abnormal neuronal activity seen in PD. However, due to the logistical difficulties inherent to systematically studying DBS parameter space in patients, this hypothesis has yet to be rigorously tested. Here, we developed a novel mouse model of STN DBS and used it to assess the parameter space. Contrary to the predominant theory, we find that the composite measure of average electrical power, rather than stimulation frequency, most strongly predicts therapeutic efficacy, and that this effect is borne out through retrospective analysis of human data.

**Disclosures: J. Schor:** None. **A. Nelson:** None.

**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

**Location:** SDCC Halls B-H

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**Topic:** C.03. Parkinson's Disease

**Support:** CONICYT graduate scholarship
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**Title:** Exploring the role of non-invasive spinal cord stimulation in a parkinsonian rat model

**Authors: *M. F. ALAMOS**[1], S. GALLEGOS[2], A. MARTINEZ[2], C. JURI[1], R. A. FUENTES[3]
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**Abstract:** Epidural electrical stimulation of the spinal cord has shown positive outcomes addressing motor symptoms of Parkinson Disease (PD), increasing its potential as a new clinical treatment. However, spinal cord stimulation (SCS) requires a surgical procedure and therefore is not exempt from the complications associated to chronic implants. In this study we explored, for the first time, the effects of a less invasive method for neuromodulation of the spinal cord. Using adult Sprague Dawley male rats with unilateral nigrostriatal dopaminergic lesions induced by 6-hydroxydopamine (6-OHDA), we evaluated the effectiveness of Non-Invasive Spinal Cord Stimulation (NISCS) by measuring the neural activity in the cortico-basal ganglia circuit and the motor function. For the first outcome, we compared the local field potential (before, during and after stimulation) from 5 different areas of the motor circuit, using the uninjured hemisphere as a control. For the second outcome, we evaluated the motor performance during 11 days of stimulation, using the cylinder test and the amphetamine-induced rotation test. We compared the motor performance between the treated and non-treated (control group) parkinsonian rats. NISCS was able to modulate the pathological neural activity and also motor function. Since this strategy is less expensive, safer, and easier to administer than other neuromodulation techniques, our findings might be relevant to the clinical practice.

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**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 756.19/FF12

**Topic:** C.03. Parkinson's Disease

**Support:** NIH R21 NS085539
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**Title:** Characterization of spontaneous and evoked neural activity in the substantia nigra pars reticulata for the accurate placement of deep brain stimulation electrodes

**Authors: *H. LI**, G. C. MCCONNELL
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**Abstract:** The Substantia Nigra pars reticulata (SNr) is a promising target for deep brain stimulation (DBS) to treat the gait and postural disturbances in Parkinson's Disease (PD). The effects of DBS in subregions of the SNr on the treatment of gait and postural disturbances in PD is not clear. We recorded spontaneous and evoked neural activity of subregions of the SNr and the ventral tegmental area (VTA) using single tungsten microwire electrodes in anesthetized rats (n=17) as an approach to predict the placement of the electrodes. The location of each recording site was confirmed by immunohistochemistry. Analysis of neural recordings included action potentials and local field potentials (LFPs) during spontaneous and evoked responses to 0.5 Hz stimulation at 25 μA and 50 μA. Action potentials were analyzed based on temporal features (firing rate, amplitude, interspike interval (ISI) correlation, ISI variance, firing regularity) and waveform shape (amplitude, signal-to-noise ratio, half width at peak, half width at valley, latency). Spectral analysis was performed on action potentials and LFPs in the delta, theta, beta and gamma bands. For spontaneous activity, ISIs were positively correlated in VTA and lateral SNr (lSNr) but negatively correlated in medial SNr (mSNr); amplitudes of spikes in VTA were significantly higher than mSNr, and amplitudes in mSNr were significantly higher than lSNr; signal-to-noise ratio of spikes in VTA were significantly higher than mSNr; power of spikes in VTA were significantly higher than lSNr in the high beta (20-30 Hz) and low gamma (30-40 Hz) bands, whereas it was higher than mSNr in the high beta (20-30 Hz) band; power of LFPs in VTA was significantly lower than lSNr in low gamma (30-50 Hz), whereas it was significantly lower than mSNr in theta (4-10 Hz), low beta (10-20 Hz), high beta (20-30 Hz), and low gamma (30-50 Hz); the power of LFPs in mSNr was significantly lower than lSNr in the high gamma (70-80 Hz) band. For evoked activity, during 25 μA stimulation the waveform of spikes changed to a thinner and less asymmetric shape in mSNr but not in lSNr, and the power of spikes in high beta (20-30 Hz) decreased in mSNr but not lSNr. During 50 μA stimulation, ISIs changed from negatively correlated to positively correlated in both mSNr and lSNr, but the power of spikes

under mid gamma (50-60 Hz) increased in lSNr but not mSNr. Our findings suggest that action potentials and LFPs provide complementary information that correlate with the location of microelectrodes within the SNr. The results shed light on a rich set of features to aid in the accurate placement of microelectrodes within the SNr for future studies of SNr DBS.

**Disclosures: H. Li:** None. **G.C. McConnell:** None.

**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 756.20/FF13

**Topic:** C.03. Parkinson’s Disease

**Title:** Measure of the phase-amplitude coupling in a rat model of Parkinson's disease

**Authors: *J. VOLLE**, A. WOźNIAK-KWAśNIEWSKA, A. EVRARD, C. RUGGIERO, C. ROUCARD, Y. ROCHE, V. DUVEAU
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**Abstract:** Movement disorders (MD) represent a wide range of neurological syndromes with different origins. The best-known disorders, such as Parkinson’s and Huntington’s diseases, are neurodegenerative but MD can also be caused by infection, inflammation, trauma or even medication. Despite recent advances in the development of new drugs, MD symptoms are not entirely alleviated by pharmacological treatments. The development of more advanced analysis methods opened up new potential for both clinical and preclinical electroencephalography (EEG) applications. An EEG approach can provide reliable biomarkers and quantifiable measures to assess the efficacy of a compound. These new findings can help developing new compounds in the field of movement disorders treatment. In particular, Parkinson's disease (PD) is a target of choice for such an approach. In both, parkinsonian patients and animal models, an increased power of beta frequencies has been observed. This abnormal beta oscillation was suppressed by dopaminergic treatments, along with motor symptoms. In addition, chronic L-DOPA treatment induced prominent gamma resonant oscillations, associated with abnormal involuntary movements (AIMs), in the motor cortex of both hemiparkinsonian rats (Halje et al. 2012) and patients (Oswal et al. 2013). More recently, an exacerbated phase-amplitude coupling (PAC) between beta-phase (13-30 Hz) and gamma-amplitude (50-200 Hz) has been characterized in the motor cortex of PD patients (de Hemptinne et al., 2013). The aim of this project was to evaluate the PAC in an animal model of PD, the unilaterally 6-OHDA-lesioned rat. We identified a strong coupling between the phase of theta (4-6Hz) and the amplitude of high gamma (90-160Hz) in the ipsilateral motor cortex of lesioned rats. This EEG signature is correlated with the locomotor activity of the animal: a high theta-gamma PAC is associated to an elevated locomotor activity. In addition, anti-parkinsonian drugs like L-Dopa, apomorphine or SKF-38393-2, significantly

suppressed this theta-gamma PAC. This theta-gamma PAC signature in an animal model of PD can be used as a new preclinical biomarker, thus providing a stable, quantifiable, reliable and objective endpoint for the development of new therapies against PD.

**Disclosures: J. Volle:** A. Employment/Salary (full or part-time):; SynapCell SAS. **A. Woźniak-Kwaśniewska:** A. Employment/Salary (full or part-time):; SynapCell SAS. **A. Evrard:** A. Employment/Salary (full or part-time):; SynapCell SAS. **C. Ruggiero:** A. Employment/Salary (full or part-time):; SynapCell SAS. **C. Roucard:** A. Employment/Salary (full or part-time):; SynapCell SAS. **Y. Roche:** A. Employment/Salary (full or part-time):; SynapCell SAS. **V. Duveau:** A. Employment/Salary (full or part-time):; SynapCell SAS.

**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 756.21/FF14

**Topic:** C.03. Parkinson’s Disease

**Title:** L-DOPA-induced striatal gamma oscillations split into low- and high-frequency components following ketamine exposure in an animal model of L-DOPA-induced dyskinesia

**Authors: *T. YE**[1], M. J. BARTLETT[2], T. FALK[2], S. L. COWEN[3]
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**Abstract:** Preclinical evidence from our group indicates that a single extended 10 hour exposure to sub-anesthetic ketamine leads to a weeks-to-month long reduction in L-DOPA-induced dyskinesias (LID) associated with the treatment of Parkinson’s disease (PD) (Bartlett et al., 2016). Considerable evidence also indicates that ketamine exposure provides lasting relief of treatment-resistant depression and chronic pain. Despite advances in its therapeutic application, the systems-level mechanisms underlying ketamine’s effectiveness are not understood. A common component of disorders treated with ketamine is the presence of hypersynchronous oscillatory activity. Our general hypothesis is that ketamine disrupts oscillatory activity associated with these disorders. In the present study, we investigated whether ketamine reduces hypersynchrony associated with LID. To answer this question, local-field recordings were acquired from rodent models of PD and LID (unilateral 6-OHDA-lesioned male rats; for the LID model PD animals were primed for 21 days daily with L-DOPA; 7 mg/kg, *i.p.*). Dyskinetic rats with abnormal involuntary movements (AIMs) scores of 33.6 ± 6.6 (mean ± SD) were implanted with electrode arrays in motor cortex (M1), dorsolateral striatum (DLS), dorsomedial striatum (DMS), and the nucleus accumbens (NAc). Neural recordings were acquired over 11 hours during which LID ($n$=7) and PD rats ($n$=7) were administered five ketamine (20 mg/kg *i.p.*) or saline injections every 2 hrs. As previously reported, we determined that L-DOPA administration (7 mg/kg, *i.p.*) was associated with wideband gamma oscillations (40-90 Hz) in M1 and DLS,

and that, contrary to our hypothesis, the power of these oscillations was not affected by ketamine administration. In the present investigation, we performed a more detailed analysis of the effects of ketamine on frequencies within the wideband gamma range (40-90 Hz). Analysis of this signal during LID revealed that ketamine administration resulted in this wideband signal splitting into a clearly discernable low-gamma (30-50 Hz) and high-gamma (70-90 Hz) component ($p$=0.005). This effect was not observed when ketamine or L-DOPA were administered separately. These observations suggest that an influx of dopamine produced by L-DOPA paired with NMDA receptor blockade by ketamine engages distinct gamma-generating networks in the striatum. This also suggests ketamine's therapeutic could be due to ketamine engaging distinct striatal networks.

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**Poster**

**756. Parkinson's Disease: Preclinical Animal Studies: Stimulation and Physiology**

**Location:** SDCC Halls B-H

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**Topic:** C.03. Parkinson's Disease

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**Title:** The relationship between local field potential activity in the basal ganglia and sleep-wake behavior in parkinsonism

**Authors: *E. MARSHALL**, S. DEYO, D. ESCOBAR, A. AMUNDSON, J. ZHANG, M. D. JOHNSON, G. MOLNAR, L. JOHNSON, J. VITEK
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**Abstract:** More than 75% of people with Parkinson's disease (PD) have significant sleep disturbances. In some cases, sleep-wake disorders can be more disabling and resistant to treatment than the motor symptoms of PD and there is a critical need for therapies to improve sleep quality in these individuals. Basal ganglia dysfunction is a hallmark of PD and likely contributes to disordered sleep in PD patients, yet relatively little is known how basal ganglia activity changes during different stages of the sleep-wake cycle in the parkinsonian brain. In this study we examined neural activity from the basal ganglia during the sleep-wake cycle of a non-human primate (NHP) made parkinsonian using the neurotoxin MPTP. We acquired and

analyzed muscle (EMGs), eye (EOGs), and cortical (EEG) activity (polysomnographic signals typically used for evaluating sleep stages), along with local field potentials from deep brain stimulation (DBS) leads targeting the subthalamic nucleus (STN) and internal segment of the globus pallidus (GPi), basal ganglia nuclei typically used as targets for treating the motor symptoms of PD. To record activity during the animal's standard sleep-wake cycle (6pm-6am), the NHP was fitted with an Avatar EEG, a device mounted on the head of the animal that enabled free moving wireless data collection (1kHz sampling rate). Using the standards for scoring sleep adapted from the American Academy of Sleep Medicine, sleep was manually scored using the polysomnography signals in 30 second epochs to get an accurate representation of the sleep staging throughout the 12-hr sleep-wake cycle. Sleep architecture was highly fragmented with minimal REM sleep epochs, similar to that previously reported in MPTP-treated NHPs. Power spectral analysis of local field potentials from the STN and GPi revealed that each structure had unique identifiable features during each sleep stage. These findings increase our understanding of how basal ganglia activity changes during different stages of the sleep-wake cycle and also suggest that a sleep classification scheme based on DBS field potentials is feasible. The ability to identify sleep stages based on neural recordings from DBS leads could contribute to the development of next generation of neurostimulation devices that monitor sleep architecture and tailor DBS parameters to improve disordered sleep in PD patients.

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**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 757.01/FF16

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** SAF2016-08573-R
Fundación Ramón Areces, Spain

**Title:** Alterations in Lamin B1, a new pathological mechanism in Huntington's disease

**Authors: M. GARCIA-FORN**[1,2,3], R. ALCALÁ-VIDA[1,2], J. CREUS-MUNCUNILL[1,2,3], C. CASTANY-PLADEVALL[1], K. CRESPÍ-VÁZQUEZ[1], J. ALBERCH[1,2,3,4], *E. PEREZ-NAVARRO[1,2,3,4]
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**Abstract:** Huntington’s disease (HD) is a hereditary neurodegenerative disorder caused by an expansion of a CAG repeat in the huntingtin (htt) gene, resulting in an aberrant form of the protein. HD patients and mouse models present hippocampal and corticostriatal alterations, but the molecular mechanisms causing selective neuronal dysfunction are not clear yet. Our group has previously showed increased lamin B1 levels in several brain regions of the R6/1 mouse model and HD patients. Lamin B1 is part of lamins family, the major structural proteins inside the nuclear lamina. Lamins functions are crucial for the structure and functionality of cellular nucleus; indeed, alterations in their genes are linked to some diseases, called laminopathies. Through imaging flow cytometry (FACS), we aimed to identify the specific neuronal populations affected by alterations in lamin B1 in each brain region. We found that lamin B1 protein is specifically increased in striatal medium-sized spiny neurons (MSN) and neurons from the CA1 hippocampal region, together with an alteration in nuclear morphology. These data suggest that altered lamin B1 levels may lead to alterations in nuclear structure that could play a role in HD symptoms. Moreover, we show that chronic treatment with betulinic acid improved cognitive function in R6/1 mice, in good correlation with a normalization of lamin B1 protein levels in the hippocampus. Altogether, our results show that alterations in lamin B1 may participate in the pathophysiology of HD, and the modulation of its levels may have a therapeutic benefit in this neurodegenerative disease.

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**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 757.02/FF17

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** Huntington Society of Canada

**Title:** Assessing the effect of ceftriaxone on glutamate dynamics and synaptic plasticity in the Q175FDN mouse model of Huntington's disease

**Authors: *C. WILKIE**, C.-L. BENSON[1], M. P. PARSONS[2]
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**Abstract:** Huntington Disease (HD) is an inherited neurodegenerative disorder characterized by motor, cognitive, and psychiatric symptoms. Subtle cognitive deficits can be detected in HD mutation carriers upwards of 15 years prior to diagnosis, and many HD patients report cognitive

symptoms to be the most debilitating aspect of the disease. Very little is known regarding the cellular mechanisms underlying HD-associated cognitive symptoms. Rapid clearance of synaptically-released glutamate by membrane-bound transporters, particularly glutamate transporter-1 (GLT-1), is necessary to promote robust synaptic plasticity and healthy cognitive function. GLT-1 impairments have been observed in various HD mouse models, leading us to hypothesize that poor glutamate clearance may contribute to weak synaptic plasticity and the cognitive symptoms associated with HD. Ceftriaxone, a FDA-approved beta-lactam antibiotic that increases GLT-1 expression, improves motor symptoms in the R6/2 HD mouse model; whether increasing glutamate clearance can improve HD-associated cognitive symptoms remains to be seen. Here, we used a combination of electrophysiology and high-speed imaging of iGluSnFR, a fluorescent sensor of extracellular glutamate, to assess the effect of Ceftriaxone on long-term potentiation (LTP) and glutamate dynamics in the hippocampus of 6-month Q175FDN HD mice and age-matched wild-type (WT) littermates. To our surprise, we found that at this age, Ceftriaxone significantly decreased GLT-1 expression in the hippocampus and had no effect on glutamate clearance rates at CA3-CA1 synapses, regardless of genotype. While the magnitude of CA3-CA1 LTP was reduced in Q175FDN mice compared to WT, Ceftriaxone was unable to restore Q175FDN LTP to WT levels. In fact, Ceftriaxone significantly reduced LTP magnitude in WT mice. Overall our results demonstrate clear detrimental effects of a FDA-approved drug on synaptic plasticity in the healthy brain, and suggest that Ceftriaxone is unlikely to be a suitable agent for the effective management of HD symptoms.

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**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 757.03/GG1

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** NINDS/NIH R01 NS084298
Hereditary Disease Foundation Leslie Gehry Brenner Award

**Title:** A novel assay for sensitive and automated detection of pathological progression-related seeding activities in HD patient cerebrospinal fluids

**Authors: *C. LEE**[1,2], N. WANG[2], K. SHEN[4], M. STRICOS[2], P. LANGFELDER[2], K. H. CHEON[1], E. P. CORTES[5], R. DAMOISEAUX[3], H. V. VINTERS[6], J. G. VONSATTEL[5], N. WEXLER[7,8], J. FRYDMAN[4], X. W. YANG[2]
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NY; [6]Dept. of Pathology and Lab. Med., David Geffen Sch. of Med. at UCLA, Los Angeles, CA; [7]Departments of Neurol. and Psychiatry, Columbia Univ., New York, NY; [8]Hereditary Dis. Fndn., New York, NY

**Abstract:** Huntington's disease (HD) is caused by an expansion mutation of the CAG trinucleotide repeat encoding polyglutamine (polyQ) near the N-terminus of Huntingtin (HTT). Identification of the pathogenic mutant HTT (mHTT) species and their correlation to disease progression remains to be the central question to study HD pathogenesis. However, the present methods are restricted to detecting soluble and likely monomeric or at most oligomeric HTT species. And it is unclear if there are certain mHTT species that could seed mHTT aggregation and be detected by a sensitive and automated assay. In the current report, we developed a stable cell line expressing a modified form of HTT N-terminal fragment tagged with GFP (HTT-GFP), which does not form aggregates by itself at the baseline. In contrast, HTT-GFP was induced to aggregate extensively by extracellular application of preformed mHTT aggregates, brain tissues from old but not young Q175 mice, or postmortem brain tissues and CSF from HD patients but not healthy controls. Importantly, the induced aggregation is specific with mHTT species, since it could not be elicited with fibrillar Aβ, phosphorylated tau, or CSF and brain lysates from control AD and PD patients. We further studied the correlation of the seedability of CSF with the disease progression using the CSF samples from the PREDICT-HD collection. The results demonstrated that the seedability of CSF significantly increases as the individuals are near the onset or diagnosed for HD. Importantly, the seedability of CSF increases as the disease progress, which is measured by various clinical assessments. In conclusion, we demonstrated that modified mutant HTT N-terminal fragments can sensitively detect HTT species in the HD patient biosamples. Importantly, our new assay is optimized for high-throughput automation. Our results suggest that the ability of CSF to induce mHTT aggregation could be a potential biomarker for measuring disease progression, and support future studies of their potential roles in the dsiease.

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**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 757.04/GG2

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** CHDI Foundation

**Title:** Integrative mouse genetics and systems biology to dissect Huntington's disease pathogenesis and aging in mice

**Authors: *N. WANG**[1,2], P. LANGFELDER[1], J. RICHMAN[1,2], M. STRICOS[1,2], F. GAO[1], X. GU[1,2], C. ZHU[1], L. RAMANATHAN[1,2], C. PARK[1,2], L. YANG[1], T. VOGT[4], J. AARONSON[4], J. ROSINSKI[4], G. COPPOLA[1], S. HORVATH[3], X. W. YANG[1,2]
[1]Semel Inst. for Neurosci. and Human Behavior, [2]Ctr. for Neurobehavioral Genetics, Dept. of Psychiatry and Biobehavioral Sci., [3]Dept. of Human Genetics, David Geffen Sch. of Med., UCLA, Los Angeles, CA; [4]CHDI Foundation/CHDI Mgmt. Inc., Princeton, NJ

**Abstract:** Integrative systems biology has been a powerful approach to elucidate novel molecular networks in Huntington's disease (HD). We previously reported a large-scale RNA-seq and proteomics study to examine an allelic series of murine Huntingtin (Htt) knock-in mice, and defined Htt CAG-length dependent co-expression gene modules that involve multiple pathways in HD pathogenesis (Langfelder et al., 2016, PMID: 26900923). In this study, we applied systems biology to examine a possible interaction between mutant Htt (mHtt) CAG repeat expansion and aging in HD neuropathogenesis. From a clinical perspective, the products of mutant Huntingtin CAG repeat length and age (i.e. CAP score) is one of the best predictors of HD progression (Ross et al., 2014, PMID: 24614516). Moreover, our previous study using a DNA methylation biomarker of age (called epigenetic clock) showed that postmortem HD patient brains exhibit evidence for accelerated aging (Horvath et al., 2016, PMID: 27479945). Here we analyzed transcriptomes of wildtype mice across multiple adult ages from 2 to 10m and build age-dependent co-expression networks for multiple brain regions (striatum, cortex, hippocampus and cerebellum) and one peripheral tissue (liver). These age-dependent gene modules are enriched with known biological changes associated with aging (e.g. inflammation). Interestingly, when we compared the aging network and Htt-CAG-repeat dependent network in multiple brain regions, there is only a strong positive correlation found in the striatum, consistent with the concept of mHtt possibly accelerating aspects of striatal molecular aging. Importantly, we now begin to utilize both environmental and genetic perturbations that are known to affect the aging process in the HD mouse models to test the idea that targeting the aging process could modify HD pathogenesis in vivo.

**Disclosures: N. Wang:** None. **P. Langfelder:** None. **J. Richman:** None. **M. Stricos:** None. **F. Gao:** None. **X. Gu:** None. **C. Zhu:** None. **L. Ramanathan:** None. **C. Park:** None. **L. Yang:** None. **T. Vogt:** None. **J. Aaronson:** None. **J. Rosinski:** None. **G. Coppola:** None. **S. Horvath:** None. **X.W. Yang:** None.

**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 757.05/GG3

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** NIH:NINDS 1P01NS092525-01A1

**Title:** Using TRiC or TRiC-based reagents to rescue cortico-striatal atrophy in Huntington's disease

**Authors: *C. CARMONA**[1], Z. BABIC[2], Y. GU[2], J. RAUS[2], C. WU[3], W. C. MOBLEY[3]
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**Abstract:** Huntington’s disease (HD) is caused by expansion of the Poly Q domain in Exon 1 of the gene for Huntingtin, leading to production of the mutant Huntingtin protein (mHTT). We demonstrated previously that TRiC, a molecular chaperonin, afforded neuroprotection against mHTT in neurons of the BACHD model of HD. Significantly, using microfluidic cultures in which we recreated the cortico-striatal circuit, we showed that overexpressing individual subunit(s) of TRiC acted to induce neuroprotective effects through increased delivery of BDNF from cortical neurons to striatal neurons. To further define the pattern of degeneration and cellular mechanism(s) responsible for defects in BACHD circuits, and the times at which TRiC reagents would act to protect these circuits, we established long-term microfluidic cortical-striatal cultures. We found that such cultures could be studied for up to 21 days in vitro (DIV). BACHD neurons in microfluidic cultures demonstrated significant, persistent deficits in synapse formation between cortical and striatal neurons; remarkably, while BACHD cortical neurons were deficient in supporting the trophic status of striatal neurons, there was little impact of mHTT on cortical neuron size or cortical axon growth. As in earlier studies, we examined the impact of adding the apical domain of TRIC 1 subunit, ApiCCT1, to cortical neurons in BACHD cultures. When added at DIV1, ApiCCT1 prevented both striatal atrophy and defects in retrograde axonal transport of BDNF. Our study further supports the utility of cortico-striatal cultures for exploring the biology of HD and a potentially important role for using TRiC derived reagents to intercept HD pathogenesis. Our current studies are focused on expanding our findings to other TRiC-based reagents and in the newly generated deltaN17BACHD mouse model.

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**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 757.06/GG4

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** This work was supported by the CHDI foundation

**Title:** Changes in specific PT and IT corticostriatal projections in the Q175 mouse model of Huntington's disease

**Authors: *T. PANCANI**[1], V. BEAUMONT[2], J. KONDAPALLI[3], D. WOKOSIN[3], D. SURMEIER[4]
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**Abstract:** Huntington's disease (HD) is a neurodegenerative disease characterized by severe motor alterations. The neuropathological occurrences underlying behavioral changes are extensive and include significant loss of striatal and cortical parenchyma. Direct communication between cortex and striatum is ensured by glutamatergic corticostriatal (CTX-STR) fibers which play a pivotal role in shaping motor behavior. Not surprisingly, a growing body of evidence is revealing significant alterations of these fibers in several mouse models of HD. CTX-STR axons are mainly originating from two distinct classes of cortical neurons: intratelencephalic (IT) and pyramidal tract (PT) neurons. IT neurons project within the telencephalon ipsi- and contralaterally to cortex and striatum forming the main component of the callosal commissure. Conversely, PTs project only ipsilaterally to extratelencephalic regions such as thalamus or brainstem forming also *en passant*synapses in striatum. The severe and progressive reduction of corpus callosum fibers seen in HD clearly suggest that CTX-STR IT and PT projections are altered in HD. However, alterations of corticostriatal fibers originating from specific cortical neuronal subpopulations and specific cortical regions has not been studied in the context of HD. Using the Q175 mice and IT and PT - Cre expressing mouse lines, together with optogenetics and electrophysiology techniques, we found that *M1-originating* IT CTX-STR glutamatergic transmission onto both direct and indirect pathway SPNs is surprisingly increased in 8 - month-old Q175 symptomatic mice. Studies performed using a CRACM approach and confirmed by mGRASP reveal an increase in IT-SPNs synapses specifically in the dorsolateral quadrant of striatum. Conversely, in Q175 PT axons originating from M1 are not altered at this age.

**Disclosures: T. Pancani:** None. **V. Beaumont:** None. **J. Kondapalli:** None. **D. Wokosin:** None. **D. Surmeier:** None.

**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 757.07/GG5

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** CHDI

**Title:** Cell type-specific transcriptome profiling of Huntington's disease mouse models

**Authors: *M. THERRIEN**[1], M. HEIMAN[2]
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**Abstract:** Huntington's disease (HD) is a fatal neurodegenerative disorder caused by CAG repeat expansions in the first exon of the *Huntingtin* gene (*HTT*). Disease severity is highly correlated with the size of the repeat expansion, wherein higher CAG repeat numbers correspond to an earlier age of disease onset. Changes to gene expression are a major hallmark of HD pathogenesis, and one of the earliest phenotypes observed in patients and in disease models. However, the causes and consequences of these changes are poorly understood with regard to disease progression and severity. In this project, we hypothesized that the identification of early changes in transcription in a cell type-specific manner could highlight important pathways of disease pathogenesis. We therefore characterized the transcriptome of different striatal cells and of corticostriatal neurons, the most affected cells in the HD brain. To do so, we have used the cell type-specific translating ribosome affinity purification (TRAP) methodology to carry out TRAP-Seq in *Drd1*- and *Drd2*- expressing striatal medium spiny neurons, striatal astrocytes, striatal interneurons, and corticostriatal projection neurons. Also, we have used five different allelic HD model knock-in mice (Q20, Q50, Q111, Q170 and zQ175) at 6 months of age, to capture early or pre- symptomatic stages of disease progression. Our study will identify early, cell type-specific changes in gene expression that are dependent on the *HTT* CAG expansion length in a cell type-specific manner. This project will lead to the identification of the cell types and pathways that are the most and earliest affected in HD and open new therapeutic avenues

**Disclosures: M. Therrien:** None. **M. Heiman:** None.

**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 757.08/GG6

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** Charles River performed this work as a CRO for CHDI

**Title:** Development of hit validation and deconvolution assays to triage potential small molecule modulators of mutant Huntingtin levels identified in a phenotypic screen in q48 human embryonic stem cells

**Authors: *D. MACDONALD**[1], V. LAZARI[2], B. NANCOLAS[2], M. MATEUS[2], A. MUKONOWESHURO[2], E. THATCHER[2], M. IOVINO[2], A. BARNARD[2], T. LADDUWAHETTY[2], P. BRECCIA[2], I. MUNOZ-SANJUAN[1], C. DOMINGUEZ[1], J. VOIGT[1],

E. DOHERTY[1], G. MCALLISTER[1]
[1]CHDI Management, Inc., Los Angeles, CA; [2]Charles River, Saffron Walden, United Kingdom

**Abstract:** We have developed a phenotypic screen in HD-patient derived, polyQ48 embryonic stem cells (ESC) to identify compounds that reduce mHTT levels. This homogeneous time resolved fluorescence (HTRF) multiplex 384-well high throughput screen (HTS) was developed and optimized to measure both mutant HTT (mHTT) and total HTT (tHTT) protein levels. In order to efficiently process the output from a 150,000 compound screen, performed to identify novel modulators of mHTT, we have developed a series of hit deconvolution assays designed to characterize hits in relation to their on and off-target activities.Using an In Cell Western assay, we have developed assays enabling orthogonal detection of HTT, as well as measures of protein selectivity, by determination of TBP and actin levels after compound treatment. As additional measures of protein selectivity, we have also used the HTRF platform to determine changes in the key cellular proteins, AKT and CREB after compound treatment. Compounds which show the required levels of selectivity are then progressed into a branched DNA assay which determines whether the compounds act through repression of translation, either at a general level or more specifically to Htt. Assays are under development to determine compounds which block HTT translation or enhance its clearance. We aim to use these assays in profiling hits from the CHDI collection whilst expanding our search for novel molecules which lower HTT by additional screening of diverse chemical matter.

**Disclosures: D. Macdonald:** A. Employment/Salary (full or part-time):; CHDI. **V. Lazari:** A. Employment/Salary (full or part-time):; Charles River. **B. Nancolas:** A. Employment/Salary (full or part-time):; Charles River. **M. Mateus:** A. Employment/Salary (full or part-time):; Charles River. **A. Mukonoweshuro:** A. Employment/Salary (full or part-time):; Charles River. **E. Thatcher:** A. Employment/Salary (full or part-time):; Charles River. **M. Iovino:** A. Employment/Salary (full or part-time):; Charles River. **A. Barnard:** A. Employment/Salary (full or part-time):; Charles River. **T. Ladduwahetty:** A. Employment/Salary (full or part-time):; Charles River. **P. Breccia:** A. Employment/Salary (full or part-time):; Charles River. **I. Munoz-Sanjuan:** A. Employment/Salary (full or part-time):; CHDI. **C. Dominguez:** A. Employment/Salary (full or part-time):; CHDI. **J. Voigt:** A. Employment/Salary (full or part-time):; CHDI. **E. Doherty:** A. Employment/Salary (full or part-time):; CHDI. **G. McAllister:** A. Employment/Salary (full or part-time):; CHDI.

**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 757.09/GG7

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Title:** Optimization of rho kinase inhibitors towards potent, selective and CNS-penetrant molecules suitable for proof-of-concept studies in HD models

**Authors: *V. BEAUMONT**[1], P. MITCHELL[2], D. TODD[2], T. LADDUWAHETTY[2], K. MATTHEWS[2], L. URBONAS[2], E. THATCHER[2], C. LUCKHURST[3], A. HAUGHAN[2], M. BARNES[2], A. CHAUHAN[2], E. SAVILLE-STONES[2], A. STOTT[2], H. PATEL[2], L. BLOM[2], G. MCALLISTER[1], R. CACHOPE[1], M. MAILLARD[1], M. ROSE[1], M. LEE[1], I. MUNOZ-SANJUAN[1], C. DOMINGUEZ[1]
[1]CHDI Mgmt., Los Angeles, CA; [2]Charles River, Saffron Walden, United Kingdom; [3]Mission Therapeut., Cambridge, United Kingdom

**Abstract:** Enhanced expression of ROCK, as well as dysregulation of its downstream elements, has been reported in Huntington's disease (HD) and other neurodegenerative disorders. More importantly, ROCK inhibition is reported to promote neuronal survival, decrease mHtt aggregation and improve synaptic function in HD cell and animal models, suggesting that ROCK inhibitors may have therapeutic potential in HD. A number of ROCK inhibitors exist, including marketed drugs such as fasudil and ripasudil (for glaucoma and ocular hypertension), although no known ROCK inhibitor combines a suitable kinase selectivity profile with good oral bioavailability and CNS exposure properties necessary for chronic efficacy studies in HD mouse models. Using literature-based information on known ROCK inhibitors and structure-based drug discovery methods we have conducted lead optimization activities to identify potential PoC tool compounds from two distinct chemical series with different selectivity profiles. Through implementation of a screening cascade, we have optimized compounds for ROCK biochemical and cellular potency, to achieve a CNS applicable pharmacokinetic profile and to maximize selectivity over key related kinases. We have applied an *ex vivo* target engagement approach (KiNativ™) and biomarker readouts to help guide dose selection for planned chronic efficacy studies in HD mice. Resulting lead compounds demonstrate good *in vivo* potency and selectivity and sustained brain exposure above levels predicted to result in inhibition of the target. We have utilized KiNativ™ technology to confirm dose-dependent target engagement and kinase selectivity *in vivo*. Lead molecules from both series offer promising potential to assess the therapeutic benefit of inhibiting ROCK in HD mouse models as orally bioavailable, brain penetrant and selective tool compounds.

**Disclosures: V. Beaumont:** A. Employment/Salary (full or part-time):; Charles River. **P. Mitchell:** A. Employment/Salary (full or part-time):; Charles River. **D. Todd:** A. Employment/Salary (full or part-time):; Charles River. **T. Ladduwahetty:** A. Employment/Salary (full or part-time):; Charles River. **K. Matthews:** A. Employment/Salary (full or part-time):; Charles River. **L. Urbonas:** A. Employment/Salary (full or part-time):; Charles River. **E. Thatcher:** A. Employment/Salary (full or part-time):; Charles River. **C. Luckhurst:** A. Employment/Salary (full or part-time):; Mission Therapeutics. **A. Haughan:** A. Employment/Salary (full or part-time):; Charles River. **M. Barnes:** A. Employment/Salary (full or part-time):; Charles River. **A. Chauhan:** A. Employment/Salary (full or part-time):; Charles River. **E. Saville-Stones:** A. Employment/Salary (full or part-time):; Charles River. **A. Stott:** A. Employment/Salary (full or part-time):; Charles River. **H. Patel:** A. Employment/Salary (full or

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**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 757.10/GG8

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** FRM Postdoctoral fellowship SPF20140129323
EMBO Lon Term Fellowship ALTF 693-2015

**Title:** Spatial $Ca^{2+}$sensing of vesicles determine their directionality along microtubules

**Authors: *C. SCARAMUZZINO**[1,2], F. SAUDOU[1,2,3]
[1]Grenoble Inst. Des Neurosciences, La Tronche, France; [2]INSERM Res. Ctr. U1216, Grenoble, France; [3]CHU Grenoble Alpes, Grenoble, France

**Abstract:** Mutation of huntingtin (HTT) leads to Huntington disease (HD), a neurodegenerative disorder characterized by the preferential dysfunction of cortical and striatal neurons. Whereas death of striatal neurons starts to be elucidated, the mechanism leading to the degeneration of cortical neurons remain unclear. One potential mechanism could involve the retrograde axonal transport of endosomes in cortical neurons that is known to induce survival of projecting neurons in various paradigms. We used state-of-the-art microfluidics to analyze distal-axonal TrkB trafficking in response to synaptic BDNF infusion. We observed that BDNF leads to a massive but transient retrograde flow of TrkB vesicles in cortical neurons, which requires receptor activation, the subsequent induction of the PLCγ pathway and Calcineurin (CaN) activation. Interestingly, we previously reported that vesicular HTT regulates transport directionality via its dephosphorylation of S421 by CaN promoting retrograde transport. Moreover, we found by mass spectrometry that CaN is present on vesicles. We observed via high-resolution microscopy that CaN localize on TrkB vesicles, suggesting that calcium released upon TrkB activation would be sufficient to drive the endosomal retrograde flow. Finally, we showed that TrkB re-routing requires HTT dephosphorylation using neurons derived from mice carrying point mutations on HTT at the S421 (S421D). Together these findings suggest that vesicles are able to sense calcium rich environments and modify the activity of their molecular motors via a CaN-HTT dependent mechanism on-board of vesicles. Furthermore, vesicles purified from mouse brains were perfused on *in vitro* polymerized microtubules and their movement was recorded by TIRF

microscopy after calcium uncaging. Preliminary data show that vesicles are able to sense the increase of calcium, which in turns would activate CaN leading to HTT dephosphorylation and to the reversion of trafficking directionality.In conclusion, we used microfluidic devices reproducing the corticostriatal connection in order to identify the BDNF-TrkB-PLCγ-CaN-HTT as a major pathway involved in the retrograde routing of TrkB signaling endosomes in cortical axons. Strikingly, we found that CaN localizes with HTT on board of TrkB vesicles and is able to direct the retrograde transport of vesicles. Together this study reveals HTT dephosphorylation as a crucial molecular event to induce axonal retrograde transport of neurotrophin signalling in neurons.

**Disclosures: C. Scaramuzzino:** None. **F. Saudou:** None.

**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 757.11/GG9

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** ARO Grant #W911NF-16-1-0311
VA Grant #1I01BX003303-01
HDSA Grant GR009606

**Title:** Mutant Huntingtin proteotoxicty suppression by NAD salvage pathway proteins

**Authors: *A. RUETENIK**[1], A. BARRIENTOS[2]
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**Abstract:** Huntington’s disease is caused by a single genetic abnormality in which the number of trinucleotide repeats encoding polyglutamine in exon 1 of the huntingtin gene expands past a threshold number of repeats to cause disease. This abnormally high number of glutamine repeats causes dysfunction and misfolding of the resulting huntingtin protein, neurodegeneration, and early death of patients with the disease. As no current treatments exist to prolong lifespan, we are interested in better understanding pathways and proteins that can protect against the toxic effects of mutant huntingtin. Previously, our laboratory discovered that several proteins that form a crucial salvage pathway in yeast protected against the toxic effects of a mutant huntingtin fragment in a yeast model of Huntington’s disease and degraded mutant huntingtin aggregates in the cell. Our continuing studies into these proteins demonstrate that their ability to protect against mutant huntingtin is independent of their catalytic function, and that they confer protection both during exponential growth and during experiments that parallel neuronal aging. Our data supports our hypothesis that these NAD salvage pathway proteins may confer protection through a previously undiscovered secondary role in the cell as molecular chaperones.

**Disclosures: A. Ruetenik:** None. **A. Barrientos:** None.

**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 757.12/GG10

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** CIHR Foundation grant 2017-2022
CHDI Foundation 2016-2018

**Title:** Palmitoylation and phosphorylation of huntingtin (HTT) regulate each other and promote HTT degradation

**Authors: *F. L. LEMARIE**[1,2], D. D. O. MARTIN[3], S. S. SANDERS[2], M. R. HAYDEN[2]
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**Abstract:** Huntington disease (HD) is a neurodegenerative disorder characterized by motor, cognitive and psychiatric disturbances. HD is caused by a CAG trinucleotide expansion in the *HTT* gene coding the huntingtin (HTT) protein. HTT is a scaffold protein subjected to multiple posttranslational modifications (PTMs) such as phosphorylation, proteolytic cleavage and fatty acylation (palmitoylation) that regulate its function. In the presence of the HD mutation, some PTMs of HTT are significantly altered. Several PTMs have therapeutic relevance, as they modulate the toxicity of mutant HTT (muHTT). Mouse models expressing muHTT harbouring mutations that block or mimic specific PTMs exhibit drastic changes in the disease phenotype: blocking caspase cleavage at Asp586 (Asp to Glu mutation) suppresses muHTT toxicity; blocking phosphorylation at Ser421 (Ser to Ala) exacerbates HD phenotypes while mimicking phosphorylation (Ser to Asp) ameliorates muHTT-induced neurodegeneration. Palmitoylation involves the formation of a labile thioester bond between a cysteine thiol side chain and a saturated palmitic acid. This type of lipidation promotes protein-membrane association as well as protein-protein interaction, and therefore plays a vital role for many neuronal and scaffold proteins. We previously demonstrated HTT palmitoylation at Cys214 catalyzed by the acyltransferase huntingtin interacting protein 14 (HIP14). We showed that muHTT is less palmitoylated in vitro and in YAC128 HD mouse model leading to increased formation of inclusions and neuronal toxicity. The objective of this study is to characterize the interactions between HTT palmitoylation and specific HTT PTMs that are protective against muHTT toxicity, and therefore evaluate the therapeutic interest of normalizing palmitoylation of muHTT.
**Results - Methods** We show that palmitoylation level is dysregulated in various HD mouse models (6-month BACHD and humanized HD mice). We investigate the interactions between palmitoylation and key PTMs of HTT (phosphorylation at Ser421, caspase cleavage) using cell

lines and HD mouse models expressing the muHTT protein carrying various mutations blocking/mimicking PTMs. We demonstrate that protective phosphorylation of HTT at Ser421 and palmitoylation regulate each other. Additionally, we show that HTT palmitoylation promotes HTT clearance. **Conclusion** This work demonstrates that HTT palmitoylation regulates neuroprotective PTMs of HTT and promotes muHTT degradation. These results support the hypothesis that normalizing muHTT palmitoylation level would constitute a therapeutic strategy to reduce muHTT toxicity.

**Disclosures: F.L. Lemarie:** None. **D.D.O. Martin:** None. **S.S. Sanders:** None. **M.R. Hayden:** None.

**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

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**Program #/Poster #:** 757.13/GG11

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** Novo Nordisk Foundation
Lundbeck foundation
CHDI

**Title:** Glial progenitor cells derived from Huntington's disease hESCs exhibit a cell-autonomous defect in the terminal differentiation of glia

**Authors: *A. BENRAISS**[1], M. OSIPOVITCH[2], S. DHALIWAL[1], A. CORNWELL[1], L. ZOU[1], D. CHANDLER-MILITELLO[1], S. WANG[1], X. LI[1], S.-J. BENRAISS[1], R. AGATE[1], A. C. LAMPP1[2], A. ASENJO-MARTINEZ[2], M. S. WINDREM[1], S. A. GOLDMAN[1,2]
[1]Univ. of Rochester Med. Ctr., Rochester, NY; [2]Fac. of Hlth. and Med. Sci., Univ. of Copenhagen, Copenhagen, Denmark

**Abstract:** Huntington's Disease (HD) is an autosomal dominant neurodegenerative disorder characterized by progressive impairment of motor function and cognition, and an invariably fatal outcome. HD is caused by a polyglutamine expansion at the N' terminal of huntingtin (HTT) protein, the accumulation of which causes striatal neuronal degeneration; but it is also associated with myelin loss, suggesting a mutant-HTT-dependent dysfunction of myelin-producing oligodendrocytes. In order to test this hypothesis, we have generated glial progenitor cells (GPCs) from human embryonic stem cells, derived from either mutant huntingtin (mHTT) embryos or controls, to assess the mHTT-dependent changes in gene expression by RNA sequence analysis (RNAseq). We found consistent downregulation of genes associated with astroglial and oligodendroglial differentiation in mHTT-expressing GPCs. Specifically, the expression of several myelin biosynthesis genes was significantly down-regulated, most notably,

MYRF and SOX10, transcription factors that tightly control the expression of a number of genes necessary for myelin formation, including MBP, MAG, OMG, PLP1 and MOG. All of these genes were significantly down-regulated in HD-derived GPCs but were restored upon over-expression of MYRF/SOX10. As predicted by the RNAseq data, when engrafted into neonatal myelin-deficient mice (Shiverer mice), mHTT-GPCs displayed a significant delay in myelination, resulting in hypomyelinated white matter and poor axonal ensheathment compared to control mice which had been engrafted with healthy GPCs. In addition, the incidence and density of HD-derived human astrocytes was lower in engrafted shiverer mouse brain than in age-matched controls. Furthermore, the HD-derived astrocytes had fewer, longer and less regularly distributed processes with gaps in radial coverage. These data suggest that glial differentiation in human HD exhibits a cell-autonomous defect in the terminal glial differentiation of mHTT-expressing GPCs, the pathology of which, rather than being secondary to neuronal loss, may be a major contributor to the etiology of HD.
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**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

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**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** CIHR Foundation Grant

**Title:** Intranasal delivery of mutant huntingtin-silencing antisense oligonucleotide nanoparticles for Huntington's disease therapy

**Authors: *A. E.-E. ALY**, N. S. CARON, H. FINDLAY-BLACK, M. R. HAYDEN
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**Abstract:** Huntington disease (HD) is an autosomal dominant, progressive neurodegenerative disorder caused by a CAG trinucleotide repeat expansion in the huntingtin gene (HTT). Silencing mutant HTT using antisense oligonucleotides (ASOs) is a promising approach that has shown great therapeutic potential in pre-clinical studies and is currently being evaluated in clinical trials for HD. However, the therapeutic potential of ASOs in HD patients is limited by their inability to cross the blood-brain barrier (BBB) after systemic administration. In non-human primates, intrathecal infusion of ASOs results in limited brain distribution, with higher ASO

concentrations in superficial regions and lower concentrations in deeper regions. Thus, there is a strong need for a non-invasive means of administrating ASOs to the brain that results in a more widespread distribution and greater target engagement in the brain regions most affected in HD, the deeper layers of the cortex and striatum.
Here, we are evaluating the therapeutic potential of in-house nanoparticle (NP) formulations as novel delivery vehicles for mutant huntingtin-lowering ASOs to the CNS after intranasal administration. The intranasal route of administration offers a non-invasive approach for direct delivery to the brain of therapeutic macromolecules and results in widespread brain distribution. We have optimized NP formulations composed of a scaffolding (or reporter) protein and phospholipids that achieve ASO loading efficiencies between 60-70% while maintaining low polydispersity and particle sizes ranging from 15-20 nm. The first goal of this study was to demonstrate the ability of these NPs to bypass the BBB after intranasal delivery in an HD mouse model. Following intranasal administration of NPs, reporter protein levels were elevated along the rostral-caudal brain axis, with highest levels in the most rostral brain regions including the olfactory bulb and frontal cortex. Our second goal was to determine the cellular pattern of distribution of the reporter protein in brain after intranasal delivery of these NPs. Double-label IHC indicates that the reporter protein primarily colocalizes with CD31+ capillary endothelial cells throughout the brain, but was also found in neuronal, astrocytic, and microglial cells. Ongoing studies will examine mHTT-lowering efficacy of ASOs delivered to the brain using NPs in HD mice.
This approach could represent a novel non-invasive means for improving delivery and brain distribution of oligonucleotide therapies and enhance likelihood of efficacy. Improved oligonucleotide delivery to the brain has widespread application for treatment of many other CNS disorders.

**Disclosures: A.E. Aly:** None. **N.S. Caron:** None. **H. Findlay-Black:** None. **M.R. Hayden:** None.

**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 757.15/DP04/GG13

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** CHDI Foundation

**Title:** Elucidating the role of DNA repair dynamics in a human neuron model of Huntington's disease

**Authors: *L. BARBÉ**, S. FINKBEINER, J. KAYE
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**Abstract:** Huntington's disease is a neurodegenerative disorder caused by the expansion of a 'CAG' repeat in the Huntingtin gene. This repeat is shown to be larger in more severe cases of the disease and DNA repair proteins were identified as the mainmolecules to create repeat enlargements. Patients with genetic variants in DNA repair genes have a later age of disease onset. However, the mechanism behind this protective effect of these genetic modifiers is unknown. Therefore, we wish to understand the contribution of DNA damage repair in Huntington's disease. We use live cell robotic microscopy to image reporters for the DNA repair proteins MSH3, MSH6, PCNA, MLH1 and FAN1 in medium spiny neuron-like cells differentiated from human pluripotent stem cells with or without a CAG expansion. We image these tagged DNA repair proteins after and before DNA damage at multiple time points on our robotic microscopy platform, which is an innovative and exquisitely sensitive method for quantifying neurological disease patterns in single cells over time in a high-throughput manner. We analyze the distribution of the DNA repair proteins using an in-house bioinformatics pipeline for segmentation, reference encoding and calculation of the number of puncta of DNA repair proteins per cell. We compare the distribution of DNA repair proteins and the response to DNA damage in CAG-expanded and control cell lines to determine the role of DNA repair in Huntington's disease.We hypothesize that the dynamics of DNA repair are altered in Huntington's disease and uncovering the activity of the DNA repair proteins may elucidate novel disease mechanism. We will report the results of our findings during this meeting.

**Disclosures: L. Barbé:** None. **S. Finkbeiner:** None. **J. Kaye:** None.

**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 757.16/GG14

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** HDSA Berman Topper HD Career Development Fellowship
NIH TG32 AG00096
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**Title:** Extracellularmatrix expression and function in Huntington's disease induced pluripotent stem cell-derived cell models

**Authors: *S. HERNANDEZ**[1], C. GEATER[1], R. LIM[1], *L. SALAZAR[1], A. REYES-ORTIZ[1], J. STOCKSDALE[1], J. WU[1], M. CASALE[1], D. KILBURN[2], L. HEISER[2], J. GRAY[2], P. GERSHON[1], L. M. THOMPSON[1], E. FRAENKEL[3], D. HOUSMAN[3]
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**Abstract:** Huntington's disease (HD) is a progressive, neurodegenerative disorder caused by a genetic expansion of a CAG repeat encoding glutamine within the Huntingtin protein. Individuals with 40 or more glutamines will eventually develop HD. HD is devastating, causing atrophy of the brain, uncontrollable movements, psychiatric disturbances, and behavioral changes. The extracellular matrix (ECM) is a highly plastic component of the cellular environment, continuously being remodeled by architectural modifications that guide cell attachment, cell motility, and cell survival. In the brain, the ECM can provide neuroprotection and loss of certain ECM components leads to phenotypes commonly observed in neurodegenerative diseases. Additionally, perturbations of the ECM can alter synaptic plasticity in the adult brain. And while there is clear evidence regarding the importance of ECM participation in critical CNS functions and neuronal dynamics, little is known about the role of the ECM in neurodegenerative diseases, including HD. Additionally, ECM molecules have shown great promise as highly druggable targets for diseases associated with traumatic neuronal loss. Therefore, taking advantage of the malleability of the ECM and the influence it has on neural plasticity through exogenous introduction of ECM molecules or agonists may allow for the prevention or reversal of disease-associated changes in the HD brain. Identification of ECM disease regulators provides molecular targets that can then be perturbed within cellular systems to elicit disease-modifying effects. To understand these processes in human cells across a range of human subjects, we are using induced pluripotent stem cells (iPSCs) to study HD by providing a source of patient-derived cells of varying polyglutamine lengths. Here, we explore HD-related ECM dysregulation in two iPSC-derived cell types: 1) medium spiny neurons (MSNs) and 2) brain microvascular endothelial cells (BMECs). In MSNs, RNAseq data implicates a dysregulation of ECM-related genes and current work is focused on defining an MSN-specific cell adhesion phenotype and optimizing mass spectrometry analysis of the MSN secretome and proteome. We recently published data indicating that iPSC-derived BMECs demonstrate an HD-related increased in angiogenesis and reduced barrier properties, implicating blood-brain barrier (BBB) deficits in HD. In BMECs, RNAseq data also demonstrates ECM dysregulation. Current data explores the relationship between the ECM, the cytoskeleton, and angiogenesis for identification of specific ECM-related molecules that can be modulated to ameliorate HD phenotypes and restore BBB dysfunction.

**Disclosures: S. Hernandez:** None. **C. Geater:** None. **R. Lim:** None. **L. Salazar:** None. **A. Reyes-Ortiz:** None. **J. Stocksdale:** None. **J. Wu:** None. **M. Casale:** None. **D. Kilburn:** None. **L. Heiser:** None. **J. Gray:** None. **P. Gershon:** None. **L.M. Thompson:** None. **E. Fraenkel:** None. **D. Housman:** None.

**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 757.17/GG15

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

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NIH Biotechnology Training Program Fellowship T32GM008334

**Title:** Bioenergetic deficits in Huntington's disease iPSC-derived neurons and rescue with glycolytic metabolites

**Authors: *S. AKIMOV**[1], A. J. DAIGLE[2], E. FRAENKEL[2], R. S. ATWAL[3], J. F. GUSELLA[3], M. E. MACDONALD[3], J. KAYE[4], S. FINKBEINER[4], V. B. MATTIS[6], C. M. TOM[6], C. SVENDSEN[6], A. R. KING[5], Y. CHEN[5], J. T. STOCKSDALE[5], R. G. LIM[5], M. CASALE[5], P. WANG[5], L. M. THOMPSON[5], T. RATOVITSKI[1], N. ARBEZ[1], C. A. ROSS[7]
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**Abstract:** Huntington's disease (HD) is a dominantly inherited neurodegenerative disorder caused by a CAG repeat expansion mutation in the *HTT* gene, and characterized by loss of neurons in the caudate and putamen at earlier ages of onset with increasing number of CAG repeats. Altered cellular metabolism is believed to be an important contributor to pathogenesis of HD, demonstrated even before the discovery of the HD CAG repeat expansion mutation. Most research has focused on mitochondrial toxicity, which can cause death of the vulnerable striatal neurons, but other aspects of metabolism may also contribute. Most previous studies have used post-mortem human brain or non-human cells. Here we studied bioenergetics in an induced pluripotent stem cell (iPSC) based model of the disease. We found decreased ATP levels in HD cells compared to controls, across differentiation stages and protocols. Proteomics data and multi-omics network analysis revealed normal or increased levels of mitochondrial messages and proteins, but lowered expression of glycolytic enzymes. Metabolic experiments showed decreased spare glycolytic capacity in HD neurons, while maximal and spare respiratory capacities driven by oxidative phosphorylation were largely unchanged. ATP levels in HD neurons could be rescued with addition of pyruvate or late glycolytic metabolites, suggesting a role for glycolytic deficits as part of the metabolic disturbance in HD neurons. Pyruvate or other related metabolic supplements could have therapeutic benefit in HD.

**Disclosures: S. Akimov:** None. **A.J. Daigle:** None. **E. Fraenkel:** None. **R.S. Atwal:** None. **J.F. Gusella:** None. **M.E. MacDonald:** None. **J. Kaye:** None. **S. Finkbeiner:** None. **V.B. Mattis:**

None. **C.M. Tom:** None. **C. Svendsen:** None. **A.R. King:** None. **Y. Chen:** None. **J.T. Stocksdale:** None. **R.G. Lim:** None. **M. Casale:** None. **P. Wang:** None. **L.M. Thompson:** None. **T. Ratovitski:** None. **N. Arbez:** None. **C.A. Ross:** None.

**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 757.18/GG16

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** NIH P50AG005131
UCSD Huntington's Disease Society of America Center of Excellence

**Title:** Quantification and epigenetic analysis of brain derived neurotrophic factor in Huntington's disease

**Authors: *P. A. DESPLATS**[1], A. GUTIERREZ[2], J.-C. BLOOM[3], E. A. THOMAS[4]
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**Abstract:** Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder that affects motor coordination and leads to cognitive decline. HD is caused by a trinucleotide repeat mutation in the *Huntingtin* gene (*HTT*) leading to a polyglutamine expansion in the huntingtin (htt) protein, which results in toxic aggregation that disrupts several neuronal pathways. HD neuropathology is characterized by substantial loss of medium spiny neurons in the striatum. Brain derived neurotrophic factor (BDNF) plays fundamental roles in the survival and activity of neurons, including striatal cells that die in HD. Previous reports shown substantial alterations in BDNF levels in the brains of HD cases; however, limited studies have explored the changes in BDNF across clinical stages of HD and levels present in peripheral fluids. We hypothesized that BDNF is increasingly deregulated during HD progression, and could be detected in plasma and saliva. Moreover, we propose that changes in BDNF expression may result from altered methylation on the BDNF promoter, as previously reported for other neurodegenerative disorders. Here, we examined the potential use of BDNF as a peripheral biomarker. We optimized an enzyme-linked immunosorbent assay to measure BDNF levels in plasma and saliva of patients in different HD clinical stages and control patients. We tested samples from n=14 pre-manifest patients, n=12 patients with full onset HD, and n=15 normal controls. We found significantly lower levels of BDNF in saliva samples from subjects that tested positive for the *HTT* gene mutation, regardless of HD clinical disease status in comparison to non-carriers. No significant changes in BDNF were found in plasma, although there was a trend towards lower levels in male patients. In addition, our results corroborate previous findings suggesting gender-

and age-based differences in BDNF. Further analysis of BDNF levels with clinical data showed no correlations of protein abundance with mental and physical states of subjects. Altogether, our findings suggest that the *HTT* gene mutation, gender, and age may give rise to fluctuations in BDNF, which may be detected in saliva. A larger sample and further studies will be needed to determine whether changes in BDNF levels may predict the onset of clinical symptoms in mutation carriers.
This study was supported by the UCSD Huntington's Disease Society of America Center of Excellence and the UCSD Shiley-Marcos Alzheimer's Disease Research Center NIH P50AG005131.

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**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 757.19/GG17

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** DFG (German Research Foundation)
NeuroCure

**Title:** Assessment of a selective histone deacetylase inhibitor as a therapeutic candidate in models of Huntington's disease

**Authors: K. HECKLAU**, *F. YILDIRIM
Dept. of Neuropsychiatry, Dept. of Psychiatry and Psychotherapy & Neur, Charite Med. Sch., Berlin, Germany

**Abstract:** Progressive transcriptional dysregulation in brain is an early and central feature of Huntington's disease (HD) pathogenesis. Using cell and mouse models, we and others have previously demonstrated genome-wide changes in transcription, DNA methylation and histone modification patterns that may underlie transcriptional dysregulation in HD. Thus, targeting epigenetic mechanisms for rescue of aberrant gene expression is a promising therapeutic strategy for HD. Here, we investigate potential therapeutic effects of a histone deacetylase inhibitor (HDACi) targeting selectively HDAC1 and HDAC3 in cell and mouse models. In primary striatal neurons transduced with lentiviruses carrying a mutant *HTT* fragment, HDAC1/3 inhibition resulted in beneficial effects against mutant *HTT*-induced toxicity and significantly restored mRNA levels of key genes commonly dysregulated in HD (e.g. *Drd2, Egr1, Darpp32, Arc*). In vivo, HDACi treatment of R6/1 transgenic mice improved motor learning skills in the accelerated Rotarod test. By volumetric MRI measurements, we detected that HDACi-treated R6/1 mice show reduced atrophy in various brain regions (e.g. Pallidum and Hypothalamus)

compared to vehicle-treated R6/1s. Analyses of several key HD-associated genes indicate improvement of their expression in R6/1 brain by HDAC1/3 inhibition. Overall, our findings suggest a beneficial effect of HDAC1/3 inhibition in HD. Further assays, including immunohistochemistry and RNA sequencing, to fully assess the therapeutic potentials of this specific HDACi in HD are currently ongoing.

**Disclosures: K. Hecklau:** None. **F. Yildirim:** None.

**Poster**

**757. Huntington's Disease: Molecular Mechanisms II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 757.20/HH1

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** CHDI grant to JF Cheer

**Title:** Modulation of corticostriatal networks as a biomarker for onset of prodromal impairments in Huntington's disease and as a potential target for endocannabinoid pharmacological intervention

**Authors: *A. Y. KIM**[1], N. E. ZLEBNIK[1], I. GILDISH[1], D. P. COVEY[1], J. F. CHEER[1,2]
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**Abstract:** Huntington’s disease (HD) is an inherited neurodegenerative disorder caused by a polyglutamine (CAG) expansion in the huntingtin gene. Resultant striatal and cortical dysfunction are the hallmark neuropathological features underlying dyskinesia (e.g., chorea) and akinesia at later stages. However, motivational and cognitive deficits commonly manifest during a prodromal stage that precedes motor dysfunction. Recent studies report an early loss of striatal cannabinoid receptors (CB1) as well as endocannabinoid (eCB) degradation enzymes in HD patients and rodent models. Here, we show in the Q175 mouse model of HD that impaired motivation for reward was associated with maladaptive gamma oscillations and patterned spiking activity at the NAc. Yet, precise temporal, spatial, and cell type-specific measures of neuronal network dynamics at localized brain regions affected by HD onset in a longitudinal fashion, such as the pre-frontal cortex (PFC), remain elusive. By implementing miniature, fluorescence microscopes with an implantable endoscopic gradient-refractive-index (GRIN) lens, we recorded spatial and temporal neuronal activity at the PFC in wild-type (WT) and Q175 knock-in mice performing a task for motivation (progressive-ratio schedule). Following treatment with MAGL inhibitor JZL-184, which raises tissue levels of the eCB 2-arachidonoylglycerol in HD mice, rescued motivation and attenuated maladaptive accumbal gamma oscillations along with neural ensemble activity at the PFC. Our multi-modal analyses of cortical and striatal networks in HD

progression suggest that eCB-based pharmacological interventions are promising pharmacological tools to attenuate biomarkers associated with prodromal psychiatric deficits in HD.

**Disclosures: A.Y. Kim:** None. **N.E. Zlebnik:** None. **I. Gildish:** None. **D.P. Covey:** None. **J.F. Cheer:** None.

**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 758.01/HH2

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** NIH R01NS089750-01

**Title:** BACHD/dnSNARE mice reveal the contribution of gliotransmission to Huntington's disease pathogenesis

**Authors: *A. KING**[1], T. WOOD[2], E. RODRIQUEZ[2], M. GRAY[2]
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**Abstract:** Huntington's disease (HD) is a neurodegenerative disorder characterized by the loss of the medium spiny neurons in the striatum and extends to other brain regions as the disease progresses. HD is caused by a CAG expansion in the gene encoding for the protein huntingtin. Huntingtin is widely expressed in neuronal and non-neuronal cell types. Understanding the toxic effects of mutant huntingtin (mHTT) in the various cell types in the brain is critical for identifying disease modifying therapies which target those cells specifically. Astrocytes are the most numerous and diverse set of neuroglial cells in the central nervous system (CNS). They perform a variety of tasks including synaptic support, axon guidance, ion homeostasis, transmitter synthesis, transmitter release, and transmitter removal. Previous studies showed that expression of the glutamate transporter (EAAT-2), is reduced in HD patient striatum. Impaired glutamate uptake could lead to excessive activation of glutamate receptors causing excitotoxicity. Although astrocyte involvement in HD has been suggested by recent studies, the pathogenic mechanisms have not been fully elucidated.
Preliminary data from our group showed that cortical astrocytes cultured from BACHD mice had increased SNARE-dependent vesicular glutamate release. We observed an amelioration of behavioral and neuropathological phenotypes in BACHD mice when full-length mHTT (fl-mHTT) expression was decreased only in astrocytes. Based on these findings, we **hypothesize that fl-mHTT expressing astrocytes play an important role in the progression of HD and may affect HD pathogenesis through increased gliotransmitter release.** To test our

hypothesis, we have used dominant negative (dn)SNARE mice to investigate decreased gliotransmitter release from astrocytes. The dnSNARE mice were bred to BACHD mice that contain a conditional human full length mutant huntingtin gene and display behavioral and neuropathological phenotypes reminiscent of HD patient disease. We report behavioral and neuropathological analyses of the BACHD/dnSNARE mice.

**Disclosures: T. Wood:** None. **E. Rodriquez:** None. **M. Gray:** None.

**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 758.02/HH3

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** CHDI Foundation

**Title:** Primary cortical neurons derived from zQ175 knock-in mice co-cultured with wildtype astrocytes as a model for Huntington's disease therapy

**Authors: R. VAN DE BOSPOORT**[1], A. STRIJBOSCH[1], M. DA SILVA[1], W. GRERNRUM[1], N. VAN DEN BERG[1], S. LACHIZE[1], *S. DIJKSTRA[1], P. MITCHELL[2], D. F. FISCHER[2], G. MCALLISTER[3], S.-W. JANG[4], I. MUNOZ-SANJUAN[3]
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**Abstract:** Huntington’s disease (HD) is a severe neurodegenerative disorder characterized by motor, cognitive and psychiatric effects. HD is an autosomal dominant, inherited disease that is caused by an unstable trinucleotide repeat expansion (CAG repeats) in the *huntingtin (HTT)* gene. To better understand HD pathogenesis in a relevant cellular context, we developed a primary neuronal culture of cortical neurons on an astrocyte feeder layer (co-culture) derived from one of the well-characterized knock-in models, zQ175, further engineered to remove a neomycin cassette for genomic integrity. In particular, a robust HTT quantification assay was established in the co-cultures to study the effect of candidate therapeutics on endogenous soluble mutant HTT levels. First, Homogeneous Time Resolved Fluorescence (HTRF) genotyping was performed, allowing for rapid and reliable identification of the knock-in mice in mixed genotype litters. Cortical neurons were dissected and seeded on top of a rat astrocytic feeder layer. Soluble mutant HTT levels were quantified using a Meso Scale Discovery (MSD) platform and cell survival and toxicity was quantified using nuclear condensation and DRAQ7 as high content assays as well as several biochemical assays. Previously characterized reference compounds were tested for the assessment of a robust positive control. Our results demonstrate that primary cortical neurons co-cultured with astrocytes derived from the zQ175 knock-in mice can be

utilized as a robust model system, in particular, for the study of different candidate therapeutics for HTT lowering. In addition, genetic perturbation strategies were explored for validation of targets involved in the regulation of mutant HTT levels. In order to further develop phenotypic relevant primary neuron/ astrocyte co-cultures, current efforts are focused on exploring additional models.

**Disclosures: R. Van de Bospoort:** None. **A. Strijbosch:** None. **M. Da Silva:** None. **W. Grernrum:** None. **N. Van den Berg:** None. **S. Lachize:** None. **S. Dijkstra:** None. **P. Mitchell:** None. **D.F. Fischer:** None. **G. McAllister:** None. **S. Jang:** None. **I. Munoz-Sanjuan:** None.

**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 758.03/HH4

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** NIH/NINDS R01 NS099136

**Title:** Assessing altered cortico-basal ganglia circuitry in a novel AAV-mediated non-human primate model of Huntington’s disease

**Authors: *A. R. WEISS**[1], D. BUTTON[1], J. DOMIRE[1], W. LIGUORE[1], Z. LIU[1,2], C. KROENKE[1,2], J. MCBRIDE[1,3,4]
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**Abstract:** Our laboratory has shown that AAV1-mediated expression of mHTT in the caudate and putamen of adult rhesus macaques induces motor impairments, reduced spatial working memory capabilities and disease-related striatal pathology, replicating several key hallmarks of human HD. We recently refined our model using a new vector with significantly enhanced retrograde transport (AAV2.retro). Upon injection of AAV2.retro expressing eGFP into the caudate and putamen, we saw robust eGFP expression in the striatum, and profound transduction in several cortical and sub-cortical regions. We are now in the process of creating a 2nd generation NHP model of HD using AAV2.retro to deliver mHTT into the caudate and putamen and anticipate that we will generate mHTT-related neuropathology in the striatum and in structures that project to the striatum, including frontal and motor cortices, the thalamus, amygdala and other regions in the basal ganglia. To assess this, we will query the temporal disruption of cortico-basal ganglia circuitry using advanced imaging methods and link changes in brain connectivity to cognitive, motor, and affective phenotypes in this new model. We developed touchscreen tasks to assess working memory and impulsivity and we will assess motor skills with the Lifesaver Retrieval Task and an NHP-specific neurological rating scale.

Emotional reactivity and anhedonia will be characterized using the Human Intruder test and a sucrose preference assay, respectively. Alongside these behavioral assays, we plan to collect MRI data to measure volumetric alterations of cortical and basal ganglia structures, detect changes in white and grey matter microstructure (DTI), and identify areas of decreased functional connectivity (rsfMRI). In addition, we will collect longitudinal serum and CSF samples for further HD biomarker development. These data will enhance our understanding of the mechanisms impacted by the HD mutation, validate neuroimaging measurements used to stage HD pathology in human subjects, generate new therapeutic biomarkers of disease progression and provide a second viral-vector based monkey model of HD available to the research community for evaluation of promising therapeutics. This work is supported by grants from NIH/NINDS (R01 NS099136).

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**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 758.04/HH5

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Title:** Comprehensive characterization of R6/2 transgenic mice: A longitudinal study to correlate progressive behavioral deficit with *in vivo* imaging and histological analysis monitoring the distribution of mutant Huntingtin

**Authors: *H. PARK**, K. PARK[1], S. PARK[1], M. LEE[2], Y. KIM[1], P. SWEENEY[1], W. IM[2], M. KIM[2]
[1]Naason Sci. Inc., Heungdeok-Gu, Korea, Republic of; [2]Neurol., Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of

**Abstract:** Huntington’s disease (HD) is a genetic, progressive neurodegenerative disease that is caused by an expansion of polyQ at the N-terminus of huntingtin protein. R6/2 that expresses exon-1 fragment of mutant huntingtin (mHTT) protein has been widely used as a disease model for HD. In this study, we show that R6/2 mice manifest robust, progressive decline in rotarod, open field, and grip strength performance over 6-12 weeks. We ran a comprehensive volumetric MRI in the entire brain and MRS in striatum at 6 and 12 weeks. The MRI analysis shows significant changes in volume in cortex, caudate putamen, hippocampus, thalamus, olfactory bulbs, and ventricles in R6/2 compared to those in wild type (WT) mice. In the MRS analysis, the level of Gln, Glu, Glx, Cho, tNAA, tCr, and Tau was also significantly altered in R6/2 striatum compared to those in WT striatum. To better understand the correlation between and expression of mHTT and MRI/MRS changes, we then examined the distribution of mHTT in the

regions where we observe more robust changes in imaging studies by using various histological methods including CLARITY 3D imaging.

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**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 758.05/HH6

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Title:** Astrocyte transduction is required for rescue of behavioral phenotypes in the YAC128 mouse model with AAV-RNAi mediated HTT lowering therapeutics

**Authors: *L. M. STANEK**, B. R. MASTIS, J. BU, A. RICHARDS, L. S. SHIHABUDDIN
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**Abstract:** Huntington's disease (HD) is a fatal autosomal dominant neurodegenerative disease caused by a CAG expansion translating into an elongated polyglutamine (polyQ) repeat near the amino-terminus of the huntingtin (HTT) protein. This results in production of a toxic mutant huntingtin (mHTT) protein that leads to neuronal dysfunction and subsequent neuronal death. Currently, no disease modifying treatments are available however numerous therapeutic strategies aimed at lowering HTT levels in the brain are under development. For all of these strategies, cell-type specific targeting is still an outstanding question. While it is clear that mHTT accumulation in medium spiny neurons play a role in their atrophy and ultimate death, there is mounting evidence that glial cells, and astrocytes in particular, play a key role in the disease process. Reducing levels of the disease causative mHTT protein in the brain has proven efficacious at ameliorating disease symptoms in a number of HD mouse models. To date these studies have not closely examined the contribution of mHTT reduction in neurons vs astrocytes and therefore a complete understanding of cell type specific targeting is outstanding. We sought to evaluate this question in the YAC128 mouse model of HD using AAV-mediated RNA interference (RNAi) to selectively lower HTT levels in neurons alone versus neurons and astrocytes. Previously we demonstrated that AAV-RNAi mediated HTT reduction using the AAV1 capsid (which transduces both neurons and astrocytes) is capable of ameliorating HD phenotypes in the YAC128 mouse model of HD. In the current preclinical study, a modified AAV2 capsid (AAV2-HBKO) with a similar distribution profile as AAV1 but strictly neuronal tropism showed comparable suppression of Htt mRNA and protein following injections into the striatum, however, it was not associated with correction of motor deficits in YAC128 mice. YAC128 mice show a significant rota rod deficit that was not ameliorated when mHTT levels were reduced only in neurons. As previously demonstrated, mice that received AAV1- miRNA

HTT, transducing both cells types, showed significant improvement on behavioral deficits suggesting that AAV-mediated HTT reduction in neurons alone was not sufficient to support full therapeutic benefit in the YAC128 mouse. This work indicates that astrocyte dysfunction may play a critical role in HD pathogenesis and represent an important therapeutic target. Additionally, therapeutics that target only neurons may be inadequate at restoring normal function and ameliorating all disease symptoms.

**Disclosures: L.M. Stanek:** A. Employment/Salary (full or part-time):; Sanofi. **B.R. Mastis:** A. Employment/Salary (full or part-time):; Sanofi. **J. Bu:** A. Employment/Salary (full or part-time):; Sanofi. **A. Richards:** A. Employment/Salary (full or part-time):; Sanofi. **L.S. Shihabuddin:** A. Employment/Salary (full or part-time):; Sanofi.

**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 758.06/HH7

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** CHDI

**Title:** Excitatory and inhibitory synaptic signaling is differentially affected in D1 and D2 MSNs in the Q175+/- mouse model of Huntington’s disease

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**Abstract:** Huntington’s Disease (HD) is an autosomal dominant neurodegenerative disorder caused by the replication of CAG repeats in the *Huntingtin* gene and the expression of mutant *Huntingtin* (mHtt). HD neuropathology manifests as a loss of cortical and striatal volume, and striatal medium spiny neurons (MSNs) of the direct (D1) and indirect (D2) pathways are particularly vulnerable. These neurons receive excitatory inputs from thalamo-striatal and cortico-striatal afferents and inhibitory inputs from other MSNs, from parvalbumin positive (PV+) fast-spiking interneurons (FSIs), and from other classes of local interneurons. Previous studies have shown significantly reduced excitatory and increased inhibitory postsynaptic current frequencies in unidentified MSNs from R6/2 and BACHD mouse models of HD (Cepeda et al., 2003), and a reduction in excitatory synaptic current frequency in D1 but not D2 MSNs in one year old BACHD and YAC128 mice (Andre et al., 2011). However, the anatomical underpinnings of these functional synaptic changes are not known. To address this question as well as the specificity of any changes to D1 vs. D2 MSN subtypes, we used whole-cell patch clamp recordings to characterize spontaneous excitatory and inhibitory synaptic currents in identified D1 and D2 MSNs in one year old Q175+/- x D2eGFP vs. wild-type (WT) x D2eGFP

mice. Subsequently we assessed both excitatory and inhibitory appositions on these neurons using immunohistochemistry for Vglut1, Vglut2, PV and Vgat and high resolution confocal imaging. We observed a significant decrease in excitatory synaptic current frequency in D1 but not D2 MSNs and a significant increase in inhibitory synaptic current frequency in D2 but not D1 MSNs in Q175+/- relative to WT. The number and distribution of Vglut1+ and Vglut2+ appositions on D1 and D2 MSNs did not differ between Q175+/- and WT. The number and distribution of inhibitory FSI (PV+/VGAT+) and nonspecific inhibitory appositions (PV-/VGAT+) to D1 and D2 MSNs are currently being assessed. We also assessed the morphological features of D1 and D2 MSNs, as well as of PV+ FSIs using confocal imaging and Neurolucida software-guided reconstruction. Interestingly, D1 MSNs in Q175+/- mice showed significant proliferative increases in dendritic length together with significant spine loss while the morphological features of D2 MSNs did not differ between Q175+/- and WT mice. Finally, the dendritic arbors of PV+ FSIs were significantly reduced in total length and volume in Q175+/- compared to WT mice. Taken together, these data reveal complex and nuanced changes to excitatory and inhibitory synaptic signaling in MSNs.

**Disclosures: A. Rubakovic:** None. **M. Sumioka:** None. **J.I. Luebke:** None.

**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

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**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 758.07/HH8

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** PUCE research grant
Prometheus Program grant

**Title:** Neuroprotectve effects of melatonin and RNAi in an experimental model of Huntington's disease by quinolinic acid model

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**Abstract:** Huntington disease (HD) is an autosomal dominant neuropathology associated with severe degeneration of basal ganglia neurons. It characterized by progressive motors symptoms, cognitive deficits and dementia. The gene HTT (Huntingtin) is located at the chromosome 4p163. The genetic mutation induces CAG trinucleotide repeat expansion. The CAG repeat is translated into a polyQ stretch. In this study we inoculated quinolinic acid (QA) intra cerebrally (Atlas of Paxinos and Watson, 1986: AP = +1.2 ahead of Bregma, L = +2.8 and DV = -5.5). Incisor bar location to 2 mm below the interaural line), to wistar rats in an experimental model of

Huntington Disease. The animals used as experimental design were: control (SS); QA; QA+SS; QA+RNAi: QA+Melatonin; QA+RNAi+Melatonin. We analyzed SOD Gpx, GSH, caspases 3,-6,-7,-9, Bcl2, Bax 3 and p53, GFAP, Map-2 genes by RT-PCR, western blot to proteins and histochemistry. The results showed low mRNA expression of SOD, Gpx, GSH, and high mRNA expression of caspases 3,-6,-7,-9, Bcl2, Bax 3 and p53 in QA; QA+SS animals. The levels of proteins presented the same tendency; the astrocytes immunohistochemistry evidence hypertrophy, hyperplasia; NeuN staining quantification present less number of neurons-cells in this treatment analyzed. Interestingly, the treatments with QA+RNAi ;QA+Melatonin; QA+RNAi+Melatonin present the reverse tendency in genes, proteins and histochemistry analyzed. This results suggest that melatonin and RNAi may be effective in reducing neuronal and astrocytes damage in HD

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**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 758.08/HH9

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** Packer.Wenz Endowment

**Title:** Nitric oxide as an exercise induced mitochondrial function modulator in the CAG140KI Huntington's mouse model

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**Abstract:** Abstract: Huntington’s disease (HD) is an autosomal dominant neurodegenerative disorder caused by an excessive polyglutamine (CAG) expansion in the Huntingtin (Htt) gene resulting in a mutated form of the huntingtin (htt) protein. HD is characterized by progressive decline in cognitive and motor functions with neuropsychiatric disturbances leading ultimately to premature death 10 to 15 years after onset of motor symptoms. The major pathological findings include severe degeneration of striatal medium spiny neurons (MSNs) and the cerebral cortex, particularly the prefrontal and frontal cortex. In the striatum, there is a preferential loss of the dopamine D2 receptor (DA-D2R)-containing MSNs that mediate the indirect pathway compared to direct pathway dopamine D1 receptor (DA-D1R)-containing MSNs. Defects in the respiratory chain in HD have been observed in early biochemical studies. Severe reduction in the activity of complex II/III and milder reduction of complex IV were found in post mortem samples of the caudate/putamen in HD patients. No changes were observed in pre-symptomatic patients. The

cerebral cortex showed minor changes in respiratory chain enzymes. Reduced activity of other enzymes of oxidative metabolism in the striatum was also reported. In particular massive loss of aconitase activity has been found in the caudate (~90%), and putamen (~70%). There is currently no cure for HD. Nitric oxide is a hydrophobic gas which can cross all biological membranes without mediation of channels or receptors. Nitric oxide (NO) diffuses isotropically to surrounding tissue at a greater rate than O2, CO2, and CO, making it ideal for intercellular messaging. NO is known as a highly reactive signaling molecule having a half life of a few seconds. NO is membrane permeable and has the ability to diffuse into dopaminergic neurons, thereby allowing NO receptors to be utilized for signaling transduction for intracellular communication. In this study we use the CAG140 HD mouse model, chosen for its slow progression with motor symptoms emerging at 12 months of age and provide evidence of the benefits of long-term treadmill running. HD and WT mice of two separate ages (9 and 15 months) ran for 3 months 60 min per day 5 days a week. Chronic cardiovascular exercise improved mitochondrial complex activities, motor function, cognition, and elevated nitrite/nitrate and aconitase levels in the brain. We explore a novel hypothesis that elevated NO stored as nitrosothiols from chronic exercise links mitochondrial brain metabolism and cerebral vasculature through the proposed mechanism of decreasing transglutaminase activity.

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**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

**Location:** SDCC Halls B-H

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**Topic:** C.04. Movement Disorders other than Parkinson's Disease

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**Title:** Normalizing glucocorticoid levels in R6/2 mice ameliorates metabolic and neuropathological symptoms of Huntington’s disease

**Authors: *B. D. DUFOUR**[1,2,3], J. L. MCBRIDE[2,3]
[1]Psychiatry and Behavioral Sci., Univ. of Washington, Seattle, WA; [2]Behavioral Neurosci., Oregon Hlth. & Sci. Univ., Portland, OR; [3]Oregon Natl. Primate Res. Ctr., Beaverton, OR

**Abstract:** Huntington’s disease (HD) is a fatal genetic neurological disorder caused by a mutation in the human Huntingtin (HTT) gene. This mutation confers a toxic gain of function of the encoded mutant huntingtin (mHTT) protein, leading to a robust neuropathology, including

cell loss, reduced levels of neurogenesis, and the formation of mHTT+ inclusion bodies. HD patients suffer from progressive motor, cognitive, psychiatric, and metabolic symptoms, which includes weight loss and muscle wasting. HD patients also show neuroendocrine changes, including a robust, significant elevation in circulating levels of glucocorticoids. Previously, we confirmed that the R6/2 mouse model of HD exhibits elevated glucocorticoid levels and demonstrated that experimentally elevated glucocorticoids exacerbate R6/2 HD symptomology - resulting in severe and rapid weight loss and a shorter latency to death. Given that efficacious therapeutics are lacking for HD, here we wished to investigate whether normalizing glucocorticoid levels could serve as a viable therapeutic approach for HD. Thus, we tested the hypothesis that normalizing glucocorticoids to wild-type levels would ameliorate HD symptomology. Wild-type (WT) and transgenic R6/2 mice were allocated to three treatment groups: 1) Adrenalectomy with WT-level corticosterone replacement (10ng/ml), 2) Adrenalectomy with high HD-level corticosterone replacement (35ng/ml), or 3) Sham surgery without replacement. As with human HD patients, R6/2 HD mice show increased metabolic rate, as indicated by an increase in resting oxygen consumption ($VO_2$) and decreased respiratory exchange ratio (RER) during indirect calorimetry assessment. Here, normalizing glucocorticoids to WT levels led to an improvement in metabolic rate in male R6/2 mice, as indicated by a normalization of RER values ($p<.05$). Normalizing glucocorticoid levels also ameliorated brain atrophy in female R6/2 mice and skeletal muscle wasting in both male and female R6/2 mice ($p<.05$ for all). Female R6/2 mice given WT glucocorticoid replacement also showed a reduction in HD neuropathological markers, including a reduction in mHTT inclusion burden in the striatum, cortex, and hippocampus, and improved levels of hippocampal neurogenesis ($p<.05$ for all). This proof of concept study illustrates that ameliorating glucocorticoid dysregulation can lead to a significant improvement in HD symptomology in the R6/2 mouse model. Accordingly, these findings suggest that FDA-approved cortisol-reducing therapeutics may be of value in improving HD patient quality of life.

**Disclosures: B.D. Dufour:** None. **J.L. McBride:** None.

**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 758.10/HH11

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Title:** Neurotherapeutic potential of pde 5 inhibitor againsts quinolinic acid evoked neurotoxicity in experimental Huntington's disease

**Authors: *P. SAROJ**[1], Y. BANSAL[1], R. SINGH[1], S. P. SAH[2], A. KUHAD[1]
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**Abstract:** Huntington’s disease (HD) is an autosomal, fatal, progressive neurodegenerative disorder that causes clinical manifestations such as progressive choreiformic movements, cognitive abnormality and psychiatric deterioration. In HD Aggregates of mutant huntingtin (mhtt) are found in neurons, astrocytes, and microglia result in increased production of pro-inflammatory cytokines viz. IL-1β, IL-2, IL-6, IL-8, tumor necrosis factor (TNF- $\alpha$;;) but decreased production of anti-inflammatory cytokines viz, IL-3, IL-4, IL-5 and IL-10. Decreased activity of cAMP responsive element-binding protein (CREB) and BDNF is thought to contribute to the death of striatal medium spiny neurons in Huntington's disease (HD). Therefore, therapies that increase levels of activated CREB, may be effective in fighting neurodegeneration in HD. Phosphodiesterase-5 (PDE5) has been implicated in various neurological diseases. This study has been structured to investigate the role of zaprinast, a selective PDE5 inhibitor in QA induced HD symptoms in rats. In our study, administration of Quinilonic acid (QA, 200 nmol/2µl saline) caused neurobehavioral (locomotor, motor-coordination and muscle grip strength) and biochemical alterations that mimic huntington’s disease in humans. Treatment with zaprinast significantly ameliorated the QA induced oxidative /nitrosative stress and neuroinflammation in brain striatum and cortex. Further zaprinast significantly reversed the mitochondrial dysfunction and neurochemical/neurotrophic, BDNF and CREB changes in brain. In conclusion, these results revealed the neurotherapeutic potential of zaprinast in Huntington’s disease.

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**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 758.11/HH12

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Title:** Cortical and striatal neuronal oscillatory activity in the zQ175 knock-in mouse model of Huntington’s disease

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**Abstract:** Huntington’s disease (HD), a severe genetically inherited neurodegenerative disorder caused by expansion of a translated CAG repeat in the Huntingtin (HTT) protein, is thought to be the result of impaired communication of the corticostriatal system. Brain electrical local field potentials (LFPs) are key features of behaviorally relevant neuronal processing thus can be used as a key measurement for understanding the neural basis of the HD behavioral phenotype. This study was designed to determine whether an electrophysiological biomarker could be identified

by electrocorticogram (ECoG) and striatal LFP recordings in the 6 to 10 month old zQ175 Het knock-in mouse model of Huntington's disease (HD). The coherence between oscillatory activities derived from these two brain regions was also evaluated. Our key findings are: 1. Power spectrum analysis showed increased oscillatory activity in the low gamma frequency range (30-60 Hz) in the striatum and, to lesser extent, in the motor cortex of zQ175 mice during the WAKE state. It also showed decrease in delta (0.5-4 Hz) and theta (4-9 Hz) bands, in all sleep states, for both cortical and striatal activities in the zQ175 as compared to WT animals. 2. The above power spectrum changes did not deteriorate with aging and remain similar across ages (from 6 to 10 month old). 3. Sleep duration of sleep states showed some significant differences between zQ175 and wild-type mice at certain times of the day and night. There was a trend towards zQ175 animals sleeping less during daytime and being less active during night time. 4. Genotypic differences were observed in oscillatory coherence between cortex and striatum. During WAKE, coherence values were increased in the low and high gamma bands of Q175 mice. During NREM and REM, coherence values were elevated across the frequency range except in the delta band. The current study revealed alterations in cortical and striatal oscillatory activities, resulting also in changes in coherence between motor cortex and striatal oscillations in the zQ175 mice. These changes could potentially be utilized for assessment of compound efficacy in HD.

**Disclosures:** **S. Zhong:** A. Employment/Salary (full or part-time):; Psychogenics. **P. Robichaud:** A. Employment/Salary (full or part-time):; Psychogenics. **A. Ghavami:** A. Employment/Salary (full or part-time):; Psychogenics. **V. Beaumont:** A. Employment/Salary (full or part-time):; CHDI Foundation Inc. **R. Cachope:** A. Employment/Salary (full or part-time):; CHDI Foundation Inc.

**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

**Location:** SDCC Halls B-H

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**Topic:** C.04. Movement Disorders other than Parkinson's Disease

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**Title:** Longitudinal assessment of an AAV delivered allele-specific gene modifier in the YAC128 transgenic mouse model of Huntington's disease

**Authors: *K. FINK**[1], P. DENG[1,2], J. HALMAI[1], S. DEL CAMPO[1], I. M. SANDOVAL[4], F. P. MANFREDSSON[5], J. NOLTA[3], D. SEGAL[6]
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**Abstract:** Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by the presence of a misfolded mutant *Huntingtin* (muHTT) protein. Reduction of HTT is an attractive therapeutic approach, however one must take into consideration the role of the normal, non-expanded version of *Huntingtin.* An ideal therapeutic would be able to selectively silence only the expanded allele, affect a large population of striatal neurons, and have a durable effect. We have previously shown allele-specific silencing of the *muHTT* transcript in patient-derived fibroblasts via transcriptional activator-like effectors (TALE) by targeting a single nucleotide polymorphisms (SNP) that is highly associated with the mutant allele. Furthermore, we have demonstrated significant reduction of the muHTT following injection of AAV9-TALE and an observable reduction of the muHTT protein following striatal injection into transgenic HD mice. In this study we examine the use of an adeno-associated virus (AAV) as putative delivery vehicle for our therapeutic TALE transgene in the YAC128 transgenic mouse model of HD. AAV9-TALE was directly injected into the striatum of YAC128 at both a presymptomatic (5 months of age) and early stage (9 months of age) of HD-like symptoms. Mice were then tested on a motor coordination task to evaluate functional recovery every two weeks for the duration of the experiment. All mice were evaluated until they were 12 months of age at which point brains were analyzed via IHC for expression of the TALE, colocalized of the TALE with cortical and striatal neurons, co-localization in glial linages, and for the reduction of muHTT aggregates. A subset of animals was also used for molecular assessment for reduction of muHTT at the RNA and protein level in addition to examination of other key implicated genes. The TALE was co-localization with striatal neurons and showed widespread distribution. Reduction of muHTT was also observed at via qPCR and Western Blot. An attenuation of motor deficits was observed starting 21-days following injection. Identification of a potent, widespread delivery vehicle and assessment of the long-term duration of expression and effect of our therapeutic transgene will be vital in the evaluation of our TALE as a viable therapeutic for HD.

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**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

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**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 758.13/HH14

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Title:** Comparison of intrinsic membrane and synaptic properties of striatal medium spiny projection neurons from both D1-GFP and D2-GFP x Q175 mouse models of Huntington's disease

**Authors: H. B. FERNANDES**[1], G. TOMBAUGH[1], J. SANCHEZ-PADILLA[1], S. GELMAN[1], K. KRETSCHMANNOVA[1], J. PALMA[1], A. GHAVAMI[1], V. BEAUMONT[2], *R. CACHOPE[2]
[1]PsychoGenics Inc, Paramus, NJ; [2]Translational Biol., CHDI Mgmt. / CHDI Fndn., Los Angeles, CA

**Abstract:** Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder resulting from an expanded number of CAG repeats in the Huntingtin (Htt) gene. HD patients exhibit both cognitive and affective symptoms, as well as uncontrolled movements (chorea) which are thought to reflect pathological changes in striatal medium spiny projection neurons (SPN) from both the direct (dSPN) and indirect (iSPN) pathways. The Q175 knock-in mouse model of HD has been useful in revealing functional alterations in intrinsic membrane and synaptic properties of striatal SPNs. Q175 mice have been successfully crossed with mice expressing GFP under control of the promoters of either the dopamine D1 or D2 receptor genes. To the extent that 1) D1- and D2- driven GFP expression putatively labels dSPNs and iSPNs, respectively, and 2) that unlabeled SPNs represent the complementary pathway, comparisons of GFP+ and GFP- cells in either model should be equally valid. However, testing this assumption by directly comparing independent datasets obtained from these two mouse lines has not yet been reported. In this study, we performed whole cell patch-clamp recordings from GFP+ and GFP- striatal SPNs in brain slices from 6-month old WT and heterozygous (Het) mice in D1-GFP and D2-GFP lines of Q175 mice. In cells from WT mice, membrane resistance values of putative dSPNs and iSPNs in the D1 line (i.e. GFP+ and GFP- cells, respectively) were nearly identical to those of the cognate cell types in the D2 line. Moreover, both dSPNs and iSPNs in Het mice from each line showed markedly and comparably elevated membrane resistance relative to WT controls. Similarly, both cell types in Het mice from each line exhibited significantly reduced rheobase compared to WT controls. Resting membrane potential and access resistance remained uniform between genotypes and cell types in both lines. The frequency of miniature excitatory synaptic currents (mEPSCs) in iSPNs from Het mice was selectively decreased relative to that seen in WT mice in both D1-GFP and D2-GFP lines. The average mEPSC amplitude was unchanged across cell types in both lines and no genotypic differences were observed. These symmetrical findings help confirm that both D1-GFP and D2-GFP lines of

Q175 mice can be used to assess the electrophysiological properties of putative direct and indirect pathway SPNs.

**Disclosures: H.B. Fernandes:** A. Employment/Salary (full or part-time):; Psychogenics Inc. **G. Tombaugh:** A. Employment/Salary (full or part-time):; Psychogenics Inc. **J. Sanchez-Padilla:** A. Employment/Salary (full or part-time):; Psychogenics Inc. **S. Gelman:** A. Employment/Salary (full or part-time):; Psychogenics Inc. **K. Kretschmannova:** A. Employment/Salary (full or part-time):; Psychogenics Inc. **J. Palma:** A. Employment/Salary (full or part-time):; Psychogenics Inc. **A. Ghavami:** A. Employment/Salary (full or part-time):; Psychogenics Inc. **V. Beaumont:** None. **R. Cachope:** None.

**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

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**Program #/Poster #:** 758.14/HH15

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Title:** Tissue catecholamine content in the PFC, NAS, and STR of the HttQ111/+ mouse model of Huntington's disease at 18 months of age

**Authors: L. N. HOFFMANN**, X. M. DIAS-WAUGHMAN, A. A. ALPERS, R. G. MARX, J. A. O'SELL, *J. M. FINLAY
Behavioral Neurosci. Program, Western Washington Univ., Bellingham, WA

**Abstract:** Complex cognitive deficits significantly affect the daily lives of people living with Huntington's disease (HD) even before the characteristic motor symptoms of the disease emerge. In HD mutation carriers, the prevalence and severity of cognitive symptoms increases with age; however, few studies have examined the time course of these deficits in mouse models of the disorder. Previously, we reported that the $Htt^{Q111/+}$ knock-in mouse model of Huntington's disease exhibits an age-related decline in complex cognitive function (Marx et al., *Society for Neuroscience*, 2017). Specifically, we observed that the $Htt^{Q111/+}$ knock-in mice exhibit greater deficits in response accuracy and impulsivity in a sustained attention task at 18, than 9 months of age, relative to wildtype mice. Following behavioral testing at 18 months of age, the wildtype (n=14) and $Htt^{Q111/+}$ knock-in mice (n=17) were euthanized and tissue samples were harvested for analysis of catecholamine content in the medial prefrontal cortex (PFC), nucleus accumbens (NAS), and striatum (STR) using high-pressure liquid chromatography with electrochemical detection. In the aged $Htt^{Q111/+}$ mice PFC norepinephrine (NE), dopamine (DA), and 3,4-dihydroxydopamine (DOPAC) concentrations did not differ from wildtype mice. In contrast, DA concentrations were reduced in both the NAS and STR of $Htt^{Q111/+}$ mice relative to control. NAS and STR DA concentrations in $Htt^{Q111/+}$ mice were 80±5% and 76±7% of wildtype concentrations, respectively. There was also a trend for decreased DOPAC concentrations in the

NAS and STR of *Htt*$^{Q111/+}$ mice to 91±9% and 86±9% of wildtype concentrations, respectively. Analyses are currently underway to assess whether loss of tissue DA content in the NAS and STR is correlated with impaired performance in the sustained attention task. The present neurochemical data suggest that the phenotype of *Htt*$^{Q111/+}$ mice at 18 months of age includes selective loss of tissue DA in subcortical but not cortical areas. The observation that tissue DA content is more robustly affected than tissue DOPAC concentrations is consistent with proposal that the activity of the remaining subcortical DA neurons is increased to compensate for loss of neighboring cells.

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**Poster**

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**Title:** Curcumin coated with solid lipid particles protect medium spiny neurons in YAC128 mouse model of huntington’s disease

**Authors: *S. J. HEILEMAN**[1], A. AL-GHARAIBEH[2], R. CULVER[2], J. ROSSIGNOL[4], P. MAITI[5], G. L. DUNBAR[3]
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**Abstract:** Huntington’s disease (HD) is an inherited neurodegenerative disorder with no known effective treatment to delay its onset or progression. The hallmark of the disease is neuronal degeneration which mainly involves medium spiny neurons in striata at the beginning of the disease, and affect other areas with disease progression. Recently, we have been using solid lipid curcumin particles (SLCPs), which consist of long-chain phospholipid bilayer and a long-chain fatty acid solid lipid core that coats curcumin extract from turmeric roots as a treatment for HD. We treated wild type and YAC128 HD mice at 11 months of age with oral gavage of SLCPs for two months. Then we sacrificed the mice, extracted the brains, and immersed them in Golgi-Cox

solution. We sectioned the tissue and studied the morphology and arborization of medium spiny neurons in striata of both WT and HD mice. We found that there was a reduction of dendritic arborization (number and length of dendrites) in HD mice in comparison to WT mice, but the HD mice treated with SLCPs showed increase in the number of distal dendrites compared to HD mice. We also found that there was a significant decrease in the number of dendritic spines in HD mice in comparison with WT mice, however, HD mice treated with SLCPs showed significant increase in spinal density when compared to HD mice. Our results suggest that SLCPs treatment protect medium spiny neurons and might be effective in delaying neuronal degeneration.
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**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

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Dr. Gillian Bates at UCL provides the human mHTT-exon1 construct

**Title:** Development and characterization of a novel bac transgenic mouse model of Huntington's disease with elongated pure cag repeats

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**Abstract:** Huntington's disease (HD) is caused by expansion of a somatically unstable, largely pure CAG nucleotide repeat in exon 1 of the human Huntingtin (HTT) gene. The existing full-length Htt genomic mouse models of HD either express such pure and unstable CAG repeats in the context of mostly murine huntingtin (i.e. the allelic series Htt knockin mice), or they are human genomic transgenic mouse models but express relatively stable repeats due to multiple interspersed CAA sequence within the CAG repeats (both encoding an uninterrupted polyglutamine repeat at the protein level), e.g. BACHD or YAC128. There are some noticeable

phenotypic differences between the two major model types (i.e. murine Htt knockin vs human genomic transgenic models) and it is currently unclear if this is due to the differences in the CAG repeat types or the overall amino acid and regulatory differences between human and murine Huntingtin. In this study, we begin to address this question by the development of a novel full-length human mutant HTT transgenic model carrying long stretch of pure CAG repeats in its exon1 (called BAC-CAG). In this model, we utilized the same BAC that was used to create the BACHD model, except now we replace the exon 1 of the wildtype human HTT BAC with a human HTT exon1 sequence with 139 repeats with mostly CAG (and only one CAA sequence towards the end of the repeat, gift from Dr. Gillian Bates). This patient-derived repeat sequence was the sequence used to generate a widely used HD fragment model, R6/2. We will present data from our ongoing study phenotyping BAC-CAG mice, including preliminary data on body weight, motor behaviors, mutant HTT aggregation, and transcriptome results. We hope our study could shed light on the potential differential contribution of disease mechanisms to the overall pathogenic picture in HD related to pure CAG repeat sequence, in the context of a human genomic transgenic model.

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**Poster**

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**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** This work was supported by CHDI Foundation

**Title:** Suppression of mutant huntingtin in cortical efferents improves behavioral inflexibility and corticostriatal information flow in Huntington’s disease mice

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**Abstract:** The motor symptoms of Huntington’s disease (HD), a neurodegenerative disorder caused by a mutation of the huntingtin protein (mhtt), emerge, in part, from abnormal communication between cerebral cortex and striatum. To assess the role of cortical projections on altered corticostriatal processing in HD, we evaluated local field potential (LFP) activity recorded simultaneously in primary motor cortex (M1) and dorsal striatum in BACHD mice, a

full-length gene model, as they spontaneously explored the four arms of a plus-shaped maze. Relative to wild-type (WT) controls, BACHD mice became progressively less likely to turn into a perpendicular arm with repeated testing, a sign of motor inflexibility. M1 LFP activity at the choice point of the maze also was abnormal, manifest as a decrease in delta, theta and gamma power. Coherence analysis indicated dysregulated information flow between M1 and dorsal striatum. Suppression of mhtt expression in cortical output neurons in BACHD/Emx1-Cre (BE) mice reversed these effects. BE mice turned as much as WT and corticostriatal LFP activity was intermediate between WT and BACHD. Together, our results indicate that expression of mhtt leads to impaired network activity in motor cortical areas, altering corticostriatal information flow and setting the stage for the development of motor inflexibility. Thus, cortical output neurons are a possible target for the development of therapeutic strategies to alleviate HD motor signs.

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**Poster**

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**Topic:** C.04. Movement Disorders other than Parkinson's Disease

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**Title:** Striatal neuropathology induced by hypothalamic overexpressionof huntingtin fragments using adeno-associated viral vectors in mice

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**Abstract:** The most prominent neuropathology in Huntington’s disease (HD) includes loss of medium spiny projection neurons expressing cAMP regulated phosphoprotein (DARPP-32) in the striatum. Recent studies have indicated that hypothalamic neuropathology with loss of orexin neurons is part of HD. As hypothalamic changes may in fact occur before striatal pathology in HD and ventral striatum receives projections from the hypothalamus, we hypothesized that hypothalamic expression of mutant *huntingtin* (HTT) may be involved in the development of

striatal pathology in HD. **Aims:** Our aim was therefore to investigate the striatal effects of selective mutant *HTT* expression in the hypothalamus. **Methods:** Wild-type mice were injected bilaterally with adeno-associated viral vectors expressing a mutant (79Q) or a normal (18Q) *HTT* fragment in the hypothalamus. Stereological quantification of brains processed for DARPP-32, NeuN and cresyl violet was performed in the striatum at 40-52 weeks post-injection. Retrograde labelling of the hypothalamic projection neurons to ventral striatum was achieved using a novel retrogradely transported adeno-associated viral (AAV) vector (rAAV-MNM004-Cre). **Results:** Selective hypothalamic expression of a long mutant HTT fragment (853 aa) leads to orexin loss and a specific reduction in the number of DARPP-32 and NeuN positive neurons with no increase in the number of glial cell profiles in the ventral striatum. Moreover, we found that the R6/2 model of HD recapitulates these changes with a similar loss of DARPP-32 in ventral striatum. Next, we have shown a successful retrograde labelling of hypothalamic projection neurons, which will be sufficient for chemogenic activation or inhibition of hypothalamo-striatal circuitries to investigate the underlying neuronal dysfunction. **Conclusions:** These results suggest that hypothalamic overexpression of HTT fragments can lead to loss of medium spiny neurons in the striatum and opens up the possibility that there may be a contribution of dysfunctional hypothalamic neurocircuitries to HD striatal pathology.

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**Poster**

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**Location:** SDCC Halls B-H

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**Topic:** C.05. Tauopathies, Tau-dementias, and Prion diseases

**Support:** NIH NS096994

**Title:** Early impairment of thalamocortical circuit activity and coherence in a mouse model of Huntington’s disease

**Authors: *E. J. DONZIS**[1], J. L. SHOBE[2], M. S. LEVINE[1], C. CEPEDA[1], S. C. MASMANIDIS[2]
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**Abstract:** Huntington’s disease (HD) is a progressive, fatal neurodegenerative disorder characterized by motor, cognitive, and psychiatric disturbances. There is no known cure for HD, but its progressive nature allows for early therapeutic intervention. Currently, much of the research has focused on the striatum, however, there is evidence suggesting disruption of

thalamocortical circuits that could underlie some of the early symptoms of HD. Loss of both cortical pyramidal neurons (CPNs) and thalamic neurons occurs in HD patients and cognitive, somatosensory, and attention deficits precede motor abnormalities. In addition, EEG studies have shown a suppression of alpha-activity which suggests thalamic abnormalities in HD patients. The role of thalamocortical pathways in HD progression has been understudied. Here, we measured *in vivo* local field potentials (LFPs) and single unit activity from 256-channel electrodes implanted in the thalamus and primary motor cortex of 3-4 month-old male and female Q175 mice during a 10 min baseline session and a 40 trial behavior session where the mouse licked for milk in response to a previously trained auditory cue. All data were analyzed offline with custom Matlab scripts. Q175 mice showed significantly increased response lick-latency to the auditory cue. During both the baseline and behavior sessions, Q175 mice showed decreased thalamocortical coherence compared to wildtype mice. In addition, neural activation was attenuated in M1 CPNs and delayed but persistent in M1 fast-spiking interneurons (FSIs) of Q175 mice following the reward trigger. No changes were found in the activity of thalamic neurons following the auditory trigger. These data suggest that impaired cortical activation of both CPNs and FSIs following an auditory cue and impaired thalamocortical coherence may play an important role in cognitive and learning deficits in HD patients. Re-establishment of thalamocortical coherence could be an important early target for therapeutic intervention.

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**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

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**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** NIH NS096994

**Title:** Alterations in the intrinsic properties of thalamic somatosensory and motor nuclei neurons in the R6/2 mouse model of Huntington’s disease

**Authors: *S. M. HOLLEY**, K. D. OIKONOMOU, J. BARRY, E. J. DONZIS, A. DONG, C. CEPEDA, M. S. LEVINE
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**Abstract:** In humans, the main histopathological feature of Huntington’s disease (HD) is the significant loss of neurons in the caudate nucleus and putamen. However, with disease progression, neurons in the cerebral cortex, hippocampus, hypothalamus and thalamus also are lost. Although most mouse models of HD show minimal cell loss in the striatum, both principle

neurons and interneurons exhibit signs of degeneration (smaller somas, decreased dendrite arborization and reduced dendritic spine density). Here, we show neurons in the motor (VAL) and somatosensory (VPM) nuclei of the thalamus also are altered in the R6/2 mouse model of HD. Injection of a retrograde tracer in somatosensory and motor cortices allowed identification of VAL and VPM projection neurons in the thalamus. Using whole-cell patch clamp electrophysiological techniques we recorded from these thalamic neurons in brain slices of 2-month-old wildtype (WT) and symptomatic R6/2 mice and found significant differences in passive membrane properties. R6/2 cells in both nuclei had smaller cell membrane capacitances, faster decay time constants and increased input resistance compared to WT cells. Changes in cell capacitance and input resistance suggest the potential for degenerative processes in thalamic neurons. Moreover, cells in the VPM of R6/2 mice had more depolarized resting membrane potentials (RMPs) compared with R6/2 VAL neurons while RMPs of WT cells in each nuclei were similar. In addition, cells in both nuclei showed increased excitability (more action potentials to depolarizing current injections) in R6/2 compared with WT mice, probably due to increased membrane input resistance. These data indicate both similar and contrasting alterations in VPM and VAL neurons in R6/2 mice. Of importance, these findings point to the possibility that alterations outside the basal ganglia and cortex will contribute to the development of the HD phenotype.

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**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

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**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** NIH NS41574
NIH NS093813

**Title:** Mechanisms underlying the upregulation of GABA responses in external globus pallidus neurons in a mouse model of Huntington’s disease

**Authors: *J. BARRY**, M. S. LEVINE, C. CEPEDA
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**Abstract:** In mouse models of Huntington’s disease (HD), optogenetic activation of striatal direct and indirect pathway medium-sized spiny neurons (MSNs) leads to differential outcomes in their target regions; substantia nigra pars reticulata and external globus pallidus (GPe), respectively (Barry et al., 2018). While GABA responses evoked by selective activation of direct

pathway MSNs (dopamine D1 receptor-expressing) are reduced in amplitude, GABA responses evoked by activation of indirect pathway MSNs (dopamine D2 receptor-expressing) display significantly longer decay times. In the present study, optogenetics and whole-cell patch clamp recordings were used in symptomatic R6/2 (>60 days) mice to examine the mechanism underlying the increased response duration of GPe neurons in this mouse model. Two different mechanisms could be implicated; reduced expression of GABA transporters or changes in postsynaptic $GABA_A$ receptor subunits (e.g., alpha1). As previous studies have demonstrated reduced expression of $GABA_A$ receptor subunits, here we concentrated on examining the role of GABA transporters in the GPe (GAT-1, expressed in axon terminals and GAT-3, expressed in astrocytes). The GAT-1 blocker NNC-711 (10 μM) did not affect optically-evoked GABA responses in GPe neurons from R6/2 mice. In contrast, the GAT-3 blocker SNAP5114 (10 μM) produced differential effects; while decay times of responses evoked in wildtype mice were increased, responses in R6/2 mice were not significantly affected. This probably indicates reduced function of GAT-3 in R6/2 mice. These findings begin to elucidate the mechanisms underlying alterations in responses evoked by indirect pathway MSN terminals in the GPe, and help understand striatal output imbalance and dysfunction in HD.

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**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

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**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** NIH NS096994

**Title:** Targeting elevations of cortical intracellular calcium as a treatment for Huntington’s disease

**Authors: *K. D. OIKONOMOU**[1], X. YU[2], E. J. DONZIS[1], B. S. KHAKH[2], M. S. LEVINE[1], C. CEPEDA[1]
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**Abstract:** Huntington’s disease (HD) is a progressive neurodegenerative disorder that predominantly affects striatal medium-sized spiny neurons (MSN) and cortical pyramidal neurons (CPN). Altered neuronal $Ca^{2+}$ signaling may contribute to neurological abnormalities observed in HD patients and mouse models. For example, $Ca^{2+}$ dyshomeostasis plays a significant role in the degeneration of MSNs in the YAC128 mouse model of HD, as store-operated $Ca^{2+}$ channel (SOC) activity is enhanced in neurons expressing mutant huntingtin and

drugs that target the SOC pathway rescue spine loss. Previous studies in our laboratory demonstrated early alterations in glutamate receptor-mediated currents, as well as augmented voltage-gated $Ba^{2+}$ currents in CPNs from symptomatic R6/2 mice. In addition, functional studies revealed that somatosensory, attention, and cognitive deficits precede chorea and other motor abnormalities. Thus, examining cortical alterations before the onset of striatal dysfunction is of vital importance. To date, there have been no studies systematically assessing the role of $Ca^{2+}$ levels in CPNs of HD mouse models. To test the hypothesis that neuronal $Ca^{2+}$ signaling in CPNs of the motor cortex is significantly disturbed we used two mouse models of HD; the R6/2, an aggressive model of juvenile HD, and the Q175, a model of adult-onset HD that better recapitulates the human condition. We simultaneously utilized whole-cell patch clamp electrophysiology and two-photon microscopy to image primary motor cortex CPNs filled with a $Ca^{2+}$-sensitive dye, Oregon Green BAPTA-1 (OGB-1). Single or multiple action potentials were evoked by a series of 50 ms depolarizing current pulses from the resting membrane potential. Accompanying somatic as well as dendritic $Ca^{2+}$ influxes were compared between mutant mice and their wildtype (WT) age-matched littermates. No significant differences in $Ca^{2+}$ influx were found between pre-symptomatic HD mice and WT controls. In contrast, in symptomatic R6/2 and Q175 mice, $Ca^{2+}$ transients were significantly elevated in both somatic and dendritic compartments. Importantly, addition of the SOC blocker EVP4593 (3 μM) reduced $Ca^{2+}$ elevations. The present study provides much needed knowledge about the role of $Ca^{2+}$ in cortical alterations observed in HD and how it can serve as a potential candidate for therapeutic intervention.

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**Poster**

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**Topic:** C.06. Neuromuscular Diseases

**Support:** NNSFC grant 31401107
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**Title:** HNRNPA1-induced spliceopathy in a DM1 mouse model

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**Abstract:** Myotonic dystrophy type 1 (DM1) is a RNA-mediated hereditary disease caused by noncoding microsatellite expansions. That is, DM1 disease pathogenesis is caused by a reversion

to fetal RNA processing patterns in adult tissues due to the expression of toxic CUG RNA expansions leading to decreased MBNL, but increased CELF, alternative splicing activities. Here, we test this model in vivo using the mouse *HSA*$^{LR}$ poly(CUG) model for DM1 and rAAV-mediated transduction of specific splicing factors. Surprisingly, overexpression of HNRNPA1 shifted DM1-relevant splicing targets to fetal isoforms resulting in more severe DM1 muscle phenotypes. HITS-CLIP of rAAV-mycHnrnpa1 injected muscle revealed interactions of HNRNPA1 with these targets in vivo. Similar to CELF1, HNRNPA1 protein levels decrease during postnatal development but are elevated in regenerating mouse muscle. Our studies suggest that CUG$^{exp}$ RNA triggers abnormal expression of multiple nuclear RNA binding proteins that antagonize MBNL activity to promote fetal splicing patterns.

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**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

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**Program #/Poster #:** 758.24/II8

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Title:** Characterization of gene expression levels in zq175 knock-in delta neo minus mouse model of Huntington’s disease

**Authors: *T. HUHTALA**[1], M. VIHMA[1], T. HEIKKINEN[1], T. PARKKARI[1], L. C. PARK[2]
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**Abstract:** In this study, we characterized the gene expression levels in newly developed zQ175 KI delta neo (DN) mice, abbreviated Q175 KI neo- mice. We compared these results to those previously obtained in zQ175 KI, or Q175 KI neo+ mice that contain a neomycin cassette. Gene expression levels of multiple genes of interest were analyzed in cortical, striatal and liver tissues from 2, 6 and 9 month old Q175 neo- and neo+ mice using the QuantiGene Plex Assay (Invitrogen). This assay combines branched DNA signal amplification and multi-analyte profiling beads (xMAP) technologies. Gene expression patterns of Q175 KI neo+ and Q175 neo- mice were significantly different at few individual time points, however, no consistent or stable changes were noted in the data. The most profound changes were found in the expression levels of cortical BDNF, which was increased in the 2 and 6 month time points of female WT and HET Q175 KI neo- in comparison to Q175 neo+. In striatal samples, Htr2a expression was significantly decreased in male WT Q175 neo- mice at all time points but the effect was not seen in HET mice. Finally, in liver samples, the expression levels of Lpl were significantly decreased in male and female WT and HET Q175 neo- mice at 2 and 6 month time points. Furthermore, PPAR-alpha expression was significantly increased in male and female WT and HET Q175 neo-

mice at 2 and 9 month time points. Taken together, the expression patterns of the studied genes were very similar in both Q175 KI neo+ and Q175 neo- mice, and the majority of the differences were observed at a very early age, which is in line with the behavioral characterization of these two strains.

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**Poster**

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**Program #/Poster #:** 758.25/II9

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Title:** Characterization of white matter defects and diffusion changes in zq175dn mouse model of Huntington’s disease by diffusion tensor mri and tract-based spatial statistics

**Authors: K. LEHTIMÄKI**[1], J. KURKIPURO[1], L. TAHTIVAARA[1], *J. OKSMAN[1], L. C. PARK[2]
[1]Charles River Discovery Services, Kuopio, Finland; [2]CHDI Management/ CHDI Fndn. Inc, Los Angeles, CA

**Abstract:** White matter (WM) pathologies have not been previously characterized in zQ175DN model, neither by MRI nor by histological means. Diffusion tensor imaging (DTI) allows for good differentiation of structures in the WM. Here we present high-resolution ex vivo DTI data and use group-level whole brain statistical analysis method, tract-based spatial statistics (TBSS, Smith SM et al. 2006), to detect the WM defects.
Fifteen male HET Q175DN and 15 WT mice (CHDI-81003019) were perfused and brains post-fixed at the age of 12 months. DTI data were acquired at 9.4T using a 3D EPI at isotropic resolution of 125 µm. Fractional anisotropy (FA), axial and radial diffusion maps were analyzed in a common template using a voxel based TBSS analysis method. In addition, voxel based morphometry (VBM) read-outs for global diffusion changes were assessed.
The mean diffusion was able to detect the phenotype difference in Q175DN from WT mice at 12 months. For the most common DTI parameter, fractional anisotropy, the findings were surprisingly limited on the TBSS skeleton. FA was decreased only in the thalamic regions and non-specific complex of several trigeminal nuclei such as Pr5, 5TT, 5N, P5, Su5 and m5. In the whole brain VBM analysis, there were three different distinct regions with decreased FA; M1/M2 motor cortex regions, cingulate cortex 1 and 2, and trigeminal nucleus complex. Interestingly, mean, axial and radial diffusions were simultaneously and almost globally decreased in zQ175DN HET mice both in tract-based and VBM style analysis.
Immunohistochemical analysis revealed only minor changes in this model consistent with DTI-

based finding. Decrease in MBP positive myelin staining was detected in internal capsule and stria medularis in HET mice. No significant axonal damage was detected by APP immunohistochemistry; APP was slightly decreased in HET mice in lateral septum and internal capsule. Although the findings here reveal some specific changes in the WM, it is apparent that the zQ175DN mouse model does not present wide-spread WM pathology at 12 months of age.

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**Poster**

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**Topic:** C.04. Movement Disorders other than Parkinson's Disease

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**Title:** Novel computational approaches for signal extraction from striatal multi-color photometry recordings and evaluating high-throughput approach-avoidance learning applied to Huntington’s disease mouse model

**Authors: *A. FRIEDMAN**, E. HUESKE, S. DELCASSO, L. G. GIBB, H. LUTWAK, S. E. TORO ANNA, S. M. DRAMMIS, L. I. RAKOCEVIC, J. D. FAJARDO, J. K. XIONG, C. A. SICILIANO, D. HU, C. W. CARTER, E. D. NELSON, A. M. GRAYBIEL
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**Abstract:** Learning is a dynamic process that requires quantification and that can be influenced by internal parameters such as motivation and attention. To evaluate the mechanistic underpinnings of behavioral performance, and to disentangle motivational and attentional components, we have developed a battery of behavioral tasks (Hueske et al., SfN 2018) integrated with high-throughput multi-color photometry. Critically, we dissected behavioral choice data to estimate motivational engagement levels using modified hidden-state Markov modeling (HMM). To process and align neural signals, we developed computational toolboxes. To adapt a stationary Markov model to dynamic learning, we developed an algorithm for searching stationary periods, or bins, during the learning process. We trained and decoded choice sequences using the HMM, and we created an algorithm that could stitch multiple HMMs obtained from these bins. To our surprise, we found that a mouse model of Huntington’s disease (HD) containing a knock-in of mutant huntingtin gene (zQ175 KI) were three times more likely than wildtype controls to have trials during which they were not engaged in the task according to

HMM-based binning of states, whereas the number of engaged trials was not different between the two genotypes. This result suggests that the delay in learning in the zQ175 KI mice (Hueske et al., SfN 2018) was due to low engagement levels, not to an inability to acquire the task. We measured pupillary diameter of mice during the task as a measure of attentional state and to compare with HMM-derived engagement level, and found preliminary correspondence between the two. To evaluate neural activity recorded during behavioral performance, we developed a high-throughput multi-color, multi-fiber photometry system and a set of analytical tools to extract photometry spikes and bursts of spikes. We performed analyses of the shape of these spikes in 470 nm recording channel and 405 nm control channels. We developed principal component-based, linear regression-based and peak shape-based analyses, and found clusters attributable to noise and spike signals. We populated a matrix of measured signal-to-noise ratios of photometry recordings along with probabilities of spike identities as either noise or signal. We found that striatal cell population responses corresponded with task-related events. Our findings suggest that there are both motivational and performance-based factors that influence the ability of HD model mice to learn reinforcement-based tasks, and we are analyzing correspondences with striatal population responses.

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**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 758.27/II11

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** CHDI Foundation A-5552
NIH/NIMH R01 MH060379
Saks Kavanaugh Foundation

**Title:** Evaluation of approach-avoidance learning in mouse model of Huntington’s disease by a novel battery of cost-benefit decision-making tasks compatible with high-throughput imaging

**Authors: *E. A. HUESKE**[1], A. FRIEDMAN[1], S. DELCASSO[2], L. G. GIBB[1], H. LUTWAK[2], S. M. DRAMMIS[1], L. I. RAKOCEVIC[2], J. D. FAJARDO[2], J. K. XIONG[2], C. A. SICILIANO[2], D. HU[1], C. CARTER[1], E. D. NELSON[1], A. M. GRAYBIEL[1]
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**Abstract:** Patients with Huntington's disease (HD) are known to have cognitive and mood dysfunction. In order to establish a high-throughput behavioral assay to evaluate cognitive and mood dysfunction in conjunction with recordings of neural activity applicable to analyze HD model mice, we developed a head-fixed task for discrimination learning and cost-benefit decision-making integrated with a multi-color, multi-fiber photometry system (Friedman et al., SfN 2018). We used the zQ175 KI mouse model of HD, and trained them to discriminate two auditory stimuli associated with appetitive (sucrose solution) or aversive (mildly aversive light) outcomes. Following an auditory stimulus presentation, mice learned to lick during a 1 sec response window prior to delivery of a graded outcome dependent on response vigor (lick frequency). HD mice required significantly more sessions than wildtype (WT) mice to learn to respond differentially to cues predicting appetitive and aversive outcomes. To evaluate whether motivational differences between WT and HD mice played a role in the slower sensory discrimination learning of HD mice, we employed a receiver operating characteristic (ROC)-based analysis to measure discriminability (d') as a measure of discrimination learning and response bias as a measure of task-engagement. These analyses identified a large difference between WT and HD mice in task-engagement with a minor deficit in discrimination learning. To further evaluate whether the small discrimination learning deficit in HD mice resulted from lower overall task-engagement, we used hidden Markov modeling (HMM) to identify periods of engaged and non-engaged performance during learning (Friedman et al., SfN 2018). Re-evaluating discrimination learning (via d') in trials classified by our HMM modeling showed that HD mice learned in the same number of engaged state trials as WT mice (see Friedman et al., SfN 2018). Using this combination of behavioral and computational approaches, we are now capable of disentangling motivational influences from discriminative learning in judging performance of WT and HD mice.

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**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 758.28/II12

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** PAPIIT-UNAM IN214716 to JFR
CONACYT Ph.D. scholarchip 369794 to VG

**Title:** Visuospatial alterations in Huntington's disease: Anatomo-functional magnetic resonance findings

**Authors: *V. GÁLVEZ, SR**[1,2], G. RAMÍREZ GARCÍA[3,2], J. FERNANDEZ-RUIZ[4], A. CAMPOS-ROMO[5,2]
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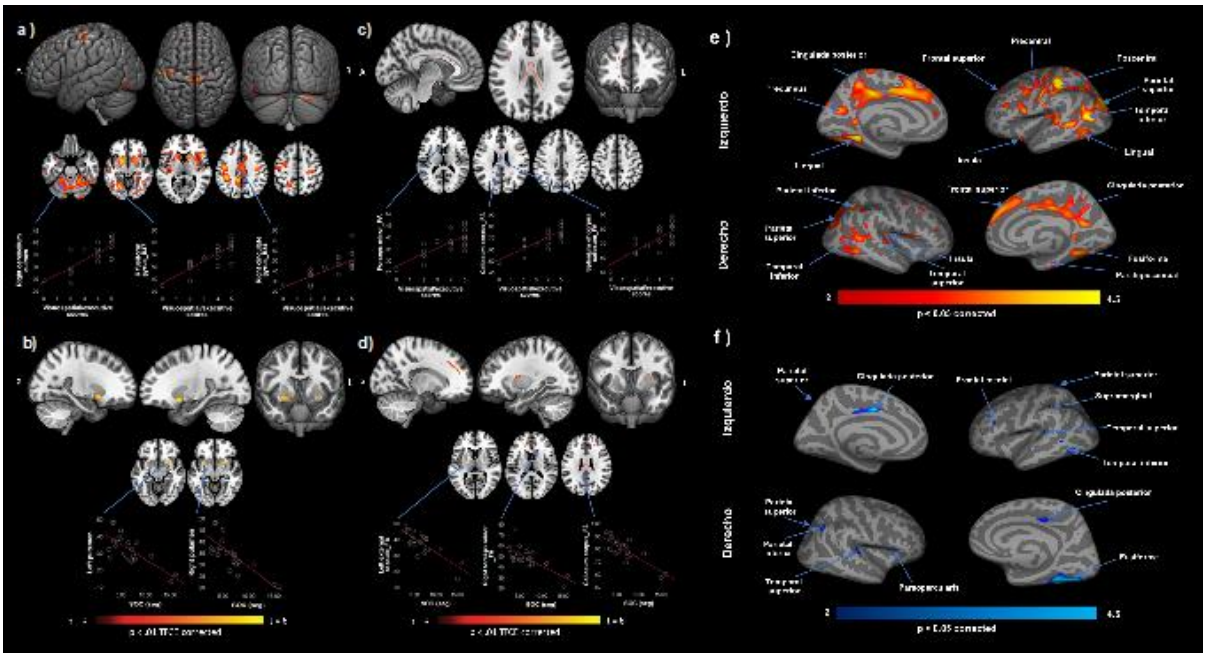
**Abstract:** Introduction: The main visuospatial alterations in patients with Huntington's disease (HD) are related to the deterioration of the striatum. However, the relationship between these first cognitive domain alterations and the preservation of white matter (WM), gray matter (GM) and cerebral cortical thickness (CT) is unknown. Objective: To characterize the WM, GM and CT changes in patients with incipient HE and describe their correlation with the main visuospatial alterations. Material and Methods: Twenty-two patients with early clinical evolution and genetic diagnosis for HD were recruited; and 22 homologated controls in sex, age and schooling, to evaluate visuospatial performance with the Montreal Cognitive Assessment Scale (MoCA), and the Stockings of Cambridge (SOC) digital visuospatial planning test. T1 structural images and diffusion tensor (DTI) were acquired by magnetic resonance to analyze, by Tract-Based Spatial Statistics (TBSS) the integrity of WM, using voxel-based morphometry for GM changes and cortical reconstruction by cortical thickness (CT). ), to finally carry out the correlation with the scores of the scale and digital test. Results: MoCA visuospatial scores showed positive correlation with minor forceps, corpus callosum, splenium of the corpus callosum (SB); right cerebellum, fusiform gyrus, right cingulate gyrus (GM); precentral and postcentral cortex, precuneus, insula, right parahipocampal, inferior temporal and superior-inferior parietal (CT). SOC scores showed negative correlation between reaction time with left external capsule, right minor forceps and corpus callosum (WM); bilateral putamen (GM); cingulate cortex, fusiform gyrus, inferior-superior temporal cortex and inferior superior parietal cortex (CT). Conclusions: We demonstrated an accurate anatomo-functional description between the first changes of WM, GM and CT and its relationship with the main visuospatial alterations of patients with HD, which will help to detect, identify and monitor potential brain therapeutic targets from relatively early stages of the illness.

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**Poster**

**758. Huntington's Disease: Animal Models and Clinical Trials**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 758.29/II13

**Topic:** C.04. Movement Disorders other than Parkinson's Disease

**Support:** NIH Grant NS090616
Azevan Pharmaceuticals, Inc

**Title:** Irritability in Huntington's disease: A phase 2 exploratory clinical trial with a novel vasopressin 1a antagonist, SRX246

**Authors: *N. G. SIMON**[1,2], S. M. HERSCH[3], K. E. ANDERSON[4], S.-F. LU[1], M. J. BROWNSTEIN[2]
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**Abstract:** Psychiatric symptoms, including irritability and aggression, are common in HD patients. These are among the most distressing aspects of the disease, adversely impact daily life,

and often result in institutionalization. Despite their frequent occurrence and severe consequences, these symptoms have received little attention. Effective treatments are lacking and well-validated scales for measuring changes in these symptoms are not available. The current Phase II clinical trial in HD patients (n=108), Safety and Tolerability of SRX246 In Irritable/Aggressive Subjects with Huntington's Disease (STAIR; NCT02507284), is designed to rigorously evaluate the tolerability of a new drug, SRX246, for the treatment of irritability and aggression; provide additional safety data; and explore various rating scales for the assessment of changes in these symptoms. The objective is to obtain critical data that can be used to plan future Phase 2b or 3 clinical trials. STAIR is a 3 arm, multicenter (22 NeuroNEXT Network sites), randomized, placebo-controlled, double-blind, 12-week dose escalation study. Following eligibility determination, subjects are randomized to receive placebo, or escalate from 80 mg (two weeks) to 120 mg, up to a maximum dose 160 mg twice daily of SRX246 for 12 weeks. Each subject has a study partner to assist with visits, taking study medication, and providing feedback about the subject's mood and behavior. As of May 2, 102 subjects were randomized and 82 have completed the protocol. Last patient in will be by May 31. Compliance has been excellent and while we are blinded, the AE profile and tolerability are consistent with other trials that show very strong safety and tolerability. The test compound, SRX246, is a first-in-class vasopressin 1a receptor antagonist. It is orally bioavailable, exhibits high affinity and selectivity for its target, has a strong safety profile in healthy volunteers and other clinical trials, and excellent pharmacokinetics. Preclinical pharmacology and an experimental medicine fMRI study in healthy volunteers showed that SRX246 has CNS effects after oral administration and that it modulates brain circuits involved in responses to stimuli that elicit aggression/fear. In a completed Phase 2 Exploratory trial for the treatment of Intermittent Explosive Disorder, SRX246 was well tolerated, no serious adverse events were reported, and exploratory analyses revealed statistically significant differences favoring SRX246 in key outcome measures of clinical benefit. These findings strongly suggested that SRX246 might have a beneficial effect on the irritability and aggression seen in a sizable proportion of HD patients.

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.01/II14

**Topic:** F.04. Stress and the Brain

**Support:** VA Grant I21 BX002085 (LPR)
VA Grant IO1 BX001804 (LPR)
VA Grant I01 BX001374 (MAW)
NIH Grant R01AG050518 (JRF)
USC Research Development Fund (LPR)
NSF Grant IOS-1656626 (CAG)

**Title:** Glutamate at the intersection between stress, pyridostigmine bromide, and immune function in a model of Gulf War illness

**Authors: *V. A. MACHT**[1], J. L. WOODRUFF[1,2], E. S. MAISSY[1], C. A. GRILLO[1,2], M. A. WILSON[1,2], J. R. FADEL[1], L. P. REAGAN[1,2]
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**Abstract:** Pyridostigmine bromide (PB) was administered to soldiers in active combat zones during the first Gulf War as a prophylactic treatment to protect against toxicity in the event of exposure to nerve agents. Although originally PB was thought to pose minimal risk, epidemiological studies have since correlated its administration with the development of a variety of symptoms in returning Gulf War soldiers, now termed Gulf War Illness (GWI). These symptoms include a variety of cognitive deficits, but since PB was not thought to cross the blood-brain barrier, the mechanism by which PB could impact the central nervous system is controversial. Changes in immune function are emerging as a hallmark feature of GWI and could be a critical point of how PB and stress could interact to influence central neurotransmission. To test this hypothesis, we used *in vivo* microdialysis in a rat GWI model to examine how combinations of PB and repeated restraint stress alter glutamatergic levels in response to a lipopolysaccharide (LPS) and a restraint stress challenge in the prefrontal cortex (PFC) and hippocampus. There were four groups in this study: vehicle-non-stressed control (NSC), vehicle-stressed, PB-NSC, and PB-stressed. Results indicate that LPS decreases glutamate levels in PB-treated rats relative to vehicle-treated rats in the PFC. In contrast, PB and stress interact to attenuate LPS-induced decreases in glutamate levels in the hippocampus. Three hours after the LPS challenge, PB-treated rats exhibited attenuated plasma IL-6 and exaggerated C-reactive protein, indicating that PB impairs the ability of the immune system to mount an appropriate inflammatory response. Although a restraint stress challenge increases glutamate in the PFC,

glutamatergic systems in PB-NSC rats fail to recover following removal from this stressor, resulting in persistent increases in extracellular glutamate relative to vehicle-treated rats. In the hippocampus, PB-stressed rats fail to exhibit habituation of the glutamate response to the restraint stress challenge relative to vehicle-stressed rats. Collectively, these results indicate that PB and stress interact to produce brain-region specific effects on glutamate systems, providing insight into the potential mechanisms underlying interactions between the immune system and persistent cognitive dysfunction in veterans with GWI.

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.02/II15

**Topic:** F.04. Stress and the Brain

**Support:** I21 BX002085
IO1 BX001804
I01 BX001374
R01AG050518
IOS-1656626

**Title:** The controversy of acetylcholine in Gulf War Illness: Interactions between stress and pyridostigmine bromide from brain neurochemistry to behavior

**Authors: *L. P. REAGAN**[1], V. A. MACHT[4], J. L. WOODRUFF[2], E. S. MAISSY[4], M. A. WILSON[5], J. R. FADEL[3]
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**Abstract:** Pyridostigmine bromide (PB) is a reversible acetylcholinesterase inhibitor which was used during the 1990-1991 Gulf War as prophylactic treatment against nerve gas exposure. Although PB was not thought to cross the blood-brain barrier, clinical and preclinical studies suggest that combinations of PB and stress from deployment interact to impair cognitive function. However, whether these cognitive deficits are associated with changes to the central cholinergic system remains controversial. In response, the current study used *in vivo* microdialysis in a rat model of Gulf War Illness to assess whether combinations of 14 days of PB and 10 days of repeated restraint stress interact to influence the prefrontal (PFC) and hippocampal acetylcholine levels in response to both an LPS and restraint stress challenge. There

were a total of four groups compared in this study: vehicle-non-stressed control (NSC), vehicle-stressed, PB-NSC, and PB-stressed. Results indicate that PB decreases the hippocampal but not PFC cholinergic response to LPS. The restraint stress challenge also produces divergent effects on the PFC and hippocampus: PB mimics the effects of stress in the PFC to attenuate the cholinergic response to restraint relative to vehicle-NSC rats, whereas PB and stress interact to increase the cholinergic response to restraint in the hippocampus relative to vehicle-stressed rats. The neurochemical effects of PB and stress on central cholinergic function are paralleled by differences in contextual and cue-based fear conditioning. PB augments stress-induced deficits in contextual fear conditioning, which is a hippocampal-dependent task. In contrast, a delayed retention test (48 hours after acquisition of the fear response) for conditioned freezing to the cue (tone) is preferentially associated with the PFC. The specific impairments in retention of the cued fear memory in PB-NSC rats further supports differences in sensitivity of the PFC and hippocampus to PB and stress. Collectively, these data suggest that PB and stress produce divergent effects on the cholinergic response to stress in the PFC versus the hippocampus, and these brain-region dependent shifts in cholinergic function parallel PFC and hippocampal-based cognitive deficits in retention of fear memories.

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.03/II16

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** CDMRP GW120037
CDMRP GW120045

**Title:** Targeting inflammatory and glucocorticoid pathways to treat Gulf War illness in a preclinical mouse model

**Authors: *L. T. MICHALOVICZ**[1], K. A. KELLY[1], J. V. MILLER[1], D. B. MILLER[1], T. J. A. CRADDOCK[2], G. BRODERICK[3], K. SULLIVAN[4], J. P. O'CALLAGHAN[1]
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**Abstract:** Gulf War Illness (GWI) is a multi-symptom disorder exhibiting many features that are similar to sickness behavior (e.g. persistent headaches, chronic fatigue, cognitive dysfunction, skin and gastrointestinal ailments). Using an exposure model combining physiological stress and

toxic chemical exposure, we have established that, like sickness behavior, GWI is associated with underlying neuroinflammation. However, current treatments for GWI tend to focus on managing symptoms as opposed to addressing the underlying cause of the illness. With ever growing support for a neuroimmune basis of GWI, several treatments have been identified that target neuroinflammatory and glucocorticoid signaling. The goal of these treatments is to restore "healthy" neuroimmune function, allowing for appropriate instead of exacerbated neuroinflammatory responses to typical immune challenge. Here, we tested the therapeutic potential of propranolol, a beta-blocker with anti-inflammatory effects, and an anti-inflammatory/glucocorticoid combination therapy of etanercept and mifepristone in our established mouse model of GWI. In this model, mice are initially exposed to the glucocorticoid, corticosterone (CORT; 200 mg/L) in the drinking water for 7 days followed by a single, acute injection of the sarin surrogate, diisopropyl fluorophosphate (DFP; 4 mg/kg, i.p.) to model the "in theater" conditions of high physiological stress and potential nerve agent exposure. This is then followed by periodic administration of CORT for 7 days every other week to a total of 5 weeks with an immune challenge (lipopolysaccharide, LPS) on the final day. The therapeutic interventions [etanercept (5 mg/kg, i.p.) + mifepristone (20 mg/kg, i.p.) spaced two days apart; propranolol (20 mg/kg, i.p.)] were given during or outside of CORT exposure to evaluate potential interactions with CORT exposure. Mice were sacrificed 6 hours after LPS challenge and brain cytokine mRNA expression was evaluated by qPCR. We found that both treatment strategies were most successful by significantly reducing the neuroinflammation instigated by the GWI exposure model when given during CORT exposure. In particular, propranolol reduced the neuroinflammation of GWI exposure group to levels comparable to the CORT+LPS "healthy sick" control group. These initial studies indicate the potential for these therapies to treat the underlying neuroinflammation associated with GWI and to return patients to a "healthy" neuroimmune functional state.

**Disclosures: L.T. Michalovicz:** None. **K.A. Kelly:** None. **J.V. Miller:** None. **D.B. Miller:** None. **T.J.A. Craddock:** None. **G. Broderick:** None. **K. Sullivan:** None. **J.P. O'Callaghan:** None.

**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.04/II17

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** CDMRP Grant GW120037
CDMRP Grant GW120045
CDMRP Grant GW150188
CDC-NIOSH intramural funds

**Title:** Spatiotemporal ACh accumulation and phosphoprotein signaling in a mouse model of Gulf War Illness

**Authors: *J. V. MILLER**[1], K. A. KELLY[1], L. T. MICHALOVICZ[1], J. A. MOUCH[2], N. PRINCE[2], J. W. BOYD[2], D. B. MILLER[1], J. P. O'CALLAGHAN[1]
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**Abstract:** It is estimated that 30% of veterans from the 1991 Gulf War (GW) suffer from a persistent form of sickness-like behavior, known as Gulf War Illness (GWI). Identifying the acute (in theater) responses to GW-relevant exposures, such as acetylcholinesterase (AChE) inhibiting chemicals and concomitant high physiological stress, that may have served as initiating events is essential for understanding the pathobiology of GWI. Following toxicant or toxin exposure(s), the organism-level response is organized via spatial (e.g., brain region and/or cell type) and temporal (e.g., acute and adaptive) cellular responses that have long-term implications with regard to disease manifestation. These early responses involve post-translational phosphorylation reactions that regulate adaptive stress pathways, which converge toward a new cellular- and ultimately organism-level steady state. Elucidation of the spatiotemporal phosphorylation responses and acetylcholine accumulation relevant to these exposures holds the potential to discern the etiology of GWI. To further investigate the early cellular changes relevant to the exposures experienced in the GW theater, we used our validated mouse model of GWI. In this model, adult male C57BL/6J mice were exposed to CORT in the drinking water for 7 days followed by a single injection of the sarin surrogate, diisopropyl fluorophosphate (DFP; 4.0mg/kg, i.p.), on the 8$^{th}$ day. To evaluate the brain-region specific effects of DFP and CORT+DFP on AChE, acetylcholine (ACh) was quantified in hippocampus (HIP) and striatum (STR) using HILIC UPLC-MS/MS. Mice were euthanized 30 min, 2 h, and 24 h post-DFP using focused microwave irradiation to ensure preservation of in vivo levels of Ach and steady state levels of protein phosphorylation. The ACh levels in the HIP and STR do not correlate with the exacerbated neuroinflammation induced by CORT+DFP exposure. Therefore, interrogation of potential aberrant phosphoprotein responses of critical signaling pathways in the HIP and STR were conducted to evaluate non-AChE targets. Over 20 phosphoprotein targets were measured using multiplex ELISA. Results from our GWI model (CORT+DFP) responses revealed numerous phosphoprotein targets with increased phosphorylation over DFP alone (e.g., ERK1/2, GSK3, IkB-a, JNK, MEK1), suggesting new potential biomolecular drivers and therapeutic targets of GWI symptomatology.

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.05/II18

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** DoD grant W81XWH-16-1-0744

**Title:** Resting state functional magnetic resonance imaging reveals brain mechanisms underlying gulf war illness

**Authors: *K. GOPINATH**[1], U. SAKOGLU[3], B. A. CROSSON[2], R. HALEY[4]
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**Abstract:** Up to 250,000 veterans of the 1991 Gulf War suffer from illness (GWI) characterized by multiple deficits in cognitive, affective, sensory, motor and pain domains as assessed through self-reported symptoms. In this study, we examined a large group of 60 GWI veterans (mean age 49.8 yrs.) and 30 matched normal controls (NC) (mean age 49.7 yrs.). The subjects were scanned in a Siemens 3T MRI scanner using a 12-channel head coil. Informed consent was obtained from all participants in the protocol approved by the local Institutional Review Board. RsfMRI data were acquired with a 10-min whole-brain EPI (TR/TE = 2000/24ms, resolution = 3mm x 3mm x 3.5mm). The preprocessed rsfMRI data for all subjects were temporally concatenated and a **G**roup spatial **I**ndependent **C**omponent **A**nalysis (GICA) was performed. For each subject, the functional network connectivities (FNCs) between the different GICA-derived ICs were assessed with cross-correlation (CC) analysis. Between-group differences in FNCs were assessed with 2-sample t-tests on z-transformed CCs. GWI veterans exhibited *impaired* connectivity within and between brain networks engaged in language, memory, attention, sensory, motor and multisensory processing. On the other hand, GWI veterans abnormally increased connectivity in pain processing networks. These results provided valuable insights into brain mechanisms underlying this multi-symptom illness. For instance, GWI veterans exhibited *decreased* (2-sample t-test $p < 0.01$) FNC between ICs representing language processing and the ICs representing different sensory (visual, auditory and sensory) inputs as well as ICs representing motor areas involved in speech production. On the other hand language networks exhibited abnormally *increased* (t-test $p < 0.02$) FNC with pain processing network ICs. Thus language deficits in GWI could arise in part from recruitment of brain areas involved in performing language tasks into an overactive pain neuromatrix caused by chronic pain. GWI veterans also exhibited *decreased* FNC between ICs representing memory function and scene and language processing ICs which could account for their episodic and semantic memory deficits. GWI veterans' inability to perform complex motor tasks could arise from impaired FNC exhibited

between primary motor, motor control, sensorimotor, visual processing and attention network ICs in GWI. These insights into brain mechanisms underlying GWI can inform future therapies for the disease.

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

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**Program #/Poster #:** 759.06/JJ1

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** Department of Defense CDMRP Award W81XWH-14-1-0572 to AKS

**Title:** Cognitive and mood dysfunction in an animal model of chronic Gulf War Illness is linked with altered leukotriene signaling in the brain and elevated systemic inflammation

**Authors: *R. UPADHYA**[1,2], S. ATTALURI[1], D. UPADHYA[1,2], M. KODALI[1,2], B. SHUAI[1,2], A. K. SHETTY[1,2]
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**Abstract:** Cognitive and mood impairments are the most conspicuous CNS symptoms of Gulf War Illness (GWI). Epidemiological studies have implied that exposures to the GW-related chemicals (GWR-Cs) and stress during the war caused illness in a significant fraction of GW veterans. The chemicals include the nerve gas prophylactic drug pyridostigmine bromide (PB), mosquito repellant DEET, and the insecticide permethrin. Our previous studies in a rat model employing exposures to these chemicals and stress have shown that cognitive and mood dysfunction in GWI is associated with the occurrence of activated microglia, reactive astrocytes and leaky blood-brain barrier (BBB). Here, we examined the molecular changes underlying neuroinflammation and BBB disruption in the brain using a rat model of chronic GWI. Specifically, we measured proinflammatory mediators in the brain and blood. These include leukotrienes (LTs), the expression of their upstream biosynthetic enzyme 5-lipoxygenase (5-LOX), and the concentration of various proinflammatory cytokines. Young male SD rats were first exposed daily to GWR-Cs, PB (2 mg/kg), DEET (60 mg/kg) and permethrin (0.2 mg/kg) and 15-minutes of restraint stress for 4 weeks. Examining with a novel object recognition test and a novelty suppressed feeding test at 6 months post-exposure confirmed the presence of persistent cognitive and mood dysfunction in GWI rats. These animals exhibited increased concentration of the leukotriene LTB4 and cysteinyl LTs (LTC4, LTD4, LTE4) in the cerebral cortex. Higher percentages of neurons and microglia in the hippocampus and cerebral cortex also displayed enhanced expression of 5-LOX. The concentration of cysteinyl LTs was unchanged in

the serum however, implying that enhanced LT signaling in GWI occurs specifically in the brain. Interestingly, these changes were associated with increased concentration of multiple proinflammatory cytokines in the circulating blood but not in the cerebral cortex. Thus, chronic GWI is linked with increased LT signaling in the brain which runs parallel to elevated systemic inflammation. These CNS and systemic changes together can have adverse effects on brain function because LTB4 is involved in recruiting leukocytes to the site of inflammation whereas, cysteinyl LTs, in addition to inducing activation of microglia and astrocytes, can cause endothelial cell dysfunction. Collectively, the findings suggest that, in GWI, increased concentration of LTs in the brain maintains chronically leaky BBB, which facilitates the entry of elevated pro-inflammatory cytokines from the blood to the brain to cause persistent memory and mood dysfunction.

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

**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.07/JJ2

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** DOD CDMRP Grant W81XWH-16-1-0626
VA Grant I01RX001520
Florida DOH Grant 4KB14
Bay Pines Foundation
Veterans Bio-Medical Research Institute

**Title:** Neurodegeneration and astrocyte responses in a pyridostigmine bromide, DEET, and chlorpyrifos Gulf War illness model

**Authors: *B. A. CITRON**[1], W. A. RATLIFF[2,3]
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**Abstract:** Gulf War Illness afflicts at least a quarter of the Veterans who were deployed during the 1990-1991 Gulf War. Neurological problems are common, in the chronic multi-symptom illnesses that are suffered, and include cognitive changes, affective disorders, and anxiety. To be able to address these problems, we must first improve our understanding of the causes. So far, it seems that the unusual prevalence and characteristics of these illnesses resulted from exposure to multiple toxins during deployments to the Persian Gulf in this time period. A factor high on the

list of detrimental exposures is the acetylcholinesterase inhibitor, pyridostigmine bromide (PB) that was administered prophylactically to counter potential nerve gas exposure. Other significant candidates include DEET-based insect repellants and organophosphate insecticides like chlorpyrifos. We have tested a mouse model of Gulf War Illness recapitulating the multidimensional toxin exposure of the Gulf War Veterans. Mice received subcutaneous administration of PB, DEET, and chlorpyrifos over the course of two weeks. Functional tests indicated that the combination insult resulted in hyperactivity and anxiety-like behavior. The effects of activation of the neuroprotective transcription factor, Nrf2, with treatment initiated long after the insult exposure, are being investigated to assess the role of this signaling pathway mechanistically and as a potential therapy. ln addition to molecular changes, we have been focusing on inflammatory responses involving glia. Coronal brain sections have been examined from toxin exposed mice. Amino cupric silver staining did not indicate significant axonal degradation. Astrocytic changes have been observed after the toxin exposure by morphological analyses after staining with glial fibrillary acidic protein and skeletonization with ImageJ. We hope that we will be able to advance the search for strategies to alleviate long-term effects in this Veteran population by identifying underlying neurodegenerative mechanisms and therapeutic targets.

**Disclosures: W.A. Ratliff:** None.

**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.08/JJ3

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** CDMRP Award W81XWH-14-1-0572 to AKS

**Title:** Monosodium Luminol improves cognitive and mood function with repression of neuroinflammation and enhancement of neurogenesis in a model of chronic Gulf War Illness

**Authors: *M. KODALI**[1,2], S. ATTALURI[1], B. SHUAI[1,2], M. L. NARAYANA[1], A. BATES[1,2], X. RAO[1,2], L. MELISSARI[1], E. MITRA[1], D. UPADHYA[1,2], B. HATTIANGADY[1,2], A. K. SHETTY[1,2]
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**Abstract:** Gulf War Illness (GWI) is associated with persistent cognitive, memory and mood impairments. Several animal model studies employing exposure to GWI-related chemicals (GWIR-Cs) and moderate stress have linked these symptoms to persistent neuroinflammation, increased oxidative stress, mitochondrial dysfunction, and decreased neurogenesis in the

hippocampus (Parihar et al., Neuropsychopharmacology, 2013; Shetty et al., Frontiers in Molecular Neuroscience, 2017). In addition, our recent study demonstrated the efficacy of monosodium luminol (MSL, BachPharma) for improving cognitive and mood function in GWI rats when administered 4 months after the exposure to GWIR-Cs and stress (Shetty et al., SFN abstracts, 2017). In this study, we examined the efficacy of MSL treatment commencing 6 months after the exposure to GWIR-Cs and stress because GWI is persistent in veterans of the first Gulf War even >25 years after the exposure. Male SD rats were exposed daily to GWIR-Cs, DEET (60 mg/kg), permethrin (0.2 mg/kg), PB (2 mg/kg), and 15-minutes of restraint stress for 4 weeks. Six months later, a cohort of GWI rats received MSL (160 mg/Kg in 0.5 ml water, oral) and another cohort received vehicle (0.5 ml water) for 16 weeks (5 times/week). An additional group of GWI rats was maintained as GWI alone group. In the $5^{th}$ week of MSL treatment, the animals also received injections of 5'-bromodeoxyuridine (once daily for 5 days, 100 mg/Kg) for analysis of hippocampal neurogenesis. Animals were subjected to a series of behavioral tests in the last 10 weeks of MSL treatment to examine cognitive, memory and mood function. The behavioral investigation sequentially comprised object location, novel object recognition, pattern separation, sucrose preference, and water maze tests. In comparison to animals in control GWI groups, animals in GWI-MSL group displayed improved ability for discerning minor changes in the environment in an object location test, recognition memory in a novel object recognition test, and spatial memory retrieval in a water maze test. Animals also displayed better mood function by showing no anhedonia in a sucrose preference test. Furthermore, the hippocampus of these animals displayed reduced levels of multiple proinflammatory cytokines (TNF-a, IL1-a, MCP-1, MIP-1a, VEGF, FGF-b, and TGF-b), reduced density of ED-1+ activated microglia, and enhanced neurogenesis, in comparison to animals in GWI-VEH or GWI alone groups. Thus, long-term MSL treatment to animals afflicted with chronic GWI leads to improved cognitive, memory and mood function with repressed neuroinflammation and enhanced neurogenesis in the hippocampus.

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.09/JJ4

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** US Army Medical Research Acquisition Activity; W81XWH-16-1-0560

**Title:** Normalizing the dyshomeostasis of glutamatergic system as a potential therapeutic strategy for Gulf War illness

**Authors: *X. WANG**[1], Z. XU[1], J. FOSTER[1], F. ZHAO[1], N. KUNG[1], K. LIN[1], K. HODGETTS[2], C.-L. LIN[1]
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**Abstract:** Cognitive difficulties and mood deficits are the most ubiquitous among the various symptoms of Gulf War illness (GWI). It is widely believe that these clinical symptoms are linked to a combination of exposures encountered by the service personnel. Literature has indicated that chronic exposure to GWI-related chemicals, such as pyridostigmine and permethrin, and war-related stress cause dyshomeostasis of glutamatergic system in the hippocampus, which may contribute to memory and mood deficits. The purpose of this study is to investigate if increasing excitatory amino acid transporter 2 (EAAT2) expression by LDN/OSU-215111, a small molecule that enhances EAAT2 translation, can normalize the dyshomeostasis of the glutamatergic system and consequently improve cognitive and mood deficits in a mouse model of GWI. Three months old C57BL/6J mice were exposed to GWI agents and chronic unpredictable stress daily for 6 weeks. At three months post-exposure, mice developed anxiety- and depression-like behaviors as assessed by several behavior tests, including open field, tail suspension, light and dark exploration, elevated plus maze, novelty suppressed feeding, and sucrose preference tests. We also observed a decrease in cognitive functions in these GWI conditioned mice as assessed by Barnes maze and novel object recognition tests. These mood and cognitive deficits worsened at six months post-exposure. An initial study was conducted to investigate if LDN/OSU-215111 can prevent mood and cognitive deficits. Mice received compound treatment daily during 6-week of GWI conditions and the treatment continued until mice were euthanized. The results showed that compound-treated GWI mice exhibited significantly reduced anxiety- and depression-like behaviors and improved cognitive functions. We observed a significant decrease in hippocampal long-term potentiation in GWI mice, but this deficit was restored in compound-treated mice. Several proteins related to glutamate system were found to be changed in GWI mouse brains, and underlying mechanisms are currently under investigation. In addition, we are currently conducting a treatment study, which GWI mice are treated with compounds at five months post-exposure when the deficits have developed. After one month of treatment, mice are evaluated for mood and cognitive functions. The results of this study will be presented.

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.10/JJ5

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** DOD Grant GW160151

**Title:** Tau pathology as a mechanism underlying microtubule-based deficits in Gulf War illness

**Authors: *P. YATES**[1], A. PATIL[1], K. SULLIVAN[2], P. BAAS[1], L. QIANG[1]
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**Abstract:** Gulf War Illness (GWI) is a chronic multisystem disorder suffered by at least 25% of the nearly 700,000 U.S. veterans who fought in the 1990-1991 Gulf War. Central nervous system symptoms include chronic fatigue, decreased information processing speeds, memory deficits, poor attention/concentration, chronic headaches, and impaired sleep. These symptoms are consistent with exposure to neurotoxicants such as organophosphate pesticides and nerve agents. Studies have demonstrated that Gulf War-relevant organophosphates induce abnormalities in neuronal microtubules (MTs) and impair axonal transport; however, the precise mechanisms are unknown, and there are no current treatments for GWI. We have shown that low doses of the sarin analog Diisopropyl fluorophosphate (DFP) that do not inhibit acetylcholinesterase, in combination with the rodent stress hormone corticosterone, reduce MT acetylation, MT dynamics, mitochondrial transport, and dopamine release in primary rat neurons, and that all of these deficits can be restored to normal by treating with the tubulin-specific histone deacetylase 6 (HDAC6) inhibitor tubacin. Now, using hiPSC-derived neurons exposed to DFP+cortisol, we confirmed the mitochondrial deficits in morphology, membrane potential, and movement. Treatment with the kinesin-5 inhibitor monastrol was able to restore most of these defects back to normal. Together, these observations suggest that drugs that affect MTs in various ways may provide treatment options for GWI, but a mechanistic basis for the observed abnormalities is still unclear. Here, we explored whether tau pathology might contribute to some of the MT-related deficits. This idea was inspired in part due to the presence of autoantibodies to tau in the peripheral blood of veterans with GWI, and in part based on earlier studies suggesting that organophosphates can make neuronal MTs thinner, presumably because of the detachment of associated proteins such as tau. We exposed hiPSC-derived glutamatergic neurons to the GWI regimen of DFP+cortisol and documented increases in total tau, as stained by TauR1, and phosphorylated tau, as stained for the early hyperphosphorylated tau marker AT8. Furthermore, we are currently studying the phenomenon in human-derived forebrain cerebral organoids in which we can investigate the effects of the GWI regimen on structures such as synapses to ascertain whether additional characteristics of tauopathy are observed. We aim to harness the

power of the hiPSCs and their derivatives to screen for potential therapies using high-throughput analyses in order to develop therapies for veterans suffering from GWI.

**Disclosures: A. Patil:** None. **K. Sullivan:** None. **P. Baas:** None. **L. Qiang:** None.

**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.11/JJ6

**Topic:** D.06. Auditory & Vestibular Systems

**Support:** CDMRP grant W81XWH-14-1-059

**Title:** Gulf War Illness is associated with reduced vestibular function that can be restored using a novel imperceptible GVS neuromodulation device based on stochastic resonance

**Authors: *J. M. SERRADOR**[1,2], M. C. SCHUBERT[3], K. BREWER[2], P. BREEN[4], S. J. WOOD[5]
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**Abstract:** Gulf War Illness (GWI) is a chronic fatigue like syndrome that plagues almost 25% of the 700,000 veterans that returned form operation Desert Storm/Desert Shield in 1990-91. To examine a possible role for vestibular inputs in this syndrome, we recruited 60 veterans with GWI, 6 Gulf War Era that were healthy and 36 age and sex matched civilians. We assessed ocular torsion (OT) during a +/-$20^{O}$ sinusoidal roll tilt at 0.03125 Hz. We found that OT gain, a vestibular ocular reflex associated with otolith function, was significantly reduced in veterans with GWI (0.13±0.06) vs Gulf War Era (0.17±0.07) and Civilians (0.19±0.07, P=0.003). Examining static balance measures between veterans with GWI and civilians we found veterans had greater mediolateral sway ($deg^2$) in all conditions: standing with eyes open (0.14±0.08 vs 0.09±0.07, P=0.010); standing with eyes closed (0.18±0.12 vs 0.10±0.06, P<0.001) and eyes open on unstable surface (0.43±0.21 vs 0.28±0.08, P<0.001). Similar results were found in anterior-posterior direction. We attempted to improve vestibular function and postural sway in GWI veterans using a novel neuromodulation device that provides imperceptible levels of random stochastic noise electrical stimulation bilaterally through ear clips (mean 0 mA, SD of stimulus of 0.02-0.4 mA, depending on veteran). Surprisingly there was no difference in OT values between sham and stim in the entire group, unlike our previous findings in elderly civilians. Further examination demonstrated that we did see improvement in 53% of the veterans with mean increases in OT of 25% (range 1-81). Improvement in OT during stimulation was negatively correlated to baseline OT (R=0.61, P<0.001), indicating that veterans with reduced

vestibular function had the greatest improvement. In contrast sway was improved in 100% of the GWI veterans. In fact, sway in the eyes open on foam condition reduced from 0.49±0.32 during sham to 0.27±0.32during stim which is lower than the 0.28±0.08 seen in age and sex matched normative data. In fact sway reduced by a mean of 42% (Range 21-63). This improvement in balance was striking since the improvement occurred in 100% of the veterans, despite OT only improving in 53%. These data highlight two important findings: 1) Vestibular hypofunction appears to be prevalent in veterans with GWI; 2) Neuromodulation using low level electrical signals that is imperceptible is able to restore vestibular function in ~50% of veterans and improve balance in 100%. These data strongly suggest that vestibular function should be assessed in GWI and that stochastic resonance may be novel treatment for vestibular loss. Supported by CDMRP grant W81XWH-14-1-0598 (PI Serrador).

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.12/JJ7

**Topic:** G.04. Mood Disorders: Depression and Bipolar Disorders

**Support:** GWIRP Grant W81XWH-17-1-0573

**Title:** Antidepressant effects of ketamine in an organophosphate rat model of Gulf War Illness

**Authors: K. PHILLIPS**[1], E. SANTOS[2], E. HAWKINS[3], *L. S. DESHPANDE[3]
[1]Neurosci., Virginia Tech., Blacksburg, VA; [2]Biol., [3]Dept Neurol, Virginia Commonwealth Univ., Richmond, VA

**Abstract:** Approximately 33% of the nearly 700,000 U.S. soldiers deployed during the First Gulf War suffer from a chronic multi-symptom disorder known as Gulf War Illness (GWI). Recent studies have shown that major depression is more prevalent in deployed Veterans than non-deployed First GW soldiers. Conventional antidepressants are limited by a delay of onset of therapeutic effects and many GW veterans do not achieve sustained remission of depressive symptoms using conventional antidepressants. Ketamine (KET) is reported to produce a rapid-onset and sustained antidepressant response, but there are no studies demonstrating the antidepressant effects of KET in GWI population. We developed an organophosphate DFP based rat model of GWI and identified hippocampal injury associated with depression and cognitive deficits similar to those reported in GWI Veterans. We postulate that GWI depression may represent a unique neuroplasticity phenomenon and therefore requires drugs with a different mechanism of action than conventional antidepressants. Male Sprague Dawley rats (3-m) were

exposed to repeated, low-dose DFP (0.5 mg/kg s.c. for 5-days) and assessed for GWI-depressive symptoms at 6-m post DFP exposure using the Forced Swim Test (FST). DFP exposed rats exhibited significantly higher immobility time in FST compared to saline-treated, age-matched control rats. GWI rats treated with KET at a low, sub-anesthetic dose (10 mg/kg, i.p.) exhibited a rapid antidepressant effect when tested at 1-h (79.04 ± 6.3s vs 24.6 ± 3.4s, n=10). This effect sustained at 24-h post KET injection (79.01 ± 4.2s vs 38.5 ± 8.2s). KET is a racemic mixture consisting of R and S stereoisomers in equal parts. Both S-KET and R-KET (10 mg/kg, i.p.) produced acute antidepressant effects (79.04s ± 6.3s vs 48.7 ± 6.5s and 45.3 ± 3.42s, n=10) that were also observed at 24-h (79.04s ± 6.3s vs 57.8 ± 6.1s and 52.6 ± 8.5s) respectively. R-KET appeared to be more potent antidepressant than S-KET. Some early effects of KET agents on motor coordination were not observable effects at 1-h post injection. The antidepressant effect of KET or its enantiomers are observed at time points when they would be eliminated from the brain, suggesting that they act by inducing long-lasting synaptic plasticity changes. Recently, we observed chronically elevated hippocampal $Ca^{2+}$ levels in GWI rat brains. Given the critical role $Ca^{2+}$ ions play in shaping synaptic plasticity and modulating behavior, it remains to be seen whether KET's effect on $Ca^{2+}$ homeostatic mechanism in GWI plays a role in mediating its antidepressant effect. Our data so far provides the first identification of antidepressant efficacy of KET and its isomers in a rat model of GWI.

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.13/JJ8

**Topic:** C.10. Brain Injury and Trauma

**Support:** NIH/NINDS-R01NS085131
CDMRP/GWIRP-W81XWH1510679

**Title:** Systemic hyperalgesia in females with gulf war illness and chronic fatigue syndrome

**Authors: *A. SURIAN**[1], J. N. BARANIUK[2]
[1]Georgetown Univ. Med. Ctr., Alexandria, VA; [2]Georgetown Univ. Med. Ctr., Washington, DC

**Abstract:** Background. The Gulf War Illness (GWI) and Chronic Fatigue Syndrome (CFS) diagnostic criteria include pain symptoms. Physical examination demonstrates systemic hyperalgesia to pressure. The relationship between pain and tenderness was assessed by dolorimetry. Methods. Pressure was applied to the 18 traditional fibromyalgia tender points and averaged in GWI, CFS, healthy control, and putative fibromyalgia (FM) women with widespread pain plus tenderness at ≥11/18 thumb pressure tender points who did not meet CFS criteria.

Results. GWI women were most tender (2.90±1.64 kg, mean±SD, n=68), followed by FM (3.46±1.25 kg, n=28), and CFS (3.72±1.85 kg, n=174) compared to controls (6.22±2.26 kg, n=133, significantly highest by ANOVA and Tukey HSD $p<0.01$). Sensitivity, specificity and concordance were 0.794, 0.827 and 0.816, respectively, in GWI at a threshold of 4 kg (AUC 0.876), and 0.759, 0.677 and 0.723, respectively, at 5 kg for CFS (AUC 0.799). Distributions of dolorimetry in GWI and CFS are shifted to the far left tail of the normal distribution, but are independent modal peaks that are distinct from the normal distribution. Conclusion. CFS and GWI women have significant systemic hyperalgesia compared to controls. The tenderness to pressure in GWI women can be used as a diagnostic physical sign in the clinic to complement their histories of Gulf War exposures and Kansas criteria items (Steele 2000) for the diagnosis of Gulf War Illness. Dorsal horn, brainstem, and cortical regions can now be interrogated to discover the mechanism(s) of systemic hyperalgesia in CFS and GWI. Measures of sensory and interoceptive dysfunction such as photophobia, phonophobia, vestibular dysfunction and irritable bowel syndrome can be examined in analogous fashion.

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.14/KK1

**Topic:** C.10. Brain Injury and Trauma

**Support:** NIH/NINDS-F30NS103563
CDMRP/GWIRP-W81XWH1510679
NIH/NINDS-R01NS085131
NIH/NIA-R25AG047843

**Title:** Characterizing dynamic functional connectivity changes following a physiological stressor in myalgic encephalomyelitis/ chronic fatigue syndrome and gulf war illness

**Authors: *R. U. RAYHAN**[1], S. D. WASHINGTON[3], R. GARNER[5], K. ZAJUR[5], F. ADDIEGO[5], J. W. VANMETER[3], K. F. MANAYE[2], J. N. BARANIUK[4]
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**Abstract:** Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Gulf War Illness (GWI) are phemenological disease states with similar phenotypes characterized by chronic widespread pain, fatigue, and dyscognition. A shared syndromic feature of both patient populations is post-exertional malaise (PEM). PEM is defined as an exacerbation of baseline

symptoms following a physically taxing or cognitively demanding activity. We previously reported a novel paradigm that modeled this hallmark symptom by utilizing fMRI scans taken before and after sub-maximal exercise. Prior studies analyzing resting state scans have led to inconsistent results of both increased and decreased functional connectivity in ME/CFS and GWI. This may be due to the methodologies used for analysis, as functional connectivity indices were averaged over the entire duration of scanning sessions. Recently, resting-state fMRI experiments have reported meaningful changes in correlational patterns that occur within one session. This dynamic behavior of functional connectivity has not been explored in ME/CFS or GWI. We recruited 49 GWI, 33 ME/CFS and 23 sedentary controls to complete the fMRI-exercise protocol. Dynamic functional connectivity (dFC) was assessed using the resting states scans acquired before and after exercise. The functional brain data was decomposed into components. Subsequent analysis then computed changes within session using sliding window analysis (40 s in length) plus k-means clustering. Prior to exercise, there was no significant differences in the dFC patterns between the groups. Following exercise, subgroups within ME/CFS and GWI revealed dFC differences between regions in the anterior insula, fronto-parietal network (FPN), and Default Mode Network (DMN). Exercise-induced alterations of dFC within large scale neural networks provides further evidence of PEM in ME/CFS and GWI. While important differences have been identified, future studies should verify these findings. Taken together, our results expand on the limited knowledge regarding the effects of PEM on cognition in ME/CFS and GWI, and strongly suggests the use of dFC analyses to better account for changes in resting state functional connectivity.

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 759.15/KK2

**Topic:** C.10. Brain Injury and Trauma

**Support:** NIH/NINDS-R01NS085131
NIH/NINDS-R2INS088138
CDMRP/GWIRP-W81XWH1510679
NIH/NINDS-F30NS103563

**Title:** Functional connectivity differences between Gulf War Illness (GWI) phenotypes during a test of attention

**Authors: *F. A. MARTINEZ ADDIEGO**[1], R. U. RAYHAN[2], S. D. WASHINGTON[3], T. CLARKE[3], J. D. JAMIESON[3], P. S. MALONE[3], J. W. VANMETER[3], J. N. BARANIUK[3]

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**Abstract:** One quarter of veterans returning from the 1990-1991 Persian Gulf War have developed Gulf War Illness with chronic pain, fatigue, cognitive and gastrointestinal dysfunction. Exertion leads to characteristic, delayed onset exacerbations that are not relieved by sleep. Exertional exhaustion was modeled by comparing magnetic resonance images from before and after submaximal exercise. One third had brain stem atrophy and developed postural tachycardia after exercise (START: Stress Test Activated Reversible Tachycardia). The remainder activated basal ganglia and anterior insulae during a cognitive task (STOPP: Stress Test Originated Phantom Perception). The role of attention in cognitive dysfunction prior to exercise was assessed by brain functional connectivity during a simple stimulus matching 0-back working memory task ("see a letter, push a button"). Three small 0-back networks of attention, task and default nodes were shared by all subjects. In addition, START (n=10), STOPP (n=18) and control (n=8) groups each had larger, unique networks of task and default nodes that formed distinct modules. Controls had a task network of right dorsolateral and left ventrolateral prefrontal cortex, dorsal anterior cingulate cortex, posterior insulae and frontal eye fields (dorsal attention network). START had a large task module centered on the dorsal anterior cingulate cortex with direct links to basal ganglia, anterior insulae, and right dorsolateral prefrontal cortex nodes, and connections through the dorsal attention network nodes in the intraparietal sulci and frontal eye fields to the precuneus and default module. STOPP had 2 separate task submodules of basal ganglia-anterior insulae, and dorsolateral prefrontal executive control regions. This STOPP task module was connected directly to the default module but not to dorsal attention or posterior insulae nodes. Instead, those nodes were embedded deep in the default module and were distant from the task networks. In conclusion, control, START and STOPP had unique connectivity patterns. START and STOPP had distinct network structures that indicate 2 patterns of cognitive dysfunction in GWI. The data support the concept of Gulf War Disease with recognizable, objective phenotypes of cognitive dysfunction.

**Disclosures: F.A. Martinez Addiego:** None. **R.U. Rayhan:** None. **S.D. Washington:** None. **T. Clarke:** None. **J.D. Jamieson:** None. **P.S. Malone:** None. **J.W. VanMeter:** None. **J.N. Baraniuk:** None.

**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.16/KK3

**Topic:** C.10. Brain Injury and Trauma

**Support:** CDMRP GR411148

NIH GR411884

**Title:** Confirmation that exercise challenge in Gulf War illness reveals two autonomic subgroups with altered brain function

**Authors: *S. D. WASHINGTON**[1], R. U. RAYHAN[3], R. GARNER[4], K. ZAJUR[1], J. W. VANMETER[1], J. N. BARANIUK[2]
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**Abstract:** Gulf War Illness (GWI) is a condition that affects 30% of the nearly 700,000 military personnel who served in Persian Gulf Theater (1990-1991). GWI is characterized by a cluster of symptoms including debilitating fatigue, chronic widespread pain, cognitive impairment, and autonomic dysfunction. A consistent complaint of GWI patients is post-exertional malaise, an exacerbation of symptoms subsequent to physical and/or mental effort. To this end, we previously demonstrated a causal relationship between exercise and cognitive deficits in GWI, after patients were phenotyped into two autonomic subgroups based on the occurrence of post-exercise postural tachycardia. However, the need for confirmatory evidence when characterizing the neurological component of any disorder coupled with recent advances in functional MRI analyses spurred us to confirm our previous findings in a second population of GWI patients (n=35). As in our previous study, we observed two GWI autonomic subgroups: one typified by orthostatic tachycardia (Reversible Tachycardia or RT, n = 12; n = 10 in prior RT subgroup) and another by exercise induced hyperalgesia (Phantom Perception or PP, n = 23; n = 18 in prior PP subgroup). We then had GWI patients and healthy controls (HC, n = 32) perform modified 2-Back tasks in a Siemens TIM Trio 3T MRI scanner both a day before and after a submaximal bicycle stress test. We then refined our previous analysis pipeline to better regress out translational and rotational motion plus exclude activity related to supporting stimuli (e.g., directions to subjects) before applying it both our previous and conformational samples. In both the previous and confirmatory samples, pre-exercise 2-Back task performance (2-Back > 0-Back) yielded robust blood oxygenation level dependent (BOLD) activity across the executive function network in HC and both the PP and RT GWI autonomic subgroups ($p < 0.01$, FDR). However, while post-exercise 2-Back task performance yielded similar or increased BOLD activity across the executive function networks of the HC group and PP subgroup, it yielded reduced activity across this network for the RT subgroup. Initial reports of basal ganglia activity in the PP group are likely linked to supporting stimuli and warrant further study. This confirmatory study enabled us to both refine and reinforce previous findings that may now provide clinicians a better understanding of the relationship between cognition and post-exertional malaise in GWI.

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 759.17/KK4

**Topic:** C.10. Brain Injury and Trauma

**Support:** NIH/NINDS-R01NS085131
NIH/NINDS-R2INS088138

**Title:** Exercise modulates mirna expression in cerebrospinal fluid of control, chronic fatigue syndrome and gulf war illness groups

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**Abstract:** Chronic Fatigue Syndrome (CFS) and Gulf War Illness (GWI) subjects have pain, cognitive dysfunction, fatigue and exertional exhaustion after exercise. miRNAs in cerebrospinal fluid were examined as biomarkers of exercise-induced mechanisms. Two groups had lumbar punctures: (i) "nonexercise" sedentary control (sc0, n=21), CFS (cfs0, n=45) and GWI (gwi0, n=21), and (ii) a separate group of sedentary control (SC, n=15), CFS (n=15), and GWI (n=64) who had LPs after submaximal exercise. Quantitative PCR levels of 380 miRNAs in 0.5 ml cerebrospinal fluid were normalized to 11 miRNAs detected in all specimens (ΔCt). Significant differences between groups were defined by ΔΔCt>2 and $p<0.05$ for ANOVA, Tukey HSD, FDR and ROC. Combinations of miRNAs were assessed for target genes (DIANA miRpathv3.0) using a novel R script to weight the highest probability targets. Targets were clustered to pathways using Ingenuity, Cytoscape, Reactome and KEGG databases. miRNA levels were higher in nonexercise than post-exercise groups (cfs0>CFS, gwi0>GWI) for miR-328, miR-608, miR-200a-5p and miR-93-3p. In addition, miR-let-7i-5p was elevated in gwi0>GWI, and miR-92a-3p in cfs0>CFS. Nonexercise controls (sc0>SC) had only significantly elevated miR-328 and miR-608. Post-exercise levels (SC>sc0) had higher miR-425-3p, miR-30d-5p and miR-204-5p. Nonexercise levels were equivalent between groups except for miR-1180 in gwi0>cfs0. The combination of miRNAs elevated in sc0>SC interfered with small signaling G proteins from the Ras GTPase superfamily, suggesting these proteins may have enhanced activity after exercise in SC. The combination in SC>sc0 interfered with Ubiquitination, PI3K/AKT Signaling and Myc Mediated Apoptosis Signaling after exercise, inferring these had higher activity in nonexercise sc0 subjects. The target genes were enriched in neuron and astrocyte transcriptomes. miRNA levels were similar in nonexercise groups, but patterns were different after exercise for SC, CFS and GWI. The changes in SC provide a foundation to understand pathophysiological effects of exercise in CFS and GWI phenotypes.

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 759.18/KK5

**Topic:** C.10. Brain Injury and Trauma

**Support:** NIH/NINDS-R01NS085131
NIH/NINDS-R2INS088138

**Title:** Targeted metabolomic and t-distributed stochastic neighbor embedding (t-sne) analysis of cerebrospinal fluid in chronic fatigue syndrome (cfs) and gulf war illness (gwi)

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**Abstract:** Metabolomics analysis of cerebrospinal fluid was used to assess pathophysiological mechanisms in Chronic Fatigue Syndrome (CFS) and Gulf War Illness (GWI). As a baseline, lumbar puncture was performed in sedentary control (n=21, 10 female), CFS (n=45, 36 female) and GWI (n=20, 11 female) subjects who had rested overnight ("nonexercise"). A separate group of control (n=7, all male), and GWI (n=21, 4 female) subjects had 2 bouts of submaximal exercise before lumbar puncture. The exercise induced transient postural tachycardia in one third of GWI (START: "Stress test activated reversible tachycardia", n=7, 1 female), but not the remainder (STOPP: "Stress test originated phantom perception", n=14, 3 female). Analyte concentrations were measured by tandem mass spectrometry and Biocrates AbsoluteIDQ® p180 Kit. Data were loaded to MetaboAnalyst. All concentrations were in normal ranges, and there were no significant differences between groups (FDR>0.16). Pearson correlation matrices of metabolite levels were examined (R Studio ggcorrplot package). Nonexercise controls had highly correlated phosphocholine levels that were slightly anticorrelated with sphingolipids. Nonexercise CFS and GWI subjects showed correlated phosphocholines but not anticorrelated sphingolipids. After exercise in controls, phosphocholines maintained their intercorrelation, but also became anticorrelated with amino acids. In contrast, post-exercise GWI became more similar to nonexercise control patterns. Follow-up by Principal Component Analysis was not productive. Metabolite concentrations were assessed by t-distributed stochastic neighbor embedding (t-SNE) that generated a linear trend that differentiated subjects by sex, exercise, and disease status. However, t-SNE analysis using Pearson correlations coefficients clearly separated nonexercise males from females, with each gender split into distinct control, CFS and GWI groups. Post-exercise controls were widely spaced away from nonexercise and the START and

STOPP GWI phenotypes. t-SNE of correlation coefficients provides a new tool to identify latent relationships within complex datasets such as metabolomics.

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.19/KK6

**Topic:** C.10. Brain Injury and Trauma

**Support:** CDMRP W81XWH-15-1-0679
NIH Neurological diseases and stroke R01NS085131

**Title:** Epidemiological trends reveal delayed neurological and cognitive onset in gulf war illness veterans

**Authors: *K. ZAJUR**[1], Y. HE[2], R. U. RAYHAN[2], R. GARNER[2], C. FAPPIANO[2], S. D. WASHINGTON[2], F. A. MARTINEZ ADDIEGO[2], J. BARANIUK[2]
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**Abstract:** The Persian Gulf War which took place between 1990-1991 has left many veterans debilitated, presenting with symptoms impairing the epithelial, abdominal, gastrointestinal, sensory, respiratory, cognitive, and nervous systems. As part of the diagnosis criteria for Gulf War Illness, a veteran must have served in theater and meet three out of the six systemic domains from the Kansas Questionnaire (Steele). Participants who met these criteria (n=47) and displayed symptoms from a case history and physical exam were asked to recall onset year (n=40) for each symptom and severity thereof (n=47) within the past 6 months. Symptoms were organized into 9 domains according to trends in prevalence between 1990-2017; fatigue and sleep, abdominal, other/mood, sensory 1, epithelial, pain, sensory 2, airways, and neurologic and cognitive. Four distinct epidemiological periods were observed, to include early onset (sharp increase between 1990-1993, with more than 20% by 1993), wide-range onset (a combination of multiple trends), delayed onset (sharp increase between 1990-1993, with less than 20% at 1993), and lagged onset (a slow onset in the 1990's and reaching 20% in 2000). Between 1991-1993 for domains excluding neurologic and cognitive, average prevalence was 18.5% and 67.6% by 2017. Exclusive to the neurologic and cognitive domain, average prevalence was 6.6% between 1991-1993 and 70.4% by 2017. Unlike other patterns, neurologic and cognitive was the only domain to present lagged onset, suggesting a slower rate of degeneration within the nervous system. Additionally, an average of 30% of participants reported moderate to severe symptoms. Our preliminary prevalence findings suggest an interdependence among symptom clusters, with a lack of correlation between epidemiological periods. Further, onset of neurological and cognitive

symptoms lags behind other domains. These patterns will now be assessed within a larger population of GWI veterans.

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.20/KK7

**Topic:** C.10. Brain Injury and Trauma

**Support:** CDMRP W81XWH-15-1-0679
Neurological Diseases and Stroke R01NS085131

**Title:** Verification of exercise-induced transient postural tachycardia phenotype in gulf war illness

**Authors: *R. GARNER**[1], R. U. RAYHAN[3], Y. HE[2], K. ZAJUR[2], S. D. WASHINGTON[2], J. BARANIUK[2]
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**Abstract:** Gulf War Illness (GWI) has affected 25% to 32% of the 700,000 veterans who served in the Persian Gulf War from 1990-1991. Along with chronic fatigue, gastrointestinal complaints, total body pain, and cognitive impairment, GWI veterans often present with signs of autonomic dysfunction and increased heart rate variability. In our verification study, we have confirmed two autonomic phenotypes based on cardiac responses to a submaximal exercise stress test. We also hypothesized that a sympathovagal imbalance would be associated with the autonomic phenotypes. Approximately one-third were identified as the Stress Test Activated Reversible Tachycardia (START) group because of the shift from a normal cardiac response to a change in posture before exercise to the occurrence of transient, orthostatic tachycardia only after exercise. Orthostatic tachycardia was defined as an increase in heart rate $\geq$ 30bpm at two or more time points upon standing after a five-minute supine period. The Stress Test Originating Phantom Perception (STOPP) phenotype had normal cardiac responses upon a change in posture both before and after exercise. An unanticipated finding was a unique GWI subgroup of patients who presented with Postural Tachycardia Syndrome (POTS). The START phenotype differed from POTS because START subjects developed postural tachycardia only after exercise, while POTS subjects exhibited orthostatic tachycardia at each time point. For START subjects, the most profound cardiac effects were observed within the first four hours after exercise, suggesting an acute pathophysiological response to exercise. These findings verify that one-third of GWI

subjects develop transient postural tachycardia after a submaximal exercise stress test. The START phenotype was different from POTS. Additional studies are required to examine this phenomenon in other illnesses and to determine pathological mechanisms.

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 759.21/KK8

**Topic:** C.10. Brain Injury and Trauma

**Support:** NIH/NINDS-R01NS085131
CDMRP/GWIRP-W81XWH1510679

**Title:** Factor analysis of the center for epidemiological studies - depression (cesd) domains in chronic fatigue syndrome and gulf war illness

**Authors: *Y. HE**[1], R. U. RAYHAN[2], R. GARNER[1], J. N. BARANIUK[3]
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**Abstract:** Chronic Fatigue Syndrome (CFS) and Gulf War Illness (GWI) are defined by a constellation of fatigue, cognitive, pain, sleep and other somatic complaints. CFS and GWI have been considered psychosomatic or depressive disorders because these disease-defining somatic symptoms overlap with fatigue, cognitive and sleep problems that are confirmatory features of depression. The 20 item Center for Epidemiological Studies - Depression (CESD) questionnaire has a 4 factor structure of Depressed, Anhedonia, Somatic and Interpersonal domains, yet only the threshold score of 16 out of 60 is used to “define” depressive risk. Methods: Threshold and domains were evaluated in sedentary control (n=2814), CFS (n=137) and GWI (n=190) subjects to determine their relative importance. Results: Confirmatory factor analysis verified the 4 factor model in CFS and controls but not GWI. Threshold scores ≥16 identified depression in 77.4% of GWI, 57.7% of CFS, and 19.2% of controls. Somatic domain scores (maximum score=21) were significantly higher in GWI (11.77±4.10, mean±SD) than CFS (9.90±3.94) and controls (3.67±3.50) (ANOVA, Tukey HSD<0.05). Somatic scores were driven by fatigue, cognitive and sleep disruption that are fundamental elements of CFS and GWI diagnostic criteria. Depressed and Anhedonia domain scores were twice as high in GWI and CFS as controls. Conclusions: The outsized impact of these Somatic items undermines the validity of CESD in screening for depression in CFS, GWI, other somatic, chronic medical and inflammatory disorders. Instead, we propose that the underutilized domain scores may have merit as independent variables to

deconvolute somatic and affective dysfunction when used as covariates in resting state MRI and other assays

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.22/KK9

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** DoD GWI grant #W81XWH-15-1-0340.

**Title:** Vagus nerve stimulation reverses the pyridostigmine bromide and permethrin-induced increase in astrocytes in the hippocampus in a model of Gulf War illness

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**Abstract:** Gulf war Illness (GWI) refers to a myriad of symptoms that are differentially observed in a large percentage of men and women who served in the Persian Gulf War. GWI symptoms include cognitive impairments (memory and concentration problems), headaches, migraines, widespread pain, fatigue, gastrointestinal and respiratory issues, as well as other unexplained abnormalities that do not fit into classical medical diagnostic criteria. Among the numerous potential etiological factors, it is possible that the exposure to the anti-nerve gas drug, pyridostigmine bromide (PB), and the insecticide permethrin (PER), may contribute to the origin of GWI in veterans that participated in the 1991 Persian Gulf War. Various studies utilizing mouse models have shown the interplay of these chemical agents in increasing neuroinflammation, which may underlie some of the symptomology of GWI. Astrocytes, a type of neuroglial cell, are key players in the neuroinflammatory response. Astrocyte meditate chemical exchange in synaptic transmission, and in pathological conditions, are involved in the secretion of neuroinflammatory cytokines and chemokines. Astrocytes can be identified by immunohistochemical staining with anti-glial fibrillary acidic protein (GFAP), which stains the intermediate filaments in the cytoplasm of the astrocytes. The size, shape and number of astrocytes can be indicative of their activation state and can provide information on neuroinflammation. Thus, the use of anti-GFAP allows for the quantitative and morphological analysis of GFAP-labeled astrocytes. Vagus nerve stimulation has been previously shown to be anti-inflammatory, and anti-neuroinflammatory. Thus, using chronically implanted vagus nerve

stimulators in a mouse model of Gulf War Illness, we tested the hypothesis that exposure to PB and PER would lead to lasting changes to GFAP-labeled astrocytes in the hippocampal dentate gyrus, and that this effect could be reversed by stimulation of the cervical vagus nerve. The results show that 9 months after exposure to the Gulf War agents PB and PER, there is an increased number of GFAP-labeled astrocytes in the hilus and molecular layer of the dentate gyrus. There were also trends towards increased astrocytes in Stratum Radiatum of CA1 and CA3. The results also show that chronic vagus nerve stimulation initiated at 8 months after exposure to Gulf War agents, reversed the increase in astrocyte number in the dentate gyrus. The results demonstrate that PB + PER can alter hippocampal astrocyte number, that can be reversed by vagus nerve stimulation.

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 759.23/KK10

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** two CDMRP awards (GW1300045 and GW150056)
VA Merit award (1I01CX000469)

**Title:** Oleoylethanolamide treatment reduces neurobehavioral deficits and the brain pathology in a mouse model of Gulf War illness

**Authors: *U. JOSHI**[1], J. EVANS, 34243[2], N. SALTIEL[2], H. LANGLOIS[2], S. OBERLIN[2], J. OJO[1], B. MOUZON[1], F. CRAWFORD[1], M. MULLAN[1], L. ABDULLAH[1]
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**Abstract:** There are nearly 250,000 veterans from the 1991 Gulf War who suffer from a multisymptom condition called Gulf War Illness (GWI) which to date remains untreatable. We performed a pilot study with samples from veterans with GWI and control to assess lipids associated with peroxisomal function then examined if targeting peroxisomal β-oxidation by oleoylethanolamide (OEA) restores these lipids and mitigates neuroinflammation and neurobehavioral deficits in a well-established mouse model of GWI. 9 weeks-old C57BL6 mice were co-administered 0.7 mg/kg of PB and 200 mg/kg of PER in a single intraperitoneal injection (i.p.) in dimethyl sulfoxide (DMSO) for 10 days daily to generate the mouse model. At 5-months post-exposure, OEA was administered at 10 mg/kg/day (based on 5 g daily food intake) in mouse chow for up to 6 months. We examined different neurobehavioral such as learning, spatial memory, anxiety and fatigue. Six months after OEA treatment, mice were

euthanized for lipidomic, biochemical and immunohistochemistry analyses. We were able to reverse chronic neurobehavioral and neuroinflammation that are key hallmarks of GWI pathology. This study shows that stimulating peroxisomal beta-oxidation with OEA corresponds with cognitive benefits and a reduction of fatigue and disinhibition like behavior in GWI mice. Biochemical and molecular analysis of brain tissue showed reduced astroglia and microglia staining, as well as decreases in NF-κB phosphorylation, chemokines and cytokines. We also observed accumulation of very long chain fatty acid (VLCFA) in the brains of GW agent exposed mice. In addition, we also provide pilot clinical studies showing alteration of lipids that are specifically metabolized in peroxisomes in veterans with GWI compared to healthy GW veterans, further supporting a translational value of targeting peroxisomes in GWI. We expect that OEA may be a potential therapy for treating the neurobehavioral symptoms and the underlying lipid dysfunction and neuroinflamamtion associated with GWI. In particular, OEA is available as a natural supplement for human consumption, making it highly appealing for future translational studies in humans.

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.24/KK11

**Topic:** B.06. Synaptic Transmission

**Support:** DOD Grant W81XWH-16-1-0586

**Title:** Septotemporal-specific effects of a Gulf War illness sarin surrogate, diisopropylfluorophosphate, on synaptic transmission in the mouse hippocampus

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**Abstract:** Diisopropylfluorophosphate (DFP) is a common surrogate for nerve agents used in rodent models of Gulf War Illness (GWI) and is known to alter hippocampal synaptic transmission. Although there has been increased appreciation for functional differences in the hippocampus between the dorsal (dH) and ventral (vH) sectors, there is a paucity of information characterizing the effects of DFP and GWI-relevant chemicals in the dH and vH. We explored the effects of acute DFP exposure on different neurophysiological measurements in mouse hippocampal slices using extracellular recordings from dH and vH slice preparations. Basal synaptic transmission was monitored by recording the population spike (PS) response in the CA1

stratum pyramidale. DFP was washed-in for 30 min while PS amplitude and PS paired-pulse ratio (PPR) were monitored. Following wash-in of 30 μM DFP, PS amplitude in the dH and vH was significantly decreased from baseline compared to control slices (-12% and -21%, respectively). Compared to slices treated with DFP alone, pretreatment with atropine (ATR) significantly enhanced PS amplitude in the dH (+9%) whereas PS inhibition was still observed in the vH (-7%). Pretreatment with mecamylamine (MEC) facilitated DFP-induced PS inhibition in both the dH (-32%) and the vH (-58%). Coapplication of ATR and MEC prevented DFP-mediated PS inhibition in the dH (0%) but unexpectedly, the antagonists had no effect on DFP-mediated PS inhibition in the vH (-16%). Pirenzepine (PZP) wash-in partially prevented PS inhibition in the dH and vH. PS PPR in dH and vH slices exposed to DFP exhibited significantly increased PPR (+15% and +36%, respectively). Interestingly, we observed persisting enhancement of PPR in the vH compared to dH with either ATR, MEC, or ATR+MEC antagonist pretreatment experiments. The DFP-mediated decrease in PS magnitude suggests an inhibitory effect on the hippocampal glutamatergic network in CA1, an effect mediated via a non-cholinergic mechanism in the vH. Partial blockade of PS inhibition by PZP as compared with ATR indicates muscarinic receptor subtype-specific effects of DFP may be present in the dH. In addition, enhanced PS PPR indicates that DFP exposure also alters the interneuron network activity in CA1, resulting in disinhibition of the pyramidal cell response. Furthermore, the facilitated PS PPR present in vH as compared to dH slices suggests a functionally distinct level of inhibition activity between the two sectors. Such differential functionality along the hippocampal septotemporal axis should be accounted for when interpreting neurophysiological and behavioral data obtained from studies employing DFP in GWI rodent models.

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**Poster**

**759. Gulf War Illness: Mechanisms, Causes, and Interventions**

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**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 759.25/KK12

**Topic:** B.10. Epilepsy

**Support:** Defense Threat Reduction Agency

**Title:** *In vivo* real-time measurements of brain acetylcholinesterase activity through a modified microdialysis procedure following nerve agent exposure in the guinea pig

**Authors: P. A. RIORDAN, Jr.**[1], C. E. KAROLENKO[1], D. L. SPRIGGS[1], *J. W. SKOVIRA[2]
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**Abstract:** Acetylcholinesterase (AChE) levels are a metric of particular interest following nerve agent exposure. Measurements of the enzyme are typically taken from blood or tissue samples collected at varying time points after nerve agent exposure or are measured post-mortem. These sampling paradigms require multiple groups of animals to be used for each time point and yield results that are limited in temporal resolution (minutes to hours between samples for a complete time course). Here we have developed a technique utilizing microdialysis to measure the activity of AChE in the brain continuously in real time. This method allows for a complete time course of measurements to be taken from each animal, which reduces animal use and variability. One week prior to the experiment guinea pigs were surgically prepared to record brain electrical activity and implanted with a guide cannula. On the day of the experiment a microdialysis probe with 8 mm of exposed membrane was inserted into a guide cannula to establish a sampling surface across a targeted brain region. Acetylthiocholine was then perfused through the probe, and the returning dialysate was mixed with Ellman's reagent before passing through a flow cell where measurements were taken using a spectrometer. The nerve agent GB (0.1 - 20.0 µg) was delivered through the microdialysis perfusate. AChE activity was continuously measured for 4 hr after nerve agent exposure. The results show that consistent measurements of brain AChE activity can be obtained using this technique.

**Disclosures: P.A. Riordan:** None. **C.E. Karolenko:** None. **D.L. Spriggs:** None. **J.W. Skovira:** None.

**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.01/LL1

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Ketamine induces adverse effects on the development of monoaminergic neurons in zebrafish

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**Abstract: Key words:** ketamine; zebrafish; developmental toxicity; serotonin; tyrosine hydroxylase
Ketamine, a phencyclidine derivative, is a non-competitive antagonist of the calcium-permeable N-methyl-d-aspartate (NMDA) receptor. A pediatric anesthetic, ketamine has been implicated in cardiotoxicity and neurotoxicity including modulation of monoaminergic systems in mammals and zebrafish. Here, we show ketamine's effects on the development of monoaminergic neurons in the zebrafish embryos. Using whole mount immunohistochemistry, we monitored the effects of ketamine on the brain serotonergic (5-HT) neurons and tyrosine hydroxylase-immunoreactive

(TH-IR) neurons. Exposure to ketamine began at 28 hours post-fertilization (hpf) embryos and static exposure continued for 20 h. Ketamine, at a dose that produces an internal embryo exposure level comparable to human anesthetic plasma concentrations, significantly reduced the areas occupied by 5-HT neurons in the brain of the 48 hpf embryos. In these embryos, TH-IR neurons in the brain and TH-IR cells in the trunk were also significantly reduced with ketamine treatment. These results indicate that longer exposure even with an anesthetic dose of ketamine can induce adverse effects on the development of both serotonergic and dopaminergic neurons.

**Disclosures: B. Robinson:** None. **Q. Gu:** None. **M. Dumas:** None. **J. Kanungo:** None.

**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.02/LL2

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NCTR E07285.01

**Title:** Early life anesthesia with ketamine, sevoflurane, or isoflurane can decrease motivation in the rhesus monkey as measured by performance on a progressive ratio responding task

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**Abstract:** A growing body of research suggests that early life exposure to prolonged anesthesia may have lasting negative consequences for neurodevelopment. For example, we have shown that exposure on post-natal day (PND) 5 or 6 to ketamine, sevoflurane, or isoflurane mixed with nitrous oxide can cause increased neuronal apoptosis and necrosis in the infant rhesus monkey. However, it is unclear if these neuronal changes result in clinically relevant behavioral changes. To determine if perinatal exposure to anesthesia can cause lasting changes to behavior, rhesus monkeys were treated with ketamine (24h), sevoflurane (2.5% 8h), or isoflurane (1% 8h) with nitrous oxide (70%) on PND 5 or 6 and later trained on the NCTR Operant Test Battery (OTB). The OTB is a translational cognitive test battery, designed to test children and nonhuman primates under nearly identical conditions. The OTB is composed of 5 core tasks, each requiring monkeys to press levers or press-plates in response to a variety of rules to earn food pellet rewards. Here, we report the effects of different anesthesia regimens on the performance of the progressive ratio task (PR), which is used to measure motivation. Animals treated with sevoflurane or a combination of isoflurane and nitrous oxide showed significantly reduced levels of responding on each biweekly block of 5 PR sessions for the first several years of life. Animals treated with ketamine have an apparent permanent reduction in responding, showing a reduced

number of lever presses even 10 years after the initial exposure. These data indicate that early life exposure to anesthesia can result in lasting motivational impairments in the rhesus monkey. Moreover, the fact that effects were seen with different anesthetic agents with different mechanisms of action indicate that these effects are not compound specific, and instead may generalize to the experience of anesthesia itself. Motivational deficits may be an area of clinical concern after early life exposure to general anesthesia.

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**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.03/LL3

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** a Grant-in-Aid from the Ministry of Health, Labor and Welfare, Japan, for Research on Intractable Diseases.

**Title:** Clioquinol enhances excitatory synaptic transmission in spinal ventral horn neurons by activating N-type voltage-gated channels

**Authors: N. IZUMI**[1,2], *W. TANIGUCHI[1], N. NISHIO[1], M. YAMANAKA[1], M. SONEKATSU[1], S. TSUTSUI[1], S. YOSHIDA[2], T. NAKATSUKA[3], H. YAMADA[1]
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**Abstract:** Subacute myelo-optico neuropathy (SMON) is the harmful effects of a medicine, Clinoquinol, which was used as antidiarrheal. SMON is an iatrogenic disease of the nervous system leading to a disabling paralysis, blindness. However, the cellular mechanism about Clioquinol-induced neurotoxicity in spinal ventral horn is not fully understood. We investigated the effect of Clioquinol on excitatory synaptic transmission in ventral horn of the rat spinal cord by using the whole-cell patch-clamp methods. The application of Clioquinol significantly increased the frequency of spontaneous excitatory postsynaptic currents (sEPSCs) in rat ventral horn neurons. In the presence of a $Na^+$ channel blocker, tetrodotoxin (TTX), the application of Clioquinol increased the frequency of miniature EPSCs (mEPSCs). And then, in the presence of an AMPA receptor blocker, 6-Cyano-7-nitroquinoxaline-2,3-dione (CNQX) the application of Clioquinol did not enhance sEPSCs. We next investigated the mechanism about Clioquinol-induced increase of sEPSC frequency. In general, it is known that the frequency of spontaneous synaptic events correlates with presynaptic $Ca^{2+}$ concentration. In $Ca^{2+}$-free ACSF, Clioquinol superfusion had little effect on sEPSC frequency. Finally we checked which calcium channel

was involved in Clioquinol-induced increase of sEPSC frequency. In the presence of ω-Conotoxin (ω-Ctx), a N-type voltage-gated calcium channels blocker, the frequency of sEPSCs was unaffected by Clioquinol treatment. These results indicate that Clioquinol enhances the spontaneous release of glutamate from the presynaptic terminals onto the ventral horn neurons through activating N-type VGCCs on the presynaptic terminals. This mechanism could lead Clioquinol-induced neurotoxicity in spinal ventral horn.

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**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.04/LL4

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** Kuwait University Grant RW01/14

**Title:** Intraventricular infusion of quinolinic acid in young rats dysregulates the expression of various signaling and structural proteins involved in learning and memory

**Authors: *A. RAHMAN**[1], M. S. RAO[2], K. M. KHAN[3]
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**Abstract:** Quinolinic acid (QA), a metabolite of the kynurenine pathway of tryptophan metabolism, is a known neurotoxicant and an NMDA receptor agonist. QA levels in the brain are increased in response to oxidative stress and inflammation. We have previously shown that intraventricular infusion of QA results in learning and memory deficits in young rats. We investigated the effects of QA infusion on the expression of various signaling molecules involved in learning and memory. These include NMDA receptor subtypes (NR1 and NR2A), molecules involved in synaptogenesis and synaptic stability (synaptophysin and PSD-95), serine (S)/threonine protein phosphatases (PP1 and PP2A), cytoskeletal protein tau, and signaling molecule CREB. QA (9 mM) was infused into the right lateral ventricle of 21-day old rats (n=5) for 7 days using mini osmotic pumps. Rats infused with the same volume of normal saline (n=5) served as vehicle control (VC). Rats were sacrificed at postnatal day (PND) 45 or PND 60, brains were dissected out and the expression of various proteins in the brain homogenate was determined by Western blot. QA-infusion did not affect the expression of NR1, CREB, or synaptophysin, either at PND45 or at PND60. Phosphorylation of NR1 (at $S^{897}$) and CREB (at $S^{133}$) were also not affected. The expression of NR2 was not affected at PND45, whereas at

PND60 QA decreased the expression of this subunit ($p<0.05$). Phosphorylation of NR2 (at $S^{1303}$) was not affected by QA. The expression of PSD-95 was decreased ($p<0.05$) by QA at PND45, but not at PND60. The expression of PP1 was not affected at PND45, whereas it was decreased ($p<0.05$) at PND60 in the QA-infused rats. PP2A expression was decreased ($p<0.05$) at both PND45 and PND60 by QA. The expression of total tau was not affected by QA-infusion at either age, whereas its phosphorylation at threonine 231 (AT180 site) was significantly increased at PND45 but not at PND60. These results suggest that QA-induced neurotoxicity involves dysregulation of NMDA receptor subunit composition, phosphorylation of proteins (like tau) at serine/threonine residues and synaptic stability. Further research is needed to elucidate the signaling pathway(s) affected by QA in order to understand the mechanism of QA-induced neurotoxicity.

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**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.05/LL5

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Connexin 43 mediated glutamate excitotoxicity in rat hippocampus upon exposure to chronic hypobaric hypoxia

**Authors: *A. DHEER**[1], V. JAIN[1], M. PANT[2], N. KUSHWAH[1], R. KUMAR[1], D. PRASAD[1], P. SETH[2], S. B. SINGH, 110054[3]
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**Abstract: Introduction:** Ascend to high altitude encounters a decrease in atmospheric pressure resulting in low $O_2$ availability to the tissues. Such condition is referred to as “Hypobaric Hypoxia” (HH). Brain is reported to be one of the first organs to be affected with oxygen deprivation. HH has severe effects on the central nervous system. Neuronal apoptosis, glutamate excitotoxicity, oxidative stress and cognitive decline have been associated with hypobaric hypoxia. The effect of HH on neuronal population in time dependent fashion has been previously reported but there have been only scarce reports on the associations of hypobaric hypoxic and glial cells. The extent of damage is a direct effect of the degree and duration of hypoxic exposure. Owing to the significance of glial cells in monitoring various vital brain functions the present study was carried out to understand the role of glial cells in HH condition. We studied morphological changes in glial cells (Microglia and astrocytes) and inflammatory markers in the CA1, CA3 and DG regions of the hippocampus in a time dependent manner. We are further

looking into the possible mechanism of glutamate excitotoxicity in HH by investigating the role of connexin43 which form hemichannels and gap junctions primarily in the astrocytes.
**Materials:** In vivo studies were performed on Healthy adult male Sprague dawley rats (200-220gms), exposed to hypobaric hypoxia in an animal decompression chamber with altitude: 25000ft, Temperature: 25°C, Humidity: 55%. Airflow was maintained, food water provided *ad libitum.*
**Results:**
Our study revealed that chronic hypobaric hypoxia (HH) exposure (7 and 14 days) led to activation of astrocytes and microglial cells in the rat hippocampus along with an increase in pro-inflammatory cytokine levels.
Further we found upregulated expression of connexin43 and reduced glial glutamate transporter (GLT-1/EAAT2) levels suggesting role of astrocytes in glutamate excitotoxcity upon hypobaric hypoxia exposure.
Further research needs to be carried out to understand the neuro-glial interactions under hypobaric hypoxia condition. A deeper understanding would provide better therapeutic targets to ameliorate the harmful effects of hypobaric hypoxia on brain functions like memory and cognition.
* DRDO headquarters life sciences,
1 Neurobiology division, DIPAS, DRDO, Delhi; 2 National Brain Research Center, Gurgaon, Manesar.
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**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.06/LL6

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

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**Title:** Arsenic exposure promotes the bioenergetic dysfunction in an Alzheimer's disease model

**Authors: *S. A. ESQUIVEL NIÑO**[1], A. MORALES-MARTÍNEZ[2], S. DIAZ-CINTRA[3], F. PEREZ[2], M. JIMÉNEZ-CAPDEVILLE[4], S. ZARAZÚA[1]
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**Abstract:** Worldwide, every year there is an increase in the number of people exposed to inorganic arsenic (iAs) via drinking water. Human populations present impaired cognitive function as a result of prenatal and childhood iAs exposure, while studies in animal models in similar conditions demonstrate neurobehavioral deficits accompanied by protein and enzyme alterations associated to Alzheimer´s disease (AD). In primary cultures of Tg2576 mouse brain, exposure to iAs promotes the release of Aβ and increases the activity of β-secretase. In order to determine whether iAs promotes the pathophysiological progress of AD, we used the 3xTgAD mouse model since it mimics the development of amyloid plaques, neurofibrillary tangles and behavioral dysfunction. Male and female 3xTgAD mice (25-30 g) were divided into 2 groups: 1) control without arsenic; and 2) exposed to 3 ppm sodium arsenite in drinking water. Animals received the treatment from gestation until 6 months. We investigated the locomotor behavior and Morris water maze (MWM). Adenosine triphosphate (ATP), reactive oxygen species (ROS), lipid peroxidation (LPx) production and secretase-αλπηα and beta were evaluated by fluorescence. Respiration rates of mitochondria were measured from isolated hippocampus, cortex and antioxidant components detected by inmunoblots. Immunohistochemical studies were performed to reveal AD markers and N-methyl-D-aspartate (NR2B subunit). As-3xTgAD did not show alterations in their locomotion activity; longer escape latencies and higher number of failures to reach the platform were found in the iAs group than in the control group in the MWM. The bioenergetic profile revealed decreased ATP levels accompanied by the decline of complex I, and an oxidant state in hippocampus compared to control. On the other hand, in cortex our results showed no changes in oxidant stress and complex I, however, the antioxidant system was increased. Secretase-βeta enzymatic activity was significantly increased and secretase-alpha was decreased; immunopositivity to tau/Aβ in sections of hippocampus and frontal cortex resulted in significantly immunoreactivity; NR2B showed changes in immunopositivity in the iAs exposed group as compared to the control group. These results are confirm that changes in bioenergetics induced by environmental exposure are linked to neurodegeneration.

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**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.07/LL7

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

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**Title:** Effects of early life manganese exposure on synaptic markers in primary motor cortex

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**Abstract:** Early life manganese exposure is associated with motor impairments in children, and a better understanding of how manganese affects the development of motor circuits could inform strategies to mitigate or prevent effects of early life manganese exposure. Chronic, pre-weaning manganese exposure in rats leads to fine motor dysfunction and disrupts catecholaminergic signaling in striatum and prefrontal cortex, brain regions important for control of skilled motor function. The primary motor cortex (M1) also plays a role in motor skill learning and performance; however, it is not known how M1 circuits are affected by early life manganese exposure. Our objective was to determine how synapses in M1 are affected by early life manganese exposure. We carried out quantitative immunohistochemistry for excitatory and catecholaminergic synaptic markers in M1 of adolescent and adult mice that had been orally exposed to manganese daily prior to weaning. We found that catecholaminergic innervation of M1, identified by tyrosine hydroxylase immunoreactivity, is not significantly different between manganese-exposed and control mice. Our results also suggest that the density of vesicular glutamate transporter (VGluT) 2, a marker for thalamocortical excitatory boutons, is altered in M1 following early life manganese exposure. Taken together, these findings suggest that early life manganese exposure may disrupt the development of thalamocortical excitatory synapses in M1. Further work will determine how other synapse populations in M1 are affected by early life manganese exposure, and how these synaptic alterations contribute to impairments in motor skill learning and performance.

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**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.08/LL8

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Training Grant T32 ES007051

**Title:** Developmental deltamethrin exposure alters dopaminergic activity and long-term potentiation in Sprague-Dawley rats

**Authors: *E. M. PITZER**[1,2], M. T. WILLAIMS[1,2], C. V. VORHEES[1,2]
[1]Univ. of Cincinnati, Cincinnati, OH; [2]Neurol., Cincinnati Children's Res. Fndn., Cincinnati, OH

**Abstract:** Pyrethroids are synthetic insecticides that act through voltage gated sodium channels to prolong channel opening leading to depolarization. Pyrethroids are used in many settings where children are present. Epidemiological studies find that developmental exposure to pyrethroids is associated with neurological and developmental abnormalities. The effects of Type II pyrethroids, such as deltamethrin (DLM), on development have received relatively little attention. We previously showed that Sprague-Dawley rats exposed to DLM from P3-20, had deficits in egocentric and allocentric learning and memory. Rats treated with DLM had no differences compared with controls during acquisition of the Morris water maze (MWM), but rather displayed deficits in reversal learning in this hippocampal dependent task. In addition, the Cincinnati water maze, a striatally dependent task, revealed that males, but not females, exhibited increased latencies and errors. In our newest experiment, we exposed Sprague-Dawley rats to 0 or 1.0 mg/kg/day DLM by gavage. Long term-potentiation (LTP), a cellular correlate of spatial learning and memory, was assessed at P25-35 in brain slices in CA1. Both males and females treated with DLM had increased LTP compared with controls ($P<0.0001$). Amphetamine-stimulated dopamine release was assessed via microdialysis. DLM-treated males exhibit a trend ($P<0.1$) towards decreased extracellular dopamine release. Microdialysis testing is continuing. Real-time reverse transcription polymerase chain reaction (qPCR) revealed that DLM-treated males had decreased D1 dopamine receptor (*Drd1*) mRNA expression in the neostriatum ($P<0.05$) compared with controls. However, Western blots revealed that DLM-treated males did not differ in DRD1 or DRD2 protein expression in the nucleus accumbens, neostriatum, or hippocampus. The NMDA receptor subunit NR1 was also not affected by DLM in the hippocampus. The data indicate that rats developmentally exposed to DLM display increased CA1 LTP, decreased extracellular dopamine release, and downregulation of *Drd1* mRNA in the neostriatum that is not accompanied by similar changes in DRD1 protein. This study is ongoing and is examining the effects of developmental DLM exposure on protein expression of the dopamine transporter (DAT), vesicular monoamine transporter (VMAT2), tyrosine hydroxylase (TH), and dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32). (Supported by NIH training grant T32 ES007051).

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**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.09/LL9

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH grant R01 ES024064

**Title:** The mRNAs involved in neuronal protection were perturbed in primary spinal cord astrocytes during methylmercury exposure

**Authors: *D. WIWATRATANA**[1], W. D. ATCHISON[2]
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**Abstract:** The neurotoxicant methylmercury (MeHg) induces motor neuron (MN) cell death by mechanisms involving increased intracellular calcium, oxidative stress and excitotoxicity. The inability of spinal cord astrocytes (SCA) to protect MN could contribute to MN excitotoxicity with MeHg. Astrocytes generally provide tropic factors and antioxidant glutathione (GSH) for neuronal survival. Vascular endothelial growth factor (Vegf) plays a role in protection against MN degeneration and reduction of the calcium influx. We hypothesized that MeHg induces MN degeneration by perturbing *Vegf* expression and GSH synthesis in SCA which contributes to MN susceptibility to MeHg. After exposing SCAs to 0.5µM MeHg, mRNA expression of *Vegf* and glutamate-cysteine ligase catalytic subunit (*Gclc*), a rate-limiting enzyme for GSH synthesis, were determined as a function of time of MeHg exposure. MeHg induced fluctuations of *Vegf* and *Gclc* expression in SCA. The fluctuations of *Vegf* expression exhibited peaks of 2.5-fold increase ($p<0.05$) at 9h and 21h exposure. During the early phase of MeHg exposure, from 30min to 12h, *Gclc* levels gradually increased and were significantly higher than control level at 6h (1.51-fold), 9h (2.11- fold) and 12h (1.52 fold). At 15h, the *Gclc* level returned to basal control level. It later increased significantly at 18h (1.3-fold) and 21h (1.4-fold) before returning to basal level at 24h. The fluctuations of *Gclc* expression appeared to be lower in the second phase (1.4-fold at peak) than in the first phase (2.1-fold at peak). This suggests that the longer the MeHg exposure, the lower the GSH synthesis in SCA. MeHg-induced excitotoxicity could also affect the cystine/glutamate transporter, encoded by solute carrier7 member 11; *Slc7a11* gene. The time course of MeHg exposure in SCA showed a pronounced increase of *Slc7a11* level following 1h of exposure (8.6-fold, $p<0.005$). Prolonged MeHg exposure appeared to induce *Slc7a11* up-regulation but the effect was not statistically significant. Pretreatment of SCA with 10mM N-acetyl cysteine (NAC), a GSH precursor, 2h prior to exposure to 5µM MeHg maintained cell viability at the same level as vehicle controls for 24h. At 28h, SCA viability was reduced with NAC pretreatment prior to MeHg exposure but remained significantly higher than MeHg treatment alone. This study suggests that MeHg perturbed GSH levels in SCA and contributed to an increase of GSH substrate precursor transporter. Consequently, the elevation of $[Glu]_{ex}$ occurs due to the exchange of intracellular glutamate for extracellular cystine. This research is supported by NIH grant R01 ES024064.

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**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.10/LL10

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Testing the ability of hemostatic products and reactive skin decontamination lotion to protect against the chemical warfare agent VX in a hemorrhagic wound

**Authors: *E. D. CLARKSON, III**[1], R. P. CHILCOTT[2], C. A. HALL[2], H. L. LYDON[2], C. H. DALTON[2], R. F. RAILER[1], R. S. STEVENSON[1], K. H. SMITH[1], P. CHEN[1], S. M. SCHULZ[1], J. E. MORGAN[1]
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**Abstract:** Hemostatic agents are used to prevent soldiers from bleeding to death in the field. Reactive Skin Decontamination Lotion (RSDL) has been shown to be very effective at blocking the toxic effects of chemical warfare agents. This study addresses their effects on a bleeding wound contaminated with the highly toxic organophosphate chemical warfare agent VX. *In vitro* studies showed that a granular hemostatic agent, WoundStat™, was the most promising candidate for blocking the absorption of VX, and it was selected for *in vivo* testing. We created a non-bleeding wound in the axillary area of an anesthetized pig, applied neat VX into the wound and determined the 6-hour MLD to be 28.6 μg/kg, at which point all surviving animals were euthanized. We expanded on this work by cutting the vein/artery bundle, applying 5xMLD (143 μg/kg) of VX into the wound and when the pocket was half-filled with blood, pouring WoundStat™ into the pocket. Of the animals tested in this manner, 3 out of 6 died prior to the 6-hour endpoint. Because the granular product causes clots to form distant from the wound, it is no longer used in the field and has been replaced by a hemostatic impregnated gauze, Combat Gauze™. In the same 5xMLD bleeding wound model 5 out of 6 animals treated with the hemostatic gauze died prior to the 6-hour endpoint. We then examined adding RSDL to the treatment. As before, the bundle was cut, 5xMLD of VX was applied, an RSDL pad was inserted into the wound and rubbed three times over the application site and Combat Gauze™ was inserted behind the RSDL pad, leaving the RSDL pad in contact with the VX application site. Of the animals tested in this manner 2 out of 6 died prior to the 6-hour endpoint. Thus, although both WoundStat™ and Combat Gauze™ alone and Combat Gauze™ in conjunction with RSDL provide benefit, all failed to completely protect against a 5xMLD challenge of VX in a bleeding wound.
The views expressed in this abstract are those of the author(s) and do not reflect the official policy of the Department of Army, Department of Defense, or the U.S. Government. The experimental protocol was approved by the Animal Care and Use Committee at the United States

Army Medical Research Institute of Chemical Defense, and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966 (P.L. 89-544), as amended.

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**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.11/LL11

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant GM112696

**Title:** Excitatory and inhibitory imbalance may contribute to the propofol-induced developmental neurotoxicity through NPAS4 signaling

**Authors: *T. ARZUA**[1], S. LOGAN[1], C. JIANG[3], Y. YAN[1], X. LIU[2], Q.-S. LIU[2], X. BAI[1]
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**Abstract:** Studies in animal models show evidence of anesthetic-induced developmental neurotoxicity, which is characterized by memory and learning dysfunction following early exposure to anesthetics. The mechanisms behind this neurotoxicity, however, remain largely unknown. Information transfer in the brain relies on a balance between excitatory and inhibitory (E/I) networks. This balance involves the maintenance of appropriate ratios of E/I synaptic inputs, and imbalances are associated with brain disorders, e.g. autism. Thus, we hypothesize that neonatal propofol exposure induces long-term E/I imbalance in mice, and this imbalance might be related to anesthetic-induced cognitive deficits. Propofol is one of the most commonly used intravenous anesthetic agents in pediatric populations. Postnatal 7-day old (P7) mice intraperitoneally received either a subanesthetic dose of 50mg/kg of propofol or an intralipid vehicle control for 3 to 6h. Morris water maze (MWM) was then performed in P60 mice. Whole cell patch-clamping was conducted on the hippocampal slices of P60 mice. The expression of 35,923 mRNAs was analyzed through a microarray assay, and the dysregulated genes were then analyzed by an Ingenuity Pathway Analysis to identify possible genes involved in anesthetic-induced E/I balance. The results showed that propofol-exposed mice displayed impaired memory function in MWM when compared with the controls. Electrophysiological assays showed that propofol exposure resulted in E/I imbalance, as evidenced by a decrease in excitatory synaptic activity and an increase in inhibitory synaptic activity. Bioinformatics analysis of propofol-

induced dysregulated mRNAs indicates that downregulated NPAS4, a gene known to be a link between neuronal activity and memory formation, might play important roles in the E/I imbalance. For the first time, E/I imbalance was shown to be present in propofol-treated mice. Future studies will look into the functional link between NPAS4, E/I imbalance, and cognitive deficits following anesthesia. Through a better understanding of these mechanisms, more rational protective therapies can be designed for pediatric anesthetic use.

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**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.12/LL12

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Locomotor alterations and increase in brain kynurenic acid levels after intoxication with lead in mice

**Authors: *D. RAMÍREZ ORTEGA**, D. F. GONZALEZ ESQUIVEL, B. PINEDA, A. DIAZ RUIZ, C. RIOS, V. PEREZ DE LA CRUZ
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**Abstract:** Lead (Pb) is a heavy metal which is a health risk due to its wide use in the industry and the facility of absorption by living organisms. Pb has neurologic and neurobehavioural effects in people exposed to this metal. The main toxicity mechanisms involve calcium action imitation and oxidative stress generation, triggering an unbalance in some metabolic pathways. In this context, kynurenine pathway (KP) -which is responsible of tryptophan catabolism toward $NAD^+$ production- can be affected for the factors that unleash the intoxication by Pb. KP intermediate metabolites have redox and neuromodulator properties. Specifically, kynurenic acid (KYNA) has been characterized as an antagonist of NMDA and alpha-7 nicotinic receptors and therefore modulates cognitive processes. The aim of this work was to evaluate the effect of lead intoxication on brain KYNA production and locomotion in mice. Mice were intoxicated with Pb (500 ppm) through drinking water during 20 days. After this time period, the locomotor activity was evaluated in open field. Additionally, brains regions were obtained to quantify Pb levels, reactive oxidative species (ROS), lipoperoxidation (LP) as well as KYNA levels and kynurenine aminotransferase-II (KAT II, main enzyme to KYNA production) activity. Lead was able to settle in brain regions (hippocampus>cortex>cerebellum>striatum) which was associated with increase in ROS production and LP in these regions. Lead also increased KYNA levels in brain regions (striatum> cortex> hippocampus>cerebellum). Nevertheless, KAT-II activity was not affected by the presence of Pb. Intoxicated mice with Pb showed less distance travelled (30%) in

open field compared with control group. These results suggest that Pb poisoning modify redox environmental and increase KYNA levels in an independent way to KAT-II activity, which is also associated with reduced activity.

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**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.13/LL13

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** Baudrand Research Foundation

**Title:** IVIG delays onset of mouse Gerstmann-Sträussler-Scheinker disease

**Authors: *Y. DU**[1], H. GU[2], J. A. MASTRIANNI[3], R. C. DODEL[4], M. R. FARLOW[1]
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**Abstract:** Our previous studies showed that intravenous immunoglobulin (IVIG) contained anti-Aβ autoantibodies that might be able to treat Alzheimer's disease (AD). Recently, we identified and characterized naturally occurring autoantibodies against PrP from IVIG. Although autoantibodies in IVIG blocked PrP fibril formation and PrP neurotoxicity in vitro, it remained unknown whether IVIG could reduce amyloid plaque pathology in vivo and be used to effectively treat animals with prion diseases. In this study, we used Gerstmann-Sträussler-Scheinker (GSS)-Tg (PrP-A116V) transgenic mice to test IVIG efficacy since amyloid plaque formation played an important role in GSS pathogenesis. Here we provided strong evidence to demonstrate that IVIG could significantly delay disease onset, elongate survival and improved clinical phenotype in Tg (PrP-A116V) mice. Additionally, in treated animals, IVIG could markedly inhibit PrP amyloid plaque formation and attenuate neuronal apoptosis at 120 d of mouse age. Our results indicated that IVIG may be a potential effective therapeutic treatment for GSS and other Prion diseases.

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**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.14/LL14

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NSF GRFP DGE-1247271
NSF CAREER 1150125
NIH R01 NS092754
NY State C32245GG

**Title:** Characterization of a hypothermic coating to target neuroinflammation resulting from intracortical microelectrode implantation

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**Abstract:** Brain-machine interfaces are impactful instruments that enable patients with paralysis to regain basic lost functions. Unfortunately, when intracortical microelectrodes that signal to local neurons are implanted, this results in neuroinflammation, causing electrode recording ability to diminish over time. As systemic hypothermia has resulted in neuroprotection in cases of traumatic brain and spinal cord injury in the clinic, we would like to apply mild hypothermia to electrode implantation. **We are fabricating an electrode coating that produces a mild, sustained cooling to dampen neuroinflammation.** This coating avoids the risks of systemic hypothermia by localizing the hypothermia proximal to the electrode. We will encapsulate potassium chloride nanocrystals (nanoKCl) using a temperature-sensitive polymer [poly(acrylamide-co-acrylonitrile)] on the surface of electrodes. The nanoKCl, which is an endothermic salt, is slowly released and lowers the local temperature no more than 2°C. The nanoKCl has been characterized by scanning electron microscopy, averaging 177 ± 21 nm per side length of each cube, and x-ray diffraction, confirming the identity of the salt. The identity of the polymer is confirmed by infrared spectroscopy, and the temperature sensitivity is confirmed by measuring the transmittance of polymer suspension using UV-visible spectroscopy at 670 nm. A toxicity assay for nanoKCl has been conducted to assess biocompatibility *in vitro* using P2 rat mixed cortical cultures. At DIV 14, KCl (10 µM-100 mM) was administered to the media (no KCl = control). The supernatant was collected and a lactate dehydrogenase cell death assay was conducted 24 hours post-exposure. KCl was toxic at 100 mM and thus will be incorporated into the coating at levels below 10 mM. Following toxicity and material characterization, the efficacy of the coating will be assessed using an *in vivo* rat electrode implantation model (uncoated electrode=control). Electrodes will be implanted within the motor cortex of 8-week old Sprague

Dawley rats (male and female) for 8 weeks to study whether neurodegeneration can be mitigated. Ultimately, this study presents a novel strategy to produce a local cooling effect to protect cortical tissue *in vivo*.

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**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.15/MM1

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** Chemical Management Plan, Government of Canada, Canada

**Title:** *In vitro* screening for potential developmental neurotoxicity by quantification of developmentally-regulated gene transcripts conserved across mammalian brain development

**Authors: *B. K. PADHI**, M. SINGH, G. PELLETIER
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**Abstract:** The developing brain is highly vulnerable to injury from exposure to environmental chemicals. However, due the expensive and time-consuming nature of *in vivo* animal testing, developmental neurotoxicity data is available only for a fraction (<0.1%) of marketed chemicals. Thus, there is an obvious need for cheaper and faster alternative methods to identify potential developmental neurotoxicants. Gene expression markers are increasingly recognised as suitable toxicity endpoints. This study aims to determine if the expression of key genes involved in neurodevelopmental processes in rat primary cerebellar granule cells (CGCs) grown *in vitro* can be used for the screening of potential developmental neurotoxicity hazards. A panel of genes involved in neuronal cell differentiation and synapse formation were selected for expression analyses by reverse transcription real-time quantitative PCR. The gene primers were designed based on comparative gene sequence analyses in rat, mouse and human, prioritizing orthologous sequence regions showing conserved expression across species. Alternative splice variants of these genes were taken into consideration by measuring the expression of individual splice variants. The culture of primary CGCs isolated from 8 day-old rat cerebellum was optimized. Neuronal differentiation appeared on the fourth day *in vitro* (DIV4), while synapse network formation was observed by DIV8, mirroring the developmentally-regulated expression patterns observed in developing rat brain *in vivo.* The CGCs' response to the first proven neurotoxicant administered (Chlorpyrifos/Chlorpyrifos oxon) was evaluated at or below concentrations inducing cellular toxicity (as assessed by conventional cell integrity assays). Quantitative gene expression analyses revealed perturbation of key genes involved in neuronal differentiation,

notably for neurofilament genes (*Nfl* and *Nfh*), and synaptic components (*Syp* and *Syn1*) at sub-lethal pesticide concentrations. These results suggest that perturbation of gene expression in primary CGCs *in vitro* can be a good indicator of potential developmental neurotoxicity. Other proven neurotoxic chemicals acting through different molecular mechanisms and non-neurotoxic controls will be used to further assess the usefulness of this approach for the prediction of neurotoxicity hazard. In conjunction with other *in vitro* bioassays, this proposed approach may prove useful to screen a larger number of untested chemicals for potential developmental neurotoxicity and to prioritize the ones requiring further *in vivo* testing.

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**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.16/MM2

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** PAPIIT, UNAM, IN219617

**Title:** Oxidative effect of L-Dopa in nuclei with innervation of the substantia nigra in intact rats

**Authors: *A. MARTÍNEZ ARZATE**[1], M. AVILA-COSTA[4], C. CALDERON[2], M. IBARRA[3], J. ESPINOZA[3], V. ANAYA-MARTINEZ[5]
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**Abstract:** Oral administration of L-Dopa, usually in combination with a peripheral inhibitor of dopa decarboxylase, is the drug for excellence in the treatment of Parkinson's disease (PD) and the clinical improvement is notorious, however, the initial effect it produces sooner or later it begins to disappear and the symptoms of the disease return, progressively; they even get worse with the appearance of side effects. This leads to opposing evidence that it is toxic and, on the other hand, that it has neuroprotective effects. Given the spectrum of such evidences, our aim was to investigate if the oral administration on L-Dopa in clinical doses and healthy rats is capable of inducing the formation of reactive oxygen species (ROS) and thus initiate lipid peroxidation, we use brain areas that receive dopaminergic innervation; we evaluated in dopaminergic neurons of the substantia nigra pars comparta (SNpc), in neurons of hippocampus, globus pallidus, striatum and cortex, the nuclei most labile to oxidative stress, specifically to lipid peroxidation. In this study 21 male rats of the *Wistar* strain were used, they were divided into two groups: control group and treatment group. The last group was given an oral dose daily

of L-Dopa (10 mg/kg 1mg/kg of carbidopa) for three months. After three months of treatment, both groups were sacrificed by intracardiac perfusion, the tissue was fixed with paraformaldehyde and with formalin, for the different histological techniques. The tissue fixed with paraformaldehyde was used for immunohistochemistry with tetramethylbenzidine (TMB) which allows revealing sites of lipid peroxidation. The tissue that was fixed with formaldehyde was used for histology with hematoxylin and eosin to mark neuronal damage; this tissue was also used for immunofluorescence (IF) with caspase-3 activated to reveal immune positive cells to this protein. Finally, a count of neurons marked with TMB and morphologically damaged neurons was performed; likewise, micrographs of the processed tissue were obtained with all the techniques used. The data show that three months after administering L-Dopa to rats, oxidative damage was observed in most of the nuclei studied, lipid peroxidation mainly in substantia nigra and globus pallidus, as well as the expression of caspase-3 activated in all nuclei. This allows us to affirm that in intact rats the L-Dopa, in clinical doses, produces damage to the neurons of the nuclei involved, in the EP, by oxidative processes (lipid peroxidation) that can end in neuronal death, specifically inducing apoptosis.

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**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.17/MM3

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant P20MD006988

**Title:** Role of PI3K/mTORC2/AKT pathway on docosahexanoic acid (DHA) protection against lipotoxicity in Schwann cells

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**Abstract:** Docosahexaenoic acid (DHA) exhibits neuroprotective properties and has been shown to preserve nerve cells following trauma and ischemic injury. In this study, we investigate mechanisms by which DHA protects primary Schwann cells (pSC) undergoing palmitic acid (PA-induced lipotoxicity, PA-LTx). Primary Schwann cells (E18) were cultured with high level of palmitic acid (PA) (PA: BSA, 300 µM: 150 µM) for 24 to 48 hrs, then cells viability and apoptosis were measured by crystal violet and Hoechst staining. Cellular Protein expressions were measured by Western blots. Our results showed that palmitic acid decreased cell viability and induced chromatin condensation. Palmitic acid presence also inhibited AKT phosphorylation

in pSC cultures in a time-dependent manner. In order to address the potential neuroprotective properties of DHA, it was added to the pSC undergoing PA-LTx. We found that co-treatment with DHA inhibited loss of cell viability and apoptosis caused by PA overload. This treatment with DHA (50 μM) inhibited chromatin condensation and stimulated AKT phosphorylation in these cells. This protective effect of DHA was observed if added within six hours after PA exposure. Additionally, the DHA protective effect was diminished when these pSC cultures were treated with PI3K inhibitors LY294002 and BMK120. When further exploring mTOR pathways, it was Torin 1 (mTORC2 inhibitor) but not Rapamycin (mTORC1 inhibitor) that blocked the protective effects of DHA. In conclusion, DHA protects primary Schwann cells from PA-LTx through a mechanism that involves the PI3K/mTORC2/AKT kinase pathway.

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**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.18/MM4

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant NS091546

**Title:** Evidence for glutamate toxicity at the *Drosophila* neuromuscular junction

**Authors: *C. CHIEN**[1,2], P. GOEL[1,3], C. HAN[4], D. K. DICKMAN[1]
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**Abstract:** Glutamate is the major excitatory neurotransmitter in mammalian central nervous system and can lead to toxicity when ambient levels are increased during conditions of high synaptic activity and neuronal injury, stress, and disease. Indeed, excess glutamate can cause cellular dysfunction through excitotoxicity, which can ultimately drive neurodegeneration. Hence, robust and adaptive mechanisms in the central nervous system exist to maintain stable glutamate concentrations. However, less is known about glutamate toxicity in the periphery, a system with many experimental advantages but that has not been extensively studied because acetylcholine is the neurotransmitter in most model systems. The *Drosophila* neuromuscular junction (NMJ) is glutamatergic, and therefore provides a unique system to study glutamate toxicity in a tractable and defined nervous system. Excess synaptic glutamate release and glutamate imbalance can be induced through neuronal overexpression of the vesicular glutamate transporter (vGlut-OE) in *Drosophila*. vGlut-OE causes toxicity and neurodegeneration in the fly central nervous system, and glutamate imbalance at the NMJ. However, glutamate toxicity at the NMJ has not been reported. Here we characterize the three principle cells of the NMJ - motor

neurons, muscle, and peripheral glia - to determine if excess glutamate induces toxicity. We find that high levels of synaptic glutamate release leads to apparent toxicity on neurons, and may also negatively impact glia. Detailed analysis of peripheral glia will be presented to determine how glia respond to excess glutamate and to identify whether adaptive mechanisms are induced. Together, this establishes a tractable model to elucidate the pathological mechanisms of glutamate toxicity and determine adaptive responses in a well-defined nervous system.

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**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.19/MM5

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** Conacyt-Grant CB-2015-255087
Conacyt Fellowship 423462

**Title:** Translational control by silica nanoparticles exposure in glial cells

**Authors: *A. G. RODRÍGUEZ**, A. DE VIZCAYA-RUIZ, E. LÓPEZ-BAYGHEN, A. ORTEGA
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**Abstract:** Bergmann glia cells (BGC), a type of radial glia, is important in brain development and in the prevention of excitotoxic insults. Since neurons are highly vulnerable to oxidative stress, neuroglia as the first physiological barrier represents a target of interest to the effects of xenobiotics in long and short term. Silica nanoparticles ($SiO_2$ NP) considered to be non-toxic, cheap and easy to manufacture, have been quite attractive for different applications including electronics, food and medicine. Due to their small size, these particles can enter the central nervous system (CNS) causing an oxidizing microenvironment, an event associated with neurodegeneration pathologies. In current molecular neurotoxicology, the effects on translational control as an event prior to physiological deterioration and cell death are poorly studied. The aim of this work was to evaluate the effect of $SiO_2$ NP in the regulation of elongation phase of the translation process using BGC as *in vitro* cell system. To this end, a treatment scheme was settled to evaluate the cell viability at different concentrations of $SiO_2$ NP, once determined a harmlessness concentration we evaluated the phosphorylation levels of some factors of the translational machinery such as eEF2, eEF2K and eIF2α after treatment with 4.8 μg / mL of $SiO_2$ NPs at short times, in parallel we evaluated *de novo* protein synthesis by [$^{35}$S]-Methionine labeling. We were able to find that $SiO_2$ NP do not affect significantly cell viability at low concentrations at the times analyzed (6 and 12 h). Tracing the *de novo* synthesized proteins with

[$^{35}$S]-Methionine, we observed an increase at 15 min, restoring the baseline protein synthesis level after 30 min. This kinetic behavior is indicative of a biphasic and transient change, in agreement with the eEF2 phosphorylation level, which is downregulated at 15 min and with the phosphorylation pattern of its kinase eEF2K which increases at 10 and 15 min of treatment. These results suggest that nanoparticles, probably through a modification of the cellular redox status, modifies the protein repertoire in glia cells.
**Keywords:** Bergmann's glia, translational control, eEF2, eEF2K, eIF2α, $SiO_2$ NPs.

**Disclosures: A.G. Rodríguez:** None. **A. De Vizcaya-Ruiz:** None. **E. López-Bayghen:** None. **A. Ortega:** None.

**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.20/MM6

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** Science and Technology Department of Sichuan Province (Grant No. 2017HH0059)
Dr. London was supported by endowments from theThomas P. and Katherine K. Pike Chair in Addiction Studies and the Marjorie M. Greene Trust

**Title:** Gray-matter volume in chronic methamphetamine users: Changes over the course of abstinence

**Authors: *L. NIE**[1,2], D. GHAHREMANI[3], J. LI[2], E. D. LONDON[3]
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**Abstract:** Background: Studies of gray-matter differences between methamphetamine (MA) users and healthy controls have provided conflicting reports of greater or smaller volume and thickness. The common use of relatively small sample sizes suggests the possibility of underpowered results. Methods: Here gray-matter volumes of subcortical structures and cortical thickness were compared between a relatively large sample size of chronic MA users (n = 100; 51 male/49 female) and healthy controls (HC) (n = 86; 52 male/41 female), using Freesurfer with data from T1-weighted structural MRI scans. The effects of age, gender and years of education were controlled using a GLM ANCOVA model. Results: Of 16 subcortical structures tested, the bilateral thalamus proper, hippocampus, amygdala, ventral diencephalon (unsegmented subcortical nuclei), left caudate and right putamen showed greater gray matter volume in MA users versus HC (Ps<0.05, uncorrected). Findings in the bilateral amygdala and the ventral di-

encephalon retained statistical significance after Bonferroni correction (Ps*16<0.05). Evaluation of whole brain parcellations indicated areas within bilateral frontal cortex showed greater thickness (Ps<0.05 corrected by Monte Carlo Null-Z Simulation). Further, correlation analysis showed a negative correlation of right hippocampal volume with the duration of abstinence (P=0.008). No regions showed less thickness/volume in MA users than in HC. Discussion: Although several studies have reported less grey matter thickness and volume in MA users, our relatively large-sample study systematically found more. Chronic MA use was associated with greater frontal and subcortical gray matter thickness and volume, respectively. Less volume in the right hippocampus with greater abstinence duration suggests post-abstinence adaptation associated with recovery. Further studies with even larger samples are needed to extend these results.

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**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.21/MM7

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** CONACYT grant #241911 to FPS

**Title:** Oleic acid induces neuroprotection by the BDNF TrkB signaling pathway in an excitotoxic damage model

**Authors: *J. JIMÉNEZ-GÓMEZ**[1], P. E. MARTÍNEZ-GOPAR[2], C. RIOS[3], F. PÉREZ[3], A. MORALES[4]
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**Abstract:** Oleic acid (OA), a monounsaturated fatty acid, has been mainly studied by its antioxidant properties. Besides, OA is an endogenous agonist of the three isoforms of the peroxisome proliferator-activated receptor (PPARs) and it is known that PPARγ activation leads to increased BDNF expression and this in turn binds to its TrkB receptor, leading to different signaling pathways. Also, it has been shown that BDNF prevents neuronal death in the excitotoxic Huntington´s disease model induced by Quinolinic Acid (QUIN), where OA restores GABA levels in striatum, diminishing the motor disorder. Until now the exact pathway that OA follows to produce neuroprotective effect is unknown. Therefore, the main objective in this study was to assess the BDNF-TrkB pathway after OA administration in the excitotoxic model induced by QUIN. For this purpose, C57BL/6 male mice (25-30 g) were orally administered with vehicle

(CMC 0.5%) or OA (60 mg/Kg) during 3 consecutive days. Subsequently, saline solution 0.9% or QUIN (30 nmol/µL) were instrastriatally administered. Two and 24 h after QUIN instrastrial administration, the cortical and striatal expression of BDNF, GAD65, TrkB and p-TrkB were analyzed. Additionally, motor coordination by rotarod and open field test were performed. Our results showed in OA treated groups an increasing in BDNF expression in striatum 2 h after QUIN lesion. QUIN groups showed diminished motor coordination. On the other hand motor activity increases with QUIN lesion but OA decreases the movements, thus OA group could confer a partial protective effect for these tests. OA influences motor coordination and motor activity in QUIN excitotoxic model. These changes could be mediated by BDNF increase in striatal neurons followed by GABA increase. This data suggests OA induced BDNF-TrkB pathway in order to restore GABA levels in QUIN damaged striatum, possibly through GAD65 transcription.

**Disclosures: J. Jiménez-Gómez:** None. **P.E. Martínez-Gopar:** None. **C. Rios:** None. **F. Pérez:** None. **A. Morales:** None.

**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.22/MM8

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** RIP-1 inhibitor protects hippocampal neurons from excitotoxic cell death in lithium-pilocarpine-induced status epilepticus

**Authors: J.-C. H. HSIEH**[1,2], *D. G. FUJIKAWA[4,3]
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**Abstract:** Necroptotic pathway has been described in cell culture studies of non-neuronal cells after inhibition of the caspase-dependent, apoptotic pathway. It is unclear if the necroptosis is implicated in the acute neuronal injury in vivo by prolonged epileptic seizures, which has been well described to occur by programmed excitotoxic cell death mechanisms. We evaluated the neuroprotective effects of 7-Cl-O-Nec-1, an inhibitor of receptor-interacting protein 1 (RIP-1), a key enzyme in the necroptotic pathway, in lithium-pilocarpine (LPC)-induced status epilepticus (SE) in the rat. Twelve male Wistar rats were implanted with EEG electrodes, intracerebroventricular (ICV) cannulae and telemetric body temperature sensors intraperitoneally. Six days after surgery, two groups of animals underwent LPCSE; Group 1 (SE vehicle control, n=5) received 3 ICV injections of vehicle (20% DMSO 5µL) at the beginning, middle and the end of 3-hour SE period before the seizures were terminated by diazepam and phenobarbital, while Group 2 (SE experimental, n=4) received 3 ICV injections of 5µL 8mM of

7-Cl-O-Nec-1 at the same times as SEcontrol rats. After 3-hour SE and a 6-hour recovery period, animals were euthanized and transcardially perfused for histology. Animals in Group 3 (no-SE control group, n=3) also received ICV vehicle injections and diazepam and phenobarbital. All brain sections were cut in 60μm thickness and stained with hematoxylin and eosin (H&E). Unbiased stereological cell counting was carried out with Microbrightfield Bioscience's optical fractionator in the dorsal hippocampal hilus (CA4). EEG power spectrum analysis was performed on the EEG recording of the two SE groups for any potential differences in seizure discharges. The estimated numbers of acidophilic (necrotic) neurons in the hilus in SE vehicle control group and SE experimental group were 10,699 ± 966 and 7,634 ± 760 (mean ± SEM) respectively, while the total numbers of neuronal cell counts were the same in all three groups. The RIP1 inhibitor reduced the neuronal death by 29% ($p < 0.024$). There was no significant difference in the EEG power spectrum of epileptiform discharges in the two SE groups. Inhibition of RIP1 reduced seizure-induced neuronal necrosis without reducing epileptic seizure discharges. This suggests that in addition to excitotoxicity, the necroptotic pathway is activated in LPCSE and contributes to seizure-induced neuronal necrosis. The degree of cross-talk between these two pathways will be determined by future research.

**Disclosures: J.H. Hsieh:** None. **D.G. Fujikawa:** None.

**Poster**

**760. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 760.23/MM9

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant R01DC012829

**Title:** The effects of multiple doses of cyclophosphamide on circumvallate papillae

**Authors: *B. C. JEWKES**[1], S. SOCIA[2], J. G. GIRARDIN[3], R. J. DELAY[3], E. R. DELAY[3]
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**Abstract:** Patients who undergo chemotherapy treatment often report taste disturbances, nausea, and appetite loss, which can delay recovery. The chemotherapy drug cyclophosphamide (CYP) has cytotoxic effects on the taste sensory cells of the murine taste system when mice are given a single 75 mg/kg dose. This study used mice to compare the effects of two different dosing regimens of CYP: four doses of saline and a single large dose (75 mg/kg) of CYP against a dose fractionation approach in which five small doses (15 mg/kg) of CYP were given one per day for five days. Immunohistochemical markers including Ki67 (proliferating cells), PLCB2 (Type II cells), and SNAP25 (Type III cells) were used to assess population differences in circumvallate

taste papillae over eight different time points up to 16 days post injection. Both CYP dosing strategies similarly decreased the number of Type II and Type III taste sensory cells to the greatest extent 10 days post treatment ($P < 0.05$). Both dosing methods also similarly reduced the number of proliferating cells involved in taste cell renewal, but the dose fractionation strategy increased the duration of this disruption by several days. Thus, in spite of the assumption that dose fractionation of chemotherapy may produce fewer side effects for the patient, this approach may actually increase the duration of its disruptive effects of the drug on the patient's taste system.

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**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.01/MM10

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** National Multiple Sclerosis Society Grant RG-1501-02646

**Title:** Role of PACAP/PAC1 signaling in protecting neurons and reducing inflammation in a model of multiple sclerosis and optic neuritis

**Authors: *C. VAN**[1], M. C. CONDRO[2], A. Q. HOANG[2], K. LOV[2], N. NGUYEN[3], H. H. KO[2], R. ZHU[2], A. DIEP[2], J. A. WASCHEK[2]
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**Abstract:** Multiple sclerosis (MS) is an autoimmune disease which affects 2.5 million people worldwide and is the number one cause of non-trauma-related disability in young adults. MS is characterized by autoreactive cells destroying myelin, resulting in loss of neurons and their axons in the central nervous system, which includes the brain, spinal cord, eye, and optic nerve. Most descriptions of MS describe the paralysis that occurs in the limbs of these patients. However, it is not commonly known that the specific pathological state in the optic nerve, optic neuritis—often experienced initially as blurred vision—is the presenting clinical symptom in about 20%, and eventually occurs in about 70% of those diagnosed with MS. Even in the absence of clinical optic neuritis, progressive loss of retinal ganglion neurons—the principle neurons that transmit visual signals to the brain—and their axons has been documented in MS patients. We focus this study on the roles of pituitary adenylate cyclase-activating polypeptide (PACAP), an endogenous, evolutionarily highly conserved protein which is upregulated in response to injury,

ischemia, and inflammation and has been shown to protect neurons and reduce inflammation in models of neurodegeneration, including MS. PACAP and its PAC1 receptor are both expressed in retinal ganglion neurons. Furthermore, protective effects of intravitreal PACAP treatment have been demonstrated in multiple *in vivo* models of retinal degeneration, and studies in mice deficient in PACAP have greater neuron loss after chemically-induced damage. In these studies, we investigate how PACAP/PAC1 signaling in a model of MS and optic neuritis, called experimental autoimmune encephalomyelitis, provides direct protection to neurons and their axons in the retina and optic nerve. We use a Cre/Lox recombination system to delete PAC1 and found that deletion of PAC1 in the eye led to loss of a subset of retinal ganglion neurons and their axons. In the optic nerve, we observed increased pathological axonal ovoids, greater immune cell infiltration into the optic nerve, and a defect in microglia/macrophage activity. These findings implicate PACAP/PAC1 as a candidate for development of therapies to treat optic neuritis and other inflammatory, neurodegenerative diseases.

**Disclosures: C. Van:** None. **M.C. Condro:** None. **A.Q. Hoang:** None. **K. Lov:** None. **N. Nguyen:** None. **H.H. Ko:** None. **R. Zhu:** None. **A. Diep:** None. **J.A. Waschek:** None.

**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.02/MM11

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Exercise is neuroprotective following partial motoneuron depletion: Run for your dendrites

**Authors: *C. CHEW**[1], D. R. SENGELAUB[2]
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**Abstract:** We have previously demonstrated that partial depletion of motoneurons innervating the quadriceps muscles induces dendritic atrophy in remaining motoneurons. Furthermore, systemic treatment with supplemental androgens is neuroprotective and dendritic atrophy following partial motoneuron depletion is attenuated. Circulating levels of androgens have previously been shown to increase following exercise, and exercise has been demonstrated to be neuroprotective in a variety of other neurodegenerative and injury models. Thus, we hypothesized that allowing animals to exercise following partial motoneuron depletion would produce neuroprotective effects similar to treatment with supplemental androgens. Motoneurons innervating the vastus medialis muscle in adult male rats were selectively killed by intramuscular injection of cholera toxin-conjugated saporin. Following saporin injections, some animals were allowed free access to a running wheel attached to their home cages. Four weeks

later, motoneurons innervating the ipsilateral vastus lateralis muscle were labeled with cholera toxin-conjugated horseradish peroxidase, and dendritic arbors were reconstructed in three dimensions. Compared with intact normal males, partial motoneuron depletion resulted in decreased dendritic length in remaining quadriceps motoneurons. Early data suggests that exercise can completely protect against this dendritic atrophy, with exercised males showing dendritic arbors lengths significantly longer than saporin and testosterone-treated animals, and of similar length to intact normal animals. These findings suggest that exercise may be a viable means of protecting against collateral dendritic atrophy. The upregulation of testosterone release following exercise combined with our previous data showing the neuroprotective effects of androgen treatment suggest that the neuroprotective following exercise may be attributable to systemic androgen upregulation.

**Disclosures: C. Chew:** None. **D.R. Sengelaub:** None.

**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.03/MM12

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Neuroprotective comparison of Curcumin and Neurobion® treatments on the sciatic nerve crush injury rat model

**Authors: *W. M. RENNO**[1], H. L. SADEK[2], J. KUMAR[2], P. GEORGE[2]
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**Abstract:** Curcumin is a compound found in the dietary spice turmeric Curcuma longa. It has been used as a traditional medication for thousands of years. Curcumin has a broad spectrum of pharmacological activities including antioxidant, anti-inflammatory, anti-cancer, and neuroprotective effects on the CNS and PNS. The present study was designed to compare the therapeutic effect of curcumin and the widely used medicine Neurobion® on sciatic nerve regeneration, neuroprotection of spinal neurons and sensory-motor functional recovery in the sciatic nerve crush injury model. **Methods:** Adult male Wistar rats were assigned to, i) Sham, ii) Sciatic nerve crush treated with saline, iii) Sciatic nerve crush treated with Curcumin (100 mg/kg orally for 14 days), iv) Sciatic nerve crush treated orally with Neurobion and v) Sciatic nerve crush treated with both Neurobion and Curcumin groups (n=12/group). All rats were tested for the motor and sensory neurobehavioral parameters from the week -1 to week 5 (Hoping reflex, hot plate test, tail flick test, extensor postural thrust, foot position, toe spread test, mechanical hyperalgesia test). At the end of the study, sciatic nerve and spinal cord tissues were harvested and processed for morphometric and stereological analysis.**Results:** CRUSH+Curcumin group

showed significant improvement in sensory and motor behavioral tests compared to CRUSH+Saline and CRUSH+Neurobion groups. Morphological examination showed a remarkable increase in the number of myelinated nerve fibers, with better myelination pattern in all the treated groups. Spinal cord ventral horns showed a significant increase in the number of NeuN-immunoreactive neurons in the CRUSH+Curcumin treated group compared to CRUSH+Saline and CRUSH+Neurobion groups. **Summary:** Curcumin and Neurobion® have a significant potential for protecting the degenerating spinal cord neurons and enhancing the regeneration of injured sciatic nerve following sciatic nerve crush injury.

**Disclosures: W.M. Renno:** None. **H.L. Sadek:** None. **J. Kumar:** None. **P. George:** None.

**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.04/MM13

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** The Korea Healthcare Technology R&D Project, Ministry of Health & Welfare (HI15C1928 and HI16C2210)
The National Research Foundation of Korea (NRF-2016R1D1A3B03931424 and NRF- 2017R1A2B4002675)

**Title:** Protection of nigral dopaminergic neurons by AAV1 transduction with Rheb(S16H) against neurotoxic inflammation *in vivo*

**Authors: *S. KIM**[1], J. M. LEE[1], D. YOON[1], U. J. JUNG[3], S. R. KIM[1,2]
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**Abstract:** We previously reported that adeno-associated virus serotype 1 (AAV1) transduction with constitutively active ras homolog enriched in brain [Rheb(S16H)] could protect nigral dopaminergic (DA) neurons through the production of neurotrophic factors in animal models of Parkinson's disease (PD). In the present study, we have further examined the effects of Rheb(S16H) transduction of nigral DA neurons under a neurotoxic inflammatory environment induced by prothrombin kringle-2 (pKr-2), which has been reported as an endogenous microglial activator. Similar to the neuroprotective effects against neurotoxin-induced toxicity, Rheb(S16H) transduction protected the nigrostriatal DA system against pKr-2-induced neurotoxic inflammation *in vivo*, even though there were similar levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1-beta (IL-1β), by upregulation of pKr-2.

In addition, we observed that the neuroprotective effects were mediated by the activation of neurotrophic signaling pathways following Rheb(S16H) transduction of DA neurons. Thus, our results demonstrate that Rheb(S16H) transduction of DA neurons is able to activate the production of neurotrophic factors, and that the upregulation of neurotrophic factors contributes to a resistance to the extracellular neurotoxic inflammation, consequently resulting in protection of adult DA neurons.

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**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.05/MM14

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Development of MSC-NTF cell exosomes for the treatment of neurodegenerative diseases

**Authors: *R. KERN**, N. ABRAMOV, H. KASPI, Y. AIZNER, C. LEBOVITS, R. ARICHA
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**Abstract: Introduction:** MSC-NTF cells are autologous bone marrow derived mesenchymal stem cells (MSC) induced under culture conditions to produce high levels of neurotrophic factors and distinct miRNAs that support neuronal growth and survival, leveraging the potential therapeutic benefits of MSCs that includes anti-inflammatory and immunomodulatory properties.MSC-NTF derived exosomes may possess unique features for the enhanced cell to cell delivery of therapeutics to the brain, including proteins, microRNA, RNA and other signaling molecules, due to their ability to cross the blood brain barrier and distribute widely within the brain and spinal cord.**Methods:** We scaled up the manufacturing process and isolated high-purity exosomes secreted by MSC-NTF cells using tangential flow filtration. Quantification, size and integrity were verified by Nanoparticle Tracking Analysis and transmission electron microscopy. Immunomodulatory and neuro-regenerative properties were studied in vitro on PBMC and neural precursor cells.**Results:** MSC-NTF derived exosomes inhibited T cells proliferation, decreased secretion of inflammatory cytokines in a dose-dependent manner and increased the proportion of Treg cells. Co-culture of the exosomes with neural precursor cells accelerated neuronal differentiation and neurite outgrowth. **Conclusion:** MSC-NTF cells-derived exosomes may leverage the benefits of the cells of origin by providing an option to deliver bio-active molecules to the brain in a non-invasive administration, thus creating a novel and promising therapeutic strategy for neurodegenerative diseases.

**Disclosures:** **R. Kern:** A. Employment/Salary (full or part-time):; rainStorm Cell Therapeutics full time employee. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock ownership BrainStorm Cell Therapeutics. **N. Abramov:** A. Employment/Salary (full or part-time):; rainStorm Cell Therapeutics full time employee. **H. Kaspi:** A. Employment/Salary (full or part-time):; rainStorm Cell Therapeutics full time employee. **Y. Aizner:** A. Employment/Salary (full or part-time):; rainStorm Cell Therapeutics full time employee. **C. Lebovits:** A. Employment/Salary (full or part-time):; rainStorm Cell Therapeutics full time employees. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Brainstorm Cell Therapeutics. **R. Aricha:** A. Employment/Salary (full or part-time):; rainStorm Cell Therapeutics full time employee.

**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.06/NN1

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH Grant AG022550
NIH Grant AG027956
Felix and Carmen Sabates Missouri Endowed Chair in Vision Research

**Title:** Control of neuronal ryanodine receptor activity by steroid hormone receptors in the nucleus

**Authors:** ***P. KOULEN**, A. A. LOPEZ
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**Abstract:** Controlling the nucleoplasmic concentration of free calcium ions ($Ca^{2+}$) is essential for the physiological activity of neurons, such as gene expression and neuronal survival under disease conditions. At the same time, the steroid hormones progesterone and the estrogen 17β-estradiol have been identified as neuroprotective and critical for proper neuronal viability as transcription factors directly controlled by extracellular hormone signaling. The present study determined novel mechanisms of action how signaling mediated by the interaction of ryanodine receptors with steroid hormone receptors in the nuclear envelope control the $Ca^{2+}$ concentration of the nucleoplasm in neurons. Specifically, it was identified how direct binding of estrogen receptors to ryanodine receptors on the nucleoplasmic face of the nuclear envelope affects the activity of this major type of ligand-gated intracellular $Ca^{2+}$ release channels in the nuclear envelope of neurons. Using immunochemistry, optical imaging and electrophysiology, as well as immunochemical assays for determining protein-protein binding, changes in the activity of

ryanodine receptors in the nucleus after binding of steroid hormone receptors were determined. Binding of steroid hormone receptors to the intracellular $Ca^{2+}$ release channel resulted in distinct changes in both channel open frequency as well as the number of channel openings at the single channel level and preservation of key biophysical parameters of the channels such as single channel conductance. These molecular changes in channel open probability were mirrored at the cellular level by altered release of $Ca^{2+}$ from the nuclear envelope and in the nucleoplasm as well as altered susceptibility of neurons to stimuli selectively elevating nucleoplasmic $Ca^{2+}$ levels. The work indicates that neuronal $Ca^{2+}$ signaling in the nucleus mediated by ryanodine receptors as $Ca^{2+}$ dependent intracellular $Ca^{2+}$ release channels is critically modulated by steroid hormone receptor binding. Such nucleoplasmic signaling controlled by protein-protein interactions in central nervous system neurons potentially provides a novel mechanism for both genomic as well as non-genomic actions of steroid hormone receptors as a new avenue for drug development in the area of neurodegeneration.

**Disclosures: P. Koulen:** None. **A.A. Lopez:** None.

**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.07/NN2

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** JSPS KAKENHI 17H04198
JSPS KAKENHI 17K08311
JSPS KAKENHI 17K18001

**Title:** The effects of the ethanol extract of brazilian green propolis that contains flavonols against mutant copper-zinc superoxide dismutase-mediated toxicity

**Authors: *M. INDEN**[1], T. UEDA[1], S.-I. SEKINE[1], H. KURITA[1], S. GO[1], N. TAKASE[1], K. ICHIHARA[2], I. HOZUMI[1]
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**Abstract:** Amyotrophic lateral sclerosis (ALS) is characterized by the degeneration of motor neurons and by the formation of intracellular protein aggregations that form in motor neurons. While 95% of ALS is sporadic, 5% is inherited. Among the inherited ALS (also known familial ALS), the mutations in copper-zinc superoxide dismutase (SOD1) are the major autosaomal dominant inherited cause for ALS. Propolis is made from a sticky substance that honeybees produce by mixing their own waxes with resinous sap obtained from the bark and leaf-buds of certain trees. The properties and constituents of propolis also differ with its geographical origin.

Propolis presents numerous biological and pharmacological properties, such as anti-bacterial, anti-inflammatory, and anti-oxidative activity. However, the effect of propolis and the active components against ALS-associated mutant SOD1-mediated toxicity is not well known. To examine whether propolis and the active components have neuroprotective effect against ALS-associated mutant SOD1-induced neurotoxicity in a cellular model, we used the ethanol extract of Brazilian green propolis (EBGP). We also further investigate whether autophagy is involved in the neuroprotection of kaempferol and k*aempferide,* the active ingredients of EBGP, against mutant SOD1-related neurotoxicity via the AMP-activated protein kinase (AMPK) - the mammalian target of rapamycin (mTOR) pathway. As results, EBGP protected N2a cells against mutant SOD1-induced neurotoxicity and reduced aggregated mutant SOD1 by induction of autophagy. K*aempferide* and kaempferol also inhibited mutant SOD1-induced cell death and reduced the intracellular mutant SOD1 aggregates. Both k*aempferide* and kaempferol significantly suppressed mutant SOD1-induced superoxide in mitochondria. Western blot analysis showed that kaempferol, but not k*aempferide,* potentially induced autophagy *via* the AMPK - mTOR pathway. These results suggest that EBGP containing the active ingredient against mutant SOD1-mediated toxicity is a promising medicine or health food for prevention and treatment of ALS.

**Disclosures: M. Inden:** None. **T. Ueda:** None. **S. Sekine:** None. **H. Kurita:** None. **S. Go:** None. **N. Takase:** None. **K. Ichihara:** None. **I. Hozumi:** None.

**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.08/NN3

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** JSPS KAKENHI Grant Number 17H04198

**Title:** Effect of 5-aminolevulic acid against low inorganic phosphate in SH-SY5Y cells

**Authors: *S.-I. SEKINE**, N. TAKASE, H. KURITA, S. GO, T. UEDA, M. INDEN, I. HOZUMI
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**Abstract:** Idiopathic basal ganglia calcification (IBGC), also known as Fahr disease or primary familial brain calcifications (PFBC), is a rare neurodegenerative disorder characterized by calcium deposits in basal ganglia and other brain regions, causing neuropsychiatric and motor symptoms. PiT-1 (encoded by SLC20A1) and PiT-2 (encoded by SLC20A2) are type-III sodium-dependent phosphate cotransporters (NaPiTs). Recently, SLC20A2 mutations have been

found in patients with IBGC, and were predicted to bring about an inability to transport Pi from the extracellular environment. Here we investigated the effect of low Pi loading on the human neuroblastoma SH-SY5Y and the human glioblastoma A172 cell lines. We also examined whether 5-aminolevulinic acid (5-ALA) inhibited low Pi loading-induced neurotoxicity in SH-SY5Y cells. At 24 h after low Pi loading, SH-SY5Y cells treated with 0 mM Pi exhibited cell death, but those treated with 0.5 and 1 mM Pi did not. On the other hand, A172 cells treated with 0, 0.5 and 1 mM Pi did not exhibit cell death at 24 h after low Pi loading. In SH-SY5Y cells, mRNA expressions of SLC20A1 and SLC20A2 were not affected by low Pi loading for 24 h. On the other hand, SLC20A1 mRNA expression in A172 cells was significantly increased by treatment with 0 mM Pi, although SLC20A2 mRNA expression did not change. We found that SLC20A1 mRNA expression was not changed in SLC20A2-knockdowned SH-SY5Y cells, compared with non-targeted siRNA controls. Concomitant application of 5-ALA (25-75 microM) with low Pi loading markedly attenuated low Pi-induced cell death. Low Pi loading significantly enhanced ROS production and 5-ALA decreased low Pi-induced ROS production. Quantitative RT-PCR analysis showed increase of phosphorylated p38, phosphorylated ERK 1/2 MAPK and HO-1 by treatment of 5-ALA. The results show a different sensitivity to low Pi loading and differential regulation of type-III NaPiTs in these cells. Treatment of 5-ALA markedly attenuated low Pi-induced cell death and mitochondrial dysfunction via HO-1 induction through p38 MAPK. The findings provide us with novel viewpoints to understand the pathophysiology of IBGC, and give a new insight into the clinical prevention and treatment of IBGC.

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**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.09/NN4

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Protective effects of nicotinamide mononucleotide against oxidative stress induced PC12 cell death via mitochondrial enhancement

**Authors: S. ITO**[1], *K. NAGAI[2]
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**Abstract:** Oxidative stress is involved in most of the neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease. Although it has been reported that $NAD^+$ precursor

nicotinamide mononucleotide (NMN) improves oxidative stress associated disease models, the detailed mechanisms have not been elucidated, yet. NMN is a precursor of $NAD^+$ which activates class III histone deacetylase sirtuin, and cytosolic sirtuin Sirt1 was reported to activate mitochondrial biogenesis regulator Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α). Thus, we hypothesized that NMN attenuates oxidative stress induced cell damage via sirtuin activation and mitochondrial increase. In this study, to study whether NMN can protect the neuronal cells from oxidative stress via enhancement of the mitochondrial function, we used PC12 cells treated with 6-hydroxydopamine (6-OHDA) and hydrogen peroxide ($H_2O_2$) as oxidative stress models. Regarding cytoprotective effects, pretreatment with 1mM NMN significantly reduced 6-OHDA and $H_2O_2$ induced cell death, and these protective effects were prevented in the presence of sirtuin inhibitor sirtinol. Moreover, these protective effects were prevented by siRNA-mediated knockdown of PGC1α. These data suggests that NMN protects the cells via sirtuin activation followed by mitochondrial increase. Thus, to clarify if NMN actually increases mitochondrial amount, intracellular mitochondria were evaluated by cytometric analysis stained with mitochondrial membrane potential dependent fluorescent dye JC-1. NMN clearly increased intracellular active mitochondria, and the increase was attenuated by sirtinol. In addition, we also evaluated mitochondria-associated sirtuin Sirt3 and antioxidative protein Superoxide dismutase (SOD2), and found that NMN treatment increased these proteins. These data suggests that NMN treatment not only increase the amount of mitochondria, but also increase the antioxidative activity. Our data suggest that NMN protects neuronal cells from oxidative stress via sirtuin activation followed by the mitochondrial enhancement.

**Disclosures: S. Ito:** None. **K. Nagai:** None.

**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.10/NN5

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Quantitatively predicting and grading the clinical efficiency of β-lactams in neuroprotective therapy of fatal encephalitis

**Authors: *V. PAREEK**[1], P. K. ROY[2]
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**Abstract: Abstract**
Encephalitis is rare but potentially life-threatening inflammation of the brain occurence in people of all ages however the incidence is higher in the pediatric population **[1]**. Fatal Encephalitis

caused by infection with Neurovirulent Strains (NSV) leads to Neuronal cell death taking in account of three processes: (a) Virus Replication, (b) Glutamate Excitotoxicity and (c) Neuroinflammation [2]. Here, we analyze various β-Lactam antibiotics such as Cefixime, Cefsulodin, Cefmetazole, Cefamandole and Ceftriaxone for neuroprotective activity. We utilize systems biology analysis using MetaDrugTM platform (Gene-Go) to predict drug for maximum efficacy and functional recovery, pertaining to the drug interactions *in-silico*. For estimating the efficacy, we devise quantitative metrics based on (i) topological index of the molecular pathway networks [3] and (ii) the functional p-value coefficient as a measure of the likelihood weight of the neuronal processes involved in the systems pathway. β-Lactams offer neuroprotection by increasing glutamate transporter (GLT) expression [4]. We compare Cephalosporin's to find a suitable Active Pharmaceutical Ingredient (API). Ceftriaxone is found to have neuroprotective activity against glutamate excitotoxicity. It is also involved in the regulation of synaptic plasticity via the cSrc-Myosin VI pathway. Ceftriaxone is FDA approved for pediatric use and shows good penetration into CSF compartment. Combinational therapy with Ceftriaxone (Neuroprotection), Talampanel (Anti-inflammatory agent) [1] and thieno[3,2-b] pyrrole-based inhibitors (Antiviral Drugs) may provide the active therapy regimen for Fatal Encephalitis. The possibility of collateral clinical evidence pertaining triple-drug approach to Fatal Encephalitis is delineated.

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2. Ivorlyne P. Greene, et al. Protection from fatal viral encephalomyelitis: AMPA receptor antagonists have a direct effect on the inflammatory response to infection. Proceedings of the National Academy of Sciences of the United States of America March 4, 2008: vol. 105 no. 9: 3575-80.
3. Gonzalez-Diaz H, Vilar S, Santana L, et al. Medicinal chemistry and bioinformatics-current trends in drugs discovery with networks topological indices. Current Topics in Medicinal Chemistry 2007; 7(10): 1015-29.
4. JD Rothsteine et.al. Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. Nature. 2005 Jan 6;433(7021):73-7.

**Disclosures: V. Pareek:** None. **P.K. Roy:** None.

**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.11/NN6

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NSERC Canada 1641

**Title:** Knockdown of Hsp70 heat shock proteins enhances the sensitivity of human neuroblastoma cells to the chemotherapeutic agent cisplatin

**Authors: *C. A. DEANE**, I. R. BROWN
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**Abstract:** Cancer cells express elevated levels of heat shock proteins (Hsps) which contribute to the ability of cancer cells to resist cell death. In addition, chemotherapeutics can further enhance Hsp levels. Cisplatin is employed to treat several types of cancer, including neuroblastoma. In this study, cisplatin increased the expression of heat shock protein HSPA1A (Hsp70-1) in human SH-SY5Y neuroblastoma cells. The sensitivity of neuroblastoma cells to cisplatin was enhanced following siRNA knockdown of HSPA1A and also knockdown of constitutively expressed HSPA8 (Hsc70). A higher level of apoptosis was apparent in the knockdown cells. Administration of cisplatin *in vivo* results in exposure to both cancerous and non-cancerous tissues. Differentiated human neuronal SH-SY5Y cells, obtained by treatment with retinoic acid that inhibits cell division and promotes growth of neuronal processes, were better able to tolerate cisplatin compared to dividing neuroblastoma cells. HSPA1A and HSPA8 knockdown increased the sensitivity of differentiated neuronal cells to cisplatin, although to a lesser degree than dividing cells. The targeting of Hsps to the ends of neuronal processes identified these locations as cisplatin-sensitive sites in differentiated neurons. Peripheral neuropathy is a side effect of chemotherapy that is associated with damage to nerve endings. Development of nanoparticles that target cisplatin and Hsp70 knockdown siRNAs to the tumor microenvironment would be advantageous to enhance the anti-tumor effectiveness of cisplatin while minimizing side effect damage to differentiated neurons.

**Disclosures: C.A. Deane:** None. **I.R. Brown:** None.

**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.12/NN7

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** Charles E. Kaufman Foundation
NIH Grant NS043277

**Title:** Neuroprotection induced by zinc-dependent translation of hepatitis C-derived neuroprotective protein NS5A targeting Kv2.1 potassium channels

**Authors: J. JUSTICE**[1], D. T. MANJOORAN[2], C.-Y. YEH[1], A. J. SCHULIEN[1], K. A. HARTNETT-SCOTT[1], S. MAMMEN[1], M. J. PALLADINO[2], *E. AIZENMAN[1]
[1]Neurobiology/PIND, [2]Pharmacol. and Chem. Biology/PIND, Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA

**Abstract:** Although the progressive neuronal cell loss that occurs in chronic neurodegenerative diseases proceeds via multifaceted processes, there are injurious signaling components that may be common to most disorders. These likely include oxidative stress, as well as the cell death-enabling loss of cytoplasmic potassium ions. With this in mind, we have designed an innovative molecular neuroprotective strategy, and provide proof-of-concept for its implementation, that relies on the injury-mediated activation of a normally silent ectopic genetic construct, whose product, when translated, prevents the pro-cell death enhancement of ionic currents mediated by the voltage-dependent potassium channel Kv2.1. As oxidative injury leads to the liberation of zinc from intracellular metal-binding proteins, we have tapped onto the zinc-activated metal regulatory element (MRE) transcription factor 1 (MTF-1) system to drive neuronal expression of the hepatitis C viral protein NS5A, a protein previously shown to be neuroprotective by preventing Kv2.1-mediated cellular potassium loss. We demonstrate rapid (3-5 hr) expression of MRE-driven products in cortical neurons *in vitro* following cadmium-induced intracellular zinc liberation. Moreover, we report that MRE-driven expression of NS5A, induced by a DL-*threo*-β-benzyloxyaspartic acid excitotoxic stimulus, functionally blocks apoptogenic Kv2.1-mediated currents, and provides neuroprotection. We suggest that this form of "on-demand neuroprotection" could provide a novel, tenable strategy to prevent neuronal cell death in neurodegenerative disorders.

**Disclosures: J. Justice:** None. **D.T. Manjooran:** None. **C. Yeh:** None. **A.J. Schulien:** None. **K.A. Hartnett-Scott:** None. **S. Mammen:** None. **M.J. Palladino:** None. **E. Aizenman:** None.

**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.13/NN8

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** PNSD 2015/005

**Title:** Alcohol binge episodes disrupts proteins conforming the intestinal and blood-brain barriers. Study of the protective effects of oleoylethanolamide

**Authors: *L. ORIO**[1], M. ANTÓN[2], A. BALLESTA[2], F. ALÉN[3], Y. GARCÍA[2], J. CASO[2], B. GARCÍA-BUENO[2], F. RODRÍGUEZ DE FONSECA[5], A. RODRÍGUEZ-GONZÁLEZ[4]
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**Abstract:** Alcohol binge drinking induces peripheral inflammation that may affect the brain promoting neuroinflammation and cognitive decline. Pharmacological pretreatment with the biolipid oleoylethanolamide (OEA), which is part of the acylethanolamide family, has shown to reduce both peripheral inflammation and neuroinflammation in rodents. In this study we tested whether the alcohol-induced peripheral inflammation and neuroinflammation are related with disruptions in the intestinal barrier and in the blood-brain barrier using an animal model of alcohol binge drinking, and the possible protective effects of OEA. Adults male Wistar rats weighting 200 g were exposed to alcohol binge episodes by intragastric administrations of 3g/kg of alcohol every 8h during 4 consecutive days. Samples of brain frontal cortex and colonic intestinal tissue were collected to measure the integrity of proteins conforming the intestinal and blood-brain barriers. Data were analyzed by 2-way ANOVA comparing the factors alcohol/water oral administration versus OEA/vehicle i.p. treatment, followed by Bonferroni *post hoc* test when appropriate. Results showed that alcohol binge episodes alter the expression of colonic occludin and claudin-3, with no effect in intestinal zona-occludens-1 (ZO-1), indicative of some alterations in the tight junction proteins that conform the intestinal barrier. Alcohol-binge episodes decrease also the expression of laminin, occludin and ZO-1 in frontal cortex, indicative of damage to the blood-brain barrier in this area. Pharmacological pretreatment with OEA before each alcohol binge prevents the decrease in occluding and claudin-3 in alcohol-treated animals, whereas OEA increases the expression of ZO-1 both in alcohol and control groups. Exploratory research regarding the blood-brain barrier fail to detect any protective effect of OEA in alcohol-induced decreases in laminin, occluding and ZO-1 in frontal cortex. These results suggest that the anti-inflammatory actions of OEA may be due in part by a local action of this biolipid in the intestine, protecting from the alcohol binge-induced tight junction
protein disruption and highlight a role of OEA in the regulation of the gut-brain axis altered by alcohol abuse.

**Disclosures: L. Orio:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent holder. **M. Antón:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent holder. **A. Ballesta:** None. **F. Alén:** None. **Y. García:** None. **J. Caso:** None. **B. García-Bueno:** None. **F. Rodríguez de Fonseca:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent holder. **A. Rodríguez-González:** None.

**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.14/NN9

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** MICINN Grant BFU2015-68149-R
Junta de Castilla y León PhD Fellowship EDU/1883/2013
European Social Fund; Operational Pro-gramme for CyL

**Title:** Apolipoprotein D-mediated regulation of lysosomal membrane integrity preserve lysosomal function and promotes cell survival in Niemann-Pick type A disease

**Authors: *M. D. GANFORNINA**[1], R. PASCUA-MAESTRO[1], M. LEDESMA[2], D. SANCHEZ[1]
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**Abstract:** Lysosomal Storage Diseases (LSDs) are genetic, early onset, neurodegenerative diseases that result in poor survival and both systemic and nervous system dysfunction. All LSDs are associated to leukodystrophy or myelination problems.
We have recently discovered that the Lipocalin Apolipoprotein D (ApoD) is essential for the maintenance of lysosomal functional integrity in glial cells. ApoD function ensures processes as diverse as cell survival upon oxidative stress (by reverting membrane permeabilization and loss of pH gradients), adequate compaction of myelin (by controlling glycolipid recycling processes), or proper phagocytic activity after nervous system injury. The crucial role of ApoD within the lysosome led us to study the potential effects of ApoD on a particularly devastating LSD, the Niemann Pick type A disease (NPA)**,** caused by loss of function mutations in the gene encoding for acid sphingomyelinase, which results in sphingomyelin accumulation in lysosomal and plasma membranes. NPA patients rapidly develop progressive neurodegeneration, cerebral and cerebellar atrophy, significant Purkinje cell loss, and myelin deficiencies. No treatment is available today, in spite of various attempts with pharmacological, enzyme-replacement, or cell-based strategies.
Using two independent NPA-patient derived fibroblasts cell lines and two healthy control lines, we here demonstrate that, as in glial cells and neurons, ApoD is targeted to lysosomes of NPA fibroblasts. While oxidative stress induces an accelerated entry of ApoD into the lysosomal compartment of healthy cells, such accelerated targeting is lost in the diseased cells, contributing to the vulnerability of NPA lysosomes. We assessed lysosomal functional integrity and cell survival, using L-leucyl-L-leucine methyl ester as positive control for lysosomal membrane

rupture, and pre-treatment of healthy control cells with sphingomyelin as a phenocopy of NPA disease.
By measuring cathepsin B activity (Magic Red assay), galectin-3 subcellular location, and lysosomal pH (Lysosensor Yellow/Blue DND-160 ratiometric assay), we demonstrate that exogenously added ApoD is able to significantly reduce lysosomal permeabilization and NPA-promoted lysosomal alkalinization. ApoD addition reverts the accumulation of oxidized products in lysosomes (revealed by lipofuscin signal) and of lipid peroxidation (4-hydroxynonenal signal) in NPA cells, resulting in a significant increase in cell survival.
Our results reveal that ApoD protection of lysosomal integrity is able to counteract biological deterioration in NPA cells, and open therapeutic opportunities for this devastating disease.

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**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.15/NN10

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** AHA Fellowship 16PRE29170009
Tsinghua-Pittsburgh Joint Program
NIH Grant NS043277

**Title:** Neuroprotection by small molecule inhibition of Kv2.1-syntaxin interaction

**Authors: *C.-Y. YEH**[1,2,3], Z. YE[6], S. GAUR[2,3], A. MOUTAL[7], A. M. HENTON[4], S. KOUVAROS[4], J. L. SALOMAN[2], K. A. HARTNETT-SCOTT[3,2], K. HE[3], T. TZOUNOPOULOS[4,2], R. KHANNA[7], C. J. CAMACHO[5], E. AIZENMAN[2,3]
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**Abstract:** Neuronal cell death-enabling loss of cytoplasmic potassium is mediated by a large increase in the number of Kv2.1 potassium channels in the plasma membrane. This process relies on the binding of syntaxin to Kv2.1 within a critical 9-amino acid sequence (HLSPSRKWKW, C1aB) of the channel's proximal c-terminus. Competitively disrupting the Kv2.1-syntaxin interaction using a blood-brain-barrier permeable peptide derived from this sequence, TAT-C1aB, improves neuronal viability following acute injury both *in vitro* and *in vivo*. Here, using molecular modeling, we predict and experimentally validate the key amino acids within C1aB

that mediate its binding to syntaxin. Critical for this binding is a ring-stacking interaction between a C1aB tryptophan and syntaxin residue F34, the latter of which is a component of a peripheral binding site to the SNARE modulator Mammalian UNCoordinated 18 (munc-18). Leveraging these findings, we virtually screened a database of 26 million commercially available compounds, discovering the small molecule F5 as an inhibitor of Kv2.1 C1aB-syntaxin binding in a far Western spot array assay. Moreover, F5 at high concentrations (100 μM) effectively displaces munc-18 from syntaxin in co-immunoprecipitation studies. We show that F5 (10 μM) suppresses Kv2.1-mediated pro-apoptotic $K^+$ currents and provides neuroprotection without altering intrinsic electrical or synaptic properties of cortical neurons. Collectively, our findings reveal an important molecular component of syntaxin's role in cell death, and validate a highly relevant cellular target for neuroprotective therapeutics.

**Disclosures: C. Yeh:** None. **Z. Ye:** None. **S. Gaur:** None. **A. Moutal:** None. **A.M. Henton:** None. **S. Kouvaros:** None. **J.L. Saloman:** None. **K.A. Hartnett-Scott:** None. **K. He:** None. **T. Tzounopoulos:** None. **R. Khanna:** None. **C.J. Camacho:** None. **E. Aizenman:** None.

**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.16/NN11

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** HKU Alzheimer's disease Research Network

**Title:** Forced resistant exercise preconditioning reduces postoperative cognitive dysfunction in aged mice by enhancing synaptic plasticity in the hippocampus

**Authors: *Y. LIU**[1,2], J. C. M. TAK[1,2], R. C. CHANG[2,3], G. T.-C. WONG[1]
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**Abstract:** Postoperative cognitive dysfunction (POCD) is characterized by dysfunctions of memory, focusing and learning after surgery, which usually develop in elderly patients. Although there is a growing knowledge for the pathogenesis of POCD, potential therapeutic options are still limited. In the current study, we test the hypothesis that a preconditioning period of resistant training can reduce postoperative cognitive decline, probably by enhancing synaptic plasticity in the hippocampus.
C57BL/6 mice with 18-month-old were trained using a ladder-climbing protocol for 5 weeks with 3-4 training sessions per week. For each session, mice were forced to climb up a 1-meter

ladder with progressively larger weight attached to tail for 15 times with 2 minutes rest during each trail. Effects of resistance training on cognition and muscle strength were checked by Y-maze and weight lifting test, respectively. Laparotomy was then performed using aseptic procedures under sevoflurane (3-4%) as anesthesia (~20 min). Cognitive functions were assessed by Y-maze test and novel object recognition (NOR) test 2 weeks afterwards. Levels of synaptic proteins in hippocampus were detected by western blot. Golgi staining was used to examine dendrites process complexity and spine density.
After 5 weeks of resistance training, mice in exercise group showed less errors and shorter latency in Y-maze test, lifted heavier weight in weightlifting test and had lower body weight. In Y-maze test, which was conducted 14 days after laparotomy, mice in laparotomy group displayed more errors and longer latency compared to control group. Mice with resistant exercise preconditioning showed significant less errors and shorter latency compared with laparotomy group. The above changes were verified by NOR test. For synaptic proteins, phosphorylation of NR2A (Y-1246) was significantly increased, while total NR2A was down regulated in hippocampus by laparotomy, and exercise preconditioning offset these changes. There were no changes of the expression lever of NR2B, Synapsin1, PSD 95, Synaptobrevin, Synaptotagmin and Synaptophysin. Golgi staining showed that mice in resistance exercise preconditioning group had increased process complexity and spine density compared to laparotomy group.
These findings demonstrated that 5 weeks of resistant exercise preconditioning ameliorates laparotomy-induced cognitive impairment in aged mice, which may be due to the modulation of synaptic plasticity in the hippocampus.

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**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.17/NN12

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** 2012R1A6A1028677
2015R1D1A1A01058350

**Title:** Phycoerythrin peptide from pyropia yezoensis alleviates endoplasmic reticulum stress caused by perfluorooctane sulfonate-induced calcium dysregulation

**Authors: *J. OH**, E.-Y. KIM, H. PARK, T.-J. NAM
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**Abstract:** Perfluorooctane sulfonate (PFOS), a stable fluorosurfactant, causes endoplasmic reticulum (ER) stress in the brain. This study was designed to investigate whether a phycoerythrin-derived peptide of *Pyropia yezoensis* (PYP) reduces PFOS-induced ER stress associated with calcium dysregulation. The protective effects of PYP were determined by cell viability, immunoblotting for ER stress response protein glucose-regulated protein 78 (GRP78) and calcium-dependent protein kinases in rat frontal cortical neurons. PFOS-induced decrease in cell viability was attenuated by PYP pretreatment (1 μg/mL) for 24 h, which was downregulated by inhibiting tropomyosin-receptor kinase B (TrkB). PYP pretreatment downregulated the increase in intracellular calcium levels and phosphorylation of calcium/calmodulin-dependent protein kinase II and c-Jun N-terminal kinase which are associated with a PFOS-induced increase in GRP78. The PFOS-induced increase in GRP78 was downregulated via activation of TrkB receptor-linked extracellular signal-regulated kinases 1/2 (ERK1/2) by PYP pretreatment. Moreover, PYP microinjections (1 μg/kg, 0.54 nmol) attenuated the GRP78 expression in rat prefrontal cortex caused by PFOS (10 mg/kg) exposure for 2 weeks. These findings demonstrate that PYP enhances frontal cortical neuron viability via activation of TrkB receptor-ERK1/2 signaling and attenuation of ER stress in rat prefrontal cortex against PFOS exposure, suggesting that PYP might prevent neuronal dysfunctions caused by PFOS-induced ER stress.

**Disclosures: J. Oh:** None. **E. Kim:** None. **H. Park:** None. **T. Nam:** None.

**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.18/NN13

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH R01 NS40433

**Title:** Cellular sources and immune regulation of a neuroprotective interleukin-10 signaling pathway in the facial motor nucleus after axotomy

**Authors: *E. M. RUNGE**[1,2], D. O. SETTER[1,2], A. K. IYER[1,2], F. M. KENNEDY[1,2], V. M. SANDERS[3], K. J. JONES[1,2]
[1]Anat. and Cell Biol., Indiana Univ. Sch. of Med., Indianapolis, IN; [2]Res. and Develop., Richard L. Roudebush VA Med. Ctr., Indianapolis, IN; [3]Med. Virology, Immunology, and Med. Genet., The Ohio State Univ. Wexner Med. Ctr., Columbus, OH

**Abstract:** Interactions between the nervous and immune systems are critical for maintaining motoneuron (MN) survival after peripheral axotomy. Of particular interest to our laboratory is interleukin-10 (IL-10), an anti-inflammatory cytokine. We have previously found that CD4+ T

cells mediate MN survival after facial nerve axotomy (FNA) in an IL-10-dependent manner, although CD4+ T cells are not the requisite source of IL-10. The precise cellular source of IL-10 as well as the details of CD4+ T cell participation in this IL-10 signaling cascade after axotomy are unknown. The aims of this study are to elucidate the cell-specific expression and role of IL-10 in mediating neuroprotection after FNA, and to investigate the manner in which CD4+ T cells modulate IL-10 receptor expression after nerve injury. Immunohistochemistry, IL-10/GFP transgenic reporter, and fluorescent in situ hybridization collectively revealed that astrocytes were positive for IL-10 protein after FNA, whereas microglia produced *Il10* mRNA without evidence of downstream protein translation. MN themselves appeared to be major constitutive producers of IL-10 protein. To determine whether any single source of IL-10 is critical for MN survival, we generated Cre/lox mouse strains to selectively knock out IL-10 in microglia, astrocytes, and neurons. In agreement with our localization data reflecting concerted IL-10 production by multiple cell types, no single cellular source of IL-10 was necessary for MN survival. We are currently evaluating whether IL-10 expression restricted to the central compartmental is sufficient for neuroprotection after axotomy by performing lentiviral transduction of the *Il10* coding sequence into facial MN of IL-10 null mice. To determine the role of the immune system in modulating the central IL-10 signaling cascade, we performed semi-quantitative PCR analysis of wild-type, immunodeficient, and immune cell-reconstituted animals, which revealed that CD4+ T cells are necessary for full upregulation of central IL-10 receptor expression after FNA. Whether this is due to direct expression of the IL-10 receptor by infiltrating T cells, or rather due to T cell-mediated upregulation of the IL-10 receptor on another cell type, is currently under investigation. In conclusion, it is likely that central IL-10 production by both neurons and astrocytes acts via CD4+ T cell-mediated upregulation of the IL-10 receptor to modulate the cellular response to neuronal injury in a neuroprotective manner.

**Disclosures: E.M. Runge:** None. **D.O. Setter:** None. **A.K. Iyer:** None. **F.M. Kennedy:** None. **V.M. Sanders:** None. **K.J. Jones:** None.

**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.19/NN14

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH grant NS043277

**Title:** A seven amino acid cell permeant peptide derived from the PRC-domain of Kv2 channels effectively declusters Kv2.1 and inhibits injury-induced enhancement of pro-apoptotic $K^+$ currents

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**Abstract:** Lethal stimuli resulting in oxidative stress induce syntaxin-dependent trafficking of Kv2.1 and augmented Kv2.1-dependent currents essential for apoptotic neuronal cell death. Previously, we overexpressed a protein derived from the C-terminus of Kv2.2 (Kv2.2CT) and observed a calcineurin-independent disruption of Kv2.1 somato-dendritic clusters in rat cortical neurons *in vitro*. Furthermore, we found that Kv2.2CT-expressing neurons were both less susceptible to oxidative stress-induced cell death and that the increased current density of Kv2.1 mediated currents associated with oxidative injury were effectively blocked. This novel finding supported the critical role of Kv2.1 somato-dendritic clusters for apoptotic delivery of Kv2.1 channels to the plasma membrane. Here, we narrowed down the critical amino acids of the Kv2.2 sequence required for the disruption of Kv2.1 somato-dendritic clusters to a critical 7 amino acid sequence (DP2). We demonstrate that a cell-permeant peptide containing this sequence (TAT-DP2) was sufficient to cause both declustering and inhibit apoptogenic trafficking of Kv2.1 compared to a scramble peptide (TAT-DP2Sc). All cultures used for imaging were transfected with a GFP-tagged Kv2.1 construct. Twenty-four hours later, images of rat primary cortical neurons were obtained with a Nikon A1 confocal microscope following a 1-2 hour treatment with either DP2, DP2Sc (10 μM) or vehicle. Neurons pretreated with TAT-DP2 had approximately 2.2 fold less Kv2.1 clusters/$\mu m^2$ (n=16) compared to neurons treated with a TAT-DP2Sc scramble (n=8) or vector controls (n=21); $p<0.001$. This effect was similar to the effectiveness of Kv2.2CT in dispersal of Kv2.1 somato-dendritic clusters (n=6); $p<0.001$. For whole cell recordings, neurons were also pretreated with either DP2, DP2Sc or vehicle for 1 hour. Following pretreatment, neurons were exposed to vehicle or DTDP (2,2'-dithio-bis-nitrobenzoic acid), a thiol-reactive, zinc-releasing oxidizing agent that leads to increased trafficking of Kv2.1. Neurons not pretreated with either peptide that were exposed to DTDP had approximately a 2.4 fold increase in mean current density compared to vehicle control (n=17/group). A similar effect was found with neurons exposed to DTDP following pretreatment with DP2Sc which led to a 1.8 fold increase in mean current density compared to vehicle control (n=22/group) $p<0.01$. Critically, neurons pretreated with DP2 effectively inhibited the DTDP-induced increase in current density (n=14/group). These data further support a critical role of Kv2.1 somato-dendritic clusters in injury-dependent enhancement of pro-apoptotic $K^+$ currents.

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**Poster**

**761. Neurotoxicity, Inflammation, and Neuroprotection: Neuroprotective Mechanisms: Preclinical**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 761.20/NN15

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** 123240.1
123280.0

**Title:** The extracts of Tilia modified the establishment of full kindled of in rats

**Authors: *G. CONTRERAS-MURILLO**[1], J. C. ESCOTTO-RAMÍREZ[2], S. ALMAZAN-ALVARADO[2], E. M. GONZALEZ-TRUJANO[2], V. M. MAGDALENO-MADRIGAL[2]
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**Abstract:** Tilia species have been used as a depressant of the central nervous system for many years in different parts of the world, mainly as an anxiolytic. In Mexico, the infusion of flowers are commonly used for the treatment of migraine, to alleviate pain, nervous tension, some types of spasms, and alterations of the liver and bladder, but also in epilepsy. Few scientific studies have investigated the anticonvulsant activity attributed to the *Tilia americana* var. *mexicana*; however its high contained in flavonoid-type constituents, among others, considered as modulators of $GABA_A$ and serotonin inhibitory $5\text{-}HT_{1A}$ receptors suggests its potential in the study of paroxistic activity. The goal of this study was to evaluate the effects of the extracts of Tilia on the evolution of amygdala kindling (AK). Adult male Wistar rats were implanted in the left amygdala and the left motor cortex. Animals were divided in three groups: Methanol (MeOH) group receiving an injection of the Tilia MeOH extract (100 mg/kg, i.p.); Ethyl acetate (AcOEt) group administrated with an injection of the Tilia AcOEt extract (100 mg/kg ip.), and the vehicle (VEH) group that received an injection of the vehicle [0.2% tween 80 in saline solution (s.s.) or s.s.]. Every 24 h all the rats were injected 30 min before the AK (1 sec, 60 Hz, 100-500 μA) until rats reached stage 5 of AK. Rats were classified as follows: (a) responders, animals that did not show progress of the AK process and remained in seizures of stages II and III. (b) Non-responders, rats that developed the AK process as in the VEH group. The effects of both MeOH and AcOEt extracts in the responders animals induced an increase in the parameters of duration and frequency compared to the VEH group. In addition, a decrease in the severity of seizures, only in the AcOEt group was observed. On the other hand, an increase in the frequency of AcOEt group and a decrease of MeOH group were observed. Our data indicate that extracts of the Tilia promote anticonvulsive effects on the amygdala kindling.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.01/NN16

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH
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**Title:** Investigation of the neuroprotective role of N-terminal beta amyloid fragments against beta amyloid-induced toxicity in glia

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**Abstract:** A chief hallmark of Alzheimer's disease (AD) is the accumulation of soluble, oligomeric beta amyloid (Aβ) peptide, promoting neurodegeneration and chronic neuroinflammation. Chronically elevated Aβ levels induce persistent glial cell activation that exacerbates neuronal death by limiting synaptogenesis, upregulating phagocytic activity to remove synapses, and increasing the secretion of pro-inflammatory species into the neuronal environment. Currently, there is no effective cure for AD, but controlling neuroinflammation may be critical for developing a successful anti-inflammatory AD treatment.
Previously, we have shown that the endogenous N-terminal fragment of $A\beta_{1-42}$, termed $A\beta_{1-15}$, and its critical hexapeptide core sequence, $A\beta_{10-15}$ (Aβcore), protect against full-length $A\beta_{1-42}$-induced cellular neurotoxicity and synaptic dysfunction in neurons. Our objective was to investigate whether the neuroprotective functions of these N-terminal Aβ fragments extend beyond neurons to glia cells. In this study, we examined the neuroprotective potential of the N-terminal Aβ fragments against $A\beta_{1-42}$-induced toxicity in primary astrocytes and microglia. Primary glia, cultured from mouse cortex, were treated with media (control) or 2.5 μM $A\beta_{1-42}$, $A\beta_{1-15}$ or Aβcore, alone or in combination, over the course of several days prior to examining alterations in cellular toxicity (oxidative stress: ROS assay, nuclear disintegration: Hoechst stain and cell viability: direct cell counts), calcium homeostasis (live cell calcium imaging) and mitochondrial membrane potential disruption (TMRE staining) due to calcium overload. Our results demonstrate that co-treatment with either 2.5 μM $A\beta_{1-15}$ or Aβcore mitigates the cytotoxic actions of $A\beta_{1-42}$. Elevated levels of $A\beta_{1-42}$ have been shown to disrupt calcium homeostasis in glia to evoke persistent activation of many cellular pathways. We have shown that co-treatment with the N-terminal Aβ fragments prevent the pronounced Aβ-triggered increase in neuronal

intracellular calcium levels. We expect the N-terminal Aβ fragments will compete with $A\beta_{1-42}$, producing differential responses in intracellular calcium concentrations in primary microglia and astrocytes while remaining bound to target Aβ receptors, similar to that seen in neurons.
In conclusion, the findings of this study provide insight into the protective function of the N-terminal Aβ fragments in primary glial cells. These results provide a basis for the development of novel approaches for maintaining the neurosupportive role of astrocytes and microglia in AD by reducing or reversing $A\beta_{1-42}$-induced glial toxicity.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.02/OO1

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Impact of traumatic stress on t cell repertoire complexity

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**Abstract:** A large segment of ongoing investigations on stress response and immune dysregulation primarily focus on global analysis of immune mediators such as cytokines and chemokines and tissue molecular signatures in stress responses, but not on specific immune cell behavior. Immune cell phenotype analysis in a few studies has yielded limited insight into how stress induces and/or maintains an inflammatory state, which underpins the low grade chronic systemic inflammation observed in Post-Traumatic Stress Disorder (PTSD) and contributes to the various pathologies and co-morbidities associated with this disorder. The purpose of this study is to survey the T cell receptor (TCR) repertoire complexity in a mouse model with key (PTSD)-like features in order to gain better insight into how clonal diversity is affected as a functional measure of disrupted immune regulation in an antigen free setting. The model involves exposure of an intruder (male C57BL/6) mouse to a resident aggressor (male SJL) mouse for 10 consecutive days. Thymus and lymph node were harvested for T cell receptor (TCR) repertoire analysis after one day rest following the 10-day trauma. To our surprise, we observed trauma induced clonal expansion in the lymph nodes of aggressor exposed mice, but not control mice, which remained largely diverse in their clonal repertoire. Thymic T cell

diversity remained even both in aggressor exposed and control mice. If these implications of stress mediated clonal expansion in mice may help explain the etiology of PTSD and its co-morbidities, we are interested in exploring if this initial observation translates to humans. Currently, we are assessing the T cell receptor (TCR) repertoire complexity in retrospectively collected blood specimens from OIF/OEF veterans diagnosed with PTSD and controls in age, sex, race, and HLA (Human Leukocyte Antigen) matched settings. Disclaimer: Research was conducted in compliance with the Animal Welfare Act, and all other Federal requirements. The views expressed are those of the authors and do not constitute endorsement by the U.S. Army.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.03/OO2

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

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**Title:** Identification of immune cells infiltrating nociceptive circuitry in CB2 cannabinoid receptor reporter mice using flow cytometry

**Authors: *L. M. CAREY, IV**[1,2], Z. XU[3], G. RAJIC[3], J. ROMERO[5], C. HILLARD[6], K. MACKIE[7,2,4], A. G. HOHMANN[3,2,4]
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**Abstract:** Immune cell infiltration into nociceptive circuitry, and subsequent secretion of pro-inflammatory factors, is thought to contribute to neuroinflammation, which may underlie the development and maintenance of pathological pain states. Cannabinoid type 2 receptors (CB2) are present at varying levels in virtually all immune cells, where their activation regulates many aspects of immune cell function, including immune cell activation status, chemotaxis/infiltration

to sites of injury and the release of pro-inflammatory factors. However, immunohistochemical identification of CB2 receptor expressing cell populations in the nervous system has been problematic due to a lack of specificity of available antibodies. We, therefore, developed mice with green fluorescent protein (GFP) following the coding sequence of CB2 in the endogenous CB2 locus to identify CB2-expressing cell types within nociceptive circuitry (Lopez et al. (2018) J. Neuroinflammation, in press). However, several common methods of tissue fixation used in preparation for histological procedures have been reported to compromise GFP function/fluorescence and elevate autofluorescence in other native proteins, possibly leading to decreased sensitivity in detecting GFP signals. The present studies compared the ability to detect native GFP fluorescence in the spleen, sciatic nerve, dorsal root ganglia (DRG) and spinal cord using both traditional histological procedures and using flow cytometry staining procedures carried out in intact, living cells. In formaldehyde-fixed tissue harvested from CB2 GFP reporter mice a strong GFP signal was observed in spleen and DRG, but GFP fluorescence in the sciatic nerve and spinal cord was below the threshold for detection. More work is necessary to determine whether tissue fixation may compromise GFP fluorescence and limit ability to detect smaller populations of GFP-positive cells. By contrast, using flow cytometry procedures we were able to detect small, discreet populations of GFP-expressing cells, as marked by CD45 expression, in spleen, spinal cord, sciatic nerve and DRG. Moreover, no differences in distributions of CD45-labeled immune cells were observed in untreated CB2f/f relative to wildtype mice in spleen, sciatic nerve or lumbar spinal cord, further validating use of CB2f/f mice in the present studies.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.04/OO3

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** SAH-induced hippocampal disturbances

**Authors: *G. W. BRITZ**, E. I. BOVSHIK, A. S. REGNIER-GOLANOV, E. V. GOLANOV
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**Abstract:** Overwhelming majority of subarachnoid hemorrhage (SAH) survivors (up to 95%) experience various long-term memory and cognitive abnormalities along with chronic fatigue, depression, and seizures. Atrophy of the temporomesial area observed in SAH survivors is suggestive of hippocampal abnormalities following SAH. We hypothesize that SAH induces

long term pathological changes in hippocampal formation, which lead to various neurocognitive aberrations. We explored morphological and functional changes in hippocampus (Hpc) in subacute period (4 days) following the SAH induced by perforation of the circle of Willis in mice (male C56BL/6J, 10-14 weeks old). SAH was induced in anesthetized animals, and they were allowed to recover. Four days following the SAH animals were anesthetized and transcardially perfused with saline followed by 4% formaldehyde solution. In a separate group of animals LTP in dentate gyrus (DG) in response to perforant pathway stimulation was explored *in vivo*. Brains were extracted, sliced and histologically processed (immunohistochemistry, Golgi, Nissl staining) to explore histopathological consequences of SAH. Upon histological examination we did not observe blood in the ventricles. Prussian blue staining did not reveal presence of iron in Hpc. Using Nissl stained images, we counted number of cells in Hpc CA1 and DG areas. Number of cells was comparable in naïve and SAH animals. We did not observe fluoro-jade C or activated caspase 3 positive cells in CA1 or DG. However, immunohistochemistry revealed significant activation of astro- and microglial cells in CA1 and DG areas ($p=0.035$) compared to naïve or sham animals. Immunoreactivity of glial fibrillary acidic protein (specific astrocyte marker), increased two-fold ($p=0.013$) compared to sham control suggesting activation of astroglia. Immunoreactivity of ionized calcium-binding adapter molecule 1 (microglial marker) increased by 1.5-fold ($p=0.038$). Hpc neuroinflammation was accompanied by loss of dendritic spines of the DG and CA1 neurons ($p<0.001$). Intensity of MAP2 staining decreased ($p=0.031$). Loss of dendritic spines was accompanied by suppression of LTP in DG in response to perforant pathway stimulation. Intraperitoneal injection of anaphylatoxin receptor C3aR antagonist, *SB*290157, reversed suppression of LTP. Our data demonstrate that 4 days following the perforation of Willis circle hippocampal neuroinflammation developed while no neuronal death was observed. The reversal of functional Hpc abnormalities by block of complement C3aR receptors suggests involvement of complement system in SAH-induced hippocampal disturbances.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

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**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH R01NS093362
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**Title:** Loss of progranulin (PGRN) dysregulates blood and brain immune cells populations and may contribute to neuroinflammation and neurodegeneration in frontotemporal dementia (FTD)

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**Abstract:** Heterozygous mutations in the progranulin gene (*GRN*) cause frontotemporal degeneration (FTD) by reducing levels of progranulin (PGRN) and granulins (GRNs). Furthermore, elevation of PGRN is neuroprotective and decreases amyloid β (Aβ) deposition in APP transgenic mice. Strategies to increase PGRN have been proposed to treat PGRN-deficient FTD and Alzheimer's disease (AD). Although expressed in neurons, PGRN is also highly expressed in microglia and peripheral immune cells. Moreover, *Grn* deficiency in mice is associated with marked increases in CD68+ myeloid cells, pro-inflammatory cytokine production, and circuit-specific synaptic pruning via complement activation. However, it is not known how PGRN loss in central and peripheral immune cells affects neuronal survival. Therefore, we focused on understanding how PGRN loss in microglia and peripheral immune cells may promote neurodegeneration. We performed immunohistological, proteomic, and deep-immunophenotyping by flow cytometry on brain, spleen, and peripheral blood of *Grn* KO and WT mice ages 3-30 months. We found that in aged *Grn* KO mice microglia the CD45 intermediate; CD11b high population in the brain is increased relative to WT mice and a large fraction of them express MHCII and CD68 relative to WT mice, suggesting that peripheral immune cells have infiltrated the CNS. In the blood, we also found 1) a generalized increase in total numbers of immune cells, 2) an increased frequency of total T cells in *Grn* KO vs WT mice, 3) a decreased frequency of MHCII+ cells within Ly6C lo monocytes (alternative activation), and 4) increased CD68 on Ly6C- monocytes. *Grn* KO mice also displayed decreased Natural Killer (NK) and B cells, and macrophages in the spleen with decreased expression of MHC-II. We identified unique functional profiles of lysosomal-associated proteases, cathepsin D and pan-cysteine cathepsins, among peripheral immune cell subsets with the greatest activity in $CD44^{high}CD11b^{high}$ monocytes. Proteomics and immunohistology also support the conclusion that peripheral immune cells infiltrated the CNS of *Grn* KO to a greater extent than in WT mice. These novel findings suggest that loss of PGRN leads to disruption of innate and adaptive immune responses. Analysis of peripheral immune cells may shed light on the mechanism of PGRN in FTD and AD patients with *GRN* mutations or SNPs.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

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**Title:** Anti-depressive effects of ChaiHu ShuGan formula and its possible neuroinflammation modulation mechanism in the reserpine induced ratdepressive-like model

**Authors: *J. ZHAO**, X. S. GAO[1], A. N. WANG[1], Y. Z. WANG[1], Z. Z. WEI[2], Y. B. ZHANG[1], L. WEI[1,2], N. WU[3], L. LI[1]
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**Abstract:** Introduction: The ChaiHu ShuGan Formula (CHSG) have shown improved effects in treating depressive symptoms. In this investigation, we utilized the reserpine-induced rat depression model to study the mechanisms underlying anti-depressive and neuroinflammation-modulatory effects of CHSG. Methods: We used fluoxetine, a selective serotonin reuptake inhibitor (SSRI), to analyze the comparable results for anti-depressive effects. Male SD rats were divided into 4 groups (n=12 per group): sham group, depression group, depression and CHSG group, and depression and fluoxetine group. These animals were given reserpine (0.3mg/kg, intraperitoneal, daily). CHSG and fluoxetine (10 mg/kg) were both orally administered. Our data showed that 14-day treatment was able to induce depressive behaviors in the animals. The current study used manual evaluation, automated open field test (OFT), and the forced swimming test (FST) to assess the anxiety and depression. We measured inflammatory factors in the serum by ELISA. The study also attempted to measure their expression level in the Raphe Nuclei regions by RT-PCR. Results: Animals in the depression groups demonstrated horripilation, back like standing, low activities, and irritability in their home cage. There was a slower body weight-gain rate in depression groups of animals. The OFT results showed significantly less travel distances. The FST results showed significantly increased immobility time. In the treatment groups, CHSG and fluoxetine both significantly increased body weight-gain rates, increased the travel distance in the OFT test, and reduced immobility time in the FST

test compared to the reserpine alone group. Levels of IL-1β, IL-6, and TNF-α in both serum and brain were increased in the reserpine alone group and reverted after CHSG and fluoxetine treatment. Conclusion: The study confirmed that CHSG could improve the general and depressive symptoms in the reserpine-induced depressive rats and reduce brain inflammation.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.07/OO6

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH grant NS036232

**Title:** Loss of huntingtin-associated protein 1 alters glucocorticoid-mediated hypothalamic responses in mice

**Authors: *X. CHEN**[1,2], S. LI[1], X. LI[1]
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**Abstract:** Abstract: Huntingtin-associated protein 1 (HAP1) was originally identified as a neuronal protein that interacts with the Huntington's disease protein, huntingtin. HAP1 is highly expressed in the hypothalamus, and is known to be critical for postnatal hypothalamic function and growth. It is also known that glucocorticoids (GCs) and glucocorticoid receptor (GR) regulate stress response and hypothalamic function. It is not yet clear whether HAP1 has a role in GR-mediated stress response. We used germline Hap1-KO mice to investigate GR expression in postnatal day 1 (P1) pups. We found the expression or distribution of GR was not significantly different in CNS of P1 HAP1-/- mice as compared with P1 HAP1+/+ or HAP1+/- mice. However, in P1 Hap1-KO mice injected intraperitoneally with dexamethasone (1 mg/Kg), the number of GR immunoreactive cells was dramatically decreased in hypothalamus compared with P1 WT and HAP1+/- mice while the expression of GR had no change in the cortex and cerebellum. These findings suggest that the HAP1 is involved in glucocorticoid-mediated stress response in the hypothalamus in mice, which may account for the fact that loss of HAP1 affects the survival and growth of animals.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.08/OO7

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Alterations in the density and signaling of the hippocampus histamine $H_3$ receptors in a rat model of Diabetes Mellitus I

**Authors: *W. MONTEJO-LOPEZ**[1], J. ARIAS-MONTANO[2]
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**Abstract:** Diabetes Mellitus type I (DM-I) is a complex metabolic disease with impaired insulin production and hyperglycemia. Streptozotocin (STZ)-induced diabetes results in morphological and functional alterations in the rat hippocampus, such as decreased neuronal plasticity (proliferation and neurogenesis), neurochemical changes and modifications in insulin signaling pathways. The histamine $H_3$ receptor ($H_3R$) is abundantly expressed in the hippocampus, where it regulates the release of histamine, acetylcholine, noradrenaline and glutamate. In diabetic rats, the content of histamine and telemethyl-histamine, its main metabolite, increases throughout the brain, and we inferred that increased histaminergic transmission may contribute to cognitive deficits in diabetic rats. The aim of this work is therefore to evaluate $H_3R$ density and function in the hippocampus of STZ-treated female Wistar rats. In membranes from hippocampal synaptosomes, which contain mainly pre-synaptic receptors, $H_3R$ density, evaluated with [$^3$H]-NMHA binding, increased significantly on days 14 and 21 after STZ treatment ($B_{max}$ control animals: day 7, 161 ± 2 fmol/mg protein; day 14, 213 ± 4; day 21, 163 ± 4; $B_{max}$ treated animals: day 7, 263 ± 32; day 14, 810 ± 30; day 21, 1231 ± 23). In membranes from the whole hippocampus (total receptors), $H_3R$ density was also significantly larger ($B_{max}$ control animals: 285 ± 34 fmol/mg protein; treated animals: day 7, 663 ± 56; day 14, 825 ± 82; day 21, 1150 ± 110). $H_3Rs$ couple to $G\alpha_{i/o}$ proteins and trigger several signaling pathways, including the activation of the MAPK and Akt/GSK-3β pathways. In hippocampal slices from STZ-treated rats, ERK-1/2 phosphorylation induced by the $H_3R$ agonist immepip (1 μM) was significantly attenuated, with maximum phosphorylation (168.4 ± 18.8% of basal at 5 min) reduced to 52.3 ± 3.4%, 56.2 ± 17.5% and 54.6 ± 2.7% at 7, 14 and 21 days after STZ administration, respectively). $H_3R$ activation (60 min) increased Akt phosphorylation ($Ser^{473}$) to 253 ± 25%, 295 ± 6% and 441 ± 29% of basal values at 7, 14 and 21 days after STZ administration, whereas in slices from control animals phosphorylation was significantly lower (163 ± 11% of basal). These results indicate that the induction of DM-I alters $H_3R$ density and signaling in the hippocampus of female rats.

**Disclosures: W. Montejo-Lopez:** None. **J. Arias-Montano:** None.

**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.09/OO8

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

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**Title:** Mutant FUS inhibits repair of oxidative genome damage in amyotrophic lateral sclerosis

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**Abstract:** Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the selective and progressive death of upper and lower motor neurons. This leads to progressive muscle weakness and death of the patient usually within 2 to 5 years after the start of the symptoms. The mutation of *FUS* (Fused in Sarcoma) gene has been linked to approximately 5% of familial ALS and 1% of sporadic ALS patients. Most missense point mutations in *FUS* are clustered in the DNA sequence encoding the nuclear localization sequence (NLS) in the C-terminus and induce nuclear depletion and cytosolic aggregation of FUS. Although FUS is associated with multiple genome repair pathways, its role in the DNA damage repair is poorly understood. In this study, we investigated the mechanism(s) responsible for the accumulation of oxidative DNA damage in the neuronal genome after the loss of FUS. We have characterized the interaction of FUS with DNA oxidative single strand break repair (SSBR) proteins and shown that FUS facilitates SSBR. The connection between FUS mutations and SSBR defects was examined in multiple model systems, including CRISPR/Cas9-mediated FUS knockout (KO) cells, familial ALS patient-derived induced pluripotent cells (iPSCs) with FUS mutations, motor neurons differentiated from these patient-derived iPSCs, and spinal cord tissue with FUS pathology from ALS patients. Notably, we found that different mutant versions of FUS cause

defects in DNA ligation via different mechanisms. Together, results of our study provide novel molecular insights into a previously unknown SSBR defects in FUS-associated ALS, and suggests that SSBR- targeted therapies may prevent or reduce disease progression.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

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**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

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**Title:** Hippocampal neurons require high glutathione content to sustain dendrite integrity and cognitive function

**Authors: *J. P. BOLANOS**[1,2,3], S. FERNANDEZ-FERNANDEZ[1], V. BOBO-JIMENEZ[2], J. ROS[4], A. ALMEIDA[2]
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**Abstract:** Loss of brain glutathione has been associated with cognitive decline and neuronal death during aging and neurodegenerative diseases. However, whether glutathione fall precedes or follows neuronal dysfunction has not been unambiguously elucidated. Previous attempts to address this issue were approached by abolishing glutathione, a strategy causing abrupt lethality or premature neuronal death that led to multiple interpretations. To overcome this drawback, here we aimed to moderate glutathione loss by genetically knocking down the rate-limiting enzyme of glutathione biosynthesis in mouse neurons in vivo. Biochemical and morphological analyses of the brain revealed a modest glutathione decrease and redox stress throughout the hippocampus, although neuronal dendrite disruption and glial activation was confined to the hippocampal CA1 layer. Furthermore, the behavioral characterization exhibited signs consistent

with cognitive impairment. These results indicate that the hippocampal neurons require a high content of glutathione to sustain dendrite integrity and cognitive function.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.11/OO10

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** Supporting Fund for Undergraduate Thesis of the University of Costa Rica's Vicerrectory of Research

**Title:** Chronic corticosterone administration without posterior immune challenge induces depressive-like behavior and microglia priming but not proliferation in young adult and middle age rats

**Authors: *D. QUESADA-YAMASAKI**[1], J. F. FORNAGUERA-TRÍAS[2], A. MORA-GALLEGOS[3]
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**Abstract:** Microglia cells play an important role regulating the proinflammatory signaling in the brain and their activation state is suggested to be affected by chronic stress and age. Therefore, this study aimed to assess the amount of microglial cells in three different brain regions as a measure of their proliferation due to stress-driven activation. Briefly, young (21 post-natal days [PND], *Y*) and middle age (330 PND, *MA*) male Sprague Dawley rats were treated for 14 consecutive days with subcutaneous injections of: a) 40 mg/kg corticosterone (*CORT*, n=10), b) a saline vehicle containing 2% v/v polysorbate 80 (*VEH*, n=10) or c) received no treatment at all (*NT*, n=12). From day 15, a set of behavioral tests were carried out: Open Field Test (*OFT*, day 15), Elevated Plus Maze (*EPM*, day 16) and Fear Conditioning (*FC*, days 17-19). Animals continued to receive their respective treatment (every day after each behavioral test) until euthanasia, where rats were anesthetized and transcardially perfused, first with a 0.9% saline followed by a 4% formaldehyde solution. Subsequently, brains were extracted, frozen and sliced. Sections corresponding to medial prefrontal cortex (*mPFC*), dorsal hippocampus (*dHPC*) and amygdala (*AMG*) were stained using fluorescently marked anti-Iba1 antibodies and mounted on slides with a DAPI-containing medium. Regarding behavioral testing, in both *Y* and *MA* rats, the *CORT* group exhibited lower weight gain across time and less locomotion in *OFT* than *VEH* and

*NT* controls, which has been associated in previous studies with depressive-like behaviors. In *EPM*, only age-related differences were found, with *Y* rats spending more time in open arms, as well as showing less risk assessment behaviors, which can be interpreted as reduced anxiety-like behavior compared with *MA* rats. During FC, all animals showed an increase of freezing percentage over time in both training and test sessions, but no differences by group or by age were observed. Finally, microglial cell count (expressed as Iba1+ cells/100 DAPI-marked nuclear elements) was lower in *CORT* when compared to *NT* rats in *mPFC* and *dHPC*, whereas no group differences were found in *AMG*. Altogether, these results confirm that chronic glucocorticoid treatment induces depressive-like behavior but not anxiety-like behaviors in rats, while suggesting that exposure to chronic stress may sensitize microglial cells but is not sufficient to induce an activation-triggered proliferation of these cells.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.12/OO11

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** PFCE 2017-18-BUAP CA 154

**Title:** Comparison of the temporal proinflammatory process of two traditional Parkinsonian models *in vivo*

**Authors: *I. PARRA**, I. MARTÍNEZ GARCÍA, E. HERNÁNDEZ ARRAMBIDE, D. I. LIMÓN, F. LUNA, V. ALATRISTE, L. MENDIETA
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**Abstract:** Parkinson’s disease (PD) is a progressive neurodegenerative disease characterized by the 80% of loss of dopaminergic neurons. Parkinson's Disease’ etiology mechanism continue being unknown, nevertheless, the activation of cellular innate immune response has been related to this suffering. In this work, we studied the proinflammatory response of microglial cells and their consequences in the dopaminergic cells of the nigrostriatal pathway in two animal models of PD. Adult Male Wistar rats received an injection of 6-hydroxydopamine (6-OHDA; 16 µg/2µL) or lipopolysaccharide (LPS; 32µg/2µL) in the dorsolateral striatum by stereotaxic surgery. The progression of proinflammatory response was followed during 1, 7, 14 days post-injection, then TNF-alpha, IL-1-beta and NLRP-3 markers were examined in striatum or substantia nigra pars compacta (SNpc). In addition, we evaluated the morphological changes in

the microglial cells by IBA-1-marker and, finally, we studied the toxicity of 6-OHDA or LPS on the motor asymmetry using the cylinder model and neurodegeneration of the nigrostriatal pathway by TH staining in striatum and SNpc. Our results demonstrated that both agents, 6-OHDA, and LPS caused a motor asymmetry behavior and decrease the TH staining from striatum and SNpc after 14 days. However, the proinflammatory response was found different in each animal model of PD, at the time that LPS caused a higher IBA-1-staining and the classical activation form of microglia respect to 6-OHDA-treated animals. In summary, both PD animal models were able to cause a proinflammatory response, though each one has a particular way to regulate its inflammatory answer of microglial cells from striatum and SNpc.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 762.13/OO12

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

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**Title:** Kv1.3 as a target to inhibit detrimental M1 microglia functions in ischemic stroke, Alzheimer's and Parkinson's disease

**Authors: *H. WULFF**[1], H. M. NGUYEN[1], Y.-J. CHEN[1], I. MAEZAWA[2], S. SARKAR[3], L.-W. JIN[2], A. G. KANTHASAMY[3]
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**Abstract:** 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. In fact, the Kv1.3 blocking peptide ShK-186 has recently been found to be effective in a psoriasis Phase-1b study. Based on the observation that Kv1.3 is also expressed on microglia in postmorten Alzheimer’s disease (AD), Parkinson’s disease (PD) and stroke brains we hypothesized that Kv1.3 blockers might also be useful for reducing neuroinflammation. Starting with cultured microglia, we found that Kv1.3 expression is up-regulated in pro-inflammatory M1-like microglia and that Kv1.3 blockers preferentially reduce the production of IL-1beta, TNF-alpha and NO without affecting IL-10

production. In organotypic hippocampal slices exposed to hypoxia/aglycemia or AβO Kv1.3 blockers significantly reduced microglia activation and increased neuronal survival. We further found increased Kv1.3 channel activity in acutely isolated microglia from 5xFAD mice or the infarct area of MCAO mice. *In vivo* treatment experiments with PAP-1 revealed that Kv1.3 blockade reduced infarction and improved neurological deficit when administered 12 hours after reperfusion in both mouse and rat models of ischemic stroke. PAP-1 was similarly effective in two models of amyloid-induced neuropathology: In mice receiving intrahippocampal injections of AβO daily oral PAP-1 for 8 days improved performance in the step-through passive avoidance test, while PAP-1 medicated diet administered for 5 months to APP/PS1 mice starting at 9 months of age improved memory deficits, and reduced cerebral Aβ-amyloid load and inflammatory marker expression. Parallel experiments in PD models demonstrated that Kv1.3 inhibition reduced aggregated α-synuclein induced inflammation in cell culture and exhibited anti-inflammatory and neuroprotective effects in the MPTP mouse model and reversed behavioral deficits and dopamine loss in MitoPark mice, a progressive model of PD. We propose Kv1.3 inhibitors as potential therapeutic agents for preferentially inhibiting pro-inflammatory M1 microglia functions in multiple neurological diseases.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.14/OO13

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Title:** Andrographolide exerts neuroprotection by inhibiting NF-κB associated NLRP3 inflammasomes in chronic unpredictable mild stress model

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**Abstract:** Depression is a stern neuro-psychiatric hitch with a lifetime prevalence exceeding 15% and has become the fourth leading cause of disability worldwide. Emerging evidence suspect the role of inflammation induced by NLRP3 inflammasomes in the pathogenesis of depression. Therefore inhibiting NLRP3 inflammasomes could provide a therapeutic benefit in halting the progression of the disease. Hence the present study was designed to investigate the hypothesis that andrographolide exerts neuroprotection by inhibiting the inhibiting NF-κB associated NLRP3 inflammasomes in chronic unpredictable mild stress (CUMS) model. Rats

exposed to CUMS showed behavioral deficits in physical state, the sucrose preference test (SPT) and the forced swimming test (FST) and exhibited a significant increase in oxidative-nitrosative stress markers, inflammatory mediators, including tumor necrosis factor-alpha (TNF-a) and interleukin-1β (IL-1β), activation of the nuclear factor kappa B (NF-κB) signaling pathway. Andrographolide treatment significantly reversed the decrease of sucrose consumption, the loss of body weight, the reduction of immobile time in the tail suspension tests (TST) and forced swimming tests (FST) induced by CUMS paradigm. Our results further demonstrate that, andrographolide negatively regulated the activation of the nod-like receptor protein (NLRP3) inflammasome/caspase-1/IL-1β axis in the hippocampus of CUMS rats. These results confirm that andrographolide exerts antidepressant-like effects, which may be mediated by enhanced antioxidant status and anti-inflammatory effects on the brain tissue via the inhibition of NF-κB signaling activation and the NLRP3 -inflammasome/caspase-1/IL-1β axis. Our findings provide new information to understand the antidepressant action of andrographolide, which is targeted to the NLRP3-inflammasome in the brain.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.15/OO14

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** Peter Deane Trust
Hope for Depression Research Foundation

**Title:** The monocytic inflammatory response to head trauma is contained by Apobec1-mediated RNA editing

**Authors: *E. M. O'CINNEIDE**[1], J. D. GRAY[1], N. F. PAPAVASILIOU[2], L. MOLLA[1], B. S. MCEWEN[1], K. BULLOCH[1]
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**Abstract:** Mild traumatic brain injury (mTBI) is the most common form of brain injury in humans and can result in long-term sensory, cognitive, and motor deficits accompanied by neurological symptoms. The neurological damage resulting from a traumatic impact is characterized by a complex neuroinflammatory response consisting of microgliosis, astrocytosis, activation of pro-inflammatory cytokines and infiltration of peripheral immune cells. Microglia

(MG) play an important role in regulating the neuroinflammatory response by producing pro- and anti-inflammatory cytokines, clearing cellular debris, and secreting neurotropic factors. Our lab has previously identified a subset of brain resident immune cells which express CD11c and are functionally distinct from $CD11c^{neg}$ microglia (defined as $CD45^{int}/CD11b^{hi}$) (Bulloch et al., 2008). Post-transcriptional modification, such as RNA-editing by Apobec1 (apolipoprotein B editing complex 1) is involved in the regulation of the microglial response to damage in the CNS. Apobec1 deletion in mice leads to neuroinflammation with increases in pro-inflammatory cytokines produced by MG, abnormal myelination, and MG clustering which are accompanied by cognitive and motor deficits (Cole et al 2017). The current study examines the possible influence of Apobec1-mediated RNA-editing in CD11C+ and MG function following mTBI. In mice subjected to mTBI, there was an increase in the number of CD11c-$EYFP^{+}$ cells in the olfactory bulb and subventricular zones, indicating a state of inflammation within the post-natal neurogenesis pathway. We also observed increases in CD11C+ cells in other white matter areas prone to damage from diffuse injury, such as the corpus callosum and optic tract. Apobec1-KO mice showed significantly more motor impairment following mTBI compared to wildtype mice also subjected to mTBI. This data suggests lack of Apobec1-mediated RNA-editing may exacerbate the secondary injury response and alter mTBI-induced neurogenesis.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

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**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NEI RO1-EY024320
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**Title:** Responses of both microglia and monocytes to neurodegeneration *in vivo*

**Authors: *E. MILLER**[1], P. ZHANG[2,3], R. J. ZAWADZKI[3,2,4], E. N. PUGH, Jr[3,2,4], M. E. BURNS[1,4,3]
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**Abstract:** Both resident microglia and infiltrating monocytes have been implicated in the sterile immune response to neurodegeneration, but the role(s) of each cell type during disease

progression are unclear. Using non-invasive, *in vivo* retinal imaging of Cx3CR1+/gfp and CCR2+/rfp mice, we have recently quantified the spatiotemporal dynamics of microglia and monocytes during both widespread and localized acute photoreceptor degeneration. In healthy retina, microglia are reliably located in the synaptic and fibrillary layers of the retina. However, within 24-48 hours of the onset of widespread degeneration, microglia extend processes axially across retinal layers and migrate to the damaged photoreceptors where they phagocytose stressed and dying neurons. Over the same time period we visualized massive monocyte extravasation from blood vessels and migration into the parenchyma. Monocytes were absent from healthy retina, but began to adhere to the vessels before eventually crossing the vascular barrier and entering the retina. When the insult was more mild and localized, in vivo time-lapse imaging revealed microglia begin to migrate toward the damaged photoreceptors by eight hours, and cells are progressively recruited over the first 24 hours, resulting in a dense cluster of Cx3CR1-gfp+ cells at the damaged location. The microglia in the local area clearly migrated, resulting in a loss of microglial density in the retina surrounding the damage. Remarkably, monocytes also extravasated in response to this mild neuronal stress, appearing in the retina roughly 48 hours after onset of damage. The response of microglia and monocytes abated as the signs of neuronal damage faded over a period of weeks. This is the first evidence that both microglia and monocytes simultaneously respond to mild (cell-autonomous) neuronal stress and a convenient model for studying the activation and resolution of the heterogeneous innate immune response to degenerative disease.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

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**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

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Danish National Association for Multiple System Atrophy

**Title:** Epigenome-wide association study on prefrontal cortex tissue from multiple system atrophy patients shows indications of an activated immune system

**Authors: *R. RYDBIRK**[1], T. BRUDEK[2], B. PAKKENBERG[2], J. TOST[3], S. AZNAR[2]
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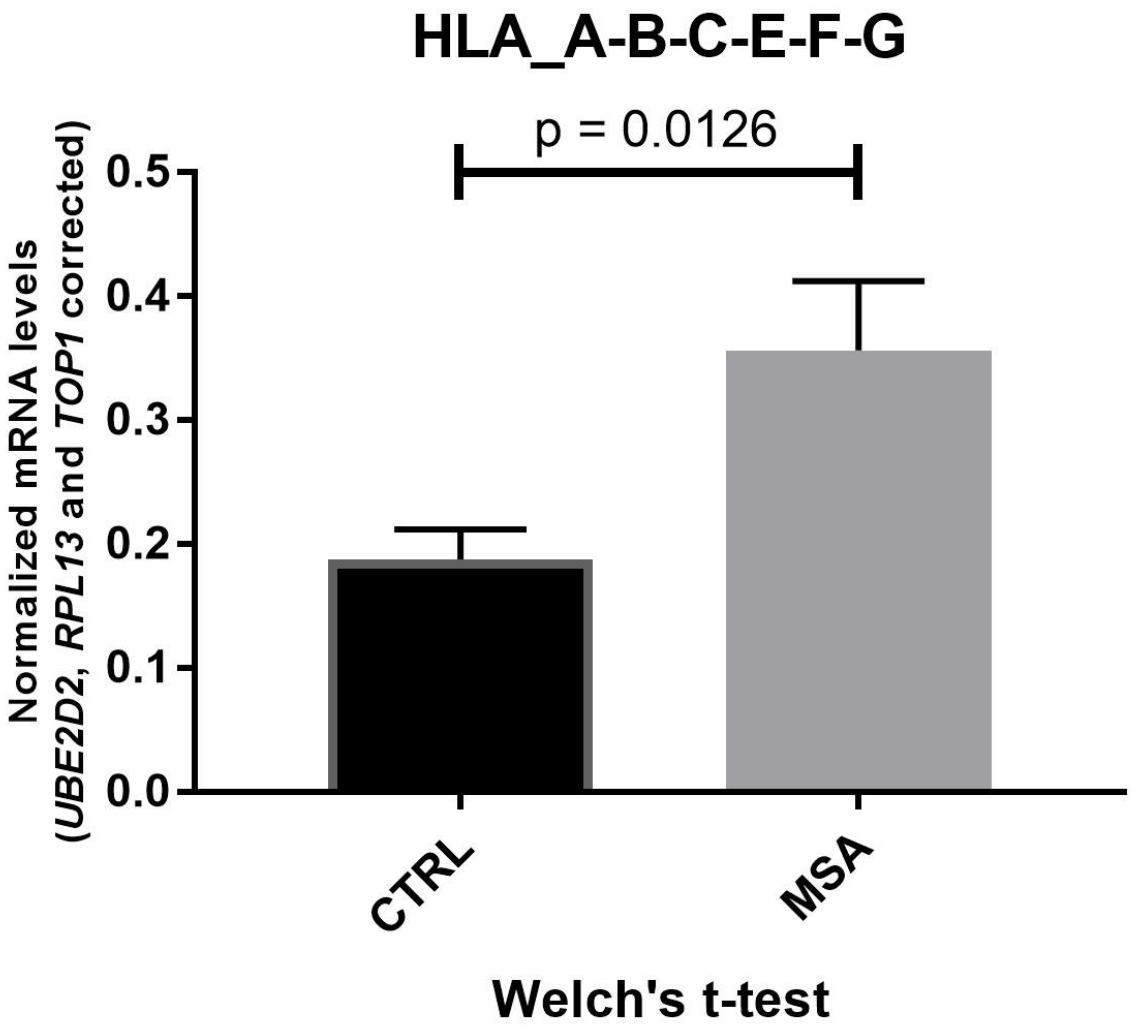
**Abstract:** Multiple System Atrophy (MSA) is a rare, fatal, neurodegenerative disease with an estimated survival time of eight years after diagnosis. The clinical diagnosis is difficult since in MSA, as in similar parkinsonian disorders, the disease is caused by accumulation of the protein alpha-synuclein in brain cells. Due to its low incidence, knowledge regarding the aetiology and progression of MSA is still very limited. In a previous study we found altered cytokine levels in MSA brains as an indicator of neuroinflammatory processes. In the present study, using a *state-of-the-art* approach, we screened for epigenetic changes in order to identify genes that may be transcriptionally altered through epigenetic modifications which will aid in mapping affected regulatory pathways. We isolated DNA from the dorsomedial prefrontal cortex of 37 MSA patients and 41 controls from brain banks at Bispebjerg Hospital (DK) and Kings College London (UK). We applied a conventional DNA extraction method and treated the DNA with a commercial kit (CEGX) that allowed us to quantify both methylated cytosines (5mC) and hydroxymethylated cytosines (5hmC) of the DNA. Infinium MethylationEPIC kits (Illumina) were run on an Illumina IScan instrument. Bioinformatic analyses were performed in R based on the ChAMP pipeline. We used the 2,000 most significant differently methylated positions for Gene Set Enrichment Analyses using the Gene Onthology database. The most significant pathways were related to antigen processing and presentation, autoimmunity and natural killer cell activity. We then performed Leading Edge Analyses to identify overrepresented genes involved in the top 10 pathways. We identified several genes related to antigen presentation, including HLA-A, -E and -F. Finally, using RT-qPCR we identified an overall increase in MHC class I expression in MSA patients compared with controls. In line with our previously results we find indications of an activated immune system in MSA. Future validation studies will determine the exact role of these mechanisms in relation to disease development and progression.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

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**Title:** The efficacy of Toll-like receptor 2 & 4 inhibitors in cultured human monocytes and in a novel rat model of Parkinson's disease

**Authors: *A. KOULI**, W.-L. KUAN, K. M. SCOTT, R. A. BARKER, C. H. WILLIAMS-GRAY
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**Abstract:** Background: Neuroinflammation is well described in the Parkinson's disease (PD) brain and we have shown that it is associated with faster cognitive decline during life. Toll-like receptors (TLRs) may be a key mediator of this neuroinflammatory response. Recent studies show that pathological aggregates of α-synuclein can initiate inflammatory responses via TLRs. Thus, blocking TLRs may be an effective therapeutic strategy for reducing neuroinflammation and slowing down disease progression. This study aimed to investigate the timecourse of neuroinflammatory response and TLR expression in a novel rat PD model and to test the efficacy of TLR-blocking agents in vivo, as well as in human PD monocytes *in vitro*.
Methods: Our novel rat PD model is based on the transvascular delivery of α-synuclein fibrils. Changes in TLR2/TLR4 levels in the brain were determined by Western blot at 2, 4 and 6 months. Subsequently, rats injected with α-synuclein fibrils were treated for 2 months with one of two TLR-blockers (TAK242 or Candesartan cilexetil) or vehicle. TLR2/TLR4 expression was evaluated in monocytes by flow cytometry at baseline, 1 and 2 months. After 2 months, TLR-levels were measured in the brain by Western blot. To determine the effect of TLR-blockers in human cells, monocytes derived from PD patients and control blood samples were incubated with TAK242, Candesartan or saline and subsequently stimulated with oligomeric α-synuclein or LPS. The inflammatory response was measured through quantifying TNFα and IL1β production using ELISA after 24 hours in culture at 37°C.
Results: Our data has shown an increase in Iba1 and TLR4 levels in the brainstem of the rat model starting at 2 months, and reaching significance at 6 months post α-synuclein injection. After a 2-month treatment, TAK242 led to a decrease in both TLR2+ and TLR4+ rat monocytes, while Candesartan did not. TLR levels in the brainstem were also decreased after TAK242 treatment, but not Candesartan. This suggests that TAK242 is a more effective TLR-blocking agent. Additional data on the human monocyte work is currently being collected.
Conclusion: Neuroinflammation in our novel PD rodent model is associated with an increase in TLR4 expression. Our pilot data indicates that TAK242 is an effective inhibitor of TLRs *in vivo*. We are now investigating its effects on human cells in vitro and its long-term impact on neurodegeneration in our rat model, which may have implications for treating human PD.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.19/OO18

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** The Michael J. Fox Foundation, Target Advancement, 13491

**Title:** Novel TLR2 small molecule antagonists inhibit alpha synuclein-induced pro-inflammatory signaling and cytokine release

**Authors: *A. M. HABAS**, S. NATALA, J. WONG, W. WRASIDLO, M. GILL, D. BONHAUS
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**Abstract:** Synucleinopathies are a family of central nervous system (CNS) degenerative disorders characterized by deposition of insoluble alpha-synuclein aggregates, neuronal and/or glial cell death and inflammation. Toll-like receptors (TLRs) play a critical role in the innate immune system response to damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). In Parkinson's disease, increased TLR2 expression was reported in patient brains and correlated with increased deposition of alpha-synuclein. TLR2 associates with TLR1 or TLR6 to form heterodimeric receptor complexes. DAMP/PAMP-mediated activation of TLR1/TLR2 or TLR2/TLR6 heterodimers triggers NFκB signaling resulting in pro-inflammatory cytokine release. Recently, secreted alpha-synuclein aggregates derived from over-expressing rodent neuroblastoma cells were shown to stimulate pro-inflammatory signaling in CNS-derived microglia. Genetic- and antibody-mediated TLR2 inhibition occluded this signaling cascade, suggesting TLR2 inhibition may be a viable strategy to disrupting alpha-synuclein-mediated inflammation. Here, using stable TLR2-expressing HEK, naïve monocyte/macrophage-derived heterologous cell lines and human microglia we confirm that TLR2 agonists activate pro-inflammatory signaling. Neuropore has developed different classes of novel, small molecule TLR2 antagonists to block alpha-synuclein-mediated inflammation. We demonstrate that allosteric but not competitive TLR2 inhibitors block TLR2-mediated signaling induced by endogenous agonists, suggesting that these inhibitors might be more effective against inflammation induced by alpha-synuclein. To that aim, we show that alpha-synuclein pre-formed fibrils (PFFs), generated from recombinant alpha-synuclein monomer, induce TLR2 signaling. We demonstrate using blocking antibodies, that specific inhibition of TLR1/TLR2 but not TLR2/TLR6 occludes alpha-synuclein-mediated pro-inflammatory signaling in TLR2-expressing HEK cells. However, the lack of reproducibility of generating large batch of alpha synuclein PFFs capable of activating TLR2 signaling has limited high-throughput screening efforts to identify specific modulators of higher order alpha synuclein

species-induced signaling. We actively are forming a collaboration network to establish of quality control standards for generation of alpha-synuclein PFFs which reliably activate TLR2 signaling. In summary, small molecule inhibition of TLR2 pro-inflammatory signaling is a feasible and intriguing therapeutic modality for reducing Parkinson's disease-related inflammation.

**Disclosures: A.M. Habas:** A. Employment/Salary (full or part-time):; Neuropore Therapies Inc. **S. Natala:** A. Employment/Salary (full or part-time):; Neuropore Therapies Inc. **J. Wong:** A. Employment/Salary (full or part-time):; Neuropore Therapies Inc. **W. Wrasidlo:** A. Employment/Salary (full or part-time):; Neuropore Therapies, Inc. **M. Gill:** A. Employment/Salary (full or part-time):; Neuropore Therapies, Inc. **D. Bonhaus:** A. Employment/Salary (full or part-time):; Neuropore Therapies, Inc..

**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.20/PP1

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIA Grant AG044919

**Title:** CX3CL1 isoforms display differential activity and rescue cognitive deficits in CX3CL1 knock out mice

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**Abstract:** Fractalkine (CX3CL1) is a chemokine expressed predominately by neurons that mediates communication between neurons and microglia. Microglia, the innate immune cells of the CNS, mount an inflammatory response when challenged by injury or infection in addition to playing a critical role in establishing and refining neural circuits. By regulating microglial activity, CX3CL1 can mitigate the damaging effects of chronic inflammation within the brain, a state that plays a major role in aging and neurodegeneration. CX3CL1 possesses two isoforms, a full-length membrane-bound form and a soluble form, generated by cleaving membrane-bound CX3CL1. Levels of soluble CX3CL1 decrease with aging, which could lead to enhanced inflammation, deficits in synaptic remodeling, and subsequent declines in cognition. Recently, the idea that these two isoforms may display differential activities within the CNS has garnered increasing attention, but has not been extensively explored. Here, we assessed the consequences

of CX3CL1 knock out on the cognitive behavior and therapeutic potential of the two different CX3CL1 isoforms in mice. CX3CL1 -/- mice displayed impaired long-term retention of a contextual fear conditioning task at 3 months of age. Moreover, CX3CL1 -/- mice tested on Barnes maze learned the location of an escape hole at a similar rate as wild type controls, but displayed an altered search pattern in a subsequent probe trial, spending less time in the target zone than their wild type counterparts. Cognitive impairments correlated with altered synaptic plasticity and impaired long-term potentiation (LTP), as well as decreases in neurogenesis within the hippocampus. Treating CX3CL1 -/- mice at 2 months of age with a viral vector expressing soluble (s)- CX3CL1 rescued the effects on LTP in addition to enhancing neurogenesis within the hippocampus. Treatment with s-CX3CL1 partially rescued the deleterious effects of CX3CL1 knock out on the Barnes maze task, however did not show rescue of long term memory retention on the contextual fear conditioning task. Studies of m-CX3CL1 are also being studied. These data suggest that the two different isoforms of CX3CL1 may possess differential activities within the CNS affecting cognition and highlight the therapeutic potential of treatments that enhance CX3CL1 signaling.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.21/PP2

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** 1I01BX000595
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1R01AG044919

**Title:** Pathway analysis of aging rat microglial proteome demonstrates therapeutic effect of polyphenols

**Authors: *A. JALLOH**[1], C. HUDSON[2], D. CHAPUT[2], S. STEVENS, JR[2], P. C. BICKFORD[3]
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**Abstract:** Microglia are the brain's resident macrophage that dynamically respond to pathogenic invasion, cellular damage, or cytokine signaling to initiate and resolve the immune response.

“Activated” microglia assume a pro-inflammatory phenotype, secreting cytotoxic factors. An additional process mediated by anti-inflammatory molecules, inhibits the pro-inflammatory phenotype and shifts microglial toward a restorative phenotype that promotes debris clearance and tissue repair. Aging perturbs microglial biology such that aging microglia become hyper-responsive to pro-inflammatory stimuli, generate excess cytotoxic factors, and become insensitive to anti-inflammatory molecules. Aged microglia are also increasingly unable to assume an anti-inflammatory phenotype. In this way, dysfunctional microglia become neurotoxic and increase CNS vulnerability. We have previously described age-related changes in rodent microglia using mass-spectrometry-based proteomics. Pathway analysis of differentially expressed microglial proteins from young (3 mo.) and aged (20 mo.) animals highlighted several cell functions altered with age. Functions annotated included transcriptional regulation, energy metabolism, and cytoskeleton remodeling. We identified RICTOR, a subunit of mTORC2, as an upstream regulator predicted inhibited with age. Our data indicated that RICTOR was a potential driver of the aging microglial phenotype, and highlighted its role as a possible therapeutic target. In this study, we evaluated the effect of polyphenol supplementation on mTORC2-related signaling pathways in aged rats. We isolated microglia from aged rats fed either a standard diet or a diet supplemented with NT-020, a proprietary blend of polyphenols including blueberry extract, green tea extract, l-carnosine, and vitamin D-3. Mass-spec analysis showed a predicted reversal of age-related RICTOR inhibition that accompanied decreased inflammation and actin cytoskeleton remodeling, as well as predicted altered chemotaxis and phagocytosis. We also identified Rho GTPases, Rac1 and Cdc42, as inflammatory mediators and cytoskeleton-remodeling proteins that signaled with RICTOR and were downregulated with NT-020 treatment. We validated our pathway analysis with functional assays measuring chemotaxis and phagocytosis, as well as PCRs measuring Rac1 and Cdc42 expression in HAPI cells. This study highlights the utility of polyphenols as therapeutic agents against age-associated microglial pathology.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.22/PP3

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** VA MRS I01BX000231

**Title:** Role of T cells in alpha-synuclein model of Parkinson's disease

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**Abstract:** Parkinson's disease (PD) is the second most prevalent movement disorder. It is characterized by up to 70% loss of dopamine (DA) secreting neurons and accumulation of Lewy bodies, deposits composed of α-synuclein (α-syn), in the remaining DA neurons of the substantia nigra pars compacta (SNpc). Accumulation of α-syn activates microglia, the immune cells of the central nervous system (CNS). Microglial over-activation causes inflammation and subsequently leads to neurodegeneration and tissue destruction. Inflammation caused by the activated microglia and dendritic cells has been associated with the pathogenesis of PD and several other neurodegenerative disorders. Recently, apart from microglia, CD4 and CD8 T cells have been shown to be recruited to the area of damage where they may either mediate neurodegeneration or act in a neuroprotective manner. The communication pattern between T cells, microglia and dendritic cells in PD patients is unknown. Previous work has shown that injection of human α-syn into the SNpc of the brain failed to induce neurotoxicity in MHCII (the marker for activated microglia) deficient mice, suggesting that T cell and microglial communication is necessary for the neurotoxic process. Here, we assessed the role of T cells in an α-syn model of PD in T cell deficient (male athymic nude) and T cell competent (male heterozygous nude) rats. Injection of AAV9 expressing human α-syn unilaterally to the SN of heterozygous nude rats at 3 months of age caused deficits in a cylinder test for paw bias in comparison to GFP-treated controls when the rats were tested 2 months post-injection. On the other hand, nude rats injected with α-syn showed no deficit in the cylinder test when compared to the controls. The percentage of tyrosine hydroxylase (TH) positive neurons in SNpc was significantly lower in α-syn injected T cell competent rats when compared to their T cell deficient rat counterparts. These data suggest that T cells may play a major role in DA neuronal loss and confirm that T cell communication with microglia is necessary for α-syn mediated neurodegeneration in Parkinson's disease.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.23/PP4

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** Indian Council of Medical Research, Govt. of India
Department of Biotechnology, Govt. of India

**Title:** Chitotriosidase modulates gliosis ensuing neurodegeneration in Amyotrophic Lateral Sclerosis

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**Abstract: INTRODUCTION:** Cerebrospinal fluid of Amyotrophic Lateral Sclerosis patients (ALS-CSF) induces neurodegenerative changes in motor neurons and gliosis in sporadic animal models of ALS. Search for identification of toxic factor(s) in ALS-CSF revealed a significant up-regulation of Chitotriosidase (CHIT-1) compared to normal CSF (NCSF) indicating its role as a biomarker for ALS. **AIM:** To determine the role played by CHIT-1 in pathophysiology of ALS. **METHODS:** Recombinant CHIT-1 at various doses was added to NSC-34 cells or intrathecally injected into Wistar rat neonates. The dosage for CHIT-1 treatments were based upon the average amount of CHIT-1 present in CSF of ALS patients (i.e, approximately 18 pg/ µl). Cell viability assay and immunocytochemistry of Choline Acetyl Transferase (ChAT), caspase 3 and TDP-43 was performed on NSC-34 cells after 48 hours of exposure. The expression of Iba1, arginase, inducible Nitric Oxide Synthase (iNOS), Glial Fibrillary Acidic Protein (GFAP) and Choline Acetyl Transferase (ChAT) was assessed in lumbar spinal cord of neonatal rats. **RESULTS:** CHIT-1 at various concentrations did not induce death of NSC-34 cells while, the positive control, i.e. ALS-CSF reduced their viability by 40% compared to buffer control or normal control. However, CHIT-1 exposure resulted in mild reduction in the florescence intensity of ChAT and slight increase in the florescence intensity of Caspase 3 even though not statistically significant. Intrathecal administration increased number of microglial cells and astrogliosis in both, white and grey matter of the ventral horn region of spinal cord. Several amoeboid shaped Iba1 immunopositive cells and GFAP immunopositive astroglia bearing long processes were present around the central canal. CHIT-1 altered the expression of arginase and iNOS in rat spinal cord. Also, CHIT-1 at a higher dose (500pg/µl) resulted in the death of motorneurones in rat neonates. **CONCLUSION:** CHIT-1 activates microglial and astroglial cells and prime them to attain a toxic phenotype which can result in neuroinflammation induced motor neuronal death.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.24/PP5

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NS061867
Barrow Neurological Foundation

**Title:** Biomarkers for astrocyte and microglia activation in als

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**Abstract:** ALS is a highly complex disease with multiple molecular mechanisms of disease resulting in a heterogeneous patient population. Enriching this population into subsets that exhibit a particular pathogenic mechanism would aid in identifying patients that could benefit from specific therapeutic approaches. However, one challenge is the absence of biomarkers for each pathogenic mechanism of disease. A number of recent ALS clinical trials have targeted inflammation (NP001 and Actemra). Therefore, additional biomarkers of neuroinflammation would be quite useful for stratification. Chitinases such as chitotriosidase (Chit-1), chitinase 3 like protein 1 (CHI3L1) and chitinase 3 like protein 2 (CHI3L2) have recently been explored as candidate biomarkers of neuroinflammation for ALS. Chit-1 and CHI3L2 are expressed by activated microglia while CHI3L1 has been shown to be expressed in both activated microglia and astrocytes. Analysis of CSF performed by our lab and others and have shown increased levels of these chitinases in ALS samples as compared to healthy controls. While levels of these biomarkers have been assessed in varying ALS sample types (biofuids and tissues), few studies have explored chitinases in longitudinal samples and no studies have looked at matching blood and cerebrospinal fluid (CSF) samples from the same patients. In this study, we assessed levels of Chit-1 and CHI3L1 in matching CSF and plasma samples from 120 ALS patients and 40 controls (diseased and healthy) using in house developed immunoassays. From a cross-sectional analysis, we observed increased levels of CSF Chit-1 in ALS samples as compared to controls. However, levels of plasma chit-1 as well as both CSF and plasma CHI3L1 exhibited no significant differences between the two groups. CSF and plasma Chit-1 levels correlated with ALS functional rating scale revised (ALSFRS-r) scores but not with disease duration indicating potential use of chit-1 as a diagnostic biomarker. CSF and plasma CHI3L1 did not correlate with these clinical variables. Longitudinal analyses of these chitinases in both CSF and plasma showed steady levels over time suggesting stability of these proteins in both biofluids. Additionally, absolute levels of CSF Chit-1 and CSF CHI3L1 were able to segregate patients

based on disease progression rates (fast vs. slow progressing ALS) indicating potential prognostic utility. Collectively, our results highlight the potential use of chitinases for diagnosis and predicting prognosis of ALS.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.25/PP6

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** Scientific Research 23111006
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**Title:** Innate immune adaptor TRIF confers neuroprotection in ALS mice by eliminating abnormal astrocytes

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**Abstract:** There is compelling evidence that glial-immune interactions contribute to the progression of neurodegenerative diseases. The adaptive immune response has been implicated in disease processes of amyotrophic lateral sclerosis (ALS), but it remains unknown if innate immune signaling also contributes to ALS progression. Here we report that deficiency of the innate immune adaptor TRIF, which is essential for certain Toll-like receptor (TLR) signaling cascades, significantly shortens survival time and accelerates disease progression of SOD1-ALS mice. While MyD88 is also a crucial adaptor for most TLR signaling pathways, MyD88

deficiency had only a marginal impact on disease course. Moreover, TRIF-deficiency reduced the numbers of natural killer (NK), NK-T, and CD8-T cells infiltrating into the spinal cord of ALS mice, but experimental modulation of these populations did not substantially influence survival time. Instead, we found that aberrantly activated astrocytes expressing Mac2, p62, and apoptotic markers were accumulated in the lesions of TRIF-deficient ALS mice, and that the number of aberrantly activated astrocytes was negatively correlated with survival time. These findings suggest that TRIF pathway plays an important role in protecting a microenvironment surrounding motor neurons by eliminating aberrantly activated astrocytes.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 762.26/PP7

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** CNRM Grant CNRM-70-9238

**Title:** Dysregulation of the ubiquitin proteasome system promotes neuro-inflammation and neuronal cell death in CNS injuries

**Authors: *G. KHAYRULLINA**[1], B. G. BURNETT[2]
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**Abstract:** Loss of neurons due to spinal cord, brain and diffuse blast injuries account for 2 million cases in the United States alone. The inflammatory response of the CNS resident immune cells has been suggested to worsen clinical outcomes and halt recovery after injury. These cells undergo rapid proteomic changes that rely on the cellular degradation machinery. Timely recycling of proteins for peptide presentation, cytokine release and maintenance of protein homeostasis are mediated by the ubiquitin proteasome system (UPS) and central to the immune response to CNS injury. The UPS is one of the two major protein degradation systems, comprised of ubiquitin conjugating enzymes and the core proteasome; all of which have been implicated in neurodegenerative diseases. Despite this, the direct role of the UPS in CNS recovery after injury remains unclear. This study aims to characterize the spatial and temporal dynamics of the proteolytic machinery in glia following brain and spinal injuries. Utilizing a controlled cortical injury, an Infinite Horizon spinal cord contusion, as well as moderate blast

model on mice, we show altered protein ubiquitination and subunit composition of the proteasome. After insult, we have shown the constitutive proteasome, present in normal conditions, is replaced by the inducible immunoproteasome in glia. This leads to NFκB-mediated persistent pro-inflammatory cytokine expression. Through pharmacologic and genetic inhibition of the immunoproteasome, we show that modulating the UPS at critical time points following injury results in an improved cellular and functional outcome. Together, our findings suggest that better understanding of the role of the UPS in the inflammatory response after CNS injury could present a novel therapeutic approach.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

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**Program #/Poster #:** 762.27/PP8

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** State of Texas (Emerging Technology Funds to AKS)
VA Merit Award to AKS

**Title:** Curcumin nanoparticle treatment after TBI maintains better cognitive and mood function with enhanced neurogenesis and reduced inflammation in the hippocampus

**Authors: S. ATTALURI**[1], M. ARORA[2], M. KODALI[1,3], B. HATTIANGADY[1,3], D. UPADHYA[1], A. BATES[1,3], B. SHUAI[1,3], R. MAJETI[2], A. K. SHETTY[1,3]
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**Abstract:** Traumatic brain injury (TBI) may result from multiple causes including motor vehicle accidents, falls, sports-related head injury, and blast attacks by terrorists or in military operations. While severe TBI results either in mortality or significant morbidity, mild to moderate TBI can cause persistent cognitive, memory and mood impairments years after the initial brain injury. It may also lead to post-traumatic epilepsy in a significant percentage of TBI survivors. We examined the efficacy of curcumin encapsulated biodegradable nanosystems (nCUR) for preventing TBI-induced long-term impairments in cognition, memory, and mood. We subjected young mice to unilateral controlled cortical impact injury (CCI, a model of moderate TBI) and then orally administered nCUR (10mg/Kg) or vehicle (empty nanoparticles). The first treatment occurred two hours after the induction of TBI and the subsequent treatment continued once daily for 6 days. Four months after TBI and nCUR/vehicle treatment, using a

series of behavioral tests, animals were examined for cognitive and mood function and compared with the data from age-matched naïve control animals. Seven days of nCUR treatment following TBI greatly diminished several adverse effects of TBI on brain function. Animals receiving empty nanoparticles after TBI displayed lasting cognitive, memory and mood impairments. These include failure to discern minor changes in the environment in a hippocampus-dependent object location test, inability to distinguish similar but not identical experiences in a pattern separation test, impaired memory in a novel object recognition test, and increased depressive-like behavior in eating-related depression and forced swim tests. In contrast, animals receiving nCUR after TBI displayed preserved cognitive, memory and mood function to levels observed in age-matched naïve controls. Histological analyses revealed that preservation of brain function after nCUR treatment was linked to the maintenance of relatively higher levels of hippocampal neurogenesis and reduced neuroinflammation. In sharp contrast, animals receiving empty nanoparticles showing waned neurogenesis and persistent neuroinflammation in the hippocampus. Thus, oral administration of curcumin nanoparticles is efficacious for preserving cognitive and mood function after an episode of moderate TBI.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 762.28/PP9

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** NIH grant MH105319

**Title:** Modulating macrophage phenotypes as a therapeutic strategy in neurodegenerative diseases

**Authors: *E. QVALE**, I. B. BATKI, M. SWINTON, A. B. SANCHEZ, B. SOONTORNNIYOMKIJ, J. A. FIELDS, C. L. ACHIM
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**Abstract:** Macrophages are scavenger cells highly responsible for the homeostasis in tissues, and the balance of proinflammatory versus anti-inflammatory factors. In the central nervous system (CNS), the balance of brain macrophage phenotypes regulates much of the inflammatory gene expression and deposition of extracellular protein. Chronic neuroinflammation and amyloid beta deposition have been implicated by many previous studies as prospective etiologies of neurodegenerative diseases, such as HIV-associated neurotoxicity. Therefore, manipulating brain

macrophage phenotypes may represent a promising therapeutic strategy for neurodegenerative diseases. Recent studies have shown that cannabinoids reverse the neurodegenerative process in multiple transgenic animal models and are associated with therapeutic effects in humans. In these studies, a cannabinoid receptor agonist, WIN55,212-2 (WIN) was tested for its ability to block IL-1β and Aβ-induced proinflammatory and neurotoxic phenotype and HIV replication efficiency in macrophages. To model perivascular macrophages, peripheral blood mononuclear cells (PBMC) were differentiated into monocyte derived macrophages (MDMs). The MDMs were treated with WIN for 24 hours before exposure to the proinflammatory cytokine IL-1β or recombinant Aβ 1-42 for an additional 24 hours. MDMs were next analyzed for proinflammatory (IL-1β) and anti-inflammatory (TREM2) gene expression by quantitative PCR and immunoblot. TREM2 expression and MDM morphology was analyzed by fluorescent microscopy. To test neurotoxicity, primary human neurons were treated with MDM conditioned media from all treatment groups an analyzed for neuronal integrity. In parallel experiments, HIV-infected MDMs were treated with WIN; supernatants were collected at 2, 4, and 5 days post infection and analyzed for p24. These HIV-relevant stimuli reduced expression of triggering receptor expressed on myeloid cells (TREM2), and increased IL-1β and IFN-$\gamma$;. Interestingly, pretreatment of MDMs with WIN reversed these effects. WIN also altered the morphology of MDMs, promoting more elongated cells, indicative of M2 phenotype and decreased p24 HIV-1 viral load. These results suggest that initial events in HIV and AD induce a proinflammatory and neurotoxic phenotype in brain macrophages. However, this may be blocked with cannabinoid receptor agonists. These findings identify a novel role for cannabinoid receptor agonists to reduce HIV-associated neurotoxicity.

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**Poster**

**762. Neurotoxicity, Inflammation, and Neuroprotection: Neuroinflammation: Beyond Microglia**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 762.29/PP10

**Topic:** C.07. Neurotoxicity, Inflammation, and Neuroprotection

**Support:** Grant on Intractable Diseases (H26-Nanchitou (Nan)-Ippan-074) from the Ministry of Health, Labour, and Welfare, Japan
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**Title:** CCR2-positive immune cells play protective roles in amyotrophic lateral sclerosis

**Authors: *R. YAMASAKI**[1], W. SHIRAISHI[2], J.-I. KIRA[3]
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**Abstract:** Objective: Amyotrophic lateral sclerosis (ALS) causes progressive weakness associated with degeneration of upper and lower motor neurons. In mutant superoxide dismutase-1 (mSOD1)-transgenic ALS model mice, inflammatory response occurs during disease progression. Furthermore, non-neuronal cells such as macrophages from peripheral blood, resident microglia, and astrocytes are activated during disease progression. Previous reports suggest that peripheral immune cells, especially monocytes, influence the disease process of ALS. We aimed to clarify the roles of C-C chemokine receptor type 2 (CCR2), a receptor for C-C motif chemokine 2 (CCL2), which is responsible for the infiltration of peripheral immunocytes in ALS, by studying ALS model mice. Methods: We created transgenic Red-Green mSOD-1 mice in which $CCR2^{RFP}$and $CX3CR1^{GFP}$are heterozygously expressed. CCR2-positive cells (Red cells) are generally thought of as peripheral monocytes while CX3CR1-positive cells (Green cells) are regarded as microglia. Using Red-Green mSOD1 mice, we analyzed the infiltration of macrophages and microglia into the nervous tissues. We also created transgenic $CCR2^{RFP/RFP}$mSOD-1 mice in which $CCR2^{RFP}$is expressed homozygously, resulting in the CCR2 knockout phenotype. We compared the disease course of $CCR2^{RFP/RFP}$mSOD-1 with that of $CCR2^{RFP/WT}$mSOD-1 mice (hetero knockout phenotype) by measuring grip strength, body weight, rota-rod test, and clinical scores. Results: In Red-Green mSOD1 mice, peripheral macrophages infiltrated neither the spinal cord nor the cerebrum until the end stage; however, invasion of CCR2-positive cells into the sciatic nerves started at as early as 8 weeks of age (pre-symptomatic stage). $CCR2^{RFP/RFP}$mSOD-1 mice showed earlier onset than $CCR2^{RFP/WT}$mSOD-1 mice as assessed by rota-rod test, grip strength, and body weight measurement. Pathological investigation demonstrated that the sciatic nerves of $CCR2^{RFP/RFP}$mSOD-1 mice showed less CCR2-positive immune cell invasion and more mutant SOD1 protein deposition compared with $CCR2^{RFP/WT}$mSOD-1 mice. Immunohistochemical analysis revealed that these inflammatory immunocytes were M2 macrophages expressing CX3CR1, CCR2, CD33 and Arginase-1. Conclusion: In mSOD1 mice, M2 macrophages infiltrate the peripheral nerve tissues earlier than they do the central nervous system tissues. Deficiency of CCR2 results in milder disease course and less macrophage infiltration into the peripheral nerves. Therefore, CCR2-positive macrophages may act as mSOD1 scavengers and play protective roles in the ALS mouse model.

**Disclosures: R. Yamasaki:** None. **W. Shiraishi:** None. **J. Kira:** None.

**Poster**

**763. Brain Injury and Trauma: Brain: Pre-Clinical Therapeutic Strategies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 763.01/PP11

**Topic:** C.10. Brain Injury and Trauma

**Support:** UNIDEL140

**Title:** Feasibility of two novel community-based settings for investigating environmental enrichment based rehabilitation model for traumatic brain injury individuals

**Authors: *D. KUMAR**[1], J. GALLOWAY[2]
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**Abstract:** Introduction:
Environmental Enrichment (EE) is a relatively new concept in human neurorehabilitation. The influence of EE on social, physical, and cognitive domains has been widely studied in healthy and brain injured animals. However, the use of EE for clinical neurorehabilitation is much less common due to the complexity of what can be considered an EE for humans. We develop a model for Traumatic Brain Injury (TBI) rehabilitation where EE is provided through i) A Community based business model - Go Baby Go Café and ii) a person's own home - Harness House.
Materials and Methods:
Go Baby Go Café: Six Participants with a diagnosis of severe TBI took part in a 2-month intervention, 3 times a week within the Go Baby Go Café at the University of Delaware. Within the Café is a free-standing 10' x 10' mechanical structure equipped with an overhead body weight support system (BWSS) that allows the participant to freely move throughout the café while preventing falls.
Harness House: Two TBI survivor-caregiver dyads participated in a six-month study. Their home environment was equipped with a BWSS where they spent maximum time. Caregivers were asked to place the TBI participants in the BWSS and use it at least 5 days/week for a minimum of 30 minutes a day with home and community-based goals.
Measures: For both studies safety and feasibility measures were assessed. Safety was assessed through reporting adverse events. Feasibility measures include attendance, attrition, and adherence with a minimum 75% cut off to consider feasibility.
Results and Discussion:
Results suggest that both environments are feasible and safe for comprehensive intervention. No adverse events and drop outs were reported. All café subjects reported high compliance to the program with an average adherence of 90%. Reported HH activity suggested that though both

families spent time in the harness, they were unable to maintain record keeping of time spent in the BWSS.
Conclusion:
Both studies were feasible in terms of technology and compliance to a café and home-based program. This potential form of community-based and family driven rehabilitation can help fill the gaps of EE based interventions, thus preventing negative neuroplasticity once TBI individuals are discharged in the community.

**Disclosures: D. Kumar:** None. **J. Galloway:** None.

**Poster**

**763. Brain Injury and Trauma: Brain: Pre-Clinical Therapeutic Strategies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 763.02/PP12

**Topic:** C.10. Brain Injury and Trauma

**Support:** CBIR15IRG014

**Title:** Wogonin attenuates the deleterious effects of traumatic brain injury in anesthetized Wistar rat

**Authors: *V. C. CHITRAVANSHI**[1], Y. UMEMOTO[2], H. N. SAPRU[3]
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**Abstract:** Wogonin, a flavonoid (5,7-dihydroxy-8-methoxyflavone) with reported neuroprotective properties, is widely used in treating inflammatory diseases. The main goal of this study was explore the role of Wogonin in preventing deleterious cardiovascular effects of traumatic brain injury (TBI). Experiments were carried out in adult male urethane-anesthetized, artificially ventilated, Wistar rats, weighing 325-350 gm. TBI was produced by fluid percussion injury (FPI). A significant decrease in blood pressure (BP), heart rate (HR) and greater splanchnic nerve activity **(**GSNA), which lasted for up to 4 hours, was observed after the application of moderate FPI. Intracerebroventricular administration of Wogonin before and after the moderate FPI significantly attenuated the decreases in BP, HR and GSNA elicited by FPI. Administration of Wogonin also prevented the attenuation of baroreflex-induced bradycardia elicited by FPI. Based on these results, it was concluded that intracerebroventricular administration of Wogonin attenuates the deleterious effects of moderate FPI.
This work was supported by New Jersey Commission on Brain Injury Research grant # CBIR15IRG014.

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**Poster**

**763. Brain Injury and Trauma: Brain: Pre-Clinical Therapeutic Strategies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 763.03/PP13

**Topic:** C.10. Brain Injury and Trauma

**Support:** T32 NS 043126-14S1

**Title:** Non-invasive longitudinal assessment of cerebrovascular reactivity after TBI using functional near infrared spectroscopy

**Authors: *M. A. SANGOBOWALE**[1], F. AMYOT[2], H. AYAZ[3], R. DIAZ-ARRASTIA[4]
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**Abstract:** Traumatic cerebrovascular injury (TCVI) is common after TBI and is responsible for a significant portion of TBI-related disability. Development of therapies targeting TCVI will require reliable and inexpensive biomarkers to measure vascular dysfunction and document target engagement. Cerebrovascular reactivity (CVR) is impaired following TBI and methods which reliably and non-invasively measure CVR are available, making CVR an attractive candidate predictive and pharmacodynamic biomarker for TCVI-directed therapies. Changes in the concentrations of oxy- and deoxy- hemoglobin in response to a dynamic challenges measured by functional Near Infrared Spectroscopy (fNIRS) indicate local perfusion changes. This study was designed to assess CVR longitudinally after TBI in humans using fNIRS from the acute to the subacute and chronic stages. We also studied the effect of treatment with a phosphodiesterase 5 inhibitor, sildenafil citrate, in order to assess the utility of fNIRS as a pharmacodynamic biomarker in future clinical trials. Participants with complicated mild TBI were longitudinally studied in the acute (within 72 after injury, n = 21), subacute (14 days after injury, n = 19), and chronic (6 months after injury, n = 10) stages in addition to 14 age- matched healthy controls (HC), who were studied once. CVR was assessed by measuring the changes in oxygenated hemoglobin (ΔHbO) and deoxygenated hemoglobin (ΔHbR) concentration produced by mild hypercapnia (5% CO2). The change in CVR one hour after the administration of single dose of sildenafil citrate (60 mg orally) was also assessed. Mean (± SD) CVR was comparable in TBI patients and HC at 72 hours (HC: 0.176 ± 0.028%/mmHg; and TBI: CVR 0.161 ± 0.011%/mmHg, p=0.23). Sildenafil administration did not result in an increase in CVR in HC (t=1.62 df=8, p=.14) whereas TBI patients showed a significant increase in CVR at 72hrs (t=3.882 df=16, p=.001), 2 weeks (t=2.5951 df=13, p=0.03), 3 months (t=2.518 df=6, p=0.04), and 6 months (t=4.218 df=3, p=0.02) after injury. These findings support the hypothesis that

vascular injury represents a distinct and persistent endophenotype following TBI and PDE5 inhibition as a potential therapy for TCVI.

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**Poster**

**763. Brain Injury and Trauma: Brain: Pre-Clinical Therapeutic Strategies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 763.04/PP14

**Topic:** C.09.Stroke

**Support:** NIH grant NS091603

**Title:** SIRT1 activation promotes long-term functional recovery in SAH rats

**Authors: *H. SHENG**[1], D. CHU[1], X. LI[1], X. QU[1], D. DIWAN[2], G. J. ZIPFEL[2], D. S. WARNER[1]
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**Abstract: Introduction:** Sirtuin 1 (SIRT1) is an enzyme that contributes to maintenance of function during cellular stress by selective protein deacetylation. In both rats and mice subjected to subarachnoid hemorrhage (SAH), increased SIRT1 ameliorated early brain injury through inhibition of pro-apoptotic P53[1], and NF-κβ-regulated inflammation genes[2]. We hypothesized that resveratrol, a SIRT1 activator, would improve long-term functional recovery in a clinically relevant rat SAH model. **Methods:** 30 male Wistar rats were anesthetized with isoflurane, intubated and mechanically ventilated. Pericranial temperature was maintained at 37°C. Blood pressure and blood gases/glucose were monitored during surgery. Rats were subjected to SAH by injection of 450 μl autologous fresh arterial blood into the prechiasmatic cistern, as previously described[3]. Rats were then computer-randomized to intraperitoneal resveratrol (20 mg/kg) or vehicle, given twice per day for 7 days beginning 30 min after injury. Body weight and rotarod performance were measured on days 0, 3, 7 and 34 post-SAH. Neurological score was assessed 7 and 34 days post-SAH. Morris water maze performance was examined 29-33 days post-SAH. Observers were blind to group assignment. Values were compared by Student t-test and repeated measures ANOVA. **Results:** Blood pressure was increased in all SAH rats immediately after blood injection and returned to baseline within 5 min. Otherwise, no between group differences were detected for blood pressure, blood gases or glucose. SAH induced weight loss during the first 7 days post-SAH, which recovered in both groups by 34 days post-SAH. Both neurological score ($p < 0.03$) and rotarod performance ($p < 0.03$) were improved in the resveratrol group 34 days post-SAH. Latency to find the Morris water maze hidden platform was also improved in the

resveratrol group (P =0.02). Measurement of brain SIRT1 activity and regional histologic damage are in process. **Conclusions:** Treatment with resveratrol for one week significantly improved neurological score, rotarod performance, and latency to find the Morris water maze hidden platform days 34 post-SAH. This resveratrol dose has previously been shown to activate SIRT1. These long-term recovery results indicate that SIRT1 activation warrants further investigation as a mechanistic target for SAH therapy. **References:** 1. Qian C et al. Mol Med Rep. 2017, 16: 9627-9635; 2. Zhao L et al. Mol Neurobiol. 2017 54:1612-1621; 3. Sasaki T et al. Neurocrit Care. 2016, 25:293-305

**Disclosures: H. Sheng:** None. **D. Chu:** None. **X. Li:** None. **X. Qu:** None. **D. Diwan:** None. **G.J. Zipfel:** None. **D.S. Warner:** None.

**Poster**

**763. Brain Injury and Trauma: Brain: Pre-Clinical Therapeutic Strategies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 763.05/PP15

**Topic:** C.09.Stroke

**Support:** NIH grant RO1NS089901
NIH grant RO1NS101718

**Title:** MicroRNA-122 improves stroke outcomes through Pla2g2a-Nos2 pathway

**Authors: D. LIU**[1], B. P. ANDER[2], *F. R. SHARP[2]
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**Abstract:** In addition to our previous data that miR-122 mimic given at 0hr improved outcomes after middle cerebral artery occlusion (MCAO) in rats, we recently demonstrated that intravenous (i.v.) miR-122 mimic given 6 hr later decreased infarct volumes by 56% and reduced neurological deficits 24 hr after MCAO in rats. These data reveal that miR-122 mimic has broad therapeutic window at least up to 6 hours for treating stroke.
Since inhibition of Nos2 is related to extended therapeutic window and Nos2 is predicted as miR-122 target gene due to mirna.org, we hypothesized that Nos2 may be implicated in the therapeutic effects of miR-122 mimic. The data showed that miR-122 mimic given at 0hr and 6hr markedly decreased MCAO-induced Nos2 expression in brain microvascular endothelial cells (BMVECs) 24hr after MCAO. However, miR-122 did not bind to 3' untranslated regions (3'UTR) of Nos2 in luciferase reporter assays, suggesting miR-122 knockdown of Nos2 was indirect.
Alternatively, we focused on Pla2g2a, as it is an important Nos2 upstream molecule and is also predicted as miR-122 target gene. We found that miR-122 mimic given at 0 and 6hr markedly

decreased MCAO-induced Pla2g2a expression in BMVECs one day after MCAO. Luciferase reporter assays confirmed that miR-122 bound to wild-type but not mutated 3'UTR of Pla2g2a. Using the anti-sense *in vivo* Morpholino oligos (MO)-Pla2g2a that specifically competes with miR-122 for the 3'UTR binding sites of Pla2g2a, our data showed that *in vivo* MO-Pla2g2a blocked miR-122 induced down regulation of Pla2g2a in leucocytes and BMVECs after MCAO in rats.
In conclusion, these data show that miR-122 mimic has a broad therapeutic window that may relate to direct knockdown of Pla2g2a and in turn decrease of Nos2 in BMVECs, and probably in leucocytes, platelets as well.
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**Poster**

**763. Brain Injury and Trauma: Brain: Pre-Clinical Therapeutic Strategies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 763.06/PP16

**Topic:** C.10. Brain Injury and Trauma

**Support:** The Moody Project for Translational Traumatic Brain Injury Research

**Title:** Non-invasive transcranial nano-pulsed laser therapy corrects aberrant hippocampal neurogenesis in a rat model of traumatic brain injury

**Authors: *E. MOCCIARO**[1], A. GRANT[1], R. ESENALIEV[2,3], I. PETROV[2], Y. PETROV[2], E. BISHOP[1], K. JOHNSON[1], I. BOLDING[1], M. PARSLEY[1], D. PROUGH[1], M. MICCI[1]
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**Abstract:** Traumatic Brain Injury (TBI) occurs after a head trauma and can lead to chronic diseases including neurodegenerative disorders such as Parkinson's and Alzheimer's disease. One of the brain regions most affected by TBI is the hippocampus that plays a critical role in learning and memory and one of the only two regions in the brain where neurogenesis occurs throughout life. Aberrant migration of hippocampus neural progenitor cells into the hilus has been previously reported in animal models of TBI. Additionally, we have shown that TBI results in significant changes in the expression of regulatory miRNAs in the hippocampus subgranular zone (SGZ). Here we tested the ability of the transcranial delivery of Nano-Pulsed Laser Therapy (NPLT), that combines near-infrared laser light (NIL; 808 nm) and laser-generated, low-energy optoacoustic waves (OA), to correct TBI-induced neurogenesis dysfunctions in the rat fluid percussion injury (FPI) model. Adult male rats were treated with a single 5 minutes application

of NPLT, one hour after FPI or sham surgery. Doublecortin (DCX)-positive neural progenitors cells were identified by immunohistochemistry. Laser Capture Microdissection (LCM) was used to collect the SGZ for qRT-PCR analysis of specific miRNAs known to regulate neurogenesis (miR9, mir25, miR29, miR124, miR137 and 186). Also, select miRNAs (miR9, mir25, miR29) were analyzed i*n vitro* in hippocampal NSC treated with NPLT or its components, NIL and OA. We show that NPLT significantly reduced aberrant migration of DCX-positive progenitor cells in the hilus and prevented FPI-induced upregulation of regulatory miRNAs in the SGZ. *In vitro*, NPLT increased the expression of miR9, mir25, and miR29 while OA treatment decreased their expression. In conclusion, our data show that NPLT prevents aberrant neurogenesis after FPI, at least in part, by modulating the expression of specific miRNAs.

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**Poster**

**763. Brain Injury and Trauma: Brain: Pre-Clinical Therapeutic Strategies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 763.07/PP17

**Topic:** C.10. Brain Injury and Trauma

**Support:** Moody Project for Translational Traumatic Brain Injury Research

**Title:** Non-invasive nano pulsed laser therapy (NPLT) reduces neurodegeneration after traumatic brain injury

**Authors: *A. C. GRANT**[1], J. GUPTARAK[1], M. A. PARSLEY[1], I. J. BOLDING[1], K. M. JOHNSON[1], I. Y. PETROV[2], Y. PETROV[2], R. O. ESENALIEV[2], D. S. PROUGH[1], M. A. MICCI[1]
[1]Anesthesiol., [2]Ctr. for Biomed. Engin., Univ. of Texas Med. Br., Galveston, TX

**Abstract:** Each year in the US 1.7 million people are inflicted with a Traumatic Brain Injury (TBI). The neuropathological consequences of these injuries can persist years after injury. We designed and built a novel, medical grade, Nano-Pulsed Laser Therapy (NPLT) system that combines near-infrared laser light (808 nm) and laser-generated, low-energy optoacoustic waves. Here we tested the ability of NPLT to reduce neurodegeneration, preserve myelinated axons and reduce loss of brain volume in a rat model of fluid percussion injury (FPI). Twenty-nine adult male rats were randomly assigned to receive FPI or sham surgery. They were further randomized to receive NPLT, applied 1 hour after injury, or no treatment. The rats were euthanized 2 weeks after FPI and the brains were harvested and sent to NeuroScience Associates (NSA) for Amino-cupric silver (neurodegeneration) and Weil (myelin) staining. Brain volume analysis and

quantification of histological stains were performed ipsilateral and contralateral to the injury between Bregma levels -2.04 mm and -7.8 mm using BZX-Analyzer software. Statistical analyses were performed using multiple comparisons ANOVA with Tukey's correction. We found that NPLT significantly decreased silver staining after FPI in the ipsilateral side (FPI=27.65±0.57%, FPI+NPLT=20.47±0.44%; p=0.0001), and the contralateral side (FPI=15.93±0.15%, FPI+NPLT=14.46±0.33%; p=0.0002). NPLT also significantly reduced loss of Weil staining after FPI in the ipsilateral side (FPI=19.55±0.2535%, FPI+NPLT=21.47±0.223%; p=0.0003), and the contralateral side (FPI=20.57±0.1987%, FPI+NPLT=21.95±0.2045%; p=0.0041). Finally, NPLT reduced loss of brain volume after FPI (FPI=498643±9709 $mm^3$, FPI+NPLT=534889±7065 $mm^3$, p=0.0170). Our data show that NPLT reduces neurodegeneration, prevents loss of myelinated axons and reduces volume loss following FPI. This further supports the therapeutic value of the NPLT treatment for brain injury survivors.

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**Poster**

**763. Brain Injury and Trauma: Brain: Pre-Clinical Therapeutic Strategies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 763.08/PP18

**Topic:** C.10. Brain Injury and Trauma

**Support:** NS085046
NS096012

**Title:** Progress toward an interneuron cell therapy for traumatic brain injury

**Authors: B. ZHU**, *R. F. HUNT
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**Abstract:** Traumatic brain injury is a devastating disorder characterized (in many cases) by cortical hyperexcitability and loss of GABAergic interneurons. Cell therapies that introduce new interneurons into damaged brain regions might have therapeutic value by restoring GABA-mediated inhibition in the injured brain. In previous work, we developed a GABA cell transplantation strategy for treating epilepsy and other common behavioral "co-morbidities" associated with the disease (Hunt et al., 2013). MGE progenitors are capable of migrating up to 1.5 mm in adult recipients, where they generate a nearly pure (&gt95%) population of cells with immunohistochemical, molecular and electrophysiological properties similar to endogenous native-born interneurons and selectively enhance synaptic-synaptic inhibition in the host brain. We are now developing a MGE-based interneuron transplantation protocol for the purpose of

reversing existing deficits in a rodent model of traumatic brain injury. In these studies, interneuron progenitors derived from the embryonic MGE were transplanted into hippocampus of control and adult brain injured mice. A series of molecular, anatomical, and electrophysiological techniques were used to characterize GABAergic neuron subtypes and functional integration of MGE-derived cells. In addition, we are investigating the therapeutic potential of MGE interneuron transplantation using in vivo electrophysiology and GCaMP6 imaging in freely behaving mice. To date, our data suggest MGE transplantation into adult brain injured hippocampus is possible and that this procedure could have therapeutic benefit.

**Disclosures: B. Zhu:** None. **R.F. Hunt:** None.

**Poster**

**763. Brain Injury and Trauma: Brain: Pre-Clinical Therapeutic Strategies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 763.09/PP19

**Topic:** C.10. Brain Injury and Trauma

**Support:** VA ORD RR&D SPIRE

**Title:** Neurotrophic factors in mTBI treatment with rTMS

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**Abstract:** A disturbing number of our service members experience a mild traumatic brain injury (mTBI) and return as Veterans suffering from chronic post-concussive symptoms. These symptoms can be debilitating, such as headache, disturbed sleep, loss of emotional regulation and memory problems. Unfortunately, treatment options are limited because the mechanisms of conversion to chronic symptoms is unclear. However, repetitive transcranial magnetic stimulation (rTMS) is a new treatment that harnesses the processes of plasticity to help improve neurological function. Investigating the biochemical mechanisms of neural plasticity in mTBI and how rTMS can facilitate this process could be key to optimizing treatment options for our Veterans. In particular, this study investigates the relationship between BDNF signaling and chronic mTBI symptoms during rTMS treatment. Plasma BDNF was measured in 47 Veterans using ELISA and Western Blot approaches. Genotype for the val66met BDNF single nucleotide

polymorphism was measured as a potential moderator of treatment response. At baseline the Val/Val homozygotes had higher circulating BDNF than the met carriers, with no difference in the precursor, proBDNF, between the genotypes. After 20 sessions of rTMS, there was an overall increase in BDNF and no change in proBDNF levels, as compared to sham treatment. However, rTMS treatment increased BDNF and decreased proBDNF in the met carriers more than the Val/Val homozygotes. Therefore, in the case of chronic mTBI, rTMS does appear to increase BDNF but the met carries may be more likely to response to treatment than the Val/Val homozygotes.

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**Poster**

**763. Brain Injury and Trauma: Brain: Pre-Clinical Therapeutic Strategies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 763.10/PP20

**Topic:** C.10. Brain Injury and Trauma

**Title:** Cordycepin attenuatesinflammatory responses after traumatic brain injury via modulating microglia/macrophage polarization

**Authors: *P. WEI**[1], C. LUO[1], W. MIAO[1], W. ZHANG[1], X. HU[1,2], J. CHEN[1,2], Y. GAO[1,2]
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**Abstract: Aims**: Traumatic brain injury (TBI) triggers systemic pro-inflammatory responses, which impact brain injury and brain repair processes. Therapeutic strategies that target at inflammatory responses after TBI may therefore preserve brain tisuues and promote recovery. Cordycepin, a cordyceps militaris extract, has been reported to modulate microglia activation. In the present study, we investigated the potential therapeutic efficacy of cordycepin for neuroprotection and immune modulation in a TBI model. **Methods**: TBI was induced in adult male C57BL/6J mice by controlled cortical impact (CCI). Cordycepin (10mg/kg, twice daily) was administered by intraperitoneal injection, starting 2h after TBI, and continued for 7 consecutive days. Rotarod, wire hanging tests and grid walking were used to evaluate the effects of Cordycepin on neurological functions. Neuronal loss, White matter integrity and microglia/macrophage activation were assessed using electrophysiological recording and immunofluorescence staining. Cytokine levels were measured using real-time PCR and a protein

array. **Results**: Cordycepin treatment improved both short term and long-term neurological functions, as revealed by wire hanging, grid walking and rotarod tests. Besides, cordycepin reduced brain tissue loss, increased NF-200 protein expression and enhanced compound action potential. Immunofluorescence staining showed that cordycepin enhanced CD206 expression and shifted microglia/macrophage polarization towards anti-inflammatory phenotype. In consistent, protein array results indicated that cerebral CCL3, IL-1β, IL-2, and IL-17a levels after TBI were reduced by cordycepin treatment. Also, CCL3, CCL2, IL-1β, TNF-,αIL-17a and CD16 mRNA decreased, while CD206 and IL-10 mRNA increased in brain tissue after TBI. **Conclusion**: These results suggest that cordycepin improves long-term recovery and relieves inflammatory responses after TBI by modulating microglia/macrophage polarization toward M2 anti-inflammatory phenotype. **Key words**: cordycepin, traumatic brain injury, inflammation, microglia/macrophage

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**Poster**

**763. Brain Injury and Trauma: Brain: Pre-Clinical Therapeutic Strategies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 763.11/PP21

**Topic:** C.10. Brain Injury and Trauma

**Support:** The Moody Project for Translational Brain Injury Research

**Title:** Identifying novel compounds to treat brain injury and depression by genomic profiling

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**Abstract:** The search for treatments for traumatic brain injury (TBI) has thus far produced many potential candidates but virtually no winners. There is a disconnect between the successful results gained from pre-clinical models and unsuccessful translation to clinical efficacy. Based on our *hypothesis* that drugs with neuroprotective properties act on a common set of molecular targets, our *objective* is to identify these common molecular targets - associated with cell death or survival - of compounds that have neuroprotective effects in pre-clinical studies. Our *rationale* is that this identified molecular signature of neuroprotection can be used as a screening tool to test drug candidates as potential treatments for TBI. *Methods:* Using the fluid-percussion injury (FPI) model in male Sprague-Dawley rats (300 - 350g), we compared the genomic response, in hippocampal tissue, to three treatments that are known to be neuroprotective, 17β-estradiol, JM6, or PMI-006. Rats were anesthetized using isoflurane and received either FPI or sham injury, and

treated with one of the drugs or vehicle one hour after injury. Twenty-four hours after surgery, brains were harvested and hippocampal tissue was collected. Total RNA isolated from the samples was reverse transcribed and subjected to genome-wide transcriptome analysis using Agilent microarrays. Microarray results were confirmed by quantitative real-time PCR analysis using Taqman probes. Results were analyzed used Ingenuity Pathway Analysis software. *Results:* All three test compounds were found to act on gene targets that were known to be involved in cell death and/or survival. Unexpectedly, *in silico* analysis revealed that many of the gene targets of these neuroprotective drugs are also targets of antidepressant drugs. Comparison of the genomic profile of JM6 to that of three FDA approved antidepressant drugs, imipramine, Prozac and Zoloft, validated this observation. The antidepressant-like effects were confirmed in the forced swim test, a classic measure of antidepressant efficacy; JM6 prolonged the latency to immobility. *Conclusion:* Our results suggest that neuroprotective compounds act on common molecular targets. These drug-induced genomic profiles may have utility in screening and identifying novel compounds with both neuroprotective and/or antidepressant potential.

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**Poster**

**764. Touch: Plasticity and Reorganization**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 764.01/PP22

**Topic:** D.04. Somatosensation: Touch

**Support:** IIMS/CTSA

**Title:** Responses to sensory stimuli and related sensory neuronal plasticity in aged mice

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**Abstract: Purpose:** Chronic and persistent pain increases with age and are major factors affecting the quality of life. It is unclear whether this increase is due to higher co-morbidity rates with other diseases observed in the elderly or due to age-related changes in nociception pathways. Studies show that higher co-morbidity rate contributes to pain chronicity in the elderly. However, there is limited understanding on age-associated changes in nociceptive pathways. Plasticity of sensory neurons and the microenvironment may play a role in altered responsiveness to sensory stimuli and pain chronicity. Here we examined changes in responsiveness to sensory stimuli during aging of naïve mice and age-dependent changes in sensory neurons, cells adjacent to sensory neuronal bodies, and peripheral terminals.

**Methods:** Responsiveness to sensory stimuli for adult (2-6 months) and aged (18-24 months) mice was measured using von Frey threshold, sensitivity to punctuate stimuli (0.4g von Frey), to light touch (0.07g von Frey), to pin-prick, to dynamic cotton touch, and sensitivity to heat and cold. Plasticity in sensory neurons and in cells surrounding sensory neuronal body and peripheral terminals was accessed by the RNA-seq and flow cytometry on DRG and paw tissues of naïve adult and aged mice.
**Results:** (1) Behavior: Sensitivity to heat and mechanical (nociceptive and touch), but not cold stimuli undergone gradual and substantial changes with age. (2) Sequencing: RNA sequencing was performed on 3-4 DRG and 3 paw samples from naïve adult (3-6mo) and aged (23-24mo) mice. Pathway analysis of upregulated and downregulated genes showed that major changes in DRG and/or paw relate to tissue abnormalities and injuries, metabolism, cell morphology and especially inflammatory responses, while ligand and voltage-gated channel expressions did not change with age. (3) Flow cytometry: Analysis of major resident immune cell types (i.e. T-cell, B-cells, leukocytes, macrophages, neutrophils and dendritic cells) in DRG and paw in adult and aged mice demonstrated that T-cell percentage increased in DRG. In contrast, no significant changes in immune cell percentage associated with age were noted for paw samples.
**Conclusions:** Nociception and touch (involving many different types of sensory fibers) altered with age. Analysis of plasticity in sensory neurons, and in cells surrounding sensory neuronal bodies as well as peripheral terminals points to degenerative processes that could affect sensory neurons and especially their terminals. This type of plasticity coupled with absence of inflammatory processes at periphery (i.e. paw) could explain the changes in responsiveness to sensory stimuli.

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**Poster**

**764. Touch: Plasticity and Reorganization**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 764.02/QQ1

**Topic:** D.04. Somatosensation: Touch

**Support:** James S. McDonnell Foundation Grant 220020516
NIH NEI R01EY022987-03
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**Title:** Alterations in somatosensory receptive fields following early blindness are shaped by the environment

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**Abstract:** The neocortex has a remarkable capacity to alter its functional organization and connectivity in response to sensory loss, particularly if this loss occurs early in life. The marsupial, *Monodelphis domestica* (short-tailed opossum), is a good animal model for the study of cortical plasticity because its nervous system is highly immature at birth, allowing us to perform experimental manipulations to the sensory receptor arrays at a very early developmental stage, equivalent to embryonic stages in placental mammals. We recently demonstrated that receptive fields for neurons in the S1 whisker representation are altered in opossums that were bilaterally enucleated on postnatal day 4, such that neural discrimination of whisker stimulus position is enhanced. We hypothesized that rearing early blind animals in a more spatially complex and dynamic environment would increase reliance on the spared sensory modalities, and influence compensatory effects observed in S1. Short-tailed opossum litters including both early blind and sighted animals were reared in cages 9x larger than standard laboratory cages, and provided with toys and climbing sticks that were changed or shifted in position every 2-3 days. Since mothers of experimental litters preferentially nested high above the ground, pups were required to rely mainly on touch to navigate along both the horizontal and vertical dimensions of the home cage. Early blind animals did not exhibit deficits in exploratory activity compared to sighted littermates, suggesting that spared sensory systems allowed these animals to effectively navigate the environment. In early blind animals reared in the enriched environment, neurons in S1 were just as selective in their responses to whisker stimuli as those reared under standard conditions. Additionally, this change was accompanied by a shift in the distribution of the shapes of receptive fields such that they were less anisotropic than standard reared animals, in which the majority of receptive fields are elongated along the horizontal axis. This change in receptive field shape from horizontally elongated to a more circular, isotropic shape may reflect their exposure to a more spatially complex three-dimensional environment. Our results show that somatosensory plasticity following early blindness is impacted by the rearing environment, suggesting that compensatory plasticity in S1 following early blindness can be directed by tactile experience.

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**Poster**

**764. Touch: Plasticity and Reorganization**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 764.03/QQ2

**Topic:** D.04. Somatosensation: Touch

**Support:** JSPS KAKENHI Grant Number JP15K16360

**Title:** Effects of cathodal tDCS on motor area on tactile threshold of the distal pulp of the hallux

**Authors: *D. ISHII**[1], S. YAMAMOTO[2], A. YOZU[1], Y. KOHNO[1]
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**Abstract:** Transcranial direct current stimulation (tDCS) has been reported to modulate cortical excitability. Many studies investigated the tDCS modulation effects on the upper extremities. Foot sole tactile sensation is essential to gait; however, little is known about the effect of tDCS on sensory function in the foot area. Here, we investigated the effects of cathodal tDCS on motor area on tactile threshold of the foot sole. Ten healthy males (mean age: 23.3 years; range: 22-34 years of age) participated in this study, which had a double-blind, sham-controlled and cross-over design. All participants underwent two tDCS conditions (with cathodal and sham tDCS) in random order. A cathodal electrode placed on the left motor cortex, represented by the C3 electrode position on the scalp according to the 10/20 EEG system. The reference electrode was placed on the contralateral supraorbital area. Before and after the both tDCS conditions, somatosensory threshold in the foot and alertness were assessed. In the tDCS condition, we applied 1.5 mA for 10-min. Our study showed that the modulation effects of cathodal tDCS on the left motor area led to a decrease in the tactile threshold of the left center of the distal pulp of the hallux. This effect was not observed in the sham condition. In addition, the vigilance levels were not changed before and after the tDCS. These results suggest that sensation on the sole of the left foot could be modulated by cathodal tDCS on the left motor area.

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**Poster**

**764. Touch: Plasticity and Reorganization**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 764.04/QQ3

**Topic:** D.04. Somatosensation: Touch

**Support:** F31NS103275
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R21AG05533301
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K25NS083754

**Title:** The effect of sensory deprivation-induced plasticity on global cortical networks

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**Abstract:** Sensorimotor deprivation is an understudied therapeutic maneuver that may be used to enhance neural plasticity after injury. For example, casting of limbs has been used to promote functional recovery in human stroke patients. In order to substantiate this clinical practice, we seek to understand the mechanistic relationship between sensorimotor deprivation and plasticity in brain networks. We have recently shown that after a focal ischemic injury to the mouse forepaw sensory cortex, depriving input to the adjacent whisker barrel cortex enhances its receptivity to competitive takeover by the injured forepaw circuit (termed remapping), while significantly improving functional recovery of forepaw sensation. In this study, we further reveal novel effects of whisker sensory deprivation on plasticity in global patterns of resting state functional connectivity (fc). To assess how sensorimotor deprivation affects global connectivity, we performed wide-field fluorescence imaging of neural activity of healthy mice expressing a genetically-encoded calcium indicator (GCaMP6f). Eighteen 3-month-old male *Thy1*-GCaMP6f transgenic mice underwent imaging of their awake resting state cortical activity as well as mapping of whisker, forepaw, and hindpaw sensory cortices, before being divided into three groups (n=6 each): 1. Full trim - complete removal of all right mystacial whiskers, 2. Single trim - removal of all right mystacial whiskers except for the D1 whisker, and 3. Control - no trimming. Mice were serially imaged for a period of 8 weeks while maintaining their sensory deprivation. Compared to prior studies done in juvenile mice, adult mice show diminished remapping of preserved sensory modalities into deprived areas. However, we observed novel changes in functional connectivity in both whisker deprived groups. Full-trim mice exhibit a weakening of both homotopic connectivity and local connectivity with the deprived barrel cortex when compared to untrimmed controls. Interestingly, single trim mice exhibit the opposite effect - increased fc locally and homotopically with the deprived barrel cortex. These changes in resting state fc appear to occur independently of gross remapping of non-deprived sensory modalities into the deprived barrel cortex. This study will lay the foundation for future work on the mechanisms of sensory deprivation-induced network plasticity and therapeutic targets to enhance or mimic the process.

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**Poster**

**764. Touch: Plasticity and Reorganization**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 764.05/QQ4

**Topic:** C.11. Spinal Cord Injury and Plasticity

**Support:** NIH Grant NS 067017
NIH Grant NS16446
Craig H. Neilsen Foundation

**Title:** Reorganization of higher-order somatosensory cortex after sensory loss from the hand in squirrel monkeys

**Authors: *H. X. QI**[1], C.-C. LIAO[2], J. L. REED[2], J. H. KAAS[3]
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**Abstract:** It is well known that the adult central nervous system is mutable after injury. In the somatosensory system, most studies have focused on the reorganization of cortical areas 3b and 1 after nerve cut, amputation, or dorsal column lesion (DCL). Little is known about reactivations that likely occur in other higher order somatosensory areas. We hypothesize that higher-order somatosensory areas rely on 3b activation via the injured dorsal column (DC) pathway. To this end, we recorded neuronal responses to light touch or taps in areas 3a, 3b, 1, secondary somatosensory (S2), parietal ventral (PV), and occasionally 2/5 in the same monkeys after unilateral DCLs. Like area 3b, areas 1, 2/5, S2, and PV became reactivated over weeks of recovery.[CL1] We quantified results within each monkey and performed statistical comparisons across cases of varying DCL extents and recovery times in 13 adult male squirrel monkeys (3 *Saimiri sciureus, 10 S. boliviensis*). Major findings are as follows. **1**) After incomplete unilateral DCLs and weeks of recovery, the hand regions in areas 1, S2, PV were responsive to touch on the contralateral hand and forelimb, with patterns similar to those of area 3b. After complete or nearly complete unilateral DCL with intermediate recovery times (~6 weeks), neurons in scattered sites of the deprived hand region in area 3b responded to touch on digits, and somatotopy was similar to that of normal monkeys. Neurons in the hand regions of 3a, 1, S2, PV were either unresponsive or weakly responsive to touch/taps to most of forelimb. However, after longer recovery times (8 - 9 months) from nearly complete DCLs, areas 3b, S2, and PV underwent large-scale reorganization, revealed by face and forelimb responses in affected hand regions. Areas 3a, 1, and 2/5 were less responsive. **2**) Receptive fields of neurons in deprived hand regions of areas 3b and 1 were usually larger with more extensive lesions, and this was reflected in S2 and PV. **3**) Unexpectedly, neural responses to tactile stimulation at some sites in S2 and PV were stronger than those of area 3b. However, across DCLs and recovery times, the reactivations of areas 1, S2, and PV closely resembled that of area 3b. The few stronger responses in deprived and reactivated hand regions in S2 and PV may suggest the convergence of activating inputs from cortical areas, such as 3b and 1, and the thalamus. Overall, the reorganization of higher-order somatosensory cortex relies on the DC pathway and area 3b, with some differences in responsiveness. Thus, the properties of reactivated higher order somatosensory areas may be important in understanding the recovery of behavior guided by tactile perception after spinal cord injury in humans.

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**Poster**

**764. Touch: Plasticity and Reorganization**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 764.06/QQ5

**Topic:** D.04. Somatosensation: Touch

**Support:** NIH Grant GM109040
NIH Grant NS097775
Charleston Conference on Alzheimer's Disease New Vision Award

**Title:** Multi-scale imaging of the plasticity of sensory representations in somatosensory cortex

**Authors: *M. LEVY**[1], C. BURTON[1], R. I. GRANT[1], A. Y. SHIH[1,2]
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**Abstract:** During the weeks and months following a cortical stroke, patients often spontaneously recover some of the sensorimotor functions lost to the injury. Animal studies suggest that stroke recovery is associated with reorganization of somatotopic maps at the macroscopic level (Nudo et al. Science 1996, Jenkins and Merzenich Prog Brain Res 1987), and involves axonal sprouting, spine remodeling and the formation of new structural circuits at the microscopic level (Brown et al. J Neurosci 2009, Carmichael et al. Exp Neurol 2017). However, whether these new synapses represent reorganized sensory inputs is still unclear. To address this question, we imaged the plasticity of whisker responses after stroke at both the areal and synaptic levels. We implanted chronic cranial windows over the vibrissae representations in the primary and secondary somatosensory cortices (S1v and S2v) and imaged hemodynamic responses to single whisker stimulations using intrinsic signal optical imaging (IOS). We then induced a microinfarct in S1v by photothrombotic occlusion of a single penetrating arteriole. IOS responses in intact barrels were strongly depressed and slowly recovered over the course of 8 weeks. In contrast, IOS responses in S2v were back to normal 1 week after stroke and further increased during the course of 8 weeks after stroke. Interestingly, stimulating whiskers whose barrels were destroyed by the infarct evoked responses only in S2v, suggesting remapping in that area. To study the changes in synaptic function associated with stroke-induced remapping, we sparsely labeled neurons in S1v and S2v with GCaMP6s (Chen et al. Nature 2013) and longitudinally imaged spine calcium responses *in vivo* with two-photon microscopy. In agreement with previous studies (Varga et al. PNAS 2012), spine responses in S1v were sparse: 14% of the spines responded to whisker stimulation on any single day, including a core of stable spines which responded every day. Spine responses in S1v were whisker-selective (76% responded to a single whisker) and, despite day-to-day variations in the identity of responding spines, whisker preference at the population level remained well correlated to the preference of the barrels where spines were located. In S2v,

spine responses were similarly sparse, but less selective than in S1v (42% responding to a single whisker). We are currently exploring whether whisker preference in S2v spines is affected by the induction of a microinfarct in S1v. These studies provide new information about the stability of synaptic function *in vivo* and may help uncover the substrates of sensory representations plasticity in the adult brain.

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**Poster**

**764. Touch: Plasticity and Reorganization**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 764.07/QQ6

**Topic:** D.04. Somatosensation: Touch

**Support:** CIHR
HSFC
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**Title:** Longitudinal *in vivo* calcium imaging reveals functional resiliency of disinhibitory vip interneuron circuits following stroke

**Authors: *M. MOTAHARINIA**[1], K. A. GERROW[2], E. R. WHITE[3], C. E. BROWN[4]
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**Abstract:** Stroke leads to a profound suppression of cortical network activity and lasting changes in the function and synaptic structure of excitatory pyramidal neurons. However, little is known about its impact on cortical interneurons which play a critical role in regulating cortical excitability. In particular, interneurons expressing vasoactive intestinal peptide (VIP) specialize in inhibiting other classes of inhibitory neurons, and thus serve to modulate cortical sensory processing. To understand how stroke disrupts this circuit, we imaged VIP neuron structure and function (using GCaMP6s) before and after focal stroke in forelimb somatosensory cortex. Stroke led to a significant increase in the remodelling of peri-infarct pre-synaptic boutons and dendritic spines in the first two weeks of recovery, with loss of these structures dominating the first week followed by a wave of bouton/spine production. Larger-scale changes, such as pruning and growth of axons and dendritic branches was observed, albeit on a limited scale and restricted to within the first 2 weeks. Functionally, the fraction of forelimb responsive VIP interneurons (~40-50%) and their response amplitude and fidelity was significantly reduced in the first week which progressively recovered to near pre-stroke levels. The initial loss of responsiveness was most evident in highly active VIP neurons, whereas less active neurons were minimally affected. Of note, a fraction of VIP neurons that were minimally active before stroke, became progressively more responsive from 2-4 weeks recovery. Lastly, stroke related changes to

synaptic structure and response properties were both restricted to within 500µm of the infarct border. These findings reveal the dynamic and resilient nature of VIP neurons and suggest that a sub-population of these cells are more apt to lose sensory responsiveness during the initial phase of stroke, whereas other less responsive cells are progressively recruited into the forelimb sensory circuit.

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**Poster**

**764. Touch: Plasticity and Reorganization**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 764.08/QQ7

**Topic:** D.04. Somatosensation: Touch

**Support:** NIH R01 NS094450 (DJM)
New Jersey Commission on Brain Injury Research CBIR16IRG032 (DJM)

**Title:** Imaging the immediate and long-term effects of focal traumatic brain injury on cortical network activity

**Authors: Y. BIBINEYSHVILI**[1], N. FLISS[1], A. SUVARNAKAR[1], J. FANG[1], *D. J. MARGOLIS[2]
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**Abstract:** Traumatic brain injury (TBI) is associated with immediate and prolonged changes in brain functional activity. The immediate response of cortical hyper-excitation is followed by a period of suppressed excitability (Ding et al, 2011; Hartings et al, 2014). The prolonged effect involves biochemical, physiological and behavioral changes that take place over days to months. Since TBI is progressive disorder, it is critical to correlate changes in brain function and behavior before, during, and after TBI. We used wide-field calcium imaging in transgenic reporter mice to measure longitudinally the immediate and long-term effects of TBI on spontaneous and sensory-evoked cortical activity.
We used widefield Ca imaging to visualize fluorescence changes in awake head-fixed Thy1-GCaMP6s-GP4.3 mice (injury: n=9 male, 8 female; sham: n=7 male, 6 female) in response to mild controlled cortical impact (CCI) TBI applied to whisker motor cortex (M1) (CCI parameters: 0.5 mm impactor tip diameter, 4 m/s velocity, 85 ms impactor dwell time, 1.8-1.9 mm contusion vertical depth at 38-42 degree angle). In addition to the immediate response during CCI, spontaneous and sensory evoked cortical Ca transients were imaged for the same animals repeatedly 4 times before and 7 times after the injury (from 20 min to 8 weeks), along with behavioral observations (grooming, rearing, digging) after every imaging session.

Following M1 CCI, we observed a massive wave of Ca signal fluorescence that started at the injury site and propagated over most of the ipsilateral hemisphere in the posterior direction with a velocity of approximately 0.1 mm/s and amplitude of 200-500% DF/F (20-100 times larger than average pre-TBI sensory-evoked activity). The excitatory wave was followed by a wave of suppression (-20 to -50% DF/F), that propagated in the same direction and velocity but with differently-shaped wave-front. 20 minutes post-TBI, the area of the whisker-evoked sensory map in the primary somatosensory barrel cortex (S1) increased by 34%, while the amplitude was unchanged. 60 minutes post-TBI, the response amplitude decreased by 31%, while the area had returned to baseline. Behavioral analysis indicated that mice decreased grooming and rearing immediately and 20 minutes post-TBI. Initial two-photon imaging experiments showed strong activation of all observed neurons in S1 during the immediate Ca wave, while the effects on subsequent sensory-evoked cellular activity were heterogeneous amongst neuronal populations. Ongoing experiments are investigating the relationship between the immediate Ca wave and TBI-induced changes in sensory maps and spontaneous network activity in individual mice.

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**Poster**

**764. Touch: Plasticity and Reorganization**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 764.09/QQ8

**Topic:** D.04. Somatosensation: Touch

**Support:** Univ of Tennessee Health Science Center Research Council Grant

**Title:** Remapping of hand-to-face representation in primary somatosensory (SI) cortex in rat following unilateral forelimb amputation

**Authors: *A. L. CURRY**[1], V. PELLICER MORATA[2], J. W. TSAO[3], O. V. FAVOROV[4], R. S. WATERS[5]
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**Abstract:** Introduction: In some patients, upper limb amputation can result in phantom limb pain (PLP) and phantom limb sensation (PLS) in the amputated limb immediately after the injury and may persist for years. Human reports indicate upper limb amputation results in remapping the deafferented forelimb onto the face in primary somatosensory (SI) cortex, examined 6 months after injury. Previous studies in forelimb-amputated rats have shown forelimb-to-shoulder remapping in SI cortex, but whether forepaw-to-face remapping occurs is unknown. Here, we

examined delayed SI remapping following unilateral forelimb amputation using a rodent animal model employing forepaw and lower jaw (LJ) representations in the rat barrel field in SI cortex.
Methods: Under aseptic conditions, adult Sprague-Dawley rats were anesthetized with isoflurane. A circumferential skin incision was made around the upper left forelimb. The skin and shoulder muscles were reflected around the humerus, the forelimb nerves and the brachial artery were ligated and sectioned, and the limb was amputated at the glenno-humeral joint. At 7-9 weeks following amputation, rats were anesthetized with Ketamine/Xylazine (100-mg/kg) and SI cortex was opened. Carbon fiber electrodes were used for extracellular recordings, and mechanical and electrical stimulation were used to map LJ [chin, lip, lower jaw] representations in LJ and forepaw barrel subfields (FBS) and in the boundary between the representations in layer IV of SI cortex. Electrolytic lesions were made at select sites for subsequent histological reconstruction of electrode penetrations.
Results: Neurons in LJ representations received input only from their respective peripheral locations. Responses to LJ input were found in deafferented forepaw SI cortex in presumptive digits and digit pad representations in both FBS adjacent and distal to LJ barrel field as well as in central FBS. Shoulder and rostral side/trunk responses were also found in FBS as in previously reported studies. Histological reconstruction of electrode penetration sites confirmed location of LJ responses.
Conclusion: Delayed forepaw-to-face remapping in the border, central, and distal region of rat forepaw SI cortex, adjacent to LJ cortex, occurs following unilateral forelimb amputation. We propose that new LJ input is likely relayed from similar subcortical (thalamic) pathways as previously reported for new shoulder input following forelimb amputation. Our finding may assist in identifying cortical and subcortical mechanisms relevant to remapping human cortex subsequent to limb deafferentation.

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**Poster**

**764. Touch: Plasticity and Reorganization**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 764.10/QQ9

**Topic:** D.04. Somatosensation: Touch

**Support:** Wellcome Trust 209998/Z/17/Z

**Title:** What factors drive the somatotopic organization of the hand representation in human somatosensory cortex?

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**Abstract:** In primary somatosensory cortex (S1) the representation of the hand is organized somatotopically, with neighboring locations on the hand represented by adjacent cortical neurons. However, the size of cortical regions is not proportional to that of their physical counterparts, and specific regions, such as the fingertips, can be magnified beyond their physical size. What leads to this size variance in cortex? As previously proposed, the magnification of some regions may be due to the variance in receptor density across the hand, which increases from the palm towards the fingertip. However, electrophysiological recordings from monkeys and, more recently, advanced neuroimaging techniques in humans have demonstrated that the hand representation also changes depending on the nature of tactile input. Finally, although there are general similarities in mapping, exact representation varies across participants. This may reflect personal hand use, which alters the input received by cortex, but might also reflect random variation in the way the maps are initially established. To investigate the contribution of these factors, we adapt a computational model that has been successful in simulating the development of visual retinotopic maps to the sense of touch. We employ a two-step process. First, we use a recently-developed large-scale simulation that reconstructs the responses of tactile afferent populations to create realistic peripheral response inputs. This model enables us to systematically vary the stimulus statistics and afferent density. Second, we use both principal component analysis and self-organising map algorithms to model and investigate the resulting somatosensory representation. We compare modelled and real somatosensory maps, by adapting typical methods used to interrogate fMRI hand representations, such as the cortical size of the areas representing individual digits, distances between digits, and representational overlaps. Our results demonstrate a complex relationship between receptor density, touch statistics and the predicted cortical mapping of digits. We also find that quantitative measures of cortical representations that are commonly used in fMRI experiments are differently affected by the input parameters and random noise; our results therefore pave the way for more robust and grounded analysis techniques.

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**Poster**

**764. Touch: Plasticity and Reorganization**

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**Program #/Poster #:** 764.11/QQ10

**Topic:** D.04. Somatosensation: Touch

**Title:** Effect of auditory feedback on finger force control

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**Abstract:** Our ability to finely control finger movements is important when we use tools. For patients with movement disorders, the faculty is often impaired. To help their motor rehabilitation, visual feedback was commonly used. But the efficacy of other sensory modality is not yet fully revealed. In this study, we examined whether feedback in auditory modality could help to control finger force.
Three subjects (22 to 28 years old) who were right-handed participated as subjects. They had no movement disorders and had normal hearing level. All experiments were conducted in a soundproof room, and subjects sit down wearing a headphones. They placed their three fingers (index finger, middle finger, ring finger) of non-dominant hands on three different keys of a MIDI keyboard, which measured the fingertip's force, and they were instructed to press the kay with three levels of intensity following the instruction on the screen. In "with-feedback condition (WF condition)", auditory feedback (instrumental sound) was presented through the headphones when subject press the key, and its sound intensity was proportional to fingertip's force. In "without-feedback condition (WOF condition)", no feedback was presented. In 1 session, instruction of different fingertip's force (3 types) was presented 5 times for each finger (3 fingers) in random order, therefore, total of 45 trials (3 fingers $\times$ 3 forces $\times$ 5 times) was conducted. Subjects performed 6 sessions (3 sessions of WF + 3 sessions of WOF). Results showed that correct answer rate of each subject in WF was 34.8%, 63.7% and 50.4% and that in WOF was 31.9%, 55.6%, and 33.3%, demonstrating that all subjects performed better in WF than WOF condition. It suggested that auditory feedback improves fine control of finger force. To calcify the neural basis of the improvement, we will replicate the experiment in fMRI and compare brain activities of WF and WOF. Furthermore, different acoustic parameters, other than intensity (e.g., frequency, timbre), and combinations of these will be tested to improve efficacy of the feedback.

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**Poster**

**765. Touch: Central Representation of Stimulus Features**

**Location:** SDCC Halls B-H

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**Topic:** D.04. Somatosensation: Touch

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**Title:** Noise enables multiplexed coding of the amplitude and frequency of periodic signals in mouse primary somatosensory cortex

**Authors: *M. KAMALEDDIN**[1,3], S. PRESCOTT[1,2,3]
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**Abstract:** One of the greatest challenges facing neuroscience is to understand how sensory stimuli are encoded in the brain. Sensory information is often encoded by spike rate, but spike timing can also be important. There is mounting evidence that both coding schemes may be used simultaneously to encode different aspects of a stimulus. Indeed, for vibrotactile stimulation driven by periodic signals of 100-600 Hz, spike rate is thought to encode stimulus intensity whereas spike timing is thought to encode stimulus frequency. However, pyramidal neurons in primary somatosensory cortex (S1) fire at rates << 100 Hz, which means that spiking does not phase lock to the periodic stimulus, or at least not on every stimulus cycle; indeed, if a spike occurred on every stimulus cycle, spike rate would necessarily be modulated by stimulus frequency. Further complicating matters, background noise is liable to disrupt spike timing, though other lines of evidence have shown that noise can help rather than hinder some forms of neural coding. How noise affects rate and temporal coding of high-frequency periodic inputs associated with vibrotactile input is yet to be fully resolved.
We recorded from pyramidal neurons in mouse S1 slices using whole-cell patch clamp recording. Using the dynamic clamp technique to simulate a high-conductance state with different noise levels, we applied a periodic stimulus directly to the cell and found that spikes occur at a preferred phase of the cyclic stimulus, consistent with temporal coding of stimulus frequency. Moreover, firing rate was positively correlated with stimulus amplitude, consistent with a rate coding. Indeed, spikes occur at a preferred phase of a stimulus cycle - the basis for temporal coding of frequency - but a different number of stimulus cycles are skipped between consecutive spikes depending on stimulus intensity - the basis for rate coding of stimulus intensity. We showed that spike rate and spike timing encode different features of the stimulus, consistent with multiplexed coding. Moreover, we found that noise plays an important role insofar as it causes an irregular pattern of skipping, thus preventing a regular pattern that lead to aliasing. Notably, skipping was achieved at physiological noise levels whereas spike phase was only disrupted at higher noise levels. Thus, our findings suggest that a physiological level of noise is not only not detrimental to the temporal coding of stimulus frequency, it is also beneficial for the rate coding of stimulus intensity.

**Disclosures: M. Kamaleddin:** None. **S. Prescott:** None.

**Poster**

**765. Touch: Central Representation of Stimulus Features**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 765.02/QQ12

**Topic:** D.04. Somatosensation: Touch

**Support:** NIH R01 NS102808

**Title:** Decoding of object position in L5b of mouse S1 during active behavior

**Authors: *J. A. CHEUNG**[1], P. S. MAIRE[1], J. KIM[1], K. LEE[1], J. SY[1], S. A. HIRES[2]
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**Abstract:** How the brain represents abstract tactile features, such as object position, in cortical regions is still poorly understood. Here, we utilize a reward paradigm that incentivizes head-fixed mice to whisk using a single whisker and identify a pole along a continuous range of object positions along an anterior-posterior axis. During active behavior, juxtacellular loose-seal electrophysiological recordings were targeted to L5b of the barrel column of the single whisker. Excitatory and inhibitory cell types were discriminated through optogenetic-tagging of inhibitory cells. Our preliminary results have identified 29 of 55 excitatory cells in L5b that represent tuning to the azimuthal angle of the whisker at touch. This tuning for object location is independent of touch force and does not reflect differences in the number or probability of touches at a location. These object location tuned cells are also found in naïve mice, suggesting that this code does not require any specialized training. Neurons in L5b display a range of preferred positions and tuning widths that tile a large proportion of the space explored during active whisking. Using a GLM, spike count for single neurons or for the whole population of neurons reveal that object location can be decoded with 5 degree resolution at levels significantly above chance (12.5%) in 6 of 55 neurons and with 39% accuracy when pooling spikes of the complete recorded population. Adding a spike timing component results in 34 of 55 single neurons predicting object location to 5 degrees at rates significantly above chance, suggesting that neural decoding schemes that use both spike count and timing information could be more precise. These results together with the known anatomy of S1 inputs suggest a circuit model for how L5b excitatory neurons encode the azimuthal angle of objects at touch and how mice discriminate object along the horizontal axis in S1.

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**Poster**

**765. Touch: Central Representation of Stimulus Features**

**Location:** SDCC Halls B-H

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**Topic:** D.04. Somatosensation: Touch

**Support:** NIH DP2 1DP2OD024308-01

**Title:** Object angle representation in barrel cortex during active touch

**Authors: *J. KIM**[1], S. A. HIRES[2]
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**Abstract:** Object angle perception is one of the key components of shape recognition. How object angle is represented in primary somatosensory cortex during active tactile exploration is not yet understood. To investigate the perception of object angle, we trained mice on a novel head-fixed single whisker task: two-choice discrimination of forward (45°) or backward (135°) angled poles. During the behavior, whisker shape was video-recorded in both top- and front-view simultaneously using a single mirror. Points of whisker-pole contact were calculated using 3-dimensional geometric distribution of coordinates determined by the intersection of the whisker and the pole from each view and the anterior-posterior pole position. Throughout learning, neuronal activity of barrel cortex was observed by two-photon microscopy of GCaMP6s in excitatory cells (tetO-GCaMP6s;CaMKIIα-tTA mice). We volumetrically imaged layers 2-4 at 7Hz, in two different volumes of 160 μm in depth with 4 planes each. Mice learned to differentiate pole angle in 1-3 weeks of training. The average correct rate was ~85% after learning. Jittering the anterior-posterior and medio-lateral pole position relative to the face did not affect task performance, indicating the mice were discriminating angle rather than position. Before and after learning, we also presented the pole in varying angles of 15° steps on the interval from 45° to 135°, to investigate neuronal angle tuning. After learning, mice categorized a range of pole angles into matched reward response, grouping 45-75° and 105-135° separately. Both before and after learning we identified a large proportion of touch-activated neurons that showed angle selective tuning in all three layers. We found that mice can learn to differentiate object angles using a single whisker, and that there is an intrinsic neuronal representation for different angles in layer 2-4 of primary somatosensory cortex in naïve mice. Our results support a circuit model of neuronal representations of tactile shape recognition, their role in shape perception, and reorganization of these representations during sensory-motor learning.

**Disclosures: J. Kim:** None. **S.A. Hires:** None.

**Poster**

**765. Touch: Central Representation of Stimulus Features**

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**Topic:** D.04. Somatosensation: Touch

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Canada Foundation for Innovation (to IRW)
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**Title:** *In vivo* two-photon calcium imaging of evoked and spontaneously active excitatory and inhibitory networks in the limb associated somatosensory cortex of mice

**Authors: *M. V. BANDET**, B. DONG, X.-M. LI, I. R. WINSHIP
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**Abstract:** To distinguish between somatosensory modalities (pressure, vibration, etc.), the somatosensory cortex should process dissimilar stimuli with different patterns of activation. However, a population based study of neuronal encoding of complex somatosensory stimuli has never been reported within the limb associated somatosensory cortex of rodents. Here we used in vivo two-photon $Ca^{2+}$ imaging to measure somatosensory evoked activity of neuronal networks of up to 250 neurons per optical section. We found that individual neurons within the somatosensory cortex can be tuned to particular frequencies of mechanical limb stimulation or broadly tuned to multiple frequencies of stimulation, thereby forming a population code for sensory processing. These population codes may result from preferential activation of different subsets of cutaneous and musculoskeletal receptors that respond to particular stimuli features. We show that for short stimulus presentations, stimulus frequency is not encoded by the overall strength of a population's response, but is instead primarily dependent on the particular subset of neurons activated and the relationship between the activity of these neurons. In contrast, longer stimulus durations result in greater overall population activity, and greater correlation within the population responses, despite continuing to show a degree of preferential activity within selective subsets of neurons of the population response. To examine the contribution of cell type specific responses to the population code within cortical networks, additional studies using genetically encoded indicators and cell type reporters were performed. To examine evoked activity in parvalbumin-expressing (PV+) inhibitory interneurons and CaMKII-expressing glutamatergic neurons in anesthetized animals, adeno-associated viral vectors were used to express GCaMP6F in CaMKII and PV+ neurons (also co-expressing a red reporter protein). We

show that PV+ cells are primarily tuned to stimulus intensity, likely as a means to inhibit prolonged activity in excitatory networks. Moreover, transgenic B6(Thy1-GCaMP6S)(Pvalb-tdTomato) mice were used to confirm PV+ and non-PV+ cell-type contributions to the spontaneous and evoked activity of somatosensory cortical networks using both awake behaving and anaesthetized preparations. Future studies will use these imaging preparations to investigate the functional consequences of changes in inhibitory tone that result from cortical injury such as stroke.

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**Poster**

**765. Touch: Central Representation of Stimulus Features**

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**Topic:** D.04. Somatosensation: Touch

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**Title:** Secondary somatosensory cortex response properties during whisker mediated object localization

**Authors: *P. S. MAIRE**, J. CHEUNG, S. HIRES
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**Abstract:** The whisker system has proven a useful model for understanding neural circuits in anesthetized, awake and awake-behaving contexts. While the primary somatosensory cortex (S1) has been well studied during these contexts, the secondary somatosensory cortex (S2) is rarely studied during active whisking behaviors, especially in granular and infragranular layers.
Here we investigate how S2 neurons respond to sensory, motor and choice variables during an active whisking behavior. In our behavior mice must discriminate the position of an object along a single continuous axis. Two distinct regions of this axis are assigned as either a go or a no-go region. The mouse must actively whisk a single whisker to determine in which region the object is, and then respond accordingly.
The S2 region corresponding to the C2 whisker (task-whisker) was determined by first localizing the C2 barrel in S1 using intrinsic image signaling while stimulating the whisker. Then coordinates (1.284 mm lateral, 0.388 mm posterior) from the center of S1-C2 were used to target S2-C2. Single-units were obtained via juxtacellular loose-seal electrophysiological recordings, targeted to S2-C2.
We report results from 56 cells, recorded across all layers of S2. Our preliminary analysis of 12 cells show that 9 are responsive to touch, 9 are modulated by whisking and 6 to licking or

reward. Further analysis will include how variables like choice, direction of whisker deflection, and reward signals correlate with the neural response.

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**Poster**

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**Topic:** D.04. Somatosensation: Touch

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**Title:** Multiplexed coding using differentially synchronized spikes: Theory, simulations and experiments

**Authors: *M. LANKARANY**[1], D. AL-BASHA[2], S. RATTE[3], S. A. PRESCOTT[4]
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**Abstract:** Multiplexing, in engineering systems, refers to the simultaneous transmission of multiple signals through a single communication channel. Mounting evidence suggests that the brain also multiplexes but it remains unclear how this occurs. We hypothesized that the brain can form multiplexed representations of first- and second-order stimulus features (i.e. stimulus intensity and abrupt variations therein) using spikes that are differentially synchronized across a set of neurons receiving common input. Specifically, the rate of asynchronous spikes encodes the slow signal (first-order feature) whereas the timing of synchronous spikes encodes the fast signal (second-order feature). We employ both *computational* and *experimental* approaches to test our hypothesis.*Computationally*, we built a feed-forward neural network comprising Morris-Lecar model neurons receiving a common mixed input. It constructed from two distinct signals, slow and fast, plus uncorrelated fast noise. To assess the feasibility of the multiplexed coding, we fit linear-nonlinear (LN) rate models to PSTHs from our conductance-based spiking models. In a conventional LN model, input passes through a linear filter and then through a static nonlinearity whose output is firing rate. We constructed a multiplexing LN model with two parallel streams; the same mixed signal is presented to both filters but the output of each filter passes through a different nonlinearity. Unlike the two input streams, which represent input from two differently specialized sets of sensory neurons, the two streams within the LN model represent two operating modes - integration (low-pass filtering) and coincidence detection (high-pass filtering).

*Experimentally*, we recorded extracellularly from single units in the primary somatosensory cortex of sedated rats. Computer-controlled mechanical stimuli were applied to the whisker pad as discrete steps of increasing force. We asked whether we could decode (1) the force intensity based on the rate of asynchronous spikes and (2) the onset and offset of the step based on the timing of synchronous spikes. Using 17 neurons, we constructed PSTH in two ways: (i) with a broad Gaussian kernel ($\tau$ = 500 ms), we found that the magnitude of firing rate tracks the intensity of the force and (ii) with a narrow Gaussian kernel ($\tau$ =5 ms), we found that abrupt changes in the force were reflected by transient synchronization. Applying a synchrony threshold to the latter PSTH yielded 86% sensitive and 100% specific detection of stimulus transients. Our results show that a set of cortical pyramidal cells can implement multiplexing by simultaneously encoding slow and fast features of a mixed signal.

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**Poster**

**765. Touch: Central Representation of Stimulus Features**

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**Topic:** D.04. Somatosensation: Touch

**Support:** Max Planck Institute for Human Cognitive and Brain Sciences

**Title:** Somatosensory detection and localization across the cardiac cycle

**Authors: *E. AL**[1,2], F. ILIOPOULOS[2], N. FORSCHACK[2], T. NIERHAUS[2], V. NIKULIN[2], P. MOTYKA[2], M. GRUND[2], M. GAEBLER[2], A. VILLRINGER[2,1]
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**Abstract:** We have recently shown that the detection of somatosensory near-threshold stimuli is higher in diastole than in systole of the cardiac cycle. In this study, we aimed (i) to confirm this finding, (ii) to determine if this enhanced detection goes along with improved “objective” performance of stimulus localization, and (iii) to identify neural correlations of differential somatosensory perception during the cardiac cycle using EEG. 40 healthy volunteers (21 female, 27±4 years) expected an electrical stimulus on the index or the middle finger of their left hand in every trial. After stimulation, they performed a “Yes/No Detection” and a “Two Alternative Forced Choice Localization” task. ECG and EEG data were recorded continuously. We show that near-threshold electrical stimuli are more likely to be detected at later phases of the cardiac cycle (diastole). However, this increase in detection does not go along with an increase in correct stimulus localization. These variations of somatosensory perception during the cardiac cycle are reflected in differences of the event related potentials (ERP). We observe significantly higher

ERP amplitudes when the stimulation occurred in diastole compared to systole in a 376-600ms time window over right somatosensory areas (contralateral to the stimulated hand; Monte-Carlo P<0.001 corrected for multiple comparisons in time and space). Both, detection performance and ECG phase modulate N200-P300 peak to peak amplitude while localization performance does not affect it. Additionally, we observe that frontally located neural events locked to heartbeats ("Heart evoked potential") before stimulus onset predict stimulus detection during diastole. Furthermore, we confirm that this differential response is not due to differences in cardiac electrical activity which could affect EEG by volume conduction. These findings suggest that the link between our heart and brain shapes our subjective experience of somatosensory stimuli.

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**Poster**

**765. Touch: Central Representation of Stimulus Features**

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**Title:** Identifying sensory representation of finger segments in people with tetraplegia

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**Abstract:** The development of bidirectional brain-computer interface (BCI) systems that convey sensory feedback through intracortical microstimulation (ICMS) will provide a new level of independence to people with tetraplegia equipped with robotic prosthetic hands (Flesher et. al. 2016). Because the bulk of our manual interactions involve the fingertips (Johansson & Flanagan 2009), these systems will ideally interface with areas of somatosensory cortex that encode contact events at the fingertips to provide intuitive sensory feedback about contact events involving the prosthetic hand.
The only published studies of ICMS in somatosensory cortex evoked tactile sensations primarily at the base of the fingers (Flesher et. al. 2016) or in the arm (Salas et. al. 2018). To better guide intraoperative electrode array placement, we are developing a functional magnetic resonance imaging (fMRI) protocol to differentiate somatosensory representations of the base and tips of the fingers for insensate subjects.
Flesher et. al. used a paradigm where the subject imagined being touched while watching a video of individual fingers being touched to differentiate between the representation of fingers in somatosensory cortex. The sensations evoked by ICMS were consistent with the expected finger representation from the presurgical imaging (Flesher et. al. 2016: Fig 1C), demonstrating that imagined touch can provide an accurate map of sensory representation in a subject with a spinal cord injury. Sanchez-Panchuelo et. al. (2012) were able to separate the three phalanges of the index finger by stimulating them in sequential order using vibrotactors. Our approach consists of combining the imagined touch approach with the sequential stimulation method to subdivide the representation of the fingers in somatosensory cortex.
To validate this approach, we tested, in able-bodied subjects, the BOLD response to sequential patterns of imagined movements, imagined touches, and vibrations. We then examined the responses to imagined touch within- and between-digits and compare these to their mechanically evoked counterparts.

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**Poster**

**765. Touch: Central Representation of Stimulus Features**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 765.09/QQ19

**Topic:** D.04. Somatosensation: Touch

**Title:** Duration and intensity perception, in parallel, through leaky integration of sensory input

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**Abstract:** To investigate the effect of two stimulus features - intensity and duration - on two perceived properties of the stimulus - again, intensity and duration - we designed two different experiments based upon tactile vibrations. We carried out the experiments both in human subjects, to whom vibration were delivered to left index fingertip, and in rats, to whom the same vibrations were delivered to the whiskers. In Experiment 1, on every trial, subjects received two vibrations - Stimulus1 of duration T1 and Stimulus2 of duration T2 - separated by a fixed, 500ms and 2 s delay for humans and rats respectively. Rats and humans learned to compare either the relative intensities (dictated by the physical mean speed) of Stimulus1 and Stimulus2, or else their relative durations. In Experiment 2, human subjects had to estimate either the duration or the intensity of a single vibration by scaling their judgment through a software slider. In both experiments and in both species, perceived duration was dependent on stimulus intensity while, symmetrically, perceived intensity was dependent on stimulus duration. This symmetrical effect suggests that the brain computation that underlies the formation of these two percepts could be overlapping. We constructed a model based on the hypothesis that perceived intensity and duration are constructed by integrating, with task-specific levels of leak and speed sensitivity, the raw sensory input over time. The model replicates the observed behavior in both rats and humans, suggesting that the network or networks involved in both perceptual modalities share broad architectural features but differ in parameter tuning.

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**Poster**

**765. Touch: Central Representation of Stimulus Features**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 765.10/QQ20

**Topic:** D.04. Somatosensation: Touch

**Support:** DARPA contract N66001-15-C-4014
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**Title:** A biomimetic model to restore touch in bionic hands through a nerve interface

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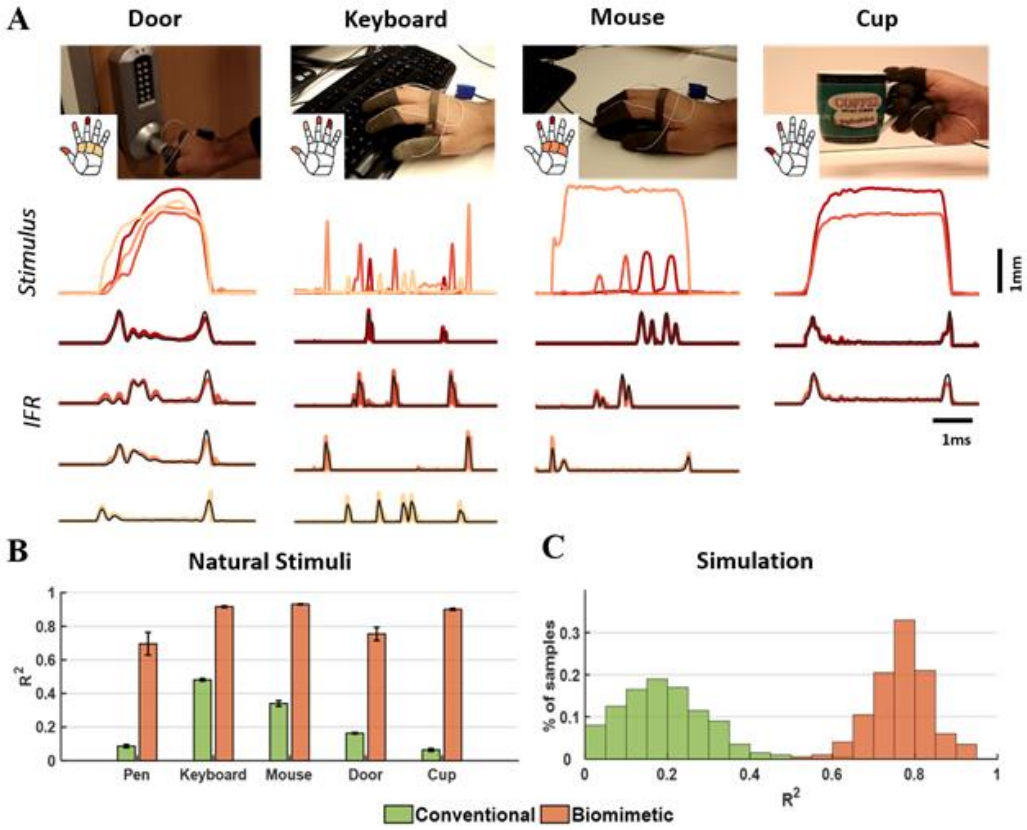
**Abstract:** Hand function can be restored in upper-limb amputees by equipping them with anthropomorphic prostheses controlled using signals from residual muscles. The dexterity of these bionic hands is severely limited in large part by the absence of tactile feedback about interactions with objects. We propose that, to the extent that artificial touch mimics its natural

counterpart, these sensory signals will be more easily integrated into the motor plan for object manipulation. Here, we describe an approach to convey tactile feedback through electrical stimulation of the residual somatosensory nerves that mimics the aggregate activity of tactile fibers that would be produced in the nerve of a native hand during object interactions. For that, we build a parsimonious model that maps a handful of stimulus parameters, namely time-varying indentation depth, indentation rate, and acceleration, into continuous estimates of the time-varying population firing rate and size of the recruited afferent population. The simple model can reconstruct afferent responses to a wide range of stimuli, including those experienced during activities of daily living. We discuss how this model can be implemented with a peripheral nerve interface and show that it leads to improved dexterity for prosthetic hands.




**Disclosures: Q. He:** None. **E.V. Okorokova:** None. **S.J. Bensmaia:** None.

**Poster**

**765. Touch: Central Representation of Stimulus Features**

**Location:** SDCC Halls B-H

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**Topic:** D.04. Somatosensation: Touch

**Support:** NRF of Korea Grant 2016M3C7A1904984
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**Title:** Contact force inhibits vibrotactile neuronal response: A submodality interaction in primary somatosensory cortex

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**Abstract:** Human tactile perception is gradually formed through the interaction of various somatosensory inputs. Previous study has shown that high gamma (HG) response in human primary somatosensory cortex may represent the neuronal processing of specific submodality afferent, such as RA1 (Rapidly Adapting type 1) and PC (Pacinian Corpuscle). However, it remains unclear as to whether these primary responses preserve their specific population activity patterns when complex stimuli activating multiple afferent types are delivered. If these responses are independent each other, the information from each submodality might be separately encoded in S1. Alternatively, submodality interaction might occur at the early-stage of cortical area. To address this question, we recorded human electrocorticography (ECoG) data in the S1 during passive texture stimulation with different contact force, ramp-and-hold pressure, and complex vibrotactile stimulation to the index finger. We found that neuronal HG activity in S1 is strongly inhibited depending on the level of contact force during tactile texture stimulation. In the minimal contact force condition, S1 HG response was analogous to that from complex vibrotactile stimulus. In the high contact force condition, however, the response was almost identical to that from ramp-and-hold pressure stimulus. More specifically, the power level of HG activity during steady-state period was substantially decreased compared to the minimal contact force condition. Interestingly, neuronal population responses of RA1 and PC afferent activations were less dependent each other in S1. Our results suggest the following: (1) dynamic submodality interaction occurs in the human S1, and (2) sensory information from pressure- and vibrotactile-sensitive afferents is categorized differently in human S1, so that these two different neuronal processing might be affected by winner-takes-all mechanism.

**Disclosures: S. Ryun:** None. **J. Kim:** None. **C. Chung:** None.

**Poster**

**765. Touch: Central Representation of Stimulus Features**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 765.12/QQ22

**Topic:** D.04. Somatosensation: Touch

**Support:** OEDIT Award, State of Colorado
City of Fort Collins match for OEDIT
Colorado State University, College of Veterinary Medicine and Biomedical Sciences
College Research Council Award
Sapien LLC match for OEDIT

**Title:** Analysis of tongue features to enhance lingual electrotactile stimulation for sensory substitution applications

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**Abstract:** Sensory substitution is a method of providing information to the brain using an intact sensory system when a different sensory system has been damaged. Research indicates that the tongue is an intrinsically favorable platform for sensory replacement through electrotactile stimulation (ETS). The moist environment of the mouth provides ideal conditions for electric conduction and its secluded nature allows signals to be kept isolated from interference. The anterior tip of the tongue has very small receptive fields, comparable to those of the finger tips, allowing for precise two point discrimination and high tactile sensitivity in this region. However, there is substantial variation in ETS perception across the tongue surface and between individuals, decreasing the efficacy of lingual sensory substitution for some individuals. To enhance electrode array design, we are investigating whether specific neuroanatomical and physiological features are associated with enhanced ability to perceive active electrodes. Specifically, the experiments described here were designed to test whether: 1) sensitivity to 6-n-propylthiouracil (PROP, a bitter compound), 2) density of fungiform papillae, or 3) sex, are associated with the ability to detect and discriminate electrotactile stimulation. Male and female adult participants were included in the studies, which involved rating the bitterness of filter paper treated with PROP, application of blue dye to the tongue followed by photography, classification and quantification of fungiform papillae, and multiple sessions of perception reporting during electrotactile stimulation of the tongue. Data were compiled and subjected to rigorous statistical analysis. Our results indicate that the ability to detect PROP is not associated with ETS perception. In contrast, fungiform papillae density is positively associated with discrimination ability, and preliminary data indicate that women tend to perceive active electrodes as more intense. These data indicate that customization of electrode arrays for lingual sensory substitution applications will increase the efficacy of information transfer to individuals.

**Disclosures: L.M. Stone-Roy:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **P. Turk:** None. **T.S. Allison:** None. **J. Moritz:** A. Employment/Salary (full or part-time):; President, Sapien LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder.

**Poster**

**765. Touch: Central Representation of Stimulus Features**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 765.13/QQ23

**Topic:** D.04. Somatosensation: Touch

**Title:** Behavioral and neural correlates of laryngeal tactile stimulation in spasmodic dysphonia

**Authors: *S. KHOSRAVANI**, A. MAHNAN, I.-L. YEH, P. J. WATSON, Y. ZHANG, G. GODING, J. KONCZAK
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**Abstract:** Spasmodic dysphonia (SD) is a voice disorder resulting in involuntary spasms of laryngeal muscles, resulting in interrupted and strangled speech. Evidence is indicative of impaired somatosensory processing in spasmodic dysphonia. Here we are addressing whether somatosensory processing in SD can be modulated through vibro-tactical stimulation (VTS) in order to normalize pathological speech.This study evaluated the effect of cutaneous laryngeal VTS on voice quality in 10 SD patients. VTS was applied through wearable low voltage vibratory motors attached externally over the laryngeal area. Standard evaluations of voice quality, for abductor and adductor SD types, were performed pre- and post-VTS, and the *number of voice breaks* and *cepstral peak prominence* (CPP) of voice signals were derived; CPP is a prominent measure of voice quality and a reliable predictor of dysphonia. Moreover, cortical activity of somatosensory and motor cortical areas was captured via EEG-recording in order to evaluate the neural correlates of VTS.**RESULTS:** 1) Considerable improvements of voice quality was observed after the application of VTS in 8/10 patients. This was documented as a reduction in the number of voice breaks and a prominent rise in CPP. 2) SD participants exhibited higher levels of theta- and alpha-band oscillatory activities over laryngeal somatosensory and motor cortical areas during vocalization, compared to healthy controls. 3) The elevated cortical activities declined with the application of VTS.**DISCUSSION:** Our finding confirms elevated low-frequency cortical activities in SD -as was reported in other forms of focal dystonia as well. Improvement of voice symptoms was correlated with a decline in low-frequency cortical hyper activity. A similar phenomenon was observed in cervical dystonia patients as they successfully performed *sensory trick* (a tactile maneuver alleviating abnormal contractions). Accordingly, laryngeal VTS in SD may activate the same neurophysiological mechanism underlying effective sensory tricks, ultimately leading to meaningful improvements in voice quality in spasmodic dysphonia.

**Disclosures: S. Khosravani:** None. **A. Mahnan:** None. **I. Yeh:** None. **P.J. Watson:** None. **Y. Zhang:** None. **G. Goding:** None. **J. Konczak:** None.

**Poster**

**765. Touch: Central Representation of Stimulus Features**

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** Human Frontier Science Program (http://www.hfsp.org; project RGP0015/2013)
European Research Council advanced grant CONCEPT (http://erc.europa.eu; project 294498)

**Title:** Dynamic updating of history bias shapes perceptual judgements

**Authors: *S. REINARTZ**, I. HACHEN, R. BRASSELET, M. E. DIAMOND
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**Abstract:** Current perceptual judgements are influenced by past events, such as the previous experience of stimuli and reinforcement. Some form of weighted averaging of the relevant stimulus attribute of preceding events can even be utilized to build and update a decisional criterion, according to changes in the environment. However, what are the exact dynamics by which such biases arise and evolve? What are the relative contributions of sensory and decisional factors?

To address the above issues, we employed a tactile discrimination task where rats (n = 8) had to categorize a set of 'noisy' vibrations according to their mean speed (in humans, mean speed is perceived as vibration intensity or strength). Trials were initiated when rats placed their whiskers in contact with a plate. The plate was then vibrated by a shaker motor, with mean speed of each stimulus scaled from 1-9. After the stimulus termination, an auditory cue instructed the animal to select a spout. According to vibration amplitude just one spout, either left or right, was rewarded, e.g. left spout for vibration speeds 1-4 and right spout for speeds 6-9. For vibrations at the boundary (mean speed 5), reward location was random.

We found a systematic influence of the past trials on rats' decisions relative to each stimulus and characterized the temporal dynamics of this effect on different time scales. By manipulating the task parameters, we further sought to disentangle decisional and sensory related factors. Based on our data, we developed a series of statistical models that allow prediction of rats' decisions, depending upon the history of recent trials.

Overall, our findings suggest that perceptual judgements are better modeled by including the previous context rather than by considering animals as unbiased 'ideal observers', and highlight the essential contribution of past sensory experience to the function of perceptual systems. In conclusion, our results indicate neural mechanisms accounting for the behavioral observations that can be tested in candidate cortical areas.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 766.01/QQ25

**Topic:** D.06. Auditory & Vestibular Systems

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Fondazione Neurone
National Research Foundation of Korea (No. 2016R1A2B4010897)

**Title:** The physiological origin of cortical evoked potentials

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**Abstract:** Event-related potentials (ERPs) have been used for decades for neuroscientific research and for clinical diagnosis of neurological disorders. ERPs are usually categorized by the type of event that they arise from, e.g., auditory evoked potentials (AEPs) or motor evoked potentials (MEPs), and are further categorized by the latency and polarity of their constituent components (e.g., N1, P1, P2). Prior research has primarily considered three main mechanisms to give rise to ERPs: (1) additive contributions to ongoing activity; (2) phase resetting by a sensory stimulus; (3) oscillatory voltage asymmetry. While different previous work has provided some evidence for each of these three possibilities, their specific quantitative contribution to each of an ERP's individual components has not yet been determined. This lack of knowledge greatly impedes detailed physiological interpretation of ERPs and the generation of more general models that such data could inform. In our study, we began to address this important issue by quantifying the specific contribution of each of these mechanisms in the context of AEPs and MEPs. In our study, eight human subjects who were implanted with electrocorticographic (ECoG) electrodes over STG and M1 motor cortex participated in a simple reaction time task. In this task, the subjects responded to a salient auditory stimulus by pressing a push button with the thumb contralateral to the ECoG implant. To determine the specific contribution of each of the three possible generating mechanisms to AEP and MEP responses, we assessed the fraction of the overall signal accounted for by each of them. Our results demonstrate that MEPs are largely generated through additivity (88%) but not through phase reset (12%). The P1 and N1

components of the AEPs are mostly generated by phase reset (94%), while the P2 component is generated by additivity (57%) and phase reset (36%). Oscillatory voltage asymmetry only marginally contributed to these ERP components. These results sheds light on the previously unknown contribution that additive, phase reset, and asymmetric amplitude mechanisms have on the generation of AEPs and MEPs. They should greatly facilitate the physiological interpretation of AEPs and MEPs, and should also be important for the creation of general models of evoked responses and their relationship to behavior.

**Disclosures: H. Cho:** None. **P. Brunner:** None. **L. Moheimanian:** None. **S.C. Jun:** None. **G. Schalk:** None.

**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 766.02/QQ26

**Topic:** D.06. Auditory & Vestibular Systems

**Support:** BBSRC grant BB/N008731/1

**Title:** Mechanisms of selectivity and invariance in the mouse auditory cortex

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**Abstract:** Any sensory system must exhibit two fundamental properties. Firstly, it must be sufficiently selective to enable the animal to discriminate between stimuli. In the auditory system, this might mean the ability to differentiate between phonemes in speech. Secondly, it must support a degree of invariance to non-informative stimulus variations. For example, it is nearly always necessary to identify a stimulus in the presence of background noise.
It has been proposed that these properties emerge from computational functions implemented by individual neurons. Neurons may become selective to increasingly complex stimulus features by responding in a supralinear way to stimulus combinations, analogous to a logical AND function. Conversely, invariance may be implemented by neurons responding in a sublinear way, computationally similar to a logical OR. We aimed to characterise to what extent neurons in the auditory cortex implement these functions whilst processing natural sounds.
Ultrasonic vocalisations (USVs) are produced by mice in various social contexts and appear to serve a communicative function. Thus, they constitute behaviourally relevant, complex, natural stimuli. We recorded the responses of single neurons to USVs in the auditory cortex of anaesthetised mice and characterised their spectro-temporal receptive fields using the maximum noise entropy (MNE) method.
For each neuron, we defined acoustic stimuli corresponding to individual receptive field

components and presented these both separately and simultaneously whilst recording responses from the same neuron. The neuron's combination function was then specified using the summation index, a metric that quantifies the extent to which this function reflects supralinear (AND-like) or sublinear (OR-like) operation. Furthermore, to verify that the stimuli excited neurons through independent inputs, we measured the extent to which adaptation caused by repeated presentations was stimulus-specific.
In summary, we present a method to investigate neuronal combination functions from responses to natural sounds, which is generalisable to other sensory modalities. We show that neurons in the mouse auditory cortex have receptive fields comprising multiple, independent components, which may be estimated from responses to natural vocalisations.

**Disclosures: M.A. Steadman:** None. **A.S. Kozlov:** None.

**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

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**Topic:** D.06. Auditory & Vestibular Systems

**Support:** NSF Grant 1515587

**Title:** Inhibitory inputs to medial geniculate body modulate nonlinear population auditory cortical responses after midbrain stimulation

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**Abstract:** The auditory colliculo-thalamocortical mouse brain slice, which retains synaptic connectivity between inferior colliculus (IC), medial geniculate body (MGB), and auditory cortex (AC), enables the examination of the role of the MGB in signal transmission from the IC to the AC. Low-magnification flavoprotein autofluorescence and calcium imaging as well as cortical local field potentials showed all-or-none cortical responses without any change in IC and MGB responses following IC stimulation. Low stimulating current amplitude and short inter-stimulus-interval increased the frequency of the missing cortical responses. In contrast, direct stimulation of MGB or the white matter produced only linear cortical responses. Bath perfusion of gabazine, $GABA_A$ receptor blocker, was capable of retrieving the missing cortical responses. However, focal injection of gabazine into MGB, not AC, retrieved the missing cortical responses and linearized cortical and MGB responses. Further, current and voltage clamp recording from

layer 4 or 2/3 showed similar all-or-none responses with showing no evidence for local inhibitory events during the missing cortical responses. However, voltage clamp recording of MGB cells showed that MGB receives a higher inhibition/excitation ratio during the missing cortical response. Intrestingly, opto- and chemogenetic silencing of NTSR-positive layer 6 corticothalamic neurons retrieved the missing cortical responses which modulates feedback inhibition of MGB to control the gain of thalamocortical neurons. Further, current clamp recording of MGB cells showed that not all MGB cells fire in a response to IC stimulation. Similarly, calcium imaging of MGB showed a spatiotemporal heterogeneity of MGB cellular responses following each IC stimulation, and the latencies of calcium signal peak of MGB cells had a higher variance during the missing cortical responses. Network analysis of the MGB responses based on calcium imaging showed that the size of the network shrinks to intensify the edges between certain nodes during cortical activation only. These data suggest that the thalamus may recruit cortical ensembles rather than linearly encoding ascending stimuli, and that GABAergic cortical thalamic inhibition from the thalamic reticular nucleus may play a role in selecting cortical ensembles for activation.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 766.04/RR2

**Topic:** D.06. Auditory & Vestibular Systems

**Support:** NIH R01 2DC05660
Max-Planck-Society

**Title:** Neural computational principles of auditory processing revealed by magnetoencephalography and deep neural networks

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**Abstract:** Acoustic information is processed by the auditory system in a hierarchical manner - detailed acoustic information is extracted and represented at the low level (e.g. sub-cortical structures and primary auditory cortex) while relatively abstract information of category and identity of sounds is formed at higher levels (e.g. superior temporal gyrus, superior temporal sulcus and frontal areas). Uncovering this hierarchical principle of information processing,

neurophysiologically and computationally is of foundational significance. To approach this, we ask, neurophysiologically, how pitch and timbre information is extracted along the auditory hierarchy temporally and spatially using magnetoencephalography (MEG). We simulate, computationally, how deep neural network (DNN) represents such information across different layers. We selected three different musical instruments and 8 different notes from the Nsynth Database and presented each sound 100 times to listeners while recording MEG signals. We classified different musical notes and reconstructed each sound along auditory ventral pathway from reconstructed MEG source signals. Taking advantage of the large number of sound samples available to train a DNN from the Nsynth Database, we trained a DNN to classify different notes and, corresponding to the MEG paradigm, studied the representation of acoustic details and classification performance on each layer of the DNN. We hypothesize that the stimulus reconstruction performance decreases and classification performance increases along the auditory hierarchy; in parallel, in middle layers of the DNN, representation of detailed acoustic information becomes degraded but performance on classification of notes is improved on top layers of the DNN. By combining results from neurophysiology and DNN, we can begin to decipher auditory processes in the brain, temporally, spatially, and computationally.

**Disclosures: X. Teng:** None. **D. Poeppel:** None.

**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

**Location:** SDCC Halls B-H

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**Topic:** D.06. Auditory & Vestibular Systems

**Support:** ERC Grant 523210

**Title:** Persistent activity in auditory cortex during passive listening

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**Abstract:** Persistent activity, the elevated firing of a neuron after the termination of a stimulus, is hypothesized to play a critical role in working memory. This form of activity is therefore typically studied within the context of a behavioural task, which includes a working memory component. Here we investigated whether persistent activity is observed in sensory cortex and thalamus in the absence of any explicit behavioural task. We recorded spiking activity from single units in the core area of auditory cortex (fields A1, R and RT) and thalamus of awake, passively-listening marmosets. We observed persistent activity that lasted for hundreds of

milliseconds following the termination of the acoustic stimulus, in the absence of a behavioral task. Persistent activity was observed following onset and sustained responses during the stimulus and showed similar stimulus tuning as the evoked responses. Persistent activity was also observed following suppression in firing during the stimulus. These response types were observed in all cortical fields tested, as well as in thalamus. Thalamic persistent activity was of shorter duration than the responses observed in cortex, indicating that cortical persistent activity is not simply inherited from thalamus. Given that the persistent activity is observed in auditory cortex of passively listening marmosets it may have functional importance beyond storing behaviourally relevant information in working memory.

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OPERA and RIG, BITS PILANI

**Title:** Classifying the neural code of concurrently presented vowels

**Authors: *S. S. SMITH**[1], A. CHINTANPALLI[2], M. N. WALLACE[1], A. HOCKLEY[1], M. G. HEINZ[3], C. J. SUMNER[1]
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**Abstract:** Listeners use multiple cues to help them understand speech despite interfering sounds (e.g. pitch, onset/offset asynchronies, dynamics). Historically, special attention has been paid to fundamental frequency (F0) cues and how they benefit the task of identifying concurrently presented vowels, denoted the ‘F0 benefit’ (review: Micheyl and Oxenham, 2010; Hear. Res. 266: 36-51). The classical model of concurrent-vowel identification can replicate an ‘F0 benefit’ only qualitatively (Meddis & Hewitt, 1992; JASA 91: 233-245). The model’s utilisation of F0 cues requires temporal processing that is unverified by neurophysiological studies. Moreover, the model makes deterministic decisions resulting in very poor predictions of listener confusions. Significant flaws in this model, and within others, imply we do not understand how listeners solve this simple instance of the ‘cocktail party problem’.

We present our model of concurrent-vowel identification, based on ideal observer principles. Our model takes expected neural responses to concurrent-vowel pairs, generated from a 'linear' simulation of the auditory nerve, as input. Likelihood functions predicting neural responses to each vowel combination are stored as templates. A high dimensional naïve Bayes classifier optimally compares raw input to these stored templates, and produces a confusion matrix. Our model can qualitatively and quantitatively replicate an 'F0 benefit'. This is despite having no explicit temporal processing of F0 cues. Simply, when there are larger F0 differences between vowels there is more information available for classification. Additionally, the model makes quantifiable predictions of listener confusions with a high degree of accuracy ($R>0.9$). The model's generality allows it to also handle data produced by a 'nonlinear' simulation of the auditory nerve, or neural responses recorded from multi-unit electrodes in the guinea pig inferior colliculus. Overall, our model is much closer to predicting human performance at the concurrent-vowel identification task than previous models. The work promotes the use of ideal observer principles to develop our understanding of how listeners solve the 'cocktail party problem'.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 766.07/RR5

**Topic:** D.06. Auditory & Vestibular Systems

**Support:** BBSRC New Investigator Award BB/M010929/1
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**Title:** Processing of reverberant sound in the auditory system

**Authors: *A. Z. IVANOV**, B. D. B. WILLMORE, K. M. M. WALKER, A. J. KING, N. S. HARPER
The Univ. of Oxford, Oxford, United Kingdom

**Abstract:** Every natural sound is accompanied by many delayed and distorted copies of itself (echoes or reverb). Unless the environment is very echoic, our brains cope effectively with reverberation. In contrast, reverberation can cause severe difficulties for speech recognition algorithms and hearing-impaired people. How might the healthy auditory system cope so well with reverberation? A major feature of auditory neurons is their ability to adapt to the sound statistics such as the mean or variance of the sound level (Dean et al. 2005, Rabinowitz et al. 2011). We posit that such adaptive phenomena could reduce the difficulties associated with

reverberation. To test this hypothesis, we used a large data set of anechoic natural sounds and a room simulator to generate reverberant sounds. Both anechoic and reverberant sounds were passed through a model of the cochlea to produce 'cochleagrams'. We then trained a linear model to find the best mapping from the reverberant to the anechoic cochleagrams. The transformation learned by the units in this normative model displayed similar characteristics to the spectro-temporal receptive fields (STRFs) of auditory neurons, such as narrow frequency tuning and lagging inhibition similar to that observed in auditory neurons (Dean et al. 2008). For each model unit we measured a time constant of adaptation from this inhibition. The units showed time constants that were frequency-dependent, consistent with previous experimental data (Dean et al. 2008). The model also provided new predictions which we tested experimentally. First, the model's time constants increased with the amount of reverberation. Second, the ratio of inhibition to excitation in model STRFs increased with the amount of reverb. We tested these predictions in the auditory cortex of anaesthetised ferrets by recording responses extracellularly using Neuropixels probes. Our data suggest that the inhibitory time constants of real neurons, and the ratio of inhibition to excitation, both increase with the amount of reverb, similar to the model predictions. These findings suggest that the adaptive (Rabinowitz et al. 2011) and meta-adaptive (Robinson et al., 2008) properties of auditory neurons may play an important role in the processing of reverberant sounds.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

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**Topic:** D.06. Auditory & Vestibular Systems

**Support:** Hellen Stafford Summer Research Fellowship Fund
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**Title:** Identifying the acoustic and neural basis of mate recognition in two Xenopus species

**Authors: *J. LAKE**, J. DEROCHOONEE, E. ZORNIK
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**Abstract:** Vocal-dependent courtship and mating behaviors are governed by the linkage between auditory processing and motor production. Male frogs in the genus *Xenopus* produce unique advertisement calls to attract female mates of their own species. While vocal production mechanisms in *Xenopus* have been studied in detail, the auditory and sensorimotor processing mechanisms that regulate behavioral responses to vocalizations remain mostly unknown.

Comparative experiments within the *Xenopus* phylogeny provide an opportunity to understand the evolution of auditory vocal processing. *X. laevis* and *X. petersii* are two closely related species whose advertisement calls differ in spectral and temporal properties. In this study, we investigated whether females of each species exhibit preferences for conspecific calls, and what acoustic features are used to distinguish between conspecific and heterospecific calls. We used natural and modified playbacks of male *X. laevis* and *X. petersii* advertisement calls, and found that call preferences depend on the reproductive state of the target female. In order to pinpoint brain regions associated with vocal processing, we measured two molecular signatures of neuronal activity, the phosphorylated ribosomal protein S6 (pS6) and the immediate early gene c-fos. Correlations between behavioral responses to call playbacks and expression levels in key auditory centers—central nucleus of the amygdala (CeA), the bed nucleus of the stria terminalis (BNST), and the torus semicircularis—contribute to distinguishing activity patterns responsible for auditory reception and species recognition. Together, our results are uncovering neural pathways involved in mate and species recognition behaviors in *Xenopus*.

**Disclosures: J. Lake:** None. **J. Derochoonee:** None. **E. Zornik:** A. Employment/Salary (full or part-time):; Reed College.

**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

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**Title:** Component modeling of electrocorticography (ECoG)

**Authors: *S. V. NORMAN-HAIGNERE**[1,2,3], P. BRUNNER[4,5], A. RITACCIO[4,5], G. SCHALK[4,5,6], N. KANWISHER[2]
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**Abstract:** Many neural signals are low-dimensional: much of their response can be captured by a small number of canonical response patterns (“components”). Thus, component analysis can be useful for understanding high-dimensional population data by distilling its key features into a small number of response patterns. At the same time, inference of these latent components is challenging, because it requires making assumptions about the statistical structure of the population response. Here, we explore component models of sensory cortical responses measured from electrodes placed directly on the surface of the human brain (electrocorticography or ECoG). Each component was defined by a time-varying response to a set of stimuli (here a set of natural sounds) and a pattern of weights that specified the contribution of that response to each electrode. Most component methods rely one of three assumptions: (1) component responses or weights are sparse (i.e., “sparse coding”); (2) component responses are temporally smooth (e.g., “slow feature analysis” or “Gaussian process factor analysis”); or (3) component responses or weights are non-negative (e.g., “NMF”). We develop a simple model that incorporates all three of these properties: each electrode is modeled as the weighted sum of a small number of component response patterns, using sparse non-negative weights; and each component response pattern is modeled as the convolution across time of sparse, non-negative activations with a temporal smoothing kernel that is learned separately for each component. We show that this model is better able to predict ECoG broadband gamma responses (70-140 Hz) on unseen data than simpler models that only assume one or two of these constraints (non-negativity, sparseness, or smoothness). We also find that the inferred components are substantially more reliable than individual electrodes (i.e. higher test-retest correlation across repetitions of the same stimuli), and exhibit interpretable structure, showing selectivity for both acoustic features and sound categories (speech, music, and singing). Our optimization framework makes it easy to change the model’s assumptions (e.g. allow the responses to be positive), and thus may be broadly useful in modeling time-varying sensory responses.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

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**Topic:** D.06. Auditory & Vestibular Systems

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**Title:** Frequency dependent interaction of dual sound representations in monkey inferior colliculus

**Authors: *S. M. WILLETT**, V. C. CARUSO, S. T. TOKDAR, J. M. GROH
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**Abstract:** Behaving in complex environments requires the segregation and preservation of multiple, often overlapping stimuli. Neural codes relying on rate are potentially ill suited for the coding of multiple stimuli. A neuron cannot fire at two rates simultaneously. How, then, do neurons encode multiple stimuli that fall within their receptive fields? A useful structure to investigate this question is the primate inferior colliculus (IC); which possesses neurons with broad response functions in the spatial and frequency domains. Recent work showed some neurons in the monkey IC fluctuate between activity patterns that could permit encoding of simultaneously presented sounds across time (Caruso et. al., BioRxiv, 2017; Willett et. al., Soc Neuro Abstr 2016, Willett et. Al., Soc Neuro Abstr 2017). However, it remains uncertain what determines how a given neuron responds to a given combination of stimuli. The current study evaluates how the frequency separation between the pairs of sounds impacts the observed response pattern. Single unit IC activity was recorded while rhesus macaques performed a dual sound localization task involving either a single saccade to the location of one sound or a sequence of two saccades to the location of each of two simultaneously presented sounds (bandpass noise of different center frequencies). We found that fluctuating activity patterns were more common on dual sound trials when the two stimuli were closer in frequency, and that when the stimuli were well separated, the responses more closely resembled the response to one of the two sounds when it was presented in isolation. Together, these findings suggest that fluctuating activity contributes to coding when the stimuli individually evoke activity in a highly overlapping population of neurons, but when the stimuli are well separated, this is not necessary.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

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**Title:** Parallel processing of sound dynamics across mouse auditory cortex via spatially patterned thalamic inputs and distinct areal intracortical circuits

**Authors: *J. LIU**[1], M. R. WHITEWAY[2], A. SHEIKHATTAR[3], D. A. BUTTS[5], B. BABADI[4], P. O. KANOLD[1]
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**Abstract:** The auditory system encodes spectral information in sound through tonotopic organizations. However, it is not fully known how the temporal information of sound, e.g. sound offset, are represented in the auditory cortex. To investigate the spatial representation of sound offset, we performed widefield imaging in awake mouse ACX expressing GCaMP6s and found large-scale areal differences in onset (On-R) and offset-response (Off-R). We also found that Off-Rs were tonotopically organized and more spatially extensive than On-R. To further investigate these differences, we performed 2-photon imaging of ACX layer 2/3 neurons and found that On- and Off-R neurons were largely non-overlapping populations and that locally Off-R were also more widely distributed in space. We further performed network-level functional connectivity analysis using Granger causality, which revealed that ACX contains On- and Off-networks of different sizes, suggesting a differential recurrent processing. To investigate the origin of cortical On/Off-R spatial patterns, we performed 2-photon imaging of medial geniculate body (MGB) terminals, which provide input to ACX, and found that MGB terminals show a consistent spatial pattern with that of cellular response. Our analysis suggests that cortical spatial representations of On/Off-R were tightly related to MGB input. Together, our results demonstrate a differential spatial organization of sound onset/offset processing across ACX due to locally spatially patterned projections from the MGB as well as differing intracortical connectivity.

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**766. Auditory Processing: Neural Coding, Experiment, and Theory**

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**Topic:** D.06. Auditory & Vestibular Systems

**Title:** Two-talker attention decoding from EEG with nonlinear neural networks and linear methods

**Authors: *C. J. SMALT**[1], G. A. CICCARELLI[1], M. NOLAN[1], J. PERRICONE[1], P. CALAMIA[1], J. A. O'SULLIVAN[2], N. MESGARANI[2], T. QUATIERI[1]
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**Abstract:** A particular challenge with hearing impairment is difficulty in attending to a single speaker in a multi-talker environment. This study is a confirmatory study that hypothesizes that nonlinear neural networks (NN) may provide an advantage to linear methods in auditory attention decoding from recorded electroencephalograph (EEG) waveforms.
Nine subjects gave written, informed consent to participate in an EEG-auditory collection protocol approved by the MIT review board. Each subject wore a 64 channel EEG and was presented with two collocated talkers (one male, one female) reading different passages. Subjects were directed to attend to one of the two speakers. The audio presentation was randomly stopped and subjects were asked to repeat back the last sentence from the target speaker to check for adherence to the task. There were approximately 35 segments of approximately 45 seconds duration per subject.
We trained three different NN architectures to map from the collected EEG to the perfectly separated speech envelope. We tested one NN with convolutional layers, one with a single hidden layer, and one that was a linear transform (no hidden layers). Attention was decoded by comparing the predicted auditory envelope using all 64 EEG leads to the target auditory envelope and the distractor envelope using Pearson correlation. Accuracy, as defined by whether the system correctly predicted the person was attending to the target talker, was determined over the course of a complete segment, and training and testing was performed with leave-one-segment out cross validation. The training and testing procedure was the same among the architectures but due to reserving two segments for nested validation the training sets were highly overlapping but not identical among architectures.
To date, we've analyzed four subjects. Mean and standard deviation for the convolutional, one hidden layer, and linear networks are: 0.63 (0.15), 0.56 (0.15), 0.51 (0.13).
This work provides additional evidence that auditory attention decoding is possible from EEG, and preliminary evidence that a convolutional architecture may provide better decoding accuracy than non-convolutional architectures.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

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**Topic:** D.06. Auditory & Vestibular Systems

**Support:** F31 DC014888
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**Title:** Dissociation of task engagement and arousal effects in auditory midbrain and cortex

**Authors: *D. SADERI**, Z. P. SCHWARTZ, C. R. HELLER, S. V. DAVID
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**Abstract:** It is well-established that changing behavior state has diverse effects on auditory brain activity, but these findings have yet to be integrated into a coherent theory of how internal state influences sensory coding. Many previous studies have focused on the effects of a single state variable, and interpretation of these results is complicated if the variable of interest is correlated with other, uncontrolled changes in state. To isolate effects of different state variables on auditory processing, we developed a paradigm to simultaneously control task engagement and monitor fluctuations in arousal during single-unit recording from the inferior colliculus (IC) and primary auditory cortex (A1) of ferrets. To control task engagement, neural activity was recorded during a tone *versus* noise discrimination task and during passive presentation of task stimuli. Arousal was measured via pupillometry. We used a generalized linear model to isolate the effects of engagement and arousal variables on spontaneous and evoked activity in the IC and A1. As expected from previous studies, fluctuations in pupil-indexed arousal were correlated with changes in task engagement, but their effects could be dissociated in most data sets. In both areas, individual neurons could be modulated by either engagement or arousal or by both variables. However, engagement and arousal effects in the IC were about half the magnitude of those in A1. Engagement effects could be enhancing or suppressing in both areas. Arousal effects also had variable sign in IC, but arousal was mostly positively correlated with spike rate in A1. Taking both state variables into account revealed a smaller measured influence of task engagement than when arousal was not considered. These results indicate that some changes attributed to task engagement in previous studies should in fact be attributed to global changes in arousal. Moreover, these arousal effects may explain differences in neural activity observed between passive conditions pre- and post-behavior. This same approach can be used to account for other state variables, such as selective attention and behavioral effort, providing a general method for dissociating the influence of continuous and discrete behavioral state variables.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 766.14/RR12

**Topic:** D.06. Auditory & Vestibular Systems

**Title:** I can hear you but Ican not catch you: The neural representations of hierarchical linguistic structures in a complex scene

**Authors: *Y. GAO**
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**Abstract:** A common case in a noisy auditory scene is that listeners hear acoustic signals to an extent but fail to understand the meaning of the target speech. Although there are plenty of works discussing the neural encoding of speech stimuli, which and how neural representations reflect the process of speech comprehension remain unclear. To address this question, we composed a target speech with hierarchical linguistic structures of syllable and word at the rate of 4 and 2 Hz, respectively, in an envelope-modulated speech-shaped noise masker. Manipulating the signal-to-noise ratio (SNR) at 0, -3, -6 dB, we measured both the electroencephalography (EEG) and speech intelligibility of listeners. While the SNR was decreasing, the neural tracking of both target words and syllables decreased. Discriminatively, the cortical oscillation only at the rate of target words but not of target syllables correlated to the speech intelligibility. These results demonstrate the particularity of speech comprehension from the signal-based auditory perception and suggest a new aspect of the neural decoding of speech in a complex scene.

**Disclosures: Y. Gao:** None.

**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

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**Topic:** D.06. Auditory & Vestibular Systems

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Wellcome Trust WT108369/Z/2015/Z

**Title:** Temporal prediction as a principle behind cochlea tuning

**Authors: *F. TRINH**, B. D. B. WILLMORE, A. J. PARKER, N. S. HARPER
Dept. of Physiology, Anat. and Genet., Univ. of Oxford, Oxford, United Kingdom

**Abstract:** Neurons in the sensory systems are tuned to diverse but specific features of the sensory environment. Over the years, several theoretical principles - notably sparse coding - have been proposed which explain how this specific tuning may be the result of adaptation to the statistical regularities of natural sensory stimuli. The cochlea transduces sound waves into electrochemical signals by filtering them using impulse response functions that can be approximated using gammatone filters. It has been suggested that the shape of these filters can be accounted for by efficient, sparse representation of sound in the cochlea (Lewicki, 2002, Nat Neurosci 5:356-363; Smith & Lewicki, 2006, Nature 439:978-982). We suggest an alternative principle: that the peripheral auditory system is governed by temporal prediction, meaning that predictive information of auditory stimuli is preferentially encoded. Recent experimental findings indicate that retinal neurons might be optimised for temporal prediction (Palmer et al., 2015, Proc Natl Acad Sci 112:6908-6919), and theoretical work also suggests that temporal prediction may explain many aspects of receptive fields in both primary auditory and visual cortex (Singer et al., 2017, bioRxiv). We ask if the same principle can explain the features of the peripheral auditory system, more specifically the cochlea. We trained a feedforward network with one hidden layer to predict the immediate future values of raw sound waveforms based on the most recent past values. We used an auditory dataset that is representative of the natural soundscape, and a crucial component of our model was the addition of Gaussian noise to the training set. We interpret the input weights to each hidden unit as the impulse response of a section of the basilar membrane. The tuning characteristics of the hidden units show ringing and resemble gammatone filters, which approximate the impulse response functions reported for both the basilar membrane and auditory nerve fibres. The hidden units are tuned to frequencies over a wide range, and their density is inversely proportional to best frequency, while the filter bandwidth is proportional to best frequency. The filters are asymmetric in time and enable biologically plausible real-time encoding. Overall, a simple model optimized for temporal prediction can capture several distinct features of the peripheral auditory system.

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**Support:** Clarendon Fund Scholarship

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**Title:** Investigating the temporal window of sensory representation in the auditory cortex

**Authors: *M. RAHMAN**, C. Y. C. LEUNG, A. J. KING, N. S. HARPER
Dept. of Physiology, Anat. and Genet., Univ. of Oxford, Oxford, United Kingdom

**Abstract:** In this study, we investigated the temporal window represented by the neural population in auditory cortex; how far into the past does the population represent auditory information, and how far into the future can it predict, and what kind of mechanisms might be involved in this representation. We played 20 natural sound clips, each of 5 s duration, to 6 anaesthetized ferrets and recorded single-unit responses in primary auditory cortical areas A1 and AAF, providing a neural population response for 73 neurons. We then processed the sound clips through a simple cochlear model to provide a time-dependent frequency decomposition (a 'cochleagram'). Then, using linear decoding, we estimated the past and future cochleagram from a 5 ms window of neural population response at the present. We could reconstruct about 0.7 s into the past, and predict about 0.3 s into the future, with at least some fidelity. We also performed the same analysis for a neural population response in the inferior colliculus (30 neurons). For the inferior colliculus, we could reconstruct only 0.1 s into the past and predict 0.15 s into the future. We investigated if the capacity for prediction and reconstruction could be explained by the linear spectrotemporal response properties of auditory neurons plus a static nonlinearity, i.e. a linear-nonlinear-Poisson (LNP) model. For both the cortical and collicular datasets, neuronal activity estimated low frequency spectral components of future sounds more faithfully than the LNP model, but estimated past sounds and high frequencies in future sounds with less accuracy. This suggests nonlinear mechanisms that increase some capacities for prediction may be involved in auditory processing, potentially at the expense of representation of the past. However, it should be noted that both datasets were dominated by high frequency tuned neurons, and the natural sound clips tended to have most power at low frequencies, which are points to consider in interpretation. We also examined decoding using different time windows of neural response (spans of 1, 5, and 10 time bins of 5 ms duration each). Longer time windows tended to improve the LNP model's capacity to estimate the past relative to that of the real neural responses, but had little effect on prediction of the future.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

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**Title:** Neural correlates of abnormal sensorimotor integration during speaking in Alzheimer's disease

**Authors: *K. RANASINGHE**[1], H. KOTHARE[2], N. KORT[3], L. B. HINKLEY[7], A. J. BEAGLE[3], D. MIZUIRI[3], S. HONMA[3], B. L. MILLER[4], K. A. VOSSEL[8], J. F. HOUDE[5], S. S. NAGARAJAN[6]
[1]Univ. of California San Francisco, San Francisco, CA; [2]Univ. of California, San Francisco, San Francisco, CA; [4]Neurol., [5]Dept of Otolaryngology -- Head and Neck Surgery, [6]Radiology and Biomed. Imaging, [3]UCSF, San Francisco, CA; [7]Radiology, UC San Francisco, San Francisco, CA; [8]Univ. of Minnesota, Minneapolis, MN

**Abstract:** Accurate integration of sensory inputs and motor commands is essential to achieve successful behavioral goals. In a previous study we demonstrated impaired sensorimotor integration in patients with Alzheimer's disease (AD) with an abnormally increased pitch reflex compared to controls. In this study we examined the neural correlates of the abnormal pitch reflex. We examined the high-gamma band (65-150Hz) neural responses using magnetoencephalography and their specific correlates to behavioral response, as the participants (n=16, patients; n=13, age-matched controls) phonated the vowel /a/ while a real-time signal processor briefly perturbed (100 cents for 400 ms) the pitch of their auditory feedback. We found that AD patients show significantly reduced left prefrontal activity during the early phase and increased right middle temporal activity during the later phase, of the pitch reflex, compared to controls. The left prefrontal (Figure-1 A &B) and right middle temporal (Figure-1 C & D) activity significantly predicted the degree of peak behavioral response in pitch reflex. The left prefrontal and right middle temporal high-gamma band activity showed significant independent associations with the peak behavioral response when controlled for the degree of executive function abilities, global cognitive performance and age. Furthermore, the high-gamma activity of the left prefrontal cortex was significantly correlated with the degree of executive function abilities, after regressing on the peak behavioral response, in the combined cohort of patients and controls. These results demonstrate the neural substrates of the abnormal pitch reflex in patients with AD and identify the neural circuit dysfunctions that may likely impact both low-level sensorimotor and high-level executive functions in AD.

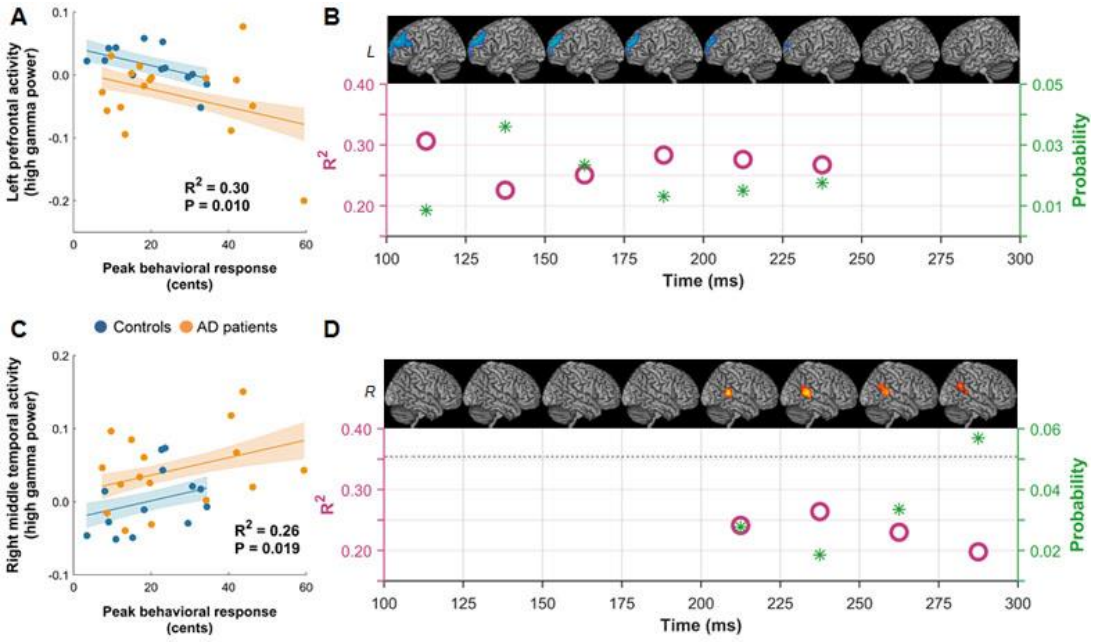


**Figure 1: Left prefrontal activity and right middle temporal activity predict peak behavioral response in pitch reflex.** In an analysis of covariance model (ANCOVA) on the combined cohort of both patients and controls, the average high-gamma activity of left prefrontal cortex across the 100 – 250 ms post-perturbation-onset was significantly negatively correlated with the peak behavioral response (A). The $R^2$ of the model predictions (pink circles; left-side Y axis) and the p-values (green stars; right-side Y axis) of the association between left prefrontal activity and peak behavioral response in each 25 ms window (B). The average high-gamma activity of the right posterior middle temporal cortex across the 200 – 300 ms post-perturbation-onset was significantly positively associated with the peak behavioral response (C). The R2 of the model predictions (pink circles; left-side Y axis) and the p-values (green stars; right-side Y axis) of the association between right middle temporal activity and peak behavioral response in each 25 ms window (D). Abbreviations: AD = Alzheimer's disease; L = Left hemisphere; R = Right hemisphere.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 766.18/SS2

**Topic:** D.06. Auditory & Vestibular Systems

**Support:** NSF Grant 1738285
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**Title:** Sparse linear dynamical models for micro-electrocorticography responses in the auditory cortex

**Authors: *M. EMAMI**[1], P. PANDIT[1], M. SAHRAEE-ARKADAN[1], M. TRUMPIS[3], B. BENT[3], J. VIVENTI[3], S. RANGAN[4], A. FLETCHER[2]
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**Abstract:** Modern micro-electrocorticography (μECoG) measurements in the rat auditory cortex have demonstrated that responses to auditory stimuli can be complex and not fully described by simple linear models such as spectrotemporal receptive fields (STRFs). In this work, we propose a novel model for the auditory cortex where responses are the output of a low-dimensional linear dynamical system driven by sparse inputs. The low-dimensional linear dynamical system can be represented compactly in a state-space form that dramatically reduces the number of parameters to be estimated in comparison to standard convolutional filters. The reduction in parameters is particularly pronounced when the response times are long. The sparse generative model inspires a novel neural decoding method based on iterative Kalman smoothing for the linear dynamical stage and thresholding for the sparse input stage. Parameter fitting for the decoder can leverage subspace methods. The method is illustrated for neural decoding of the rat primary auditory cortex (A1) using a high-resolution flexible electrode array. The array has 61 electrodes with 400 μm spacing. It is shown that the proposed method can offer improved performance over standard decoding methods, particularly in awake animals where there are large numbers of confounding stimuli.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

**Location:** SDCC Halls B-H

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**Title:** Nominally non-responsive frontal and sensory cortical cells encode task-relevant variables via ensemble consensus-building

**Authors: *M. INSANALLY**[1], I. CARCEA[1], R. E. FIELD[1], C. C. RODGERS[2], B. DEPASQUALE[3], K. RAJAN[4], M. R. DEWEESE[5], B. F. ALBANNA[6], R. C. FROEMKE[1,7]
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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. These results suggest that nominally non-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 nominally non-responsive (64/103 AC cells and 43/74 FR2 cells from 15 animals had neither significant tone-modulated activity or ramping activity; $p < 0.05$,5,000 bootstraps). To understand the role of all recorded cells we devised a novel, spike-timing-based algorithm for single-trial decoding. Our algorithm evaluates the extent to which singe-unit responses encode task variables on individual trials (stimulus category and behavioral choice) by using the statistical prevalence of the interspike interval (ISI) on trials of a certain stimulus category (target vs. nontarget) or behavioral category (go vs. no-go). Using this analysis, we have made four discoveries: 1) Nominally non-responsive cells reveal hidden task information. The activity of cells that seem unresponsive when trial-averaged often encode task-relevant information at levels comparable to responsive cells. 2) Nominally non-responsive cells are better predictors of single-trial behavioral errors. 3) Frontal cortex is more informative about task-relevant auditory stimuli than auditory cortex. 4) Ensemble consensus-building underlies ISI-based task information. Neural ensembles coordinate the behavioral meaning of spike timings, essentially achieving consensus on the representation of task variables on correct but not error trials. This unbiased approach allows for the contribution of all recorded neurons - particularly those without obvious task-modulation - to be assessed for behavioral relevance on single trials.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 766.20/SS4

**Topic:** D.06. Auditory & Vestibular Systems

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**Title:** From microscale structure to population coding of normal and learned behavior

**Authors: *B. J. FISCHER**[1], W. M. DEBELLO[2], M. H. ELLISMAN[3], E. A. BUSHONG[4], J. L. PENA[5]
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**Abstract:** How ensemble activity, network architecture, and synaptic specializations coordinate natural and learned behavior is not known. We predict that orienting to auditory targets is implemented by readout of activity of an entire neural population, approximating statistical inference. This is being tested in barn owls, as they provide easy access to a complete population representing auditory space in both normal and learned conditions and the correlated synaptic and network microanatomy can be determined by advanced 3D microscopy methods. Microelectrode arrays (MEA) are used to map the activity of the population to sound, and decoders are designed to test how the population is readout to drive behavior. Preliminary results using MEAs and tetrodes support the central hypothesis. In addition, tetrode recordings of distant and nearby neurons were used to measure response correlations, providing preliminary evidence inconsistent with the alternative hypothesis that information-limiting correlations cause underestimation for sounds in the periphery. The second goal is to produce correlated anatomical mapping, at synaptic resolution, of the circuit that feeds the population code. We will test the hypothesis that high noise correlations arise from divergence in the ascending sensory pathway. Using a combination of new nested marker technologies, key regions are processed for serial block EM reconstruction and mapped by x-ray microCT, to ensure a direct connection to sites of electrophysiological recordings. Partial 3D EM reconstructions have already led to discovery of a new type of dendritic spine whose distinct patterns of synaptic convergence suggest they are both independent computational subunits and cellular loci of plasticity. A third goal is to investigate how behavior, physiology and microanatomy change during learning. We use prismatic adaptation, a paradigm that produces learned adjustments in orienting behavior, and developed a novel design now shown to reduce site-to-site variability. This provides a reliable

pipeline to recapitulate the experiments described above. The data will be assembled into models to determine the decoding mechanism in learned circuitry.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

**Location:** SDCC Halls B-H

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**Topic:** D.06. Auditory & Vestibular Systems

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Pennsylvania Lions Club Hearing Research Fellowship Maria Neimark Geffen

**Title:** Increased cortical gain facilitates the detection of targets in noise

**Authors: *C. F. ANGELONI**[1], M. N. GEFFEN[2]
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**Abstract:** To function in highly variable acoustic contexts, it is necessary to adapt to persistent stimulus features to reliably differentiate sounds within the statistical regime of the current environment. A recent body of work demonstrated that neurons in auditory cortex (AC) adjust their gain to match their dynamic range of their spiking responses to the spectrotemporal characteristics of the stimulus (Rabinowitz et al., *Neuron*, 2011; Natan et al., *Cereb. Cortex*, 2017). Adaptive control of neural gain benefits loudness discrimination in environments with varying dynamic range (ie. different contrasts), but the effect of gain adaptation on target-in-noise detection is unknown. Here, we tested whether and how gain adaptation to different noise environments shapes neural and behavioral responses to embedded targets and examined the temporal dynamics of this process. To address these questions, we manipulated the contrast of a noisy background and embedded broadband targets at different temporal offsets relative to a change in contrast. Then, we recorded neural activity in AC of mice performing a target-in-noise detection task. In the neural population and behavior, target detection changed as predicted by

gain adaptation to each noise environment, such that detection was facilitated by high gain and hindered by low gain. These observed behavioral and neural results were predicted by neurons simulated in a linear-nonlinear model, in which the gain of the output nonlinearity of the simulated neurons was parametrically adapted over time. Our results suggest that gain adaptation, while useful for conserving discriminability across a range of stimulus contexts, can either facilitate or diminish target detection, depending on the statistics of the noise background.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 766.22/SS6

**Topic:** D.06. Auditory & Vestibular Systems

**Support:** National Institute of Health, NIDCD, DC014279

**Title:** Reconstructing intelligible speech from human auditory cortex

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**Abstract:** Auditory stimulus reconstruction is an inverse mapping technique which finds the best approximation of the acoustic stimulus from the population of evoked neural activity. Ever since the reconstruction method was applied to decode speech from the human brain, the prospect of using this technique as a speech-brain computer interfaces (BCI) has received considerable attention. The ultimate goal of a speech neuroprosthesis is to restore communication to people who have lost their ability to speak. The practicality of a neuroprosthetic device to restore speech communication was further supported by studies showing successful decoding of speech during both covert and overt conditions. While previous studies have established the feasibility of reconstructing speech from the neural data, the quality of the reconstructed speech they achieved is relatively low. This is currently the major limiting factor in their utility as a reliable BCI technique. A natural choice is to directly estimate the parameters of a speech synthesizer from the neural data, but this has not been attempted previously because it requires accurate estimation of several sound dimensions which is hard to achieve with traditional machine learning techniques.
To advance the state of the art in speech neuroprosthesis, we combined the recent advances in deep learning with the latest innovations in speech synthesis to reconstruct closed-set intelligible speech from the human auditory cortex. We considered two parameters that directly affect the

reconstruction accuracy: the regression technique (linear versus nonlinear) and the representation of speech to be reconstructed (spectrogram versus speech vocoder). Our results show that the deep neural network model that estimates the parameters of a speech synthesizer (WORLD vocoder) achieves the highest objective and subject scores compared to spectrogram and linear regression models. Specifically, the subjective evaluation of the reconstructed waveforms shows a %75 intelligibility score in a closed-set digit recognition task (%65 improvement over baseline), and is rated %62 higher in mean-opinion-score quality measure. These results pave the way toward the next generation of BCI systems which can be used to enhance communication with patients.
**Index Terms:** speech reconstruction, deep neural networks, convolutional neural networks, vocoder-based reconstruction

**Disclosures: H. Akbari:** A. Employment/Salary (full or part-time):; Department of Electrical Engineering, Columbia University, New York, NY 10027, USA. **B. Khalighinejad:** None. **J.L. Herrero:** None. **A.D. Mehta:** None. **N. Mesgarani:** None.

**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 766.23/SS7

**Topic:** D.06. Auditory & Vestibular Systems

**Support:** National Institute of Health, NIDCD, DC014279

**Title:** Predicting the neural responses to speech in human auditory cortex using deep neural network models

**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]
[1]Electrical Engin., Columbia Univ., New York, NY; [2]Mortimer B. Zuckerman Mind Brain Behavior Institute, Columbia Univ., New York, NY; [3]Neurosci., Feinstein Inst. for Med. Res., Manhasset, NY; [4]Neurosurg., Hofstra-Northwell Sch. of Med. and Feinstein Inst. for Med. Res., Manhasset, NY

**Abstract:** Recently, interest has grown 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. However, linear models 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 investigated 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 perisylvian auditory cortex of five patients undergoing surgery for the treatment of epilepsy, as they listened to continuous speech. As deep convolutional neural networks (CNN) have shown great promise in capturing non-linear relationships, we trained a CNN with rectified linear 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.
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%. We analyzed the nonlinear function that the network implements to determine the computation of the auditory pathway and identified several properties that differentiate the linear and nonlinear functions. In addition, we examined the response dimensions in which the DNN excels at prediction, compared to the linear model. Finally, we examined the relation between the properties of the linear and nonlinear functions and the electrode anatomical locations. This study further shows that by interpreting complex nonlinear models that outperform their linear counterparts, we can gain invaluable insight into the workings of the brain, that are simply not possible with the traditional linear approach.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

**Location:** SDCC Halls B-H

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**Topic:** D.06. Auditory & Vestibular Systems

**Support:** NIH Grant GOTOL0292B
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**Title:** Behavior state-dependence of correlated neural population activity in ferret primary auditory cortex

**Authors: *C. R. HELLER**, D. SADERI, Z. P. SCHWARTZ, S. V. DAVID
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**Abstract:** Sound-evoked spiking responses in primary auditory cortex (A1) neurons are often variable across repeated presentations of identical acoustic stimuli. Simultaneous recordings of multiple neurons in A1 have shown that some trial to trial fluctuations are correlated across the population. Moreover, the average magnitude of these spike count correlations ($r_{sc}$) changes with

behavioral state, suggesting that they reflect underlying neural computations supporting acoustic perception and behavior. However, the dynamics with which $r_{sc}$ changes over time and its dependence on behavioral state is not well understood. To address these questions, we recorded neural activity from A1 of awake, behaving ferrets using a linear 64-channel multi-electrode array and used pupillometry to simultaneously measure arousal. The linear array provided access to several (5-20) closely spaced single units within a single cortical column. We found that, on average, spike count correlations decreased during periods of high arousal and active task engagement, confirming previous work. To investigate the state dependence of individual pairwise correlations over time, we created a linear model in which each neuron's response was predicted by scaling its average sound-evoked response by the activity of each other neuron in the population. Therefore, the predictive strength of the model for a given pair served as a measure of $r_{sc}$ magnitude between the two neurons. This analysis revealed that less than 10% of neuron pairs showed significantly non-zero $r_{sc}$ measurements within a cortical column. Evaluation of the model over short time windows showed that $r_{sc}$ strength was strongly modulated by both task engagement and arousal for most of these coupled pairs. The strength of coupling changed smoothly with continuous changes in arousal. For the remaining coupled pairs, $r_{sc}$ varied over time, but independent of changes in the task and arousal. Collectively, these results suggest that pairwise correlations in A1 are dependent on multiple processes, including arousal state and task-engagement. State space analyses are currently being pursued to further investigate the effect of behavior and arousal state on population dynamics in A1.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

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**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 766.25/SS9

**Topic:** D.06. Auditory & Vestibular Systems

**Title:** Attention modulates the ensemble activity in mouse auditory cortex

**Authors: *P. YAO**[1], J. SHEN[3], A. P. CHEN[2], S. GE[4], Q. XIONG[5]
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**Abstract:** Attentional modulation is believed to be essential for sensory processing by amplifying neuronal responses to the behaviorally relevant sensory stimuli while suppressing responses to distraction stimuli. However, despite decades of studies, attentional modulation of the mammalian cortical auditory system remains controversial. The amplification of the sound evoked response in the auditory cortex to the attending target was observed in early ferret

studies. Contrary to this, in rats, it was reported that the sound evoked response in the auditory cortex would be suppressed when animals were engaged in the task context. More recently, two-photon calcium imaging studies on the auditory cortex reveal that both enhancement and suppression can happen in the auditory cortical neurons when animals were attending to the auditory stimuli. Several factors may contribute to these controversial results. First, previous studies did not discriminate the "ignoring audition" state from the "passive" state, which served as control states in the previous attention modulation studies. On the other hand, the heterogeneous feature of the cortex makes it less meaningful to conclude the modulation on single cell level. The modulation of ensemble activity may provide another insight to understand how attention modulates the information process in sensory cortex. Considering all these factors, we developed a novel two-alternative forced choice task to let the animal either attend to or ignore the auditory stimuli. Taking the advantage of the microendoscopic system and cell-type specific calcium imaging in freely-moving mice, we compared the neuronal activity in the auditory cortex during different behavioral condition, including attending to audition, ignoring audition and passive state.We found the 'ignoring the audition' and the 'passive states' were two different states in terms of the neuronal activity in auditory cortex. On the single neuron level, the modulation of amplitude and time scale of the sound response was shown in both the 'attend to sound' context and the 'ignore sound' context. On the population level, the accuracy of the decoder to the auditory stimuli was different between the two contexts, suggesting that the information quality in auditory cortex was modulated differently depending on whether the mouse was ignoring the sound or in passive attendance.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

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**Program #/Poster #:** 766.26/SS10

**Topic:** D.06. Auditory & Vestibular Systems

**Support:** NIH Grant DC014950

**Title:** Nonlinear coding of naturalistic sound streams in marmoset auditory cortex

**Authors: L. A. SHAHEEN**, *S. V. DAVID
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**Abstract:** The human auditory system is adept at isolating and comprehending a single sound source out of multiple sources (auditory streaming). The early auditory system encodes the incoming signal across a population of neurons, each sensitive to distinct low-level features, such as spectral frequency, spatial location, and modulation frequency. Because natural sound sources

can contain overlapping features, the activity of individual neurons reflects a mixture of multiple sources. As signals pass through the auditory hierarchy, they undergo a series of nonlinear transformations which have been proposed to support emergent stream segregation. Such nonlinear responses are well-documented for static, synthetic stimuli in auditory cortex (ACtx). How completely the mechanisms identified in this work extend to natural, dynamic stimuli such as human speech is unknown.
To study streaming of naturalistic sounds at the single-neuron level, we recorded ACtx activity in passively-listening marmosets during presentation of a two-"voice" stimulus that retained the temporal dynamics of speech but had static spectra. Each voice consisted of a harmonic complex tone (HCT) with a unique fundamental frequency, modulated by a temporal envelope drawn from human speech. The envelope could be the same for both voices (coherent) or different (incoherent). Coherent voices were perceived as originating from a single source, and incoherent voices as two sources.
Responses to two dynamic HCTs were poorly predicted by responses to static HCTs, and by the sum of responses to each voice in isolation. Instead, responses were mostly suppressed relative to the sum of the isolated responses. However, periods of nonlinear enhancement were also observed. Nonlinear interactions varied with coherence. Greater suppression was observed for incoherent stimuli, possibly reflecting differences in streaming between conditions. A linear-nonlinear (LN) encoding model incorporating a spectro-temporal filter followed by a static nonlinearity was able to predict some nonlinear interactions (ex. saturation), but most neurons remained poorly predicted. Ongoing efforts will determine if a model incorporating nonlinear adaptation and/or multiple LN units is sufficient to predict responses in these conditions.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

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**Topic:** D.06. Auditory & Vestibular Systems

**Support:** 1R01DC013961

**Title:** Contribution of correlated cortical activity to identity-preserving changes in sounds

**Authors: *F. A. RODRIGUEZ CAMPOS**[1], B. KARPOWICZ[2], M. SCHAFF[2], Y. E. COHEN[3]
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**Abstract:** Abstract: Our environment is filled with acoustic stimuli that our brains transform from low-level sensory responses into perceptual representations called auditory objects. These

objects are the foundational building blocks of our auditory-perceptual world and are the computational result of the brain's capacity to detect, extract, segregate, and group the regularities in an acoustic environment, a process often referred to as "auditory scene analysis". Listeners are tolerant to substantial changes in the spectral and temporal features of auditory objects. For example, as a singer moves across a stage, we can recognize their unique voice and understand the song although the acoustic features vary dramatically with location. In order to enable such invariance, the hierarchy of cortical areas must develop neuronal representations of auditory objects that are increasingly independent of their naturally occurring transformations in time. However, the brain areas, neural mechanisms, and computations that provide the basis for a listener's tolerance to these identity-preserving changes are unknown. To address the neuronal basis of invariant sound recognition, we conducted large-scale recordings (MicroProbes' 96-electrode Microwire Brush Array) from the auditory cortex (anterolateral belt [AL], middle-lateral belt [ML], and primary auditory cortex [A1]) of rhesus monkeys while they listened to natural-sound exemplars (animal vocalizations and natural background noises) and identity-preserving transformations of these exemplars. These transformations included changes in the location of the stimuli and changes in room reverberation. Additionally, as controls, we presented scrambled versions of these sounds. These scrambled versions were statistically matched to the natural exemplars but could not be identified as originating from the same sound source as the original stimuli. We report how noise correlations vary with the identity-preserving transformations inflicted by our sound ensembles. In particular, we describe how the spiking activity and population activity in those three brain regions support representations of invariance.

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**766. Auditory Processing: Neural Coding, Experiment, and Theory**

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**Topic:** D.06. Auditory & Vestibular Systems

**Support:** NIDCD/NIH

**Title:** Correlations improve accuracy in predicting population codes in macaque auditory cortex

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**Abstract:** Our understanding of the function of the auditory cortex derives almost exclusively from experiments that study the coding properties of single neurons. Although these studies have

shed important information, they are limited because they have not considered how neuron-to-neuron (i.e., pairwise) correlations may affect population coding. We, therefore, sought to determine whether, in the primate auditory cortex, pairwise correlations contribute information to population coding above and beyond the information provided by the independent firing of auditory-cortex neurons. We recorded neuronal activity in the primary auditory cortex and the anterolateral belt region of the auditory cortex in two rhesus monkeys. Neuronal activity was recorded either with tetrodes or multi-contact linear u-probe electrodes. While recording neuronal activity, the monkeys participated in a "hearing-in-noise" task in which they reported hearing a target stimulus that was embedded in a noisy background. We titrated task difficulty by varying the sound level of the target stimulus, relative to the background. Based on either (1) the independent spiking activity of these neurons or (2) the independent spiking activity plus their pairwise correlations, we generated "Ising" models. Ising models are the maximum-entropy distributions that are consistent with experimentally observed firing rates and pairwise correlations without any mechanistic assumptions. We report whether Ising models more accurately predict the experimental probability of population dynamics when pairwise correlations are taken into account along with independent spikes. We also test whether Ising models better represent population dynamics in primary auditory cortex than in the anterolateral belt. This study lays groundwork for future studies that determine the relative importance of correlations in processing different types of acoustic stimuli.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 766.29/DP06/SS13

**Topic:** D.06. Auditory & Vestibular Systems

**Support:** NIH Grant DC03180
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**Title:** Multiscale calcium imaging of auditory cortex in awake marmoset monkeys

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**Abstract:** The common marmoset (*Callithrix jacchus*), a highly vocal New World monkey species, has emerged in recent years as a promising non-human primate model for neuroscience research. Because the marmoset brain is lissencephalic (smooth), nearly all cortical areas are

accessible directly under the skull with optical imaging methods. Two-photon calcium imaging with genetically encoded calcium indicators (GECIs) has been previously implemented in marmoset somatosensory cortex. Two-photon imaging in the auditory cortex is technically challenging since a mechanically vibrating laser scanner can generate sounds that are audible to the animal and thus interferes with the experimental design. In the current study, we developed a flexible, agile, yet silent two-photon microscope based on an acousto-optical deflector (AOD) scanner. An optical window with a quarter-inch diameter was implanted over the auditory cortex of awake marmosets. A clear tonotopic structure can be observed through intrinsic signal imaging at both green and blue wavelengths. Multiple virus injections carrying GCaMP were made through the silicone-based optical window. A dual-virus strategy was used to separate controls over expression specificity and expression level. A clear macroscopic wide-field fluorescence response was observed starting 10 days after virus injections, at sound levels as low as 10 dB lower than hearing thresholds. The tonal response recorded from wide-field fluorescence imaging was consistent with intrinsic signal imaging results and was also limited mainly within the primary auditory cortex. By using complex sound stimuli, such as music or marmoset vocalization recordings, strong and widespread cortical responses ($\Delta F/F$>10%) can be evoked in both primary and secondary cortical areas. The silicone-based window can be replaced by a glass coverslip-based window. And a customized silent two-photon microscope was used to measure responses of individual neurons at a microscopic scale. The general response patterns within each two-photon field-of-view were consistent with wide-field imaging results. However, individual neurons' responses can be heterogeneous even for close-by neurons. The multiscale calcium imaging approach reported here thus provides a new experimental paradigm for functional mapping of the marmoset auditory cortex in the awake condition in a high throughput way over conventionally electrophysiology methods.

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**Poster**

**766. Auditory Processing: Neural Coding, Experiment, and Theory**

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**Title:** Auditory texture synthesis from task-optimized convolutional neural networks

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**Abstract:** Models of sensory systems have traditionally been built from engineering principles and experimental observations, but modern-day machine learning allows models to be learned from data. We sought to compare hand-engineered and learned models of the auditory system by generating synthetic sounds that were matched to particular natural sounds according to the features in the model. We used automated gradient-based optimization to synthesize sounds for this purpose. Models that replicate perceptual representations should produce model-matched sounds that sound like the natural sounds to which they are matched. We synthesized stimuli that produce the same time-averaged values in a model's representation as those measured from a natural texture. Such stimuli should evoke the same texture percept if the model replicates the representations underlying texture perception. We compared textures generated from: (1) the first layer of filters from three task-optimized convolutional neural networks, (2) a model of primary auditory cortex consisting of spectrotemporal filters, and (3) the McDermott and Simoncelli (2011) texture model (consisting of cochlear and temporal modulation filters and their correlations). The task-optimized networks were trained on a word in noise task, a speaker identification task, or a music genre classification task. Sounds generated from any of the task-optimized filter banks were more recognizable and realistic than those from the hand-engineered filter bank. To explore the origins of this difference, we constrained sounds to additionally match marginal statistics of the cochlear representation. The inclusion of cochlear statistics caused the quality of sounds from the hand-engineered model to improve to the level of those from the learned filter bank. By contrast, including cochlear statistics did not improve the quality of sounds from the learned filters. Synthesis from the learned filters was comparable to that from the McDermott and Simoncelli model, which also required cochlear statistics to produce realistic textures. The trained filters evidently retain task-relevant information from earlier processing stages that is discarded by conventional models. Further, sounds generated from random filters were less recognizable and realistic than the task-optimized filters, suggesting that features learned during training are necessary for texture synthesis. The results illustrate that better auditory models can be obtained by task-optimizing sensory representations.

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**Poster**

**767. Visual Cognition: Decision Making II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 767.01/TT1

**Topic:** D.07. Vision

**Support:** CIHR Grant 380343

**Title:** Letter classification based on nominal vs. physical criteria in a right-hemispherectomy subject with blindsight: A forced-choice paradigm

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**Abstract:** In 1967 a letter classification task was described by Posner & Mitchell which required subjects to judge letter pairs as 'same' or 'different' based on criteria set by the experimenter. The two criteria were defined as 'nominal', where the subject must judge a letter pair based on their name (nominal identity: NI), and 'physical', where the subject may only take the letter's shape into consideration (physical identity: PI). This task not only evaluates the capacity of the subject to make correct decisions involving the same letters based on varying criteria, but it can also test the reaction time (RT) needed for the subject to respond appropriately to each stimulus. While some patterns of behavior have emerged in this field, there are many competing hypotheses that attempt to explain the data. In order to further investigate, we have tested this task on a complete right-hemispherectomy subject - DR (where the entire cortical mantle has been removed due to uncontrollable epilepsy) who has very well documented blindsight in her presumed blind visual field. For this experiment, NI and PI were examined in separate blocks. Within each block, there were 5 runs of 96 trials (48 same + 48 different). Within each run, DR was asked to judge the letters based on either NI or PI criteria, and to respond as fast as possible by pressing one button for same, and another for different. 5 healthy controls were recruited for this study. A within-subjects ANOVA (3x2) revealed a nominal-physical disparity, which has been previously reported in the literature, and was confirmed in healthy controls. This effect describes faster RT observed for PI as compared with NI matches. Interestingly, DR was able to match the letter pairs under NI criteria with above-chance accuracy but failed under PI conditions. More specifically, her error rate was significantly higher when the letter pairs were different, i.e. she exhibited a false-same effect. Proctor (1981) suggested that under PI criteria, when different letter pairs are presented simultaneously, there is an inhibition that occurs with the input of competing 'letter codes' from either hemifield. This triggers an internal checking mechanism that confirms that the letter pair is different. With DR, it is possible that in the absence of the right cerebral hemisphere, this inhibition does not occur due to a lack of processing by the appropriate pathway leading DR to mistakenly identify the two letters as same. Since DR was able to accurately perform the task only under NI criteria, we suggest that judgements based on NI and PI are processed independently by different pathways. These results thus lend support to the inhibition theory proposed by Proctor.

**Disclosures: L. Georgy:** None. **A. Ptito:** None.

**Poster**

**767. Visual Cognition: Decision Making II**

**Location:** SDCC Halls B-H

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**Topic:** D.07. Vision

**Support:** NIH T32
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Defense Advanced Research Projects Agency
Champalimaud Neuroscience Programme

**Title:** Evidence for nonlinear integration of visual motion evidence in motor cortex during a perceptual discrimination task

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**Abstract:** We have recently shown that it is possible to decode, in real time, a neural correlate of a monkey's decision from populations of neurons in dorsal premotor (PMd) and primary motor (M1) cortex (Peixoto et al., SfN 2016). The decoded "decision variable" (DV) is highly predictive of the monkey's upcoming choice in a random dot motion discrimination reaching task. We used the DV to trigger changes in the stimulus on individual trials. In the current study, we used this closed-loop paradigm to interrogate whether motion evidence is linearly integrated by injecting small pulses of motion information into the stimulus, triggered on distinct DV thresholds. Previous work has shown that the behavioral and neural effects of similar pulses decrease with elapsed time of stimulus presentation (Huk and Shadlen, 2005; Kiani et al., 2008). Here, we provide evidence that the motor cortical population response to pulses of motion evidence varies as a function of the instantaneous state of the DV itself at pulse onset.
In each of two monkeys performing the motion discrimination task, we estimated the instantaneous DV (log odds of a rightward choice) every 10ms from the preceding 50ms of activity on 96-192 channels from 1-2 Utah arrays in PMd/M1. The DV was calculated from a decoder trained on a previous session. We set threshold DV values that, if reached, triggered a 200ms pulse of additive motion evidence (±2%/±4.5% for monkey H/F), randomly assigned to be either congruent with or opposite to the dominant motion direction in the baseline stimulus. On average, we found that motion pulses slightly but significantly biased animals' choices in the direction of the pulse (equivalent to changing the overall stimulus coherence by 0.38%/0.55% for

monkey H/F; p < 1E-13/1E-3). After a delay of approximately 200ms from pulse onset, the DV on average was also biased in the direction of the pulse for approx. 400ms.
In the case of simple linear integration, we expect the magnitude of DV change in response to a fixed motion pulse to remain constant, regardless of the DV at pulse onset. However, pulses presented at smaller DV magnitudes led to larger subsequent changes in the DV. This result held even when analysis was restricted to the shortest third of stimuli, suggesting that time of pulse onset does not entirely explain the variation with the triggering DV level. Thus, simple linear integration of evidence does not appear to explain the evolution of the DV in these experiments. Future work will attempt to elucidate the nature of the nonlinearity suggested in our data, which might emerge from decision bounds, or attractor dynamics that reduce the impact of pulses on the neural activity at larger DV values (Wong et al., 2007).

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**Poster**

**767. Visual Cognition: Decision Making II**

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**Program #/Poster #:** 767.03/TT3

**Topic:** D.07. Vision

**Support:** the National Natural Science Foundation of China (31771151).

**Title:** Role of mouse secondary motor cortex in flexible categorization of visual stimuli

**Authors: *T.-Y. WANG**, J. LIU, H. YAO
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**Abstract:** Flexible adaptation to changes in stimulus-action association is essential for the survival of animals. To elucidate neural processes underlying such behavioral flexibility, we developed a flexible visual categorization task in freely moving mice. The mouse categorized a grating stimulus in each trial as low or high spatial frequency, and the categorization boundary changed between a lower and a higher frequency across blocks of trials. As the categorization boundary changed, the mouse was required to change its choice to the reversing stimulus. After the boundary switch, the mice' performance for reversing stimulus dropped and gradually increased over trials.
We found that chemogenetic inactivation of secondary motor cortex (M2) impaired the performance for reversing stimulus in the early trials after boundary switch, without affecting the performance for non-reversing stimuli. Electrophysiological recordings from M2 in behaving mice showed that the spiking activity of M2 neurons was sensitive to the categorization boundary.
We are currently building decision models to examine how behavioral choice and M2 responses

are influenced by recent experience (sensory, action, reward) on a trial-by-trial basis , and exploiting machine learning methods (support vector machine, etc.) to examine whether M2 activity is sufficient to predict the animal's choice to the reversing stimulus in different epochs after boundary switch.

**Disclosures: T. Wang:** None. **J. Liu:** None. **H. Yao:** None.

**Poster**

**767. Visual Cognition: Decision Making II**

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**Program #/Poster #:** 767.04/TT4

**Topic:** D.07. Vision

**Support:** Wellcome Trust 205093
Wellcome Trust 108726

**Title:** Effects of learning an orientation comparison task on mouse visual cortex

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**Abstract:** Many choices faced by an animal involve not only recognizing an ideal stimulus feature but also comparing that ideal to other presently available alternatives. What role do sensory areas of the brain play in this behavior? One possibility is that sensory areas themselves perform computations to help determine the optimal choice. Additionally, sensory areas may optimize the representation of relevant task stimulus features over the course of learning.
To address this question, we trained mice in a two-alternative forced-choice orientation comparison task. The task is an adaptation of a similar task that we developed for contrast discrimination (Burgess et al., 2017). At the start of each trial, two Gabor patches were presented simultaneously in opposite visual hemifields. The Gabor patches could each take one of three possible orientations with equal probability (90°, 68°, and 45°). We rewarded mice for correctly identifying the Gabor patch whose orientation was at or closest to the ideal 45°. Thus, the intermediate orientation (68°) would be either correct or incorrect, depending on its pairing.
We implanted an imaging window over the visual cortex of mice expressing GCaMP6s exclusively in excitatory cells of the cortex (Wekselblatt et al., 2016). To record the activity of a large population of neurons, we performed multiplane two-photon imaging across layer 2/3 and upper layer 4 of primary visual cortex.
To relate neural activity to task behavior, we used a linear encoding model for predicting each cell’s activity on each trial based on the stimulus shown and trial choice. As expected, the stimulus presented was able to predict neural activity for many cells. However we found a negligible impact of choice on activity; additionally, a classifier was poor at decoding trial

choice from neural population activity.
To investigate whether learning of the task had changed the cortical representations of task stimuli, we presented drifting gratings in passive conditions before and after learning. Following the learning of the task, we found an apparent increase in the number of neurons preferring the orientations of task stimuli. We are currently investigating whether this increase reflects changes in the orientation selectivity of neurons, or is the impact of arousal on visual responses.

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**Poster**

**767. Visual Cognition: Decision Making II**

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**Program #/Poster #:** 767.05/TT5

**Topic:** D.07. Vision

**Support:** Sir Henry Wellcome Fellowship 106101/Z/14/Z
Wellcome Trust 205093

**Title:** Dopaminergic and frontal signals for reward learning in perceptual decisions

**Authors: *A. LAK**, M. OKUN, M. MOSS, H. GURNANI, M. WELLS, C. BAI REDDY, K. D. HARRIS, M. CARANDINI
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**Abstract:** Efficient decision making requires combining immediate sensory evidence with learned reward values. It is not known how the brain performs this combination and learns from the outcome of the resulting decisions. We trained mice in a decision task that requires combining sensory evidence and past rewards: mice performed a visual detection task (Burgess et al, 2017) in which reward size for correct choices changed across blocks of trials. Mice behaved optimally in this task, shifting their psychometric curves so that reward size had a larger influence in trials with low contrast stimuli, where perceptual uncertainty is higher. Their choices were well described by a reinforcement learning model that learns the values of stimulus-action pairs and combines them with sensory evidence (Lak et al, 2017). The model computes two key internal variables for each choice: the predicted reward associated with the choice and the reward prediction error. These variables depend not only on reward size but also on trial-by-trial perceptual uncertainty. We established a neural correlate of the first variable - uncertainty-dependent predicted reward - by recording from populations of neurons in prelimbic frontal cortex. These neurons were mainly responsive before and during choice execution, and a subset of them reflected the predicted reward associated with the animal's choice, in close correspondence with model predictions. We established a necessary and sufficient correlate of the second variable - uncertainty-dependent prediction error - by imaging and optogenetic

manipulation of midbrain dopamine neurons. Fiber photometry revealed that the activity of these neurons matches the model-driven prediction errors and their dependence on reward size and perceptual uncertainty. Optogenetic activation of these neurons mimicked a positive prediction error, shifting the psychometric curves in a similar way as when we changed reward size. Optogenetic suppression of these neurons shifted the curves to the opposite direction.Similar effects were seen with optogenetic manipulation of dopaminergic terminals in ventral striatum, indicating prediction error is signaled by projections to ventral striatum. Conversely, activation of dopaminergic terminals in dorsal striatum affected choice execution rather than mimicking prediction errors. These results provide a unified framework for studying decisions guided by reward and sensory signals in mice, and reveal neuronal computations that enable the brain to learn and make efficient choices when challenged with internal and environmental uncertainty.

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**Poster**

**767. Visual Cognition: Decision Making II**

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**Topic:** D.07. Vision

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**Title:** Re-examining the behavioral evidence for evidence accumulation in perceptual decision-making

**Authors: *G. M. STINE**[1], A. ZYLBERBERG[2], J. DITTERICH[3], M. N. SHADLEN[4]
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**Abstract:** Accumulating information over long time-scales is fundamental to cognition. To study the neural mechanisms of this process, the field has exploited perceptual decision making tasks, because their normative solutions often involve accumulating sensory evidence over time. Indeed, models of bounded evidence accumulation fit behavioral data well, and psychophysical reverse correlations (e.g., choice-conditioned stimulus averages) show ostensibly that subjects use information throughout the entire stimulus presentation epoch. Are these observations sufficient to infer that subjects accumulate evidence over time? To address this question, we aimed to identify the observations required to achieve such an inference, relying solely on behavioral measurements. We considered fixed stimulus-duration, variable stimulus-duration

(VSD), and reaction-time (RT) paradigms and compared the predictions of bounded evidence accumulation to those of models that do not involve evidence accumulation. We found that the two classes of models make surprisingly similar quantitative predictions; within any single task-paradigm, both model classes can fit behavioral data well and can qualitatively match psychophysical reverse correlations. We also found that it is challenging, and in some circumstances impossible, to disentangle the models without reaction-time measurements and decision times that are substantially longer than the stimulus autocorrelation. However, we were able to disentangle the models by comparing data across task-paradigms and empirically testing the models' predictions of the non-decision time (i.e. the portion of reaction time that is not accounted for by evidence evaluation). Only bounded evidence accumulation could parsimoniously explain data from well-trained monkeys discriminating random dot motion in both a RT and VSD paradigm. Preliminary data from humans discriminating motion in two different stimuli suggest that subjects might adopt alternative strategies depending on the stimulus, even if such a strategy is suboptimal. Our results underscore the difficulty of inferring subjects' strategies in perceptual decision-making tasks and thus have implications for interpreting neurophysiological recording and perturbation experiments that assume subjects accumulate evidence over time.

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**Poster**

**767. Visual Cognition: Decision Making II**

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**Topic:** D.07. Vision

**Support:** KAKENHI 16K18380
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**Title:** Subthreshold decision-making in a visual cue detection task in rats

**Authors: *Y. OSAKO**[1], Y. SAKURAI[2], J. HIROKAWA[3]
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**Abstract:** The dissociation between a subjective-criterion performance and forced performance in a sensory detection can provide critical insights into the neural correlates of sensory awareness. Here, we established a behavioral task for rats to test their spatial-visual cue detection ability, using a two alternative choice task with and without a third choice option where animals

get rewards only in the objective absence of a visual cue. In the trials without the third option, spatial choice accuracy decreased from near perfect to near chance levels as the visual cue brightness decreased. In contrast, with the third option, the rats exhibited >90% spatial choice accuracy regardless of the cue brightness. The rats chose the third choice option less frequently when the cue was brighter, suggesting that rats have a generalized strategy to make spatial choices only when their internal detection criterion is met. Interestingly, even when the animals chose the third option, they can still significantly and correctly choose the direction of the visual stimuli if they were forced. Our data suggest that the rats' variable detection performance with identical set of stimuli is derived from stochastic processing of visual signals with a certain internal detection threshold rather than general motivational threshold.

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**Poster**

**767. Visual Cognition: Decision Making II**

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**Program #/Poster #:** 767.08/TT8

**Topic:** D.07. Vision

**Support:** ERC parietal Action 323606

**Title:** The role of posterior parietal cortex in actions discrimination

**Authors: *S. FERRI**[1], A. PALTONOV[3], G. A. ORBAN[2]
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**Abstract:** Growing evidence indicates that observation of distinct action classes activates different parts of human posterior parietal cortex (PPC). In particular, Ferri et al 2016 have shown that passive observation of skin displacing and manipulative actions specifically activated a PPC region straddling OP1 and PFop and putative human AIP (phAIP) respectively. To provide further support for this view, we conducted an fMRI experiment in which the featural attention of the subjects was manipulated during the observation of identical videos clips. Subjects (n=12) viewed videos showing a female or male actor executing a skin displacing action

(massaging or scratching) toward either its torso or cheek, fixated a point in the middle of the action trajectory and performed three 2-alternative forced choice tasks regarding the action, body part or gender of the actor. To avoid lateralisation bias, the position of the actor was flipped in half of the blocks. This yielded 8 videos per action exemplar presented to half of the subjects. In the other half of the subjects the size of the videos was additionally manipulated (small, large) as well as the position of the video in the visual field (left, middle, and right), yielding 48 videos per action exemplar.The fMRI session included 8 runs in which the three discrimination and the fixation conditions were repeated twice. Eye tracking data showed that all subjects fixated well during scanning averaging 8 saccades/min with no significant differences among conditions. Mean response accuracy was high in all three tasks: action = 97% (SD=1.2), gender = 96% (SD=1.1), body part 98% (SD=1.3), but mean reaction time were longer for action discrimination (1.12s, SD 0.64) than for gender (0.69, SD 0.43) or body part discrimination (0.84s, SD 0.34s). Univariate analysis revealed activation of left OP1 and its boundary with PFop (first half 15 voxels , second half 22), left supramrginal gyrus (PFt) (fist half 12 voxels, second half 18) as well as bilateral MT cluster (LH hemi cluster size : first half 36 voxels , second half 20, RH hemi cluster size : first half 32 voxels , second half 13 )in the contrast action discriminating relative to the two other discriminations. However the MT cluster activation decreased with increasing number of videos per action exemplar, while the PPC activations increased . A priori ROIs analysis showed that phAIP was not activated confriming the specificity of the latter region for manipulative actions. Thus the present study along with the previous two that used 2 AFC task with manipulative actions exemplars ( Ferri et al sfn 2016), strongly suggests that different PPC sites process different observed action classes.

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**Title:** The neuroscience of legal evidentiary rules: Using electroencephalography to test whether contemporaneity is a safeguard against deceit

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**Abstract:** While neuroscience has arguably influenced substantive legal policy, such as in juvenile justice, it has yet to affect any procedural rules which govern the day to day workings of trials. This study applied electroencephalography (EEG) and behavioral techniques to test one of the assumptions underlying a specific rule of the Federal Rules of Evidence (FRE), which determine what evidence federal juries see and don't see, and in what form. Despite playing a pivotal role in the accuracy, efficiency, and legitimacy of trials, the rules are premised on untested psychological assumptions. The Present Sense Impression (PSI), is an exception to the general ban against hearsay. FRE Article VIII excludes hearsay evidence because we want the primary observer to testify about the observed event while under oath, in the presence of the fact finder, and while subject to cross examination. Exceptions to the hearsay exclusion, however, have evolved when it is believed that the traditional risks of errors in perception, memory, narration, and deceit associated with hearsay are lessened. The PSI assumes that contemporaneity is a safeguard against deceit. Here, we used a novel behavioral paradigm and EEG measures to assess several event-related potential components (ERP) associated with deception. These ERPs were used to test the hypothesis assumed by the PSI exception that distinct cognitive processes underlie lies about contemporaneous events, lies about past events, and truthful responses. One possibility is that lies about contemporaneous events are processed as errors while lies about past events are processed as conscious misstatements. Our results suggest that there is no difference in the error related negativity (ERN) or error positivity (Pe) amplitudes between truth telling, lying about past events, and lying about contemporaneous events. However, we did find a significant difference in late parietal component for lying about contemporaneous events compared to truth telling, but not when lying about a past event. This difference suggests that individuals may be holding two representations of the stimuli in working memory when lying and merits further research to test the hypothesis that lying, especially about contemporaneous events, may be cognitively demanding due to the need to maintain additional information in working memory. By empirically testing the assumptions behind the FRE, neuroscience can facilitate the formulation of rules that better reflect human cognition and thus help achieve the goals of a more just legal system.

**Disclosures: G. Woodman:** None.

**Poster**

**767. Visual Cognition: Decision Making II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 767.10/TT10

**Topic:** D.07. Vision

**Support:** NSF Grant 1156601

**Title:** Second guessing in perceptual decision-making

**Authors: *J. DITTERICH**
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**Abstract:** Perceptual decision-making studies have initially focused on choice accuracy and response times, which can both be explained by integration-to-threshold models. Later studies have also investigated decision confidence. When choosing between more than two alternatives, however, the decision-maker might not only have access to the outcome of the decision and an associated confidence, but potentially also to information about the competitiveness of the non-chosen options. To test whether this is the case, we asked human observers to make a decision about the strongest component of motion in a 3-component random dot motion stimulus. We recorded this choice and the associated response time. On every single trial the subject then also reported a second guess. We told the subjects to indicate which of the remaining options they would rather go with, assuming they got their first choice wrong. We demonstrate that subjects do not make a random second guess, but that they are more likely to choose the alternative that was supported by the stronger sensory evidence. We further show that the same integration-to-threshold model that can explain the distribution of first choices and the associated response times can also explain how subjects distribute their second guesses.

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**767. Visual Cognition: Decision Making II**

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**Title:** Bidirectional control of orienting behavior by distinct prefrontal circuits

**Authors: *R. HUDA**[1], G. O. SIPE[1], E. ADAM[1], V. BRETON-PROVENCHER[1], G. PHO[1], L. GUNTER[1], I. R. WICKERSHAM[2], M. SUR[1]
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**Abstract:** Animals respond to their environments using complex and diverse motor movements, but are limited by being able to enact only single actions at a time. Hence, voluntary control over behavior requires context-dependent mechanisms that select appropriate actions and suppress complementary but inappropriate ones. Such duality of behavioral control is readily apparent in sets of commonly displayed opposing behaviors, such as freeze/flight, approach/avoidance, and exploration/exploitation. The prefrontal cortex (PFC) has been widely implicated in dynamically coordinating behavior by biasing the flow of activity in downstream cortical and subcortical structures, but a fundamental outstanding question is how the anatomical organization of inputs to and outputs from the PFC enables its proposed role. Here we use multiple approaches to analyze a visual two-alternative task and deconstruct the circuit logic of the anterior cingulate cortex (ACC), a subdivision of the mouse PFC. We trained mice to perform a leftward-rightward forepaw orienting movement in response to bilaterally presented visual cues. Using a combination of virus-mediated anatomical tracing, projection-specific optogenetic manipulation and multiphoton imaging, we show that the ACC integrates and routes discrete sensory inputs to anatomically segregated populations of projection neurons in order to promote and inhibit goal-directed visual orienting responses. ACC outputs to the superior colliculus principally inhibit incorrect orienting movements. A projection-based activity model predicts that feedback from the ACC to the visual cortex via a non-overlapping set of neurons is critical for correct orienting, which we confirm. Our results suggest that integrating anatomically distinct but functionally complementary projections for bidirectional control may be a general organizing principle for PFC circuits.

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**Poster**

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**Location:** SDCC Halls B-H

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**Topic:** D.07. Vision

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Richard A. and Susan F. Smith Family Foundation
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**Title:** Rats optimize reward rate and learning speed in a binary choice task

**Authors: *J. A. MASIS**[1], A. SAXE[2], D. D. COX[1]
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**Abstract: AIMS**: At the heart of perceptual decision-making research is the question of the speed-accuracy trade-off. When speed and accuracy are balanced to optimize reward rate in free response two-alternative free response tasks, behavior converges to an optimal performance curve (OPC). We wanted to explore whether rats act optimally in a two-alternative free response task, and if so, what is their trajectory to optimality?
**METHODS**: We trained rats on a visual object recognition psychophysical task. We then developed a model to explain their learning trajectory using a deep linear neural network.
**RESULTS**: Like humans, a subset of animals approach the OPC, generally with lower error rates, while many respond too slowly and remain above the OPC. We tracked the rats' development throughout learning and found that, like humans, rats tended to respond too slowly early in learning, and improved error rate before lowering reaction times. We develop a tractable theory of learning in free response binary choice tasks based on error corrective learning in deep linear neural networks. Our theory predicts the entire learning trajectory in speed-accuracy space, and shows a decisive advantage to slowing early trials in order to learn faster.
**CONCLUSIONS**: To our knowledge, our study is the first analysis of optimal behavior in this context in rats, and our theory is the first to directly incorporate the learning process into free response binary choice models.

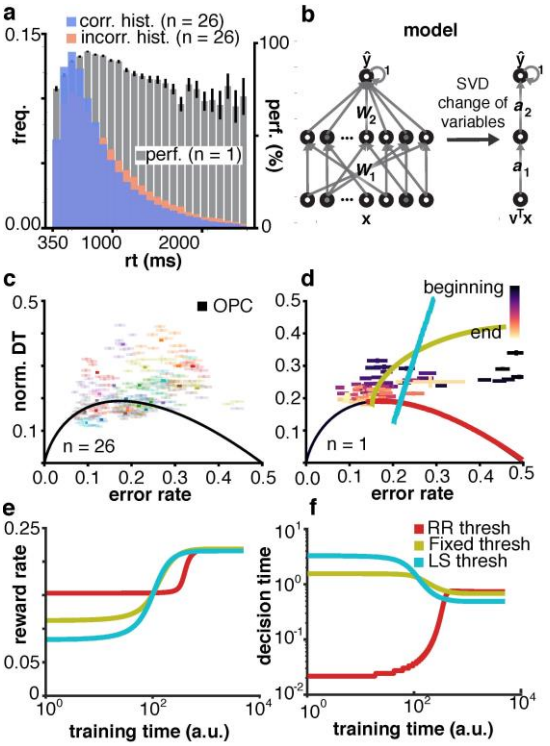


**Fig 1: (a)** reaction time (RT) histogram for 10 latest sessions of 26 trained animals separated by correct and incorrect trials and RT binned by task performance (perf.) from one example animal **(b)** *deep linear model:* noisy perceptual inputs pass through two layers of tunable synaptic connections which feed into a perfect neural integrator. **(c)** 10 latest sessions of fully trained animals (translucent) and respective means (opaque). **(d)** learning trajectory of model and one example animal from beginning to end of training. **(e) and (f)** *model performance:* reward rate (RR) increases faster and decision time decreases slower for fixed and learning speed (LS) thresholds (norm. DT = normalized decision time). (OPC = optimal perf. curve). All errors bootstrapped.

**Disclosures: J.A. Masis:** None. **A. Saxe:** None. **D.D. Cox:** None.

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**Topic:** D.07. Vision

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**Title:** Contribution of history-dependent modulation of neuronal activity in visual area MT to the temporal dynamics of visual motion processing in monkeys

**Authors: *H. LEFUMAT**, L. DING, A. DALLSTREAM, J. I. GOLD
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**Abstract:** Performance on visual discrimination tasks can depend strongly on how the brain processes incoming visual information as a function of time. A well-studied example is a visual motion direction-discrimination task that relies on sensory evidence about visual motion that is represented in the middle temporal (MT) area and accumulated over time to form a direction judgment. However, our understanding of how MT neuronal activity contributes to the temporal dynamics of this decision process is limited in two important ways. First, it is well established that MT neurons adapt to visual motion stimuli, but this adaptation is often not considered models of evidence accumulation. Second, a number of studies have begun to highlight the importance of adaptive temporal dynamics to form decisions in dynamic environments, but the role of MT in these processes has not yet been examined. The goal of this study is to test the hypothesis that MT adaptation reflects recent stimulus dynamics in a manner that can help to optimize perceptual judgments about dynamic motion signals.To test this hypothesis, we measured single-unit responses in MT in monkeys performing a “dots-reversal task” in which coherent motion can switch back-and-forth within a trial. Monkeys are rewarded for correctly choosing, with a saccadic eye movement, the final direction of motion presented on a given trial. Under these conditions, the normative decision-maker should adaptively adjust temporal integration times in accordance with the switch rate of the motion stimulus, such that high/low switch rates promote short/long integration times. Consistent with our previous studies with human psychophysical subjects, preliminary data from one monkey indicates decisions that reflect this adaptive process. In particular, the monkey’s accuracy increased as a function of viewing time following the final direction change-point in the stimulus, but with a shallower rate-of-rise in blocks with high versus low switch rates. We also have preliminary MT recordings showing that adaptation time constants depend on the switch rate of the immediately preceding stimulus, with longer integration times corresponding to lower switch rates. We suggest that a downstream decision-maker that integrates these adapted responses over time can produce

decisions that are consistent with the normative model. Further work is needed to: 1) confirm the observed trends in our behavioral and neural data; and 2) assess more carefully if and how the magnitude and time course of MT adaptation depend on recent stimulus history.

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**Title:** Choice history biases sensory representations in visual and parietal cortex

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**Abstract:** Perceptual choices under uncertainty are biased by previous choices, a phenomenon referred to as choice history bias. Choice history biases arise mostly from preceding choices, rather than the associated motor responses (Braun, Urai & Donner, J Neurosci, 2018). Previous choices bias the evidence accumulation, rather than the starting point, of the current decision (Urai, de Gee & Donner, bioRXiv, 2017). This suggests that choice history may bias sensory cortical responses encoding the sensory evidence, or their readout in association cortex. Here, we used magnetoencephalography (MEG) to test this idea in the human brain.
61 observers performed a two-interval motion coherence discrimination task, where they viewed two successive random dot stimuli with varying coherence and had to judge whether the second interval contained stronger or weaker motion than the first (Urai, Braun & Donner, Nat Commun, 2018). We recorded MEG during task performance and used source reconstruction to estimate the time-course of band-limited activity in 5 retinotopically organized regions of visual, temporal, and posterior parietal cortex (Wang et al., Cereb Cortex, 2015). Gamma-band responses in dorsal visual field maps have been shown to encode visual motion coherence (Siegel et al., Cereb Cortex, 2007).
Across visual field maps, we found stronger gamma-band (65-95Hz) responses to stronger than weaker visual motion in the second interval, thus encoding the decision-relevant feature in our task. Critically, this visual gamma-band response also reflected the previous choice: on trials following a ‘stronger motion’ choice, gamma-band activity was increased compared to trials

following a ‘weaker motion’ choice. This choice history signal was particularly prominent in dorsal occipital (V3A/B) and intraparietal sulcus (IPS0-5) regions. It was present already before the onset of the second (decision-relevant) motion stimulus, and combined additively with the stimulus-induced gamma-band response.
We conclude that choice history biases the baseline state of sensory cortex, leading to the integration of stimulus-independent information that biases observers towards repeating their previous choices.

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**Poster**

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**Program #/Poster #:** 767.15/TT15

**Topic:** D.07. Vision

**Support:** NSF IOS-ORG 1456830

**Title:** Animal habitat as an evolutionary driving force for the development of planning systems

**Authors: *U. MUGAN**[1], M. A. MACIVER[2]
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**Abstract:** The relationship between sensory input and behavior can be conceived along a spectrum. On one end of the spectrum is “reactive behavior” — a simple and rapid transformation of the sensory input — and on the other end is “deliberative behavior” — a choice from many internally simulated sequences of actions and corresponding potential outcomes, referred to as planning. Our prior work on the computational visual ecology of the vertebrate invasion of land revealed that eyes took in a largely blurry world at a short range in ancestral aquatic environments. Just prior to moving on to land, eyes tripled in size after morphological changes that suggest aerial vision while still living in water. The increase in eye size and switch to aerial vision extended the visual range by a factor of 100. Due to the increase in visual range and environmental complexity, the move onto land may have provided a selective benefit to animals that evolved deliberative behavioral control, enabling them to plan extensively. To test this hypothesis, we created a survival task for virtual prey acting in random worlds with varying distributions of occlusions calculated based on entropy, a proxy for environmental complexity. In each trial, the prey used a predetermined visual range and planning depth (for a tree-like planning system) to get to a goal position while avoiding the predator. Across trials, we independently manipulated prey visual range, planning depth, and predator start location. For the low entropy world with no occlusions, we found that there is no benefit in

planning when prey visual range is short. In the same environment, for longer visual ranges survival rate is only modestly increased for high planning depths. For an environment with midrange complexity, we found that at long visual ranges an increase in planning depth greatly increases survival rate, since the prey is able spot the predator and then use the occlusions to aid its survival. In contrast, an increase in planning depth does not have as great of an effect on survival rate for short visual ranges, indicating that independent of environmental complexity, high planning depths are not beneficial for short-sighted prey. In very low or very high entropy environments, independent of predator start location, there only two trajectories that lead to success with high probability, allowing for reactive strategies to succeed. However, at midrange entropies, the distribution of successful paths is diffuse, placing greater reliance on higher planning depths. These results provide insight into a fundamental question about the selective advantage of planning and competing behavioral control strategies that arise as a function of animal habitat.

**Disclosures: U. Mugan:** None. **M.A. MacIver:** None.

**Poster**

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**Program #/Poster #:** 767.16/TT16

**Topic:** D.07. Vision

**Title:** Temporal integration of sensory evidence revealed by wholebrain imaging

**Authors: *E. I. DRAGOMIR**, V. ŠTIH, R. PORTUGUES
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**Abstract:** The behavior of animals is, to a large extent, driven by external sensory stimuli. When making a behavioral choice, there are neural mechanisms that first need to process the incoming sensory input, integrate this momentary sensory evidence such that it can be evaluated over longer timescales, and use this valuation to plan the appropriate motor actions. Neural activity related to these mechanisms have been identified in a number of brain regions, however, their explicit contribution to the decision-making process remains unclear. Here we present a novel assay for studying perceptual decision-making in larval zebrafish, adapted from the well-established random dot motion paradigm (RDM) used in primate, rodent and human decision-making studies. We rely on a robust untrained behavior, the optomotor response, which induces fish to align themselves and swim in the direction of perceived visual motion. We show that various parameters of the behavior improved with increasing stimulus strength, and that both sensory and motor history were involved in the selection of the current behavioral choice. Using cellular resolution wholebrain imaging in intact, behaving animals, we identify all neural signals relevant to the different stages of the decision-making process, from momentary sensory

processing, accumulation of this sensory evidence and behavioral output. Fitting the neural responses representing sensory evidence with a general model of sensory integration, we find a continuous distribution of time constants, with different units integrating evidence over varying time windows. These units are also distributed across different regions, suggesting that decision-making activity is represented broadly across the brain.

**Disclosures: E.I. Dragomir:** None. **V. Štih:** None. **R. Portugues:** None.

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**Title:** Examining early sensory activity and motor preparation during rapid value-biased sensorimotor decisions

**Authors: *A. MARTINEZ RODRIGUEZ**, E. A. CORBETT, K. MOHR, S. KELLY
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**Abstract:** The aim of this study is to investigate the effects of value on early sensory neuronal responses and motor preparation dynamics, during rapid sensorimotor decisions. Different accounts have been developed that try to explain the mechanisms underlying value biases during the decision making process. The starting point bias account suggests a shift in the starting point of the evidence accumulation process, in the direction of the more valuable of two opposing bounds. An alternative model suggests that the mean tendency of the decision variable (drift rate), varies as a function of value. While most studies have supported a starting point bias approach, recent work (Afacan-Seref et al., 2018) suggests that drift rate biases may also be invoked during the decision process. One possible source of such drift rate biases is the modulation of the sensory representations of evidence in the low-level visual cortex. Our study examines these by recording EEG (Biosemi), eye-position (Eyelink) and EMG of the flexor policis brevis muscle activity, while participants perform a value-biased orientation discrimination task under a strict deadline. The relative value of the two sensory alternatives (left- or right-tilted orientation) changes across trials, offering participants the possibility to earn 40 or 10 points in every correct trial.
Preliminary analyses of this ongoing study show a clear effect of value on reaction time and accuracy. There was an evident increase in accuracy for the high value condition compared to the low value one. Reaction time was significantly faster for correct high value trials ($p<.001$), but low value errors were faster than the high value ones ($p<.01$). Regarding the neural processes

underlying these phenomena, the lateralized motor preparation reflected in the lateralized readiness potential (LRP), showed signs of a starting point bias mechanism around cue onset, across the different value conditions. However, the initial, "C1" component of the visual evoked potential (VEP), thought to reflect primary visual cortical activation, is showing no signs of significant value modulation. Our preliminary results seem to suggest that even though behaviour is strongly biased by value, affecting also motor preparation signals (LRP) under conditions of time pressure, there is no evidence of a value modulation of the earliest sensory activity.

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**Topic:** D.07. Vision

**Title:** Leveraging visual search patterns in the trail-making task to understand cognitive errors following a stroke

**Authors: *C. PERRY**[1], T. SINGH[4], T. M. HERTER[2], A. HARRISON[3]
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**Abstract:** Efficient patterns of eye movements and fixations (visual search) are needed to accurately perform visuomotor skills such as driving a car. Visual search collects task relevant information from the environment in order to make accurate decisions about future motor actions (Ex. stopping for pedestrians). Inefficient patterns of eye movements are associated with poor visuomotor performance and increases in number of errors. Survivors of a cerebral stroke often exhibit altered visual search patterns and make more errors when performing visuomotor tasks. However, it is not known if visual search patterns associated with task errors differ from visual search patterns associated with non-error performances in those with stroke. To investigate this, a total of 32 participants with chronic stroke were recruited to perform a virtual trail making task. Participants were seated in a height adjustable chair at an upper-limb kinematic apparatus with an integrated eye tracking system. To perform the task, participants grasped a manipulandum with their least affected hand. Participants were instructed to use their hand, represented as a white circle, to accurately and quickly connect labeled targets in the correct order while alternating alphabetical and numerical sequences (trail making part B). Participants that made at least one error while performing the trail-making task (n=19) were included for future data analysis. Analysis of intra-participant eye movements was performed on the visual search

patterns between error and non-error trials. Error trials were divided into the two primary error types in the task: 1) “non-switch” errors (failure to alternate alpha-numeric sequences) and 2) “switch” errors (successfully alternate alpha-numeric sequences). Results show that during non-switch error trials, participants exhibited few fixations ($p<0.001$) and shorter foveation durations of their destination target ($p<0.001$) compared to non-error trials. In addition, non-switch error trials were uniquely characterized by indiscriminate foveation durations of all visual stimuli. During switch error trials, participants exhibited visual search patterns similar to that of non-error trials. Based on the results, it can be inferred that non-switch and switch errors are likely the result of impairments of two distinct neural processes involved in task performance. This experiment provides evidence that visual search patterns can provide insight into the neural mechanisms that underlie visuomotor errors in those with stroke.

**Disclosures: C. Perry:** None. **T. Singh:** None. **T.M. Herter:** None. **A. Harrison:** None.

**Poster**

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Wellcome grant 108726
Wellcome doctoral fellowship 109004/Z/15/Z

**Title:** Different tasks engage distinct populations in mouse parietal cortex

**Authors: *J. LEE**, M. KRUMIN, K. HARRIS, M. CARANDINI
UCL, London, United Kingdom

**Abstract:** A challenge for the brain is to represent a vast variety of potential situations. One way to deal with this challenge is to distribute representation of multiple processes across the same neurons. For instance, in decision tasks, individual neurons in posterior parietal cortex (PPC) show “mixed selectivity” - that is, overlapping representation of diverse task features (Meister et al., 2013; Park et al., 2014, Raposo et al., 2014; Goard et al., 2016). Another way is to allocate distinct neuronal populations for different processes, as seen in primate PPC across adjacent parietal areas (Snyder et al., 1998). To distinguish between these possibilities, we recorded from the same population of PPC neurons using two-photon calcium imaging, in mice trained to perform two visual detection tasks. In one task, the mouse turned a steering wheel to report whether a visual grating was on the left or right side. In the other task, the mouse navigated through a virtual T-maze and turned at the end to report whether a grating appeared on the left or right wall. Although both tasks involved visual detection, decision-making, and orienting

behavior, they engaged distinct populations of PPC neurons. Most neurons were exclusively active in one or the other task, while few were active in both. Neurons active in one task or the other were spatially intermingled, and their selectivity was consistent across multiple days. Among these task-selective neurons, some neurons maintained their selectivity across passive replay conditions that preserved the means of decision report (ball vs. steering wheel). However, other neurons were active only during the tasks but not during passive replay conditions. In conclusion, PPC seems to follow two strategies - perhaps encoding task features in a given task using mixed selectivity within the same neurons, yet allocating distinct neuronal populations for different tasks. Distinct task characteristics, such as means of decision report, may provide a global signal for the selection of active ensembles. Within these active ensembles, single neurons could encode for task-relevant features such as choice, reward, or stimulus. Further work will study whether neurons active in both tasks, but not in passive conditions, share selectivity for the same kinds of task features.

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**Poster**

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Cold Spring Harbor Laboratory

**Title:** A normative explanation for lapses in perceptual decisions

**Authors: *S. PISUPATI**, L. CHARTARIFSKY, D. M. MAHARJAN, A. K. CHURCHLAND
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**Abstract:** During perceptual decisions, even well-trained subjects have a constant rate of errors that lead to imperfect asymptotic performance on easy stimuli. Such stimulus-independent errors are assumed to arise from inattention or motor error. For this reason, they are often referred to as “lapses” and have long been viewed as a nuisance. Proper treatment of lapses is known to be crucial for accurate estimation of decision parameters, but the factors that influence them remain poorly understood. Here, we demonstrate that perceptual uncertainty modulates the probability

of lapses, and propose uncertainty-driven exploration as the underlying cause, rather than inattention or motor error. Specifically, we manipulated uncertainty on a multisensory rate discrimination task in rats using 4 strategies: 1) Presenting unisensory vs. multisensory events with matched rates, 2) Varying the signal intensity of the unisensory events, 3) Presenting multisensory "catch" trials in which one stimulus was uninformative and 4) Comparing with "sure bet" trials on which a salient LED unambiguously indicated the rewarded side. In all cases, conditions with higher uncertainty also showed an increased probability of lapses, ruling out fixed probability explanations such as motor error. Inattention-based explanations were insufficient because we observed increased lapses on multisensory catch trials with uninformative stimuli, despite them being as salient as normal, matched trials. The effects were parsimoniously explained by an alternate model not normally used for perceptual decisions - uncertainty-guided exploration. This is a well-known heuristic in reinforcement learning that balances exploration and exploitation. Surprisingly, the model favored by BIC (17 rats) was a Bayesian ideal observer followed by an exploratory "softmax" decision rule, with the exploratoriness modulated by uncertainty. Since the explanation for lapses in this model is intimately tied to reward, we tested its predictions by increasing the reward magnitude for one decision outcome relative to the other. The uncertainty-guided exploration model correctly predicted that this would shift the probability of lapses in favor of this decision in uncertain conditions, while leaving "sure bet" trials unaffected. All other models incorrectly predicted a criterion shift with no effects on the lapse probability. In summary, we propose a new explanation for lapses in perceptual decisions, that they are driven by uncertainty-guided exploration. Our new model suggests that lapse rates are not a nuisance, but are instead informative about an individual animal's exploration-exploitation tradeoff.

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**Title:** Model-free decoding of likelihood functions from sensory cortical population reveals trial-to-trial probabilistic computation in visual cortex

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**Abstract:** Organisms typically base their perceptual decisions on noisy and ambiguous sensory observations. Bayesian models of behavior postulates that organisms maintain a representation of uncertainty about the task relevant sensory variable to make better decisions, rather than just carrying a point estimate. In an earlier work, we introduced a simple orientation classification task with controlled top-down (ambiguity) and bottom-up (noise) sensory uncertainty for which optimal performance requires the observer to utilize sensory uncertainty on a trial-by-trial basis, and demonstrated that both humans and monkeys do so. However, the neural code underlying the representation of uncertainty in a cortical population has remained unclear. The theoretical framework of probabilistic population coding (PPC) postulates that the brain decodes sensory uncertainty from a noisy pattern of population activity as a "likelihood function" over the stimulus. This function represents the probability of the observed pattern given each hypothesized stimulus value, and the width of this function is a proxy of sensory uncertainty. Rigorously testing this hypothesis has been challenging due to: 1) the need for simultaneous cortical population activity recorded in a task in which uncertainty information is behaviorally important and 2) the lack of generalizable methods for decoding distributed activity without a need for specific parametric assumptions. Here, we overcome these challenges: we trained macaques in a visual categorization task where trial-to-trial uncertainty about orientation is relevant for the decision, recorded multi-unit activity in primary visual cortex (V1) as they performed the task, and developed a novel technique using deep learning to decode the trial-by-trial uncertainty information from V1 population responses in the form of the likelihood function over orientation with no explicit parametric assumptions employed. We find that a Bayesian decision model utilizing the entire likelihood function predicts the monkey's trial-to-trial decisions better than a non-Bayesian model using only a decoded point estimate of orientation. This remains true when we perform analysis conditioned on the stimulus, suggesting that internal fluctuations in neural activity drive behaviorally meaningful variations in uncertainty. Our work provides a key finding in how neural populations encode uncertainty, and in particular provides population-level physiological evidence in support of the PPC framework, which may be a general principle of the neural code.

**Disclosures: E.Y. Walker:** None. **R.J. Cotton:** None. **W. Ma:** None. **A.S. Tolias:** None.

**Poster**

**767. Visual Cognition: Decision Making II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 767.22/TT22

**Topic:** D.07. Vision

**Support:** Wellcome Trust 205093
Wellcome Trust 108726

**Title:** Lateralized role of mouse parietal cortex during virtual navigation

**Authors: *M. KRUMIN**, J. REYNOLDS-CLARK, C. REDDY, K. D. HARRIS, M. CARANDINI
Univ. Col. London, London, United Kingdom

**Abstract:** In rodents, posterior parietal cortex (PPC) has been implicated in both decision making and spatial navigation. Here, we asked if mouse PPC plays a causal role in visually-guided navigation and decision making.
We trained mice to perform a two-alternative forced choice (2AFC) task in virtual reality (Krumin et al. biorRxiv, 2017). Subjects were required to navigate through a T-Maze, with a vertical grating of varying contrast presented on one of the walls of the main corridor. They reported the position of the grating by turning to the right or to the left at the end of the T-Maze. Correct trials were rewarded by a droplet of water, wrong trials were indicated by a brief auditory white noise sound.
We tested the causal role of PPC in this task using optogenetic photoinactivation (Olsen et al, Nature 2012, Guo et al, Neuron, 2014) . Transgenic mice (n=3) expressing Channelrhodopsin-2 in Parvalbumin-expressing interneurons (Ai32 ChRh2-EYFP (floxed) x Pvalb-IRES-Cre) were implanted with a headplate to facilitate head-fixation, and the skull was exposed and covered by UV-curing cement to allow optical access to the cortex. Optical inactivation was performed by focusing a 462 nm laser at the cortical surface (FWHM of the spot size < 150 μm). The location of the stimulation was controlled by a custom galvo-mirror based system. We performed unilateral and bilateral inactivation of PPC (defined by the stereotactic coordinates of -2 mm AP, and +-1.7 mm ML relative to bregma) throughout the duration of the trial.
We found that unilateral inactivation of the parietal cortex introduced ipsilateral bias into mouse behavior. Inactivation of right PPC increased the fraction of rightward choices, and vice versa. The effects were seen both in an increase in bias, which shifted the psychometric curves horizontally, and in a change in lapse rates, which shifted the psychometric curves vertically. The effects of bilateral inactivation were not nearly as clear, and we are currently examining whether they were significant.
We conclude that mouse posterior parietal cortex plays a lateralized causal role in decision making during visually-guided navigation.

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**Poster**

**768. Cerebellum: Human Studies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 768.01/TT23

**Topic:** E.02. Cerebellum

**Support:** Grant-in-Aid for Young Scientists (B) No. 15K19503 from the Japan Society for the Promotion of Science

**Title:** Short-term follow-up of type 1 metabotropic glutamate receptor availability in patients with spinocerebellar ataxia type 6

**Authors: K. ISHIBASHI**[1], Y. MIURA[2], K. WAGATSUMA[1], J. TOYOHARA[1], *K. ISHII[3]
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**Abstract:** Objectives: Imaging of type 1 metabotropic glutamate receptor (mGluR1) has recently become possible using $^{11}$C-ITMM positron emission tomography (PET) with the finding that mGluR1 in healthy subjects is exclusively localized in the cerebellar cortex [1]. In the cerebellum, mGluR1 is predominantly expressed on the dendrites of Purkinje cells, and is involved in excitatory neurotransmission, suggesting that mGluR1 plays a critical role in the physiology and pathophysiology of Purkinje cells. Previous studies using small animals have shown that reduction in cerebellar mGluR1 expression is associated with the occurrence of cerebellar ataxia. More recently, we have confirmed that cerebellar mGluR1 availability is decreased in patients with cerebellar ataxia using $^{11}$C-ITMM PET [2]. As an extension of the previous study, we report the course of cerebellar mGluR1 availability in some of the patients. Methods: Two patients with spinocerebellar ataxia type 6 (SCA6) and 25 healthy subjects were included in this study. Patient-1 underwent $^{11}$C-ITMM PET at ages 74, 75, and 76; Patinet-2 at ages 68 and 70. The $BP_{ND}$ value was calculated to estimate GluR1 availability using the simplified reference tissue model with the visual cortex as a reference region. Cerebellar ataxia was scored with the Scale for the Assessment and Rating of Ataxia (SARA). Results: The cerebellar $BP_{ND}$ values were 1.84, 1.90, and 1.96 at ages 74, 75, and 76, respectively, in Patient-1, 1.05 and 1.07 at ages 68 and 70, respectively, in Patient-2, and 2.49 ± 0.23 in the control group. The SARA scores were 6.5, 6.5, and 7 at ages 74, 75, and 76, respectively, in Patient-1, and 21 and 22 at ages 68 and 70, respectively, in Patient-2. Conclusions: The degree of cerebellar ataxia almost unchanged over the short-term follow-up period in two patents with SCA6. Although cerebellar mGluR1 availability remained below the normal range, cerebellar mGluR1 availability tended to increase with advancing age in both patients with SCA6. These results may indicate that cerebellar mGluR1 availability does not continue to decline throughout the course of SCA6. References: [1] Toyohara J, Sakata M, Oda K, Ishii K, Ito K, Hiura M, Fujinaga M, Yamasaki T, Zhang MR, Ishiwata K (2013) Initial human PET studies of metabotropic glutamate receptor type 1 ligand 11C-ITMM. *J Nucl Med* 54, 1302-1307. [2] Ishibashi K, Miura Y, Ishikawa K, Zhang MR, Toyohara J, Ishiwata K, Ishii K (2016) Relationship between type 1 metabotropic glutamate receptors and cerebellar ataxia. *J Neurol* 263, 2179-2187.

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**Poster**

**768. Cerebellum: Human Studies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 768.02/TT24

**Topic:** E.02. Cerebellum

**Support:** ZSE Tuebingen

**Title:** Motor training improves motor performance at the preclinical stage of degenerative cerebellar ataxia

**Authors: *W. ILG**[1], J. GOEDDEL-SAND[2], C. SCHATTON[1], A. JAHN[1], Z. FLESZAR[2], M. A. GIESE[1], L. SCHOELS[2], M. SYNOFZIK[2]
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**Abstract:** *Background:* It is well known for many neurodegenerative diseases that subtle movement changes often occur years before clinical manifestation, corresponding to a neurodegenerative disease process starting many years before clinical onset. In earlier work[1], we have shown that increasing complexity of balance and gait tasks allow to unravel dysfunctions in preclinical stages of degenerative spinocerebellar ataxia (SCAs). This calls for early intervention strategies aiming to slow down disease progression already at the preclinical stage of the disease as a promising window of opportunity for intervention. Here, we examined the effects of a 6-weeks exergaming-based coordination training in preclinical mutation carriers of SCA. *Methods:* The motor exercise program consisted of five whole-body controlled video games based on Microsoft Xbox Kinect™ (e.g. Juggling, Hacky Sack, Light Race). Subjects received a two-day introductory training, followed by six weeks of home training, We recruited three intervention groups 1.) EARLY: 5 patients with early stage SCA [SARA[2] score: 3-8]; 2.) PRE: 14 preclinical mutation carriers for SCA types 1,2,3 or 6; [SARA<3]; 3.) CON: 8 age-matched healthy controls. The effects were examined within an intra-individual control study design by quantitative movement analysis. We assessed (i) stance (Romberg test) in different complexities including closed eyes and on an elastic mat as well as (ii) walking and tandem walking on hard and soft ground. *Results:* Before intervention a difference in body sway was observed in all Romberg conditions between the groups EARLY and CON ($p<0.001$) as well as between EARLY and PRE ($p<0.02$). Differences between PRE and CON were identified in Romberg on the mat with closed eyes ($p<0.002$). For tandem walking and tandem walking on a mattress PRE showed significant increased variability in step length and in step cycle time compared to CON ($p<0.006$). After intervention, subjects of groups CON and PRE improved in stance and tandem tasks with high complexity (Romberg on the mat with closed eyes: reduced body sway, $p<0.02$; tandem on the mat: reduced temporal step cycle variability, $p<0.03$). Improvements in tandem

gait correlated with improvements in the game score in a goal-directed stepping task game ($p<0.02$).*Discussion:* We identified features in complex stance and gait tasks, which differentiate pre-clinical SCA mutation carriers from controls. These features improved after a 6-weeks exergaming-based motor intervention revealing specific motor improvements in preclinical SCA mutations carriers. 1 Ilg et al Mov Disord. 2016;31(12):1891-1900. 2 Schmitz-Hübsch et al, Neurology. 2006;66(11):1717-20

**Disclosures: W. Ilg:** None. **J. Goeddel-Sand:** None. **C. Schatton:** None. **A. Jahn:** None. **Z. Fleszar:** None. **M.A. Giese:** None. **L. Schoels:** None. **M. Synofzik:** None.

**Poster**

**768. Cerebellum: Human Studies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 768.03/UU1

**Topic:** E.02. Cerebellum

**Support:** NIH Grant R15MH106957
Mellon Doctoral Dissertation Award

**Title:** Effect of active electrode position on brain activation after cerebellar tDCS

**Authors: *L. BLEVINS**[1], A. M. D'MELLO[4], S. E. MARTIN[2], B. C. DRURY[3], C. G. BARRETT[3], A. R. LILLIAN[3], M. E. MARKO[3], C. J. STOODLEY[1]
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**Abstract:** Cerebellar transcranial direct current stimulation (tDCS) has been proposed as a potential treatment for multiple disorders, including aphasia, schizophrenia, and autism. However, its method of action has yet to be determined, and current methods of electrode placement are based on skull landmarks rather than individual brain anatomy. The present study combined tDCS and functional MRI (fMRI) to investigate the relationship between tDCS effects and electrode position relative to brain anatomy. Healthy males (n=9, 20.78 yrs) completed three tDCS-fMRI sessions. In each session, right cerebellar lobule VII was targeted by positioning a 5x5 cm electrode 1 cm down and 4 cm lateral to the inion. Participants received 20 min of 1.5 mA tDCS (anodal, cathodal, or sham) in the scanner and completed a serial reaction time task (SRT; 50 randomly-ordered trials, followed by 15 repeats of a 10-item sequence, followed by 50 randomly-ordered trials). The order of tDCS condition was counterbalanced across all subjects. Electrode placement was quantified as the distance between the electrode center and the center of the target region using structural MRI scans and the SUIT atlas in individual subject space. The mean distance from electrode center to the target lobule was 137.1 mm (SD 11.0 mm; range

113.5-155.35 mm). To examine the neural effects of active tDCS, post-tDCS brain activation patterns were compared between active and sham tDCS conditions (anodal vs. sham, cathodal vs. sham; $p<0.001$, $k>50$). Then, using multiple regression, the resulting maps were correlated with electrode placement values to highlight differences in activation patterns that were associated with electrode distance from target. There were no regions where the activation difference between active and sham tDCS was associated with electrode distance to target. These initial findings suggest that tDCS electrode placement using skull landmarks does not lead to significant inter-individual differences in post-tDCS brain activation when using 5x5 cm electrodes.

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**Poster**

**768. Cerebellum: Human Studies**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 768.04/UU2

**Topic:** E.02. Cerebellum

**Support:** Mercur Pr-2015-0010
SFB1280 (TP A05 and A06)

**Title:** Physiological mechanisms and computational modelling of cerebellar transcranial direct current stimulation in humans

**Authors: *G. BATSIKADZE**[1], Z. REZAEE HASSAN ABADI[3], D.-I. CHANG[2], M. GERWIG[2], S. HERLITZE[4], A. DUTTA[5], M. A. NITSCHE[6], D. TIMMANN[2]
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**Abstract:** *Background.* Recently, transcranial direct current stimulation (tDCS) emerged as a popular method to non-invasively modulate cerebellar excitability and plasticity in healthy subjects and various patient populations. However, ctDCS parameters are poorly standardized. The aim of the present study was to compare the physiological effects of three different return electrode positions. Additionally, a modeling approach was used to compare the distribution of the induced electric field within the cerebellum between these electrode montages. *Methods.* 15 healthy participants took part in two Experiments, with the exception of one subject participating in Exp. 1 only. In both experiments, the target tDCS electrode was placed over the right cerebellar cortex. In Exp. 1, the return electrode was placed over one of the following three

positions: the right buccinator muscle, the left supraorbital area or the right deltoid muscle. In Exp. 2, it was positioned over the right buccinator muscle. CBI was measured by a double-TMS protocol. The conditioning stimulus (CS) was applied over the right cerebellum with an intensity of 5% below the brainstem motor threshold (BMT). The test pulse followed over the left primary motor cortex 5ms later. For a CBI-recruitment curve (CBI-RC), five different CS intensities were used (-5, -10, -15, -20, -25 below BMT). After-effects were measured before and for two hours after application of 15 minutes 2mA anodal or cathodal cerebellar tDCS. Additionally, an anatomically accurate head model was built based on an individual MR image and the electric field distribution was modelled for each of the electrode montages. *Results.* In Exp. 1, both tDCS polarities significantly decreased CBI for at least two hours compared to both sham and pre-stimulation values. No significant differences between different return electrode positions were observed. In Exp. 2, CBI was significantly increased after anodal and was decreased after cathodal tDCS with low CS intensities. Simulation data revealed no significant differences in the ctDCS-induced electric field distribution between the three return electrode positions. *Conclusions*. The present results show that the return electrode position has no significant impact on physiological ctDCS after-effects and model-based cerebellar electric field distribution. The recruitment of the cerebellar-M1 connection, however, varies depending on ctDCS polarity and cerebellar TMS intensity, suggesting that tDCS differently affects neurons in different layers of the cerebellar cortex. This polarity-specific dependence should be considered for tDCS applications and addressed in future studies.

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**Poster**

**768. Cerebellum: Human Studies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 768.05/UU3

**Topic:** E.02. Cerebellum

**Support:** NSERC

**Title:** Cerebellar inhibition modulates attentional control of irrelevant stimuli

**Authors: *D. ANDREW**, M. S. ADAMS, W. R. STAINES
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**Abstract:** Recent findings of cerebellar activation during non-motor tasks and its projections to non-motor cortical areas have led to the hypothesis that in the same way that the cerebellum aids in coordination of movement, perhaps it contributes to the coordination of cognitive tasks. To

accomplish these higher order processes within multisensory environments, we need to orient our attention to important stimuli and ignore distractions. Studies have shown nodes of the cerebellum to be active during attentional tasks, although the exact mechanism of its action is not clear. Understanding the mechanisms and networks by which we alter our attention is critical, as a deficit in its control may be a contributing factor to the deleterious symptoms observed in various behavioural disorders.

This study therefore sought to examine the cerebellum's role in attention by assessing changes to somatosensory and visual stimuli within a sensory conflict task. 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 were asked to make a graded motor response to the amplitude of visual or tactile stimuli that were presented either individually or simultaneously. Attention was altered by having participants respond only to tactile or visual stimuli as instructed, prior to the start of each task block. This resulted in conditions in which participants received a relevant stimulus, an irrelevant stimulus, or a distractor stimulus. Somatosensory ERPs and performance were measured using electroencephalography (EEG) and grading accuracy, respectively. These measures were collected pre and post cTBS to the right lateral cerebellum (centre of coil placed 1 cm below and 3 cm to the right of the inion).

Preliminary results demonstrate that the somatosensory N70 was 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 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. Following transient inhibition of the cerebellum, participants are less likely to gate stimuli that are not relevant, indicating that the cerebellum may serve as a regulator of top-down control of attention orienting.

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**Poster**

**768. Cerebellum: Human Studies**

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**Topic:** E.02. Cerebellum

**Support:** European Commission's 7th Framework Programme (#602450, IMAGEMEND)
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**Title:** Common genetic variants influencing human cerebellar grey matter volume - a genome-wide association study of 12578 healthy participants

**Authors: *T. MOBERGET**[1], D. VAN DER MEER[2], J. ROKICKI[2], T. KAUFMANN[2], A. CORDOVA-PALOMERA[2], F. BETTELLA[2], N. T. DOAN[2], D. ALNAES[2], O. A. ANDREASSEN[2], L. T. WESTLYE[2]
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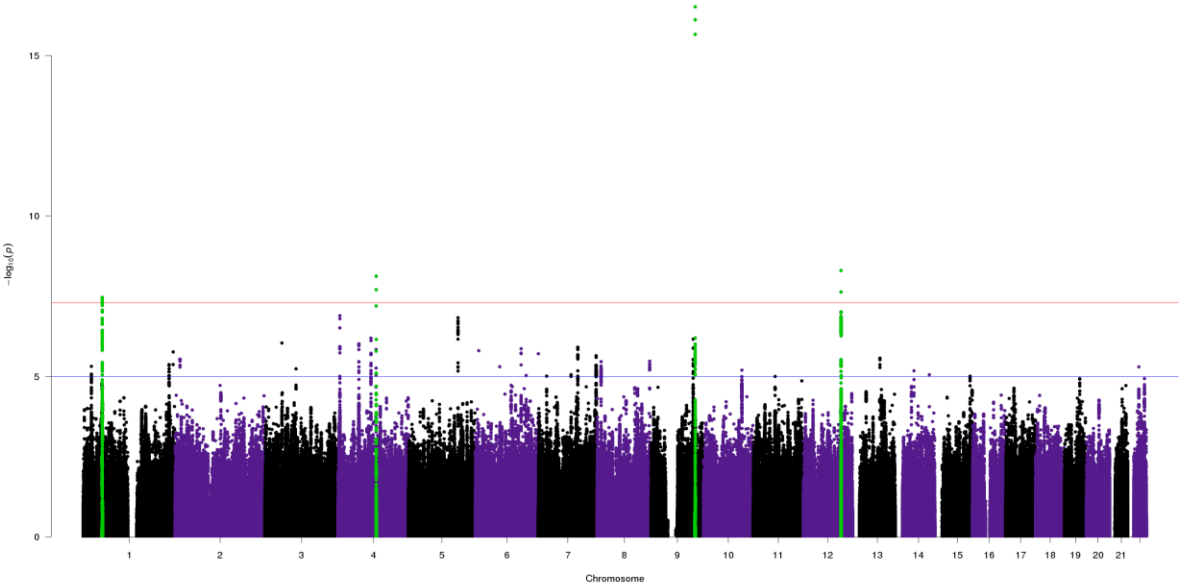
**Abstract: Background:** The cerebellum contains >70% of all neurons in the human brain and is increasingly being linked to a number of cognitive functions, as well as to a number of neuropsychiatric and neurological disorders. However, compared to supra-tentorial brain structures, the cerebellum has been relatively neglected in research targeting the genetic determinants of brain structure and function. Thus, we here sought to identify genetic variants influencing cerebellar volume in a large sample of healthy participants. **Methods:** T1-images from the UK Biobank (n= 12578) were processed using a combination of Freesurfer 5.3 and the SUIT-toolbox (optimized for cerebellar-specific structural and functional MRI-analyses) running on MATLAB. Total cerebellar grey matter volume was defined as the sum of 28 cerebellar regions of interest in the SUIT-atlas, and these total volumes were adjusted for effects of sex, age and estimated total intracranial volume using generalized additive models. We next calculated their SNP-based heritability using genetic complex trait analysis (GCTA) and ran a genome-wide association analysis (GWAS) to identify SNPs significantly associated with total cerebellar grey matter volume. Finally, the functional significance of these genes was explored using FUMA (http://fuma.ctglab.nl/). **Results:** Total cerebellar volume showed a SNP-based (i.e., narrow-sense) heritability of .27 (SE: 0.03, $p < 1e\text{-}16$. GWAS identified 4 independent whole-genome significant loci (on chromosomes 1, 4, 9 and 12; see Fig 1), which were mapped to 12 genes in FUMA (TTC39A, RNF11, C1orf185, SLC39A8, BANK1, PAPPA, IGF1, NUP37, CCDC53, DRAM1, PMCH, PARPBP). There was significant enrichment for genes previously found to be associated with height, QRS duration, blood pressure and systemic lupus erythematosus. **Conclusions:** In this first GWAS on cerebellar volume, we identified four novel whole-genome significant loci. Functional annotation of mapped genes suggests common biological pathways with height, cardiovascular and autoimmune disorders.

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**Poster**

**768. Cerebellum: Human Studies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 768.07/UU5

**Topic:** E.02. Cerebellum

**Support:** NIH Grant NS105839
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**Title:** Dissociable effects of cerebellar degeneration on adaptation and online correction across motor domains

**Authors: *B. PARRELL**[1], H. E. KIM[2], A. BRESKA[3], R. IVRY[4]
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**Abstract:** The cerebellum has been hypothesized to be a critical component of a network that allows us to adapt future movements in response to sensory errors. When presented with external

manipulations that perturb the sensory feedback, neurologically healthy participants show adaptation, iteratively recalibrating their movements over time to cancel out the perturbation. Patients with cerebellar degeneration are impaired in their ability to adapt, an impairment that has been observed across a wide variety of motor and sensory domains, including somatosensory and visual feedback during reaching, visual feedback of saccades, somatosensory feedback during walking, and auditory feedback during speaking.

In addition to its role in adaptation, sensory feedback is also integral to the online control of movement, including rapid movements like reaching and speech. However, how cerebellar degeneration impacts online control is not well understood. In contrast to adaptation, there may be significant differences across motor domains: Previous studies have shown that sensory feedback control is equivalent to that of controls in walking, whereas our recent work has shown increased sensitivity to feedback in the online control of articulation and pitch control while speaking.

To further explore this issue, we employed a within-subject design, testing patients with cerebellar degeneration on reaching and speech tasks, using perturbations designed to either test adaptation (changes across trials) or on-line feedback control (changes within trials).To test adaptation, we introduced external perturbations of either the visual feedback during reaching (20° visuo-motor rotation) or of the vowel formants (125 Mel alteration) during speech. To test online compensation, we measured the magnitudes of within-trial corrective responses to self-produced errors in both reaching and speech tasks.

Relative to controls, adaptation in the patient group was reduced for both reaching and speech, with evidence suggesting a larger reduction in reaching. However, there was no correlation between the patients' behavior in the two domains, similar to previous work showing that adaptation to visuomotor and force-field perturbations are dissociable in this population. Most striking, there was a large difference in online control between the two domains: Although the patients exhibited normal on-line corrections to speech errors, they showed attenuated on-line corrections during reaching compared to controls. These results suggest that, following cerebellar damage, impairments in the use of sensory feedback for both adaptation and online control are domain-specific.

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**Poster**

**768. Cerebellum: Human Studies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 768.08/UU6

**Topic:** E.02. Cerebellum

**Support:** Fundação para a Ciência e Tecnologia

**Title:** An activation likelihood estimation (ALE) meta-analysis of sensorimotor feedback manipulations

**Authors: *J. F. JOHNSON**[1], M. BELYK[2], M. SCHWARTZE[1], A. P. PINHEIRO[3], S. A. KOTZ[4]
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**Abstract:** As we move in the present, we employ sensory feedback to fine-tune our future actions. The forward model is a computational process that compares predicted with actual sensory consequences of a motor action. A common strategy for testing the forward model is to analyze "prediction errors" by comparing patterns of neural activation of self-generated movements under conditions of natural as opposed to altered feedback. Although it is established that this process engages the cerebellum, more fine-grained functional specification within this structure remains elusive. This discrepancy likely indicates methodological variability but also that various sub-regions of the cerebellum might respond to prediction error induced by different kinds of feedback alterations. We performed an activation likelihood estimation (ALE) meta-analysis of studies that manipulated the type and timing auditory and visual feedback from self-generated movements. A dataset of 379 foci from 25 human neuroimaging feedback manipulation studies was compiled via the PubMed database. The ALE analysis conducted on this dataset revealed clusters in the bilateral superior temporal gyrus and premotor cortex, left supplementary motor area, and right inferior frontal gyrus and intraparietal lobule, with no significant clusters in the cerebellum. Additionally, contrast analyses between subsets of foci from auditory and visual feedback manipulations revealed no modality specific cerebellar involvement. A secondary ALE analysis was conducted on only the 9 experiments that reported cerebellar activity to determine if these foci converged on similar sub-regions, or were randomly distributed. Two cerebellar clusters emerged: lobule VI a functional region involved in auditory and visual sensory processing and lobule VIII in sensorimotor processing. We reveal that the current body of feedback manipulation research does not serve as a general probe for the cerebellar role in the forward model and provide suggestions for future investigation. Foremost, we advise employing unpredictable conditions of manipulation in event-related designs as opposed to block to avoid habituation. Manipulation in a continuous task allowing for motor adjustment may probe the cerebellar sensorimotor area, while unexpected changes to sensory feedback irrelevant to movement correction may probe sensory processing areas. Finally, this functionally distributed involvement of the cerebellar cortex exemplifies the necessity to consider localization at the scale of the functional zone as opposed to general involvement of the structure when studying the intricate role of the cerebellum in the forward model.

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**Poster**

**768. Cerebellum: Human Studies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 768.09/UU7

**Topic:** E.02. Cerebellum

**Title:** Improved motor evoked potentials after craniovertebral decompression in Chiari malformation type II may help avoid duroplasty

**Authors: *S. ROMER**[1,2], J. CASTLE[2], A. TEWARI[2]
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**Abstract:** Chiari Malformation Type II (CMII) is a potentially life-threating disease during infancy and childhood. Also known as Arnold-Chiari malformation, the disease is characterized by a structural defect in the cerebellum causing caudal herniation of the cerebellar tonsils through the foramen magnum. Posterior fossa decompression surgery can stop the progressive damage to the nervous system and alleviate symptoms, however, a general consensus has not been reached about incorporating duroplasty into the surgery. While, duroplasty can improve clinical outcomes in some patients, it is also associated with significantly more complications, increased hospitalizations stays and increased medical costs. For the first time, using intraoperative neuromonitoring of transcranial motor evoked potentials (TcMEPs) in CMII infant patients undergoing decompression surgery, we report a significant 26% increase TcMEP amplitudes in 6/9 patients (abductor pollicis brevus muscle, p=0.013, paired t-test). The increase in TcMEPs is likely a result of enhanced conduction in the descending motor spinal pathways following effective decompression. In 5/6 of these patients, the significant increase in TcMEPs occurred after the C1 laminectomy with subsequent duroplasty offering no further motor benefit. Thus, the use of standardized TcMEPs intraoperatively in infants can be used as real-time tool, that together with ultrasonography and CSF dynamics, can be used to assess the necessity of performing duroplasty and reduce morbidities in CMII patients.

**Disclosures: S. Romer:** A. Employment/Salary (full or part-time):; Evokes, LLC. **J. Castle:** None. **A. Tewari:** None.

**Poster**

**768. Cerebellum: Human Studies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 768.10/UU8

**Topic:** E.02. Cerebellum

**Title:** Mapping of cerebellar patterns of activity using EEG

**Authors: *E. TORRES, JR**
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**Abstract:** In EEG, electrical potentials measured at the scalp are typically associated with the synchronous activity of large populations of cortical pyramidal cells over relatively short timescales (ms range) due to their organization and structure. Purkinje cells in the cerebellum share many of these characteristics. Here, we used EEG activity obtained during a sensorimotor control task to localize task-related cerebellar activity in the cortico-cerebellar networks that support motor control.
EEG was collected from 7 subjects (mean= 26 years) as they performed a target tracking task using an actuated wrist manipulandum with their right hands. The subjects' task was to use the manipulandum to place a visual cursor onto a pseudo-randomly moving target presented on computer display. As subjects tracked the target, force impulses were applied intermittently via the manipulandum at one of five levels (0.3, 0.5, 0.7, 0.9, and 1.1 N-m). EEG data was collected using a 64-channel cap and pre-processed in EEGLab to remove drift and eye blink artifacts. EEG signals were then epoched into one-second trials centered on the force impulse and the activity baseline corrected. For each force level, trials were averaged to obtain the evoked response associated with subjects' correction to the induced movement error. Source imaging analyses was performed in Brainstorm using a weighted-minimum norm to localize EEG activity to the surface of the cortex and cerebellum for each subject. Following source localization, source maps were morphed onto the ICBM152 anatomy and averaged across subjects to characterize the cerebellar-cortical networks associated with error correction during goal-directed movements.
Source activity was characterized in task-related regions of interest, including somatosensory, premotor , and primary motor cortex, and cerebellar lobes. The time course of error-related activation showed early an onset in S1 (=125ms) with activity in premotor (=125ms) and motor cortices (=125ms). Significant Cerebellar activity was seen to be present ipsilaterally at 100ms, bilaterally at 200ms, and once again ipsilaterally at 300ms and 400ms. Cerebellar activity peaked at 250ms coinciding with a peak in activity for the other ROI's . The spatiotemporal pattern of activity points to an early cortical registration of movement error in sensory and motor areas, followed by a cerebellar-cortical activity associated with sensorimotor prediction of the corrective action. The results support a role for the cerebellum in forward prediction of sensory

responses to motor actions and indicate that EEG source localization can be used to characterize cerebellar activity in humans.

**Disclosures: E. Torres:** None.

**Poster**

**768. Cerebellum: Human Studies**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 768.11/UU9

**Topic:** E.02. Cerebellum

**Support:** NIH Grant NS094946

**Title:** Force and time control in SCA6

**Authors: B. YACOUBI**, A. CASAMENTO-MORAN, R. BURCIU, S. SUBRAMONY, D. E. VAILLANCOURT, *E. A. CHRISTOU
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**Abstract:** Spinocerebellar ataxia type 6 (SCA6) is a genetic disease causing cerebellar degeneration with significant motor control impairments. Our purpose was to characterize motor control in SCA6 during isolated contractions and determine its association with brain activity, muscle activity, and functional capacity. Twenty-two individuals diagnosed with SCA6 (60.4 ± 8.8 yrs., 15 F) and 8 healthy controls (55.3 ± 9.7 yrs., 4 F) performed 50 submaximal ballistic goal directed contractions (15% maximum at 180 ms) with ankle dorsiflexion. We quantified the following: 1) Motor control - dysmetria and endpoint variability in force and time during ankle dorsiflexion; 2) Brain activity - using resting functional connectivity and free-water diffusion magnetic resonance imaging analyses; 3) Agonist muscle activity - TA EMG burst and burst variability during ankle dorsiflexion; 4) Functional capacity - using the International Cooperative Ataxia Rating Scale (ICARS), the Scale for the assessment and Rating of Ataxia (SARA), and a manual dexterity test. We identified two distinct groups of SCA6 patients based on time endpoint variability. The first group (n=12) exhibited low time variability (<15%; time invariant group). The second group (n=10) exhibited time variability comparable to healthy controls (>20%; time variant group). The time invariant SCA6 group exhibited impaired functional capacity as evidenced from greater scores in ICARS ($P<0.05$) and SARA ($P<0.05$), and lower scores in the manual dexterity test ($P<0.05$). Time variability was predicted by the TA EMG burst duration variability ($R^2=0.67$; $P<0.05$) and activity of the cerebellum ($R^2=0.86$; $P<0.05$). Our findings provide novel evidence that there is a distinct subtype of SCA6 characterized by invariance in time endpoint. This group of SCA6 exhibit impaired functional capacity, and differential activation of the brain and muscle.

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**Poster**

**769. Histologic Responses to Electrode Insertion**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 769.01/UU10

**Topic:** E.05. Brain-Machine Interface

**Support:** NIH NINDSR01NS094396

**Title:** Microelectrode implantation induces pericyte reactivity and vascular bed reorganization as revealed by two-photon microscopy

**Authors: *S. WELLMAN**, T. D. Y. KOZAI
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**Abstract:** Integration of neural interfaces with minimal tissue disruption in the brain is ideal to develop robust tools that can address essential neuroscience questions and combat neurological deficiencies. However, implantation of intracortical devices provokes severe tissue inflammation, which requires a high metabolic demand to support a complex series of cellular events mediating tissue degeneration and wound healing. Pericytes, peri-vascular cells involved in blood-brain barrier maintenance, vascular permeability, waste clearance, and angiogenesis, have recently been implicated as significant participators in neurodegenerative disease. While the intimate relationship between pericytes and the vascular bed have been explored under other diseased states, its behavior following microelectrode implantation, which is responsible for direct blood vessel disruption and permeability, is currently unknown. Using two-photon laser scanning microscopy, NG2+ vascular pericytes labeled by a red fluorescent reporter (*Cspg4-Ds.Red*) were observed during microelectrode implantation. Non-functional 4-shank microelectrode probes were inserted into the adult mouse cortex and imaged every 12 hours for a minimum of 2 weeks following insertion. Reactive changes in pericyte morphology and structural changes to the vascular bed were monitored around implanted electrode shanks. No obvious changes were noted in pericyte structure within the first 24 hours following insertion. After 2-3 days, pericytes began to hypertrophy, displaying enlarged cell bodies. Shortly afterwards, morphological deformations in pericyte soma coincided with the formation of new blood vessels within the vicinity of the electrode. These new blood vessels displayed a significantly larger diameter compared to pre-injury capillaries, indicating an increase in blood flow perfusion following microelectrode implantation. Beginning 5-7 days following injury, fluorescent pericyte coverage of the tissue area surrounding the electrode increased independent of angiogenesis suggesting potential encapsulation of the device. Preliminary data suggests that alterations in the physiological behavior of vascular-bound pericytes is attributed to insertion of a

microelectrode array. Since pericytes are important facilitators of blood-brain barrier restoration, it is possible their reactivity is induced by vasculature damage sustained during implantation. These novel insights on the fluctuating tissue dynamics around neural interfaces within the brain provide an additional framework for analysis in an effort to improve long-term device stability and performance.

**Disclosures: S. Wellman:** None. **T.D.Y. Kozai:** None.

**Poster**

**769. Histologic Responses to Electrode Insertion**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 769.02/UU11

**Topic:** E.05. Brain-Machine Interface

**Title:** Development of tools for a 3D reconstructed intracortical volume around microelectrode arrays

**Authors: *A. NAMBIAR**, N. NOLTA, M. HAN
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**Abstract:** Extensive research using penetrating electrodes implanted in the central and peripheral nervous systems has been performed for many decades, with significant advances in recent years such as deep brain stimulation and brain-machine interfaces. 2D histological studies have been insightful in identifying and quantifying foreign body responses responsible for chronic failure around the implant sites. However, there are significant limitations of 2D histological studies in providing a holistic picture of the problems occurring at the electrode-tissue interface. In this study, we present a 3D reconstruction of serial sections to overcome these limitations. The image data was from an animal study using hybrid arrays having 8 Blackrock electrodes, 4 NeuroNexus probes, 4 short Microprobe microwires and 4 long Microprobe microwires inserted in the right and left cerebral cortex of 11 adult male cats. XuvStitch, AutoAligner, and Imaris (Bitplane AG) were used to correct image artifacts and reconstruct a 3D volume of the intracortical tissue section. A dewarping algorithm was written in MATLAB and interfaced with Imaris to correct image artifacts like tissue distortions and eliminate dark out-of-focus slices. Artificial electrode tips were drawn in the reconstructed 3D volume. Neurons and astrocytes were volume rendered using Imaris and their densities determined in different zonal bins from the electrode site in increments of 25 µm up to 200 µm. Quantifications indicate the severity of foreign body response to microwires was less than that to Blackrock microelectrodes. The 3D examination of intracortical tissue volumes made possible by these software tools expands the capabilities of histological analysis and is faster and less labor-intensive than our previous method.

**Disclosures: A. Nambiar:** None. **N. Nolta:** None. **M. Han:** None.

**Poster**

**769. Histologic Responses to Electrode Insertion**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 769.03/UU12

**Topic:** E.05. Brain-Machine Interface

**Support:** NIH/NINDS R21 NS094900

**Title:** Structural and functional changes of pyramidal neurons in primary motor cortex at the site of an implanted multielectrode array

**Authors: *B. GREGORY**[1], J. SALATINO[2], M. RAILING[1], T. O'MALLEY[1], J. SEYMOUR[4], J. BEATTY[1], C. COX[1], E. PURCELL[3]
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**Abstract:** Implanted microelectrode arrays (MEAs) have created unprecedented opportunities to study brain function and treat neurological diseases and injuries. However, the rapid growth in the usage of these technologies has outpaced clear understanding of their interaction with surrounding brain tissue and the source(s) of variable device longevity and chronic performance. While reactive gliosis and neurodegeneration are well-known to occur following device insertion, the link between the tissue response and cell-specific changes in excitability are unknown. Focal lesions of neocortex can produce long-term changes in dendritic spines including decreased density and a shift towards immature/silent synapses. Our studies explore potential mechanisms of signal loss over time by characterizing dendritic morphology and intrinsic excitability of pyramidal neurons closely associated with an MEA. Our experiments measured spine density in segments of apical and basal dendrites from fluorescently-labeled pyramidal neurons in L5/6 of male Sprague Dawley rats in primary motor cortex. We employed 2-photon laser scanning microscopy in brain slice preparations containing a polyimide-based MEA device taken 1 week after insertion into the primary motor cortex. Pyramidal neurons with somas <100 μm (near-device) and >500 μm (distant-device) from the device surface, and non-implanted controls were investigated. Regular-spiking and intrinsically bursting pyramidal neuron sub-types were grouped and analyzed separately. Results show a decrease in spine density and limited dendritic arborization in near-device cells compared with distant-device and naïve controls. In addition, whole-cell intracellular recordings showed two central observations in near-device neurons in comparison to distant and non-implanted tissues: (1) neurons typically displayed a depolarized resting potential, lower input resistance, and lack of action potentials in response to current injection, or (2) neurons were characterized by a hyperpolarized resting potential, but varied in input resistance and spike firing properties. These data suggest that device

insertion does impact dendritic architecture, while also altering the excitability of near-device cells. The results propose a novel role of local structural and functional plasticity surrounding devices in chronic signal loss and instability.

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**Poster**

**769. Histologic Responses to Electrode Insertion**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 769.04/UU13

**Topic:** E.05. Brain-Machine Interface

**Support:** KTIA 13 NAP-A-IV/1-4,6
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EU FP7 Grant No. 600925 NeuroSeeker
NKFIH NN 116550

**Title:** Biocompatibility of the SU-8 in the central nervous system

**Authors: *K. TÓTH**[1], E. Z. TÓTH[1], L. WITTNER[1], R. FIÁTH[1,2], D. MESZÉNA[1,2], I. PÁL[1], E. L. GYőRI[1,2], D. PINKE[2], Z. BERECZKI[3], G. ORBÁN[1,4], A. PONGRÁCZ[5], I. ULBERT[1,2], G. MÁRTON[1]
[1]Inst. of Cognitive Neurosci. and Psychology, HAS, Res. Ctr. For Natural Sci., Budapest, Hungary; [2]Fac. of Information Technol. and Bionics, Pázmány Péter Catholic Univ., Budapest, Hungary; [3]Dept. of Control Engin. and Information Technol., Budapest Univ. of Technol. and Econ., Budapest, Hungary; [4]Óbuda Univ. Doctoral Sch. on Materials Sci. and Technologies, Budapest, Hungary; [5]Ctr. for Energy Res., HAS, Inst. of Tech. Physics and Materials Sci., Budapest, Hungary

**Abstract:** Multichannel microelectrodes implanted in the brain are important both in basic science and in clinics. The majority of the neural probes are silicon based. The advantage of the SU-8 material compared with the silicon is that it is more flexible, allowing a smoother coupling with the soft brain tissue. Despite the widening use of SU-8 nowadays in the production of neural sensors, a detailed systematic quantitative study concerning its biocompatibility in the central nervous system was not performed yet. In this project, we examined the biocompatibility of the SU-8 photoresist polymer by studying the neuron density near the device surface and by assessing the gliosis surrounding the device. 62 probes were implanted in the brains of 31 rats. After 2 months, neurons or glial cells were labeled with NeuN- or GFAP-immunostaining. Neuronal densities were calculated in 20 µm wide regions up to 400 µm on the 4 sides of the tracks. The density values of each sector were normalized to the average values of the 200 to 400

μm regions. The severity of the gliosis around the probe tracks was investigated in the same way, the average pixel intensities were calculated. The severity of gliosis, and the synaptic density near the track were analyzed at the electron microscopic level. The density of neurons significantly decreased in the first 20 μm. The average normalized densities were 0.24±0.28 in the 0-20 μm distance. From 40 μm the density of neurons was control-like. The intensity of the GFAP-staining is reduced with increasing distance from the implantation site. In average, the astroglial reaction was the most intense in the upper layers and it was gradually attenuated towards the deeper layers. At a 40 μm distance from the electrode track several GFAP-positive elements were visible at the electron microscopic level. At a larger distance (180 μm) the amount of GFAP-immunostained elements was markedly decreased. The first synapses appear at a distance of 24 μm. From 30 μm the density of synapses was comparable with a distance of 120 μm. Our results indicate that SU-8 material enables a better neuronal survival in the close vicinity of the implant than the different types of silicone based probes which cause a significant neuronal loss typically between 50 and 100 microns from the implant surface.

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**Poster**

**769. Histologic Responses to Electrode Insertion**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 769.05/UU14

**Topic:** E.05. Brain-Machine Interface

**Support:** Neural Engineering SEED Grant

**Title:** Effect of deferoxamine on neuroinflammation, oxidative stress, and blood-brain barrier (BBB) disruption in intracortical silicon microelectrode implants

**Authors: *C. BENNETT**, F. MOHAMMED, A. ALVAREZ-CIARA, M. A. NGUYEN, A. PRASAD
Biomed. Engin., Univ. of Miami, Miami, FL

**Abstract:** The use of microelectrode arrays as an invasive, intracortical recording device has gained significant attention in being able to not only help restore motor functions to paralysis patients but can also be used to study brain function in various neurological disorders. However, the use of intracortical electrodes elicits a foreign body response (FBR) that varies on various factors. Vasculature, or blood-brain barrier (BBB), disruption has been hypothesized as one of the most influential factors that results in electrode-implant induced trauma. During vascular disruption following electrode implant, ferric iron released from intracranial hemorrhage can

further escalate the FBR and its subsequent events. In this work, we evaluate the use of a US FDA-approved iron chelator, deferoxamine mesylate (DFX), on inflammation, BBB-integrity, and oxidative stress following implant of silicon microelectrode array in the rat cortex. A total of n=50 adult, male Sprague Dawley rats were used in the study. Animals were divided into control and DFX-treated groups. We used quantitative polymerase chain reaction (qPCR) to quantify the expression of genes directly involved in inflammation, oxidative stress, and BBB-disruption. For qPCR, we evaluated DFX-treated animals implanted for 24-hr, 48-hr, 72-hr, and 7-day time points (n=5 per group) with matched non-treated controls (n=5) for each time point. We used n=10 rats as naïve controls with no implant or surgery to obtain a baseline of the expression in healthy, unimplanted animals. Gene expression was quantified using the $RT^2$ PCR primers for key genes mediating the inflammatory response, key substrates involved in reactive oxygen species (ROS) production involved in oxidative stress, and tight and adherens junctions proteins that form the endothelial barrier necessary for the functionality of the BBB. Our results indicate significant inflammation throughout the study. The BBB, although initially downregulated, returns to at or above baseline levels by 7-days with a significant increase at 7-days with the help of DFX. Levels of oxidative stress were monitored at 7-days suggesting presence of cellular stress due to increased inflammation and ROS. The results further delve into the pathophysiological events—which could be used as potential therapeutic agents—occurring after electrode implantation that could give rise to the electrodes rejection and failure. In general, DFX-treated animals showed reduced BBB-dysfunction over time compared to untreated controls. The study further provides mechanistic insights following microelectrode insertion into inflammation, oxidative stress, and BBB-disruption.

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**Poster**

**769. Histologic Responses to Electrode Insertion**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 769.06/UU15

**Topic:** E.05. Brain-Machine Interface

**Title:** Long-term neural and vascular structural and functional changes to intracortical microelectrode arrays

**Authors: *K. SOLARANA**[1], M. YE[1], Y.-R. GAO[2], H. RAFI[1], D. X. HAMMER[1]
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**Abstract:** Cortically-implanted microelectrode arrays provide a direct interface with neuronal populations in the motor cortex and are used to restore movement capabilities to patients with

paralysis or amputation. Penetrating electrodes produce higher neural signal fidelity and spatial resolution than surface electrodes shortly after implantation, but inexorably experience high rates of signal degradation that limit effectiveness and lead to device failure within the first year. Biological responses, including blood-brain barrier disruption, glial encapsulation, and neurodegeneration, as well as mechanical and material failures can all contribute to decreases in the quality of the recorded signal. Here, we use a multimodal approach combining electrophysiology and optical imaging *in vivo* to assess vascular and cellular changes over time in animals with implanted electrodes, and examine the correlation between the brain tissue response and electrical signal quality. Thy1-YFP transgenic mice were implanted with 16-channel single-shank, Michigan-style microelectrodes 200-400 µm deep in the motor cortex. Optical coherence tomography (OCT)-guided two-photon microscopy (TPM) was then performed through a cranial window concurrent with electrophysiological recordings periodically for durations exceeding a year. Cerebral blood vessels, dendritic tufts at the cortical surface (<50 µm deep), neuronal dendrites and capillaries near the electrode tip (200-400 µm), cell bodies in deeper layers (450-700 µm), neuronal single unit activity, and local field potential (LFP) were analyzed. At acute timescales, we observe structural damage from the mechanical trauma of electrode insertion, evidenced by severed dendrites in the electrode path and local hypofluorescence. We also see superficial vessel growth and remodeling within the first few weeks, while the deeper capillary network remains stable over six months. After longer periods of implantation, there is evidence of degeneration of the severed dendrites superficial to the electrode path and re-orientation of dendrite tracks parallel to the electrode, while dendritic tuft density at the cortical surface remains relatively stable. Single cell spike recording amplitude decreased after the first month, probably a result of gliosis. The LFP signal remained relatively constant up to 6 months, particularly in the high-gamma band, indicating long-term electrode viability. This multifaceted approach will provide a more comprehensive picture of the ongoing biological response at the brain-electrode interface and will identify biomarkers of tissue damage that can predict device failure.

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**Poster**

**769. Histologic Responses to Electrode Insertion**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 769.07/UU16

**Topic:** E.05. Brain-Machine Interface

**Support:** NIH R21NS084492-01

**Title:** Do micromotion-induced cyclical stresses induce a physiological response in neurons around chronic brain implants?

**Authors: *J. L. DUNCAN**, S. SAMPATH KUMAR, A. SRIDHARAN, J. MUTHUSWAMY
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**Abstract:** Brain micromotion can arise from physiological events such as vascular pulsation (2-4 μm) and breathing (10-30 μm) and can induce cyclical stresses in the order of 0.2-4 KPa on the brain tissue in the micro-enviroment surrounding a microelectrode under acute and chronic implantation conditions. However, there is little understanding of the effects of these stresses on single neurons in the vicinity of the electrode. Many studies have also reported significant membrane potential changes of 20-30 mV in neuronal intracellular recordings from rodents with frequencies in the order of ~1 Hz (breathing) and ~3 Hz (vascular pulsations). However, it is not known if these membrane potential changes are physiological or artifactual. The objective of this study is to determine if micromotion induced compressive and/or shear stresses can result in an electrophysiological response in single neurons. In this study, we mimicked micromotion in Aplysia neurons (n = 5) by applying compressive cyclical (at 1 Hz) stresses of magnitudes ranging from 0.6 to 4 KPa on the neurons using an extracellular microelectrode. The membrane potential changes in response to the applied cyclical stresses were measured using penetrating glass micropipettes. No membrane potential oscillations were observed for stresses <1.5 KPa in all cells tested. Downward and upward stresses of magnitudes >1.5 KPa resulted in hyperpolarization and depolarization of membrane potential respectively. Also, the change in membrane potential increased linearly with increase in magnitude of applied stresses (n=5). Interestingly, action potentials were generated in response to upward stresses (>3 KPa) in some silent neurons (n=2) and change in firing rates in neurons that were already firing, such that the neurons fired in response to upward stresses and remained silent in response to subsequent downward stresses (n=3). The generation of action potentials in response to only upward stresses indicates that the associated membrane potential changes may be physiological, rather than artifactual. Preliminary drug studies in Aplysia neurons with serotonin (5-HT) suggest the involvement of the mechanosensitive receptors, SK channels, in the generation of action potentials in response to stresses. We are currently investigating the mechanisms underlying the membrane potential changes observed in Aplysia neurons as well as rat cortical neurons in vivo in response to micromotion. The results of this study will 1) significantly improve our understanding of neuronal responses to chronically implanted electrodes and 2) help design improved neural interfaces in which relative micromotion is minimized.

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**Poster**

**769. Histologic Responses to Electrode Insertion**

**Location:** SDCC Halls B-H

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**Topic:** C.03. Parkinson's Disease

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**Title:** Differences in the reaction of the electrode-tissue interface to chronically implanted active and inactive deep brain stimulation electrodes

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**Abstract:** Chronically implanted stimulation or recording electrodes provide a critical interface for therapeutic and rehabilitation interventions including deep brain stimulation (DBS), brain machine interfaces and neural control of prostheses. DBS is an established treatment in Parkinson's disease (PD), dystonia and essential tremor, and is being explored for other disorders. Efficacy of these systems degrades over time due to several factors including changes at the electrode-tissue interface. Long-term implantation causes impedance changes in the surrounding tissue due to glial scar formation, but the exact electrical and structural properties of the tissue formed, and its effect on the recording or stimulation ability of electrodes is not fully established. Furthermore, the influence of the current or voltage applied during active stimulation on these mechanisms is unknown. The aim of this study was to investigate changes in electrical impedance and tissue histology surrounding chronically implanted DBS electrodes in a rodent model. Experiments were approved by the UCD Animal Research Ethics Committee and licenced by the Health Products Regulatory Authority of Ireland. Bipolar concentric electrodes were implanted in the subthalamic nucleus, a common DBS target in PD, of 6 male Wistar rats (400 g). Rats were followed for 4-8 weeks during which 2 rats received DBS (130 Hz, 100 µA, 60 µs duration biphasic rectangular pulses) and 4 received no stimulation. Continuous stimulation was applied via wireless programmable, inductively charged headstages. Electrical impedance of the electrode-tissue interface was monitored using impedance spectroscopy. For the assessment of brain tissue reaction, brains were fixed by cardiac perfusion with 10% neutral buffered formalin and 5 µm sections were labelled for astrocytes (GFAP) and microglia (Iba-1) by immunohistochemistry. Baseline impedance was 19.8 kΩ ± 4.1 kΩ. Impedance decreased in the first days after surgery, then increased above baseline and stabilized after 14 days. Six weeks

after surgery impedance was 49.3 kΩ ± 4.4 kΩ in the non-stimulation and 29.3 kΩ ± 3.5 kΩ in the stimulation group. A glial reaction at the electrode-tissue interface was observed in both groups. However, the density of astrocytes and activated microglia observed in a concentric ring of up to 400 µm around the electrode was markedly increased in stimulated compared to non-stimulated rat brains. The preliminary results indicate that the electrode-tissue interface reacts stronger to actively stimulated electrodes than to passive electrodes and this difference in reaction is accompanied by lower impedance at the electrode-tissue interface.

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**Poster**

**769. Histologic Responses to Electrode Insertion**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 769.09/DP07/UU18

**Topic:** E.05. Brain-Machine Interface

**Support:** DARPA

**Title:** Penetration mechanics in brain tissue

**Authors: *A. M. OBAID**[1], Y.-W. WU[3], M.-E. S. HANNA[2], W. NIX[2], J. DING[3], N. MELOSH[2]
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**Abstract:** While penetrating microelectrodes have been used effectively in experimental neuroscience for decades, important quantifications of the force and work exerted on the brain tissue during insertion are not well described. The most critical theme of these microwire electrodes is to have the wires insert into the brain without buckling but also have them small enough so that they can insert and reduce physiological damage. Mechanical measurements of single wire insertion into the brain are important quantifications of the force and work exerted on the brain tissue during insertion, and may help identify lower-damage microelectrode designs and surgical procedures.
Many aspects of the mechanics of insertion remain unknown, such as the effects of wire diameter and tip shape. To address the limitations of typical force transducers, we have devised a high-resolution mechanical measurement system to probe the ultra-compliant properties of the brain at much higher force and temporal resolution than previous measurements. We perform a systematic study of the insertion mechanics into traditional brain mimics, freshly removed murine brains (ex-vivo), and in-vivo for a series of different microwire diameters (7.5 um to 125 um) and tip geometries (flat, angled, and electrosharpened). We find clear trends in the forces and displacements necessary to penetrate into the brain, with the brain dimpling > 10 times the

diameter of the wire before puncture. The data from brain insertion was strikingly different from those in traditional brain mimics, and provide the first clear view of how insertion mechanics depend on wire geometry.
These ultra-sensitive force measurements were coupled with live 2-photon microscopy and epifluorescence imaging, providing a unique visualization of the insertion process with simultaneous force measurement. We found no disruption of local astrocytes and/or micro/macro vasculature with wire diameters of 25 um or less, while damage is clearly observed with diameters greater than or equal to 50 µm. These are the first measurements of their kind and provide a framework to understanding insertion mechanics into the brain, as well as providing key design principles for BMIs.

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**Poster**

**769. Histologic Responses to Electrode Insertion**

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**Program #/Poster #:** 769.10/UU19

**Topic:** E.05. Brain-Machine Interface

**Support:** Wallace H Coulter Center for Translational Research – Neural Engineering SEED Grant

**Title:** Determining baseline tissue response to tungsten microwire arrays in neural implants

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**Abstract:** Brain machine interfaces (BMIs) aim to improve the quality of life of people who are paralyzed or have severe motor disabilities. Long-term BMI performance is severely compromised by intracortical electrode failure due to multiple factors that occur at varying time scales. Among these factors, the foreign body response (FBR), blood-brain barrier (BBB) disruption, and the oxidative stress that occur as a result of electrode implants, affect the chronic electrode-tissue interface stability. The BBB provides a physical and metabolic barrier in the brain that regulates cerebral homeostasis while protecting the central nervous system (CNS) from pathogens and toxic compounds. The damage leads to multiple biochemical cascades responsible for neuronal dysfunction and degeneration. Among these pathways, BBB disruption is one of the most dominant pathways resulting in hemorrhage, edema, ischemia, microglial activation, and the release of pro-inflammatory neurotoxic cytokines and has been indicated as key determinant affecting the chronic electrode-tissue interface stability. In this work, we use a combination of techniques that include immunohistochemistry, electrophysiology, and quantitative polymerase

chain reaction (qPCR) to evaluate the pathophysiology at the electrode-tissue interface following implantation of 16-channel tungsten microwire array (MWA) in the rat cortex. We evaluated rats (n=5/ group) implanted with MWA for 3-day, 7-day, 15-days, and 30-days implant duration, respectively. For immunohistochemistry, we used the contralateral brain tissue as control whereas for qPCR, we used n=10 rats as naïve controls with no implant to obtain a baseline of gene expression in healthy animals. Our preliminary results indicate significant upregulation in multiple chemokines and cytokines involved in proinflammatory cascades. We also observed significant downregulation, at earlier time-points, of genes involved in the regulation of tight and adherens junction proteins of the BBB, indicative of BBB-disruption. Further, we also observed significant upregulation of genes related to ROS, RNS, and oxidative stress pathway indicative of formation of oxidative stress around implant sites. The study provides further mechanistic insights related to FBR, BBB-disruption, and oxidative stress following the implant of slow-inserted MWAs.

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**Poster**

**769. Histologic Responses to Electrode Insertion**

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**Topic:** E.05. Brain-Machine Interface

**Support:** UF Preeminence Start-up Funds
W.M. Keck Foundation
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**Title:** Investigating changes in glial and neuronal responses to implantable neural interfaces: How the unique regenerative abilities of the African spiny mouse could impact current understanding of the foreign body response in the brain

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**Abstract:** Mammalian tissue injury typically results in the formation of a fibrotic tissue-based scar at the site of injury. In the field of neural interfaces, chronically implanted neural interfaces

in the CNS leads to an encapsulating glial scar. Glial encapsulation of the implanted neural recording electrodes serves as an ionic barrier, thus reducing the signal to noise ratio of nearby action potentials and the overall functionality of the device. While other non-mammalian species have shown remarkable ability to fully regenerate tissue, such as the axolotl, the African Spiny Mouse (ASM) is the only known mammal able to fully regenerate injured tissues with minimal scarring. The unique regenerative abilities of this mammalian species make it a prime candidate for investigating the foreign body response (FBR) to implanted devices, which has traditionally been a highly variable and complex system to understand, especially in the context of neuroprostheses.

Without a clear understanding of the FBR's biological mechanism, research focused on FBR minimization has typically focused on reducing the physical size or altering the material properties of the device. Thus, the current trend in neural electrode design is device modification to better suit the biology, rather than biological modification to better suit the device. While this can be effective in FBR mitigation, it too can negatively impact the functionality of the device. If the biological mechanism of the FBR could be identified and targeted, the FBR could be reduced or eliminated completely, allowing next generation device design to be optimized while still achieving a favorable tissue response.

This study presents a baseline examination of the cellular morphology of the ASM brain in the context of implantable neural interfaces. Traditional cryo-sectioning and advanced immunohistological techniques, including CLARITY and whole-tissue light sheet microscopy, are used to compare the ASM and a more common lab model used for neural recordings, the C57BL/6 mouse. This work is intended as the first step in investigating how the unique regenerative abilities of the ASM could impact the current understanding of the FBR and neuroregeneration with respect to the field of neural prosthetics.

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**Poster**

**769. Histologic Responses to Electrode Insertion**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 769.12/UU21

**Topic:** E.05. Brain-Machine Interface

**Support:** N66001-17-C-4013

**Title:** An engineered *in vitro* model of foreign-body response to chronic neural implants

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**Abstract:** Chronically implanted neural devices rely on a stable device-tissue interface in order to maintain long-term recordings, and thus performance. However, such interfaces often fail due to acute inflammation and a chronic foreign-body response around the device. Numerous strategies have been employed to mitigate the chronic tissue reaction, including the development of mechanically pliable devices, increasingly small devices, and local drug delivery from the surfaces of devices. Evaluation of potential treatments of the chronic tissue reaction require a 4 month implantation time, sufficient for the body to respond fully to the implanted foreign-body. The long timeframe of in vivo incubation for large scale testing of treatments is impractical for drug optimization or iterative device development. Current short-term in vitro alternatives for efficacy testing rely on traditional monolayer primary cultures, which do not replicate the complexity of three-dimensional device-tissue interactions, diffusion of inflammatory mediators, or cell migration. Here we present a tunable, engineered in vitro model of the chronic foreign-body response suitable for screening potential strategies for neural device-tissue interfaces. In the model, primary cortical self-assembled microtissues, a three-dimensional in vitro model of the brain, were supplemented with inflammatory mediators to elicit an accelerated, and controllable inflammatory response to implanted microwires. The increased inflammatory reactivity to foreign-bodies was assessed by immunohistochemisty in cleared microtissues for three-dimensional analysis of the device-tissue interface. Use of such three-dimensional tissue models may provide a more efficient means of testing and development for potential drug and material treatments of the device-tissue interface.

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**Poster**

**770. Spinal Prosthetics and Stimulation**

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International Paraplegic Foundation

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**Title:** Utility and versatility of asynchronous switch neural decoders based on regularized gaussian mixture models for neuroprosthetic applications

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**Abstract:** Intracortically recorded activity of neuronal ensembles has been used to control multiple continuous degrees of freedom to enable accurate, dexterous and effective control of computers and robotic limbs. Nonetheless, asynchronous switch-based brain-controlled neuroprostheses, in which one or more decoded binary commands control the effector, remain widely used. Furthermore, the majority of brain-controlled neuroprostheses based on continuous effector commands also utilize switch commands.
Over the past decade, we have established a computational framework based on regularized Gaussian Mixture Models to design, calibrate and validate asynchronous switch neural decoders in a variety of functional tasks. In the past, we applied this framework to detect error-related neuronal responses from human electrocorticography. We also developed a decoder that used intracortical neural signals to trigger lumbar spinal cord stimulation that restore weight-bearing locomotor movements in monkeys with a spinal cord injury. Additionally, we engineered an LFP-based decoder that enabled stable and repeated use of a text-entry computer application by people with tetraplegia over up to four and a half months.
Here, we show how our improvements of this framework delivered more versatile and dexterous control. Intracortical neural signals allowed us to trigger cervical spinal cord stimulation protocols using decoded initiation of reach and pull movements. A multiclass extension of this framework allowed us to decode four motor actions from EEG in humans. We used the same extension to engineer an intracortical brain-spine interface that alleviated gait deficits in a monkey model of Parkinson's disease. Moreover, we demonstrate accurate and reliable decoding of gait events from calcium imaging signals in rats. Finally, we applied a mixture-of-experts approach to decode both the time and the magnitude of stepping movements of monkeys

crossing an obstacle course.
These numerous applications with clear therapeutic targets indicate the utility and versatility of our decoding framework. Our preliminary results open promising avenues for evaluating the therapeutic potential in people with Parkinson's disease, paraplegia, tetraplegia, and locked-in syndrome.

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**Poster**

**770. Spinal Prosthetics and Stimulation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 770.02/VV1

**Topic:** E.05. Brain-Machine Interface

**Support:** WCP-034

**Title:** Nonhuman primate model of subcortical stroke

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**Abstract:** Recovery of motor functions after subcortical stroke correlates with the degree of corticospinal tract damage. Typically, extensive corticospinal tract lesions result in near-permanent loss of hand dexterity. Instead, sparing of corticospinal tract fibers leads to an extensive motor recovery that involves compensatory changes in intact brain regions. For example, imaging and electrophysiological experiments have suggested that reorganization of projections from the ipsilesional ventral premotor cortex to the primary motor cortex plays a pivotal role in this recovery. To test this hypothesis, we used pathway-specific anatomical tracing and chemogenetics in a new nonhuman primate (NHP) model of subcortical stroke. We employed the clinical Fischer thermo-coagulator to interrupt the upper limb component of the corticospinal tract within the internal capsule. For this, we planned the trajectory of the probe, to

avoid the motor and premotor cortex, using the Medtronic Neuronavigation Stealth Station. Brain anatomy was obtained using magnetic resonance imaging (MRI) scan while the animals were secured within a personalized dental mold in an MRI-compatible stereotaxic frame. We evaluated the functional impact of the lesion on reaching and grasping movements using the Modified-Brinkman board task. The lesion led to a complete paralysis of the hand. Gross movements improved during the first month, but dexterous hand movements remained permanently impaired. The location and size of the lesion were confirmed using a combination of ex-vivo MRI and virus-mediated tract tracing of the corticospinal tract. We are currently combining intersectional tract tracing and CRE-dependent expression of DREADDs to probe the anatomical reorganization and functional contribution of the projections from the ventral premotor cortex to the primary motor cortex in the partial recovery of hand function.

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**Poster**

**770. Spinal Prosthetics and Stimulation**

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**Topic:** E.05. Brain-Machine Interface

**Support:** The Whitaker Foundation
Wyss Center for Bio and Neuroengineering in Geneva
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**Title:** Personalized brain-spine interfaces in freely-behaving non-human primates

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**Abstract:** Various studies have shown the ability of brain-controlled electrical spinal cord stimulation to alleviate gait deficits in rodent and non-human primate models of spinal cord injury and Parkinson's disease. Currently, spinal implants are designed with a standard size and predefined electrode placements. The electrodes target proprioceptive afferent fibers in the individual dorsal roots. However, anatomical differences between—and within—species, as well as differences in the location and type of spinal cord injury may have important implications on the optimal positioning of the electrodes over the spinal cord. To overcome this limitation, we developed a framework for next-generation neuroprosthetics that enables personalizing the position of the electrodes to the anatomical features and residual function of each individual. Here, we applied this framework to design a wireless brain-spine interface in non-human primates. Using combinations of magnetic resonance imaging and computed tomography with 3D modeling and 3D printing technologies, we personalized the surgical protocols and placement of the electrodes in the spinal implant in order to target the individual dorsal roots of the lumbosacral spinal cord. We used similar methods to personalize the shape and positioning of a titanium mesh screwed onto the skull. The mesh is covered with hydroxy-apatite, which favors the osteo-integration of the mesh and thus increases its resistance profile. The incorporation of multiple pedestals onto the mesh allowed the long-lasting implantation of multiple iridium oxide probes into the motor cortex (M1), and premotor cortex (PMd) in conjunction with up to 14 pairs of electrodes inserted into muscles to record electromyographic (EMG) activity. Wireless transmitters are screwed onto the pedestals to record broadband signals from the intracortical probes and muscles without the need for tethered connections. We developed two-tier mixture of experts models to decode kinematic events and the magnitude of muscle activity from neural recordings in real-time. We then linked the decoded commands to stimulation protocols reinforcing these features during different locomotor tasks. Personalized neuroprosthetics that optimize stimulation efficacy may provide a practical path to establish a similar framework for clinical applications in humans.

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**Poster**

**770. Spinal Prosthetics and Stimulation**

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**Topic:** E.05. Brain-Machine Interface

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Swiss National Science Foundation program Ambizione
Swiss National Science Foundation program Sinergia
Swiss National Science Foundation program Sino-Swiss Science and Technology Cooperation
Swiss National Science Foundation program SpineRepair

**Title:** A wireless brain-spine interface that alleviates gait deficits of Parkinson's disease

**Authors: *T. MILEKOVIC**[1,3], F. RASCHELLÀ[4], S. SUN[3,6], M. G. PERICH[2], G. SCHIAVONE[4], Y. JIANZHONG[7,8], G. ANDREA[2], C. HITZ[3], W. K. D. KO[7,8], Q. LI[7,8], Q. CHUAN[7], M. CAPOGROSSO[3], S. P. LACOUR[4], S. MICERA[4,9], J. BLOCH[10], E. BEZARD[7,8,11], G. COURTINE[5,10]
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**Abstract:** Levodopa and deep brain stimulation alleviate most of the symptoms associated with Parkinson's disease. However, axial gait disorders are less responsive to these treatments. These deficits include short and slow steps, balance deficits and episodes of gait freezing, during which the affected persons are unable to initiate locomotion. We recently engineered a brain-spine interface - a neuroprosthetic system that reinforced intended movements - that restored weight-bearing locomotor movements of monkeys with the paralyzed leg as early as 6 days after spinal cord injury. Here, we adapt the brain-spine interface framework to alleviate axial gait deficits observed in parkinsonism. We demonstrated the therapeutic effects in MPTP-treated Rhesus macaque monkeys - the gold standard model of Parkinson's disease symptomatology. Two MPTP-treated rhesus macaques were implanted with the wireless brain-spine interface. Brain recordings of the left and right leg motor cortex were used to detect neural states related to flexion and extension movements of both legs while the animal walked freely overground or over a horizontal ladder. The detection of these gait events controlled an implanted pulse generator that delivered electrical stimulation through two electrode array implants covering the dorsal aspects of the lumbar and sacral spinal cord. The brain-spine interface instantly improved gait execution when compared to the non-stimulation condition. These improvements manifested in increased speed along the corridor and the ladder, and in the absence of falls on the horizontal

ladder in contrast to the frequent misplacements that occurred without stimulation. These preliminary results open promising avenues for evaluating the ability of the wireless brain-spine interface to alleviate gait deficits in people with Parkinson's disease.

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**Poster**

**770. Spinal Prosthetics and Stimulation**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 770.05/VV4

**Topic:** E.05. Brain-Machine Interface

**Support:** Queen Elizabeth II Graduate Scholarship
CIHR
Alberta Innovates - Health Solutions

**Title:** Online prediction of phases of the gait cycle for control of intraspinal microstimulation

**Authors: *A. DALRYMPLE**[1], D. G. EVERAERT[3], R. S. SUTTON[2], V. K. MUSHAHWAR[3]
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**Abstract:** The goal of this project was to produce over-ground walking with intraspinal microstimulation (ISMS) in a model of hemiplegia. ISMS is an electrical stimulation technique that activates hind-limb muscles by delivering small currents through microwires implanted in the ventral horn of the lumbosacral enlargement. ISMS has produced over-ground walking in a model of complete spinal cord injury (SCI). For restoring walking after incomplete SCI, the control strategy needs to utilize residual function and deliver stimulation to compensate for deficits. In this study the adaptable control was accomplished using Pavlovian control. Pavlovian control was used to learn predictions (conditioned stimulus - CS) and coupled the predictions to a fixed stimulation output (conditioned response - CR). Reinforcement learning produced general value functions (GVFs) for limb loading and angular velocity to predict the phases of the gait cycle. An anesthetized cat was partially suspended in a sling over a walkway. An experimenter manually moved one hind-limb through the gait cycle, mimicking voluntary control of that limb. The learned predictions of signals indicating phases of the gait cycle from the experimenter-moved limb (CS) were coupled to fixed stimulation outputs (CR), that controlled the movements of the other limb to produce alternating walking. Learning predictions of gait phases were either initialized at zero or were built upon learned predictions from previous trials. Whether the

learning parameters were initialized to zero or learning continued between walking trials, 3 of the 4 phases of the gait cycle were successfully predicted within 2 steps on average, and produced alternating walking over the walkway. Learning predictions for each phase occurred at different rates; early swing and propulsion were most often learned after a single step. Predicting the mid-stance phase required the most steps for learning (average = 5 steps). The learned predictions translated from one walking trial (crossing a 3m walkway) to another, where the end and start points in the gait cycle differed. Results from testing on previously recorded trials on a treadmill indicated that learned predictions could also be translated from one cat's trials to another, needing a maximum of one step to adjust predictions. In this study predictions were continuously learned; therefore, they were quickly adaptable step-by-step and may be adaptable to different subjects. Pavlovian control was able to produce walking in a hemiplegia model. Hence, Pavlovian control may be a viable option for restoring walking after other neural injuries or disorders.

**Disclosures: A. Dalrymple:** None. **D.G. Everaert:** None. **R.S. Sutton:** None. **V.K. Mushahwar:** None.

**Poster**

**770. Spinal Prosthetics and Stimulation**

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**Program #/Poster #:** 770.06/VV5

**Topic:** E.05. Brain-Machine Interface

**Support:** Research was sponsored by the U.S. Army Research Office and the Defense Advanced Research Projects Agency (DARPA) was accomplished under Cooperative Agreement Number W911NF-15-2-0016.

**Title:** Closed-loop stimulation of cervical spinal cord and dorsal roots in upper-limb amputees to enable sensory discrimination

**Authors: *S. CHANDRASEKARAN**[1], A. C. NANIVADEKAR[2], D. M. WEIR[2], E. R. HELM[2], M. L. BONINGER[1], J. L. COLLINGER[1], R. A. GAUNT[2], L. E. FISHER[2]
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**Abstract:** Intuitive and timely sensory feedback could enable upper-limb amputees to achieve fine control of their prosthesis and effectively modulate grasp force. Electrical stimulation of the peripheral and central nervous system is the focus of extensive research as a means of providing this sensory feedback. In this study, we targeted stimulation to the dorsal spinal cord and roots (DSCR) using FDA-cleared spinal cord stimulation (SCS) leads. The DSCR provide a clear separation between sensory and motor pathways, thereby avoiding concurrent activation of motor pathways that could contaminate a myoelectric control interface. Stimulation was carried

out through three 8- or 16-contact SCS leads percutaneously in the lateral epidural space near the cervical DSCR. Stimulation was delivered using a custom stimulator during testing sessions for up to 4 weeks following implant, after which the electrodes were removed. The first few sessions of testing with the subject established the receptive field, detection thresholds and just-noticeable differences for various chosen electrodes using a structured reporting system. The scaling of intensity of the evoked percepts in relation to stimulus parameters was also determined. Here, we present observations from closed-loop experiments performed while stimulating the DSCRs in three upper-limb amputees. While deprived of visual feedback, the subject was asked to interact with an object using a sensorized prostheses and determine its properties like size or compliance in a closed-loop setup. The subject used a DataGlove worn on the contralateral intact hand to control either a sensorized DEKA hand or a virtual hand in MuJoCo to grasp objects of various sizes and compliances. The sensor data was used to trigger stimulation and scale the stimulus amplitude. The subject verbally reported the size and compliance of each object while being blinded to the task. We observed that the amplitude and frequency of stimulation evoked a corresponding linear increase in perceived intensity within the ranges tested (1-6 mA and 20-300 Hz). In the closed-loop task, for both real and virtual environments, the subject determined the object properties at a level better than chance (33% accuracy). However, the subject was consistently more adept at determining object size (73% mean accuracy) than object hardness (46% mean accuracy). Thus, stimulation of the DSCR can evoke sensory percepts in the missing limb which could be utilized intuitively by the subject for control of a prosthesis and determine the size or compliance of the object being handled by the prosthesis.

**Disclosures: S. Chandrasekaran:** None. **A.C. Nanivadekar:** None. **D.M. Weir:** None. **E.R. Helm:** None. **M.L. Boninger:** None. **J.L. Collinger:** None. **R.A. Gaunt:** None. **L.E. Fisher:** None.

**Poster**

**770. Spinal Prosthetics and Stimulation**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 770.07/VV6

**Topic:** E.05. Brain-Machine Interface

**Support:** Canadian Institutes of Health Research (Open Operating Grants Program (MOP); #130520)
the US Department of Defence (Congressionally Directed Medical Research Program – Spinal Cord Injury Research Program; #SC110029)

**Title:** Requirements of intraoperative testing of intraspinal microstimulation in humans

**Authors: *A. TOOSSI**[1], D. G. EVERAERT[2], R. UWIERA[3], D. S. HU[2], J. L. JAREMKO[4], K. ROBINSON[5], C. C. KAO[6], P. E. KONRAD[7], V. K. MUSHAHWAR[8]

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**Abstract: Background**: Intraspinal microstimulation (ISMS) of the lumbar enlargement of the spinal cord is a neuroprosthetic approach for restoring lower limb mobility after paralysis. This method involves the implantation of a microelectrode array into the spinal cord, targeting motor networks controlling leg movements. ISMS has shown important benefits such as producing longer standing durations (~5x) and walking distances (~10x) than those with intramuscular implants in cats. The present study aimed to prepare ISMS for intraoperative testing in human volunteers by: 1) developing a stereotactic system for precise targeting of the gray matter of the spinal cord (targeting error <0.5 mm), and, 2) evaluate the effect of a clinical neurosurgical anesthesia protocol on the responses evoked by ISMS. **Methods**: 1) *Stereotaxic Frame:* A spine-mounted stereotactic system with 6 degrees of freedom was developed along with ultrasound imaging to guide the implantation trajectory of the electrodes. The spatial targeting error of the system was assessed in 7 pigs. 2) *Anesthesia Protocols:* The intraoperative responses of ISMS in animals have been classically measured under pentobarbital anesthesia. Functional neurosurgical procedures in clinical practice, however, commonly use Propofol infusion. Possible differences in the evoked responses under these anesthesia protocols were assessed in 6 pigs. In these experiments, the ISMS evoked joint torques and stimulation thresholds were compared. Animals were first anesthetized with Propofol infusion followed by a 1 hr-washout period, before testing under pentobarbital. **Results**: 1) The stereotactic system was quick to setup (<10 min) and provided sufficient stability and range of motion to reach ISMS targets reliably. In pigs, the largest electrode alignment error using ultrasound guidance was 0.37, 0.01 and 0.17 mm in the frontal, sagittal and vertical axes. 2) The stimulation thresholds for evoking movements and joint torques produced under the tested anesthesia protocols were not significantly different from each other. **Conclusions**: We developed an ultrasound-guided stereotactic system for precise implantation of ISMS implants with <0.5 mm targeting accuracy. The similarity between the ISMS responses under Propofol and pentobarbital anesthesia suggests that clinical anesthesia will not suppress the ISMS responses in the first intraoperative experiments in humans, and responses will be comparable with the intraoperative observations in animals.

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**Poster**

**770. Spinal Prosthetics and Stimulation**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 770.08/VV7

**Topic:** E.05. Brain-Machine Interface

**Support:** CHIR
US Department of Defense

**Title:** Safety of intraoperative intraspinal microstimulation - Implications towards functional mapping of the spinal cord

**Authors: *D. S. HU**[1], D. G. EVERAERT[2], A. TOOSSI[2], A. N. DARLYMPLE[2], R. R. E. UWERIA[2], T. ROBINSON[3], R. FOX[2], P. E. KONRAD[4], H. SHAH[4], V. K. MUSHAHWAR[1]
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**Abstract:** The overall goal of this project was to demonstrate the safety of our intraspinal microstimulation (ISMS) paradigm for human implantation. Exploration of the neural circuits in the spinal cord dates to the work of Sherrington. ISMS has garnered attention as an attractive approach for exploring and activating these circuits. Here, we tested the safety of using ISMS in the lumbar region of the cord in an intraoperative setting. This work provides the translational support for the use of ISMS to investigate spinal neural networks in humans.
Experiments were conducted in 8 Yucatan minipigs (37-47 kg, 10-11 month old). The pigs were trained to walk across a 3-m walkway. Gait analysis was performed based on bilateral 3D kinematics and wireless surface electromyography. Both experimental (n=5) and sham groups (n=1) underwent a two-level laminectomy to expose the lumbar-enlargement of the spinal cord and a stereotactic frame was mounted. Small cuts in the pia mater to advance microelectrodes in the spinal cord were made in both groups, but only the experimental group received electrode insertions in 8-12 different locations in one side of the spinal cord. For each insertion, electrical stimuli were delivered (biphasic pulses, 50 Hz, 200 μs, up to 150uA in amplitude) and the movements evoked in the ipsilateral hindlimb were quantified. Over a 4-week period post-operatively, motor function was assessed with gait analysis and a quantitative grading scale developed for swine, the Porcine Thoracic Injury Behavioral Scale (PTIBS). Examination of sensory and autonomic functions focused on observations of pain-like behaviors, reflexive responses, and bladder function.
Results to date show that as early as 2 weeks post-operatively, PTIBS scores return to their baseline levels. Interestingly, during the first 1-2 weeks, both sham and experimental groups exhibited similar transient bilateral functional deficits that were corroborated with their PTIBS scores. All reflexes remained present post-operatively and no signs of spasticity were seen post-operatively.
These preliminary findings suggest that intraoperative use of ISMS may be a safe procedure for exploring the neural circuits in the spinal cord and may be used for investigating the functional organization of locomotor networks in humans. We also demonstrate that ISMS produces functional leg movements in an animal model (Yucatan pigs) with spine and spinal cord morphologies that best resemble those of humans.

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**Poster**

**770. Spinal Prosthetics and Stimulation**

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**Program #/Poster #:** 770.09/VV8

**Topic:** E.05. Brain-Machine Interface

**Support:** RGPIN-2014-05498
RGPIN-2016-06329
NSERC Alexander Graham Bell Canada Graduate Scholarship-Doctoral Program

**Title:** Discriminating naturally evoked compound action potentials from nerve cuff recordings with convolutional neural networks

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**Abstract:** Neural signals from the peripheral nervous system could provide information for robust control in neuroprosthetic and neuromodulation applications, but it is difficult to develop methods to extract this encoded information reliably without damaging the nerve. Extraneural recordings from multi-channel nerve cuff electrodes can reflect the location of neural sources within the nerve and their conduction velocity. Spatiotemporal patterns across contacts in these devices can thus be used to characterize compound action potentials (CAP) associated with specific neural sources of interest. Based on these spatiotemporal patterns, this study used convolutional neural networks (CNN) to discriminate naturally evoked CAPs from different neural pathways.

9 Long-Evan rats were implanted with a 56-channel spiral nerve cuff electrode (7 rings x 8 contacts) on the sciatic nerve. Afferent activity was selectively evoked within three fascicles of the sciatic nerve (tibial, peroneal, sural) using mechanical stimuli. After spike detection, the spatiotemporal patterns of the CAPs recorded (56 contacts x 100 time samples) were used as inputs into a CNN that assigned each CAP to a neural source. For comparison, these same inputs were used to create a tailored match filter for each neural activity, as described in previous literature.

Two factors affecting the spatiotemporal patterns were additionally investigated for their effects on the discriminability of CAPs: the reference montage (tripolar, common average and tripole applied based on groups of 3 consecutive rings), and the ordering of contacts (by ring vs by row in the 7x8 grid, to emphasize spatial vs temporal information).

3-fold cross-validation of detected CAPs was used for evaluation, and performance of the CNN

was measured based on the classification accuracy and $F_1$-score. The mean classification and $F_1$-score for the 3-class problem can be seen in Table 1.

This study demonstrates that CNNs can be used to classify naturally evoked CAPs using a multi-contact nerve cuff electrode. These findings are a significant step in achieving closed-loop applications in neuromodulation and neuroprosthetics.

**Table 1**. Classification accuracies and corresponding $F_1$-score

| **Tripolar Reference** | Classification Accuracy (%) | $F_1$-score |
|---|---|---|
| Match Filter – SE | 51.0±10.8 | 0.446±0.157 |
| Match Filter – TE | 43.3±7.6 | 0.395±0.072 |
| CNN – SE | 75.9±12.5 | 0.672±0.119 |
| CNN – TE | 75.0±12.4 | 0.662±0.113 |
| CNN – SE + TE | **78.0±11.5*** | **0.696±0.116*** |
| **Common Average Reference** | | |
| Match Filter – SE | 50.3±11.1 | 0.440±0.050 |
| Match Filter – TE | 42.8±6.7 | 0.388±0.065 |
| CNN – SE | 76.3±11.8 | 0.679±0.110 |
| CNN – TE | 74.4±12.7 | 0.658±0.117 |
| CNN – SE + TE | **77.8±11.8** | **0.694±0.118** |
| **cTPR Reference** | | |
| Match Filter – SE | 49.3±10.6 | 0.429±0.053 |
| Match Filter – TE | 41.8±8.4 | 0.375±0.080 |
| CNN – SE | 71.7±11.8 | 0.624±0.107 |
| CNN – TE | 68.6±12.4 | 0.595±0.105 |
| CNN – SE + TE | **73.5±11.7** | **0.642±0.114** |

* Highest score from all configurations,
SE – Spatial Emphasis
TE –Temporal Emphasis
cTPR – Tripole applied based on groups of 3 consecutive rings

**Disclosures: R. Koh:** None. **A.I. Nachman:** None. **J. Zariffa:** None.

**Poster**

**770. Spinal Prosthetics and Stimulation**

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**Program #/Poster #:** 770.10/VV9

**Topic:** E.05. Brain-Machine Interface

**Support:** DOD W81XWH-15-0332
NIH 1DP2EB022357-01

**Title:** Spinal cord neural interface for neuroprosthetics in a primate model

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**Abstract:** Due to the loss of voluntary control over arm and hand movements, individuals with spinal cord injury has to depend on caregivers to perform activities of daily living. In these individuals, restoring upper extremity functions would lead to an increased level of independence and improved quality of life. In this work, we describe efforts to construct a spinal cord neural interface in a primate model to explore the feasibility, long-term stability, and decoding capability of signals recorded from a marmoset spinal cord. The common marmoset (*Callithrix jacchus*) has been proposed as a suitable bridge between rodents and larger primates. Two adult male marmosets were used in this study. Neural data was recorded from 16-channel tungsten microwire arrays, (Tucker Davis Technologies, Alachua FL) and spinal data from 13-channel floating microelectrode array, (MicroProbes, Gaithersburg, MD). Recordings were collected using a Tucker Davis Technologies RZ2 system sampling at 24,414Hz and a band-pass filter 300-5000Hz. Local Field Potentials (LFPs) were acquired with a 1-500Hz band-pass filter. Spikes and LFPs of cortical signals were compared against spinal cord signals. The mutual information between the motor and spinal cord channels were calculated. A linear support vector machine was used for decoding rest, plan and move states. Subpopulation of the pairs of spinal cord units analyzed, synchrony occurred during planning, at movement onset, or during movement. The decoder was able to separate the rest/plan/move states from spinal cord signals with 60%-70% accuracy, where the chance performance was 33%. Results indicated that there were task related modulation in activity from both neuronal spiking and LFP activity, with the high gamma frequency band following a similar trend to multiunit activity. Temporal changes in power with respect to baseline were used to illustrate the relationships between LFP to spiking activity in the MI of the marmoset. The SVM algorithm could classify the target directions for features of both spiking and LFPs. The ability to chronically record cortical and spinal signals for neural prosthetics applications in the common marmoset extends the potential of this small non-human primate model in neural interface research.

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**Poster**

**770. Spinal Prosthetics and Stimulation**

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**Program #/Poster #:** 770.11/VV10

**Topic:** E.05. Brain-Machine Interface

**Support:** NIH Grant K12HD073945

**Title:** Intraspinal microstimulation for motor rehabilitation modulates neural transmission in pain pathways of the deep dorsal horn

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**Abstract:** Spinal cord injury (SCI) results in dramatic changes in neural excitability below the lesion, leading to debilitating motor impairments, dysregulation of reflexes, and neuropathic pain. Broadly, voluntary motor output is reduced below the lesion, whereas the spinal effects of sensory feedback become pathologically increased, contributing to hyperreflexia and neuropathic pain. Therapies seeking to restore sensorimotor function after SCI therefore face a dual challenge: increasing spinal motor output in response to descending motor commands while decreasing the spinal responses to sensory feedback that contribute to hyperreflexia and pain. Here, we characterized the ability of electrical intraspinal microstimulation (ISMS) of the ventral horn, which can increase spinal motor output, to concurrently reduce transmission in spinal pain pathways. All experiments were approved by the FIU IACUC and conducted in adult Sprague-Dawley rats under urethane anesthesia. After T13-L2 laminectomy, electrode arrays were implanted at the L5 dorsal root entry zone. Electrodes locations for ventral ISMS targeted Laminae 8-9 and electrode locations for quantifying transmission in pain pathways targeted Laminae 3-6 of the dorsal horn. We then identified convergent interneurons in the deep dorsal horn based on their responses to painful and non-painful mechanical stimulation of the peripheral receptive field.
We delivered open-loop ventral ISMS while recording extracellularly from convergent interneurons. Prior to and after ISMS, we mechanically stimulated the peripheral receptive field by applying controlled forces of varying magnitude (ranging from non-painful to painful). We found that even short periods of ventral ISMS could modulate transmission in convergent interneurons of the deep dorsal horn, often reducing neural transmission associated with painful peripheral stimuli. We also report band-specific changes in intraspinal local field potential power throughout the ventral and dorsal horns associated with ventral ISMS. The mechanisms by which ventral ISMS reduces transmission in deep dorsal horn pain pathways are unknown, but could be related to trans-synaptic activation of low-threshold, non-pain-related inputs to convergent interneurons, which could suppress, or gate, their response to painful stimuli.

Our results demonstrate that neuroprosthetic therapies using ventral ISMS to increase motor output have the potential to simultaneously reduce transmission in spinal pain pathways. Future work is required to optimize these effects and to establish limits for avoiding unintended increases in pain-related neural activity.

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**Poster**

**770. Spinal Prosthetics and Stimulation**

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**Program #/Poster #:** 770.12/VV11

**Topic:** E.07. Rhythmic Motor Pattern Generation

**Support:** The Scottish Government Health Directives

**Title:** The impact of BDNF rs6265 mutation on changes in explosive jump performance after direct current spinal stimulation

**Authors: *H. R. BERRY**[1,2], R. J. TATE[3], B. A. CONWAY[2]
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**Abstract:** We recently found that anodal transcutaneous spinal direct current stimulation (tsDCS) alters the performance of repeated countermovement (CM) vertical jumps via effects on central fatigue mechanisms, however there was significant between subject variability. Brain-derived neurotrophic factor (BDNF) is a key mediator of activity-based neuroplasticity. Carriers of the *BDNF* rs6265 (p.valine66methionine) single nucleotide polymorphism (Met SNP) secrete less BDNF and have altered neuroplastic responses to tsDCS compared to wildtype Val66Val carriers. Accordingly, we investigated whether *BDNF* rs6265 Met SNP carriers display differential changes (Δ) in jump performance when compared to wildtypes following sham and anodal tsDCS. Using a double-blind, randomized, crossover design, 27 (18 male) healthy participants performed 3 sets of 5 explosive jumps prior to and at 20 and 60 min after a single application of sham and active anodal tsDCS. Performance was assessed from ground reaction force (GRF) measurements and cheek swabs were taken for *BDNF* genotyping. Informed consent was provided and the study was approved by the University of Strathclyde Ethics Committee. Irrespective of treatment, Met SNP carriers (12; 8 male) differed from wildtypes (mean difference, 95% CI) in the magnitude and direction of change in ΔCM deceleration (-13%, -22, -5%, $p = 0.001$), velocity (-4%, -8, -1, $p = 0.014$) and power (-7%, -11, -2% $p = 0.005$), transition phase GRF (-11%, -17, -4%, $p = 0.001$) and peak jump GRF (-4%, -7, -1%, $p = 0.019$). After anodal tsDCS, wildtypes reduced, and Met SNPs increased their CM duration (11%, 4—17%, $P < 0.001$) but the post-sham fatigue in final take off velocity was prevented for both

groups (2%, 1, 3%, p = 0.029). Effects were similar at 20 and 60 min and for both sexes (p > 0.05). Our results demonstrate lasting but differential changes in jump performance according to *BDNF* rs6265 genotype and tsDCS treatment, which were most pronounced during CM. Irrespective of tsDCS treatment, Met SNP carriers experienced greater deterioration in peak CM performance and transition GRF than wildtypes. After active tsDCS, and compared to sham, they slowed but maintained their CM performance, GRF values and take off velocity, whereas wildtypes increased their CM speed and performance, peak jump GRF and maintained take off velocity. The results highlight jump phase dependent differences in fatigue processes and response to tsDCS between *BDNF* genotypes. We conclude that genetic profiling is an important consideration when investigating neuromodulation interventions for sports training or neurorehabilitation.

**Disclosures: H.R. Berry:** None. **R.J. Tate:** None. **B.A. Conway:** None.

**Poster**

**771. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 771.01/VV12

**Topic:** E.09. Motor Neurons and Muscle

**Support:** NIH R01 HD090642
NIH F31NS093855
Banting Postdoctoral Fellowship

**Title:** Muscle spindle Ia afferent firing rate mirrors eccentric muscle fiber force

**Authors: *B. C. HORSLEN**[1], K. S. CAMPBELL[2], K. P. BLUM[1], T. C. COPE[3], P. NARDELLI[4], L. H. TING[1]
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**Abstract:** We hypothesize actin-myosin crossbridge cycling dynamics in intrafusal muscle fibers govern muscle spindle movement-history-dependence that is thought to impact human postural behaviors. History dependence manifests in muscle spindle Ia afferent dynamic responses when the muscle has been held at a constant length and then stretched, similar to what occurs to a muscle during perturbations to standing balance; if the muscle is stretched, shortened, and stretched again, the muscle spindle afferent response is attenuated, i.e. history dependent. This history-dependence has been attributed to history-dependent changes to in-series muscle fiber short-range stiffness (SRS). However, we do not know how small pre-stretch amplitudes, on the

order of human postural sway, impact muscle spindle and muscle fiber SRS history dependence. Therefore, our objective was to perform parallel experiments in muscle spindles and isolated muscle fibers to characterize responses to eccentric stretch profiles after a range of conditioning stretch amplitudes and time intervals. We predicted larger conditioning stretch amplitude and shorter time intervals between conditioning and test stretches would reduce Ia afferent firing rate and muscle fiber SRS, consistent with a common crossbridge mechanism of history-dependence.We targeted stretch amplitudes within the range of healthy human postural sway (<1% length change) as well as large amplitudes analogous to destabilizing balance perturbations (up to 3.8% length change). Large 3.8% conditioning stretches (fibers: 0.046 μm/half sarcomere; spindles: 1.67mm) caused significant reduction in SRS and afferent firing at 1ms time intervals, yet SRS and initial burst amplitude returned to unconditioned levels by 1s and 3.2s, respectively. SRS and initial burst amplitudes also decreased as conditioning amplitude increased. However, consistent with the idea that healthy sway does not impede robust early reactions to perturbations, both muscle fiber SRS and muscle spindle initial burst were unaffected by conditioning stretches smaller than 0.4%.We conclude history-dependence in muscle spindle Ia afferent firing rate is determined by muscle fiber mechanics because changes to muscle spindle Ia afferent firing rate mirror changes to muscle fiber stiffness. While small amplitude conditioning stretches had minimal impact on Ia afferent firing or SRS, we hypothesize increasing amplitude of sway variability (e.g. with aging or neurological disorder) may lead to balance and general motor impairment by reducing muscle spindle stretch encoding, and ultimately diminishing and/or delaying sensorimotor responses.

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**Poster**

**771. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 771.02/VV13

**Topic:** E.09. Motor Neurons and Muscle

**Support:** NIH P01 NS-057228

**Title:** Relocation of the axonal initial segment in lumbar motoneurons of rats receiving chemotherapy

**Authors: *D. I. CARRASCO**, P. NARDELLI, S. N. HOUSLEY, T. COPE
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**Abstract:** Preliminary findings from our lab (see Nardelli et. al. poster) show that chronic treatment with Oxaliplatin (C-OX) disrupts repetitive firing of rats motoneurons (MNs), i.e. C-OX significantly *reduces* MN excitability. Other preliminary findings from our lab (see Housley et. al. poster) show that acute OX treatment (A-OX) significantly increase the spontaneous activity of rat MN i.e. A-OX *increases* MN excitability. We hypothesize that the chronic hypo-excitability reflects a compensatory mechanism. Among possible mechanisms, we considered the change in the MN axon initial segment (AIS). Recent studies have shown that increased neural activity can displace the AIS away from the soma and reduce neuron excitability. These observations led us to evaluate AIS location in MNs of C-OX rats. Spinal cord sections from C-OX and untreated controls rats were incubated with an antibody that recognized Ankyrin-G (Ank-G), a membrane scaffold protein present mainly at the AIS, and the voltage-gated sodium channel isoform 1.6 (NaV1.6). These preliminary results show that the average AIS distance from the soma was 52% longer in C-OX than in the untreated controls. AIS length showed no significant difference among groups. NaV1.6 relocated together with Ank-G. These findings are consistent with a compensatory response to hyperexcitability in A-OX rats, whereby AIS shifts away from the MN soma to reduce excitability.

**Disclosures: D.I. Carrasco:** None. **P. Nardelli:** None. **S.N. Housley:** None. **T. Cope:** None.

**Poster**

**771. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 771.03/VV14

**Topic:** E.09. Motor Neurons and Muscle

**Support:** P01 NS-057228

**Title:** Chronic defects in repetitive of spinal motoneurons from a decrease in persistent inward current after chemotherapy

**Authors: *P. NARDELLI**[1], S. N. HOUSLEY[1], D. I. CARRASCO[1], R. K. POWERS[2], T. C. COPE[1]
[1]Sch. of Biol. Sci., Georgia Inst. of Technol., Atlanta, GA; [2]Dept Physiol & Biophysics, Univ. Washington, Seattle, WA

**Abstract:** For years after chronic chemotherapy, Oxaliplatin (OX) causes many debilitating peripheral effects including sensory ataxia and paresthesia. Previous in vivo studies (Bullinger et al 2011, Vincent et al 2015) of rats, weeks after a full treatment course of OX, show that muscle spindle afferents have lost the ability to encode sustained muscle stretch. These findings are consistent with a decrease in Persistent Inward Currents (PICs), and encouraged us to

investigate, for the first time, if this deficit extends to a neuron in the CNS. We hypothesized that chronic OX causes deficits in the repetitive firing of motoneurons (MNs) due to a decrease in PICs. MN firing was measured in terminal experiments on adult F344-Pirc (model of colon cancer) rats anesthetized with isoflurane, following OX treatment. Repetitive firing was elicited during 5 second, square pulse current injections. In response, MN's fired erratically and included pauses of up to 1 second, decreasing force production of the motor unit significantly. Using computer simulations, decreasing the ratio of Na PIC to K conductances reproduced defective MN firing. Using dynamic clamp, in vivo, control MNs showed similar deficits in repetitive firing when decreasing PIC via manipulation of Na and K conductances predicted by the simulation. In OX treated rats, repetitive MN firing was rescued when increasing PIC via dynamic clamp which in turn rescued motor unit force. Finally, an FDA approved serotonergic agonist that increases PIC was administered acutely while recording from MNs in OX rats. The increase in PIC, also rescued MN firing and motor unit force production to control levels. Collectively, these preliminary findings support our hypothesis that defective MN firing with chronic OX results from a net decrease in PIC.

**Disclosures: P. Nardelli:** None. **S.N. Housley:** None. **D.I. Carrasco:** None. **R.K. Powers:** None. **T.C. Cope:** None.

**Poster**

**771. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 771.04/VV15

**Topic:** E.09. Motor Neurons and Muscle

**Support:** P01 NS-057228

**Title:** Origin of acute chemotherapy induced spontaneous activity

**Authors: *S. N. HOUSLEY**[1], J. A. VINCENT[2], P. NARDELLI[1], D. I. CARRASCO[1], T. C. COPE[1]
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**Abstract:** Pain, dysesthesias, cramps, fasciculations, and spasms are among the principle dose-limiting side effects afflicting nearly all cancer survivors treated with platinum-based chemotherapy. This constellation of symptoms known as chemotherapy-induced peripheral neuropathy (CIPN) diminishes quality of life and limits functional capacity. Acute CIPN is consistently attributed to spontaneous motor and sensory activity. Although the evidence is largely indirect, spontaneous activity is believed to originate at ectopic sites in the peripheral

nervous system outside the normal action potential initiation zones. *In-vitro* studies of motor, sensory, and dorsal root ganglia provide evidence for an ectopic location of origin for spontaneous firing. Unfortunately, these experimental models have failed to accurately reproduce the necessary circumstances to probe the mechanistic underpinnings of spontaneous firing. Methodological limitations that
influence excitability independent of chemotherapy (e.g. transection of the cervical spinal cord and ventral root) reduce external validity. Therefore, the goal of this study was to determine the origins of spontaneous firing induced by platinum-based chemotherapy in sensory and motor neurons. Our preclinical model in rats enabled *in vivo* implementation of electrophysiological techniques capable of localizing the origin of spontaneously activity in intact sensory and motor neurons. To determine the origin of spontaneous motor activity, we spike trigger averaged from synchronous single-unit EMG and ventral root recordings. To determine the origin of spontaneous sensory activity, we spike trigger averaged from single Ia afferents and peripheral nerves recordings. The results were unequivocal in demonstrating that spontaneous activity originated at or near the primary sensory endings of group Ia muscle afferents and at or near the soma/initial segment of motor neurons within central nervous system. Our findings provide the first *in-vivo* demonstration of the site of spontaneous motor and sensory activity and raise further uncertainty about the involvement of ectopic firing for the treatment of acute CIPN.

**Disclosures: S.N. Housley:** None. **J.A. Vincent:** None. **P. Nardelli:** None. **D.I. Carrasco:** None. **T.C. Cope:** None.

**Poster**

**771. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 771.05/VV16

**Topic:** E.09. Motor Neurons and Muscle

**Support:** NIH R01 HD090642
NIH F31NS093855

**Title:** Muscle spindle primary afferents transduce intrafusal muscle force differentially in healthy and impaired function

**Authors: *K. P. BLUM**[1], K. S. CAMPBELL[2], P. NARDELLI[3], S. N. HOUSLEY[3], T. C. COPE[4], L. H. TING[5]
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**Abstract:** To facilitate more realistic simulations and predictions of muscle spindle activity in normal and impaired sensorimotor control, we introduce a new model of muscle spindle mechanotransduction based on history-dependent forces in muscle fibers. History-dependence in muscle spindles is likely critical to normal and abnormal sensorimotor behavior mediated by spinal and brainstem circuits, as it reduces muscle spindle sensitivity to stretch based on prior movement. However, current muscle spindle models are not history-dependent, assuming a unique relationship between muscle spindle firing and muscle stretch kinematics. Here we developed a mechanistic model based on our recent work showing that muscle spindle stretch responses have a unique relationship with history-dependent eccentric muscle force and its first time derivative, yank, but not with imposed stretch kinematics (Blum et al 2017). We hypothesized that history-dependent muscle spindle spiking responses could be predicted by simulating cross-bridge population cycling kinetics in conjunction with a conductance-based model neuron. History-dependent muscle fiber forces can be reproduced by simulating muscle cross-bridge cycling kinetics, but not in phenomenological descriptions of muscle contraction often used in muscle spindle models. Ours is the first to be capable of generating muscle spindle responses to a ramp-hold perturbation classically described by initial bursts, dynamic response, and rate adaptation, as well as history-dependent responses caused by prior movement of the muscle. Surprisingly, our model predicted several features of muscle spindle firing that we did not anticipate. By varying relative sensitivities of the model neuron to simulated intrafusal force and yank, we produced a large set of spiking response phenotypes spanning experimentally-observed ranges of initial burst amplitudes and dynamic responses observed in the classical muscle spindle literature, including the history-dependence of these features. Further, our model predicted phenotypes of muscle spindle dysfunction observed in perturbed condition including reduction of sustained responses after with oxaliplatin chemotherapy, and reduction of initial bursts with nerve stimulation. Such a model could be used to simulate the effects of muscle activation level and changes in neural dynamics on muscle spindle firing, which are known to be altered in both normal and impaired sensorimotor control. Our neuromechanical muscle spindle model provides a multiscale framework for simulating the effects of muscle properties, neuron biophysics, and gamma drive on the firing of muscle spindle afferents.

**Disclosures: K.P. Blum:** None. **K.S. Campbell:** None. **P. Nardelli:** None. **S.N. Housley:** None. **T.C. Cope:** None. **L.H. Ting:** None.

**Poster**

**771. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 771.06/VV17

**Topic:** E.09. Motor Neurons and Muscle

**Title:** Human ips cell-derived motor neurons for modeling neurological diseases and drug screening

**Authors: *N. LIN**[1], D. WU[2], L. ZHANG[2]
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**Abstract:** In this study, we developed a robust method to produce highly pure, functional validated motor neurons from human induced pluripotent stem cells (iPSC), which can be used in neurological disease modeling studies. Using xeno-free differentiation conditions, we were able to produce motor neurons from human iPSC, at greater than 85% purity as measured by immunostaining of ISL1, HB9, ChAT and Tuj1. iXCells™ hiPSC-derived motor neurons are functionally verified by neuromuscular junction assay, and electrophysiological assay using a multi-electrode array (MEA) system. These cells can be cryopreserved, thawed, and cultured in defined maintenance media without glia cells. They can also be co-cultured with primary astrocytes for extended periods (>30 days) without losing featured motor neuron markers. Using iPSC lines from multiple donors, including Amyotrophic Lateral Sclerosis (ALS) patients, we have demonstrated the protocol is robust, and independent of the donor iPSC lines. We developed ALS isogenic models carrying multiple mutations in TDP-43 gene, which were used for transcriptome analysis with RNA-seq. Taken together, these data show that our protocol is reproducible in human iPSCs, and is applicable in modeling MN-degenerative diseases and in proof-of-principle drug-screening assays.

**Disclosures: N. Lin:** None. **D. Wu:** None. **L. Zhang:** None.

**Poster**

**771. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 771.07/VV18

**Topic:** E.09. Motor Neurons and Muscle

**Support:** NIH R56NS099092
NIH R01NS57190
NSF 1444932

**Title:** The role of microglia in synaptic plasticity around axotomized spinal motoneurons

**Authors: *E. T. AKHTER**[1], T. M. ROTTERMAN[2], A. R. LANE[2], A. W. ENGLISH[3], F. J. ALVAREZ[2]
[1]Cell Biol. & Physiol., [2]Physiol., Emory Univ., Atlanta, GA; [3]Dept Cell Biol., Emory Univ. Sch. of Med., Atlanta, GA

**Abstract:** Following peripheral nerve injury (PNI) there are significant alterations in the cellular properties and synaptic organization of axotomized motoneurons (MNs). These include alterations in MN membrane properties and loss of synaptic inputs on MN soma and proximal dendrites. Synaptic loss mainly affects excitatory over inhibitory synapses, but despite the partial maintenance of inhibitory synapses, their driving force decreases due to downregulation of the potassium chloride cotransporter-2 (KCC2). Most synaptic inputs and KCC2 revert to normal levels after MNs regenerate and reinnervate muscle; however, excitatory VGLUT1 synapses originating from proprioceptors (Ia and II fibers) also axotomized by PNI are permanently degraded and do not return. Synaptic plasticity, as well as KCC2 downregulation, have been related to microglial activation, but other experimental evidence has disputed microglia's role. To directly test the role of microglia we analyzed whether the microglial reaction around axotomized MNs can be attenuated by genetically deleting the gene for colony stimulating factor 1 (*csf1*) from *Chat-cre* expressing MNs. Male and female adult *Chat::csf1*$^{f/f}$ (n=5animals) or *csf1*$^{f/f}$ control (n=5) mice underwent a unilateral sciatic nerve transection one week after the lateral gastrocnemius (LG) MNs pools in both sides of the spinal cord were retrogradely labeled with Fast Blue (FB). The cell bodies of FB-labeled MNs were analyzed (blind) ipsilateral and contralateral to the injury at fourteen days after injury (peak of microglia activation) for the presence of KCC2 immunoreactivity, as well as VGLUT1, VGLUT2 and VGAT synapses. After deletion of *csf1* from MNs, ventral horn Iba1+ microglia showed no proliferation, lower tropism towards the cell bodies of axotomized MNs and lower upregulation of CD68 (a phagocytic marker); however, our preliminary data show that synaptic and KCC2 downregulation occurred normally. These findings indicate that ventral microglia are activated by *csf1* released from MNs and that despite commonly accepted ideas, microglia are not responsible for transient removal of excitatory synapses from the MN cell body or changes in the driving force of inhibitory synapses on MN following PNI. However, microglia activation seems necessary for preventing recovery of VGLUT1 synapses in animals in which regeneration was allowed and that were analyzed after muscle reinnervation 8 weeks after injury. These results suggest that microglia are more closely associated with the permanent deletion of the central synapses originating in peripherally injured axons than stripping of all types of synapses from the cell body of axotomized MNs.

**Disclosures: E.T. Akhter:** None. **T.M. Rotterman:** None. **A.R. Lane:** None. **A.W. English:** None. **F.J. Alvarez:** None.

**Poster**

**771. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 771.08/VV19

**Topic:** E.09. Motor Neurons and Muscle

**Support:** NIH Grant R56NS099092
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**Title:** Two-photon live imaging of microglia interactions with adult motoneurons axotomized after nerve injury

**Authors: *T. M. ROTTERMAN**, F. J. ALVAREZ
Physiol., Emory Univ., Atlanta, GA

**Abstract:** Microglia are in constant motion surveying the parenchyma sensing for any disruptions in homeostasis. Following sciatic nerve injury (SNI) microglia respond rapidly by retracting their processes, proliferating, and migrating towards the cell bodies of axotomized motoneurons in the spinal cord ventral horn. These changes are associated with a pro-inflammatory state, increased phagocytosis, and the stripping of synapses from motoneuron (MN) cell bodies; however, whether microglia are necessary for synapse removal remains a topic of debate. To gain insight into the interactions between activated microglia and MNs after SNI, we developed an adult spinal cord slice preparation in CX3CR1-GFP mice to image microglia and CTB-555 labeled MNs using 4D time-lapse two-photon microscopy (30-40 minutes recording sessions; 30-40 seconds per volume frame). We validated the preparation by testing microglia activation due to slicing (morphological changes, CD68 expression) and found this to be minimal during the first 4-5 hours after slicing. Then we measured the change in microglia surface area over 30-mins of recording. Individual processes or endings displayed similar motility in injured and control sides (2.2 - 4.0 µm/min), but while process elongations were matched by retractions in the control side, these occurred more randomly ipsilateral to the injury resulting in a greater rate of change of microglia surface area per frame (4.4% ±0.5 surface change; ±SEM) compared to controls (1.7% ±0.4). Microglia responding to injury also significantly increased the number of phagocytic cups compared to controls (15.8 ±2.6 cups per 30 mins of recording, control: 3.0 ±1.0). However, cups durations did not differ between conditions. Lastly, we analyzed the interaction between microglia and MNs at different times after injury. In the control side microglia broadly surveyed the surface of MNs without any specific directionality, however, 7 days after SNI microglia processes were directed towards the MN surface where they form phagocytic cups and then are retracted. Ten days after injury the nature of the interaction changed. Now microglia attached to the MN cell body surface displaying minimal movement except for filopodia constantly surveying the MN surface. In normal control animals only 3.2% ±0.6% of the MN cell body surface is in contact with microglia, however 14 days after SNI 25.3% ±2.1% of this surface is covered. Although at this time point phagocytic cups are not visible the microglia side opposite to the MN gets enriched with CD68 granules. These observations highlight the dynamic nature of microglia interactions with axotomized MNs and how it changes with time after injury.

**Disclosures: T.M. Rotterman:** None. **F.J. Alvarez:** None.

**Poster**

**771. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 771.09/VV20

**Topic:** E.09. Motor Neurons and Muscle

**Support:** NIH R01 NS 082463
Barrow Neurological Foundation

**Title:** Propriospinal and corticospinal postsynaptic potentials in lumbar motoneurons following moderate spinal cord contusion injury and exercise

**Authors: *V. V. TURKIN**[1], D. O'NEILL[1], B. T. JONES[2], T. M. HAMM[1]
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**Abstract:** Previous studies demonstrating plasticity in corticospinal pathways following either hemisection (Bareyre et al., 2004; Courtine et al. 2008) or mild contusion spinal cord injury (SCI) (Hunanyan et al., 2013) present evidence for formation of novel corticospinal pathways via propriospinal axons. To investigate such plasticity following a more severe injury, we stimulated the ventrolateral funiculus (VLF) and dorsal corticospinal tract (dCST) and recorded postsynaptic potentials (PSPs) in lumbar motoneurons after a moderate contusion SCI. We also examined the effects of exercise on these synaptic pathways following injury. Rats received sham operations (sham group) or contusion injuries (170 kdynes) at T9/T10. Injured animals were randomly assigned to standard caging (SCI-standard group) or cages with exercise wheels (SCI-exercise group) beginning 2 weeks after injury. In terminal experiments 8-10 weeks after injury, the VLF and dCST were stimulated with tungsten electrodes at T7 (Hunanyan et al., 2013) while intracellular recordings were made in tibial and common peroneal motoneurons. Trains of 5 stimuli at 100 Hz were used to examine transmission through polysynaptic as well as through mono- and di-synaptic pathways. VLF monosynaptic EPSPs found consistently in sham motoneurons were less common in injured animals, and amplitudes were reduced to ~10-20% of those in sham motoneurons. Responses from dCST stimulation were also reduced. Short-latency responses recorded in sham motoneurons, consisting of small disynaptic EPSPs or mixed EPSP-IPSPs, were observed infrequently following injury, and evidence for formation of short-latency alternative pathways to lumbar motoneurons was not found. Late, long-latency responses evident following stimulus trains were observed after both VLF and dCST stimulation. VLF responses tended to be larger in injured animals, being largest in SCI-standard rats. Late dCST IPSPs, found in a minority of cells of sham and SCI-exercise rats, were not observed in SCI-standard rats. Our results do not provide evidence of significant plasticity in short-latency VLF and dCST pathways to motoneurons, although changes occur in long-latency pathways that may be

impacted by exercise. Plasticity may be limited by substantial damage to more ventral white matter as well as dorsal spinal cord, as shown by histology. Despite the substantial loss of short-latency responses, coordination in gait is only mildly impaired at this level of injury (O'Neill et al., 2018; accompanying abstract), suggesting the importance of long-latency pathways or other mechanisms.

**Disclosures: V.V. Turkin:** None. **D. O'Neill:** None. **B.T. Jones:** None. **T.M. Hamm:** None.

**Poster**

**771. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 771.10/VV21

**Topic:** E.09. Motor Neurons and Muscle

**Support:** NIH R01 NS 082463
Barrow Neurological Foundation

**Title:** Analysis of walking gait following moderate spinal cord injury and locomotor exercise

**Authors: D. O'NEILL**[1], T. SLEEM[2], V. V. TURKIN[1], B. T. JONES[3], *T. M. HAMM[1]
[1]Div. Neurobio., Barrow Neurolog. Inst., Phoenix, AZ; [2]Arizona State Univ., Tempe, AZ; [3]Dept. of Anat., Midwestern Univ., Glendale, AZ

**Abstract:** We performed gait analysis in rats that received moderate spinal cord contusion injury to determine the residual effects of injury on coordination following recovery of walking ability. Effects of voluntary exercise on recovery and coordination were also examined. Rats received sham operations (sham group) or contusion injuries (170 kdynes) at T9/T10. Injured animals were randomly assigned to standard caging (SCI-standard group) or cages with exercise wheels (SCI-exercise group) beginning 2 weeks after injury. Video recordings were made as rats crossed a platform pre-injury and at 4 weeks (28dpi) and 8 weeks (56dpi) post injury. Both SCI-standard and –exercise groups recovered good locomotion. Patterns of foot placement were regular (90-95% regularity index), although the number of patterns increased somewhat compared to sham. Locomotion speed decreased in both injury groups with the slowest post-injury speeds recorded in SCI-exercise rats. No significant effects of injury or exercise were observed in the relation of stance/swing phase to cycle duration. Coordination between ipsilateral limbs was examined by determining axial distances between fore- and hind-limbs and stride length. Axial distances were more variable in injured rats, mainly due to a greater tendency to place the hindpaw in front of the forepaw during stepping. This was confirmed by finding that mean hindlimb stride distance was greater than forelimb stride distance after injury. These effects of injury on stride distance were exacerbated in SCI-exercise rats compared with SCI-standard rats. The base of support

(BOS), the distance between contralateral limbs, was greater for hindlimbs than forelimbs. Both hindlimb BOS and lateral distance between ipsilateral fore- and hind-limbs were greater in SCI-standard rats than in sham rats, whereas these measures in SCI-exercise rats were not different from sham. Based on observations of open-field locomotion, this narrower BOS in SCI-exercise rats compared to SCI-standard rats was accompanied by increased truncal instability during stepping, despite the apparent normalization of BOS values. We find that moderate contusion injury results in long-term impairments in coordination between fore- and hindlimbs during locomotion, consistent with loss of propriospinal and corticospinal inputs to motoneurons (Turkin et al., 2018; accompanying abstract). However, these impairments are minimal despite extensive losses in these pathways, suggesting the importance of other mechanisms of coordination. While wheel-cage exercise affects gait parameters following injury, these activity-related adjustments may not be functionally adaptive.

**Disclosures: D. O'Neill:** None. **T. Sleem:** None. **V.V. Turkin:** None. **B.T. Jones:** None. **T.M. Hamm:** None.

**Poster**

**771. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 771.11/VV22

**Topic:** E.09. Motor Neurons and Muscle

**Support:** Læge Sofus Carl Emil Friis og Hustru Olga Dorus Friis' Legat.

**Title:** Spinal motoneurones are not hypoexcitable in the G93A SOD1 mouse model of Amyotrophic Lateral Sclerosis

**Authors: *D. B. JENSEN**, C. F. MEEHAN
Dept. of Neurosci., Univ. of Copenhagen, Copenhagen, Denmark

**Abstract:** Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease with no cure. In vitro studies using embryonic or neonatal preparations from transgenic models of the disease have suggested an increased excitability of motoneurones. In vivo intracellular recordings from adult ALS mouse models however, have produced conflicting findings. Experiments using barbiturate anaesthetised G93A SOD1 mice suggested that some motoneurones are in fact hypo-excitable, defined by an inability to fire repetitively in response to intracellular triangular current injection (Delestree et al 2014). Our own recordings in the G127X SOD1 model using Hypnorm and Midazolam anaesthesia, however, showed no deficits in repetitive firing, but did show increased sodium currents at axon initial segments and increased persistent inward currents. These discrepancies may be due to either differences between models,

symptomatic stages, anaesthesias or technical differences in the recordings. The first step to investigate this was to repeat our original experiments but in the adult G93A mouse (at 71-107 days old) using the same barbiturate anaesthesia. Intracellular recordings were made from antidromically identified spinal motoneurones. Once identified, the motoneurones were tested for repetitive firing ability by intracellular current injections of regular ramps of current through the microelectrode in DCC mode (3 and 8 kHz) using an Axoclamp 2B amplifier. Only cells with membrane potentials more hyperpolarized than -50mV were accepted for analysis and this was confirmed using extracellular potentials upon exciting the cell dorsally. Particular checks were made to ensure that the microelectrodes were properly compensated and correctly passing current. Finally, cells were tested at multiple times to control for initial injury to the membrane immediately after penetration. No significant differences were found between motoneurones from wild type (WT) and G93A mice with respect to the proportion of cells able to fire repetitively (43/46 WT, 86/88 G93A, Fishers Exact Test P=0.3385). Motoneurones in G93A SOD1 mice were significantly more likely to fire action potentials spontaneously (6/62 WT, 35/94 G93A, Fishers Exact Test P<0.0001). This was most obvious upon initial entry. In conclusion, we were unable to find any evidence that spinal motoneurones in the G93A SOD1 model of ALS are hypoexcitable and if anything, the increase in spontaneous firing point towards an increased excitation in this model.

**Disclosures: D.B. Jensen:** None. **C.F. Meehan:** None.

**Poster**

**771. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 771.12/WW1

**Topic:** E.09. Motor Neurons and Muscle

**Support:** NIH R01 NS085167
NIH R01 NS094384

**Title:** Parametric optimization of Vagus Nerve Stimulation for the enhancement of plasticity and recovery of forelimb motor function after peripheral nerve injury

**Authors: *A. D. RUIZ**, M. BILAL, Z. HAIDER, A. SEYEDAHMADI, A. ABUSOMWAN, D. PARMAR, J. TRAN, M. SHETH, M. KHAN, S. HAYS, R. RENNAKER III, M. KILGARD
Texas Biomed. Device Ctr., Univ. of Texas At Dallas, Richardson, TX

**Abstract:** Previous work from our lab has shown that pairing vagus nerve stimulation (VNS) with a motor movement drives substantial neuroplasticity observed by an increase in the cortical representation of the paired movement. Additionally, we have shown that pairing VNS with

rehabilitation improves motor function in rat models of ischemic stroke, hemorrhagic stroke, traumatic brain injury, spinal cord injury and peripheral nerve injury. Currently it is unknown how different stimulation pulse trains of VNS affect functional recovery. In this study we assess three different VNS stimulation pulse trains (4 pulse, 16pulse, and 64 pulse) when paired with rehabilitative training in a model of peripheral nerve injury (PNI). Adult female Sprague-Dawley rats were trained on the isometric pull task, an automated, quantitative measure of forelimb strength. Upon reaching task proficiency, peripheral nerve injuries of the median and ulnar nerves in the right forelimb were performed. Following 5 weeks of home cage recovery, a vagus nerve cuff was implanted onto the left cervical branch of the vagus nerve. One week later, animals were randomly assigned to one of the predetermined pulse train stimulation groups, and received rehabilitative training paired with VNS for 5 weeks. Current results show that all three VNS stimulation trains help animals regain significant motor function by the final week of therapy. However, the rate at which each group shows recovery differs. Animals in the 4 pulse train group appear to recover faster than those in the 64 and 16 pulse train group.

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**Poster**

**771. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 771.13/WW2

**Topic:** E.09. Motor Neurons and Muscle

**Support:** IMSS Grant FIS/IMSS/PROT/G11/925

**Title:** Spinogenesis and plastic changes in the dendritic spines of spinal cord motoneurons after traumatic injury in rats

**Authors: *I. GONZALEZ-BURGOS**[1], E. PORTILLA-DE BUEN[1], H. SALGADO-CEBALLOS[2], D. GONZÁLEZ-TAPIA[3], N. I. MARTÍNEZ-TORRES[4], N. VÁZQUEZ-HERNÁNDEZ[1]
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**Abstract:** Spinal cord injury (SCI) is highly incapacitating, and the neurobiological factors involved in an eventual functional recovery remain uncertain. Plastic changes to dendritic spines are closely related with the functional modifications of behavior. To explore the plastic response

of dendritic spines in motoneurons after SCI, female rats were assigned to either of three groups: Intact (no manipulations), Sham (T9 laminectomy), and SCI (T9 laminectomy and spinal cord contusion). Motor function according to a BBB scale was progressively recovered from week 2 through week 8 postinjury, reaching a plateau through week 16. Dendritic spine density was greater in SCI versus control groups, rostral as well as caudal to the lesion, at 8 and 16 weeks postinjury. Thin, stubby and wide spines were more abundant at both locations and time points, whereas mushroom spines predominated at 2 and 4 months in rostral to the lesion. Filopodia and atypical structures resembling dendritic spines were observed. Synaptophysin content was lower in SCI at the caudal portion at 8 weeks, and was higher at week 16. Spinogenesis in spinal motoneurons may be a crucial plastic response to favor spontaneous recovery after SCI.

**Disclosures: I. Gonzalez-Burgos:** None. **E. Portilla-de Buen:** None. **H. Salgado-Ceballos:** None. **D. González-Tapia:** None. **N.I. Martínez-Torres:** None. **N. Vázquez-Hernández:** None.

**Poster**

**771. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 771.14/WW3

**Topic:** E.09. Motor Neurons and Muscle

**Title:** Novel nanoparticles for gene delivery in motor neurons

**Authors: *C. KHODTHONG**[1], M. L. HENDRICKSON[2], Z.-W. DU[2], L. JUCKEM[1]
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**Abstract:** Cultured human spinal motor neurons are a valuable tool to study basic mechanisms of neural development as well as motor neuron diseases. However, the lack of efficient gene transfer techniques limits the study of gene regulation and the development of gene therapy strategies for motor neuron diseases including amyotrophic lateral sclerosis (ALS) and spinal muscular atrophies (SMA).
One of the major limitations of gene delivery studies is obtaining a pure and consistent population of primary motor neurons. To overcome this, we utilized iPSC-derived human motor neurons from a commercial source (BrainXell) that were produced using a directed differentiation protocol taking human iPSCs to neuroepithelial cells to motor neuron progenitors and finally to motor neurons that were cryopreserved.
Next, we performed a gene delivery optimization and screened more than 200 candidates of cationic polymer and lipid combinations in iPSC-derived human motor neurons. The novel nanoparticles that we identified from the screen offer superior gene delivery in human motor neurons compared to leading commercially available transfection reagents. The ability to safely

and efficiently deliver genetic materials into human motor neurons will enable a wide range of scientific studies from neuronal gene expression modulations to drug discovery screening.

**Disclosures: C. Khodthong:** None. **M.L. Hendrickson:** None. **Z. Du:** None. **L. Juckem:** None.

**Poster**

**771. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 771.15/WW4

**Topic:** E.09. Motor Neurons and Muscle

**Support:** Leona M. and Harry B. Helmsley Charitable Trust
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**Title:** Submaximal marker for investigating peak muscle torque using NMES after paralysis

**Authors: *D. J. ARPIN**[1], G. F. FORREST[2], S. J. HARKEMA[3], E. REJC[1]
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**Abstract:** Spinal cord injury (SCI) results deleterious skeletal muscle adaptations, such as atrophy and loss of lower limb force generating capacity. However, paralyzed skeletal muscle still demonstrates the ability to be reconditioned through various training strategies. This adaptability is critical since mobility can be limited by muscle weakness. Therefore, it is important to assess maximal muscle torque output both before and after participation in rehabilitation protocols to assess whether muscle output may be sufficient for functional recovery, as well as to assess the effectiveness of different rehabilitation protocols on muscle function. However, methods of assessing maximal torque output with neuromuscular electrical stimulation (NMES) are limited in individuals with residual sensation and those at risk of fracture. Therefore, this study examined the relationship between NMES amplitude and muscle torque exerted (recruitment curve) in order to determine whether maximal torque output can be characterized by a submaximal marker. To this end, recruitment curves for knee extensors, knee flexors, and ankle plantarflexors were recorded from 30 individuals (female = 5, male = 25; age = 32.2 + 10.2 years) with motor complete SCI. NMES was delivered starting with an amplitude of 5 mA, and increasing by 5 mA for every subsequent stimulation until either the participant requested to stop the stimulation or the maximum stimulation amplitude (140 mA) was reached. Correlation analyses were performed between the peak slope of the recruitment curve and peak torque, as well as between peak slope and a muscle fatigability index (FI). Our results showed

significant Spearman rho correlations between peak slope and peak torque for the knee extensors ($r = 0.75$, $p < 0.0001$), knee flexors ($r = 0.68$, $p < 0.0001$), and ankle plantarflexors ($r = 0.91$, $p < 0.0001$). These correlations indicate that muscles that show a greater peak slope tend to generate a greater peak torque. Additionally, we found no correlation between peak slope and FI for any of the muscle groups, implying that peak slope is not related to the fatigability of the muscles. Based on our results as well as prior transcutaneous electrical stimulation work, we hypothesize that the peak slope calculated form the recruitment curves of this study may be an indicator of the maximal rate of motor unit recruitment during electrically stimulated contractions. More importantly, we have demonstrated that peak slope, which was achieved at a stimulation intensity that was on average 43% smaller than that corresponding to peak torque, may be used as a submaximal marker for characterizing maximal torque output in individuals with paralysis.

**Disclosures: D.J. Arpin:** None. **G.F. Forrest:** None. **S.J. Harkema:** None. **E. Rejc:** None.

**Poster**

**771. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 771.16/WW5

**Topic:** E.09. Motor Neurons and Muscle

**Support:** NIDILRR-90RE5013

**Title:** Is there a triceps response to biceps tendon tap in hemi-spastic stroke survivors

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**Abstract:** INTRODUCTION The neural mechanisms that contribute to hyperreflexia in individuals with spasticity remain largely unknown. One possibility is that the observed reduction in the reflex threshold may be a manifestation of a motoneuron pool that is easily excitable.. A largely unaddressed issue in humans is whether inteneuronal excitability is also altered. To address this we tested the stretch reflex in the biceps brachii using brisk tendon taps during a passive state on the affected and contralateral sides of four hemiparetic stroke individuals and assessed the triceps response as well. <br />METHODS The forearm was cast and immobilized in a ring mounted to a load cell to record the force exerted at the wrist. Bipolar surface EMGs were recorded from both the biceps brachii and triceps brachii muscles. Tendon reflexes were elicited in both arms of each subject at approximately five second intervals using a tendon hammer. This device contained a load cell attached at the point of contact with the forearm so as to measure the force with which the biceps tendon was struck. The subjects were

asked to remain at rest while a series of stretch reflex trials were performed. The magnitudes of the both the biceps and triceps surface EMG responses were measured by calculating the root mean square(RMS) of the reflex response. Cross correlation analysis between the triceps and biceps response was performed in order to estimate the time delay between the two responses; to assess the possibility of cross-talk. A least squares regression line was fit to the RMS EMG of the reflex responses versus the (force)magnitude of the tendon tap(TT) response, and the slope of this regression line was compared for the involved and contralateral sides of each subject for both muscles.<br />RESULTS Three of the four subjects exhibited a substantially greater slope (reflex/tap force)in the biceps on the impaired side as compared to the unimpaired side under resting conditions. This was true for the triceps response for these subjects also. DISCUSSION Our study shows an exaggerated reflex response in the biceps muscle and as well as a nonzero slope and significant increase in the triceps response to biceps taps as a function of tap force on the affected side only. This data would suggest that the motoneuron(MN) pool on the spastic side is in a hyperexcitable state during rest, and that there is a potential reduction in reciprocal inhibition or a dis-inhibition of the associated inter-neurons.

**Disclosures: N.L. Suresh:** None. **S. Chandra:** None.

**Poster**

**771. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 771.17/WW6

**Topic:** E.09. Motor Neurons and Muscle

**Support:** P01-NS-057228

**Title:** A molecular switch: Kv2.1 currents maintain or suppress repetitive firing in rat lumbar motorneurons

**Authors: S. H. ROMER**[1], *A. S. DEARDORFF[3], R. E. W. FYFFE[2]
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**Abstract:** Kv2.1 channels are widely expressed in the central nervous system including in lumbar motoneurons (MN) where they form distinct clusters in highly regulated signaling ensembles. The clustering properties of Kv2.1 are linked to the gating kinetics of the channel and can impact repetitive firing properties in other neuronal cell types. To determine the contribution that Kv2.1 clustering has on MN firing properties, the inhibitor Stromatoxin was used to block Kv2 currents in whole-cell current clamp electrophysiological recordings. In rat lumbar MNs, Kv2 currents maintain MN repetitive firing properties and membrane excitability. Kv2 currents

may relieve $Na^+$ channel inactivation, permitting shorter interspike intervals and higher repetitive firing rates. Conversely, in the presence of prolonged 10μM glutamate treatment, increased outward current through Kv2.1 channels homeostatically reduce firing rates. These results are consistent with the notion that differential modulation of Kv2.1 channel kinetics allow these channels to act in a variable way across a spectrum of MN activity states. Thus, Kv2.1 acts as a homeostatic molecular switch, and is able to reversibly shift between states to maintain or promote repetitive firing in physiological activity conditions and suppress repetitive firing in high-activity or pathologic conditions.

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**Poster**

**771. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 771.18/WW7

**Topic:** E.09. Motor Neurons and Muscle

**Support:** NIH Grant 1 R15 GM119099-01

**Title:** The marine invertebrate ciona robusta as an animal model to study neuromuscular junction and neurodegenerative disorders

**Authors: *M. HOSSAIN**[1], A. STOLFI[2,3], B. VITRINEL[3], R. WANG[1], J. MIRKOVIC[1], L. CHRISTIAEN[3], M. RUGGIU[1]
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**Abstract:** Tunicates are marine invertebrates and are the closest living relatives to vertebrates. The swimming larva of the tunicate *Ciona robusta* is an emerging animal model to study developmental and evolutionary biology. Its nervous system comprises of a mere 177 neurons distributed rostro-caudally in a brain vesicle, a motor ganglion, and a nerve cord and its larval connectome has been completely mapped. Due to its small size, cellular simplicity, rapid development, and compact genome that has not undergone the duplications seen in vertebrates, *Ciona* is particularly amenable to molecular perturbation and imaging. Here we show that *Ciona* can be a powerful model organism to study neuromuscular junction (NMJ) biology and neurodegenerative and neuromuscular disorders, including congenital myasthenic syndrome (CMS). NOVA1 and NOVA2 are neuron-specific alternative splicing factors and are target antigens in patients with an autoimmune neurodegenerative disorder. One of the targets of NOVA is a neuron-specific splice form of the ubiquitously expressed gene agrin, termed $Z^+$ agrin, that activates the MuSK signaling pathway by interacting with the transmembrane receptor

LRP4, thus promoting clustering of acetylcholine receptors (AChRs) at the postsynaptic terminal. Interestingly, agrin mutations that mimic $Z^-$ agrin cause CMS. We cloned the *Ciona* ortholog of NOVA, which is present as a single copy gene in tunicates, and that of agrin, and characterized their function and expression pattern during larval development. We discovered that, as in vertebrates, agrin also undergoes alternative splicing to generate the $Z^+$ isoforms in *Ciona*, indicating that the Nova-agrin-Lrp4 pathway for AChR clustering is shared between tunicates and mammals. Nova harbors 3 KH type RNA binding domains and specifically recognizes YCAY clusters on pre-mRNA. *Ciona* Nova requires the first 2 KH domains to mediate Z exon inclusion, and it does so via a bipartite intronic splicing enhancer downstream of Z exons. We also discovered a unique function of the N-terminus of *Ciona* Nova that acts as a regulatory switch between two different modes of splicing: a KH1- and KH2-dependent mode, and a second one that is KH3-dependent. Our work establishes the tunicate *Ciona robusta* as a model organism to study synapse biology and neurodegenerative diseases and provides new insights into the function of NOVA.

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**Poster**

**772. Motor Neurons and Muscle: Motor Unit Recordings, Kinematics, and EMG**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 772.01/WW8

**Topic:** E.09. Motor Neurons and Muscle

**Title:** Muscle activation patterns and balance during a sit-to-stand across symmetric and asymmetric initial foot positions in healthy adults

**Authors: *W. JEON**, C. V. MIHOVA, J. L. JENSEN, L. GRIFFIN
Kinesiology and Hlth. Educ., The Univ. of Texas At Austin, Austin, TX

**Abstract:** ***Introduction:*** The sit-to-stand (STS) is an essential daily task that is commonly used for muscle strength and balance assessment in clinical practice. The initial foot position (IFP) is an important strategy determinant of successful STS transfer. The purpose of this study was to examine the effects of IFP on leg muscle activation patterns and balance during and after the STS. ***Methods:*** Three symmetric IFPs (neutral; both knees at 90° flexion, and one-third (S1) and two-thirds (S2) of foot length posterior to the heel of the neutral IFP) and three asymmetric IFPs (neutral non-dominant leg with S1 dominant leg (AS1), with S2 dominant leg (AS2), and S1 non-dominant leg with S2 dominant leg (AS3)) were tested. EMG activity of the tibialis anterior (TA), gastrocnemius (Gas), soleus (Sol), rectus femoris (RF), biceps femoris (BF), and gluteus maximus (GM) were recorded along with the displacement of the center of mass (CoM) during STS in healthy adults. The standard deviation (SD) of ground reaction force (GRF), sway area

(SA) and the power spectrum of center of pressure (CoP) during the stabilization phase (period before entering quite standing after upright) was analyzed. ***Results:*** In all IFPs, the EMG activity of BF and GM was greater and had earlier onset times (15% to 23% and 12 to 19% EMGmax respectively), as IFP moved anteriorly from S2 to neutral, whereas RF decreased (35% to 30%) ($p = 0.01$). In all asymmetric IFPs, the EMG activity of RF, BF, and GM in the posterior leg was greater than the anterior leg ($p = 0.01$). In AS3, however, EMG peak of the TA was higher in the anterior leg ($p = 0.01$). The forward velocity of the CoM (fvCoM) during rising was greatest for the neutral IFP (896 mm/sec) and was smallest for AS3 (650mm/sec) ($p = 0.003$). In the stabilization phase, the SD of GRF on the A-P axis and the SA of the CoP was the largest in N ($2.14 \pm 0.21$ N, $34.94 \pm 3.21$ $mm^2/s$ respectively) and was the smallest in AS3 ($1.21 \pm 0.22$ N, $11.51 \pm 3.88$ $mm^2/s$) ($p = 0.02$, $p = 0.003$). The CoP sway during the stabilization phase in AS3 was primarily at 0-1 Hz, whereas other IFPs were slightly higher (0-3Hz, $p = 0.01$). ***Conclusion:*** The BF and GM participate more in generating forward acceleration as the CoM shifts more anteriorly during rising from a sitting position. This causes postural insatiability after completing upright posture. Thus, the posterior IFP improved balance during the stabilization phase by reducing fvCoM. Also, the greatest TA activity in the anterior leg of AS3 is likely assisted in slowing down fvCoM. Thus, the best balance occurred during the stabilization phase of AS3 with the least amount of time to enter the quiet standing.

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**Poster**

**772. Motor Neurons and Muscle: Motor Unit Recordings, Kinematics, and EMG**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 772.02/WW9

**Topic:** E.09. Motor Neurons and Muscle

**Title:** A preliminary analysis of imperceptible vibrotactile noise on motor unit discharge patterns

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**Abstract:** Gaussian noise stimulation delivered electrically or through vibration has been shown to favorably alter motor behavior (e.g. decreased tremor, increased postural stability, increased agility, etc.); however, only one study has examined the effect of electrical noise stimulation on motor unit (MU) discharge rates and variability. To date, no study examining MU discharge patterns during noise stimulation has had a sham control, nor have they explored the effect of vibration noise stimulation on MU discharge patterns. Therefore, the purpose of this current

study was to examine the MU discharge rate and variability during a constant force contraction of the flexor digitorum superficialis during both imperceptible vibrotactile noise (STIM) and sham (SHAM) conditions. Data was obtained from 18 right-handed, male subjects. Fine wire EMG was collected from the flexor digitorum superficialis while the subject's 4$^{th}$ finger held a constant force of 20% MVC for 30 seconds. The STIM or SHAM perturbation was applied during the middle 10 seconds of contraction (i.e. seconds 10-20). A subset of the data has been analyzed from six subjects, identifying 15 MUs (seven SHAM and eight STIM). This preliminary analysis utilized both frequentist and Bayesian multilevel models to examine how MU discharge rate (Hz) and discharge variability (standard deviation [SD] of rate) are altered during and after the application of STIM. The frequentist discharge rate model suggested a potential interaction effect between STIM and time (p=0.054); the Bayesian model suggests a 92% confidence that discharge rates decreased after STIM was removed (mean decrease 0.92 Hz). The frequentist model for discharge variability revealed a significant interaction between STIM and time (p=0.038); the Bayesian model suggested a 97% confidence that discharge variability decreased after STIM was removed (mean decrease 0.75 SD Hz). Based upon the results of the currently analyzed MUs, there is no effect during STIM on MU discharge patterns (seconds 10-20); however, the removal of STIM (seconds 20-30) decreased descending drive and decreased MU variability. Perceptible levels of vibration at a given frequency are known to have transient effects on MU discharge rate, increasing MU discharge in 0-5 seconds, followed by a decrease in MU discharge. It is possible that the imperceptible vibration causes an undetectable increase in discharge rate followed by a more pronounced decrease in discharge rate, only discernable after the removal of STIM. This hypothesis is partially supported by the observed decrease in MU discharge variability, which is a metric for the number of neural inputs to the lower motor neuron.

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**Poster**

**772. Motor Neurons and Muscle: Motor Unit Recordings, Kinematics, and EMG**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 772.03/WW10

**Topic:** E.09. Motor Neurons and Muscle

**Title:** Changes in corticospinal excitability in muscle shortening or lengthening during repetitive passive movements

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Kasei Univ., Sayama, Japan; [3]Sch. of Allied Hlth. Sciences, Kitasato Univ., Sagamihara, Japan; [4]Kitasato Univ., Sagamihara-Shi, Japan; [5]Kitasato Univ, Sch. Allied Hlth. Sci., Sagamihara-City, Japan; [6]Dept Physiol Sch. Allied Helth Sci, Kitasato Univ., Sagamihara, Japan

**Abstract:** Introduction: Passive movement is often used in rehabilitation for maintaining and improving the range of motion. Studies using a noninvasive brain stimulation device have shown passive movement to influence the activity of the primary motor cortex and to induce neuroplastic changes. Chye *et al.* (2010) reported that corticospinal excitability during passive movement increases with muscle shortening and decreases with muscle lengthening. Edwards *et al.* (2014) reported that the corticospinal excitability in muscle lengthening decreases with repetitive passive movement. However, the corticospinal excitability in muscle shortening has not yet been studied. Therefore, a change in corticospinal excitability on muscle shortening and lengthening during repetitive passive movement was investigated in this study.
Methods: All eight, right-handed, healthy subjects enrolled in the study were seated in comfortable positions. Passive movement induced using an isokinetic motion control device on the right wrist joint was repeated 50 times at 0.15 Hz in the range of 90° (flexion 45° to extension 45°). Transcranial magnetic stimulation (TMS) was performed on the flexor carpi radialis muscle hot spot with the wrist joint in the neutral position, and the motor evoked potential (MEP) was measured 100 times (shortening 50 times, lengthening 50 times) as an index of corticospinal excitability. Background electromyography of >20 μV for 50 ms before TMS was excluded. Z score for each subject was calculated from the obtained MEP amplitude data, and an average value from 10 repetitions was calculated.
Results: Z scores of MEP amplitude increased with both muscle shortening and lengthening by repeated passive movement, but shortening resulted in higher Z scores (initial 10 times: −0.26, last 10 times: 0.41) than lengthening (initial 10 times: −0.18, last 10 times: 0.21).
Discussion: Although corticospinal excitability increases with both muscle shortening and lengthening due to repetitive passive movement, lengthening results in a more activated inhibitory mechanism for passive movement.

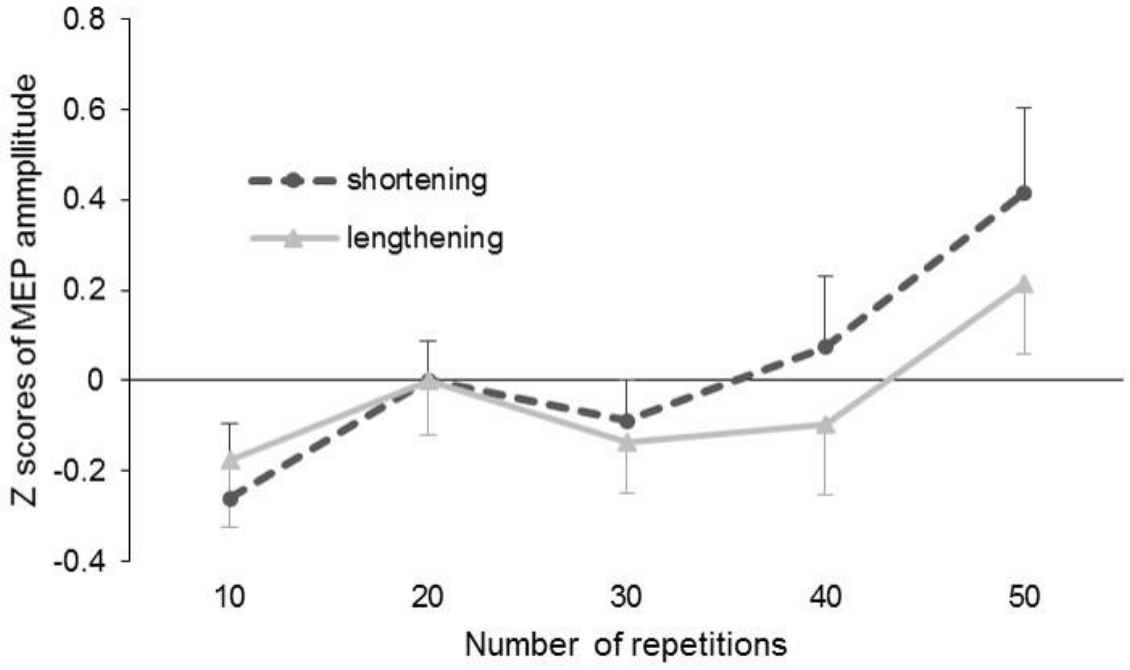


**Figure.** Z scores of MEP amplitude during passive movement

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**Poster**

**772. Motor Neurons and Muscle: Motor Unit Recordings, Kinematics, and EMG**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 772.04/WW11

**Topic:** E.09. Motor Neurons and Muscle

**Title:** Motor unit discharge rates during ischemic sustained submaximal isometric contractions

**Authors: *L. GRIFFIN**[1], R. GREGG[2], M. S. TENAN[3]
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**Abstract:** ***Introduction:*** During blood-flow-restriction exercise, muscle fatigues at a faster rate than under non-ischemic conditions. Mean motor unit discharge rates decrease under non-

ischemic and ischemic conditions during sustained maximal trials, yet to increase during intermittent, submaximal contractions. The purpose of this study was to investigate the effects of ischemia throughout a sustained, submaximal contraction of the tibialis anterior. ***Methods:*** Four males and four females (age: 21.8 ± 1.47 yrs) took part in this study. Fine wire electrodes were used to record the activity of 20 motor units (11 non-ischemic, 9 ischemic) during sustained contractions of 20% maximum voluntary contraction force. Percent change in motor unit discharge rates and the coefficients of variation in motor unit discharge rate were assessed by multilevel statistical models. ***Results:*** All motor units were monitored throughout entire fatigue task. Significant main effects were seen for time ($p < 0.001$), quadratic time ($p= 0.005$), and interaction of time and ischemia ($p=0.033$). ***Conclusion:*** Discharge rates of motor units decrease initially under both ischemic and non-ischemic conditions. While non-ischemic discharge rates recover over the course of the trial, discharge rates for ischemic conditions decreased rapidly, did not recover over the trial, and ultimately resulted in early termination of the task. This was likely due to the influence of Group III and IV afferents in response to metabolic restriction, and their influence on reducing motor neuron drive.

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**Poster**

**772. Motor Neurons and Muscle: Motor Unit Recordings, Kinematics, and EMG**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 772.05/WW12

**Topic:** E.09. Motor Neurons and Muscle

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NSF GRFP to BAC
DOD MR150091 to FJV-C

**Title:** Evaluating the learnability-dimensionality relationship in a tendon-driven finger

**Authors: *B. A. COHN**[1], A. MARJANINEJAD[2], F. J. VALERO-CUEVAS[2,3]
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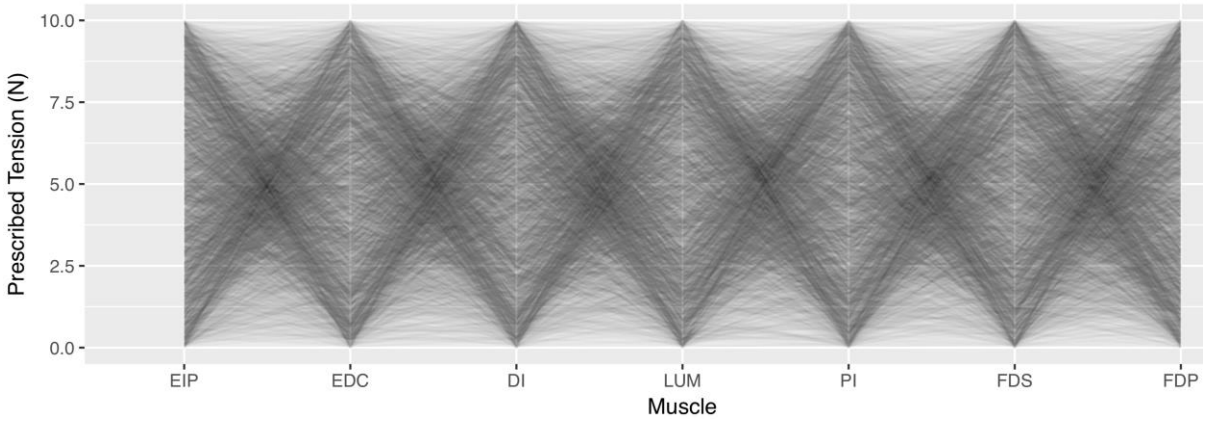
**Abstract:** Vertebrate systems operate limbs with many more muscles than degrees of freedom, which creates redundancies for isometric force production. Optimization is usually proposed as the means by which the nervous system solves such underdetermined problem. However, the learning and execution problem can also be approached from the geometric perspective of heuristic or systematic exploration of high-dimensional spaces, and exploitation of feasible regions found and remembered. We apply such approach to assess the learnability of the input-tension to output fingertip force mapping for the seven tendons of a human cadaver index finger.

We applied five thousand different 7-dimensional tension vectors, while simultaneously recording the resulting isometric fingertip force outputs. We analyzed the relationship between the input and output in both the forward and inverse directions using. a linear regression model, an Artificial Neural Network, and a data-driven Nearest-Neighbor lookup table. We find that forward models perform more accurately than inverse models and that the Nearest-Neighbor approach has a notable fit error at the edges of the input space. These results open a new front for a thorough understanding of how the actual physics of an anatomical system (i.e., the plant the brain must contend with) fundamentally affects learning, memory, and performance of motor function in health, disease, and in an evolutionary context. **Figure 1:** A parallel coordinate plot of 5000 muscle tension patterns implemented on a human cadaver finger highlights how sparsely the edges of the input space are explored with uniform sampling.

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**Poster**

**772. Motor Neurons and Muscle: Motor Unit Recordings, Kinematics, and EMG**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 772.06/WW13

**Topic:** E.09. Motor Neurons and Muscle

**Support:** MOTU - PPR-AI 1/2

**Title:** EMG-based decoding of motor tasks in trans-femoral amputees to control powered knee-ankle prostheses

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**Abstract:** Leg amputation is a severely disabling condition in which the quality of life strongly depends on the performance of the lower limb prosthesis. Recently, active prostheses have been developed to improve the walking performance of the amputees in different tasks. They are usually controlled by different kinds of sensors (e.g., inertial sensors, foot switches). However, electromyographic (EMG) signals can be also used to decode motor intentions. An EMG-based decoding could timely inform the prosthesis controller about the steps that the patient is going to perform, much earlier compared to the information given by sensors. This could help avoiding gait-related alterations which lead to several health problems such as joint degeneration, back pain and neuromuscular disorders. The aim of this pilot study was to investigate whether an EMG-based algorithm can detect motor intentions of trans-femoral amputees.
In this study, subjects with trans-femoral amputation performed different motor tasks (e.g., ground level walking, climbing upstairs, and walking on a ramp), while recording surface EMG signals from 4 muscles (Adductor, Tensor Fasciae Latae, Gluteus Medius and Rectus Femoris). In each motor task, gait events (e.g., touch down, lift off) were monitored using two wearable pressure sensors placed under the prosthetic foot.
Two time-dependent approaches were used to discriminate the performed motor tasks: (i) features extracted from the EMG signal of each muscle were used as input for a linear discrimination analysis (LDA); (ii) features extracted from pairs of muscles were used as input for a Support Vector Machine (SVM) decoding. Results showed that using both approaches it was possible to discriminate, with excellent accuracy, the different motor tasks. This result was achieved after approximately 100ms from the onset of the movement, thus ensuring that the information about the next step could be transmitted to the active prostheses with a sufficient advance to ensure its proper control.
Our results show that an EMG online decoding based on the recording of a reduced set of muscles could represent a valuable option to control powered knee-ankle prostheses for trans-femoral amputees.

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**Poster**

**772. Motor Neurons and Muscle: Motor Unit Recordings, Kinematics, and EMG**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 772.07/WW14

**Topic:** E.09. Motor Neurons and Muscle

**Support:** CONACyT DCQLCB256990 "Proyecto apoyado por el fondo sectorial de investigacion para la educacion"
CONACyT Grant IN212916 to MMG
LO591506

**Title:** Impact of aging on the sexual response of pelvic and perineal muscles in male rats

**Authors: *M. A. LARA GARCIA**[1], M. MEDEL[4], O. LARA GARCIA[2], M. MARTINEZ-GOMEZ[6,5], P. PACHECO[7,3], D. L. CORONA QUINTANILLA[5]
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**Abstract:** Sexual response has been described as the link between active sexual life persistence and progressive aging. Past studies regarding elder people sexual health have shown that sexual aging is quite diverse and heterogeneous among men. Hence, it has not been properly stated how aging affects male sexual response. However, as sexual behavior in male rat involves penile erection, emission and ejaculation of seminal fluid throughout urethra (urethrogenital reflex) as well as seminal plug placing within vaginal tract. This animal model offers an opportunity to further clarify this matter; since, the physiological reflexes involved, are mainly carried out by pelvic and perineal striated muscles i.e., bulbospongiosus (Bsm) and pubococcygeus (Pcm), whose morphology and physiology are heavily affected by gonadal hormones levels. It is interesting to explore aging effect on male sexual response through the urethrogenital (UG) reflex of Bsm and Pcm of adult and elder male rats. Here, we used Wistar male rats divided in two groups: young adult males (at least 4 months-old) and old males (at least 17 months-old). Briefly, male rats were anesthetized and using a continuous saline solution injection through the urethra, penile urethral pressure as well as Bsm and Pcm electromyograms (EMGs) were recorded before, during and after urethrogenital reflex. Results showed that elder males have an altered Pcm and Bsm EMGs during this UG reflex, threshold pressure was increased and UG reflex duration was decreased. Our results shows that aging is clearly affecting both Bsm and Pcm response during UG reflex which may lead to male sexual dysfunction, although we cannot rule out that this might be due to gonadal hormone effect on these muscles.

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**Poster**

**772. Motor Neurons and Muscle: Motor Unit Recordings, Kinematics, and EMG**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 772.08/XX1

**Topic:** E.09. Motor Neurons and Muscle

**Support:** DARPA Grant W911NF-15-2-0016

**Title:** A clustering approach to identify the locations of intramuscular electromyographic electrodes used for prosthesis control

**Authors: *M. MANSOURI**[1], C. R. BERINGER[2], S. YAKOVENKO[3], V. GRITSENKO[3], A. SOBINOV[3], M. BOOTS[3], M. C. MUNIN[1], M. L. BONINGER[1], L. E. FISHER[1], J. L. COLLINGER[1], R. A. GAUNT[1]
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**Abstract:** Highly dexterous robotic hand prostheses are becoming commercially available, leading to a significant need for intuitive methods to control such devices. Using surface EMG (electromyography) recordings, pattern recognition based myoelectric prostheses offer intuitive control but at the cost of an increased training time. The recent development of intramuscular, high channel count myoelectric recording systems, combined with model-based control approaches developed in our group offers an alternative that largely eliminates the need for training. Biomimetic models provide an intuitive control scheme by embedding the mechanical and neural coupling that naturally exist in the human hand. However, this approach relies on recording from a correctly identified set of muscles. Here, we implemented a clustering technique that can be used alongside anatomical markers, e.g. ultrasound, to identify implanted electrodes based on the patterns of muscle activities.Eleven able-bodied subjects, 4 females and 7 males, ages 22-36 years, were recruited for this study. We recorded intramuscular EMG from 16 extrinsic hand muscles placed under ultrasound guidance. Subjects were instructed to perform 45 single-joint movements that included finger and wrist flexion/extension at 1 Hz at five different wrist postures (flexed, extended, pronated, supinated and neutral). The EMG signals were recorded at 30 kHz, high-pass filtered at 100 Hz, rectified, and then low-pass filtered at 4 Hz. Hierarchical Clustering Analysis (HCA) using a Euclidean weighted average method was performed on the average peak EMG pattern during the 45 trials to classify both the movements and the muscles into groups based on the similarities in the EMG patterns across all subjects.HCA successfully clustered movement trials into distinct wrist and individual finger groups based on the EMG patterns. The 176 EMG channels (16 muscles, 11 subjects) were then clustered to 22 subgroups (assigned based on the number of unique muscles implanted), consisting of major wrist and fingers' flexor and extensor muscles. The most frequent muscle in

each cluster was then selected as the cluster name. The least frequent muscles in each cluster flagged as outliers in each subgroup and their identity were rechecked based on the EMG pattern and their physical proximity to other muscles in the cluster. Combined with the anatomical information obtained from the ultrasound, the clustering method demonstrated a promising way to identify single EMG channels based on EMG activity pattern. The HCA results can be used to improve the biomimetic mapping of myoelectric control signals from the muscles to the underlying joint mechanics.

**Disclosures: M. Mansouri:** None. **C.R. Beringer:** None. **S. Yakovenko:** None. **V. Gritsenko:** None. **A. Sobinov:** None. **M. Boots:** None. **M.C. Munin:** None. **M.L. Boninger:** None. **L.E. Fisher:** None. **J.L. Collinger:** None. **R.A. Gaunt:** None.

**Poster**

**772. Motor Neurons and Muscle: Motor Unit Recordings, Kinematics, and EMG**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 772.09/XX2

**Topic:** E.09. Motor Neurons and Muscle

**Support:** Mat Market Postural Stability Grant # MA2017
Neurological Disorders and Stroke grant #R25NS095371

**Title:** Characterization of distal lower extremity balance measuring neuromuscular effort and amplitude probability distribution function in healthy and unhealthy neuromuscular systems

**Authors: *V. M. HOMER**[1], M. HARRINGTON[2], C. MASON[3], A. KUPERAVAGE[3], C. MACKO[4], R. MACKO[4]
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**Abstract:** Our investigators are characterizing neuromuscular function using three experiments that test two hypotheses. First, that the application of Non-custom foot orthotics will significantly decrease distal lower extremity injuries directly associated with foot orthotic modality regardless of footwear type. Second, we believe this will be due to better energy dissipation in primary muscle movers of the foot and ankle complex. By the altering input signals through mechanoreceptors in the skin and muscle into the plantar foot, the orthotic will ultimately cause proper alignment and stability of the foot, changing the “muscle tuning” of the lower extremity, producing a change in muscle activity ideally dampening soft tissue vibrations with the lower extremity muscles. Both hypothesis are supported by the preferred movement pathway theory. The overall goal of my research is to characterize ankle torque and its correspondence to the damping of specific muscles in the lower extremity that are primary

movers of the ankle joint with and without a standardized intervention. The specific aims of the current project are: 1) to investigate the long term effects of monitored prophylactic application of Non Custom Foot Orthotics on foot and ankle related injury in collegiate athletes; 2) To examine the etiology of distal lower extremity injury associated with foot orthotic modality in various field and court sports by comparing changes in lower extremity neuromuscular stability and muscle tension during sport specific movement and normal walking gait parameters; and 3) To examine the interaction at the base of support between footwear, in-shoe interface and terrain. Research subjects will perform the Y-Balance excursion test which can be correlated with injury risk, while having specific joint kinematics recorded along with Electromyography in four specific muscle stabilizers of the foot and ankle. Tibialis Anterior, Peroneus Longus and the Medial and Lateral Gastrocnemius will be characterize independently and in conjunction with one another in performance of foot and ankle stabilization under various conditions. We expect to see changes in neuromuscular effort and threshold of fatigue directly relating to the economy of ankle movement during specific athletic activity with and without orthotic intervention. Characterizing ankle torque and its correspondence to damping of specific muscles that are the primary movers of the ankle joint with and without standardize intervention, we hope to quantify the effect of foot orthotics and shoes on the neuromuscular system, and to establish an innovative model for determining distal lower extremity injury risk.

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**Poster**

**772. Motor Neurons and Muscle: Motor Unit Recordings, Kinematics, and EMG**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 772.10/XX3

**Topic:** E.09. Motor Neurons and Muscle

**Support:** Center of Aging and Translational Research Pilot Grant

**Title:** Association between manual dexterity and motor unit activity

**Authors: *M. JOSHI**[1], B. HEINTZ[2], F. NEGRO[3], K. G. KEENAN[4]
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**Abstract: Introduction**
Manual dexterity is often assessed experimentally as the ability to hold a steady force during an isometric task. Impaired dexterity with age has been associated with changes in motor unit properties such as increased discharge rate variability. Research has also shown that low-frequency common modulation of discharge rates explains fluctuations in isometric force in young adults, though this association in unknown in older adults. In addition, recent findings suggest that experimental paradigms involving hybrid tasks requiring well-directed forces and motions may better reflect deficits in motor control with aging since they mimic activities of daily living (ADLs). The purpose of our study was to find associations between motor unit activity and performance on tests of manual dexterity.
**Methods**
Manual dexterity was tested in 8 healthy older adults (age: 66 – 84). Metrics of performance included force steadiness during a hybrid task and an isometric index finger abduction task. The hybrid task required pressing and moving with the index finger on the iPad surface at a cadence of 50 bpm. The steadiness task consisted of 3 trials holding a force at 5% of maximal for 30 s. High-density surface EMG (64 channels) was recorded from first dorsal interosseus (FDI) during the abduction task (EMG-USB2, OT Bioelettronica, Torino, Italy). EMG was decomposed using the convolution kernel compensation technique. Force steadiness and motor unit discharge rate variability were computed as the coefficient of variation (CV) of force and discharge rate, respectively. Percent variance explained by the first common component (FCC) was computed by running a principle component analysis on all motor unit action potential discharges.
**Results**
CV of force during the hybrid task (19.83 ± 2.4%) was significantly greater than during the abduction task (4.52 ± 2.76%; $p = 0.001$). Discharge rate variability of the motor units during abduction was correlated with performance on the hybrid task ($r = 0.795$; $p = 0.018$). CV of abduction force had moderate correlations with the discharge rate variability ($r = 0.466$) and FCC ($r = 0.459$), however these associations were not statistically significant in this small sample size.
**Discussion**
As expected, the hybrid task was more challenging for the older adults than the isometric task. Interestingly, in the regression model motor unit discharge rate variability during the abduction task explains 63.2% of the force variability during the hybrid task, consistent with previous work relating abduction task performance with other measures of manual dexterity. Future work should identify the mechanisms linking performance across tasks.

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**Poster**

**772. Motor Neurons and Muscle: Motor Unit Recordings, Kinematics, and EMG**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 772.11/XX4

**Topic:** E.09. Motor Neurons and Muscle

**Support:** ERC-2014-CoG-646923_DBSModel

**Title:** Motor unit discharge and nonlinear surface EMG features during isometric contraction in Parkinson's disease

**Authors: *L. M. MCMANUS**, M. W. FLOOD, M. M. LOWERY
Univ. Col. Dublin, Dublin, Ireland

**Abstract:** Motor unit activity in Parkinson's disease exhibits characteristic bursting patterns with evidence of doublet and triplet firing patterns during parkinsonian tremor [1]. The behavior of individual motor units during isometric contraction in Parkinson's disease, however, is less well established. The aim of this study was, therefore, to investigate motor unit discharge and nonlinear surface electromyography (EMG) features related to synchronization of motor unit activity during isometric contraction of the first dorsal interosseous hand muscle in individuals with idiopathic Parkinson's disease (PD). Surface EMG data were recorded from the first dorsal interosseous muscle during index finger abduction in subjects with idiopathic Parkinson's disease (N=10). Subjects performed separate contractions at 10, 20, 30 and 40% MVC. Motor unit firing times (MUs) were extracted from the surface EMG signals using established decomposition algorithms (Delsys, Inc.). Acceptance criteria based on the uniqueness of the motor unit action potential shapes and stability of the spike triggered averaged action potentials were applied before accepting motor units for further analysis. Differences in the structure of the surface EMG signal were quantified using determinism (%DET) and sample entropy (SampEn), two nonlinear measures of signal complexity. The motor unit and EMG parameters were compared with those of healthy subjects (N=10).
Motor unit firing rates were were not significantly different between subjects with Parkinson's disease (12.7 ± 3 Hz), when compared to the healthy subjects (12.8 ± 2.8 Hz, $p = .9$). There was no significant difference in the firing rate of the motor unit population recorded at 10, 20, 30 and 40% MVC in the PD group. However, %DET was significantly higher, and SampEn significantly lower, in the PD group. The nonlinear measures reveal a difference in the structure of the surface EMG signal between the two groups that would indicate higher MU synchrony in individuals with Parkinson's disease [2,3].
[1] Glendinning & Enoka (1994). Physical Therapy, 74(1), 61-70.[2] Webber (1995), J Appl Physiol,78(3),814-822[3] Richman & Moorman (2000): Am J Physiol Heart Circ Physiol 278(6)H2039-H2049.

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**Poster**

**772. Motor Neurons and Muscle: Motor Unit Recordings, Kinematics, and EMG**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 772.12/XX5

**Topic:** E.09. Motor Neurons and Muscle

**Support:** NIH Grant 5R25GM079300-12
NIH Grant K01HD084672-04

**Title:** Investigating the efficacy of delta 9-THC in treating spasticity following spinal cord injury

**Authors: *O. A. SHELTON**, D. V. BIRCH, A. C. PURITZ, C. K. FRANZ, V. M. TYSSELING
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**Abstract:** Spinal cord injuries (SCI) are commonly associated with motor paralysis, but most people with spinal cord injury also develop involuntary muscle contractions that can severely interfere with function.
Spinal cord injuries disrupt messages between the brain and the body distal to the injury. This results in paralysis below the injury level and makes daily function very difficult. In addition, most people with spinal cord injury develop hyperreflexia and involuntary muscle contractions, or spasms, that cause even more movement dysfunction as well as pain, contractures, and safety issues.
The most widely used anti-spasm medication is a general $GABA_B$ receptor agonist, baclofen. Although baclofen is effective at alleviating muscle spasms, $GABA_B$ receptors are ubiquitously expressed in the central nervous system, and treatment can cause a plethora of uncomfortable side effects. Anecdotal evidence from patient reports list marijuana as a very effective drug to decrease spasms, but this has not been systematically tested. In this study, we aim to test whether the administration of a synthetic THC, Marinol, reduces spinal reflexes *in vivo* and *in vitro*, and would therefore decrease spasms post injury. If so we can further investigate the therapeutic mechanism to develop a more specific future pharmacotherapy for patients who suffer from SCI. For these studies, we are using a chronic transection mouse model of SCI. We are comparing electrical outputs from muscle and nerve tissue before and after administering baclofen or Marinol in these SCI mice. To compare how muscle contractions are impacted by our drug interventions we test spasticity *in vivo* by recording the flexor withdrawal EMG response to an electrical stimulus three months post injury. To directly measure the effects of baclofen and Marinol on the spinal reflexes, we remove the sacral section of the spinal cord, stimulate the dorsal roots, and then record the electrical response through the ventral roots.
Anecdotal accounts claim that marijuana is effective at reducing spasticity following spinal cord injury. This study aims to systematically determine whether THC has a significant effect on

spasticity *in vivo* and *in vitro* and whether THC signaling pathways are a potential therapeutic target for patients with SCI.

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**Poster**

**772. Motor Neurons and Muscle: Motor Unit Recordings, Kinematics, and EMG**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 772.13/XX6

**Topic:** E.09. Motor Neurons and Muscle

**Support:** University of Wisconsin-Milwaukee CHS Graduate Student Research Grant

**Title:** Common synaptic input to the motor neuron pool is related to dorsiflexion force steadiness in older adults

**Authors: *J. J. PETERSON**[1], F. NEGRO[2], K. G. KEENAN[1]
[1]Dept. of Kinesiology, Univ. of Wisconsin-Milwaukee, Milwaukee, WI; [2]Univ. Degli Studi di Brescia, Dept. of Clin. and Exptl. Sci., Brescia, Italy

**Abstract: Background:** Functional limitations, such as in walking, climbing stairs, and maintaining balance, become increasingly prevalent as adults progress into older age. Performance on force steadiness tasks is related to functional performance in older adults. However, the neural mechanisms driving impaired performance remain unclear. Common synaptic input to the motor neuron pool at low-frequencies (< 4 Hz), termed common drive, has been identified as a mechanism which may contribute to impaired performance with advancing age. However, previous work examining common drive has produced mixed results and the influence of common synaptic input at higher frequencies on performance in older adults remains largely unknown. The purpose of our study was to examine the differences in common synaptic input between young and older adults during a 5% MVC dorsiflexion task, and to examine the relationship between common synaptic input and force steadiness.
**Methods:** 15 young (26.4 ± 3.8 yrs) and 18 older (73.6 ± 6.5 yrs) adults performed a dorsiflexion task while seated with the knee extended and ankle in a neutral position. Participants performed a series of MVCs followed by two 30 s trials at 5% MVC. Performance was quantified as the coefficient of variation (CV) of force. High-density surface EMG was collected from tibialis anterior using a 64-channel electrode (OTBioelettronica, Torino, IT) and decomposed into motor unit action potential trains. Common synaptic input was quantified as 1) variance explained by the first common component (FCC) using principal component analysis and 2) coherence in the low-frequency (0.25 – 5 Hz), alpha (5 – 10 Hz), and beta (10 – 30 Hz) bands.

**Results:** CV of force was increased for the older adults compared to the young adults (4.0 ± 2.0% and 2.3 ± 1.3%, respectively, p = .009). There was not a difference between young and older adults for any of the common synaptic input metrics (p > .07). However, for the older adults there were negative relationships between CV of force and variance explained by the FCC ($R^2$ = .38; p = .007) and between CV of force and low-frequency coherence ($R^2$ = .38, p = .007). There was a positive relationship between CV of force and beta band coherence ($R^2$ = .32; p = .014) for the older adults. None of the other relationships were significant (p > .15).
**Conclusions:** Greater low-frequency coherence and a higher percent total variance explained by the FCC is related to better performance on a dorsiflexion force steadiness task in older adults, while greater beta band coherence is related to impaired performance. These results demonstrate that common synaptic input to the motor neuron pool plays an important role in motor performance for older adults.

**Disclosures: J.J. Peterson:** None. **F. Negro:** None. **K.G. Keenan:** None.

**Poster**

**772. Motor Neurons and Muscle: Motor Unit Recordings, Kinematics, and EMG**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 772.14/XX7

**Topic:** E.09. Motor Neurons and Muscle

**Support:** NIH Grant R44NS077526
De Luca Foundation

**Title:** Motor unit measurements during exercise and functional activities

**Authors: *J. C. KLINE**, B. SHIWANI, J. P. CHIODINI, P. CONTESSA, S. H. ROY, G. DE LUCA
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**Abstract:** Current approaches for investigating motor control during training, exercise and rehabilitation rely on inertial sensors, instrumented force plates and/or motion capture systems that infer but do not directly measure the underlying mechanisms used by the central nervous system to regulate movement. However, advanced technologies for decomposing the surface electromyographic (sEMG) signal into constituent motor unit action potentials (MUAPs) provide empirical means to investigate the behavior of the central nervous system. Our group has been working to develop sensors and algorithms for automatically measuring the action potentials of individual motor units directly and noninvasively, first during isometric contractions or constrained cyclic contractions, and more recently during a broader range of exercise and functional activities. To achieve this goal, we are advancing our decomposition algorithms to overcome three primary challenges of extracting motor unit data from sEMG signals recorded

during dynamic movement: 1) tracking non-stationary changes in MUAP shapes that occur with position and length changes of the muscle fibers, 2) improving the temporal resolution of firing rate measurements across dynamically varying activities, and 3) localizing firing detections amongst complex superpositions typically encountered in functional activities. We tested the algorithms using sEMG signals recorded with the dEMG system (Delsys, Inc, Natick, MA) from n=10 consenting control subjects during eccentric and concentric biceps exercise, position and force tasks of extrinsic hand muscles, and functional tasks of the upper-limb. The algorithms were able to identify a broad range of motor units above the 90% accuracy benchmark for each activity. During each task, motor units showed clear changes in both firing rate progression and their degree of correlation with the output changes in force or joint angle. These results mark a first step towards delineating the neural contributions to motor tasks associated with human movement, and provide new research opportunities to modify exercise, guide training modalities and tailor rehabilitation protocols based on the underlying motor unit-based outcome measures of neuromuscular control.

**Disclosures: J.C. Kline:** A. Employment/Salary (full or part-time):; Delsys, Inc. **B. Shiwani:** A. Employment/Salary (full or part-time):; Delsys, Inc. **J.P. Chiodini:** A. Employment/Salary (full or part-time):; Delsys, Inc. **P. Contessa:** A. Employment/Salary (full or part-time):; Delsys, inc. **S.H. Roy:** A. Employment/Salary (full or part-time):; Delsys, Inc. **G. De Luca:** A. Employment/Salary (full or part-time):; Delsys, Inc.

**Poster**

**773. Neuroendocrine Processes: The HPG Axis**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 773.01/XX9

**Topic:** F.03. Neuroendocrine Processes

**Support:** Great Lakes Fishery Commission

**Title:** Pheromones modulate sexually dimorphic neuropeptide responses in a basal vertebrate

**Authors: *Y.-W. CHUNG-DAVIDSON**[1], U. BUSSY[2], S. D. FISSETTE[2], W. LI[2]
[1]Fisheries & Wildlife, [2]Michigan State Univ., East Lansing, MI

**Abstract:** Gonadotropin-releasing hormone (GnRH) and gonadotropin-inhibitory hormone (GnIH) are key players in the hypothalamic-pituitary-gonadal (HPG) axis. However, the function of GnIH in basal vertebrates has not been well-studied. GnIH orthologues have been identified in the sea lamprey (*Petromyzon marinus*), which possesses the most ancient HPG axis and well-studied pheromone systems. We sought to examine how olfactory inputs interact with the HPG axis to modulate reproductive behaviors and neuroendocrine responses. Based on our finding that pheromones induced sexually dimorphic behaviors in the sea lamprey, we hypothesize that

pheromones also induce sexually dimorphic neuropeptide responses in this species. We took advantage of a stimulatory (3-keto petromyzonol sulfate, 3kPZS) and an inhibitory (3-keto allocholic acid, 3kACA) sex pheromone identified in the sea lamprey to study the sexually dimorphic effects of pheromones on neuropeptide responses. We examined GnRH and GnIH concentrations in the brain and plasma in animals exposed to waterborne vehicle, $10^{-10}$ M 3kPZS or $10^{-10}$ M 3kACA over a time course (2h, 4h, 24h and 48h) using liquid chromatographic tandem mass spectrometry (LC-MS/MS). In females, exposure to 3kPZS increased plasma lamprey (l) GnRH-II levels after 24h and 48h, but had no effect in brain lGnRH-II or lGnRH-I and -III levels in the brain or plasma. On the contrary, males only responded to 3kACA exposure, showing elevated plasma lGnRH-I and -III after 2h, increased brain lGnRH-I after 4h, but decreased brain lGnRH-III after 48h. In females, both pheromones decreased brain GnIH variants (LPXRFa1a, LPXRFa1b and LPXRFa2) after 4h, but 3kPZS increased brain GnIHs after 48h, and plasma GnIHs after 2h and 48h. In male brains, 3kACA increased LPXRFa1a level after 4h, but decreased all three GnIH variants after 48h. Pheromones did not affect plasma GnIH levels in males. To summarize, lGnRH-II levels were modulated by 3kPZS in females, but lGnRH-I and -III levels were regulated by 3kACA in males. GnIH levels were controlled by both 3kACA and 3kPZS in females, but only affected by 3kACA in males. Therefore, olfactory stimuli elicited by different pheromones may activate distinct subsets of GnRH and GnIH neurons in a sexually dimorphic manner.

**Disclosures: Y. Chung-Davidson:** None. **U. Bussy:** None. **S.D. Fissette:** None. **W. Li:** None.

**Poster**

**773. Neuroendocrine Processes: The HPG Axis**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 773.02/XX10

**Topic:** F.03. Neuroendocrine Processes

**Title:** Localization and quantification of kisspeptin and gonadotropin inhibitory hormone in green anole lizards (anolis carolinensis)

**Authors: *S. TALWAR**, R. E. COHEN
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**Abstract:** It has been well supported among mammalian species that the hypothalamic-pituitary-gonad (HPG) axis is regulated positively by kisspeptin and negatively by gonadotropin inhibitory hormone (GnIH). Studies with seasonal breeding models have generally shown higher levels of kisspeptin in areas of the hypothalamus associated with reproduction, such as the preoptic area (POA) and arcuate nucleus, during the breeding season. Conversely, when examining models during the non-breeding season, studies have indicated GnIH to be higher in hypothalamic nuclei, such as the POA. However, kisspeptin’s role in regulating reproduction may not be

consistent among all vertebrate groups. While kisspeptin has been shown to upregulate reproduction in mammals, this peptide has not been detected in avian species and recent work in fish has suggested that kisspeptin may not play a regulatory role in reproduction. Relatively little is known about these peptides in reptiles and the seasonal regulation of kisspeptin and GnIH has not been investigated in this group. Green anole lizards (*Anolis carolinensis*) have a distinct breeding and non-breeding season, and during the breeding season, steroid hormone levels in the plasma are elevated, males are more territorial, and display reproductive behaviors at a higher frequency. Previous work in this species has demonstrated that, in non-breeding anoles, kisspeptin-positive neurons were present in the POA and the dorsomedial hypothalamus. It is currently unknown whether kisspeptin expression is altered in breeding lizards and there is no data available on GnIH expression in this species. We hypothesize that there is a seasonal effect on kisspeptins and GnIH in green anole lizards, with kisspeptins more highly expressed in the breeding season, while GnIH is more highly expressed in the non-breeding season. Preliminary data using quantitative PCR has revealed no significant difference between seasons in the expression of *kiss1*, *kiss2*, and *Gnih* mRNA from a dissection of the brain that contained the hypothalamus ($F_{1, 16} \leq 4.35$, $p \geq 0.053$, n = 4-6 per group). Although we did not detect a significant difference between seasons, expression in specific regions may differ. Therefore, using fluorescent *in situ* hybridization, we aim to determine the localization and expression levels of *kiss1, kiss2* and *Gnih* expression throughout the hypothalamus. This study expands upon available data and bridges the evolutionary gaps in the roles of kisspeptin and GnIH in regulating reproduction.

**Disclosures: R.E. Cohen:** None.

**Poster**

**773. Neuroendocrine Processes: The HPG Axis**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 773.03/XX11

**Topic:** F.03. Neuroendocrine Processes

**Title:** The relationship between seasonal breeding and deiodinase expression in green anole lizards

**Authors: *H. KANG**, D. S. SHARLIN, R. E. COHEN
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**Abstract:** The hypothalamus-pituitary-gonadal (HPG) axis regulates the production of gonadal steroid hormones and reproduction. Recent work in mammalian and avian models has suggested that thyroid hormone (TH) can interact with the HPG axis to alter reproduction and steroid hormone production, but it is unknown if this interaction occurs in reptiles. Green anole lizards (*Anolis carolinensis*) breed seasonally, with increased steroid hormone levels, increased

reproductive behaviors, and altered brain morphology in breeding compared to non-breeding animals. We examined whether local control of TH action in the gonads interacts with the HPG axis, which could contribute to the regulation of seasonal reproduction and behavior in green anoles. Among breeding and non-breeding lizard gonads, quantitative PCR revealed that type 2 deiodinase (Dio2), the TH activating enzyme, was upregulated in compared to non-breeding anole testes ($F_{(3, 18)} = 8.04$, $p = 0.012$, n = 5-6/group). In contrast, type 3 deiodinase (Dio3) mRNA, the TH deactivating enzyme, was upregulated in breeding ovaries ($F_{(3, 16)} = 14.78$, $p < 0.001$, n = 5-6/group). This result supports the idea that there is an interaction between the HPG axis and local control of thyroid hormone action in the anole gonad, which may regulate reproductive physiology. To study this relationship, we manipulated the HPG axis in non-breeding male lizards by subcutaneously injecting luteinizing hormone (LH; 2 μg/g) and follicular stimulating hormone (FSH; 0.15 μg/g) or saline every other day for 12 days. The gonads were collected to examine Dio2, Dio3 and steroidogenic acute regulatory protein (StAR, rate limiting step for steroidogenesis) mRNA expression. LH and FSH injected male testes were significantly larger ($t = 2.46$, $p = 0.029$, n = 6-9/group) and had increased StAR mRNA expression ($t = 2.78$, $p = 0.016$, n = 6-9/group), which indicates that the gonadotropin injections were able to activate the HPG axis in non-breeding male lizards. Surprisingly, testes Dio3 was upregulated in LH and FSH injected animals ($t = 3.68$, $p = 0.003$, n = 6-9/group), while Dio2 levels remained similar to the vehicle injected group ($t = 0.95$, $p = 0.359$, n = 6-9/group). These results suggest different roles of local TH activation in gonadal growth and maintenance. In addition, we will measure male aggressive behavior in response to the injections, as well as plasma testosterone levels to determine whether injections increased steroid hormone production. Our findings reveal a role for gonadal deiodinase expression in seasonally breeding lizards and contribute to the understanding of the relationship between the HPG axis and thyroid hormone action in the male gonad.

**Disclosures: H. Kang:** None. **D.S. Sharlin:** None. **R.E. Cohen:** None.

**Poster**

**773. Neuroendocrine Processes: The HPG Axis**

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**Program #/Poster #:** 773.04/XX12

**Topic:** F.03. Neuroendocrine Processes

**Support:** INKP 2018-52
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HBRP Grant 2017-1.2.1-NKP-2017-00002

**Title:** The fine structure of human kisspeptin neurons

**Authors: *S. F. TAKÁCS**[1], Z. BARDÓCZI[2], K. SKRAPITS[3], B. GÖCZ[3], V. VÁCZI[3], Z. MAGLÓCZKY[4], A. KÁDÁR[5], C. FEKETE[5,6], I. KALLÓ[2,7], M. WATANABE[8], W. S. DHILLO[9], I. SZűCS[10], G. RÁCZ[11], A. MATOLCSY[11], E. HRABOVSZKY[3]
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**Abstract:** Kisspeptin (KP) synthesizing neurons of the hypothalamic infundibular region are critically involved in the central regulation of fertility; these cells regulate pulsatile gonadotropin-releasing hormone (GnRH) secretion and mediate sex steroid feedback signals to GnRH neurons. Fine structural analysis of the human KP system is complicated by the use of post mortem tissues. To gain better insight into the neuroanatomy of the somato-dendritic cellular compartment, we introduced the diolistic labeling of immunohistochemically identified KP neurons using a gene gun loaded with the lipophilic dye, DiI. Confocal microscopic studies of primary dendrites in 100-µm-thick tissue sections established that 79.3% of KP cells were bipolar, 14.1% were tripolar and 6.6% were unipolar. Primary dendrites branched sparsely, contained numerous appendages (9.1±1.1spines/100 µm dendrite) and received rich innervation from GABAergic, glutamatergic and KP-containing terminals. KP neuron synaptology was analyzed with immunoelectron microscopy on perfusion-fixed specimens. KP axons established frequent contacts and classical synapses on unlabeled and on KP-immunoreactive somata, dendrites and spines. Synapses were asymmetric and the presynaptic structures contained round and regular synaptic vesicles, in addition to dense-core granules. Although immunofluorescent studies failed to detect vesicular glutamate transporter isoforms in KP axons, ultrastructural characteristics of synaptic terminals suggested use of glutamatergic, in addition to peptidergic, neurotransmission.
In summary, immunofluorescent and DiI labeling of KP neurons in thick hypothalamic sections and immunoelectron microscopic studies of KP-immunoreactive neurons in brains perfusion-fixed shortly post mortem allowed us to identify previously unexplored fine structural features of KP neurons in the mediobasal hypothalamus of humans.

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**Poster**

**773. Neuroendocrine Processes: The HPG Axis**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 773.05/XX13

**Topic:** F.03. Neuroendocrine Processes

**Support:** INKP 2018-51
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HBRP Grant 2017-1.2.1-NKP-2017-00002

**Title:** Identification of 200,000 GnRH neurons in basal ganglia of the adult human brain

**Authors: *K. SKRAPITS**[1], S. TAKÁCS[2], V. VÁCZI[2], B. GÖCZ[2], G. RÁCZ[3], A. MATOLCSY[3], E. HRABOVSZKY[2]
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**Abstract:** The neuroendocrine control of reproduction in mammals is governed by the hypothalamic gonadotropin releasing hormone (GnRH) neurons. These ~2,000 cells are born in the nasal placodes from where they migrate along the nerve fibers, enter the brain, and turn ventrally to reach their final destinations within the hypothalamus. Unexpectedly, in human embryos, in addition to this well-characterized ventral migratory pathway, a dorsal route also exists through which ~8,000 developing GnRH neurons migrate toward pallial and subpallial regions; however, there is no information available for the further fate of these cells in adulthood so far. In the present study, we hypothesized that, in human, dorsally migrating GnRH neurons settle, survive into adulthood and produce GnRH neuropeptide in extrahypothalamic regions. To examine this, we used immersion fixed post mortem human brains. Using our own GnRH antibodies, we have visualized for the first time GnRH immunoreactivity outside the hypothalamus. We identified more than 200,000 extrahypothalamic GnRH-immunoreactive neurons which were located mostly (>90%) in the striatum: the putamen and the caudate nucleus. Scattered neurons were also found in the globus pallidus, in the basal nucleus, in the accumbens nucleus and in the bed nucleus of the stria terminalis. To study the morphology of these cells we randomly labeled the immunohistochemically identified GnRH neurons using a gene gun containing the lipophilic dye, DiI. We found that extrahypothalamic GnRH cells are aspiny/sparsely spined neurons. We showed that these cells are distinct from the parvalbumin and neuronal nitric oxide synthesizing/somatostatin positive cell populations but nearly all of them contain choline acetyltransferase, a marker of cholinergic neurons. In conclusion, these novel observations provide evidence that a group of striatal cholinergic cells in human can use

GnRH/GnRH receptor signaling to influence the local dopaminergic and/or glutamatergic neurotransmission onto spiny projection neurons whereby GnRH may modulate various motor, memory and reward functions. Changes in GnRH content of cholinergic cells may serve as information for the progression of human pathologies such as Alzheimer's and Parkinson's disease.

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**Poster**

**773. Neuroendocrine Processes: The HPG Axis**

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NIH R01 HD090161

**Title:** Estradiol upregulates Kiss1 expression in the medial tuberal nucleus in mice

**Authors: *S. B. STEPHENS**[1], R. B. LIAW[1], N. P. DI GIORGIO[2], V. A. LUX-LANTOS[2], A. S. KAUFFMAN[1]
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**Abstract:** Kisspeptin, encoded by *Kiss1*, stimulates GnRH release and is required for reproduction. *Kiss1* neurons reside in the hypothalamic AVPV/PeN and ARC nuclei, and in smaller numbers in extra-hypothalamic areas, including the medial amygdala, bed nucleus of the stria terminalis, and lateral septum. Recently, a small population of *Kiss1* neurons in the lateral hypothalamic region was newly identified in sheep. We identified a similar small population of *Kiss1* neurons in this general region in mice, specifically in the medial tuberal nucleus (MTu) of the hypothalamus. In adult *Kiss1*-Cre TdTomato+ mice, a small population of TdTomato-expressing cells were found in the MTu of both male and female mice. A small population of *Kiss1* mRNA-expressing cells was also detected, using *in situ* hybridization, in the MTu of adult male mice. Nothing is currently known about the regulation and function of *Kiss1* neurons in the MTu, though estradiol ($E_2$) strongly upregulates *Kiss1* expression in the AVPV/PeN, MeA, and BnST, but downregulates *Kiss1* expression in the ARC. Because all previously-identified *Kiss1* neuronal populations are regulated by estradiol and ERα, ERβ, and aromatase are expressed in

the MTu, we hypothesized that *Kiss1* in the MTu is also regulated by $E_2$. Using *in situ* hybridization, we found that gonadectomized male and female mice had essentially no detectable *Kiss1* expression in the MTu. By comparison, $E_2$ treatment significantly increased *Kiss1* expression in the MTu of both sexes. Thus, like the AVPV and extra-hypothalamic *Kiss1* neuronal populations, *Kiss1* expression in the MTu is upregulated by $E_2$. Additional research is needed to further characterize the regulation and potential functions of this small population of newly identified *Kiss1* neurons in the MTu.

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**Poster**

**773. Neuroendocrine Processes: The HPG Axis**

**Location:** SDCC Halls B-H

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**Topic:** F.03. Neuroendocrine Processes

**Support:** National Science Foundation of Hungary (K115984)
Hungarian National Brain Research Program

**Title:** Effects of estradiol on GABA and glutamate neurotransmission to mouse GnRH neurons during the positive estrogen feedback

**Authors: *F. BÁLINT**[1], I. FARKAS[2], E. FARKAS[3], C. VASTAGH[2], C. FEKETE[3], Z. LIPOSITS[2]
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**Abstract:** Although our knowledge about central regulation of reproduction has increased in the recent decades, the feedback actions of estradiol (E2) during the female reproductive cycle have not fully been elucidated. During positive E2 feedback period, the increasing serum estradiol triggers the surge release of gonadotropin-releasing-hormone (GnRH), which is essential for activation of pituitary-gonadal-unit at late, proestrous afternoon. The present study describes molecular mechanisms through which E2 exerts positive feedback regulatory actions directly on GnRH-GFP neurons of mice. Whole-cell patch-clamp measurements from intact mice demonstrated that high physiological dose of E2 (200 pM) significantly increased mPSC frequency at proestrous afternoon (153.2 ± 17.33 % of the control value), whereas decreased it at metestrous afternoon (80.6 ± 7.54% of the control value), and no change was observed at proestrous morning (112.7 ± 9.65% of the control value). This direct effect of E2 requires the involvement of estrogen receptor beta (ERβ) in GnRH neurons since inhibition of ERβ signaling attenuated the excitatory effect of E2. Intracellular blockade of Src kinase or PI3K or scavenging

of nitric-oxide (NO) also prevented the facilitatory effect of E2 indicating the involvement of ERβ/Src/PI3K/Akt pathway in activation of neuronal NO-synthase (nNOS). The immunocytochemical analysis revealed the localization of the NO-receptor soluble guanylate cyclase in both glutamatergic and GABAergic terminals innervating GnRH neurons. Furthermore, blockade of $GABA_A$-R and glutamate/AMPA-R eliminated the facilitatory effect of E2. These results indicate that estradiol acts directly on GnRH neurons via the ERβ/Akt/nNOS pathway at late proestrus, generates NO that retrogradely accelerates GABA and glutamate release and increases mPSC frequency. The newly explored mechanism contributes to the preparation of GnRH neurons for surge release, a fundamental prerequisite of ovulation.

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**Poster**

**773. Neuroendocrine Processes: The HPG Axis**

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**Program #/Poster #:** 773.08/YY2

**Topic:** F.03. Neuroendocrine Processes

**Support:** HD042635
UL1TR001881

**Title:** Estrogen-responsiveness of female mouse hypothalamic astrocytes: A developmental study

**Authors: *M. A. MOHR**, B. J. LAHAM, B. A. FALCY, P. E. MICEVYCH
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**Abstract:** Puberty involves the maturation of female reproductive circuits to the point of supporting estrogen positive feedback that elicits a luteinizing hormone (LH) surge, triggering ovulation. We have shown that in post-pubertal female rodents, peripheral estradiol (E2) increases progesterone synthesis in hypothalamic astrocytes (neuroP), initiating an LH surge. Interestingly, E2-facilitated neuroP synthesis occurs in adult females but not in males or prepubertal females. The focus of the current study was to determine changes in female astrocytes during puberty that allow E2 to facilitate neuroP synthesis. Of particular interest are levels of estrogen receptor-alpha (ERα)-- trafficked to the cell surface by interaction with caveolin 1 (Cav1) proteins—that are required to mediate E2's induction of neuroP synthesis by activating protein kinase A (PKA), and the phosphorylation of protein kinase B (AKT) by which E2 facilitates cell proliferation. Hypothalamic astrocyte cultures were established from female mice at postnatal day (PND) 23 (prepubertal), PND 35 (pubertal), and PND 60 (adult) and treated with 1nM E2 or vehicle. Surface biotinylation and western immunoblotting determined

changes in membrane ERα, Cav1, phosphoPKA, and phosphoAKT. We observed a developmental increase in phosphoAKT and Cav1 proteins (ANOVAs, main effects of age, p values < 0.005; n = 2-5/treatment/age) and a trend toward an increase in phosphoPKA protein. These results suggest that the levels of membrane ERα increase to adulthood, and initial investigations with surface biotinylation and western blotting reveal an age-related increase in mERα (ANOVA, main effect of age, $p < 0.05$, n = 2-3/treatment/age). Ongoing experiments to increase power may reveal an interaction between age and estrogen treatment. These experiments highlight how cellular signaling changes during puberty in hypothalamic astrocytes to allow for neuroP biosynthesis that contributes to estrogen positive feedback. Supported by HD042635 and UL1TR001881.

**Disclosures: B.J. Laham:** None. **B.A. Falcy:** None. **P.E. Micevych:** None.

**Poster**

**773. Neuroendocrine Processes: The HPG Axis**

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**Topic:** F.03. Neuroendocrine Processes

**Support:** NIH Grant RO1HD042635
NIH Grant RO1HD058638

**Title:** Progesterone receptor-Src family kinase interdependent signalig mediates neuroprogesterone induction of the luteinizing hormone surge

**Authors: *C. E. CARLSON**[1], T. CHUON[2], S. ONDREJIK[2], P. E. MICEVYCH[3], K. SINCHAK[2]
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**Abstract:** Astrocyte-neuronal interactions regulate estrogen positive feedback. Initial actions of estradiol upregulates classical progesterone receptors (PGR) in kisspeptin (kiss1) neurons of the rostral periventricular region of the third ventricle (RP3V). Positive feedback estradiol levels induce neuroprogesterone (neuroP) synthesis in hypothalamic astrocytes. This neuroP stimulates kisspeptin neurotransmission that triggers the luteinizing hormone (LH) surge. In an *in vitro* model of RP3V kisspeptin neuron (mHypoa51 neurons), progesterone signals through PGR-Src signaling complexes to induce the release of kisspeptin. Therefore, we tested the hypothesis that neuroP induction of the LH surge is mediated by PGR-Src signaling. In Experiment I, ovariectomized/ adrenalectomized (ovx/adx) rats were subcutaneously injected with 2μg EB which primes LH surge circuits but does not induce an LH surge. Rats received two sequential infusions into the RP3V. The first infusion was either DMSO or PP2 (Src antagonist, 50 nmol;

Tocris) 51.5 hours after EB. The second infusion 4.5 hours later was either a Src agonist (Src Family Activator, 50 nmol; Santa Cruz Biotechnology) or DMSO. Two hours later, rats were anesthetized, then trunk blood and brains were collected. Src activation significantly increased serum LH concentrations compared to DMSO controls. PP2 inhibited the Src activator induced increase in LH. In Experiment II, animals received 50μg EB which induces neuroP and the LH surge. For three consecutive days, PP2 (50 nmol) was infused into the DBB to inhibit Src activity. PP2 blocked the EB-induced LH surge. In Experiment III, ovx/adx animals primed with 2 μg EB received an infusion of a PGR-specific agonist (R5020, 50 nmol, PerkinElmer) into the RP3V. R5020 induced a robust LH surge similar to progesterone-treated animals. This LH surge was attenuated by pretreatment with either PGR antagonist (RU486, 50 nmol, Sigma-Aldrich) or PP2. Taken together, these results indicate that PGR and Src signaling in the RP3V are each sufficient and interdependent for inducing the LH surge. Our lab demonstrated that PGR-Src complex in RP3V neurons, therefore our results support the idea that neuroP activates a membrane-associated PGR-Src complex to trigger the LH surge.

**Disclosures: C.E. Carlson:** None. **T. Chuon:** None. **S. Ondrejik:** None. **P.E. Micevych:** None. **K. Sinchak:** None.

**Poster**

**773. Neuroendocrine Processes: The HPG Axis**

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**Program #/Poster #:** 773.10/YY4

**Topic:** F.03. Neuroendocrine Processes

**Support:** JSPS KAKENHI 16K18984
JSPS KAKENHI 17K08526

**Title:** Expression of IL-18 in gonadotropin-releasing hormone neurons was observed in the hypothalamus

**Authors: *H. YAGI**[1], S. KUWAHARA-OTANI[2], Y. MINATO[2], S. MAEDA[2], H. OKAMURA[3]
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**Abstract:** The hypothalamic-pituitary-gonadal (HPG) axis controls reproductive functions. Gonadotropin-releasing hormone (GnRH), which is released by GnRH neurons in the hypothalamus, controls the secretion of gonadotropin from the pituitary. GnRH neurons are the key output cells of neuronal networks regulating reproduction and fertility. It is well known that inflammation and stress can influence reproduction at the level of hypothalamus, and the depression of reproductive functions in the hypothalamus is related to several inflammatory cytokines. It has been shown that interleukin-18 (IL-18) plays a role in local immune reactions

and in modulating immunological responses under neuropathological and stressful conditions. However, there is limited information on the interaction between IL-18 and the HPG axis, and the detailed localization of IL-18 and its receptor in neuroendocrine cells has not yet been addressed. Therefore, we examined the expression of IL-18 and the alpha chain of its receptor (IL-18Rα) in the hypothalamus. We performed double-label immunofluorescence for GnRH with IL-18Rα or IL-18. IL-18Rα was expressed in approximately 60% of GnRH-immunopositive perikarya, while IL-18 was distributed in all GnRH-immunopositive perikarya. We next confirmed the expression of IL-18 and its receptor in GT1-7 cells, a GnRH-producing cell line. We also detected the expression of other inflammatory cytokines, TNF-α, IL-1β, and IL-6, and their receptors in GT1-7 cells. Our observations indicate that these inflammatory cytokines may exert direct effects upon GnRH neurons via their specific receptors. There is a possibility that these cytokines regulate the function of GnRH neurons in an autocrine or paracrine manner.

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**Poster**

**773. Neuroendocrine Processes: The HPG Axis**

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**Program #/Poster #:** 773.11/YY5

**Topic:** F.03. Neuroendocrine Processes

**Support:** NICHD (R00HD058044)

**Title:** Tet1 regulates Fgf8 expression in the developing hypothalamus during gonadotropin-releasing hormone neuron emergence

**Authors: *M. L. LINSCOTT**[1], W. C. CHUNG[2]
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**Abstract:** Fibroblast growth factor 8 (FGF8) is a potent morphogen that regulates the ontogenesis of gonadotropin-releasing hormone (GnRH) neurons, which control the hypothalamus-pituitary-gonadal (HPG) axis, and therefore reproductive success. Indeed, FGF8 and FGFR1 deficiency severely compromises vertebrate reproduction in mice and humans and is associated with Kallmann Syndrome (KS), a congenital disease characterized by hypogonatropic hypogonadasim associated with anosmia. Our laboratory demonstrated that FGF8 signaling through FGFR1, both of which are KS-related genes, is necessary for proper GnRH neuron development in mice and humans. Perturbations in this signaling system disrupt the ontogenesis and physiological function of GnRH neurons. Here, we investigate the possibility that non-genetic factors, such as the epigenome, may contribute to KS onset. For this purpose, we developed an embryonic explant model, utilizing the mouse olfactory placode (OP), the

birthplace of GnRH neurons. In our first study, we found that *Fgf8* expression is controlled by both bivalent histone modifications and demethylation events. Specifically, we found that in the embryonic day (E) 9.5 OP, *Fgf8* harbors both H3K4me3 and H3K27me3, while at E13.5, only H3K27me3 is present, indicating a possible role for Fgf8-dependent histone modifications in specifying GnRH neuron fate. Next, we profiled the OP at E10.5 and E13.5 and found an upregulation of all three ten-eleven translocation (TET) enzymes. Tet1, an enzyme involved in the process of demethylation, which converts 5-methylcytosine residues (5mc) to 5-hydroxymethylated cytosines (5hmc), has also been shown to maintain histone bivalency. Accordingly, we directed our studies towards determining the role of Tet1 on *Fgf8* and *Fgfr1* transcription during GnRH neuron ontogenesis. Our immunoprecipitation studies demonstrate that *Fgf8* in the E9.5 OP is enriched with both 5hmC and Tet1 at specific CpG islands, which decreases with age. Recently, we have shown through siRNA experiments that both *Fgf8* and *Fgfr1*, are regulated by Tet1, indicating Tet1 may be an important upstream epigenetic factor involved in the regulation of KS genes. Together, these studies underscore the significance of epigenetics and chromatin modifications to temporally regulated genes involved in KS. Future studies will determine how epigenetic changes affect other KS-related genes and whether these changes result in reproductive deficits.

**Disclosures: M.L. Linscott:** None. **W.C. Chung:** None.

**Poster**

**773. Neuroendocrine Processes: The HPG Axis**

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**Title:** Classical progesterone receptor and Src family kinase are co-expressed and form complexes in the plasma membrane of RP3V neurons

**Authors: *M. FERI**[1], T. CHUON[1], S. ONDREJIK[1], C. CARLSON[1], P. E. MICEVYCH[2], K. SINCHAK[3]
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**Abstract:** In response to proestrous estradiol concentrations in the female rat, hypothalamic astrocytes synthesize and release neuroprogesterone (neuroP), which stimulates neurons in the rostral periventricular region of the third ventricle (RP3V) to release kisspeptin (kiss) that triggers the luteinizing hormone (LH) surge. This neuroP acts through classical progesterone receptors (PGR) that are upregulated by estradiol. Previously, our laboratories have demonstrated that interdependent PGR-Src family kinase (Src) signaling is necessary for inducing the LH surge *in vivo*, and stimulates kiss release (*in vitro*; mHypo51a neurons modeling RP3V kiss neurons) (Mittelman-Smith et. al, 2017) . Based on this PGR-Src interdependence, we tested the hypothesis that a subpopulation of RP3V neurons coexpress PGR and Src, and PGR and Src are in close proximity to form signaling complexes in the plasma membrane. In Experiment I, we established that PGR and Src are colocalized in the RP3V using double-label immunohistochemistry in tissues from ovariectomized (ovx) rats treated with oil or 17β-estradiol benzoate (EB, 2μg). The number of cells expressing PGR in the RP3V were upregulated with EB treatment in comparison to oil controls. EB also increased the number of neurons that coexpress PGR and Src colocalization. In Experiment II, we showed that PGR and Src are in close proximity (40nm) in the RP3V neurons using a Duolink Proximity Ligation Assay from tissues of ovx rats treated with 2μg EB or oil. EB also upregulated Duolink PGR-Src interactions compared to oil controls. In Experiment III, rats were treated with either oil or 50μg EB, and plasma membrane and cytosolic fractions were extracted from RP3V block dissections. Co-immunoprecipitation experiments indicated that PGR and Src form complexes on the plasma membrane and cytosol. The co-expression, close proximity, and physical complexes of PGR-Src support our hypothesis that neuroP signals through RP3V membrane PGR-Src complexes to induce the LH surge.

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**Poster**

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**Title:** Acute stress rapidly inhibits *in vivo* LH pulses and alters Rfrp and Kiss1 neuronal activation in male mice

**Authors: *J. A. YANG**, J. HUGHES, R. PARRA, K. VOLK, A. KAUFFMAN
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**Abstract:** Multiple types of stress, including psychosocial stress, disturb reproductive hormone secretion, but it is not fully understood how or where in the brain this reproductive suppression occurs. Reproductive neural populations upstream of GnRH neurons, such as kisspeptin, neurokinin B, and RFRP-3 (GnIH) neurons, are possible targets for stress to inhibit reproductive hormone secretion, but this has not been well-examined. These upstream populations are either stimulatory (kisspeptin, neurokinin B) or inhibitory (RFRP-3) to the reproductive axis. Our previous work in ovariectomized female mice demonstrated that short-term restraint stress significantly and rapidly reduces *in vivo* LH pulsatility and *Kiss1* neuronal activation, while increasing RFRP-3 neuronal activation. Given reported sex differences in stress hormone secretion and sensitivity to stress exposure, the current study examined whether one-time acute restraint stress also alters endogenous LH pulsatility and neuroendocrine gene expression in male mice. We found that, similar to ovariectomized females, *in vivo* LH pulses in castrated male mice are strongly suppressed by acute restraint stress. This LH pulse suppression is observed in as little as 12 min, suggesting rapid effects of restraint stress on reproductive inhibition. Although hypothalamic *Kiss1*, *Tac2*, and *Rfrp* gene expression did not change at 45, 90, or 180 min restraint stressed males, *Kiss1* neural activation in the arcuate nucleus was decreased by 180 min. Conversely, hypothalamic *Rfrp* neuronal activation was markedly increased on a more rapid scale, after just 45 min of restraint stress, but was attenuated to levels even lower than controls by 180 min of restraint stress, similar to the pattern previously observed in females. Our findings indicate that in the absence of gonadal sex steroids, the neuroendocrine reproductive axis of males responds rapidly to acute stress exposure, similar to females, with increased *Rfrp* neuronal activation and decreased pulsatile LH secretion occurring quickly and decreased *Kiss1* neuronal activation occurring later, after longer stress durations. Additional studies are currently identifying whether the effects of acute restraint stress on reproductive dysfunction are stress hormone-dependent.

**Disclosures: J.A. Yang:** None. **J. Hughes:** None. **R. Parra:** None. **K. Volk:** None. **A. Kauffman:** None.

**Poster**

**773. Neuroendocrine Processes: The HPG Axis**

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**Topic:** F.03. Neuroendocrine Processes

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**Title:** Identifying roles for gonadotropin-releasing hormone and kisspeptin neurons in the development of opioid-induced hypogonadism

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**Abstract:** One understudied aspect of opioid use is the development of opioid-induced hypogonadism, which occurs in the vast majority of opioid users regardless of sex, route of administration, or duration of use. Hypogonadism is characterized by low levels of estrogen and testosterone. The hypothalamic-pituitary-gonad axis consists of Kisspeptin (Kiss1) neurons that stimulate gonadotropin-releasing hormone (GnRH) neurons. Pulses of GnRH stimulate pulses of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary to act on the gonads to promote the production of estrogen and testosterone. We are exploring the actions of opioids and mu-opioid receptor signaling in Kiss1 and GnRH neurons. We have identified the mu opioid receptor (MOR) in the immortalized kisspeptin neurons, KT-aR cells, and GnRH neurons, GT1-7 cells, using qPCR and dermorphin-A594 binding. We have also found that morphine or DAMGO treatment decreases Kiss1 and GnRH transcriptional activity. GT1-7 cells transfected with a GnRH-luc reporter showed reduced GnRH transcription following morphine treatment. KT-aR cells treated with DAMGO show a marked decrease in Kiss1 mRNA using qPCR. These studies suggest a direct effect of MOR on Kiss1 and GnRH transcription, which may contribute to the development of opioid-induced hypogonadism. Responsiveness of GnRH neurons to kisspeptin can be measured by the increase in serum LH following exogenous kisspeptin challenge. The increase in LH following kisspeptin administration was abolished in acutely morphine-treated mice, indicating morphine interference of GnRH neuron responsiveness. Overall, our preliminary findings are beginning to establish the roles of the kisspeptin and GnRH neurons in the etiology of opioid-induced hypogonadism.

**Disclosures: K.J. Tonsfeldt:** None. **L.J. Cui:** None. **P.L. Mellon:** None.

**Poster**

**773. Neuroendocrine Processes: The HPG Axis**

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**Program #/Poster #:** 773.15/YY9

**Topic:** F.03. Neuroendocrine Processes

**Title:** Restricted feeding disrupts circadian timing in the HPG axis in mice

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**Abstract:** In mice, when food availability is restricted to a 4-hour window during the light phase of the light-dark (LD) cycle, a period of food anticipatory activity (FAA) develops for approximately three hours prior to feeding. This anticipatory activity is not under the regulation of master circadian clock in the suprachiasmatic nucleus (SCN), and is thought to be driven by a food entrainable oscillator, the location of which in the brain or body is unknown. Clocks in the ovaries regulate reproductive function, and these clocks are normally synchronized with the overt behavioral rhythms driven by the SCN. Here we hypothesized that under conditions of timed daily restricted feeding the ovarian clock would become desynchronized from the SCN, and that this would have a negative impact on the HPG axis and reproductive function. Herein we examine how circadian timing in the HPG axis is regulated during timed restricted feeding. After entraining to LD conditions, mice (n=30) were placed on restricted feeding (4h) for 14 days in either middle of the light at *zeitgeber time*, ZT6 (RF-day; ZT6-10; ZT0 = lights onset) or in middle of the dark phase at ZT18 (RF-night: ZT18-22). Control group mice were maintained in *ad libitum* food condition. At end of the experiments, mice (n=5) were sacrificed every 4h at six time points starting with ZT0. SCN, pituitary and ovaries were collected and processed for RT-PCR to study genes of interest involved in clock, feeding and reproductive functions. In animals fed ad libitum, estrous-cycle dependent locomotor activity rhythms are apparent, with heightened wheel running activity seen most commonly every fifth day. In animals on restricted feeding regimes, this pattern is lost. AL animals maintain their body weight through the experiment (mean gain 0.1 g). The RF-day animals lost 1.2g on average and the RF-night animals gained 1.9g on average. The differences between feeding conditions were statistically significant ($p < 0.001$). Interestingly, RF-night animals had higher water intake as compared to RF-day group. In both, day and night RF mice, we observed a compromised reproductive system with a significant reduction in uterine horn diameter. Pilot data from qPCR experiments suggests an advance in the rhythm in *per2* expression in the ovary but not the SCN during RF-day, indicating possible desynchrony between clocks in these tissues.These data suggest that desynchrony between the SCN and the ovary may influence reproductive function.

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**Poster**

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**Topic:** F.03. Neuroendocrine Processes

**Support:** NCSU OUR Award

**Title:** Evidence that undernutrition reduces kisspeptin neuron expression in wethers

**Authors: A. N. RENWICK**[1], A. M. THOMPSON[2], A. MATTHEWS[1], M. J. CUMMINGS[1], J. R. SOMMER[1], *C. M. MERKLEY[1], C. C. NESTOR[1]
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**Abstract:** Hypothalamic gonadotropin-releasing hormone (GnRH) neurons are the final central pathway controlling reproduction, and stimulate luteinizing hormone (LH) secretion from gonadotropes in the anterior pituitary. While undernutrition has been shown to suppress GnRH/LH secretion, the central mechanisms that govern this regulation remain to be determined. Since several lines of evidence support the idea that hypothalamic kisspeptin neurons are responsible for the generation of GnRH/LH pulses and thus are essential for reproduction, we hypothesized that undernutrition would reduce the number of kisspeptin neurons in the arcuate nucleus of the hypothalamus of male sheep. Six wethers (approximately 5 months of age) were evenly divided into either a fed to maintain body weight (Fed) group or a feed restricted to lose 15% pre-study body weight (FR) group. Weekly blood samples (every 12 minutes for 4.5 hours) were taken via jugular venipuncture and plasma was stored at -20C until the time of radioimmunoassay. Weekly body weights were recorded and feed amounts were adjusted to achieve desired body weights. At Week 13, animals were euthanized following blood collection, and brain tissue containing the hypothalamus was collected. Hypothalamic tissue was sectioned and immunohistochemistry for kisspeptin in the arcuate nucleus was performed on free-floating sections. At Week 13, the average percent change in body weight was clearly evident (Fed, 10.23 $\pm$ 7.2% vs FR, -17.03 ± 2.8%), and although not significantly different between Fed and FR groups, mean LH was dramatically reduced in two of three FR wethers compared to controls. Interestingly, the number of kisspeptin-immunoreactive neurons was significantly less in FR animals (51.5 ± 12.0 cells/section), compared to Fed animals (153 ± 34.4 cells/section). Therefore, the reduction in kisspeptin cell numbers observed here may be an important contributor to the decrease in GnRH/LH pulses that occur in an undernourished state, and this work provides the first evidence that kisspeptin plays a role in the central mechanism governing GnRH/LH secretion during times of undernutrition in male sheep.

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**Poster**

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**Topic:** F.03. Neuroendocrine Processes

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PAPIIT 216015

**Title:** Transitory inhibition of the suprachiasmatic nucleus´ electric activity by tetrodotoxin microinjection at 14:00 of every stage of the estrous cycle results on a blockade of ovulation in the rat

**Authors: *C. C. SILVA-MENDEZ**[1], G. D. CORTÉS[2], C. Y. JAVIER[2], A. FLORES[2], R. DOMÍNGUEZ[2]
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**Abstract:** The earth is a cyclic world and several environmental variables change in a 24-h basis as a result of its rotation around its own axi. The physiology of lifeforms evolving on it exhibit temporal programs that allows them to be coherent with the external environment. In this sense, they can synchronize to predictable time cues in order to save energy and increase survival chances. Reproduction is not the exception, as a highly timed process depends on both, the reproductive and the circadian system. The core oscillator of the circadian system of mammals resides at the suprachiasmatic nuclei (SCN) and it is pivotal for the regulation of the preovulatory surge of gonadotropins in females. There is evidence to suggest that the SCN may be involved in the regulation of neuroendocrine events that are essential for ovulation and that occur prior of proestrous day. In the present study we explore this possibility by means of temporal inactivation of the SCN. Female rats were implanted with guide bilateral cannulas aimed to the SCN. After full recovery of estrous cycles animals were connected to a micro-infusion system and injected with either tetrodotoxin (TTX) or saline while freely moving on their cages. Injections were performed at 14:00 h of each stage of the estrous cycle and animals were euthanized on the next predicted estrous. The number of ova shed was counted and intact estrous-rats were used as absolute control. All intact animals ovulated (7/7). Saline-treated rats displayed an inhibitory effect that depends on the stage of the estrous cycle when the treatment was performed (proestrous 7/7, metestrous 6/9, diestrous 2/7*, estrous 2/9*; *$p \leq 0.05$ Fisher test vs intact). On the other hand, TTX blocked the ovulation irrespectively of the stage of the cycle (proestrous 0/5*, metestrous 1/4*, diestrous 0/7*, estrous 1/4*; *$p \leq 0.05$ Fisher test vs intact). These results support the idea that the SCN is required for the regulation neuroendocrine events that occur before the preovulatory surge of gonadotropins. Other studies suggests that it may be involved with the preparation of the system to respond to rising levels of estradiol. Experiments designed to disclose the deleterious effect of saline solution are in progress.

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**Poster**

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**Topic:** F.03. Neuroendocrine Processes

**Support:** NCSU OUR Award

**Title:** Activation of central melanocortin signaling stimulates LH secretion in male sheep

**Authors: A. M. THOMPSON**, A. N. RENWICK, A. N. MATTHEWS, M. J. CUMMINGS, J. R. SOMMER, *C. C. NESTOR
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**Abstract:** Insufficient nutrient intake has been shown to impair gonadotropin-releasing hormone (GnRH), and subsequently luteinizing hormone (LH) release, but the central mechanism underlying this reduction during times of undernutrition remains largely unknown. Since others have shown a role for melanocortin regulation of LH secretion in food restricted adult ewes, we hypothesized that central activation of melanocortin signaling would stimulate LH secretion in feed restricted young male sheep. Eight wethers (approximately 5 months of age) were neurosurgically implanted with a chronic guide tube targeting the right lateral ventricle, and fourteen days later were placed into either a fed to maintain body weight group (Fed; n = 4) or a feed restricted group (FR; n = 4) that was fed to lose 15% pre-study body weight. Weekly body weights were recorded and feed amount was adjusted to achieve desired body weights. Weekly blood samples (every 12 minutes for 4.5 hours) were collected and plasma was stored at -20C. When the FR group reached the desired 15% weight loss, all wethers underwent jugular blood sampling while receiving either a central infusion of a melanocortin receptor agonist (MTII) or vehicle, followed by the opposite treatment four days later. At Week 10 the Fed group was at 3.75 $\pm$ 3.8 % of their pre-study body weight, while the FR wethers lost 16.99 $\pm$ 2.0 % of their pre-study body weight. Mean LH was shown to increase in both Fed (20.16 $\pm$ 2.5 ng/ml) and FR (22.97 $\pm$ 2.4 ng/ml) animals with an infusion of MTII, compared to infusion of vehicle (Fed, 16.14 $\pm$ 0.6 ng/ml; FR, 18.46 $\pm$ 1.0 ng/ml). In addition, an infusion of MTII increased LH pulse frequency in one of three Fed animals and three of four FR animals compared to vehicle-treated controls. Thus, central melanocortin signaling appears to be an underlying component of GnRH/LH secretion in both fed and feed restricted wethers, and further work will elucidate the central pathways by which this GnRH regulation occurs.

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**Poster**

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**Topic:** F.03. Neuroendocrine Processes

**Support:** NIH R01 HD082165
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**Title:** Morphological evidence for sexual dimorphism of NK3R-containing neurons in the retrochiasmatic area of sheep

**Authors: *J. LOPEZ**[1], R. MCCOSH[3], M. BEDENBAUGH[4], E. BOWDRIDGE[1], A. LINDO[1], S. HILEMAN[1], R. L. GOODMAN[2]
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**Abstract:** Neurokinin B (NKB) is critical for fertility in humans and stimulates GnRH/LH secretion in humans, primates, and sheep. In sheep, NKB actions in the retrochiasmatic area (RCh) contribute to the induction of the preovulatory LH surge. We previously demonstrated that the LH response to administration of the NKB receptor agonist, senktide, in the RCh is sexually dimorphic. These results raise the possibility that sexual differences in the RCh account, in part, for the inability of estrogen to induce an LH surge in male sheep. In this study, we determined if a neuroanatomical basis exists for sexual dimorphism. Specifically, we characterized sex differences in expression of NK3R- and NKB-containing neurons the arcuate nucleus (ARC), and the amount of NKB-immunoreactive contacts onto NK3R-containing cells in the RCh. To normalize steroid milieu, yearling wethers (rams castrated at 6 weeks of age, n=6) and acutely ovariectomized ewes (9 - 10 months, n=5) of a similar age were treated with estradiol and progesterone (CIDR) implants that mimicked luteal phase concentrations of these steroids. After one (female) and two (male) artificial luteal phases, CIDRs were removed and LH surge-inducing levels of estradiol were administered via subcutaneous implants. Animals were sacrificed the following day and hypothalamic blocks were removed for immunohistochemical and confocal microscopic analysis. In the ARC, the average number of NKB neurons/section was higher in females than males (60.3 ± 4.5 females, 24.8 ± 4.5 males), and the percentage of NKB cells with cytoplasmic NK3R expression was 18.4 ± 3.5 % in females and 12.8 ± 2.6 % in males. There was a greater total number of NK3R-containing neurons in the RCh of females than males (133.8 ± 9.7 females, 81.0 ± 10.7 males) and there were more NKB contacts onto NK3R-containing neurons in the RCh in females (4.59 ± 1.16 contacts/cell) compared to males (0.41 ± 0.32 contacts/cell). These data demonstrate that morphological differences exist between the

sexes in the expression of components of the NKB-NK3R signaling system and support the hypothesis that sex differences in the RCh contribute to the sexual dimorphism of the estrogen induced-LH surge in sheep.

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**Poster**

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**Support:** NIH R01 HD082135
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**Title:** Evidence that the LH surge in ewes involves both neurokinin B-dependent and -independent actions of kisspeptin

**Authors: *R. L. GOODMAN**[1], J. A. LOPEZ[1], M. N. BEDENBAUGH[1], J. M. CONNORS[1], S. L. HARDY[1], S. M. HILEMAN[1], L. M. COOLEN[2], M. N. LEHMAN[3]
[1]West Virginia Univ., Morgantown, WV; [2]Physiol. & Biophysics, [3]Univ. of Mississippi Med. Ctr., Jackson, MS

**Abstract:** It is generally recognized that kisspeptin plays a key role in induction of the LH surge in sheep and we have reported evidence that neurokinin B (NKB) does so as well. Specifically, disrupting NKB signaling in the retrochiasmatic area (RCh) using either an antagonist to its receptor, NK3R, or lesions of NK3R-containing neurons in the RCh with a saporin conjugate (NK3-SAP) reduced the amplitude of the estrogen-induced LH surge by 50%. Because a KISS1R antagonist (p271) also produced a 50% decrease in surge amplitude, we hypothesized that these two systems are organized in series with NKB actions in the RCh stimulating kisspeptin release. If this is the case, then the combination of NK3R lesions and a KISS1R antagonist should produce the same inhibition as either treatment alone. This experiment tested this prediction using a 2 x 2 design. Breeding season ewes were ovariectomized and immediately given an estradiol (E) implant sc and two progesterone implants (CIDRs) intravaginally that produced luteal phase levels of these steroids. Ewes then received bilateral injections of either NK3-SAP (n=6) or Blank-SAP (n=5) into the RCh. Three weeks later, an artificial follicular phase was produced by inserting four 3 cm long E implants 24 hrs after CIDR removal and either saline or p271 was infused into the lateral ventricle for 16-24 hrs after E implantation; LH was monitored every 2-4 hrs for two days. CIDRs were then reinserted and the protocol repeated in a cross-over design so that all ewes received saline and p271 treatment. In Blank-SAP ewes, p271

decreased the peak of the LH surge from 61.2 ± 7.6 to 27.4 ± 4.6 ng/mL and delayed it 8 hrs (from 26.5 ± 0.5 to 34.1 ± 1.2 hrs post E implantation). The NK3-SAP injections alone decreased the peak of the LH surge to 29.7 ± 10.7 ng/mL compared to Blank-SAP, but the peak was not further inhibited by p271 in these NK3-SAP-treated ewes (24.4 ± 1.4 ng/mL). However, p271 delayed the peak of the LH surge (from 28.8 ± 1.2 to 34.8 ± 2.1 hrs post E implantation) in the ewes injected with NK3-SAP. Based on these results, we propose that kisspeptin has two roles in the LH surge in ewes: it initiates the surge independent of NKB signaling in the RCh, and maintains LH secretion during the surge by a NKB-dependent system.

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**Poster**

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**Title:** Kisspeptin, neurokinin B, and dynorphin mRNA regulation by ovarian steroids in the arcuate nucleus of the ewe: Simultaneous analysis of all three KNDy mRNAs in individual neurons

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**Abstract:** Neurons of the hypothalamic arcuate nucleus (ARC) that co-express kisspeptin, neurokinin B (NKB) and dynorphin (Dyn), termed KNDy cells, play a pivotal role in controlling pulsatile secretion of gonadotropin-releasing hormone (GnRH) and the negative feedback influence of estradiol (E) and progesterone (P), on GnRH secretion.Studies of steroidal regulation of KNDy peptide expression provided the basis for their proposed role in negative feedback but interpretation of changes at a cellular level has been limited by analyses of a single KNDy peptide mRNA at a time. In addition, co-expression of all three KNDy peptides has largely been based on co-localization of only two peptides at a time. To circumvent these limitations, we performed triple-label *in situ* hybridization to simultaneously examine co-expression and steroid regulation of transcripts for all three peptides in the same KNDy neuron. Four groups of breeding season ewes (n=4/ea) were used: ovariectomized(OVX), OVX+E,

OVX+P, and OVX+E+P ewes. E and P implants were inserted at the time of OVX and produced levels similar to those seen during the luteal phase of the ovine estrous cycle. Tissue was collected 7-10 days post OVX, perfused and blocks containing the hypothalami were dissected. Coronal sections were cut on a cryostat and processed for triple-label detection using RNAscope for ovine kisspeptin, NKB, and Dyn in the middle division of the ARC (3 sections/animal). The results show 94% co-localization of all three transcripts (independent of experimental treatment), confirming the high degree of co-expressionof KNDy peptides. However, there was substantial heterogeneity among KNDy neurons in the relative amount of labeling for each transcript, due in part to differential effects of steroid treatments on the mRNA content of individual neurons for each peptide. Preliminary data indicates that E treatment decreased kisspeptin mRNA, increased NKB mRNA and had no effect on Dyn mRNA compared to OVX animals. P treatment decreased NKB and Dyn mRNA levels compared to OVX ewes but had no effect on kisspeptin mRNA. Finally, OVX+E+P animals showed increased NKB mRNA levels and decreased Kiss and Dyn mRNA compared to OVX animals. Results are consistent with previously observed inhibitory effects of E on kisspeptin in the sheep ARC, but E appears to be stimulatory to NKB mRNA expression in the same KNDy neurons, in contrast to its inhibition of NKB peptide in previous work. The inhibitory effect of P on Dyn mRNA differs from previous results that OVX decreased expression compared to ovary intact, and raises the possibility that ovarian factors, other than E and P, may control expression of Dyn mRNA.

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**Poster**

**773. Neuroendocrine Processes: The HPG Axis**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 773.22/YY16

**Topic:** F.03. Neuroendocrine Processes

**Support:** NIH R01 HD082135
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**Title:** Evidence that nitric oxide from somatostatin-containing neurons is critical for the LH surge in sheep evidence that nitric oxide from somatos evidence that nitric oxide from somatostatin-containing neurons is critical for the LH surge in sheep

**Authors: *R. MCCOSH**[1], J. A. LOPEZ[2], M. N. BEDENBAUGH[2], J. M. CONNORS[2], S. L. HARDY[2], S. M. HILEMAN[2], R. L. GOODMAN[3]
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**Abstract:** Three groups have proposed that somatostatin (SST) neurons within the ventral lateral aspect of the ventral medial nucleus (vlVMN), that contain estrogen receptor alpha, contribute to the generation of the LH surge in sheep because c-Fos expression in these SST neurons increases during the surge. However, SST generally inhibits LH secretion in sheep and we recently reported that neither a SST receptor 2 agonist nor antagonist altered the timing or amplitude of the LH surge. One simple explanation for the discrepancy between the pharmacological and c-Fos data is that the activated SST cells contain another signaling molecule important for the LH surge and, based on colocalization data in the rat, we hypothesized that this second molecule is nitric oxide (NO). The first experiment tested this hypothesis by determining if c-Fos expression only increased in SST neurons that also contained neuronal NO synthase (nNOS). Triple-label immunohistochemistry was performed on hypothalamic tissue collected from sheep during the luteal phase (n=4), the early follicular phase (n=4) or during the LH surge (n=4). The percentage of SST cells that contained nNOS was not altered by phase of the estrous cycle (51.6 ± 5.3%). The total population of SST cells in the vlVMN had a significant increase in c-Fos expression during the surge compared to other phases as reported previously. Interestingly, the population of SST cells that also contained nNOS, but not the population that only contained SST (nNOS immuno-negative) had an increase in the percentage that contained c-Fos during the surge. To determine whether NO is critical for the LH surge in sheep we infused L-NAME, a NOS inhibitor, or saline into the third ventricle of 5 ewes in a cross-over design. An LH surge was induced using a well characterized model involving progesterone pretreatment followed by insertion of 4 estradiol implants. L-NAME (0.04mmoles/hr) or saline (60uL/hr) was infused from 14-24 hrs after estradiol implantation and blood samples collected every 2-4 hrs were assayed for LH. This procedure was repeated, so that each animal received L-NAME and saline (2 weeks apart). Normal LH surges were observed in 4 of 5 ewes while infused with saline (amplitude: 49.6 ± 8.6 ng/mL); the remaining ewe was excluded from further analysis. Three out of 4 animals had no detectable LH surge when treated with L-NAME, the other ewe had an LH surge that began before the start of L-NAME infusion. These findings clarify the contradictory data on a role for SST in the LH surge and support the hypothesis that NO produced by a population of SST neurons in the vlVMN is critical for the LH surge in sheep.

**Disclosures: R. McCosh:** None. **J.A. Lopez:** None. **M.N. Bedenbaugh:** None. **J.M. Connors:** None. **S.L. Hardy:** None. **S.M. HIleman:** None. **R.L. Goodman:** None.

**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

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**Topic:** F.03. Neuroendocrine Processes

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**Title:** Thyrotropin-releasing hormone (TRH) in the brain and pituitary of the teleost, Clarias batrachus and its role in regulation of hypophysiotropic dopamine neurons

**Authors: *O. SINGH**[1], S. KUMAR[1], D. R. PRADHAN[1], A. J. SAKHARKAR[2], R. M. LECHAN[3], P. S. SINGRU[1]
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**Abstract:** Thyrotropin-releasing hormone (TRH) is a principal regulator of the hypothalamic-pituitary-thyroid axis in mammals. It also regulates prolactin secretion directly or indirectly via its action on tuberoinfundibular dopamine neurons. Although the peptide is abundantly expressed in the brain of teleosts and believed to mediate neuronal communication, empirical evidence is lacking. To this end, we analyzed expression of pro-TRH mRNA and mapped TRH-immunoreactive (TRH-ir) elements in the brain and pituitary, and explored its role in regulation of hypophysiotropic dopamine (DA) neurons in the adult, female catfish, *Clarias batrachus*. Partial pro-TRH transcript from *C. batrachus* transcriptome showed six TRH progenitors repeats. Using qRT-PCR, pro-TRH transcript was observed in a number of different brain regions. Immunofluorescence using specific TRH antiserum, showed TRH-ir cells/fibers to be particularly abundant in the olfactory bulb, telencephalon, preoptic area (POA), hypothalamus, midbrain and hindbrain. In the pituitary, TRH-ir fibers were seen in the neurohypophysis, proximal pars distalis, and pars intermedia but not in rostral pars distalis. In POA, distinct TRH-ir cells were seen in nucleus preopticus periventricularis anterior (NPPa). Compared to postspawning and resting phases, a significant increase ($P<0.001$) in TRH-ir was observed in NPPa of fish collected during preparatory and prespawning phases, reaching a peak in the spawning phase. Although TH neurons in the NPPa project to the pituitary, none of the TRH neurons in this region retrogradely accumulated DiI following implants into the pituitary. However, approximately 87±1.6% NPPa TH neurons were densely innervated by TRH-containing fibers. Superfused POA slices containing NPPa treated with TRH (0.5-2 μM) significantly reduced ($P<0.001$) TH concentrations in the tissue homogenate and the percent fluorescent area of TH-ir in the POA sections containing the NPPa. We conclude that TRH in the brain of *C. batrachus* regulates a range of physiological functions but in particular, serves as potential regulator of hypophysiotropic DA neurons and reproduction.

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**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 774.02/YY18

**Topic:** F.03. Neuroendocrine Processes

**Title:** TRH and TRH-like peptides participate in the interaction of oxytocinergic and serotonergic systems of the male rat hypothalamus and epididymis

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**Abstract:** Oxytocin (OT) analogs and mimetics have exciting potential as therapeutics for an array of psychiatric illnesses including major depression, autism, social anxiety disorder, and Prader-Willi syndrome. Carbetocin, a long-acting OT analog, stimulates the release of TRH and TRH-like peptides throughout male rat brain and peripheral tissues. TRH and TRH-like peptides ameliorate the effects of depression, anxiety, epilepsy, neurodegeneration and aging, and are responsive to changes in serotonin levels. TRH-like peptides have the structure pGlu-X-Pro-$NH_2$, X-TRH, where "X" can be any amino acid residue. Serotonin has been reported to participate in the anxiolytic effects of OT. This suggests that these tripepides also participate in the interactions of OT with serotonin. We therefore have ip injected young adult male Sprague-Dawley rats, divided into 4 groups, 4 rats/group, with either saline, carbetocin, ritanserin, a long-acting 5-$HT_{2A/2C}$ receptor antagonist, or carbetocin plus ritanserin to assess the role of TRH and TRH-like peptides as mediators of the neurobiochemical, metabolic, and reproductive effects of OT and serotonin. TRH and TRH-like peptide levels were measured, by a combination of HPLC and RIA, in hypothalamus, striatum, medulla oblongata, anterior cingulate, entorhinal cortex, nucleus accumbens, amygdala, posterior cingulate, cerebellum, piriform cortex, hippocampus, adrenals, epididymis, prostate, testis and pancreas. Using 2-way ANOVA, we found the significance level for a combined action of carbetocin with ritanserin in the release of TRH by hypothalamus to be $p < 0.008$, consistent with previous reports of oxytocinergic and serotonergic interacting systems within the supra-optic and paraventricular nuclei. The corresponding significance for Leu-TRH release in response to the combined action of carbetocin and ritanserin within the epididymis was $p < 0.002$. This latter observation agrees with our previous report of increased Leu-TRH levels in epididymis in response to the highly selective serotonin reuptake inhibitor, escitalopram. We conclude that TRH and TRH-like peptides participate in the interactions of the oxytocinergic and serotonergic systems within the hypothalamus and epididymis.

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**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

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**Topic:** F.03. Neuroendocrine Processes

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**Title:** Role of prokineticin receptor 2 expressing neurons in adult mice

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**Abstract:** Kallmann Syndrome (KS) is characterized by hypogonadotropic hypogonadism coupled with anosmia. A subset of KS patients carries mutations in the prokineticin receptor 2 gene, *PROKR2*. These findings coupled with global deletion of *Prokr2* in mice have shown PROKR2 signaling to be important for GnRH neuronal migration and olfactory bulb formation during embryonic development. However, the role of PROKR2 neurons in adult physiology has not been determined. *Prokr2* mRNA is widely expressed throughout the adult brain suggestive of PROKR2 signaling in various physiological systems such as circadian rhythm, metabolism and reproduction. We have recently generated and validated a mouse model expressing Cre-recombinase driven by the Prokr2 promoter. To determine the potential roles of PROKR2 signaling in adult mice and further delineate a previously reported reproductive role, we used the Prokr2-Cre mouse model in combination with chemogenetic technology, i.e. the Designer Receptor Exclusively Activated by Designer Drugs, DREADD. We assessed the effects of chronic inhibition of Prokr2-Cre cells in adult mice. We found that mice expressing the modified inhibitory muscarinic receptor, hM4Di, in a cre dependent manner had disrupted estrous cycles, higher water intake and food intake during Clozapine N-Oxide administration. Our findings are in agreement with the expression of Prokr2 mRNA in areas associated with reproductive control (e.g., medial nucleus of the amygdala), water intake (e.g., subfornical organ) and food intake (e.g., dorsomedial nucleus of the hypothalamus and lateral parabrachial nucleus). Additional studies targeting specific Prokr2-Cre cell populations are under way to determine the neuronal populations responsible for these physiological responses.

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**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

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**Topic:** F.03. Neuroendocrine Processes

**Support:** Health Research Council of New Zealand

**Title:** Periventricular kisspeptin neurons project to the paraventricular nucleus in late-pregnant mice

**Authors: *C. H. BROWN**, M. JACKSON, R. AUGUSTINE
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**Abstract:** Oxytocin is secreted into the bloodstream from the posterior pituitary gland to stimulate uterine contractions during birth and milk let-down during lactation. Oxytocin secretion is triggered by action potentials initiated in the cell bodies of magnocellular neurons in the hypothalamic paraventricular and supraoptic nuclei. Kisspeptin is synthesised by neurons in the hypothalamic periventricular, anteroventral periventricular and arcuate nuclei. Intracerebroventricular kisspeptin administration consistently increases oxytocin neuron firing rate only in late pregnancy. Using immunohistochemistry, we have found that kisspeptin fibre density in the paraventricular and supraoptic nuclei of late-pregnant mice (gestation day 19; G19) is higher than in non-pregnant, early-pregnant (G7), mid-pregnant (G14) and lactating (post-partum day 7) mice. Retrograde tracer was injected into the paraventricular nucleus of pregnant mice under anaesthesia and four days later, on G19, the mice were deeply anaesthetised and perfused with 4% paraformaldehyde. The brains were removed and processed for immunohistochemistry to identify kisspeptin cell bodies. Kisspeptin cells were retrogradely labelled from the paraventricular nucleus in the periventricular nucleus but not in the anteroventral periventricular nucleus or arcuate nucleus. Taken together, these results suggest that periventricular kisspeptin neurons contribute to increased activity of oxytocin neurons in late pregnancy. It remains to be established whether the emergence of this excitatory kisspeptin projection is important for birth.

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**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

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**Program #/Poster #:** 774.05/YY21

**Topic:** F.03. Neuroendocrine Processes

**Title:** Oxytocin receptor expressing neurons in the perinuclear zone of the supraoptic nucleus in the mouse hypothalamus

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**Abstract:** Oxytocin is synthesized in magnocellular neurons located in the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus. Oxytocin-containing vesicles travel from the soma to axon terminals within the neurohypophysis where oxytocin is released into the general circulation in response to physiological demands. Oxytocin induces contraction of the uterus and mammary glands during parturition and milk ejection, respectively. The release of oxytocin largely depends upon the pattern of neural activity of the synthesizing neurons. The firing pattern in oxytocin neurons changes dramatically from slow random firing to short and high frequency bursts of action potentials preceding each milk ejection and uterine contraction. This bursting activity is synchronized among all oxytocin neurons in both the SON and PVN resulting in a bolus release of oxytocin into the general circulation. In addition to the release from the neurohypophysis, oxytocin is also released from the soma and dendrites of oxytocin neurons in response to physiological stimuli, such as parturition and suckling. The increased somato-dendritic release of oxytocin is essential to the onset of the milk ejection reflex and enhances the amplitude and frequency of suckling-induced bursts of action potentials that occur simultaneously in all oxytocin neurons. The effect of the somato-dendritic release of oxytocin is thought to be mediated by the oxytocin receptor (OXTR) on the oxytocin neurons themselves via an autocrine-paracrine mechanism. The present study was conducted to determine if the expression of OXTR in oxytocin neurons changes during reproductive states of females using OXTR-Venus reporter mice. Contrary to our expectation, no OXTR-Venus was found in oxytocin neurons in the SON or PVN. Instead, OXTR-Venus was found in non-oxytocin neurons in the perinuclear zone (PNZ), an area immediately dorsal to the SON. These OXTR-Venus neurons possess processes that project to oxytocin neurons in the SON. Moreover, the number of OXTR-Venus neurons in the PNZ from lactating females was significantly greater than that from virgin females or from non-pregnant post-weaning females. These findings suggest that the effect of somato-dendritic release of oxytocin on oxytocin neurons is mediated by OXTR neurons in the PNZ, instead of OXTR on oxytocin neurons themselves.

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**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

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**Topic:** F.03. Neuroendocrine Processes

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**Title:** Distribution of estrogen receptor and progestin receptors relative to estrogen receptor beta-containing neurons in the mouse hypothalamic paraventricular nucleus

**Authors: *N. H. CONTOREGGI**[1], J. PARK[1], A. C. OVALLES[1], E. M. WATERS[2], M. J. GLASS[1], T. A. MILNER[1]
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**Abstract:** The hypothalamic paraventricular nucleus (PVN) is a critical neural coordinator of brain cardiovascular circuits involved in sympathetic and neuroendocrine systems pivotal for blood pressure regulation. Gonadal steroid hormones, in particular estrogens, acting in the hypothalamus have been implicated in blood pressure. Studies from our lab and others implicate estrogen receptor beta (ERβ) within the PVN as a significant mediator of estrogen's actions on blood pressure regulation. There is also evidence that signaling at other gonadal hormone receptors with known hypothalamic distributions, including estrogen receptor alpha (ERα) and the progestin receptor (PR), play a role in central cardiovascular processes. However, the cellular and subcellular relationships of ERα and PR with ERβ in the PVN are uncertain. Using light microscopic and dual labeling immunoelectron microscopic analyses, this study examined the distribution of ERα and PR, which is regulated by estrogen levels, relative to ERβ in the PVN. Neurons expressing ERβ were identified in BAC transgenic ES2 enhanced green fluorescent protein (EGFP) expressing female and male mice. By light microscopy, ~10 times more ERβ-EGFP neurons were seen compared to ERα-immunoreactive nuclei in rostral, medial and caudal levels of the PVN. Additionally, ~3 times more ERβ-EGFP neurons were seen compared to PR-immunoreactive nuclei in these same subregions. By electron microscopy, both extranuclear ERα- and PR-labeling were primarily detected in axons and axon terminals, indicating a prominent presynaptic distribution of these proteins in the PVN. Occasionally, extranuclear ERα- and PR-labeling were detected in soma, dendrites, and in glial processes, also suggesting roles for these proteins in postsynaptic and glial signaling in the PVN. Dual label electron microscopy revealed that axon terminals containing ERα and PR sometimes synapsed on ERβ-EFGP containing soma and dendrites, and that few soma with ERα-immunoreactivity colocalized ERβ-

EGFP. Together with previous studies, these findings indicate that ERα and ERβ are expressed in distinct populations of PVN neurons and that ERα, PR and ERβ are positioned for the modulation of different signaling functions in the PVN.

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**Poster**

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**Title:** Glutamate spillover from Kiss1$^{ARH}$ neurons induces a slow inhibitory postsynaptic potential in NPY/AgRP neurons through mGluR7 in female mice

**Authors: *J. QIU**[1], M. A. BOSCH[1], T. L. STINCIC[1], O. K. RONNEKLEIV[1,2], M. J. KELLY[1,2]
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**Abstract:** Kisspeptin (Kiss1) neurons are essential for reproduction, but their role in the control of energy balance and other homeostatic functions remains unclear. Previously, optogenetic stimulation of arcuate nucleus Kiss1 (Kiss1$^{ARH}$) neurons revealed glutamatergic input to NPY/AgRP neurons, and high-frequency photo-stimulation of Kiss1$^{ARH}$ neurons generated slow inhibitory postsynaptic potentials (IPSPs) in NPY/AgRP neurons in male mice (Nester et. al., 2016). Using scRT-PCR analysis, we found that the majority of NPY/AgRP neurons expressed group III metabotropic glutamate receptors, mGluR7. To pharmacologically elucidate the postsynaptic metabotropic glutamate response in NPY/AgRP neurons, we utilized the group III selective mGluR7 allosteric agonist, AMN082 (10 μM), and found that it hyperpolarized and inhibited firing of NPY/AgRP neurons. In addition, AMN082 in the presence of TTX, CNQX and AP5 blockade induced an outward current in NPY/AgRP neurons. The I-V relationship of AMN082 induced current exhibited inward rectification and a reversal potential at $E_{K^+}$, the hallmark of activation of G protein-coupled inwardly rectifying $K^+$ channels. Importantly, AMN082 was significantly ($p$<0.005) more efficacious in NPY/AgRP neurons following E2-treatment of OVX females, indicating that there was a more robust E2-induced inhibition of NPY/AgRP neurons. Furthermore, high-frequency photo-stimulation (20 Hz) of Kiss1$^{ARH}$ neurons induced a slow IPSP in NPY/AgRP neurons, which was blocked by mGluR7 negative allosteric modulator, ADX71743 (10 μM). Therefore, NPY/AgRP neurons in females receive

frequency-dependent glutamatergic synaptic input (glutamate spillover) from Kiss1$^{ARH}$ neurons and are inhibited by activation of mGluR7, which may be a critical pathway by which Kiss1 neurons coordinate energy homeostasis and reproduction.

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**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

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**Title:** Estradiol signals via diverse receptors to inhibit KNDy peptides but increases the excitability of kisspeptin neurons in the arcuate nucleus

**Authors: *M. A. BOSCH**[1], J. QIU[1], M. J. KELLY[1,2], O. K. RONNEKLEIV[1,2]
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**Abstract:** Kisspeptin (Kiss1) neurons in the hypothalamic arcuate nucleus (Kiss1$^{ARH}$) co-express Kiss1, neurokinin B and dynorphin (KNDy), all of which are down regulated in females in the presence of elevated physiological levels of circulating 17β-estradiol (E2). Kiss1$^{ARH}$ neurons also co-express vesicular glutamate transporter 2 (vGluT2), and release glutamate. To explore a potential E2 regulation of *Slc17a6* (*Vglut2)* expression in females, we dispersed and harvested pools of Kiss1$^{ARH}$ neurons from ovariectomized (OVX) and OVX + E2-treated mice and used real-time PCR for quantitative analysis of changes in gene expression. In contrast to the peptide neurotransmitters, mRNA that encodes for vGluT2 (*Slc17a6*) was increased in Kiss1$^{ARH}$ neurons in E2-treated females by ~ 2-fold ($p<0.01$). Similarly, *Cav3.1*, *Hcn1* and *Hcn2* mRNAs, underlying T-type calcium and h-current, respectively, were increased by 2-3 fold ($p<0.01$). In addition, both T- and h-currents as well as neuronal excitability (measured as rebound excitation), were increased in Kiss1$^{ARH}$ neurons with E2-treatment. Since E2 binds to multiple receptors, we determined which estrogen receptors (ERs) were involved by harvesting pools of Kiss1$^{ARH}$ neurons from vehicle and STX (Gq-mER ligand)-treated females. qPCR analysis revealed that the pacemaker channels (*Cav3.1* and *Hcn1)* mRNA levels were increased in Kiss1 neurons from STX-treated females ($p<0.01$). In contrast *Kiss1*, *Tac2* and *Slc17a6* mRNAs were not affected by the STX treatment. Together, these studies provide evidence that the STX-

responsive Gq-mER is expressed in Kiss1$^{ARH}$ neurons and upregulates channels to increase the excitability of Kiss1$^{ARH}$ neurons, but does not down-regulate the peptide neurotransmitters. In addition, the E2-driven increased expression of *Slc17a6* could be via ERα- or ERβ-signaling. Therefore, E2 acts via diverse receptors and signaling pathways to decrease the expression of neuropeptides but increases the expression of vGluT2 and ion channels that are important for Kiss1$^{ARH}$ neuronal excitability.

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**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

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**Title:** Estrogenic signaling alters neuronal excitability and neurotransmitter release from hypothalamic POMC neurons

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**Abstract:** While the actions of estrogens are traditionally viewed as relatively slow nuclear-initiated changes in gene expression, estrogen receptors (ERs) are also capable of mediating rapid, non-genomic actions. Interestingly, the electrophysiological effects of E2 in proopiomelanocortin (POMC) neurons retain efficacy in ERα, ERβ, double ER, and GPER 1 knockout mice, indicating the presence of additional ER subtypes. The compound STX is a selective agonist for a Gαq coupled membrane-bound ER that recapitulates many of the behavioral effects of E2. Specifically, STX also produces a significant decrease in the food intake and body weight of ovariectomized (OVX) female rodents. Supporting this phenotype, STX exerts divergent effects on POMC and neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons of the arcuate nucleus of the hypothalamus (ARH), respectively enhancing or attenuating their function. We studied these ARH populations using POMC$^{GFP}$ or POMC$^{Cre}$ mice in conjunction with viral vectors for channelrhodopsin and GCaMP6. First, quantitative single cell RT-PCR and determined that the relative expression of *Vglut2* mRNA was significantly ($p<0.05$) elevated in proestrous versus OVX female mice. Next using whole cell patch clamp and optogenetics, we found that E2-treated OVX females (n=9) displayed higher glutamate release

probability compared to oil-treated OVX controls (n=12) ($p<0.05$). In preliminary experiments, we observed a rapid, STX-mediated increase in intracellular calcium levels in $POMC^{Cre}$ neurons expressing GCaMP6, which facilitates neurotransmitter release. STX has also been shown to desensitize $GABA_B$ receptors in POMC neurons (Qiu, J. Neurosci 2006) which would also enhance release. Indeed, acute bath application of 10 nM STX (20 minutes) increased glutamate release probability (n=15, $p<0.01$) even in the presence of cycloheximide (n=3). This enhanced release likely inhibits NPY/AgRP neurons through group III metabotropic glutamate receptors expressed on NPY/AgRP neurons (Qiu SFN 2018 poster). In addition, high frequency (20 Hz) stimulation generated a slow outward current that reversed near $E_{k+}$ and was antagonized by naloxone, indicative of β-endorphin release whose expression is upregulated by E2 (Thornton,J. Comp. Neurol. 1994). Finally, NPY/AgRP neurons expressed μ-opioid receptor mRNA and were potently inhibited by the selective agonist DAMGO (EC50 ≈ 90 nM, n=11). Therefore, POMC excitability and neurotransmission are enhanced by E2, which would facilitate decreased food consumption through inhibition of NPY/AgRP neurons.

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**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

**Location:** SDCC Halls B-H

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**Title:** The physiological role of insulin produced by neurons in the paraventricular nucleus of the hypothalamus (PVN)

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**Abstract:** Although there are many reports for insulin production in the central nervous system (CNS), a physiological role of locally synthesized-insulin in the CNS remains unknown. In previous work, we also identified the mechanism of insulin synthesis in the hypothalamus, but the role of hypothalamic insulin is not revealed. To address this, we tried to find an origin of hypothalamic insulin, which will introduce a target of locally synthesized-insulin anatomically. Insulin mRNA expression was found in neurons of the paraventricular nucleus of the

hypothalamus (PVN), and proinsulin positive signals were also observed in PVN neurons. C-peptide, a by-product of insulin processing, was found in the external zone of the median eminence (ME), where nerve terminals of PVN neurons are located. To determine whether insulin secreted from PVN neurons is functional or not, PVN insulin was silenced through the administration of lentiviral shRNA. The knockdown of PVN insulin significantly decreased c-peptide positive signals in the ME and phospho-AKT levels in the pituitary gland, suggesting that insulin is secreted from PVN neurons and activate insulin signaling of the pituitary gland. Collectively, these data demonstrate that insulin is synthesized locally in the PVN and secreted from the ME to the pituitary gland, and the regulation of pituitary insulin signaling is the physiological role of PVN insulin.

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**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

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**Program #/Poster #:** 774.11/ZZ3

**Topic:** F.03. Neuroendocrine Processes

**Title:** Neurodegenerative pathways in islet neuroendocrine cells in type 1 diabetes

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**Abstract:** Type 1 diabetes is a multi-stage autoimmune disease that develops over multiple years and results from insufficient numbers of functional beta-cells. Type 1 diabetes is one of the most costly diseases in the U.S. requiring life-long insulin replacement therapy and with many co-morbidities including neuropathy, retinopathy, nephropathy and cardiovascular disease. As yet, current therapies are unable to preserve or restore beta-cell function, representing a gap in our understanding of disease pathophysiology. While GWAS studies have identified the HLA and insulin genes as key determinates of risk, over 50 additional genes are associated with the disease. Beta-cells and neurons share a number of important morphological and functional similarities. We propose that characterization of the neuroendocrine phenotype of beta-cells during type 1 diabetes progression could uncover new pathways amenable to targeted therapy. The aim of this study was to determine gene expression profiles in islet neuroendocrine cells from subjects in different stages of type 1 diabetes progression. Pancreas sections were obtained from the JDRF Network for Pancreatic Organ Donors with Diabetes program (Dr. Mark Atkinson). Subjects were matched by age, gender, and BMI from 3 donor groups: donors without diabetes (controls), asymptomatic islet-related autoantibody positive (AAb+) donors, and donors with type 1 diabetes (N=4/group). Islet sections were obtained from fresh frozen samples using laser microdissection and RNA extracted using PicoPure columns (Arcturus). Quality control

analyses were performed using an Agilent Bioanalyzer for RIN and concentration. Differential gene expression and pathway analysis were performed after amplification for low sample input RNA (4 ng) using the nCounter neuropathology panel containing a panel of 770 genes with 10 housekeeping genes (Nanostring). Key pathways showing significant down regulation included transmitter synthesis and storage, carbohydrate metabolism, unfolded protein response, and transcription and splicing. Differential gene expression showing significant up-regulation included pathways associated with autophagy, activated microglia, tissue integrity, and cytokines. Interestingly, pathways were differentially regulated between AAb+ and type 1 diabetes for axon and dendrite structure, oxidative stress, neural connectivity and transmitter synthesis and response. Islets in the type 1 diabetes exhibit differential gene expression patterns associated with neurodegeneration. Future studies will be aimed at preventing neurodegeneration in human islets.

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**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

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**Topic:** F.03. Neuroendocrine Processes

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**Title:** Melanin-concentrating hormone receptor 1 (MCHR1) immunoreactivity along the reproductive cycle of the female mouse (Mus musculus)

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**Abstract:** The melanin-concentrating hormone (MCH) system is a highly-conserved neural network of peptides, receptors, and their far-reaching connections in the vertebrate central nervous system. This peptidergic system has been implicated in several biological processes,

especially on the coordination of motivated behaviors. The actions of MCH are mediated by two G protein-coupled receptors, termed MCHR1 and MCHR2. All vertebrates with available genetic information have a copy of *Mchr1* in their genome, suggesting profound and fundamental actions of this receptor on the survival of those organisms and the continuity of their species. Although a considerable body of knowledge was generated from the study of MCHR1, including its deletion and the use of agonists and antagonists, there is a paucity of information regarding this receptor synthesis and distribution in the central nervous system. Previous works have focused on the expression of the *Mchr1* gene in both rats and mouse, with little regard to the synthesis of the receptor, its subcellular localization, and the relationship between this receptor and physiological parameters of the animal, such as sex and the reproductive stage. Therefore, we proposed in this work to describe in detail the distribution of MCHR1 in the central nervous system of male and female mice, including all stages of the female reproductive stage: the four estrous cycle phases, gestation, early-, mid- and late-lactation and post-lactation. The main subcellular localization of MCHR1 is in the primary cilium, a specialized sensory structure that plays a key role in the detection of free signals on the extracellular fluid. Primary cilia immunoreactive to MCHR1 are found widespread in the central nervous system, including several cortical fields, subcortical olfactory areas, the striatum, the hippocampus, some thalamic and hypothalamic nuclei, amygdaloid subnuclei, discrete brainstem areas and the dorsal spinal cord. The most remarkable reproductive stage-linked alteration in MCHR1 synthesis we observed was in the granular layer of the dentate gyrus, with the immunoreactive signal to MCHR1 almost undetectable in estrous-cycling animals and increasing in the infrapyramidal blade of the dentate gyrus as lactation progresses. Our results indicate that MCHR1 is ideally positioned to detect free MCH in the extracellular fluid. Furthermore, the reproductive stage can alter the synthesis of this receptor, suggesting new mechanisms for MCH action on sexual and maternal behavior. We believe this work may be of significance for the several groups that study MCH and hypothalamic peptides of homeostatic control.

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**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

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**Title:** Neuroanatomical characterization of melanin-concentrating hormone [MCH] in the hypothalamus of male Neotomodon alstoni [N. alstoni] volcano mice

**Authors: *D. S. BATTAGELLO**[1], G. B. DINIZ[1], J. D. REYES-MENDOZA[2], E. RAMOS[2], C. LUNA[2], M. MIRANDA-ANAYA[3], T. MORALES[2], J. C. BITTENCOURT[1,4]
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**Abstract:** *Neotomodon alstoni*, a volcanic mouse, is an endemic and monogamic species in Mexico. Half of these animals develop obesity when feed with standard rodent chow under captive conditions. Little is known about the neural or metabolic mechanisms that lead to the spontaneous onset of their obesity. A potential candidate is melanin-concentrating hormone [MCH], a neuropeptide predominantly located in hypothalamic regions of rats and mice that is related to several functions, such as control of energy expenditure, sexual and maternal behavior, hormone secretion and REM-sleep control. The lack of a detailed morphological description of the MCH system in *N. alsto*ni impairs us from detecting particular morphological characteristics that may explain their metabolic differences. The need for an *N. alstoni* description is further strengthened by recent studies from our group that suggest anatomical differences in the MCH system among rodents. Therefore, we set to provide neuroanatomical data concerning the MCH system, through the analysis of the distribution of MCH immunoreactivity in the hypothalamus of male *N. alstoni* mice. Nissl stain of intervening sections was used to provide cytoarchitectonical reference. In this species, the lateral hypothalamic area contains most MCH-immunoreactive [MCH-ir] neurons, followed by the perifornical nucleus, anterior hypothalamic area and posterior aspect of anterior hypothalamic area, and the *zona incerta*. Despite the lack of neurochemical data, we suggest the existence of an incerto-hypothalamic area with fewer MCH-ir neurons than that described for rats and mice. Contrasting to what is observed in rats, MCH-ir cells were not found in the periventricular zone of *N. alstoni*, what agrees to what we observed in *Mus musculus* mice. In addition, an internuclear group of MCH-ir cells was found between dorsomedial hypothalamic and ventromedial hypothalamic nuclei, but it occupies a more posterior position than the rat internuclear group. At the most caudal hypothalamic levels, MCH-ir cells are located in the lateral part of the retromammillary nucleus, suggesting a larger rostro-caudal extension *in N. alstoni* than in other rodents. Our results suggest that the *N. alstoni* mouse has a distribution of MCH-ir cell bodies that is different to both rat and mouse, although the overall disposition follows a basic plan that is shared by all mammals studied so far. The presence of MCH in hypothalamic areas linked to feeding and metabolism support the investigation of this peptidergic system as a candidate for the underlying mechanism that leads to the particular metabolic behaviors observed in this volcanic species.

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**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

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FAPESP 2017/16293-8

**Title:** Effect of maternal melatonin deprivation during pregnancy and lactation on the offspring neuroimmune system

**Authors: *L. C. MOTTA-TEIXEIRA**[1], D. BATAGELLO[1], S. SILVA JÚNIOR[2], E. LEITE[1], P. R. L. GOMES[2], G. B. DINIZ[3], J. C. BITTENCOURT[4], P. LUCASSEN[5], A. KOROSI[5], J. CIPOLLA NETO[1]
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**Abstract:** Circadian disruption induced by prenatal chronic exposure to light appears to be a key contributor to offspring diseases that develop in adult life (the concept of fetal programming). Exposure to light at night leads to suppression of nocturnal melatonin pineal synthesis. This hormone is essential to photic entrainment of physiological and behavioural processes and acts as an endocrinemodulator, immunomodulator, direct free radical scavenger and indirect antioxidant and cytoprotective agent. During normal pregnancy, maternal melatonin level increases progressively until term and is transferred to the fetus, providing photoperiodic information and plays an important role in brain formation and differentiation. Alteration in maternal melatonin level has been associated with disrupted energy metabolism, brain development and spatial memory deficits in adult life. However, the underlying mechanisms that leads to theses deficits are unknown. Melatonin plays distinct effects on adult cell proliferation, differentiation, survival and apoptosis in the adult hippocampus and their regulation by melatonin receptor type1 and type2 (MT1/2)-mediated signaling. MT1/2 receptors have been identified in the embryonic and fetal hippocampus. mRNA expression of these receptors has been reported in adult precursor cells located in the dentate gyrus. Our hypothesis is that the lack

of maternal melatonin (induced by pinealectomy) during gestation and lactation could affect different stages of adult neurogenesis processs and contributes to these cognitive deficits.

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**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

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**Program #/Poster #:** 774.15/ZZ7

**Topic:** F.03. Neuroendocrine Processes

**Support:** CAPES
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**Title:** Incerto-hypothalamic area projections subserves multiple functions

**Authors: *L. V. SITA**, E. O. BARBEIRO, J. B. SILVA, D. S. BATTAGELLO, G. B. DINIZ, J. C. BITTENCOURT
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**Abstract:** The incerto-hypothalamic area (IHy) is a diencephalic region characterized by the presence of tyrosine hydroxylase- and melanin-concentrating hormone (MCH)-producing neurons. It is currently considered that IHy acts on the regulation of the maintenance of the estrous cycle through the MCH system under the influence of estrogen, but the neurochemical circuit involving IHy and brain areas related to reproductive control is still unknown. Previous hodological studies in our group have shown that this region presents sexually dimorphic connections. In female rats, we observed the innervation of areas associated with the neuroendocrine control, whereas in males there is a predominant innervation of areas related to defense behavior. Here, we injected an anterograde neuronal tracer (biotinylated dextran amine) into the IHy of female C57BL/6 mice and followed it with histochemistry and silver-gold intensification. Although the female mice IHy roughly innervates the same areas previously described in rats, it is intriguing that the female mice IHy provides a more extensive innervation of the brain. That innervation includes both projections related to reproductive control (anteroventral periventricular nucleus, medial preoptic area, and arcuate nucleus), as well as those associated with the defensive circuit (anterior hypothalamic area, ventromedial hypothalamic nucleus, dorsomedial hypothalamic nucleus, precommissural nucleus and periaqueductal gray matter). Those connections suggest that the female mice IHy is eligible to influence defensive behaviors subserving reproductive functions

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**Poster**

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**Title:** Ultrastructural analysis of melanin-concentrating hormone immunoreactive perivascular projections in the hypothalamus and neuro-hypophysis of female rats in different reproductive periods

**Authors: *J. C. BITTENCOURT**[1,2], J. L. M. CAMARGO[1,2], J. G. P. FERREIRA[1], J. C. G. DUARTE[1], G. B. DINIZ[1]
[1]Dept. of Anat., Inst. Biomed. Sci. - Univ. of Sao Paulo, Sao Paulo, Brazil; [2]Exptl. Psychology, Inst. of Psychology, Sao Paulo, Brazil

**Abstract:** Introduction: Melanin-concentrating hormone (MCH) is a neuropeptide predominantly synthesized in the lateral hypothalamic area (LHA), incerto-hypothalamic area (IHy) and zona incerta. In addition to those areas, exclusively during the lactation period, this peptide can be detected in the medial preoptic area (MPOA). Due to the functions of these areas, MCH is involved in the regulation of endocrine, autonomic and behavioral responses. Projections of the MCH-immunoreactive neurons (MCH-ir) reach, with differential densities, all cell clusters and cortical fields in the rat brain. Especially important to its neuroendocrine role, these projections can also be identified in the median eminence (ME) and neuro-hypophysis (NH), where there is a greater permeability of the blood-brain barrier. Furthermore, MCH-ir neurons and their fibers are found very close to blood vessels in the LHA. However, to date, the exact mechanism by which such MCH-ir neurons exert their functions in the hypothalamic-hypophyseal system is still unclear. Objectives: analyze and characterize ultrastructurally the MCH-ir neurons and its terminals in the periphery of blood vessels present in the LHA, EM and NH of female rats, in order to elucidate how this hormone is secreted in the bloodstream; and to correlate the incidence of perivascular MCH-ir neurons in different phases of the reproductive cycle of females. Material and Methods: Sprague-Dawley rats were grouped according to each stage of the reproductive cycle (diestrus, proestrus, estrus, metaestrus, gestation and lactation).

These animals were submitted to transcardiac transfusion and, later, collection of the hypothalamus and NH. These tissues were then processed for immunohistochemistry and analysis in transmission electron microscope and optical light microscope. Results: Through electron microscopy, the MCH-ir was detected specifically within secretion granules in neuronal pericarias of the LHA. It was also possible to observe a certain electron density similar to the nucleus of a granule in the proximities of the Golgi complex, suggesting active formation of granules containing MCH. In the neurohypophysis, granules containing neurochemical signature for MCH were found in Herring bodies (or neurosecretory bodies) and axonal terminals closely juxtaposed to the basal membrane and interstitial space of fenestrated capillaries. Conclusions: thus, so far, these data suggest that MCH exerts not only a neuromodulatory or neurotransmitter role, but also a neuroendocrine role, being secreted directly into the bloodstream towards peripheral targets.

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**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

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**Title:** Evaluation of long-term administration of melanin-concentrating hormone (MCH) and NEI peptide in lactating rats

**Authors: *M. O. KLEIN**[1], G. B. DINIZ[1], D. S. BATTAGELLO[1], J. C. BITTENCOURT[1,2]
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**Abstract:** Melanin-concentrating hormone (MCH) is a peptide that, among several other actions, plays a role in the regulation of energetic balance. Furthermore, exclusively during lactation, MCH is synthesized in the medial preoptic area (MPOA), a hypothalamic region related to the expression of maternal behaviors. This expression starts around post-partum day (PPD) 5, peaking on PPD 19 and then is vanished after weaning. Thus, MCH could be related to the signaling of lactation terminus to the mother. However, the exact physiological role of MCH

expression during lactation, a period of high metabolic demand, is not determined. Moreover, NEI peptide, which is also transcripted with MCH gene (*Pmch*) and thus share its synthesis location, does not have an elucidated role in lactation. To test these, Long-Evans rats received through a cannula implanted in the lateral ventricle attached to an osmotic pump, 8 µg/day/rat of MCH or NEI peptides from pregnancy day 15 to PPD 19. Artificial cerebrospinal fluid was used as control. Litters were culled to eight pups on PPD 1. On PPD 5, 12 and 19, dams were recorded for posterior evaluation of the expression of maternal behavior. During six consecutive hours, latency to first milk ejection, number of milk ejections and ejection intervals were assessed. Also, motivational aspects of maternal care were evaluated for 30 minutes after a short removal of pups, where the latency to retrieve first, fifth and eighth pups was calculated. Dams food intake was measured throughout pregnancy and lactation. On PPD19, dams were killed and their brains were collected to analyze MCH immune-responsive (MCH-ir) cells. Expected results for MCH group are a decrease in maternal behavior expression, as well as an impairment in milk ejection mechanisms leading to earlier lactation ending in relation to control. Energy balance may also be impaired in these dams, showing dysregulated food consumption. Furthermore, the amount of MCH-ir cells may be decreased due to the exogenous administration of the peptide. Regarding to NEI, considering that it has similar roles to MCH in other contexts, impaired maternal behavior expression may be expected, although in different levels compared to MCH. Together, these results will provide a detailed vision of both MCH and NEI physiological and temporal aspects during lactation process.

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**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

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**Title:** Oral oxytocin alters brain activation and behaviors of developing mice in a dose, age, and sex dependent manner

**Authors: *M. TABBAA**[1], E. A. D. HAMMOCK[2]
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**Abstract:** Oxytocin (OXT) regulates species typical social behaviors and interacts with early life experience to shape adult responses. Recent data from our lab characterizing oxytocin receptor (OXTR) ligand binding in the mouth and nasal cavity of pre-weanling mice suggest that OXT may affect sensory processing and subsequent development. However, it is unknown if OXT applied to the mouth alters neural activity in oral sensory circuits or acute oromotor behavior via peripheral OXTR. In a first study, to determine the acute brain response to oral OXT, we applied a high or low dose of OXT or saline to the mouths of postnatal day (P) 14 and P21 male and female OXTR:EGFP mice. We then quantified neuronal activation, fos, in the trigeminal nuclei of the brainstem, which receive sensory information from the face, and interconnected regions including the paraventricular nucleus of the hypothalamus (PVN). In a second study, we quantified the sensory dependent brain and behavioral response to oral OXT versus saline with unilateral whisker brushing in P14 and P21 males and females. In the first study, oral OXT increased the correlation of fos between trigeminal sensory and motor nuclei in P14 males and P21 males and females compared to saline. Further, oral OXT decreased the variation in fos activity in sensory and motor trigeminal nuclei in males and females of both ages. Oral OXT also increased fos activity in the PVN of P14 males compared to saline. In study 2, orofacial and locomotor behaviors were altered after oral OXT and unilateral whisker brushing compared to saline with a significant interaction between treatment and sex on oral behavior, locomotor, and resting activity. Follow up tests of simple effects suggest that compared to saline, P14 females receiving a high dose of OXT and whisker brushing had decreased grooming behavior and locomotion, and increased resting behavior. On the other hand, a high dose of OXT tended to increase oral behavior (grooming plus chewing) in P14 males compared to saline during the 10-minute behavioral test. P14 males receiving a high dose of OXT had significantly increased oral behavior but only during the first five minutes of testing compared to saline. Altogether, these data implicate an age and sex dependent coordination of the trigeminal sensorimotor feedback loop regulating oral behavior via peripheral OXTR. This study may shed light on mechanisms by which socially exchanged OXT, through breast milk or saliva for example, can organize the brain and behavior.

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**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

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**Title:** Oxytocin receptor expression in the periphery of neonatal rats and prairie voles

**Authors: *M. A. GREENWOOD**, E. A. D. HAMMOCK
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**Abstract:** Oxytocin (OXT) is an important neuropeptide known to play an integral role in mediating mother-infant attachment across mammalian species. OXT and the OXT receptor (OXTR) facilitate a mother's ability to deliver, nourish, and nurture her offspring. OXT is found in maternal peripheral fluids such as amniotic fluid, saliva, and breast milk. Potential targets were recently identified for detection of maternal OXT by infant OXTR in the infant periphery of neonatal C57BL/6J mice (*Mus musculus*). In those studies, specificity was confirmed with a congenital OXTR knockout mouse model as well as competitive binding techniques. The aim of this project was to assess peripheral sites of OXTR for cross-species comparisons in commonly used laboratory rodent models with well-characterized social behaviors. These species included Long-Evans and Sprague-Dawley rats (*Rattus norvegicus*), and Prairie voles (*Microtus ochrogaster*). Receptor autoradiography was performed on 20μm sagittal sections of whole neonatal (PD 0) males and females of each species using the $^{125}$iodinated-ornithine vasotocin ([$^{125}$I]-OVTA) radioligand. A competition binding assay was used to assess the selectivity of [$^{125}$I]-OVTA for peripheral OXTR. Radioactive ligand (0.05nM [$^{125}$I]-OVTA) was competed against concentrations of 0 nM and 1000 nM excess unlabeled OXT. Previously identified regions of significant OXTR expression in the mouse were analyzed for comparison: rostral and lateral periodontium, olfactory epithelium, ciliary bodies of the eye, whisker pads, adrenal gland, anogenital area, liver, and scapular brown adipose tissue. OXTR expression in all species was different from previous reports of OXTR receptor expression in the periphery of the C57BL/6J mouse, as well as between species compared within this project. Within species sex differences are reported for specific regions. Collectively, these data indicate that OXTR expression in the infant periphery, as is well-established in the central nervous system, is species-specific.

**Disclosures: M.A. Greenwood:** None. **E.A.D. Hammock:** None.

**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 774.20/ZZ12

**Topic:** F.03. Neuroendocrine Processes

**Support:** NIH MH114994
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Foundation for Prader-Willi Research

**Title:** Trigeminal ganglia correlates of hypothalamic oxytocin production in neonatal mice

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**Abstract:** Oxytocin (OXT) via the oxytocin receptor (OXTR) facilitates species-typical social behavior. Recent evidence indicates that sensory stimulation of the face (e.g. the whiskers) during the neonatal period can increase the production of OXT in the infant mouse brain. Our lab has identified peripheral regions expressing OXTR protein and Oxtr mRNA in neonatal C57BL/6J mice. Peripheral OXTR may modulate OXT production and release in the hypothalamus. To begin to evaluate the neural circuits by which socially acquired OXT and/or sensory input may enhance infant OXT production, we are performing anatomical and functional studies. In our first study, we further explore the specific subpopulation of trigeminal sensory neurons that express Oxtr mRNA through in-situ hybridization. The trigeminal nerve is a mixed cranial nerve, carrying sensory information from the face through 3 major branches, and supplying motor signals to the lower jaw. Double label in situ hybridization will identify which subpopulation of sensory neurons in the trigeminal ganglia express Oxtr mRNA. Because OXTR activation can promote OXT release, in our second experiment, we tested the hypothesis that congenital loss of Oxtr would impair the development of OXT production in C57BL/6J mice. Our preliminary results showed that at postnatal day 8, male Oxtr knockout mice show a 40% reduction in Oxt mRNA levels compared to WT animals determined by RT-q PCR. In this study, we further explore the congenital loss of Oxtr on Oxt expression in the PVN and SON by RT-q PCR at postnatal day 14 and adulthood. These findings suggest that socially acquired OXT acting at peripheral OXTR may influence the sensory-dependent development of neural circuits and infant production of OXT. This may represent a positive feedforward virtuous cycle of intergenerational transmission of OXT production.

**Disclosures: R. Vaidyanathan:** None. **E.A. Hammock:** None.

**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

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**Program #/Poster #:** 774.21/ZZ13

**Topic:** F.03. Neuroendocrine Processes

**Support:** CONACYT 331854

**Title:** Prolactin and testosterone induce migration in LNCaP cells

**Authors: *M. G. JIMENEZ BUENDIA**[1], J. A. LARA FUENTES[2], G. ARANDA ABREU[3], M. E. HERNANDEZ AGUILAR[3], J. MANZO DENES[3], J. M. SUAREZ MEDELLIN[3], M. E. MENDOZA GARRIDO[4], A. AQUINO GÁLVEZ, 07360[5], F. ROJAS DURAN[3]
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**Abstract:** Prolactin (PRL) is a polypeptide hormone synthesized and secreted mainly by specialized cells of the adenohypophysis. Testosterone (T) is a steroid hormone synthesized mainly in Leydig cells. Both hormones are regulated by the hypothalamic-pituitary axis. Both PRL and T are necessary for the proper functioning of the prostate, however, they are also intimately related to the progression and development of cancer. One of the characteristics of cancer, and the main cause of mortality, is metastasis, where cell migration is involved. The metalloproteinases of the matrix (MMP) participate in cellular migration, being MMP-2 and MT1-MMP the most studied. There is little information about the participation of PRL and T in cell migration, especially in prostate cancer. Therefore, we evaluated the effect of stimulation with PRL and / or T in the migration of the prostate cancer cell line LNCaP. The results show that PRL (50 nM) and T (0.1 nM) increased cell migration; which was enhanced when both hormones were used. On the other hand, in the zymography and western blot assays, an increase in the pro-form of MMP-2 with PRL and STAT-3 was observed with T and PRL + T, respectively. At the cellular level membrane extensions characteristic of migration were observed when the LNCaP cells were stimulated with the hormones. The data suggest that PRL and T may be involved in metastasis through inducing cell migration, probably due to the activation of the MMP-2 proforma and through the STAT-3 signaling pathway.

**Disclosures: M.G. Jimenez Buendia:** None. **J.A. Lara Fuentes:** None. **G. Aranda Abreu:** None. **M.E. Hernandez Aguilar:** None. **J. Manzo Denes:** None. **J.M. Suarez Medellin:** None. **M.E. Mendoza Garrido:** None. **A. Aquino Gálvez:** None. **F. Rojas Duran:** None.

**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 774.22/ZZ14

**Topic:** F.03. Neuroendocrine Processes

**Support:** Conacyt

**Title:** Effect of prolactin and estradiol in cell migration in MCF-7 cells

**Authors: *J. LARA REYES**[1], M. G. JIMENEZ BUENDIA[1], M. HERNANDEZ[2], G. E. ARANDA-ABREU[5], J. MANZO DENES[3], D. HERRERA-COVARRUBIAS[4], J. SUAREZ MEDELLIN[5], C. L. SAMPIERI[6], A. AQUINO GÁLVEZ[7], F. ROJAS DURAN[1]
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**Abstract:** Prolactin (PRL) is a polypeptide hormone synthesized and secreted mainly by specialized cells of the pituitary gland. Estradiol ($E_2$) is a sexual steroid hormone of the estrogen group and it is the most potent natural estrogen in humans. The release of both hormones is controlled by neural stimuli and their levels are regulated by the hypothalamic-pituitary axis. PRL participates in the development of the mammary gland and in the production of milk proteins in pregnancy and lactation. It exerts diverse biological effects through its interaction with specific membrane receptors that are widely distributed in the organism. $E_2$ has effects on the growth, development and differentiation of tissues, although its main action is observed in reproductive organs. In addition to both their physiological functions, it has been shown that they also participate in the development of pathologies such as breast cancer, however, it is not clear whether these hormones have any involvement in cell migration, a crucial step in the development of metastasis, even less known are the mechanisms through which these hormones may be regulating cell migration processes. Therefore, we evaluated the effect of stimulation with PRL and $E_2$ in cell migration in MCF-7 cells. The results showed that PRL (2 nM) increased cell migration in MCF-7 cells and $E_2$ seems to have no effect. The data suggest that PRL, might be involved in metastasis through inducing cell migration.

**Disclosures: J. Lara reyes:** None. **M.G. Jimenez buendia:** None. **M. Hernandez:** None. **G.E. Aranda-Abreu:** None. **J. Manzo Denes:** None. **D. Herrera-Covarrubias:** None. **J. Suarez Medellin:** None. **C.L. Sampieri:** None. **A. Aquino Gálvez:** None. **F. Rojas Duran:** None.

**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 774.23/ZZ15

**Topic:** F.03. Neuroendocrine Processes

**Support:** PRODEP BUAP-PTC-448

**Title:** Ontogeny of Kiss1R in the uterus of female Hartley guinea pigs

**Authors: *V. ALATRISTE**[1], J. DE LA ROSA PRIEGO[2], I. BARRERA SOLÍS[3], L. MARTINEZ MENDIETA[3], D. I. LIMÓN[4], I. MARTÍNEZ-GARCÍA[4], F. LUNA[4]
[1]BUAP, Puebla, Mexico; [2]Benemérita Univ. Autónoma De Puebla, Amozoc, Mexico; [3]Benemérita Univ. Autónoma De Puebla, Puebla, Mexico; [4]Benemerita Univ. Autonoma De Puebla, Puebla, Mexico

**Abstract:** Kisspeptin (Kiss) is a modulator of the onset of puberty, Kiss through Kiss1R activates GnRH neurons in the hypothalamus. Kiss and Kiss1r are in peripheral organs like testes and ovaries, and they are regulating spermatogenesis and folliculogenesis, respectively. However less is known about Kiss and Kiss1R role and localization in the uterus. Our objective was to know the ontogeny of Kiss1R receptor expression in the uterus of female Hartley guinea pigs at different postnatal ages.
We used female Hartley guinea pigs and they were randomly divided into four groups (n = 3), postnatal 0 (P0), P10, P20 and first vaginal opening (FVO), FVO was evaluated as the complete loss of the membrane vaginal. The guinea pigs of each experimental group were sacrificed with an exposure of $CO_2$ and perfused with intracardiac saline solution (NaCl, 0.9%) followed by paraformaldehyde (4%)-PBS. The uterus was dissected and fixed in 4% paraformaldehyde-PBS. The uterus was embedded in paraffin and then sectioned in microtome to get 5 μm slides. The slides were stained with hematoxylin and eosin and used to measure the thickness of the endometrium and myometrium. To located Kiss1R we performed an inmunohistochemistry technique (IHC). All measurements and the evaluation of IHC and Kiss1R positive cell were made with the NIH ImageJ software. The results correspond to the mean ± SEM, *p ≤0.05 were analyzed using ANOVA followed by the Mann-Whitney U-test. The thickness of the endometrium at P0 (*448.65 ± 9.4 μm) is lower vs FVO (465.06 ± 7.3μm). And the myometrium thickness is at P0 is 186.24 ± 2.93 μm, lower at P10 *127.57 ± 2.79 μm, also at P20 *139.29 ± 3.22 μm while at the age of FVO increased (*176.49 ± 3.42). The presence of uterine glands there are few at P0 (*10.30 ± 0.52), P10 (*11.65 ± 0.63) and P20 (*10.57 ± 0.63), and at FVO the number of uterine glands is increased (*22.27 ± 0 71). By IHC we located the Kiss1R in the endometrium, myometrium and uterine glands. By a total count we got a lower Kiss1R cells at P0 and P10 (*133±24 and *163±44, respectively), increasing at P20 and FVO (249±24 and 279±37). All the results were vs at FVO group. Our data shows than Kiss1R have a differential expression at the ages evaluated and increases in relation at age. In conclusion Kiss1R promotes del cell development of the uterus of female Hartley guinea pigs.

**Disclosures: V. Alatriste:** None. **J. De La Rosa Priego:** None. **I. Barrera Solís:** None. **L. Martinez Mendieta:** None. **D.I. Limón:** None. **I. Martínez-García:** None. **F. Luna:** None.

**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 774.24/ZZ16

**Topic:** F.03. Neuroendocrine Processes

**Support:** PRODEP BUAP-PTC-448

**Title:** Kiss1R modulates of cell development in uterus and the onset of puberty in female Wistar rats

**Authors: *J. DE LA ROSA PRIEGO**, I. BARRERA SOLÍS, L. MARTÍNEZ MENDIETA, I. MARTÍNEZ GARCIA, D. I. LIMÓN, F. LUNA MORALES, V. ALATRISTE BUENO
Benemérita Univ. Autónoma De Puebla, Puebla, Mexico

**Abstract:** Kiss1R modulates of cell development in uterus and the onset of puberty in female Wistar rats [1]Joaquina De la Rosa-Priego, [1]Irene Barrera Solís, [2]Liliana Martínez-Mendieta, [2]Isabel Martínez-García, [2]Daniel I. Limón, [2]Félix Luna, [2*]Victorino Alatriste 1 Student of School of Chemistry-BUAP 2 Laboratory of Neuroendocrinology-BUAP In hypothalamus the Kiss1R are activated by Kisspeptin (Kiss) and promotes the release of gonadotropin-releasing hormone (GnRH), GnRH is promoting the onset of puberty. Also, Kiss1R have been found in testes, ovary and placenta. However, in the uterus, a very important organ that regulates the estrous cycles and pregnancy, little is known about the localization and function of the Kiss1R. Our objective was to know the role of Kiss1R in the onset of puberty and the cell development of the uterus by in situ administration of Kiss antagonist. We use female Wistar rats, they were divided in four groups (n=5, administration was performed at P24): Control, Vehicle (administered with 0.6 IU I.S.S.), and two groups administered with Kiss antagonist (Kisspeptin-234 trifluoroacetate salt) 1nM and other 10nM. The animals were sacrificed by CO2 exposure at the age of the first vaginal opening (FOV). The uterus was dissected and fixed in 4% paraformaldehyde-PBS. The uterus was embedded in paraffin and then sectioned serial cuts of 5 μm, stained with hematoxylin and eosin, used to measure the thickness of the endometrium and myometrium. Other slides were stained with Masson's Trichromic to measure the thickness of the muscle fibers of the myometrium. And Kiss1R were located by the immunohistochemistry (IHC). All the measurements were made with the NIH ImageJ software. The results correspond to the mean ± SEM, *p ≤0.05 were analyzed using ANOVA followed by the Mann-Whitney U-test. The FOV increases Kiss antagonist 1nM (*58.5 ± 3.34) and 10nM (*46.5 ± 1.03) vs control (39 ± 0.35) and vehicle (42.3 ± 1.36). The thickness of the endometrium of the 1nM (*288.31 ± 7.15 μm) is lower vs control (372.37 ± 6.27 μm). The measurement of muscle fibers thickness is lower in the groups treated with Kiss antagonist 1nM (*40.92 ± 0.7 μm) and 10nM, (*46.74 ± 0.91 μm) vs control (51.73 ± 1.2 μm) and vehicle (54.11 ± 1.11 μm). Finally, we located the Kiss1R in the endometrium (uterine glands and myometrium). We show that the administration of Kiss antagonist in the uterus delays puberty in Wistar rats, because the cellular development of the uterus is affected. Also, the decrease in the thickness of the endometrium and muscle fibers in the 1nM and 10nM groups, as well as the increase in Kiss1R demonstrate than Kiss trough the Kiss1R are necessary for the cell development in the uterus.

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**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 774.25/ZZ17

**Topic:** F.03. Neuroendocrine Processes

**Support:** PRODEP-PTC-448-BUAP

**Title:** Expression and localization of Kiss1R receptors in the ovaries of pregnant Wistar rats

**Authors: *I. BARRERA SOLÍS**[1], J. DE LA ROSA PRIEGO[1], F. LUNA[2], L. MARTINEZ MENDIETA[1], I. MARTÍNEZ GARCÍA[1], D. I. LIMÓN[1], V. ALATRISTE[3]
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**Abstract:** Kisspeptin (Kiss) is encoded by the KISS1 gene, which its receptor is Kiss1R. Kiss and Kiss1R have a main role in the regulation of the onset of puberty and ovarian folliculogenesis through the control of the hypothalamic-pituitary-gonadal axis. Kiss1R has been found expressed in ovaries, testicles, pancreas, small intestine, placenta, central nervous system and uterus. In the ovaries, Kiss and Kiss1R are both expressed in theca cells and granulosa cells, and in other ovarian cells. However, less is known about Kiss1R expression and its role in ovaries of pregnant animals. So, in this study, we evaluated the expression of Kiss1R receptor in the ovaries of Wistar rats at different gestational ages. We used female pregnant Wistar rats, and they were divided in five groups with(n=5): gestational day 0 (G0), gestational day 5 (G5), gestational day 10 (G10), gestational day 15 (G15), and after delivery (Post Delivery). The rats were sacrificed by CO2 exposure, and perfused with intracardiac saline solution (NaCl, 0.9%) followed by paraformaldehyde (4%) in PBS, pH 7.4 (solution of PF-PBS). We dissected the ovaries and they were fixed in 4% paraformaldehyde-PBS. Then, the ovaries were sectioned with a Leica SM2010R microtome to get 3 μm slides. We located the Kiss1R by immunohistochemistry in the ovaries of female pregnant Wistar rats. The study of localization and the count of Kiss1R were performed using the ImageJ-NIH software.
We found that the expression of KISS1R in the ovaries of the pregnant rat is indeed affected by the process of pregnancy. It decreases during the G5 of pregnancy and starts to slowly rise to show a maximum expression towards the end of the pregnancy. These findings confirm the role of Kiss and its receptor, Kiss1R modulates the regulation of folliculogenesis. Also, the data suggest that the high concentration of certain hormones during pregnancy, give a negative feedback on the expression of KISS1R in the ovaries.

**Disclosures: I. Barrera Solís:** None. **J. De La Rosa Priego:** None. **F. Luna:** None. **L. Martinez Mendieta:** None. **I. Martínez García:** None. **D.I. Limón:** None. **V. Alatriste:** None.

**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 774.26/ZZ18

**Topic:** F.03. Neuroendocrine Processes

**Title:** Computational model for energy sensing and plasticity of PMv neuronal circuitry in pregnancy

**Authors: *P. LEE**, C. F. ELIAS
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**Abstract:** The energy sensing in reproduction is mainly modulated by the ventral premammillary nucleus (PMv) neurons in hypothalamus. They are sensitive to the adipocye-derived hormone leptin; some of them are excitatory to leptin, and the others are inhibitory to leptin. Recently we have characterized PMv neurons expressing dopamine transporters (DAT) suppress female reproductive function, and this is inhibited by leptin.
During pregnancy, elevated prolactin hormone induces *leptin resistance* and possibly obesity. At the same time, dopamine released from tuberoinfundibular dopaminergic (TIDA) neurons is downregulated. PMv neurons express prolactin receptors and might interplay with leptin. Even though leptin action in PMv neurons has not been associated with metabolic regulation, very little is known about the potential role in physiologic states of negative energy balance, i.e. pregnancy and lactation.
We hypothesize that 1) PMv DAT neurons depolarize AgRP neurons. PMv non DAT neurons depolarize POMC neurons, and this pathway is independent to GABAnergic projection from AgRP to POMC. The projection from PMv neurons to those arcuate nucleus neurons and feeding behavior is strengthened in pregnancy by modulation of prolactin/dopamine. 2) Hyperpolarization-activated rebounding channels ($I_h$) in PMv are main sources of conductance for neurons inhibited by leptin dopamine sensitively.
To construct a minimal neuronal circuit for energy sensing, we have developed a computational model of conductance-based electrophysiology; input signals to PMv by leptin, dopamine, and prolactin, and the output response of bursting spike frequency by AgRP and POMC neurons. For excitatory PMv neurons, leptin/prolactine-sensitive TRPC channels are incorporated. Leptin-dependent $K_{ATP}$ as well as *hypothesized* dopamine-sensitive channels are applied for DAT neurons inhibited by leptin. Both subpopulation neurons release glutamate neurotransmitters. For AgRP neurons, leptin-dependent $K_{ATP}$ channels are considered with $GABA_A$ release for projection to POMC neurons. For POMC neurons, we have incorporated leptin-dependent TRPC channels.
The computational neuronal circuit model predicts that the contribution of upregulated prolactin and DAT are significant for *leptin resistance* in pregnancy and lactation, and blocking $I_h$

channels in PMv DAT neurons also overcomes moderately the *leptin resistance* implying potential therapeutics. This will be validated by optogenetic regulations of PMV DAT neurons and leptin/prolactin receptors as well as specific pharmaceutical blockers.

**Disclosures: P. Lee:** None. **C.F. Elias:** None.

**Poster**

**774. Neuroendocrine Processes: Neuroendocrinology, Anatomy, and Physiology**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 774.27/ZZ19

**Topic:** F.03. Neuroendocrine Processes

**Support:** NIMH T32 MH019524

**Title:** The neuropeptide oxytocin and embryonic diapause

**Authors: *J. L. MINDER**[1], M. V. CHAO[2], R. C. FROEMKE[3]
[1]Mol. Neurobio., [2]New York Univ. Med. Ctr., New York, NY; [3]Otolaryngology, NYU Med., New York, NY

**Abstract:** Oxytocin is a peptide hormone involved in childcare and social behavior (Dulac et al. 2014; Froemke and Carcea 2017; Rilling and Young 2014). Previously our labs generated antibodies to the mouse oxytocin receptor (OXTR) and characterized receptor expression throughout the adult mouse brain, as well as in the cortex during postnatal development (Mitre et al. 2016). Other recent work also indicates that the OXTR is expressed early in development (Hammock and Levitt 2013). With both antibody labeling as well as via transgenic OXTR-Cre mice (Hidema et al. 2016), we have documented OXTR expression throughout the brain and body of the P0-P8 mouse pup. Therefore, we asked how early is the OXTR expressed? We examined prenatal receptor expression, detecting the OXTR as early as embryonic day three, during the blastocyst stage. This is the developmental stage where blastocysts begin implantation into the uterine endometrium, an event critical for successful pregnancy. Interestingly, rodents- like most if not all mammals- undergo a phenomenon called diapause, in which the timeframe that the embryo implants is delayed during a maternal state unfavorable for pregnancy, such as while nursing a previous litter (Fenelon et al. 2014). Embryonic diapause is thought to occur by making the uterus non-receptive to implantation in a manner regulated by the hypothalamic neuroendocrine axis, but the underlying mechanism is unknown (Renfree and Shaw 2000). Lactation requires the neuropeptide oxytocin (OT), raising circulating levels of OT that can permeate down to the embryo perhaps via maternal-fetal signaling (Stouffer and Hennebold 2014). We hypothesized that OT, released in response to the sensory stimulus of a suckling pup, might act to coordinate the pre-implantation embryo and uterine interactions to initiate diapause in mice. In support of this, we have recapitulated a developmental delay in vitro after culturing

mouse blastocysts. OT treatment delayed implantation as compared to saline-treated at 24hrs (32% delayed, OT n= 12, saline n= 17). Additionally, injections of 50 µM OT in vivo led to halted or terminated pregnancies in all cases (66% pregnancy with saline, n=6 in each group). Diapause has also been reported to occur via the introduction of an intruder male, suggesting paradigms beyond lactation where the maternal brain can dictate the timing of pregnancy progression to enhance overall reproductive success (Marois, 1982). Furthering our understanding of the uterine conditions favorable for allowing blastocyst implantation has major implications for hormone signaling, developmental biology, and reproductive medicine, including human in vitro fertilization.

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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.01/ZZ20

**Topic:** F.04. Stress and the Brain

**Title:** Change in sound features of ultrasonic vocalizations by neonatal rats separated from their mother depending on condition of the neonatal rats

**Authors: *M. NAKAMURA**[1], M. TANICHI[3], H. TODA[3], T. SAITO[3], S. MITSUYOSHI[2], S. SHINOHARA[2], Y. OMIYA[4], M. HIGUCHI[1], K. SHIMIZU[5], A. YOSHINO[3], S. TOKUNO[1]
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**Abstract:** A neonatal rat emits ultrasonic vocalizations (USVs) when it is separated from its mother. The situation of maternal separation will impact seriously on its survival, therefore the USVs in maternal separation are thought to be eliciting signals for caregiving behavior by its dam. If a rat pup's condition affects features of its USVs, we can know condition of a rat pup from its USVs, vice versa. In this study we examined relationship between features of a rat pup's USVs and conditions of a rat pup, such as distance between a pup and its dam, usage of a heating pad, and age of a pup.
We put a rat pup and its dam into two cages separately after adaptation for an hour. Then we changed distance between two cages and recorded their USVs for five minutes per each condition. In first half of each trial we increased the distance, while we decreased the distance in latter half. We divided rat pups into two groups: a pup of one group was with a heating pad while it was in a cage, and a pup of another group was without a heating pad. We also recorded USVs at different ages of a pup, one week old and two weeks old. We extracted features from recorded USVs per single USV, then features were averaged in each five-minutes recording.

We found several features of USVs showing significant difference between different conditions. Deviation of pitch in single USV became larger as a trial progressed in the group of subjects without a heating pad at one week old, while the feature remained small throughout a trial in other groups of subjects with a heating pad at one week old and two weeks old regardless usage of a heating pad. As rat pups at two weeks old grew large enough and had enough hair, subjects of the later three groups were thought to be able to keep their body temperature. On the other hand, subjects of the former group were estimated to fail to keep the body temperature. Therefore, the difference in changing of deviation of pitch might be caused by the difference in homeothermic condition.
This result infers that features of USVs by maternal separation may reflect conditions of a rat pup such as hypothermic stress and that the analysis of USVs may work as a non-invasive probe for early life stress of a rat.

**Disclosures:** **M. Nakamura:** 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.; PST inc.. **M. Tanichi:** None. **H. Toda:** None. **T. Saito:** None. **S. Mitsuyoshi:** None. **S. Shinohara:** None. **Y. Omiya:** None. **M. Higuchi:** 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.; PST Inc.. **K. Shimizu:** None. **A. Yoshino:** None. **S. Tokuno:** 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.; PST Inc..

**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.02/ZZ21

**Topic:** F.04. Stress and the Brain

**Support:** Watson Bowes Research Institute

**Title:** Behavioral and physiological consequences of mid-term drug-induced pregnancy termination in an animal model

**Authors: C. CAMILLERI**[1], R. M. BEITER[1], L. PUENTES[2], P. ARACENA[2], *S. SAMMUT[1]
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**Abstract:** Given the significant physiological changes that take place during and resulting from pregnancy, as well as the lack of objective research available on the potential effects of pregnancy termination, this study investigated the potential for developing a valid animal model to objectively assess the physiological and behavioral consequences of mid-term pregnancy termination. Female Long-Evans rats were divided into four groups (n=13-15/group), controlling for drug (mifepristone (50mg/kg, i.g.)/misoprostol (0.3mg/kg, i.g.) or vehicle (1% Carboxymethylcellulose Sodium/0.2% Tween®80 suspension), i.g.) and pregnancy. Drug administration took place at 19 weeks of age during days 12-14 of gestation. Vehicle was administered to the controls on the same days. Parameters measured included rat weight, vaginal impedance, food intake, sucrose consumption, locomotor activity, and the forced swim test. At the termination of the study, rats were deeply anesthetized using urethane, and blood, brain, and liver were collected for biochemical analysis. Relative to control rats (non-pregnant, vehicle), rats undergoing pregnancy termination displayed a significant decrease in body weight, food intake and locomotor activity-related behaviors, but not sucrose consumption. Regression analysis indicated that pregnancy termination was a predictor variable for all of the behavioral parameters measured. Moreover, vaginal impedance did not significantly decrease over time in rats carrying their pregnancy to full-term in contrast to the other groups. Biochemical analysis indicated putative drug and pregnancy specific influences on oxidative balance. Overall, our results appear to suggest benefits of carrying a pregnancy to full-term pertaining to fertility and negative behavioral effects following pregnancy termination. Thus, our findings indicate the importance for further objective investigation of the physiological and behavioral consequences of pregnancy termination in order to provide further insight into the potential effects of pregnancy termination in humans.

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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.03/ZZ22

**Topic:** F.04. Stress and the Brain

**Support:** NMRC/CG/013/2013

**Title:** Mechanistic validation of a novel relaxin-3 B-chain stapled peptide as a preclinical lead in targeting relaxin-3/RXFP3 networks

**Authors: *S. MARWARI**
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**Abstract: Background:** The neuropeptide relaxin-3, play a crucial role in the normal function of the central nervous system and its major endogenous receptor relaxin/insulin-like family peptide receptor 3 (RXFP3), hold a great promise as a therapeutic target for the treatment of several CNS disorders. However, the development of relaxin-3 peptides has been limited with the challenges such as complexity in synthesis, likely rapid metabolism and the requirement of surgical implantation into the brain providing the limitation of therapeutic development of novel compounds.
**Methods:** Introducing a "hydrocarbon-stapling" technology, we tested the series of stapled peptides and alternative stapling strategies installed at relaxin-3 B-chain sequence.
**Results:** In the present study, successful emergence of a lead stapled peptide exhibited the stabilized secondary structure and the most potent binding affinity and activition towards RXFP3 receptor. To be clinically viable, we tested and validated the intranasal administration method of a lead stapled peptide in anxiety and depression related behaviour paradigms.
**Conclusion:** Our preclinical findings suggests that this multifunctional strategy of "stapled" relaxin-3/RXFP3 system has a huge potential in the pursuit of the most effective translational pharmacological approach to reversing eating and stress related neuropsychiatric disorders.

**Disclosures: S. Marwari:** None.

**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.04/ZZ23

**Topic:** F.04. Stress and the Brain

**Title:** Social isolation-mediated hyperactivity and reduction of anxiety are not affected by Caps2 deficiency

**Authors: *Y. SHINODA**[1], M. OKA[1], N. TANAKA[1], Y. FUJIWARA[1], Y. SANO[2], T. SADAKATA[3], T. FURUICHI[2]
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**Abstract:** In rodents, social isolation during the early postweaning phase induces several behavioral abnormalities such as hyperactivity. Several studies have tried to clarify the mechanism of social isolation induced behavioral abnormality, however, the key molecular factor connecting between social isolation and behavioral abnormality is not fully understood. Hyperactivity is known to be often co-occur with the patient of autism spectrum disorder (ASD), and one of the possible reason is that ASD patients are usually isolated from social activity by themself. Therefore, we hypothesized that the molecular related to ASD is also sensitive to the social isolation-induced hyperactivity. We previously reported that calcium-dependent activator

protein for secretion 2 (CAPS2) is highly associated with ASD, and *Caps2* knock-out (KO) mice show ASD-like behavior. In the present study, we investigated the behavioral phenotype (using light-dark transition test, open field test, elevated zero maze test, marble burying test, novel objective recognition test, social interaction test) of socially isolated mice and compared the differences of the behavioral phenotype between wild-type (WT) and *Caps2* KO. In the most of experiments, socially isolated mice showed hyperactivity and reduction of anxiety; however, the magnitudes of hyperactivity and anxiety in WT and *Caps2* KO mice were almost identical. These data suggest that *Caps2* gene is not associated with social isolation-induced hyperactivity and reduction of anxiety.

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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.05/ZZ24

**Topic:** F.04. Stress and the Brain

**Support:** FAPESP grant 2015/26364-4
CNPq grant 303449/2015-2
AFIP
CAPES

**Title:** Maternal deprivation alters social investigation and corticosterone reactivity in an age- and sex-dependent fashion in adolescent rats

**Authors: *D. SUCHECKI**[1], V. C. CESCHIM[2], P. A. SUMARÁN[2], A. A. BORGES[2], C. E. N. GIRARDI[2]
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**Abstract:** Maternal deprivation induces anxiety and depression, assessed in adolescent and young adult rats, and both disorders are characterized by impairment of social behavior. In the present study, we assessed anxiety-like behavior, social motivation and testing-induced corticosterone (CORT) reactivity in male and female adolescent rats, from three groups, composed by 8 litters each: control (CTL); 24 h maternal deprivation (MD) on postnatal day (PND) 3 (DEP3); MD on PND 11 (DEP11). Litters were standardized to 4 males and 4 females on PND 1. On the day of MD, litters were transferred to another cage containing bedding from the maternity cage and placed on a heating pad set at 30-33ºC, in a far away room, for 24 h. After MD, litters and mothers were reunited and were not disturbed until weaning on PND 21, when pups were housed with their same-sex siblings. Between PNDs 40 and 45, 1 male and 1

female from each litter were non-tested (NT) and perfused or decapitated (2 males and 2 females), while 2 males and 2 females were exposed to an open field for 10 min, for assessment of anxiety-like profile (lesser activity in the center indicated more anxiety). On the next day, animals were submitted to the social investigation test, by exposing them, for 10 min, to 2 metal cylinders, 1 empty and 1 containing a conspecific (target rat). Exploratory rate was taken by the time and frequency exploring the target rat/time and frequency exploring both cylinders. At the end of the test, 1 male and 1 female were decapitated; basal values were obtained from 1 NT male and female. CORT reactivity (CR) was calculated by the equation: CR = [(post-test value x 100)/group average CORT value] - 100. The brains of perfused animals were cryoprotected for later assessment of oxytocin immunoreactivity (OT-ir) in the supraoptic and paraventricular nuclei of the hypothalamus. The results showed a clear age and sex effects: 1) DEP3 females in proestrous exhibited more anxiety-like behavior than CTL and DEP11 counterparts; 2) DEP3 males investigated the target rat less than the other groups and CTL and DEP11 females investigated the target rat less than their male counterparts; 4) CR was the greatest in DEP3 animals, and within this group, females reacted more than males. These results indicated that MD produced age-dependent effects with a clear sexual dimorphism. The assessment of OT-ir will be important to provide the neurobiological underpinning for the present results.

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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.06/ZZ25

**Topic:** F.04. Stress and the Brain

**Support:** Undergraduate Special Opportunities in Artistry and Research Program (USOAR)
NIU RIPS

**Title:** Investigating a sedentary form of environmental enrichment in a prairie vole model of social stress

**Authors: *M. L. COX**, M. C. NORMANN, W. WATANASRIYAKUL, O. I. AKINBO, S. SUJET, S. CIOSEK, N. HOLZAPFEL, A. J. GRIPPO
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**Abstract:** Social stress, such as isolation, influences psychological health, stress reactivity, and neural function. Environmental enrichment (EE), which includes interacting with inanimate objects (items of different colors and textures) and opportunities for exercise, positively stimulates the brain and may protect against social stress. Older and disabled individuals are

vulnerable to social stress but may be restricted in physical activity, therefore investigating the potential benefits of a sedentary form of EE can inform treatment strategies for these populations. This project used a prairie vole model to compare the ability of EE with and without physical activity components to protect against social isolation. Prairie voles have a similar social structure to humans and face negative effects from social isolation. Twenty female prairie voles were randomly assigned to four groups: continuous pairing with a female sibling (control- 8 wks), standard social isolation (8 wks), social isolation (4 wks) followed by the addition of sedentary EE items (4 wks), or social isolation (4 wks) followed by the addition of EE + an exercise wheel (4 wks). Prairie voles were then subjected to a forced swim test (FST- 5 min of swimming) to examine depression-like behavior and a social crowding stressor (10 min in a cage with 3 strangers) for stress reactivity. Behaviors were coded by experimentally-blind observers. Preliminary results indicate that the standard social isolation group displayed the highest levels of depression-like behavior in the FST. The paired, isolation with sedentary EE items, and isolation with EE + exercise wheel groups showed similar, lower levels, indicating that sedentary EE can be equally effective as EE with an exercise component at preventing depression-like behavior following social isolation. The standard social isolation group displayed the highest levels of freezing behavior and lowest levels of aggression, affiliative behaviors, and individual (non-social) behaviors. The paired, isolation with sedentary EE items, and isolation with EE + exercise wheel groups did not differ among these behaviors, indicating that sedentary EE and EE with an exercise component result in similar responses to a social stressor. Altered neural activity in brain regions that regulate and respond to stress, including the hippocampus (CA1 and CA3) and the hypothalamic paraventricular nucleus, may mediate the protective effects of EE and/or exercise. The data have important implications for understanding and treating social stress using environmental strategies with sedentary alternatives in humans.

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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.07/ZZ26

**Topic:** F.04. Stress and the Brain

**Support:** NIMH K02 MH087845
Brain and Behavior Young Investigator Award to KMS
ULL Graduate Student Organization

**Title:** The cost of neglect: How maternal deprivation may influence FGFR1 and brain development

**Authors: *T. L. CAIN**, J. C. COLLETTE, K. M. SMITH
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**Abstract:** Approximately 18.8 million Americans suffer from a depressive disorder in a given year. The innate stress response influences the development of affective disorders including anxiety and depression via overactivation of the Hypothalamic-Pituitary-Adrenal Axis (HPA Axis), which leads to changes in multiple gene expression patterns. Adverse childhood experiences drive HPA axis activity, and leave individuals vulnerable to future mental health problems. Some of the genes that have an altered expression pattern after long term HPA axis activation are Fibroblast Growth Factors (FGFs) and their Receptors (FGFRs). FGFs and FGFRs are a large family of signaling molecules in the brain; which are important for neuronal proliferation, differentiation, and migration. Previous research has shown that patients who have been clinically diagnosed with depression have decreased expression of FGFRs, and mice lacking FGFR1 ligands have an increased predisposition for developing anxiety. Our previous work demonstrated Fgfr1 expression is enriched in brain areas that are part of the regulation and function of the HPA axis including hippocampus, hypothalamus, and cingulate cortex. We are employing the tgFgfr1-EGFP reporter mouse as a way to examine FGFR1 expression after multiple stress paradigms. In our first experiment, we find that chronic unpredictable stress decreases Fgfr1-driven GFP expression in the hippocampus. As a continuation of these findings, our goal is to investigate changes in FGFR1 expression in mice that have experienced induced maternal neglect. We will quantitatively assess differences in FGFR1 expression in the neglected mice pups, as compared to control animals, by examining GFP levels and Fgfr1 levels by RT-PCR and microscopy. We have induced neglect, for 14 days, 3 hours per day, and are examining astrocytes within the hippocampus, hypothalamus, anterior cingulate, and frontal cortex with a combination of stereological and quantitative PCR methods to investigate changes in gene expression. Examining the interaction between FGFR signaling, stress, and affective disorders can provide a candidate drug target for novel affective disorder therapies.

**Disclosures: T.L. Cain:** None. **J.C. Collette:** None. **K.M. Smith:** None.

**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.08/AAA1

**Topic:** F.04. Stress and the Brain

**Support:** JSPS KAKENHI Grant 15K09815
JSPS KAKENHI Grant 18K07617

**Title:** Immobilization stress enhances the hippocampal mRNA expression of FKBP5 in maternal separation rats

**Authors: *H. TODA**[1], M. TANICHI[1], M. KOGA[1], T. SAITO[1], S. ENOMOTO[1], S. TAKESHITA[1], F. ASAI[1], Y. MITSUI[2], M. NAGAMINE[2], M. FUJITA[3], K. SHIMIZU[2], A. YOSHINO[1]
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**Abstract:** Previous studies have reported that increased expression of the FK506 binding protein 51 (FKBP5), especially in the amygdala and hippocampus, is associated with increased stress-related behavior. We have developed a rat model of post-traumatic stress disorder (PTSD) using a shuttle box 2 weeks after inescapable stress. In this model, maternal separation (MS) increased the number of learned helplessness behavior which was thought to be indicative of depressive symptoms. To elucidate its biological background, 30 minutes immobilization stress was undertaken as acute stress to MS group. All litters were born from timed pregnant Wistar rats and were randomly assigned to 2 groups (MS and Animal Facility Rearing, AFR groups). Litters of MS group were separated from the dams for 3 hours daily from post-natal day 2 to post-natal day 14. After the weaning at post-natal day 21, MS and AFR rats were housed in standard animal cages with 3-4rats. Thirty minutes immobilization stress was undertaken at 9 weeks old. The hippocampus, amygdala, and medial prefrontal cortex (mPFC) were dissected at 30, 60, 120, 180 minutes after the immobilization had started. FKBP5 mRNA was assessed by real-time PCR. Hippocampal, amygdala and mPFC FKBP5 mRNA levels of both AFR and MS groups at 120 and 180 minutes were more increased than at 30 and 60 minutes. Hippocampal FKBP5 mRNA level at 120 minutes of MS group was significantly increased, compared to AFR group. In case of not immobilized group, Hippocampal FKBP5 mRNA level of MS group was significantly increased at evening. FKPB5 is an important modulator of stress response and FKBP5 upregulation result in an ultrashort negative feedback loop of glucocorticoid signals. This study might indicate that MS induce stress vulnerability via the hippocampal FKBP5 upregulation. All procedures were in accordance with the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978), and the study was approved by the local Animal Investigation Committee of the National Defense Medical College.

**Disclosures: H. Toda:** None. **M. Tanichi:** None. **M. Koga:** None. **T. Saito:** None. **S. Enomoto:** None. **S. Takeshita:** None. **F. Asai:** None. **Y. Mitsui:** None. **M. Nagamine:** None. **M. Fujita:** None. **K. Shimizu:** None. **A. Yoshino:** None.

**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.09/AAA2

**Topic:** F.04. Stress and the Brain

**Title:** Neural activity in the medial prefrontal cortex during social interaction in rats: Effect of isolation rearing

**Authors: *S. ITO**, C. MINAMI, T. SHIMIZU, M. ITO, A. MITANI
Lab. of Physiology, Dept. of Human Hlth. Sci., Grad. Sch. of Medicine, Kyoto Univ., Kyoto-Shi, Japan

**Abstract:** Reduced sociability is a central symptom in various neuropsychiatric disorders, and yet the neural mechanisms underlying reduced sociability remain unclear. The medial prefrontal cortex (mPFC) has direct connection with subcortical limbic areas including amygdala and is thought to play an important role in regulating social behavior. In the present study, we recorded the mPFC neuronal activity from the infralimbic cortex (IL), prelimbic cortex (PL) and medial orbital cortex (MO) of pairs of freely moving rats during social interaction and examined the influence of isolation rearing on the activity.
Adult male Sprague-Dawley rats were used. Stainless steel wires (two wires of 50 μm in diameter) were implanted in the IL, PL or MO. Animals were allowed to recover for one week. On the test day, pairs of rats were placed in an open field box (100 x 100 x 50 cm) for 15 min, and the multi-unit activities in the IL, PL or MO were recorded in the freely behaving rats using a wireless recording system. In group-reared rats, PL neurons increased firing when the rat showed approaching behavior and also contact behavior, especially when the rat attacked the partner. MO neurons increased firing when the rat showed contact behavior. Conversely, IL neurons increased firing when the rat exhibited leaving behavior, especially when the partner left on its own accord. Isolation rearing altered social behavior and neural activity. Isolation-reared rats showed an increased frequency and decreased duration of contact behavior. The increased firing of PL neurons during approaching and contact behavior, observed in group-reared rats, was preserved in isolation-reared rats, whereas the increased firing of IL neurons during leaving behavior, observed in group-reared rats, was suppressed in isolation-reared rats. This result indicates that isolation rearing differentially alters neural activity in the mPFC during social behavior. The differential influence of isolation rearing on neural activity in the mPFC may be one of the neural bases of isolation rearing-induced behavior.

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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.10/AAA3

**Topic:** F.04. Stress and the Brain

**Title:** Establishment of a mouse model of depression induced by social isolation during adolescence

**Authors:** ***J. LIU**[1], Z. LI[2], Q. YOU[2], Y. CHEN[2], J. YANG[2], T. GAO[2]
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**Abstract:** Objective Major depressive disorder (MDD) is a highly prevalent neuropsychiatric disorder worldwide. Adolescence is a crucial developmental period and concomitant early life stressors in this period can increase susceptibility to lead to risky behaviors that result in neurological, mental health and substance-use disorders. And social isolation is a common stressor in human beings. However, it is unclear whether and how long the social isolation paradigm during adolescent leads to the depression in mice. Methods In this study, postnatal 21 (P21) and P35 male C57BL/6J mice were subjected to single housing (isolated group) or group housing with 3-5 mice per cage (control group), respectively. Sucrose preference tests were performed weekly to test whether and when the isolated mice exhibited anhedonia, a core symptom of depression. We also identified the depressive-like behaviors by employing the forced swimming test (FST), tail suspension test (TST) and learning helplessness test (LHT). Meanwhile, the anxiety-like behaviors were also examined by using open field test (OF), elevated plus maze test (EPM) and the novelty-suppressed feeding test (NSF). Results 4-week social isolation induced depressive-like and anxiety-like behaviors immediately after weaning, which can be reversed by antidepressants, whereas 10-weeks isolation was required to produce anhedonia in P35 mice. Also, the isolation paradigm increased the plasma corticosterone levels and disturbed sleep-wake pattern. Together, the symptoms after 4-week social isolation during adolescence met the principle of the construct (or etiologic) validity, face validity and predictive (or pharmacological) validity to establish an animal model of depression. Conclusions We established a mouse model of depression for studying the mechanisms of depression in adolescents.

**Disclosures: J. Liu:** None. **Z. Li:** None. **Q. You:** None. **Y. Chen:** None. **J. Yang:** None. **T. Gao:** None.

**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.11/AAA4

**Topic:** F.04. Stress and the Brain

**Support:** 2016M3C7A1914451

**Title:** The accumulated stress in early life induces depression-like behaviors and neuroinflammatory response in young adult mice

**Authors: *J. KIM**[1], E. NAM[2], Y.-H. SUH[3], K.-A. CHANG[2,1,3]
[1]Gachon Advanced Inst. for Hlth. Sci. & Technology(GAIHST), Gachon Univ., Incheon, Korea, Republic of; [2]Dept. of Pharmacol., Col. of Medicine, Gachon Univ., Incheon, Korea, Republic of; [3]Neurosci. Res. Institute(NRI), Incheon, Korea, Republic of

**Abstract: Background**
Depressions often have onset in young adulthood and contribute substantially to the global disease burden. However, its etiologies remain unclear and current treatments are not wholly effective. Because of the rapid brain development and epigenetic regulation from childhood to adolescence, early life experience can lead to anatomical and functional changes in the young adult brain. Here, we tested an animal model of accumulated stress in early life as a possible model for young adult depression.
**Methods**
To mimic accumulated adversities in early life course, we gave serial different stresses to C57BL/6 mice depending on infancy (prenatal stress, PS), childhood (maternal separation, MS), and adolescence (social defeat stress, SD). When stressed mice were 8 weeks old, we performed behavior test to assess locomotor activity, cognition, anxiety and depression-like behavior. And then we conducted Western blot, immunohistochemistry, and ELISA were to seek the pathological changes and neuroinflammation in the brain.
**Results**
Accumulated stresses significantly increased anxiety and depression-like behaviors in stressed mice compared to the control mice, but there were no differences in cognitive deficits. We found that neuronal loss, glial activation and changes of inflammation-related protein increased in hippocampus of the stressed mice. Furthermore, depression-like behaviors and pathological changes in stressed mice were attenuated by venlafaxine (10mg/kg, 21 days, i.p.), one of the SNRI antidepressants.
**Conclusion**
These results showed that accumulated mild stress in early life contribute developing depression in young adult through neuroinflammation. In addition, it suggests that an animal model of accumulated stress in early life may be a useful a model for young adult depression.

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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.12/DP08/AAA5

**Topic:** F.04. Stress and the Brain

**Title:** Developing predictors of alcohol use disorder in a chronic alcohol taking rat model

**Authors: *Y. SUN**[1], D. RIGA[2], A. B. SMIT[3], S. SPIJKER[4]
[1]VU Univ. Amsterdam, Guangdong, China; [2]CNCR, NCA, Vrije Univ., Amsterdam, Netherlands; [3]Ctr. for Neurogenomics & Cognitive Research, VU Univ., Amsterdam, Netherlands; [4]Ctr. for Neurogenomics & Cognitive Research, VUA, Amsterdam, Netherlands

**Abstract:** Alcohol is a highly addictive substance; however, its consumption does not always lead to alcohol use disorder (AUD). For instance, individual vulnerability to alcohol dependence exists and factors, such as social stress may affect the severity of AUD. Specific personality traits (related to impulsivity, compulsivity and inability to cope with stress) are important predictors for the severity of AUD in later life. Here, we searched for potential predictors of AUD-like behavior in naïve rats (no stress -NS) or rats exposed to social stress, by first examining their baseline performance in four spatial memory and social interaction tasks. Rats were subjected to the social defeat-induced persistent stress (SDPS) paradigm followed by long-term access to alcohol at their home-cage and in operant self-administration chambers. Using a 5-criteria classification of DSM-V AUD symptoms, AUD severity was assessed in NS and SDPS-exposed groups. A higher incidence of the AUD-like phenotype was detected in the SDPS group. Baseline affective behavior, measured as interaction with an adult conspecific (social approach-avoidance, SAA), was significantly correlated with most AUD criteria in controls. Notably, in the SDPS-exposed group, SAA correlated significantly with some AUD criteria in opposite direction. Furthermore, we showed that NS rats with low SAA performance seemed protected from AUD-like symptoms, whereas exposure to SDPS increased addictive-like behavior in low SAA rats. We conclude that most AUD sub-phenotypes are based on both prior genetic and environmental factors that shaped the individual's affective behavior. Exposure to social stress transforms the predictive value of affective behavior in regards to AUD-like symptoms. Disrupted affective behavior might therefore be an interesting parameter in predicting the development of AUD in humans.

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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.13/AAA6

**Topic:** F.04. Stress and the Brain

**Support:** R21MH113124

**Title:** The role of maternal peripheral serotonin 1A receptor (5-HT1AR) in programming offspring innate anxiety

**Authors: *R. J. CHEN**[1], E. LAIRD MITCHELL[2], J. GAL TOTH[2], F. TAKI[2], P. BERGIN[2], M. TOTH[2]
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**Abstract:** In addition to nutrients, mothers provide biologically active substrates to the fetus and neonate to optimize their development to the prevailing environment, referred to as predictive/adaptive maternal programming. Maternal programming is an evolutionary developed mother-offspring link that allows maternal signals to promote offspring survival and fitness. Disruptions in proper maternal signaling, due to environmental conditions or maternal disease, can lead to an increase in disease risk, such as neuropsychiatric conditions, in the offspring. Our lab has found that maternal serotonin (5-HT) and its receptor (5-HT1AR) are essential to program a proper and adaptive level of emotional regulation and immunity, because even a partial genetic reduction in maternal 5-HT1AR during gestation results in increased innate fear/anxiety and an autoimmune-like phenotype in the genetically wild-type offspring. Our data suggest that a deficiency in maternal peripheral 5-HT1AR leads to specific immune deficiencies during pregnancy, which disrupts proper maternal signaling to the fetus and results in increased offspring anxiety. Our work reveals that, in addition to its traditional CNS neuromodulatory role in regulating anxiety, 5-HT1AR in the periphery functions as a novel immunoregulator to program anxiety intergenerationally.

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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.14/AAA7

**Topic:** F.04. Stress and the Brain

**Support:** NIH Grant 1R21MH092667-01A1
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Pennsylvania State Institute for Neuroscience

**Title:** Developmental asthma leads to long-term changes in lung function, anxiety-related behavior, and expression of genes in emotion-regulation brain areas

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**Abstract:** Allergic asthma is the most common chronic condition for kids, with approximately 10% of youth affected. Developmental asthma is associated with mental health issues related to stress/emotion regulation. To understand causal mechanisms by which developmental asthma may affect emotion-related behavior, brain, and health trajectories, we developed a mouse model of developmental allergic asthma. We tested the long-term effects of developmental asthma on adult lung function, and behavior and brain gene expression associated with stress/emotion regulation. We manipulated airway inflammation and bronchoconstriction in young male and female BALB/cJ mice and measured adult outcomes three months after final asthma manipulations. Allergen exposure via administration of intranasal house dust mite extract occurred three times per week from post-natal day 7-56. This protocol led to persistent airway inflammation, mucus, collagen buildup, and elevated lung *IL-5* gene expression three months after final allergen exposure. At this same age, developmental allergen exposure led to altered brain gene expression related to stress/emotion regulation (prefrontal corticotropin releasing hormone receptor 1, hippocampal glucocorticoid receptor) and serotonin function (brainstem serotonin transporter). On the other hand, developmental acute labored breathing events (via weekly exposures to aerosolized methacholine from postnatal day 22-57) led to altered anxiety-related behavior. Importantly, these effects were modulated by mouse sex and pre-asthma fear-related behavior (rates of isolation-induced ultrasonic vocalization). Pre-asthma fear-related behavior predicted unexpected results: low-calling (low fear) neonates that were treated developmentally with methacholine demonstrated increased anxiety-like behavior compared to mice that had been categorized as high-calling (high fear) neonates. Additionally, when exposed to allergens during development, low-calling mice approached novelty more slowly and showed increased hippocampal glucocorticoid receptor expression as adults, whereas the opposite was true for high-calling mice. Developmental asthma may have long-term impacts on emotion and stress regulation mechanisms, and these influences may differ across sex and pre-asthma temperament.

**Disclosures: J.I. Caulfield:** None. **M. Caruso:** None. **R. Bourne:** None. **N. Chirichella:** None. **L. Klein:** None. **T. Craig:** None. **A. August:** None. **S. Cavigelli:** None.

**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.15/AAA8

**Topic:** F.04. Stress and the Brain

**Support:** R01 MH102729

**Title:** The children of Superstorm Sandy: The blunting of electrodermal activity by maternal depression

**Authors: *J. BUTHMANN**[1], G. VENTURA[2], J. FINIK[3], W. ZHANG[2], Y. NOMURA[4]
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**Abstract:** The prenatal environment is thought to prepare offspring for the postnatal environment, and is subject to the influence of many factors including maternal mental health. This study examines the relations between exposure to Superstorm Sandy during pregnancy, maternal prenatal depression, and offspring electrodermal activity (EDA), a measure of sympathetic nervous system activity. Superstorm Sandy, which struck the New York metropolitan region in late October of 2012, disrupted transportation and electricity, damaged property, and killed 53 people in the area. EDA was measured in children ages 2-6 during a fear-potentiated startle paradigm, in which six 90 dB startling stimuli occurred at varying intervals. The magnitude of the electrodermal responses was quantified and normalized with a log transformation. Subjects were grouped by exposure to Superstorm Sandy and exposure to prenatal maternal depression. Prior research as linked depression to hyporeactive sympathetic nervous system functioning, whereas increased stress and anxiety have been linked to hyperreactive functioning. Prenatal maternal depression was associated with blunted electrodermal responses in offspring. Of those children who were unexposed to the storm in utero, prenatal maternal depression was associated with significantly lower magnitude of electrodermal responses, while controlling for age, sex, ethnicity, and maternal marital status and education. This relation was not significant in subjects who were exposed to the storm in utero. Children exposed to Superstorm Sandy but not prenatal maternal depression had the greatest magnitude electrodermal response. Our results emphasize the enduring influence of maternal prenatal mental health, support targeted risk assessment for children who experienced an adverse prenatal environment, and the need for a deeper understanding of the interactions between maternal mood and stress on the developing child.

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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.16/AAA9

**Topic:** F.04. Stress and the Brain

**Title:** Maternal exercise during offspring postnatal development programs resiliency to acute but not chronic stress

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**Abstract:** A sedentary lifestyle is linked to various ailments while physical activity attenuates many disease-associated physical, cognitive and metabolic symptoms. However, activity and dietary patterns of the parental generation may also impact offspring physiology and behavior. Voluntary wheel running, for example, reduces proinflammatory cytokine production, while altered cytokines in maternal milk increase hippocampal (HF) proliferation and program adult offspring cognition. HF function is also linked with emotional reactivity and stress responsivity, with improved regulation of the HPA axis increasing stress resiliency. Here we asked whether maternal post-parturition exercise could program otherwise sedentary adult offspring's hormonal and behavioral responsivity to acute and chronic stress. C57BL/6 dams were provided with post-parturition access to a running wheel (runner) or standard housing (sedentary). Adult male offspring underwent four-weeks of chronic unpredictable stress (CUS) after which we assessed their emotional reactivity, specifically innate fear, sociability, and sucrose preference. Stress responsivity, measured as restraint stress-induced serum corticosterone (CORT), was assessed mid-CUS and one-week post-CUS. Stress responsivity was also assessed through daily weight measurements as an indicator of overall health. Acute stress (restraint stress followed by blood draw) resulted in comparable peak CORT levels in runner and sedentary mice, but only sedentary mice exhibited attenuated weight gain. Runner group resiliency to acute stress was lost under chronic stress, with runners showing comparable weight loss to sedentary mice. Furthermore, CUS increased restraint stress-induced peak CORT levels in both runner and sedentary mice compared to non-CUS controls. This suggests that maternal exercise-dependent resiliency is limited to acute stress and is eliminated under long-term stress conditions. Despite CUS-induced changes in stress responsivity in runner and sedentary mice, CUS failed to modify innate fear or sociability. Additionally, CUS-related increase in restraint stress-induced serum CORT levels was no longer observed one week after CUS termination, indicating that this effect is reversible in both groups. Our data show that maternal exercise during offspring postnatal development programs resiliency to acute, but not chronic stress, and that this resiliency is ablated under chronic stress. Importantly, exacerbating effects of CUS on HPA responsivity are reversible, suggesting that maternally programed acute stress resiliency may be reinstated following termination of a chronic stressor.

**Disclosures: M. Zaheer:** None. **A. Thompson:** None. **B. Zupan:** None.

**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.17/AAA10

**Topic:** F.04. Stress and the Brain

**Support:** Starr Foundation Fellowship

**Title:** Early life adversity: Role for perineuronal nets and inhibitory interneurons during anxiety-related neural oscillations in the hippocampus

**Authors: *S. MURTHY**[1,2], G. KANE[2], N. KATCHUR[2], P. MEJIA[1], G. OBIOFUMA[2], B. S. MCEWEN[3], E. GOULD[2]
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**Abstract:** Adverse experiences during early life are associated with increased risk of psychiatric disorders in adulthood, including anxiety disorders and attentional deficit hyperactivity disorder (ADHD). Interestingly, fifty percent of adults with ADHD also suffer from anxiety disorders. Maternal separation with early weaning (MSEW), a model of early life adversity, leads to increased anxiety and hyperactivity in adult mice. The ventral hippocampus (vHIP) has been associated with anxiety-like behaviors, and lesions in this region have been shown to alter anxiety-like behavior and activity levels. Neuronal oscillations of the theta frequency range (4-12Hz) have been implicated in anxiety as rodent studies have shown increased theta oscillations and theta synchrony between vHIP and mPFC during anxiety. However the electrophysiological profile of rodents that display both behavioral and neurobiological changes due to early life adversity has not been studied so far. We investigated the effects of MSEW and found that adult mice displayed small but significant increases in anxiety-like behaviors and activity levels along with increased theta power, and enhanced theta-gamma coupling in the vHIP. Additionally, MSEW mice showed reductions in densities of parvalbumin (PV) and somatostatin inhibitory interneurons in the vHIP. Our work showed that perineuronal net (PNN) intensities surrounding PV cells are increased, suggesting a role for altered PV neuron plasticity in anxiety associated with early life adversity. Intensities of OTX2, a transcription factor involved in the regulation of the critical period of plasticity of ocular dominance in the visual cortex, were also increased in the choroid plexus where it is produced, as well as in PV interneurons in the vHIP. These findings suggest causal links among PV interneurons, PNNs, OTX2, and MSEW-induced anxiety and hyperactivity and suggest potential circuit level targets for interventions to counter the negative impact of early life adversity.

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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.18/AAA11

**Topic:** F.04. Stress and the Brain

**Support:** NIH/NIAAA grants R37AA007789
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**Title:** Altered central and peripheral immune system function following prenatal alcohol exposure and/or early-life adversity: Implications for mental health

**Authors: *C. RAINEKI**, T. S. BODNAR, P. J. HOLMAN, J. WEINBERG
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**Abstract:** Brain development is a dynamic process beginning in prenatal life and extending through adolescence. Adversity and/or stress in any of these stages can alter the neurodevelopmental trajectory, putting the individual on a pathway to pathology. Alcohol is a teratogen that negatively alters brain development. However, how the early postnatal environment contributes to the pervasive effects of prenatal alcohol exposure (PAE) is poorly understood. Importantly, dysregulation of immune function may play a role in how pre- and/or postnatal adversity/stress alter brain development. Here, we examined whether PAE differentially increases vulnerability to immune dysregulation in response to early-life adversity, which may further alter brain development and lead to increased risk of psychopathology. PAE and control litters were exposed either to limited bedding (postnatal day [PN] 8-12) to model early-life adversity or to normal bedding. During early (PN30) or late (PN45) adolescence, male and female offspring were tested in the open field (OF – anxiety-like behavior) and forced swim test (FST – depressive-like behavior). Following the FST, we collected blood and brains to evaluate peripheral (serum) and central (amygdala and medial prefrontal cortex) immune function (cytokine and CRP). In females, PAE alone resulted in anxiety-like behavior in the OF. This anxiogenic profile emerged at PN30 and lasted until PN45. In males, neither PAE nor early-life adversity altered behavior in the OF. By contrast, exposure to early-life adversity resulted in depressive-like behaviors at PN45 in both male and female controls but not in PAE animals. Peripheral immune alterations following PAE and/or early-life adversity were more prevalent in males than in females. In males, PAE alone increased serum levels of TNF-α and KC/GRO at PN45 and PAE males exposed to early-life adversity showed reduced serum levels of TNF-α at PN30. In addition, early-life adversity also resulted in immune alterations in males, as serum levels of IL-5 were increased in both groups at PN30. Finally, control males exposed to early-life adversity showed reduced serum levels of IL-5 at PN45 and increased levels of IL-4 at PN30. Conversely, PAE females only showed reduced serum levels of IL-6, regardless of age. Our

results indicate that PAE and early-life adversity have unique and interactive effects on emotional regulation and immune system function, and these alterations in the immune system could be an underlying mechanism of the emotional dysregulation observed following PAE and/or early-life adversity.

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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.19/AAA12

**Topic:** F.04. Stress and the Brain

**Support:** NIGMS P20GM103643
NICHD/NIGMS 1R15HD091841

**Title:** Involvement of the CRF system on behavioral and cellular function following neonatal pain and later-life fear conditioning and sensory function

**Authors: *S. M. DAVIS**, J. ZUKE, M. RICE, V. EATON, A. STEINIS, E. HOLMQVIST, M. BURMAN
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**Abstract:** It has been established in both clinical and preclinical settings that neonatal pain and stress can lead to later-life adversity, including an increased sensitivity to pain. Our lab has demonstrated that rats exposed to repeated hindpaw needle pricks produced a disruption in cued freezing on a Pavlovian fear conditioning model, while both painful hindpaw pricks and non-painful handling produced a marked mechanical hypersensitivity when assessed at the equivalent of childhood in humans. In order to determine the role of the CRF system, male and female rat pups were pretreated with the CRF-R1 antagonist antalarmin hydrochloride before any neonatal pain manipulations were performed. Then at PND 24 or PND 66 rats were subjected to a four-day fear conditioning and somatosensory testing protocol. Results indicate that in younger rats only, neonatal handling produced a hypersensitivity in vehicle-treated males and non-injected females. Antalarmin reversed this hypersensitivity in both groups. To further explore the role of the CRF system, male and female rat pups were subjected to the same neonatal pain (hindpaw pricks) and handling procedure, however on PND 6, brain tissue was harvested 15 mins after the first neonatal pain manipulation. Brain tissue was subsequently sectioned and processed for use in either qPCR or RNAscope, a commercially available fluorescent in situ hybridization system. qPCR was conducted on dissected amygdala using CRF primers and analyzed using the ddCT method against GAPDH expression. For RNAscope, probes targeting CRF mRNA and the immediate early gene cFos were used and images were analyzed for both total CRF and cFos

expression as well as co-localization within the left and right amygdala. Results indicate that neonatal pain alters CRF and cFOS expression and a sex and hemisphere dependent manner. Taken together, these data implicate the CRF system as a potential driver behind neonatal pain and subsequent later-life behavioral and neurobiological effects.

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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.20/AAA13

**Topic:** F.04. Stress and the Brain

**Support:** NIH Grant HD091841
NIH Grant GM103643

**Title:** The effects of repeated neonatal pain on subsequent anxiety-like behaviors and corticosterone expression

**Authors: *M. RICE**, T. PAQUIN, J. RUDLONG, M. BURMAN
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**Abstract:** Premature infants who spend time in the Neonatal Intensive Care Unit (NICU) are at higher risk of developing anxiety-disorders later in life, likely due to exposure to painful/stressful events. Little is known about the mechanisms by which early life trauma might lead to later anxiety. The Hypothalamic-Pituitary-Adrenal (HPA)-axis is of particular interest as neonatal pain/stress may induce changes in its function. We hypothesized that early life pain may result in lifelong changes in HPA-axis function that may contribute to later-life anxiety.Animal models have been developed to emulate the pain that occurs in the NICU. Our lab has previously shown that early life pain in the form of needle pricks disrupts subsequent fear conditioning in rats. The current studies expand upon that by exploring how early-life pain affects subsequent anxiety-like behavior in the elevated-plus maze and HPA-axis function.For *Experiment 1:* we tested the hypothesis that neonatal pain might affect later life behaviors on the elevated plus maze (EPM) and that predator odor could act like a second trauma. To accomplish this, neonatal pain and handled groups were exposed to a predator odor (PO) or not (NPO). They were then tested on the EPM. For *Experiment 2:* we tested the hypothesis that neonatal pain might lead to changes in HPA-axis function, which could account for behavioral changes observed. To accomplish this, we analyzed the effects of neonatal paw pricks on CORT expression in rats that were either exposed to a foot shock stressor or not. The results demonstrated that repeated neonatal pain affects later anxiety-like behaviors. Neonatal pain rats were more hyperactive overall compared

to undisturbed rats. In addition, neonatal pain rats spent significantly more time in the open arms of the maze compared to handled rats. In addition, neonatal pain affected stress-related CORT release in a sex-dependent manner. Stress-induced CORT expression seems to be mildly reduced in male rats that experienced early life pain and inhibited in male rats that experienced handling. In female rats, both pain and handled groups seemed to have an increased stress response.The increased time spent in open arms in neonatal pain rats, likely suggesting a reduction in anxiety, was opposite to the effect we expected. One explanation is that the repeated brief dam-pup separations and reunions provided a protective effect. In future studies the early life pain experience can be manipulated differently by keeping rat pups separate from their mother between pain sessions.

**Disclosures: M. Rice:** None. **T. Paquin:** None. **J. Rudlong:** None. **M. Burman:** 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.; Glia LLC.

**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.21/AAA14

**Topic:** F.04. Stress and the Brain

**Support:** DGAPA-PAPIIT IN 306 918
PAPIME PE 306 318

**Title:** Effects of the exposure to alcohol and stress in the behavioral response of adolescent rats

**Authors: *M. D. VERGEL-MUNGUÍA**[1], U. TORRES-LÓPEZ[1], J. E. RAMÍREZ-SÁNCHEZ[1], P. TORRES-CARRILLO[1], O. GALICIA-CASTILLO[2], D. B. PAZ-TREJO[1], H. SÁNCHEZ-CASTILLO[1]
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**Abstract:** It has been described that in the central nervous system there are several plasticity processes along neurodevelopment, the adolescence is one of these crucial stages in which these processes happened. These changes give the organism the ability to adapt to the environmental demand, however, they also make it vulnerable to other factors, such as drug abuse and/or stress. Previous studies have suggested that alcohol consumption begins as a form of self-medication to stressful events. In addition, it is known that acute alcohol consumption produces anxiolytic effects, however, when it becomes chronic, it generates anxiogenic and depressive effects. For this reason, the purpose of this study was to investigate the effects of exposure to alcohol and

chronic unpredictable stress in the development of anxiety and depressive like behaviors in adolescent rats. Male Wistar rats (postnatal day 21) were used under standard laboratory conditions and divided in 4 groups: Alcohol + Stress, Stress + Alcohol, Alcohol and Stress. The Alcohol + Stress group was administered with alcohol at 10% v/v for 21 days and then exposed to our Chronic Unpredictable Stress Battery (CUSB), the Stress + Alcohol group was exposed to CUSB and then alcohol consumption; the Stress group was exposed to CUSB only and the Alcohol group was exposed to alcohol only. In all conditions, the anhedonic effects were evaluated with the saccharine preference test and the anxiogenic effects with the zero maze test. We hypothesize that the stress exposure before to alcohol consumption elicit an increment of alcohol intake, for this reason, the alcohol consumption of the Stress + Alcohol, Alcohol + Stress and Alcohol groups was also measured. The results indicate that the order of exposure to alcohol and stress has repercussions in the development of depressive and anxiety like behaviors. Furthermore, alcohol consumption was also affected by a consequence of this exposure order. Recently, it has been proposed that the inflammatory processes caused by stress and alcohol consumption could underlie to the impairment caused by exposure to these factors. This research highlight adolescence as a critical period for the proper development of subjects in the adulthood.

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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.22/AAA15

**Topic:** F.04. Stress and the Brain

**Support:** DGAPA PAPIIT 306918

**Title:** Endocannabinoids prevent behavioral alterations by predator scent stress in rats

**Authors: *M. MIGLIARO**[1], D. B. PAZ-TREJO[1], O. GALICIA-CASTILLO[2], H. SÁNCHEZ-CASTILLO[1]
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**Abstract:** Life-threatening experiences may lead to the development of anxiety and alterations in cognition and it has been suggested that an early pharmacological treatment after a traumatic event is viable strategy to prevent the development of posttraumatic symptomatology. The endocannabinoid system is an important regulator of stress response and has been shown to act

as a buffer by regulating the excitability of the amygdala with a mechanism that depends on the cannabinoid 1 (CB1) receptor. However, it is not known if endocannabinoids could modulate the behavioral consequences of a traumatic stressor. To evaluate if endocannabinoids can affect the development of stress-induced anxiety-like behavior and memory deficits, Wistar male rats were administered with an intraperitoneal injection of anandamide (AEA; 1, 2 or 4 mg/kg i.p.), oleamida (ODA; 1, 2 or 4 mg/kg i.p.) or vehicle (30% DMSO, 70% saline) 10 minutes prior to predator scent stress (PSS) and behavioral assessment commenced 24 hours after the stressor. Anandamide dose-dependently prevented the development of anxiety-like behavior induced by PSS in the open field test and memory deficits measured in the object recognition test. The intermediate (2 mg/kg) and higher dose (4 mg/kg) of AEA showed similar effectiveness, but the lower dose (1 mg/kg) did not affect any of stress induced alterations. It is suggested that the effects induced by AEA could be attributed to a CB1-dependent mechanism and given that AEA acts as a CB1 partial agonist, it makes sense that a higher occupancy of the receptor elicits a more distinguishable effect. On the other hand, ODA showed a poor preventive capacity, which could be due to the lower affinity to the CB1 receptor.

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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.23/AAA16

**Topic:** F.04. Stress and the Brain

**Support:** IN 306918
PE 306318

**Title:** Effects of PACAP on central amygdala on stress-related behaviors in male and female rats

**Authors: *H. SANCHEZ-CASTILLO**[1], B. ROJAS-LITE[2], S. ORTEGA-TINOCO[3], D. B. PAZ-TREJO[4], D. VELAZQUEZ-MARTINEZ[5]
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**Abstract:** Stress is a set of responses that allow the body to adapt to the demands of the environment with the aim of preserving the organism's survival. Exposure to high levels of stress, modifies the system's functionality and increases the probability of developing various pathologies such as depression, anxiety and post-traumatic stress disorder (PTSD). High levels of

PACAP have been linked to the development of PTSD. Expression of this polypeptide under stress conditions contributes to the sustained activity of the hypothalamic pituitary axis (HPA) and an increase in stress-related behaviors. PACAP is widely expressed in regions involved in the regulation of stress response, such as the paraventricular nucleus of the hypothalamus (PVN), basolateral amygdala (BLA) and central amygdala (CeA). The aim of this work was evaluate the behavioral effects of PACAP administration on the CeA in males and females to determine their role in stress responses. Wistar rats males and females were used to perform stereotaxic surgery (2.4 to 2.6 mm caudal to bregma, ± 4.4 to 4.5 mm. lateral to the midline and 5.5 to 5.6 mm below the skull surface). Rats were divided into four groups: I control females, II PACAP females, III males control, IV PACAP males and infused the drug 10 minutes prior to behavioral testing (open field and elevated zero maze). The results indicated that the animals with PACAP increased the frequency and time of anxiety-type behaviors such as crossings to the open arm and freezing. The results indicated that PACAP had no effect on stress coping behaviors such as grooming, however, males and females infused with PACAP decreased crosses and time to the open arms, indicating anxiety. In addition, the infusion of PACAP increased the freezing time only in females. We conclude that PACAP in CeA can mimetics some behaviors related to stress and its effect was more marked in females, which allows us to think that there are differential mechanisms in the anxiety and stress responses in each sex.

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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 775.24/AAA17

**Topic:** F.04. Stress and the Brain

**Support:** DGAPA-PAPIIT IN306918
PAPIME PE306318

**Title:** Influence of sex and type stressors in behavioral and neuroendocrine response to stress

**Authors: *P. TORRES-CARRILLO**[1], M. VARGAS-GOMEZ[2], J. T. MIRANDA-GUZMÁN[2], M. D. VERGEL-MUNGUÍA[4], E. J. RAMÍREZ-SÁNCHEZ[3], D. B. PAZ-TREJO[2], L. D. OCHOA-DE LA PAZ[5], H. SANCHEZ-CASTILLO[6]
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**Abstract:** Excessive and prolonged stress can lead to neuronal damage in vulnerable brain structures that is reflected with a potential negative impact on neuroendocrine and behavior response. Stress-related mental illnesses could be related to the nature and characteristics of the stressor. Previous studies demonstrated sex differences in neuroendocrine and behavioral responses to stress, being it more impaired in females, which could explain the higher prevalence in females to develop stress related disorders. On the other hand, some studies demonstrated that chronic and acute stress alters behavioral responses in males and females. Chronic Unpredictable Stress (CUS) impairs spatial memory in males but seems improve in females, whereas predator scent stress model (PSS) impairs spatial memory independent of sex or strain. The aim of this study was to compare female and male responses to different stressors vs. no-stress condition: Chronic Unpredictable Stress Battery (CUSB), PSS, and control group, respectively. Male and female Wistar rats four months old were used (n=10 per group). Animals of CUSB group were exposed to a battery of stressors for ten days. The stressors that made up the battery consisted of 1) placing animals in movement restrictors for 20 min. (3 times per day), 2) swimming in cold water for five minutes (16°C), 3) overnight light exposure (12 hours), 4) placing the rats for 12 hours (overnight) or 3 hours (on day) in their home cages with wet bedding, 5) placing the rats for 3 hours in their home cage that was tilted at 45°, and 6) overnight water deprivation (12 hours). The exposure to each stressor was randomized according to the CUSB protocol. Animals of the PSS group were exposed for 10 minutes in an exposure box that contained a bottle with scent tag impregnated with predator urine. Behavior was assessed with Open Field Test 24 hours after the final stressor exposure. The results of this study were the increased of time spent in center of open field in subjects exposed to stress but not found differences between females and males, that was consistent with several studies. Whereas, immobility time spent was higher in males than females but not differences between stress type. On the other hand, grooming time spent was higher in males than females and increases in CUSB males compared with control males. The above suggests that CUSB and PSS induced anxiety-like behaviors in males and females but not in the same way.

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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.25/AAA18

**Topic:** F.04. Stress and the Brain

**Support:** DGAPA-PAPIIT 307 715

**Title:** Behavioral effects of stress in different exposure times

**Authors: *K. B. VALENCIA**[1], U. TORRES-LÓPEZ, 04510[2], O. GALICIA-CASTILLO[3], D. B. PAZ-TREJO[4], H. SÁNCHEZ-CASTILLO[3]
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**Abstract:** Stress is the systemic response for a real or perceived threat, that enhance the survival probability of an organism. Stress response could be acute o chronic depending of the exposure time. Several mechanisms have been proposed as modulators of this response (glucocorticoid response, prefrontal and hippocampal modulation, etc.), however, when these mechanisms are not enough, and the stress response is sustained over time (chronic stress), that response could be nocive because can trigger psychiatric disorders like anxiety or depression. Research in chronic stress has developed animal models in which the exposure to stress induce anxiety-like behaviors (increased thigmotaxis, immobility, etc.), depression-like behaviors (decrease in saccharine intake) or cognitive deficits (specifically on spatial and recognition memory). Those models have become popular across the years, however, there is few researches about how the temporality to stress exposure alters significantly the behavior. Due this, the aim of this research was evaluate the behavioral effects of four exposure times to stress (5, 10, 14 and 21 days). For that, we use the chronic unpredictable stress battery (CUSB) and a behavioral battery, that include open field test (OFT), barnes maze (BM), novelty object recognition (NOR), and saccharine preference (SP). The results showed that the 10, 14 and 21 days of CUSB develop anxiety-like behaviors on OFT. In the BM and NOR only the group of 10 days of CUSB develop altered behaviors. Furthermore, since these two tests are widely related to hippocampal functioning, it could be that only 10 days of exposure causes hippocampal alterations. Finally, in the SP test all the exposure times (5, 10, 14 and 21 days of CUSB) presented depression-like behaviors. These results indicate that the exposure to 10 days of CUSB showed the greatest amount of behavioral deficits. However, since all other exposures showed depression-like behaviors, this could be the reason because why indistinct stress exposure times are used in chronic stress research.
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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.26/AAA19

**Topic:** F.04. Stress and the Brain

**Support:** NSERC (RGPIN-2014-05570)

**Title:** Sex differences in neuroinflammatory responses to systemic lipopolysaccharide treatment during puberty

**Authors: *D. KOLMOGOROVA**[1], T. VAGGAS[3], N. LEBEL[2], S. ST-PIERRE[1], E. HUDSON[3], J. G. GREGORY[4], N. ISMAIL[1,5]
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**Abstract:** The extensive neurological changes in the pubertal brain renders it vulnerable to external pathogens. In mice, systemic immune challenge during puberty induces various permanent and enduring changes in the brain and in behavior in an age- and sex-specific manner. Previous findings from our laboratory suggest that the age and sex differences in acute immune response may explain these age- and sex-specific sequelae of peripubertal immune challenge. Given that systemic immune challenge induces neuroinflammation, significant age and sex differences in the priming of microglia, the brain's resident immune cells, may also exist. This study examined sex differences in the progression of microglial activation to a systemic immune challenge during puberty. Male and female mice were treated with either the bacterial endotoxin lipopolysaccharide (LPS; 1.5 mg/kg body weight, *ip*) or 0.9% sterile saline (LPS-matched volume, *ip*) at 6 weeks of age (i.e., stress-sensitive pubertal period). Then, they were euthanized and intracardially perfused at either 24 hours, 1 week, or 4 weeks after treatment ($n$ = 8/group). Body weight changes and sickness behaviors were monitored for 48 hours post-treatment. Microglial cells labelled by immunocytofluorescence were counted in the sub-regions of the hippocampus. As expected, LPS-treated mice showed more sickness behaviours ($p < .001$) and weight loss ($p < .01$) compared to saline-treated mice, with LPS-treated females showing a slightly faster symptomatic recovery than LPS-treated males. Overall, iba-$1^+$ cell expression in the hippocampus was significantly greater among LPS-treated mice at all three time-points ($p < .05$). LPS-treated males generally showed more activated microglial cells than female counterparts at 24 hours post-treatment ($p < .05$). Although iba-$1^+$ cell expression normalized within 1 week of treatment for males exposed to LPS, the microglial response among LPS-treated females was more gradual and remained more activated compared to LPS-treated males even after 4 weeks. These results indicate a sex difference in the vulnerability of the pubertal brain to neurotoxic microglial priming from external pathogens that is biased towards females.

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**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.27/AAA20

**Topic:** F.04. Stress and the Brain

**Support:** NSERC RGPIN-2014-05570

**Title:** Probiotic amelioration of LPS-induced glucocorticoid receptor resistance

**Authors: *K. B. SMITH**[1], N. ISMAIL[2]
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**Abstract:** Puberty is a sensitive developmental period characterized by sexual maturation, and brain reorganization and remodeling. Pubertal stress exposure can disrupt normal hypothalamic-pituitary-adrenal (HPA) axis development, potentially leading to future cognitive, behavioural, and mental disorders. Improper HPA axis development can cause excessive cortisol release, eventually leading to glucocorticoid receptor resistance (GRR). The purpose of this study was to examine whether the stress ameliorating properties of probiotic administration are effective at preventing GRR in pubertal mice. Mice arrived at age 3 weeks and were separated by sex. They were separated again to either receive free access to milk control or kefir (a probiotic). Mice were given either a saline or LPS injection during puberty. Behavioural monitoring and sickness response was recorded until sacrifice at 10 weeks of age. Immunohistochemistry was used to stain for glucocorticoid receptor (GR). GR expression is currently being examined in the paraventricular nucleus, suprachiasmatic nucleus, piriform cortex, amygdala, and medial prefrontal cortex. This study intends to find decreased GR expression in all five brain regions in LPS-treated mice exposed to control milk. However, in LPS-treated mice exposed to probiotics, we expect to find to change in GR expression in the five brain regions examined. Obtaining the anticipated results would provide additional evidence that probiotics mitigate the stress response. As well, these results would suggest that timely administration of probiotics contribute to the healthy biological development of our brain. Continued research could optimize the effects of probiotics and potentially develop supplemental treatment for those suffering from stress-related disorders.

**Disclosures: K.B. Smith:** None. **N. Ismail:** None.

**Poster**

**775. Early-Life Stress: Anxiety, Social Function, and Depression**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 775.28/AAA21

**Topic:** F.04. Stress and the Brain

**Support:** NSERC grant (RGPIN-2014-05570)

**Title:** Programming effects of pubertal lipopolysaccharide treatment in male and female CD-1 mice

**Authors: *R. SHARMA**[1], B. THOMAS[2], N. ISMAIL[1]
[1]Univ. of Ottawa, Sch. of Psychology, Ottawa, ON, Canada; [2]Cardiff Univ., Wales, United Kingdom

**Abstract:** Puberty is an important developmental event that is marked by the remodeling of the brain. Exposure to stressors during this critical period of development can have enduring effects on both reproductive and non-reproductive behaviours. Neonatal studies show that exposure to immune stress during this critical period of development can alter the response to a second exposure later in life. Programming effects of pubertal immune stress remain un-investigated. Therefore, the objective of this study was to investigate age and sex differences in the programming effects of lipopolysaccharide (LPS) treatment, a bacterial endotoxin and immune stressor, in male and female CD1 mice (N=40 for experiment 1; N=80 for experiment 2) caused by pubertal LPS treatment. Mice were pre-treated with either saline or LPS at 6 weeks (puberty) or 10 weeks (adulthood) of age. After four weeks, all mice received LPS and were euthanized 10 hours later. Body temperature and peripheral and central cytokines were analyzed via telemetry dataloggers, multiplex luminex immunoassay, and RT-qPCR, respectively. Adult males that were pre-treated with LPS had a greater reduction of the hypothermic response to a second immune challenge than those that were pre-treated during puberty, suggesting age differences in the thermoregulatory programming effects. The blood serum concentrations of IL-6 and IFNγ were also attenuated by previous LPS treatment. Pre-treated adult males produced decreased levels of serum IL-6 and IFNγ whereas pre-treated pubertal males showed lower levels of IL-6. Programming effects of the neuroimmune response were localized by sex such that adult males pre-treated with LPS displayed an attenuated mRNA expression of TNFα and IL-6 in the hippocampus. Pubertal females pre-treated with LPS displayed attenuation in IL-1β, TNFα, and IL-6 mRNA expression in the prefrontal cortex. These findings suggest that puberty is a critical period for the programming of stress and immune responses, and stressor exposure during this period can alter the response to subsequent stressors. To conclude, this study found that the immune response is attenuated by a secondary treatment of LPS but further research is required to elucidate the age- and sex-specific mechanisms in programming effects.

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**Poster**

**776. Stress and the Brain: Adolescence**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 776.01/AAA22

**Topic:** F.04. Stress and the Brain

**Support:** COLCIENCIAS/Predoctoral fellowship

**Title:** Stress during puberty has differential effects on impulsive action and waiting behaviors

**Authors: *L. F. GONZALEZ MARTINEZ**, K. ABSHIRE, W. PADRON, H. J. LEE, Y. DELVILLE
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**Abstract:** Early stress exposure has a wide range of effects impacting cognition and personality, making early trauma a risk factor for development of mental disorders later in life. Our previous studies in hamsters showed that chronic social stress in early puberty results in enhanced impulsive action, in particular decreased action inhibition in a Go-NoGo task. We decided to address possible effects of early stress on the capacity to wait to respond, the other form of impulsive action. Male golden hamsters were exposed daily to aggressive adults from postnatal day 28 to 42. Later in adulthood, animals were trained to respond to a light cue by nose-poking into a lid opening that triggered the delivery of food pellets reward in a five-choice-serial-reaction-time task. During testing, we introduced random and varying delays (2 to 40 secs) between the light in the conditioning chamber and in the openings, and looked for premature nose-poking responses as an indicator of impulsive action. As delays grew longer, animals were more likely to perform premature responses. However, previously stressed animals were ca. 25% less likely to perform such actions by the longest delay. There were no significant differences between groups or between delays in accuracy, omissions or errors. As a control for this experiment, we introduce varying delays (0 to 60 secs) between the nose-poking response in the openings and the delivery of the reward. In this case, there were no significant differences between groups in accuracy, omissions, errors, or perseverative responses. However, as delays grew longer all animals were significantly less accurate, and made more errors and perseverative responses. Early social stress has opposite effects on the two components of impulsive action: decreased action inhibition, but enhanced capacity to wait to respond. Additionally, early stress has differential effects in the response to introduction of delays: enhanced tolerance to delays between conditioning cues, but no differences between groups in waiting for delayed rewards. These studies suggest complex neural changes underlying these behavioral consequences, and may help to understand the diverse patterns of impulsivity and the specificity of the long-term effects of early stress.

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**Poster**

**776. Stress and the Brain: Adolescence**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 776.02/AAA23

**Topic:** F.04. Stress and the Brain

**Support:** CIHR 376681

**Title:** The behavioural and pathophysiological effects of early life adversity on pain sensitivity

**Authors: S. SALBERG**[1], N. BURKE[4], M. WANG[2], J. VINALL[3], M. NOEL[1], *R. M. MYCHASIUK[3]
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**Abstract:** All children experience pain, and although many recover quickly a significant proportion go on to suffer from chronic pain. Chronic pain which is defined as pain that last for greater than 3 months is a growing epidemic with limited effective treatment options. It effects between 11-38% of youth, significantly decreasing quality of life for these children. Early life adversity is characterized by stressful or traumatic events early in life and is associated with cognitive, social and emotional impairment, as well as chronic pain. Therefore, this study aimed to investigate the effects of early life stress on pain sensitivity and emotional function in the Sprague Dawley rat, using maternal separation (MS) as a model of neglect. This was done via two aims: 1) Evaluate the effect of early life stress on behaviour, and 2) Evaluate the effect of early life stress on the epigenetic and pathophysiological response to pain. Our results showed decreased weights and brain size in MS groups compared to controls, as well as increased anxiety-like behaviour and an altered pain response, with increased pain thresholds indicative of chronic pain in the future. MS groups also demonstrated increased expression of genes involved in regulating the stress and fight-or flight response, mood, and neuroplasticity; as well as increased levels of inflammatory markers. With these findings, we conclude that we were able to alter the pain response both at the behavioural and molecular level using a psychological model of early life stress. This is a promising area to tease apart the causes of chronic pain; an important step in understanding the multiple factors associated with chronic pain, which may lead to more realistic and effective treatment options to deal with stressors and reduce pain.

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**Poster**

**776. Stress and the Brain: Adolescence**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 776.03/AAA24

**Topic:** F.04. Stress and the Brain

**Title:** The implications of early life stress on the endogenous dopamine system

**Authors: *G. ERICKSON**[1], T. LOVE[2], A. J. SMITH[2], J.-K. ZUBIETA[3]
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**Abstract: Background:**
Early life stress (ELS) is associated with an increased risk of anxiety, depression, and substance abuse. Some research suggests that stress, particularly stress early in life can impact activity within the mesolimbic dopamine system, a system which plays a significant role in both reward and stress. Here, we examined the relationships between age of onset of ELS, length of ELS, number of traumatic experiences, and dopamine receptor binding in a group of healthy male participants.
**Methods:**
21 healthy male participants aged 18-45 were recruited via advertisement. Participants filled out the Family Experiences Questionnaire which is a retrospective measure of childhood trauma. Three parameters of trauma were determined for analyses: age of initial trauma AoIT, which is the participants age at their first traumatic experience; length of trauma (LoT) which is the length of time between their initial and final traumatic experience; and number of traumas (NoT) is the count of traumatic experiences through childhood. These analyses were chosen because of their relation to the adverse childhood experiences questionnaire and is associated with increased risk of mortality. Participants were then scanned using positron emission tomography (PET) with the dopamine D2/3 receptor antagonist radiotracer [11C] raclopride.
**Results:**
Regression analyses indicated baseline dopamine binding was negatively correlated in the left globus pallidus with AoIT ($T=3.54$, $p=0.001$). The right putamen showed negative correlation between D2/D3 receptor binding in both the LoT ($T=3.54$, $p=0.001$) and in the NoT group ($T=3.59$, $p=0.001$).
**Discussion:**
We found relationships between dopamine binding and ELS in age of onset of stressors, length of stressors, and number of stressors. These data suggest that mesolimbic dopamine activity may be modulated by the experience of ELS, particularly when the experience occurred earlier in life or had a longer duration.

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**Poster**

**776. Stress and the Brain: Adolescence**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 776.04/AAA25

**Topic:** F.04. Stress and the Brain

**Title:** Ethanol and stress alter fear memory in adolescent rats

**Authors: *R. SIRCAR**[1,2]
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**Abstract:** In humans increased ethanol intake is thought to reduce stress, and stress exposure has been shown to increase the alcohol consumption in both humans as well as in experimental animals. Adult rats and mice exposed to chronic stress exhibit impaired memory. Also, long-term ethanol consumption impairs performance of memory tasks. Some studies in literature show that increased ethanol consumption in adult rodents exacerbates stress-induced memory dysfunction, but not others. Whether stress with or without ethanol can modulate memory functions in adolescent rats is not known. Here we report effects of stress and ethanol on fear conditioning in adolescent rats. Adolescent female rats were exposed to repeated unpredictable stress. Groups of stressed and non-stressed rats were administered daily with ethanol (2 g/kg, intraperitoneally), or equivalent volumes of vehicle. All rats were trained in the fear conditioning paradigm, and 24 hours later were tested for fear memory. Freezing during fear conditioning tasks were recorded, and freezing scores were computed for each animal. Compared to vehicle-treated control rats, ethanol-treated adolescent rats showed significant disruptions in fear memory with or without stress. Our data suggests that ethanol and stress can alter memory functions in adolescent rats.

**Disclosures: R. Sircar:** None.

**Poster**

**776. Stress and the Brain: Adolescence**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 776.05/AAA26

**Topic:** F.04. Stress and the Brain

**Support:** NSERC grant # RGPIN-2014-05570

**Title:** The effect of pubertal probiotic treatment on LPS-induced changes in TLR4 expression in the PVN in male and female CD1 mice

**Authors: *E. L. MURRAY**[1], K. MARR[1], N. ISMAIL[2]
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**Abstract:** Puberty is a critical period in development during which sexual maturity is achieved and accompanied by significant brain reorganizing and remodeling. Exposure to an immune challenge during puberty causes enduring effects on neurological processes involved in anxiety and future response to stress. The gut microbiome is a system known to modulate neurocognitive functions; however, research has yet to elucidate the role of gut microbiota on these processes during pubertal development. The present study investigated the long-term effects of exposure to lipopolysaccharide (LPS) and probiotic treatment during puberty on toll-like receptor 4 (TLR4) expression in the periventricular nucleus of the hypothalamus (PVN). Male (N = 21) and female (N = 22) CD1 mice received probiotic treatment (kefir or milk control) for two weeks and were exposed an immune challenge (LPS or saline control) at 6 weeks of age. When mice reached adulthood, they were exposed to a 30-minute restraint stress and euthanized 30 minutes later. Mice injected with LPS displayed increased TLR4 expression in the paraventricular nucleus of the hypothalamus (PVN) in adulthood compared to saline controls. Moreover, male mice display increased TLR4 expressions compared to females. In the probiotic condition, LPS-treated males display significantly more TLR4 compared to LPS-treated females. Treatment with kefir did not produce significant differences compared to milk controls. These findings suggest that pubertal exposure to LPS causes enduring changes in TLR4 receptor expression in adulthood and provides a greater understanding of the long-term effects of immune challenge, probiotics and sex differences on CNS signalling responses. Our research study is the first to examine the relationship between gut bacteria, immune challenge and its impact on pubertal development, a time when stressors are particularly impactful. This research provides an understanding sex differences and the mechanism of gut-brain interaction.

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**Poster**

**776. Stress and the Brain: Adolescence**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 776.06/BBB1

**Topic:** F.04. Stress and the Brain

**Support:** MH101729
T32 DK059803

**Title:** Fear enhanced learning after single prolonged stress prevented by previous adolescent stress exposure: Circuitry and neuronal subtype characterization

**Authors: *E. M. COTELLA**, P. LEMEN, S. MARTELLE, R. MOLONEY, M. FITZGERALD, N. BEDEL, J. HERMAN
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**Abstract:** Posttraumatic stress disorder (PTSD) is a psychiatric condition that can develop after the individual is exposed to traumatic experience. Not everybody that experiences trauma develops the disorder suggesting there must be mechanisms that confer either vulnerability to develop the condition or on the contrary, more resilience to overcome the traumatic experience. Single-prolonged stress (SPS) is one of the most studied models of fear-potentiated fear that has shown to be a suitable protocol for the study of PTSD features. To study factors affecting vulnerability and resilience, we evaluated rats using a double-hit model of stress in adolescence and SPS in adulthood. Male and female rats were submitted either chronic variable stress (CVS) for 2-weeks starting at PND44. Stressors were presented randomly twice daily (cage vibration, cold water swim, warm water swim, cold room, hypoxia, or restraint) and every 2-3 days they had overnight stressors (single housing or overcrowding). At 85 days of age, a group of the rats was subjected to single-prolonged stress (2 hour restraint, 20 minutes of group swim, 10 min recovery, exposure to ether vapor until loss of consciousness) The resulting groups were: Control, Adol CVS, SPS and the double-hit group Adol CVS+SPS. After a week, animals' performance in an auditory-cued fear conditioning paradigm was tested. There were no differences in acquisition of freezing in response to the pairing of the shock to the auditory tone in any group or sex. During extinction, SPS males increased freezing behavior during all extinction sessions ($p<0.05$). This was prevented by the previous exposure to stress during adolescence ($p<0.05$). In females, the first day of extinction, all the stressed groups had higher retrieval of the behavior ($p<0.05$). In this case, CVS+SPS group did not exhibit reversal of the extinction deficit seen in males. During recall, CVS and SPS males showed higher freezing ($p<0.05$) and CVS+SPS remained at the control level. Both males and females had increased freezing during reinstatement session and this was prevented by previous exposure to CVS ($p<0.05$ respectively). In summary, previous history of stress makes the animals resilient to the effects of SPS later in life, suggesting that some of the physiological adaptations during adolescent stress could prevent the effects of PTSD in adulthood.In order to address circuitry involved in the effect, mapping of Fos activation in areas related to the control of stress and fear responses such as medial prefrontal cortex and amygdala is currently underway to determine differential activation in excitatory versus inhibitory neurons.

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**Poster**

**776. Stress and the Brain: Adolescence**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 776.07/BBB2

**Topic:** F.04. Stress and the Brain

**Support:** FONDECYT #1140776
VRIEA 125.793/2014 PUCV

**Title:** Early-life exposure to antibiotics affects behaviour and expression of dopamine receptors in the mesocorticolimbic system of young rats

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**Abstract:** Neonatal gut colonization begins as the newborn passes through the birth canal, and later comes in contact with the mother (i.e.: breast feeding). Thus, alterations in the maternal gut microbiota, like those induced by antibiotic use through perinatal period may affect the infant's microbiota. Additionally, it has been shown that alterations in the gut microbiota affect human and animal behaviour. For instance, germ-free mice have reduced anxiety-like behaviours despite producing an exaggerated release of corticosterone upon a stressful stimuli. In addition, the use of oral non-absorbable wide-spectrum antibiotics in adult rodents reduces anxiety-like behaviours. All these observations have been made in adult animals, and very little has been done in order to address whether these finding can be replicated in early-life stages. Thus, in order to test this we administered through oral gavage a mixture of non-absorbable wide spectrum antibiotics (neomycin 100 mg/kg, bacitracin 100 mg/kg, pimaricin 5microg/kg and vancomycin 100 mg/kg) to pregnant Sprague-Dawley dams starting three days before parturition and until post-natal day (PND) 7, while a control dam group was given vehicle (0.9% NaCl solution). On PND 21 pups were weaned and behavioural studies were carried out only in males between PND 34 to PND 36. Early-life exposure to antibiotics increased the number of entries to the central area of the open field, with no effect on motor activity when compared to controls. In a novel object recognition test, males exposed to antibiotics explored the novel object, while control animals do not pay much attention to the novel object. Additionally, early-life antibiotic exposure reduced basal plasma concentration of corticosterone in comparison to control rats. In the brain, early-life exposure to antibiotics decreased the expression of tyrosine hydroxylase and dopamine receptor 2 in the ventral tegmental area, and it also reduced the expression of

dopamine receptor 1 in cingulate cortex 1, striatum and nucleus accumbens, when compared to control animals. These findings suggest that alterations in the bacteria that colonize the gastrointestinal tract during early-life (PN1-7) affect exploratory behaviours in young rodents, reduce corticosterone levels, and do not affect motor function. This findings strongly suggest that acquisition of a balanced microbiota in early-life stages is important for the development of the dopaminergic system. Moreover, these findings are observable during infancy, which suggests that further interventions can be made in order to prevent the occurrence of psychiatric-related disorders later in life.

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**Poster**

**776. Stress and the Brain: Adolescence**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 776.08/BBB3

**Topic:** F.04. Stress and the Brain

**Support:** Fondecyt 1130213

**Title:** Colon submucosal neuropathy in malnourished juvenile rats

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**Abstract:** Malnutrition disturbs several aspects of digestive physiology. Essential to the large intestine function is the enteric nervous system (ENS), which releases and responds to the same neurotransmitters found in the CNS. The ENS modulates muscle contractility and epithelial absorptive and secretory function, thanks to the actions of the myenteric plexus, immersed in the gut muscle layers, and the submucosal plexus, closer to the lumen, respectively. The ENS remarkable plasticity allows it to modify neuronal size, density of certain neuronal phenotypes and their chemical coding in response to environmental stimuli. Poor nutrient supply can impair myenteric neuron plasticity, reducing neuronal size and decreasing the number of certain neuronal types. Surprisingly, little data is available regarding the effect of malnutrition on submucosal neurons, which are in a closer location to sense gut luminal changes and are therefore a key element to the gut-brain axis.
We have previously shown that just 20 days of protein malnutrition (4% instead of 26% protein

in a control diet) generate a substantial reduction in weight gain, accompanied by disruption of the gut barrier function in the juvenile rat. Our aim was to evaluate whether protein malnutrition impairs submucosal neuron plasticity in the juvenile rat colon.
After weaning at postnatal day (PND) 21, animals received control diet until PND 40. Thereafter, they were separated into control groups, which continued under the same diet, and low protein (LP) groups, which were fed a low protein diet. Neuron morphometry and characterization of chemical coding (i.e. expression of the markers HuC/D, PGP9.5, neurofilament 200, Substance P (SP), Somatostatin, VIP and NPY) was performed at PND 40, 45, 50 and 60 by immunofluorescence of the colon submucosa.
The number of sensory neurons per submucosal ganglion, as well as the amount of total ganglion projections remained unchanged in LP-fed animals. However, protein malnutrition had a consistent effect on the size of submucosal neuron bodies, especially at the 20-day treatment group: VIPergic and NPYergic neurons, as well as sensory VIPergic and sensory SP neurons displayed significantly smaller cell body area in LP-fed animals in comparison to age-matched controls. Further studies should functionally characterize these neurons in order to evaluate the consequences of such morphological changes.
These data will aid to increase our understanding of the consequences that inadequate nutrition has on adolescent digestive physiology and their potential implications on the ability of enteric submucosal neurons to sense and communicate local information to the brain.

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**Poster**

**776. Stress and the Brain: Adolescence**

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**Program #/Poster #:** 776.09/BBB4

**Topic:** F.04. Stress and the Brain

**Support:** NIH DA038588
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**Title:** Maternal care controls the development of fear learning in adolescent nonhuman primates: Relationship with prefrontal 5ht1a receptor binding

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**Abstract:** Childhood maltreatment is associated with increased risk for psychopathology, and social and cognitive deficits. Consistent with human evidence linking early life stress (ELS), with poor emotional/stress regulation, as seen in anxiety and mood disorders, our lab has reported that maternal maltreatment (MALT) leads to increased emotional reactivity, anxiety and impulsive aggression in nonhuman primates. It is unclear if this is due to enhanced fear learning or impaired ability to modulate fear responses. These questions can be probed using acoustic startle paradigms where the inability to modulate fear-conditioned responses by safety cues have been found to be translational biomarkers for fear-related disorders in humans and animal models. This study used a well-established rhesus model of MALT, which consists of spontaneous and comorbid physical abuse and rejection, leading to infant distress. The long-term outcome of ELS on fear learning was assessed in 25 adolescent macaques (4.5-5.5 yrs), half experienced MALT (n=14; 8 M, 6 F), and the other half competent maternal care (Control: n=11; 5 M, 6 F). It was hypothesized that MALT animals would have higher baseline and fear conditioned acoustic startle, take longer to discriminate fear/safety to attenuate startle, and show impaired extinction. An AX+/BX-, fear/safety signal paradigm, measured baseline startle response as an indicator of anxiety, fear-potentiated startle, attenuation of startle with safety signals, and extinction. Baseline startle in maltreated animals, particularly females, remained high throughout baseline startle testing, suggesting impaired desensitization to the startle cue. During discrimination training, % fear potentiated startle was significantly lower in females, and MALT females showed a higher transfer of fear to the safety cue in addition to the fear cue during early training than Control females, suggesting fear generalization. Due to its role in emotional/stress regulation, prefrontal serotonin (5HT) 1A receptor binding potential (BP) was also examined using PET imaging during adolescence. There was a significant negative correlation between PFC 5HT1A receptor BP and startle measures ($r= -0.481$, $p=0.0173$), such that reduced BP was predictive of increased baseline startle amplitude, consistent with human studies on anxiety and depression. This suggests developmental alterations in fear learning related to MALT, especially in females, leading to difficulties in discrimination learning and generalized fear. This interpretation is supported by higher measures of trait anxiety in baseline startle, as well as reduced PFC 5HT1A receptor BP in maltreated animals.

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**Poster**

**776. Stress and the Brain: Adolescence**

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**Topic:** F.04. Stress and the Brain

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Yerkes National Primate Research Center (YNPRC) Base Grant OD P51OD011132

**Title:** Early hypothalamic-pituitary-adrenal axis activity predicts anxiety and sensitivity to the reinforcing effects of cocaine in adolescent macaques: Early life stress as a risk factor

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**Abstract:** Early life stress (ELS) is a known risk factor for psychopathology, including anxiety and substance use disorders, which are often comorbid. The mechanisms underlying this association, however, remain poorly understood. A likely biological link is overactivation of the hypothalamic-pituitary-adrenal (HPA) axis during critical periods of neurodevelopment. To study this relationship, our group is using a well-established, translational ELS model of infant maltreatment by the mother in rhesus macaques (*M. mulatta*). This ELS model consists of concomitant infant abuse and rejection by the mother during the first months of life. The long-term effects of ELS on anxiety and risk for psychostimulant abuse during adolescence have been examined using established fear-potentiated startle (FPS) and cocaine self-administration (COC SA) paradigms, respectively. In this study, we tested the hypothesis that elevated HPA activity reported during infancy in the ELS animals predicts elevated anxiety in FPS, and increased COC SA during adolescence (n=11; 5 females, 6 males) using bivariate correlation analysis. Our results show that higher hair cortisol accumulation during the first 6 months of life was positively correlated with both baseline startle amplitude in FPS (i.e. index of anxiety; r=0.897, p=0.003) and response rates during COC SA limited access conditions (an index of sensitivity to the reinforcing effects of COC; 0.757, p=0.049). Stepwise regression adding sex into the model found that this variable did not account for a significant portion of either relationship. These findings suggest that HPA axis activity early in life predicts later anxiety-like behavior and sensitivity to the reinforcing effects of COC. This lends credence to the suspected involvement of ELS-induced HPA axis overactivation early in life in the emergence of comorbid anxiety and substance use disorders. Further investigation will be required to determine if this relationship is causal.

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**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 777.01/DP10/BBB6

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** ERC fUS Imagine 339244
Fondation Recherche pour le Cerveau Programme Rotary Espoir en tete
Ecole Doctorale Frontières du Vivant Programme Bettencourt

**Title:** Neurofunctional Ultrasound reveals brain-wide vascular patterns during REM sleep in rats

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**Abstract:** Rapid eye movement sleep (REMS) is a peculiar brain state present in most mammalian species that combines the behavioral components of sleep and the electrographic patterns of the wake state. Long associated with dreaming and emotional content and more recently with memory consolidation, REMS is thought to exhibit a general brain state that is comparable to active behavior as both electrophysiological profiles are strongly similar. Classical models of REMS have thus assumed that the brain recreates wake conditions to perform its functions; however, the question of brain activity levels during REMS remains elusive because observations of its natural dynamics remain an experimental challenge.
Here, we reveal brain-wide spatiotemporal hemodynamics of single REMS episodes and demonstrate for the first time the close association between massive hyperemic events and fast gamma oscillations in rats. Using functional ultrasound (fUS) imaging concurrently with intra-hippocampal extracellular recordings of local field potentials (LFP), we show that REMS hemodynamics consist of a tonic increase in cerebral blood volume that is interleaved with large-amplitude brain-wide phasic hyperemia. Moreover, the intensity and spatial reach of these "vascular surges" (VS) largely outmatched wake levels, revealing brain-wide amplification that was strongest in the dorsal hippocampus and dorsal thalamus. We found LFP precursors to VS in the theta (6-10 Hz) and fast gamma (80-110 Hz) bands in the CA1 region. However, the variability of VS intensity was best accounted for by fast gamma power. Ultimately, our findings question the evolutionary benefit of such energy-demanding vascular patterns, especially considering the near-ubiquitous presence of REMS in mammalian species. Our findings also open the way for the combined controlled manipulation of local brain rhythms and global imaging of sleep hemodynamics.

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**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 777.02/BBB7

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** Australian Research Council Discovery Project (DP170101778)

**Title:** Detectability of ocular dominance and orientation preference features in primary visual cortex using fMRI

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**Abstract:** Recently developed hemodynamic model and deconvolution techniques are used to explore whether and how ocular dominance (OD) and orientation preference (OP) features in the primary visual cortex (V1) can be imaged with functional magnetic resonance imaging (fMRI). These features exist on scales of around 1 mm, which is near the current fMRI resolution limit. Moreover, hemodynamic effects extend the response of these features to localized neural activity over scales of up to several mm, which further reduces their detectability. Here, the retinotopic map from retina to V1 is used to estimate the neural response to an oriented bar stimulus, which consists of a “string of pearls” pattern of localized activated regions in V1, whose OPs correspond to the bar orientation and patchy axonal projections from the directly excited points. For OP perpendicular to OD boundaries, the separation of the directly stimulated regions ranges from about 1 mm for binocular stimuli to 2 mm for monocular stimuli; whereas, for OP parallel to OD boundaries, the separation is about 1 mm or sometimes less. Hemodynamic modeling shows that the patchy connectivity in V1 gives rise to a response that has a width of several mm, with a modulation of about 10% for 1 mm separation and about 25% for 2 mm. However, it is demonstrated that model based deblurring can resolve the underlying neural signal using a filter with noise-to-signal ratio of 1%. Up to now, the way to visualize OD and OP is through experimental studies in post-morten species. Here, the simulations show that equivalent patterns can also be visualized using fMRI. This study can guide future explorations of OD and OP features in V1.

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**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 777.03/BBB8

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Title:** Novel index to evaluate the effect of the intervention for healthy elderly, preclinical Alzheimer's disease and mild cognitive impairment subjects using the combination of cerebral hemodynamics markers with multi-task based functional near-infrared spectroscopy (fNIRS)

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**Abstract: Background:** Early and appropriate intervention in Mild Cognitive Impairment (MCI) and preclinical Alzheimer's Disease (AD) is an effective way to prevent progression of the disease. Continuity of intervention by motivating individuals is crucial issue to prevent onset of dementia, however, there is no useful index to evaluate effectiveness of the intervention. fNIRS is functional neuroimaging technology for assessment of neuronal activity by measuring the cerebral hemodynamics related to the task in a non-invasive and unconstrained manner. In this study, we developed the novel index to monitor cognitive function using multi-task based fNIRS in the daily function levels in healthy, preclinical AD and MCI subjects. **Methods:** The observation study between non-dementia control (NDC) and MCI was approved by site Institutional Review Boards with written informed consent. The inclusion and exclusion criteria of NDC or MCI were basically referred to the Alzheimer's Disease Neuroimaging Protocol (ADNI). Cerebral hemodynamics signals were acquired at total 54 channels to cover the cortex region of not only forehead but parietal and somatosensory area on age-matched 14 NDC and 12 MCI subjects using continuous-wave fNIRS system by two daily function level tasks developed by us. Each task had repeating block design and the degree of difficulty was different between $2^{nd}$ and $3^{rd}$ block so that we utilized the signal ratio between $2^{nd}$ and $3^{rd}$ block to avoid artifacts in fNIRS signals. To screen an appropriate regression model, four region-of-interest (ROI) on cerebral cortex were selected, and the ratio of fNIRS signals on each ROI were averaged respectively, then linear regression model between NDC and MCI in combination with all feature quantity of fNIRS signals was obtained. The receiver operation characteristic (ROC) analysis was done to evaluate the clinical usefulness of this model with cognitive ability index. Accuracy of this new index was evaluated using another set of subjects consisting of 17 NDC

and 8 MCI as test data. **Results:** The combination of feature quantity of oxygenated hemoglobin and signal area in both the sensory examination task and calculation task showed good performance with an area under the curve (AUC) of 0.863, 83.3% sensitivity and 78.6% specificity in NDC vs. MCI. Accuracy in cross-validation of this index in NDC vs. MCI was 65.4%. The test data from 25 subjects indicated 68.0% accuracy (NDC: 70.6%, MCI: 62.5%). **Conclusions:** fNIRS approach in present study to get the index for evaluating cognitive function may be useful to establish the monitoring system for the cognitive-normal brain activity in the daily function levels.

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**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

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**Program #/Poster #:** 777.04/BBB9

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

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ANR-10-IDEX-0001-02, INSERM
PremUp Foundation

**Title:** Large amplitude cortical cerebral blood volume variations (ΔCBV) revealed by functional ultrasound imaging are typical of neonate active sleep

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**Abstract: Research objective**
Functional Ultrasound (fUS) imaging recently opened new perspectives for neonate neuroimaging. fUS can detect the neurovascular coupling by leveraging its sensitivity (down to 1mm/s blood flow speed), temporal resolution (1ms), and spatial accuracy (250 µm). Its portability makes it an unprecedented tool for research on neonate brain activity at bedside. In a first study, fUS was able to localize ictal events in pathological patients [1]. Here, we assessed

the relevance of fUS coupled to electroencephalography (EEG) for studying neonates' sleep phases.

**Methods**

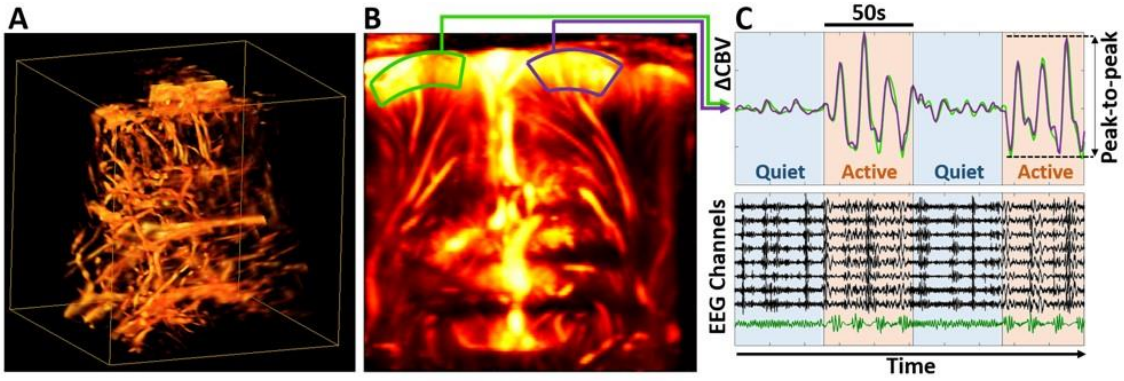
A custom ultrasonic probe was mounted into a newborn-adapted headset along with 8 electrodes. An ultrafast ultrasound research scanner was used to acquire custom fUS sequences (PRF 1950Hz) recording the ΔCBV every 1s with acoustic intensities far below FDA requirements. The probe was placed on the fontanel and could be rotated with a servo-motor. 3D scans in both coronal and sagittal views were combined to reconstruct a volume of brain vasculature. Once in the section of interest, fUS and EEG were synchronously recorded on 6 near-term healthy neonates during 60min to observe phases of quiet and active sleep.

**Results**

The 3D scan allowed probe positioning between patients in reproducible cerebral structures of interest. During sleep, fUS revealed oscillating patterns of ΔCBV (~0.05Hz), which amplitude increases more than threefold in active sleep as compared to quiet sleep. The high correlation ($r=0.8$, $p<0.0001$) between ΔCBV oscillations' peak-to-peak amplitude (> 50% of baseline) and the EEG-revealed sleep state showed the sensitivity of fUS to subtle vascular changes.

**Conclusion**

fUS proved to be sensitive enough to detect neurovascular variations during the moderate brain electrical activity changes observed in healthy neonates during sleep phases. The huge metabolic demand recorded during active sleep is questioning the role of this phase in brain development. By combining fUS, 3D navigation and synchronous EEG, this study paves the way for functional connectivity imaging [2] in neonates at bedside.




**(A) 3D reconstruction of neonate vasculature (B) fUS coronal slice at a given time (C) Time course of ΔCBV and EEG : ΔCBV peak-to-peak amplitude correlates with sleep phases visible in EEG**

[1] Demene *et al.* "Functional ultrasound imaging of brain activity in human newborns," *STM*, 2017.
[2] Hassanpour *et al.* "Neonatal brain resting-state functional connectivity imaging modalities," *Photoacoustics*, 2018.

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**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

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**Title:** Awake mouse imaging: From two-photon microscopy to BOLD-fMRI

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**Abstract:** Functional Magnetic Resonance Imaging (fMRI) in awake behaving mice is well positioned to bridge the detailed cellular-level view of brain activity, which has become available due to recent advances in microscopic optical imaging and genetics, to the macroscopic scale of human noninvasive observables. However, while microscopic (e.g., 2-photon imaging) studies in behaving mice have become a reality in many laboratories, awake mouse fMRI remains a challenge. Furthermore, due to variability in behavior between animals, performing all types of imaging within the same subject is highly desirable and would lead to a higher scientific rigor. Here, we demonstrate Blood Oxygenation Level Dependent (BOLD) fMRI in awake mice implanted with chronic glass cranial “windows” that allow a clear optical access for microscopic imaging modalities and optogenetic (OG) stimulation. We start with 2-photon imaging of single-vessel diameter changes. Next, we implement intrinsic optical imaging of blood oxygenation and flow combined with laser speckle imaging of blood flow obtaining a “mesoscopic” picture of the hemodynamic response. Then, we obtain the corresponding BOLD fMRI data. All measurements

are performed in the same mice in response to identical sensory and OG stimuli. The glass window does not deteriorate the quality of fMRI and allows going back and forth between the imaging modalities for each subject. This report provides a proof of feasibility for the multiscale imaging approach in awake mice. In the future, this protocol can be extended to include complex cognitive behaviors translatable to humans, such as sensory discrimination or attention.

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**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 777.06/BBB11

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** NMSS Grant No RG150704951
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**Title:** Neural-vascular uncoupling mediates motor performance decline in multiple sclerosis

**Authors: *K. WEST**[1], D. SIVAKOLUNDU[1], M. ZUPPICHINI[1], L. HIMES[1], M. TURNER[1], J. HART, Jr[2], H. LU[3], D. OKUDA[4], B. P. RYPMA[6,5]
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**Abstract:** Multiple Sclerosis (MS) is an immune-mediated, demyelinating disease of the central nervous system. Motor cortex (MC) dysfunction occurs in MS patients and is associated with muscular impairment, weakness, and fatigue, the prevailing symptoms of MS. Previously, we have found altered blood-oxygen-level dependent (BOLD) signal in the motor cortex of MS patients. However, BOLD is influenced by all components of the neural-vascular coupling system, specifically cerebral blood vessels, glial cells, and neurons. Effective neural functioning relies on the finely-tuned interplay between these structures. The coherent functioning of neural-vascular coupling is likely affected by MS, but the contribution of each neural-vascular component and their relationships to motor performance remain unknown.
We performed a cross-sectional study comparing relapsing-remitting MS patients and age- and sex-matched healthy controls. All magnetic resonance imaging (MRI) was conducted on a Philips 3T MRI system with a 32-channel head coil. We used a dual-echo calibrated functional

MRI (cfMRI) sequence, which provided near-simultaneous measures for both cerebral blood flow (CBF) and BOLD signal. During imaging, subjects performed a motor task which required bilateral button presses in time with a 2Hz auditory cue. An additional hypercapnia gas challenge involving inhalation of room air (4 min) followed by room air with 5% $CO_2$ (6 min) permitted measures of cerebral metabolic rate of oxygen utilization ($CMRO_2$). Data were preprocessed and analyzed using the general linear model to obtain percent signal change from baseline for each measure. A central-sulcus region of interest (ROI) was delineated using Freesurfer. The top 30% of voxels in the ROI for BOLD, CBF, and $CMRO_2$ was obtained. After scanning, participants underwent evaluations for motor performance including Trails-Making A, Box-Completion Task, and 9-Hole Peg Test. The score from each task was z-standardized and a composite motor performance score was calculated.
Neural-vascular coupling correlated with faster performance in healthy individuals. Overall, MS patients displayed significantly slower motor scores than healthy individuals. Performance in faster MS patients was supported by increased CBF, $CMRO_2$, and neural-vascular coupling compared to healthy controls. Conversely, slower performing MS patients could not sustain the additional demands of CBF and $CMRO_2$ and thus motor performance declined. These results suggest the complex effects of MS on the neural-vascular coupling system and the consequences for motor performance.

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**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 777.07/BBB12

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Title:** Assessing EEG data quality during simultaneous EEG-fMRI recording

**Authors: *J. E. GALLEGO RUDOLF**[1], M. CORSI CABRERA[2], E. PASAYE ALCARAZ[1]
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**Abstract:** Introduction: Simultaneous Electroencephalography and functional Magnetic Resonance Imaging recording (EEG-fMRI) is a multimodal neuroimaging tool that intends to

assess the electrophysiological and hemodynamic correlates of spontaneous and evoked brain activity. Nevertheless, data quality (especially for EEG) remains an important issue. Two artifacts are introduced in the EEG during EEG-fMRI: the gradient artifact (GA), produced by magnetic gradients switching during image acquisition and the ballistocardiographic artifact (BCG), produced by induced currents due to pulse-related movement of EEG sensors inside a strong magnetic field. Synchronizing the EEG amplifier with the Magnetic Resonance (MR) hardware allows Artifact Template Subtraction (ATS) approaches to eliminate the GA. However, the frequency and amplitude characteristics of the BCG artifact make the obtainment of high-quality EEG data a great challenge. Method: The aim of this study was to assess EEG data quality inside the MR environment in a healthy sample of 15 postgraduate students. We recorded eyes closed and eyes open EEG outside the MR environment, inside the MR scanner (without obtaining images) and during EEG-fMRI using an MR-compatible EEG recording system (GES 400MR, EGI) and a 3T MR scanner (GE MR750 Discovery, 32 channel head coil). For GA correction we performed ATS. For BGC correction we tested two of the most widely used algorithms to deal with the artifact: Independent Component Analysis (ICA) and Optimal Basis Set (OBS). After BCG correction, we computed the power spectra and maps for each electrode of the 10-20 system and then compared the spectrum from 1 - 50 Hz between conditions. Results: Uncorrected data is severely distorted inside the MR environment. Satisfactory gradient artifact cleaning can be performed using an ATS approach. Both BCG correction methods reduce the artifact, although efficacy varies among different electrodes (being the frontal the most affected) and individuals. Corrected signals show abnormal power spectra profiles, mainly at frequencies below 10 Hz. When comparing the two methods, more consistent results were observed with ICA, rather than OBS. Conclusion: Qualitatively interpretable EEG signals can be obtained during EEG-fMRI. However, spectral analysis showed that residual BCG artifact remains after correction, mainly affecting theta and delta bands. Careful EEG data quality inspection should be performed and caution should be taken when interpreting results. Future efforts should focus on developing new approaches for BCG artifact correction, as well as making these accessible to the growing community working with EEG-fMRI.

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**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 777.08/DP09/BBB13

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** NSF DGE 1106400
NINDS 5R01NS079698-05

**Title:** Functional and structural network connectivity explain regional differences in intrinsic activity dynamics measured with resting fMRI

**Authors: *D. J. LURIE**[1], M. D'ESPOSITO[1,2]
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**Abstract:** Brain regions vary greatly in their anatomical and functional properties. This diversity underlies functional specialization and helps define the role that each region plays within the whole brain network. Two major ways in which brain regions vary are in the dynamics of their intrinsic and evoked activity patterns, and in their connectivity to other brain areas. A growing literature suggests that these two properties are closely related, and we sought to characterize this relationship using structural and functional MRI in humans. We hypothesized that a hierarchy of intrinsic timescales across brain areas could be explained by a parallel hierarchy in network connectivity, and predicted that highly connected hub regions would exhibit slower timescales than less connected areas. Following preprocessing, regional BOLD time series were extracted from resting fMRI data collected from a large sample of healthy adults. These time series were used to estimate the intrinsic timescale of each region, as well as to construct a functional connectivity network. We used two complimentary measures of intrinsic timescale: lag-1 autocorrelation and the decay of autocorrelation over increasing lags. Structural connectivity was calculated from a population-averaged connectome atlas derived from diffusion tractography. The weighted degree (K), participation coefficient (PC), and within-module degree z-score (WMDz) of each brain region was estimated independently for the structural and functional networks. As predicted, intrinsic timescale had a significant positive correlation with the global connectivity (K) of each brain region. This was true for both structural and functional connectivity, and held for both measures of intrinsic timescale. Structural network WMDz also showed a significant positive correlation with intrinsic timescale, suggesting that structural module hubs have a slower timescale than peripheral regions. Surprisingly however, regions which connect multiple functional modules (high PC) had significantly faster timescales. In a regression model, features describing connectivity profile were able to explain up to 40% of regional variance in intrinsic timescale. These results support our hypothesis that network connectivity plays a key role in determining the dynamic functional properties of a brain region, and further our understanding of the brain as a hierarchically organized complex dynamical system.

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**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 777.09/BBB14

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** IBS-R015-D1

**Title:** MION enhanced resting-state brain networks in the anesthetized rhesus monkey: Hyperalgesia-induced effects

**Authors: *E. BAEG**[1], B.-Y. PARK[1,2], C.-U. PARK[3], H. PARK[1,4], C.-W. WOO[1], S.-G. KIM[1]
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**Abstract:** The low frequency oscillations of the resting state fMRI (rsfMRI) activities have been reported in humans, non-human primates (NHP) and even rodents. Although its functional role of oscillations needs to be further verified, it was reported that network synchronizations are modified by learning and cognitive status in humans, suggesting that rsfMRI can detect the changes of brain activities at network-level. We applied rsfMRI to determine whether capsaicin-induced hyperalgesia affects the network synchronization of rsfMRI in anesthetized NHP. Male rhesus macaques (5 yrs, 4-9 kg, n=5) were used in accordance with IACUC guidelines. During imaging, medetomidine (0.03mg/kg/hr) and isoflurane (0.3%) were used to maintain anesthesia. Animal's physiology was controlled and maintained within a normal range throughout the experiment. Tactile electrical stimulation (7~10 mA) was applied to the skin of the lower arm through attached hydrogel patch electrode (2x2 $cm^2$) without and/or with topical application of capsaicin (0.1 mg). To enhance functional sensitivity, a bolus of monocrystalline iron oxide nanoparticles (MION, 8~10 mg Fe/kg body weight) was injected through the saphenous vein. Three 12-min rsfMRI images (3T, Siemens Prisma) were collected; i) before electrical stimulation, ii) after electrical stimulation without capsaicin, and iii) after electrical stimulation and capsaicin application. The independent component analysis decomposed group-wise rsfMRI data into nine independent components reliably. Each component was compared with known macaque functional networks and previously identified networks in humans. Analysis for functional network connectivity was conducted with the identified components. Capsaicin application induced centrality changes in sensorimotor related network, which network is the major target of the capsaicin stimulation in the experiment. Our result suggests that MION-enhanced rsfMRI in NHP is a good approach to identify network-level changes because of its superiority in detecting modified functional networks, and the similarity to human network changes.

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**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

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**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

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**Title:** Comparisons of dynamic functional connectivity of neuronal and hemodynamic activity in awake mice

**Authors: *D. A. HANDWERKER**[1], S. H. KIM[2], Y. MA[2], M. SHAIK[2], D. THIBODEAUX[2], M. MONTGOMERY[2], T. ZHAO[2], J. GONZALEZ-CASTILLO[1], P. A. BANDETTINI[1], E. M. HILLMAN[2]
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**Abstract:** Neurovascular coupling is often modeled as a spatiotemporal low pass filter of neural activity. Such models have made it possible to make inferences about underlying neural activity from hemodynamic signals detected using FMRI. However, more direct determinations of this neuronal – hemodynamic relationship are critical to drawing more subtle and specific inferences about brain function. Dynamic functional connectivity (dFC) analyses are becoming a major focus in human neuroimaging studies [1], but these dynamics can be difficult to validate [2]. Here, we examine the correspondence between dFC variations over time based on simultaneously acquired optical recordings of neural and hemodynamic data in awake mice. Wide-field optical mapping (WFOM) was used to capture both excitatory neural activity (in Thy1-GCaMP6f mice) and hemodynamics across the entire dorsal surface of the awake mouse brain [3]. Data were acquired from mice across multiple days with up to 36 repeated 3-minute continuous imaging sessions per mouse.
To analyze these data, 50 regions of interest (ROIs) were defined for each mouse using k-means clustering of the GCaMP and total hemoglobin ($\Delta c_{HbT}$) time series from all runs and a mean time series was calculated for each ROI and run. The correlations between the time-courses within each pair of ROIs were then calculated for both GCaMP and $\Delta c_{HbT}$ data. The way in which correlations change across time for each data source were then examined.

As has been observed in human fMRI dFC studies, windowed dFC measures show substantial temporal variations for both GCaMP or $\Delta c_{HbT}$ data. However, even with high variation from session to session, the correlation matrices for GCaMP or $\Delta c_{HbT}$ are often very similar. In approximately two thirds of the 84 runs, the correlations between the connectivity matrices for GCaMP & $\Delta c_{HbT}$ were nearly identical (r> 0.8). The remaining runs also showed strong correlations between GCaMP and $\Delta c_{HbT}$ (all, but one r>0.4). These observations remained after low pass filtering the all data to remove high frequency fluctuations that might affect correlations of neural, but not hemodynamic activity.
These observations extend earlier work showing that hemodynamics are an accurate proxy for neural activity, including measures of functional connectivity. The variations of the magnitude of significant correlations of the FC maps between GCaMP and $\Delta c_{HbT}$ point to subtle shifts in this relationship can be used to probe factors that might affect neurovascular coupling.
1 Hutchison, Womelsdorf et al NeuroImage 2013
2 Handwerker, Roopchansingh et al NeuroImage 2012
3 Ma, Shaik et al PNAS 2016

**Disclosures: D.A. Handwerker:** None. **S.H. Kim:** None. **Y. Ma:** None. **M. Shaik:** None. **D. Thibodeaux:** None. **M. Montgomery:** None. **T. Zhao:** None. **J. Gonzalez-Castillo:** None. **P.A. Bandettini:** None. **E.M. Hillman:** None.

**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 777.11/CCC2

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** FLAG-ERA JTC 2015

**Title:** 4D functional ultrasound imaging of the whole brain activity: First evidence in rodents

**Authors: *C. RABUT**[1], V. FINEL[1], M. CORREIA[1], S. PEZET[2], M. PERNOT[1], T. DEFFIEUX[1], M. TANTER[1]
[1]Inst. Langevin / Inserm U979, Paris, France; [2]CNRS UMR 8249, ESPCI Paris, Paris, France

**Abstract:** Functional Ultrasound (fUS) Imaging is a recent powerful imaging technique to image whole-brain activation [1]. It has been applied to study functional response with high-resolution or Functional Connectivity (FC) in freely-moving or anesthetized conditions in different species (rodents, primates, ⋯). However, brain mechanisms are inherently 3D, it is thus crucial to develop a technology suitable to image the full brain in 3D with high sensitivity. We present here 4D fUS technology (3D in space+ time) for imaging whole-brain and transient changes in blood volume at unprecedented spatiotemporal resolution based on ultrafast 3D ultrasonic imaging

(1000volum/s). We demonstrate the concept on rats with visual stimulation, resting-state FC and epileptiform activity.
To address 3D imaging, the concept of ultrafast multiplane waves [2] is extended to 3D Ultrafast Volumetric Imaging. A 1024 channels custom ultrasound platform is used to drive a matrix phased array at more than 3000 frames/s.
To highlight the spatiotemporal sensitivity of 3D fUS we acquired the dynamics of blood volume in response to successive periodic visual stimuli and epileptiform activity, induced by a focal injection of a potassium channel blocker (4-AP) in trepanned, anesthetized rats. We also studied the FC at rest of both superficial and deep brain structures during several minutes.
High-quality and real time 3D vascular volumes (170µm$^3$ voxel and 2s temporal resol) are obtained in rats and show the feasibility of task-activated 4D fUS. Strong correlations are observed between stimuli and vascular responses in dedicated brain areas (fig.a,b). During epileptiform seizures, we observe the 3D propagation of different waves of activity (fig c). At rest, we identified strong contrasting spatial coherence signals in low-frequency (<0.1 Hz) spontaneous 3D fUS signal fluctuations.
The ability of 4D fUS to image volumic cerebral activity at high spatiotemporal resolution, with high sensitivity is of great interest for whole-brain neuro-imaging applications.
[1] Mace&Al 2011, NatMeth
[2] Tiran&Al 2015,PhysMedB

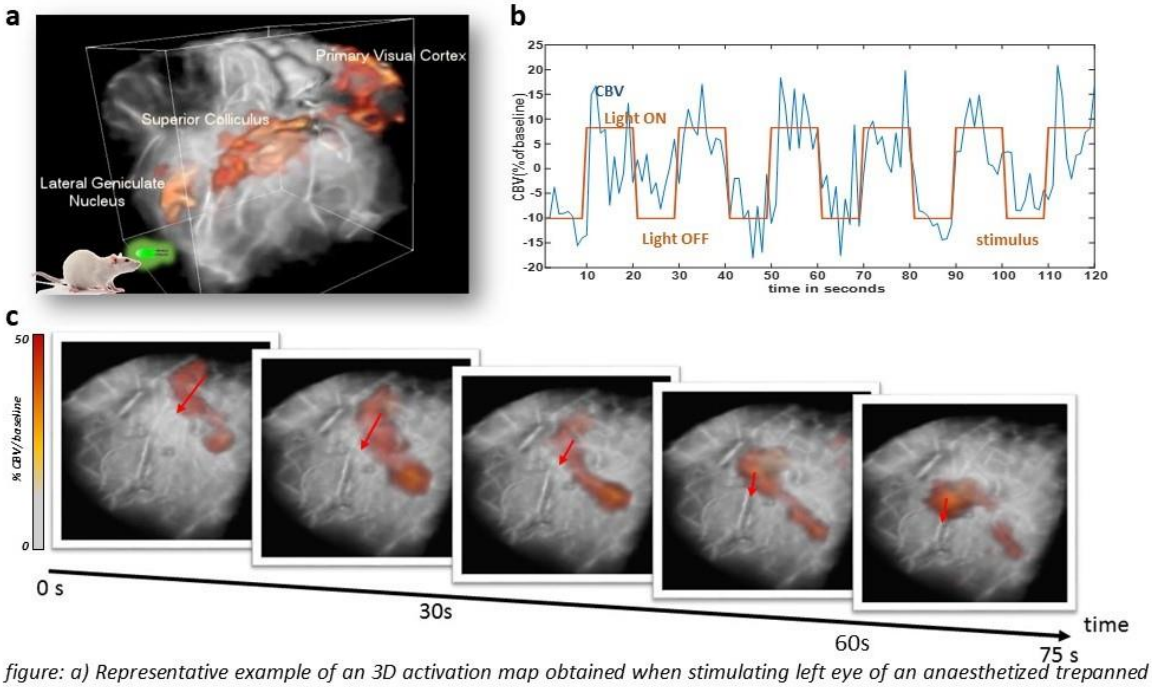


*figure: a) Representative example of an 3D activation map obtained when stimulating left eye of an anaesthetized trepanned rat with green LED. Map was obtained as the correlation coefficient between the power Doppler signal and the stimulus pattern. Cerebral visual areas labeled here were delineated from a rat brain atlas. b) Doppler Signal of task-evoked brain activation in visual areas in the rat brain. Power Doppler fUS volumes are acquired every 1.5s. The visual stimulation pattern consisted in 15s ON light (green led) and 15s OFF light repeated 6 times. c) Propagation of a cortical depression wave from the back to the front of the brain during an epileptic seizure induced by 4AP cortical injection. Power Doppler blood volume increased between 15% and 50% during ictal activity. Wave traveling speed = 2.2 ± 0.3 mm/min.*

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**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 777.12/CCC3

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** ANR-15-HBPR-0004

**Title:** Demonstration of reproducible pharmacological functional ultrasound (PhfUS) imaging in a non anesthetized preclinical rodent model during scopolamine drug injection and reversal

**Authors: *T. DEFFIEUX**[1], C. RABUT[1], J. FERRIER[2], X. MOUSSET[3], A. BERTOLO[3], B. OSMANSKI[3], Z. LENKEI[2], M. TANTER[1]
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**Abstract:** The cholinergic system is altered in neurodegenerative disorders such as Alzheimer's disease Alzheimer's or Parkinson’s diseases. Pioneering preclinical fMRI studies showed that acute cholinergic modulation might be reflected in altered resting-state functional connectivity (FC) patterns[1]. However, most brain imaging modalities require sedation/anesthesia, which may alter neuronal metabolism and neurovascular coupling, resulting in modified FC outcome and reproducibilty. Functional Ultrasound (fUS), a new highly-sensitive technique for brain imaging of the neurovascular coupling, has been recently implemented in awake and mobile rodents[2]. Here we used fUS imaging to investigate the modulatory effects of Scopolamine (ScoP), a muscarinic receptor antagonist, on resting-state FC. These effects were assessed in both anesthetized and awake mice.
Male C57BL/6 mice were anesthetized using 1.5% isoflurane + medetomidine infusion (0.1 mg/kg/hr) and ScoP was administered at 0.5 or 3mg/kg doses after 10min of baseline acquisition. For the awake protocol (n=5), a small metal frame was chronically fixed on the skull to allow magnetic fixation of the ultrasonic probe and mice were briefly trained for 4-5hr long acquisition sessions in a custom mobile cage. Imaging was performed on day 10 after surgery. After acquisition, stationary epochs were concatenated to assess FC at rest.
In anesthetized mice, a diffuse averaged (n=4) connectivity pattern was observed at baseline at the investigated coronal plane (Bregma -2.3mm). ScoP injection induced a global decrease of the

FC. Conversely, in awake mice, strong interhemispheric correlations were observed between contralateral cortical, hippocampal and thalamic regions (r=0.53) before ScoP injection with significantly lower (r= -0,23, p=0.004) inter correlations between the three networks. After ScoP injection, at both doses, the cortico-hippocampal connectivity was strongly increased (respectively r=0.65, p=0.007 and r=0.74, p=0.001). Milameline, a muscarinic agonist, induced a recovery of the specific highly-contrasted bilateral correlation pattern observed at baseline. Taken together, these results indicate the crucial role of anesthesia on functional connectivity studies asFC outcome can be opposite depending on the vigilance state. FC analysis in awake rodents using fUS might provide new insights into the brain functioning in pharmacological studies as it provides for the first time a modality for preclinical brain connectomics without anesthesia bias.
[1] Shah et al, NeuroImage 2015
[2] Sieu et al, Nature Methods. 2015

**Disclosures: C. Rabut:** None. **J. Ferrier:** None. **X. Mousset:** A. Employment/Salary (full or part-time):; Iconeus. **A. Bertolo:** A. Employment/Salary (full or part-time):; Iconeus. **B. Osmanski:** A. Employment/Salary (full or part-time):; Iconeus. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Iconeus. **Z. Lenkei:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Iconeus. **M. Tanter:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Iconeus.

**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 777.13/CCC4

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** NIH Grant NS080675
NIH Grant F30MH106253

**Title:** Studying the spatiotemporal dynamics of spontaneous brain activity with fMRI time delays

**Authors: *R. V. RAUT**, A. MITRA, A. Z. SNYDER, M. E. RAICHLE
Washington Univ. in St. Louis, Saint Louis, MO

**Abstract:** The resting-state functional magnetic resonance imaging (rsfMRI) signal corresponds to propagating electrophysiological infra-slow activity (<0.1 Hz) (Mitra et al., Neuron 98:1-9, 2018). Thus, in addition to defining the spatial topography of large-scale functional networks,

this signal exhibits interregional time delays that can be used to probe the state-dependent temporal organization of infra-slow activity existing within and between networks. Time delay estimation (TDE) will therefore be a valuable addition to conventional zero-lag functional connectivity (FC) analysis for the study of spontaneous brain activity moving forward. Although FC methodology has been extensively described, factors affecting accurate TDE in rsfMRI data are comparatively unexplored. Here we use simulated fMRI time series to demonstrate the strong dependence of TDE accuracy on data quantity, the magnitude of a given pairwise correlation, and, to a lesser extent, the temporal sampling rate. An important implication is that, while greater quantities of data are generally required for TDE compared to FC analysis, specific data requirements depend on the scope of TDE analysis: estimating temporal relationships among pairs of highly correlated regions requires far less data than modeling brain-wide propagation patterns based on all pairwise time delays. We demonstrate the effects of each of the above factors in real data by utilizing the recently published "Midnight Scan Club" dataset comprising 10 individuals each completing 10 30-minute scans. Additional sampling error arising from the exclusion of high-motion time points is found to have observable impacts on both FC and TDE within and across subjects. Defining criteria for data exclusion necessitates a tradeoff between data quality and sampling error, the resolution of which will depend on the questions of interest. Excluding high-motion time points additionally complicates TDE, which generally requires contiguous data. Because the treatment of this issue invokes the well-described bias-variance tradeoff -- which, like the data quantity-quality tradeoff, will differentially impact high- and low-motion data -- we address these tradeoffs by seeking to optimize intra/intersubject correspondence between high- and low-motion session/subjects. We demonstrate substantial improvements to these metrics by incorporating updates to our previously published approach for TDE. Finally, we present guidelines and strategies to detect and mitigate the impact of sampling error on TDE, with the goal of improving future analysis and interpretation of time delays observed with fMRI.

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**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 777.14/CCC5

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

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**Title:** Altered brain responses to binaural beats in patients with obstructive sleep apnea

**Authors: *L. EHLERT**[1], X. SONG[1], B. ROY[2], S. SINGH[1], A. SAHIB[1], D. KANG[3], R. AYSOLA[3], M. WOO[2], M. LARSON[7], R. KUMAR[1,4,5,6]
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**Abstract:** Obstructive sleep apnea (OSA) subjects suffer from fragmented sleep and show impaired cognitive and mood functions, in addition to autonomic issues. Multiple studies indicate that binaural beats, non-invasive brain stimulation procedures that utilize occurred phenomenon when two different frequencies are presented separately in each ear, may help to modify cognition, mood, and sleep. The procedure produces a third phantom binaural beat, whose frequency is equal to the difference of the two presented tones and can be used to manipulate non-invasive brain stimulation. However, the neural regulatory mechanisms underlying these effects, as well as effects of binaural beats on brain activities in OSA patients are unclear. Our aim was to examine brain responses to binaural beats, and whether such responses in OSA are altered compared to healthy controls (HC). We collected BOLD functional MRI data, using a 3.0-Tesla scanner, from 5 newly-diagnosed, treatment-naïve OSA (age, 44.1±9.6 years; 3 male) and 5 HC (age, 35.0±10 years; 3 male) while applying binaural beat frequencies on 240 Hz carrier tone with 10 Hz difference between ears (240/250 Hz binaural tone). A 90 s baseline period, followed by monaural (240 Hz) and binaural (240/250 Hz) tones were interleaved applied; each condition lasted for 60 s with three repeats with inter-stimulus period for 90 s, ending with again 90 s baseline period. After standard data preprocessing, brain activation maps were calculated and compared between OSA and HC subjects (SPM12, ANCOVA; covariates: age and gender; $p<0.05$, cluster size>27 voxels). Compared to monaural beats, binaural beats induced higher activation in the cerebellar vermis, thalamus, bilateral auditory cortices, posterior insula, precentral gyrus, as well as superior and inferior parietal lobules in HC. However, OSA subjects showed significantly lower neural responses to binaural beats in the cerebellar vermis, thalamus, left auditory cortices, bilateral putamen, posterior insula, dorsal lateral prefrontal cortices, as well as superior and inferior parietal lobules, compared to the HC. The findings suggest that binaural beats elicit higher brain activation in sensorimotor, sleep, attention, and cognitive control areas in control subjects, which may explain the beneficial effects on normal brain functions. However, OSA subjects showed compromised neural responses to binaural stimuli in areas involved in sensation and perception, cognition, attention, and sleep, indicating altered such regulatory circuitry in the condition.

**Disclosures: L. Ehlert:** None. **X. Song:** None. **B. Roy:** None. **S. Singh:** None. **A. Sahib:** None. **D. Kang:** None. **R. Aysola:** None. **M. Woo:** None. **M. Larson:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Provided sleep shepherd blue. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Is a part of Sleep Shepherd Blue company we are using his device in the research. **R. Kumar:** None.

**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 777.15/CCC6

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** NIH Grant R01NS095933
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**Title:** Dual-component model explains non-classical bold fmri contrast

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**Abstract:** The classic picture of the BOLD response implies that there is a single population of spins that have variable relaxation rate ($R_2$*) decreased by functional activation. Recent studies have challenged this theory based upon the dependence of functional contrast on echo time (TE) and flip angle (FA). We postulated that dual spin populations are involved in functional contrast, so we measured functional contrast across a broad range of TEs and multiple FAs to test this hypothesis. **Methods:** Functional MRI data were collected using a dual-echo spiral-out sequence with 1.5-mm cubic voxels and TR = 1.5 s. Data were measured across 12 TEs varying from 7—115 ms and FAs of 18°, 39°, and 72°. During each run, subjects performed a fixation task with high-contrast flickering-dot stimulus (Fig A). Signal and contrast data were obtained from retinotopically defined visual areas (V1—3) in each subject. TE-dependent signal decays were fit to the steady-state signal equation using a gridded search that yielded best-fit parameters ($M_0$, $R_1$, $R_2$*). Both single- and dual-component fits were attempted. Delta parameters ($\Delta M_{0V}$, $\Delta M_{0A}$, $\Delta R_{2V}$*) were also extracted to explain functional contrast. **Results:** Single- and dual-component models both fit the mean signal with good accuracy (R > 0.99), but the single-component fit deviates near the TE extrema (Fig B). Functional contrast measurements are much more sensitive to the dynamics. Contrast variations are much better fit by the dual-component model (black) than the single-component model (green). Delta parameters, bootstrapped across subjects ($N$ = 12), are highly significant for both spin populations (Fig C). **Discussion:** The dual-component results suggest that two spin populations are involved in the generation of functional contrast in gray matter. We identify the short-lived population as venous blood producing a “classic” BOLD response. The other population is arterial blood that reduces contrast by volume-exchange effects, expressed by $\Delta M_{0A}$. Thus, an interplay of opposing volume effects explains “non-classical” BOLD contrast.

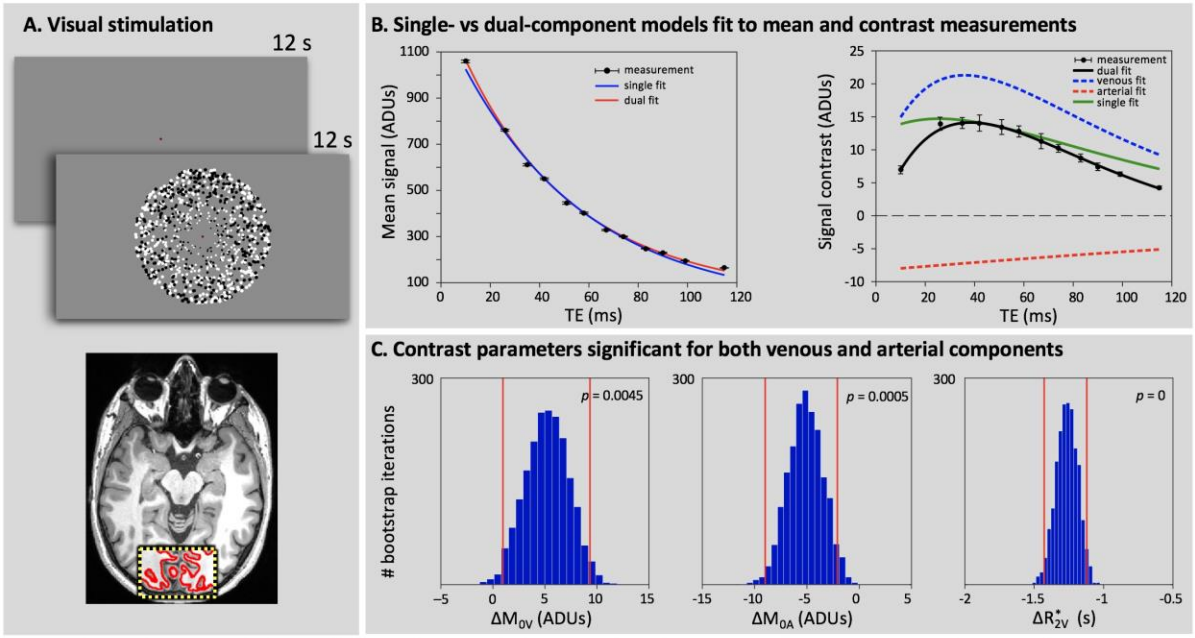


**Figure. A)** A high-contrast flickering dot stimulation with fixation task evokes strong response across visual cortex. **B)** Measurements across echo times (TE) are fit with a single component or with dual components (venous and arterial). **C)** Delta parameters from the dual-component model reveal the underlying contrast mechanisms: $\Delta M_{0V}$ and $\Delta M_{0A}$ show changes in magnetization intensity of venous and arterial components, while $\Delta R_{2V}^{*}$ shows the variation in venous relaxation time.

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**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 777.16/CCC7

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** R01 NS076628
RF1 MH114276
R01 NS063226
U19 NS104649
F30 HL128023

**Title:** Assessing the impacts of pharmacologically mediated neurovascular dysfunction in the awake, behaving mouse using wide field optical mapping (WFOM)

**Authors: *D. N. THIBODEAUX**[1], M. A. SHAIK[1], Y. MA[1], S. H. KIM[1], H. T. ZHAO[1], M. K. MONTGOMERY[1], M. M. ERLER[2], E. M. HILLMAN[1]
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**Abstract:** Localized neuronal activity in the brain leads to an increase in blood flow to the responding region. The classical response to a stimulus is an increase in oxygenated and total hemoglobin, and a decrease in deoxygenated hemoglobin. Neurovascular coupling is important for cognitive function, and this study seeks to understand how disruption in neurovascular coupling could affect both behavior and neuronal function. Utilizing Wide Field Optical Mapping (WFOM), we measured fluctuations in hemodynamic and neural activity simultaneously in head-fixed awake Thy1-GCaMP mice. WFOM allows behavioral paradigms to be implemented in these awake mice during recording, and we utilized this to measure motor responses to an aversive, randomized whisker-flicking stimulus, where a simple movement would interrupt the aversive stimulus.
In order to disrupt neurovascular coupling, we utilized commonly used clinical drugs, which we have previously found to selectively disrupt neurovascular coupling via interactions with endothelial signaling. WFOM permits neurovascular coupling dynamics to be evaluated across the whole dorsal surface of the cortex in real time, while the neural representations of the stimulus and motor response can be evaluated before and after the animal receives the drug, in parallel with real-time behavioral recordings. Preliminary analysis suggests that neurovascular perturbations that slow the onset of the hemodynamic response attenuate initial neural responses in the cortex with associated delays in the animal's motor response.
These results suggest that neurovascular uncoupling can have acute effects on neural activity in the brain, and potentially direct behavioral consequences. Controls and confounds for these observations are being explored, while experiments are continuing to assess whether neurological effects compound during longer-term exposure to these drugs.
Assessing the cognitive impacts of neurovascular dysfunction, especially dysfunction evoked by common medications as well as disease states affecting endothelial and cardiovascular health, could be a critical step towards understanding what role neurovascular coupling plays in maintaining a healthy brain. Such findings could also reveal new therapeutic targets as well as imaging biomarkers for neurovascular dysfunction.
1) Ma, Y. et al. Wide-field optical mapping of neural activity and brain haemodynamics: considerations and novel approaches. Philos Trans R Soc Lond B Biol Sci 371, doi:10.1098/rstb.2015.0360 (2016).

**Disclosures: M.A. Shaik:** None. **Y. Ma:** None. **S.H. Kim:** None. **H.T. Zhao:** None. **M.K. Montgomery:** None. **M.M. Erler:** None. **E.M. Hillman:** None.

**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

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**Program #/Poster #:** 777.17/CCC8

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** NIH Office of the Director OT2-OD023867

**Title:** Stimulus frequency modulates cardiovagal and brain responses to respiratory-gated auricular vagal afferent nerve stimulation (RAVANS)

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**Abstract:** Transcutaneous vagus nerve stimulation of auricular branch of the vagus nerve is a neuromodulatory therapy for numerous disorders involving sympathovagal disruption. As target brainstem nuclei are also modulated by respiration, our group demonstrated that neural target-engagement, such as nucleus tractus solitarii in the medulla, can be enhanced by gating stimulation to the exhalation phase of respiration (Garcia et al. 2017). However, the influence of other stimulation parameters (pulse width, frequency) is unknown. Here, we investigate cardiovagal modulation (high frequency heart rate variability, HF-HRV) and functional MRI (fMRI) brain response to respiratory-gated auricular vagal afferent nerve stimulation (RAVANS) at different frequencies. Data from 7 healthy subjects were collected at 3T MRI using a whole-brain multiband pulse sequence (2mm isotropic voxels, TR=1.25s, 400 volumes), concurrently recorded with respiration and cardiac finger pulse. After an initial sham stimulation (no current) fMRI scan, subjects experienced percept-matched exhalation-gated RAVANS (300μs pulse width, 1.5s duration). In each of four scans, stimulation was delivered at a different frequency ({2, 10, 25, 100} Hz), in randomized order. Sham stimulation, also gated to exhalation, controlled for respiratory influence on fMRI signal. R-R intervals from the pulse signal were fed to a point-process algorithm for estimation of instantaneous HRV indices (Barbieri et al 2005), thus allowing for computation of stimulus-evoked responses. GLM analyses were performed on preprocessed fMRI data (cardiorespiratory artifact correction with RETROICOR, slice-timing, motion, and distortion correction, FWHM=3mm spatial smoothing, 50s high pass filter). Stimulus-evoked HF-HRV power demonstrated post-stimulus increase, most pronounced following 2Hz RAVANS. The correspondent fMRI difference map (RAVANS>Sham, corrected $p<0.05$) demonstrated activation in a network of cortical and subcortical regions including thalamus, contralateral striatum and anterior and posterior insula, anterior and middle cingulate, and ventromedial prefrontal cortices. We also found that stimulus amplitude (current mA) was greatest for the 2Hz frequency condition (7.39±0.52mA). Although preliminary, these results support the fact that stimulation frequency is an important variable for tVNS-induced autonomic and brain response. As stimulus perception is important in cutaneous neuromodulation techniques, the interplay between stimulus amplitude and frequency effects needs to be assessed with objective outcomes reflecting potential target engagement.

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**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

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**Program #/Poster #:** 777.18/CCC9

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** NSERC - Discovery grant
NSERC - Alexander Graham Bell Canada Graduate Scholarships
FRSQ - PhD scholarship

**Title:** Dissociation between the time course of the non-specific fMRI hemodynamic response and its stimulus feature-specific component

**Authors: *S. PROULX**, R. FARIVAR
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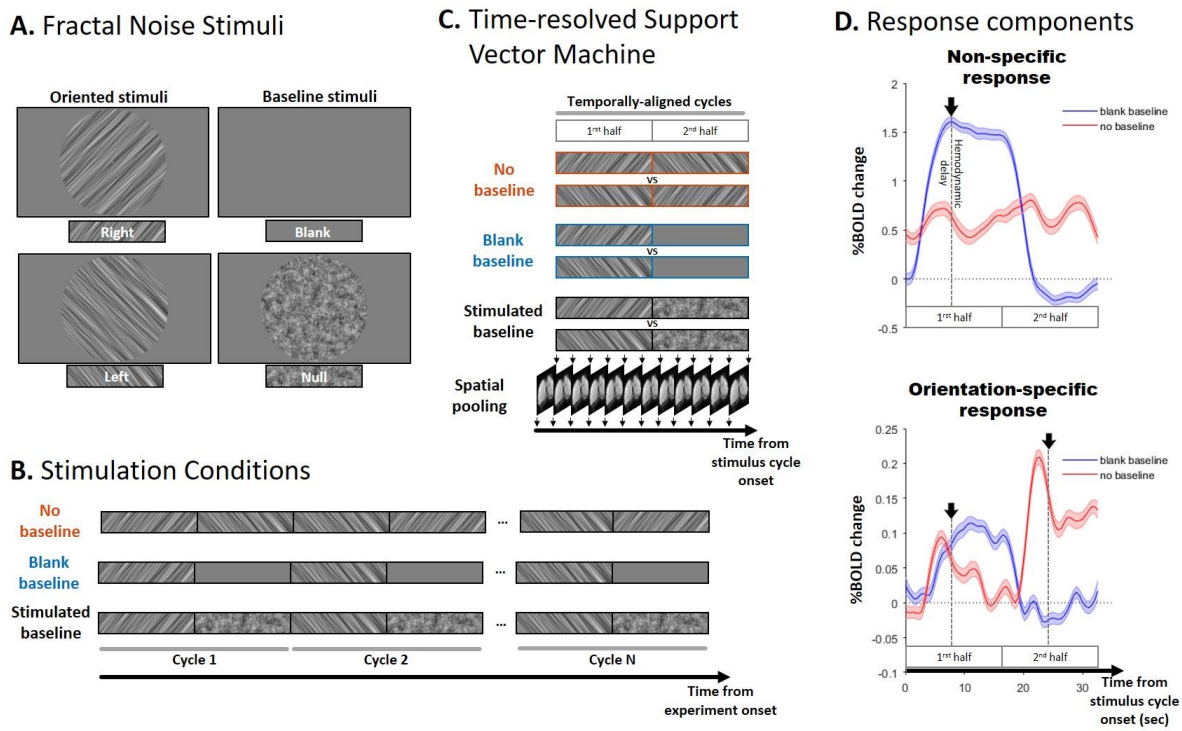
**Abstract:** A major limitation of functional Magnetic Resonance Imaging (fMRI) is its relatively weak spatial specificity. The Blood-Oxygenation-Level-Dependent (BOLD) response to stimulus presentation often spreads to neighboring non-active brain tissue — the response is composed of a large *non-specific* and a smaller *stimulus feature-specific* components. Most approaches to fMRI assume the time course of the feature-specific response to follow the hemodynamic response function derived from non-specific BOLD responses. Our findings challenge that assumption. We acquired fMRI data (3T Siemens; BOLD gre EPI; 2x2x2mm$^3$ voxels; TR 0.517ms) on two healthy humans and analysed anatomically-defined V1 voxels. Using time-resolved, cross-validated Support Vector Machine, we pooled signal across voxels discriminating two orthogonally-oriented visual stimuli (Fig1.A, B and C). Averaging across stimulus cycles yielded the time courses of the non-specific (Fig1.D, top) and orientation(feature)-specific (Fig1.D, bottom) response. Interleaving the 16-sec stimuli with blank periods (Subj1; Fig1.B and C, blank baseline condition, blue) produced a large non-specific response (Fig1D, top, blue) with the expected hemodynamic delay (black arrows), but the feature-specific response (Fig1D, bottom, blue) lagged an extra 3 seconds behind. Abolishing the non-specific response (Subj2; Fig1D, top, red) by replacing the blank periods by stimulation with the opposite orientation (Fig1.B and C, no baseline condition, red) shifted the feature-specific response to 1.5 seconds before the hemodynamic delay (Fig1D, bottom panel, red trace). This is the first report of a dissociation between the time courses of non-specific and stimulus feature-specific BOLD responses. The rising phase of the large non-specific response might disrupt the spatial pattern of the feature-specific component, increasing its delay. Our findings have implications for optimal fMRI design.




**Disclosures: S. Proulx:** None. **R. Farivar:** None.

**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 777.19/CCC10

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** NIH Grant RO1-NS094404
NIH Grant RO1-EB003324

**Title:** Effects of neuronal modulation with light-sensitive silencers on blood flow changes in primary somatosensory cortex

**Authors: *A. H. ALTAMIRANO-ESPINOZA**, M. FUKUDA, A. VAZQUEZ
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**Abstract:** Hemodynamic changes (HC) are caused by the interplay of inhibitory, excitatory neurons, glial cells and microvessels. To better understand how HC are governed by these dynamics, we investigated the effect of either strong silencing versus finely tuning neuronal activity by activating light-sensitive silencers (Syn or CAG AAV ARCHT, eNPHR or Jaws) on

sensory-evoked HC. Experiments were conducted in head-fixed awake or anesthetized mice by optical intrinsic signal imaging (OIS-CBV, OIS-BOLD) and changes in cerebral blood flow (CBF, using LDF) through a cranial window. Short pulse durations at low power photostimulation showed a decrease in sensory-evoked changes in OIS-CBV, OIS-BOLD, and CBF. While long pulse durations at higher power settings yielded opposite results. Preliminary electrophysiological recordings results indicate that these observations are possibly related to the promoter. These results suggest that HC are possibly finely tuned by specific cellular dynamics.

**Disclosures: A.H. Altamirano-Espinoza:** None. **M. Fukuda:** None. **A. Vazquez:** None.

**Poster**

**777. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging I**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 777.20/CCC11

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** National Council for Scientific and Technological Development (CNPq)
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**Title:** Let the prefrontal cortex decide whether this is good enough: Effects of self-selected music on cerebral oxygenation and exercise performance

**Authors: *L. R. ALTIMARI**[1,2], M. BIGLIASSI[2,3], V. BARRETO-SILVA[2], P. CHIEROTTI-SANTOS[2], C. F. BUZZACHERA[2]
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**Abstract:** Music-related interventions have been widely used in the realm of sport and exercise as a means by which to force attentional focus towards external sensory cues and ameliorate the effects of fatigue-related symptoms (e.g., limb discomfort). In order to select *suitable* pieces of music to be delivered during exercise-relate situations, researchers have commonly used scales and questionnaires to quantify the psychological qualities of music. However, music choice is highly personal and idiosyncratically variable, meaning that psychological measures could not be sufficiently sensitive/effective to detect the so-called "*appropriate* pieces of music". Based on this assumption, the present authors decided to use functional-near infrared spectroscopy (fNIRS) techniques to further understanding of cerebral changes that occur in response to music. It has been hypothesised that motivational pieces of music could potentially upregulate oxygenation of the frontal areas of the cortex. Subsequently, the same musical tracks were used during a 5-km run as a *counterproof* method to identify whether the selected songs could facilitate the execution of movements and enhance exercise performance. Thirteen amateur

runners (26.31 ± 3.11 years; 75.22 ± 5.51 kg; 178 ± 0.4 cm) were administered two randomized conditions during a 5-km run (MM: Motivational music; CO: Control). fNIRS (BIOPAC Systems, Inc., Goleta, CA; 16-channel forehead sensors; 10 photo detectors; 4 photo emitters; 2.5 cm interoptode distance) analysis was applied prior to commencing the exercise bouts in order to determine the motivational qualities of music and its effects on the oxygenation of the prefrontal cortex (PFC). A technician applied the fNIRS sensors in line with positions FP1-FP2 on the International 10-20 System, designed for recording data from the PFC. The results of the present experiment indicated that Oxy-Hb levels in the three regions of the PFC were significantly affected by the presence of self-select pieces of music in comparison with baseline values (right dorsolateral prefrontal cortex [RdlPFC]: 0.31 ± 0.18 ua.μM, $d$=0.84; left dorsolateral prefrontal cortex [LdlPFC]: 0.32 ± 0.21 ua.μM, $d$=0.85; medial prefrontal cortex [MedPFC: 0.22 ± 0.17 ua.μM, $d$=0.60]). The presence of music reduced the time that participants took to complete the trial from 27.02 ± 0.35 min to 25.31 ± 0.31 min ($p$<.05; ~6,33% of difference). In conclusion, fNIRS analysis was successfully used to detect changes in the regions of the PFC that are, in theory, associated with the stimulative qualities of music. The same pieces of music enhanced task performance during high-intensity aerobic/anaerobic exercises.

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**Poster**

**778. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 778.01/CCC12

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** IBS-R015-D1
NRF-2014H1A2A1020612

**Title:** Dynamics of neurovascular coupling at a single-neuron and single-vessel level during seizure events

**Authors: *H.-K. LIM**[1,2], N.-Y. YOU[1,3], B.-M. KANG[1,3], S. BAE[1,3], S.-G. KIM[1,3], M. SUH[1,3,4]
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**Abstract:** A detailed study of neurovascular coupling in the epileptic brain is extremely useful for the adequate interpretation of perfusion-based signals such as PET, SPECT and fMRI, which are widely used in clinical operations. Earlier *in vivo* studies have demonstrated a tight coupling between gamma-band activities and hemodynamic signals in non-pathological condition and one

recent study showed that the relationship was maintained in epileptic condition. However, very little is known about how individual neurons' activities are reflected both in the neural band during seizure events and in hemodynamic response, particularly at a single-vessel level. We proposed to investigate fine details of the neurovascular coupling during spontaneous recurrent seizures, which were acutely induced with 4-aminopyridine (4-AP) injection. First, we measured mesoscale cerebral blood volume (CBV) changes with concurrent measurement of local field potentials (LFP). Second, we combined two-photon vessel imaging or calcium imaging with LFP recordings to observe dynamics of single vessel or activities of individual neurons. During inter-ictal periods, we observed that calcium signals were generally depressed in a seizure focus and that arterioles had a constricted tone, which was mostly correlated with the decreases in gamma-band (30-100 Hz) power. When seizures were evoked, huge dilation of arterioles was observed immediately after the seizure onset which were strongly associated with sharp increases in alpha-band (8-13 Hz) power and the propagation of calcium signals from the seizure focus. Surprisingly, the rising slope of arteriole dilation showed a strong correlation with the degree of constriction of arterioles during the prior inter-ictal periods. On the other hand, during the maintenance of ictal events, both CBV and arteriole responses were mostly associated with gamma-band activities and synchronous calcium signals in a broad region including the seizure focus and the propagated area. Our findings provide useful insights into the underlying mechanism of neurovascular coupling in epilepsy at cellular level and may have implications for further research of epileptic brain using non-invasive imaging techniques which are based on perfusion-based signals.

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**Poster**

**778. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging II**

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**Program #/Poster #:** 778.02/CCC13

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** IBS-R015-D1

**Title:** *In vivo* and *ex vivo* study of impaired neurovascular coupling in chronically stressed mouse

**Authors: *K.-Y. HAN**[1,2], J. MIN[1,3], B.-M. KANG[1,3], J. WOO[4,5,6], H. SHIM[1,2], W. JUNG[1,3], M. LEE[1,3], T. PARK[1,3], J. YE[1,3], J. LEE[1,3], H. RYU[1,3], J. HANHN[1], C. J. LEE[4,5,6,7], S. KIM[1,2,3], M. SUH[1,2,3]
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**Abstract:** Hemodynamic signals, which are often measured by functional magnetic resonance imaging (MRI) and optical intrinsic signal (OIS) imaging, reflect blood flow change that is tightly linked to the elaborate interplay among excitatory neurons, inhibitory neurons, glia and vascular system. There are emerging evidences that hemodynamic signals have stronger correlation with the power in higher frequency ranges of local field potentials (LFPs), which is associated with the synchrony of inhibitory interneurons. We previously reported that cerebral blood volume (CBV) changes following sensory stimulus is decreased in chronically stressed animals. However, whether specific neuronal activity changes are associated with the hemodynamic signal changes is remained unclear. In this study, we investigated the alterations in neuronal activity and vascular dynamics in chronically stressed model with *in vivo* and *ex vivo* experiments. We applied restraint stress to 8-week-old male C57BL/6 mice for 6 hours per day for 3 weeks. By utilizing *in vivo* OIS imaging and electrophysiological recording techniques, CBV changes and LFPs were simultaneously measured during electrical forepaw stimulation**.** Both evoked CBV changes and the sum of LFP amplitudes following forepaw stimulation were decreased in chronically stressed animals compared to the controls. In particular, LFP power in the higher frequency bands was notably reduced in the stressed group suggesting the reduction in inhibitory interneuron's activity. To elucidate whether the excitatory and inhibitory neurons contribute differently to hypo-perfusion after the chronic stress exposure, we utilize acute brain slices which have better accessibility for dissecting complex neuronal signaling. First, we confirmed reduced vasodilation of penetrating artery under chronically stressed condition following a focal electrical stimulation. Then, we noticed the differential response of cerebral arterioles induced by drugs relating with either excitatory- or inhibitory signaling. There was a considerably dissimilar response between control and stressed groups when GABA agonists were treated. In addition, we utilized a patch clamp recording to confirm whether neuronal signaling was impaired in chronically stressed condition. The results showed the amplitude of inhibitory postsynaptic currents (IPSCs) was significantly reduced in stressed mouse whereas the amplitude of excitatory postsynaptic currents (EPSCc) was not notably changed. This study suggests that chronic stress induces impaired neurovascular coupling and these alterations may be modulated by GABA-mediated pathways.

**Disclosures: K. Han:** None. **J. Min:** None. **B. Kang:** None. **J. Woo:** None. **H. shim:** None. **W. Jung:** None. **M. Lee:** None. **T. Park:** None. **J. Ye:** None. **J. Lee:** None. **H. Ryu:** None. **J. Hanhn:** None. **C.J. Lee:** None. **S. Kim:** None. **M. Suh:** None.

**Poster**

**778. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging II**

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**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** IBS-R015-D1
NRF-2017H1A2A1044646

**Title:** Investigation of neuronal correlations with hemodynamic fluctuations in resting state using simultaneous wide-field hemodynamic and calcium imaging

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**Abstract:** Slowly varying resting state hemodynamics provide an important implication of functional brain connectivity. However, the relationship between resting state hemodynamics and underlying neural activity is still largely unknown. Only recently few studies investigating the neural basis of resting state hemodynamics in a spatial scale of whole cerebral cortex have been done. The detailed comparison between neuronal activation and slow hemodynamic signals has not fully investigated, yet. Here, we used a custom-built wide-field optical imaging system to simultaneously observe neural activity signals and hemodynamic fluctuations of resting state. In detail, 8~10 weeks old male Thy1-GCaMP6s mice with an intact skull were used. To visualize resting state neural activity and cerebral blood volume (CBV) changes, images were simultaneously acquired using alternating light sources whose wavelengths are 473 nm and 532 nm respectively. Our results showed that the resting state calcium signals, where hemodynamic contamination is corrected, has a correlation with resting state hemodynamic fluctuations throughout the whole brain. Using a seed-based cross correlation method, we also found similar functional connectivity maps between resting state calcium activity and resting state CBV fluctuation. This study may provide better understanding of the underlying neural correlates of resting state hemodynamics, such as slow fluctuation(<0.1Hz) in resting state BOLD fMRI signal.

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**Poster**

**778. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 778.04/DDD1

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** IBS-R015-D1

**Title:** Real-time *in vivo* two-photon imaging study reveals increased blood-brain barrier permeability in chronically stressed mice

**Authors: *B.-M. KANG**[1,2], J. KIM[1,3], S. LEE[1], J. MIN[1,2], H. RYU[1,2], H. KIM[1,2], M. SUH[1,2,3,4]
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**Abstract:** Chronic stress disrupts brain homeostasis and adversely affects the overall cerebro-vascular system, including blood-brain barrier (BBB) permeability. Our previous study suggests that chronic stress can cause hypoxic condition. In support of this result, mice with chronic-restraint stress are known to be associated with increased hypoxia-inducible factor-1α (HIF-1α) expression, higher levels of vascular endothelial growth factor (VEGF) and its receptor VEGFR2. Especially, VEGF has been reported to enhance BBB permeability. Most studies that have investigated the correlation between chronic stress and BBB permeability have used an endpoint assay, i.e., extravasation of Evans blue or sodium fluorescein dye. However, there are few *in vivo* dynamic studies on the effects of chronic stress on the BBB permeability. In this study, the effects of chronic stress on BBB permeability were studied using *in vivo* two-photon (2p) microscopic imaging with an injection of fluorescence-conjugated dextran. BBB permeability was investigated with two different size of tracers, i.e., 40-kDa and 70-kDa dextran. Stressed animals exhibited a greater BBB permeability to 40-kDa dextran, but not to 70-kDa dextran, suggesting weakened vascular integrity following stress. Molecular analysis further revealed significantly elevated HIF-1α, VEGFa mRNA expression and a reduction in claudin-5. Our results suggest that the sustained decreases in CBV due to chronic stress lead to a hypoxic condition that causes molecular changes, such as HIF-1α, VEGF and claudin-5, which eventually impairs the BBB. We conclude that 3-weeks chronic-restraint stress increased BBB permeability but did not induce BBB disruption.

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**Poster**

**778. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging II**

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**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** This research was supported by the Intramural Research Program of the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA.

**Title:** BOLD fMRI correlates of intermittent sympathetic vasoconstriction and autonomic EEG arousals during sleep

**Authors: P. S. OZBAY**, C. CHANG, *D. PICCHIONI, H. MANDELKOW, M. G. CHAPPEL-FARLEY, P. VAN GELDEREN, J. A. DE ZWART, J. H. DUYN
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**Abstract:** Blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) is a powerful tool to study the brain's activity and functional connectivity. fMRI signal is well established to originate from blood flow changes in response to neuronal activity through local (intracortical) neurovascular coupling. However, potential confounding contributions of the extrinsic sympathetic innervation of CNS arteries on the fMRI signal is less well known and mostly ignored by the fMRI community. Sympathetic activity is known to be highly variable during conditions of fMRI, including rest, sleep, and drowsiness and various cognitive, sensory, and emotional tasks, these variations could lead to fluctuations in heart rate and vascular tone. Our goal was to study this contribution by analyzing concurrently acquired fMRI, EEG, and peripheral vascular tone, measured with photoplethysmography (PPG) from the finger-tip, during rest and light sleep in healthy human subjects to capture fluctuations in autonomic arousal associated with K-complexes. fMRI data were obtained at 3 T (2D-EPI sequence, TR = 3 s, TE = 36 ms, voxel-size = 2.5 x 2.5 x 2 $mm^3$), and EEG and ECG were acquired concurrently with a 64-channel recorder. During time segments of NREM stage-2 sleep, we observed a high co-occurrence of the PPG amplitude drops with K-complexes in the EEG data (83% ± 0.11%, n = 6). Furthermore, we found substantial correlation (r = -0.33 ± 0.16) between EEG (1-5 Hz) and peripheral vascular tone, consistent with previous studies that linked it to sympathetic activation (Ackner and Pampiglione 1957)(Catcheside, Chiong et al. 2002) of the super cervical ganglion. Strong correlation was also found between peripheral vascular tone and fMRI signal, its spatio-temporal pattern consistent with the known vascular delay between the deep (medullary) and superficial vascular territories in periventricular white and cortical gray matter (Ozbay, Chang et al. 2018). A similar correlation pattern between peripheral vascular tone and fMRI was observed in a publicly available data base of task-based studies including emotional and cognitive stimuli.

These findings suggest a contribution to the fMRI signal from the extrinsic sympathetic innervation of the pial vasculature and is expected to be important for a range of conditions that activate the sympathetic pathway. Due to the close integration of brain stem systems that regulate sympathetic nervous activity and intracortical neuronal activity, separation of these two sources of fMRI activity is challenging and will require further research to establish a comprehensive model of the relationship between fMRI, EEG, and peripheral measures.

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**Poster**

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**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** This work was supported by the Intramural Research Programs of the National Institute of Neurological Disorders and Stroke, National Institute on Deafness and Other Communication Disorders, and National Institute of Mental Health.

**Title:** Motion during all-night functional magnetic resonance imaging sleep studies

**Authors: *N. L. JOHNSON**, J. A. DE ZWART, H. MANDELKOW, C. CHANG, P. S. ÖZBAY, P. VAN GELDEREN, J. H. DUYN, D. PICCHIONI
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**Abstract:** Functional magnetic resonance imaging (fMRI) of sleep offers new opportunities to study the brain's functional architecture and its unique signatures during the various behavioral states across the sleep-wake cycle. Unfortunately, previous studies have been hampered by the difficulty of obtaining extended amounts of sleep in the sleep-adverse environment of the scanner and have often resorted to manipulations such as prescan sleep deprivation. These manipulations limit the generalizability of the results. The current study is a methodological validation of a protocol aimed at obtaining all-night fMRI data in sleeping human subjects without the use of sleep deprivation. In addition, an analysis of motion is included to verify that sleeping prevented gross subject movements in the scanner. Preliminary analyses of these data from a subset of subjects has been previously presented (Moehlman et al., 2017). All subjects were between the ages of 18-34 and passed numerous screening criteria to increase the likelihood of typical, healthy sleep. Furthermore, subjects underwent an in-person screening and an adaptation night in the scanner. Good sleep hygiene was ensured with a two-week home-monitoring period. The last three days before scanning, subjects were asked to listen to an audio

recording of the scanner for 1 hour each day. Subjects were allowed to exit the scanner and take breaks whenever requested. Sleep scoring results from simultaneously acquired electroencephalography data indicate that subjects (n = 12) reached the full spectrum of sleep stages including slow-wave (M = 47.9 min, SD = 28.0 min) and rapid eye movement (REM, M = 40.4 min, SD = 24.8 min) sleep and exhibited a mean of 2.1 (SD = 1.1) nonREM-REM sleep cycles. Mean total time in stages N1 and N3 were significantly different between night 1 (58.7 min N1, 27.8 min N3) and night 2 (38.9 min N1, 47.9 min N3). This indicates the importance of the adaptation night. Across all scans (n = 239) of variable length (M = 41.05 min, SD = 52.26 min), maximal head displacement was M = 2.69 mm (SD = 3.03 mm). Only 7 of the 239 scans had a maximal head displacement greater than 3 SD from this mean. This shows that motion during long sleep scans is comparable to the motion in resting-state scans of shorter duration. The conclusion of this research is that by diligently applying fundamental principles and methodologies of sleep and neuroimaging science, performing all-night fMRI sleep studies without sleep deprivation may be feasible.

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**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** IBS-R015-D1

**Title:** Longitudinal study of neurovascular coupling changes associated with recovery period following soft cranial window installation in mouse

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**Abstract:** The soft-cranial window, which we previously developed using polydimethylsiloxane (PDMS) (Heo et al, 2016), allows not only a direct access into neural tissue but also chronic monitoring for a large brain area. But, the adverse-effect of PDMS to brain in long-term is still unclear. Here, we investigated the long-term effects of soft-cranial window installation on sensory-evoked cerebral hemodynamics and neuronal activity. C57bl/6 mice were used in this study. We monitored the brain tissue immunocytohistologically and sensory-evoked electrophysiological and hemodynamic responses for 6 weeks following soft-window

installation. In immunohistochemical studies, we found that the most significantly heightened reactive astrocytic level and activated microglia at 2 weeks post-installation. The animals at 6 weeks post-installation had similar expression levels of reactive astrocyte and activated microglia compared to normal control animals. Consequently, animals with soft-window installation underwent two *in vivo* experimental sessions with ketamine anesthesia at 2 weeks and 6 weeks post-operation. We recorded sensory-evoked hemodynamics of the barrel cortex during a single whisker stimulation (C2 whisker) for 4 seconds and also recorded local field potential (LFP) during a single whisker deflection at two time points. The animals at 6 weeks post-operation showed stronger hemodynamic responses and more focalized barrel mapping than responses from 2 weeks post-operation. LFP recording during a single whisker deflection also showed that the animals at 6 weeks post-operation showed larger neural activity than the animals at 2 weeks post-operation. Furthermore, we found that the expression level of proinflammatory cytokine, IL-1β was highly upregulated at 2 weeks post-operation than 6 weeks post-operation. When we treated minocycline, a drug inhibiting the production of proinflammatory cytokine, to the animals every other days during 2 weeks post-operation, the animals with minocycline showed similar hemodynamic responses compared with control animals. This suggests that proinflammatory cytokine may cause alterations in neurovascular coupling following soft-window operation.

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**Poster**

**778. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging II**

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**Title:** Prolonged cannabinoid intake leads to memory impairment and to changes in brain metabolism and brain connectivity in mice

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**Abstract:** Chronic exposure to cannabinoids can lead to cognitive deficits and increases the risk of developing psychiatric disorders. One immediate consequence of cannabis consumption is an impairment in memory consolidation, seen in both humans and laboratory animals. Brain imaging techniques gave important contributes to better understand and characterize the brain regions that are affected by long-term exposure to cannabis. However, chronic consumption studies in humans can be contaminated by confounding variables, such as lifestyle factors or mixed drug use. In the present work we used mice as an animal model and evaluated the impact of prolonged cannabinoid exposure on brain metabolism, functional brain connectivity and recognition memory. C57BL/6 mice (7-8 week old) were i.p. injected with WIN 55,212-2 (1 mg/kg of body weight) during 30 days. Recognition memory was assessed in the Novel Object Recognition test, while anxiety and locomotion were evaluated by the Elevated Plus Maze and the Open Field Test, respectively. After the behavioural tests, to determine local cerebral glucose utilization (LCGU), mice were injected i.p. (2.5 ml/kg) with 4.625 MBq/Kg of 2-deoxy-D-[14C]glucose in physiological saline. Through autoradiography image analysis, differences in LCGU between WIN and control mice were evaluated in brain regions of interest (RoI), using as reference a stereotactic mouse brain atlas. Regional functional brain connectivity was analyzed applying the Partial Least Squares Regression (PLSR) algorithm. We observed that chronic cannabinoid exposure impairs recognition memory (*P <0.05, n=19), without significantly affecting anxiety or locomotion parameters. Importantly, we show that chronic WIN 55,212-2 exposure induces hypometabolism in the hippocampal dorsal subiculum and in the mediodorsal nucleus of the thalamus, two brain regions directly involved in recognition memory. In addition, WIN 55,212 exposure induces (P<0.05, n=20) hypometabolism in the habenula with a contrasting hypermetabolism in the globus pallidus. Prolonged WIN 55,212-2 administration also altered functional connectivity in brain networks that underlie recognition memory (hippocampus-prefrontal cortex, thalamus-prefrontal cortex, hippocampus-perirhinal cortex). In addition, our results support disturbed lateral habenula and serotonin system functional connectivity following prolonged WIN 55,212-2 exposure. Overall, this study provides new insight into the functional mechanisms underlying the impact of chronic cannabinoid exposure on memory and highlights the serotonin system as a particularly vulnerable target.

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**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** BB/N009088
MR/N013700/1

**Title:** Multimodal characterisation of methylene blue's effects on rat neurovascularity and metabolism

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**Abstract:** Methylene blue (MB) is a synthetic pharmaceutical which seemingly displays neuroprotective characteristics via metabolic modulation. Low-dose MB (<5 mg/kg) reportedly enhances task-related blood oxygen level dependent (BOLD) activations in rats[1] and in humans[2], while an increase in global and regional Cerebral Blood Flow (CBF) has also been reported in rats[3]. However, MRI observations are indirect characterisations of the underlying metabolic processes and can be misinterpreted or confounded by physiological interference, e.g. the effects of anaesthesia. Further, global Cerebral Metabolic Rate of Oxygen ($CMRO_2$) has been shown to increase following injection of MB[3], but regional metabolic differences have not been established. This exploratory multimodal study pairs essential replication of previous MRI studies with the gold-standard method of quantified $^{14}$C-2-deoxy-D-glucose ($^{14}$C-2DG) *in vivo* autoradiography, to provide further insights into the neurovascular and metabolic responses to MB.

Male Sprague-Dawley rats were cannulated (femoral vein and artery) under 5% isoflurane anaesthesia. Autoradiography cohort rats (n=6-8 per group) were stabilised at low-level isoflurane (1.5%) for 30 minutes, before injection with either MB (2 mg/kg) or saline control (1 ml/kg). Following 30 minutes further stabilisation, $^{14}$C-2DG was administered intravenously. Blood glucose and $^{14}$C levels were after $^{14}$C-2DG administration at 14 intervals across 45 minutes. Rats were decapitated within 2 minutes of the final sample, their brains were cryosectioned and the sections exposed to an x-ray sensitive film. Additionally, BOLD and CBF responses were recorded from the MRI cohort (n=4-6) before and after intravenous injection of MB (2 mg/kg) with a 9.4 T Bruker scanner.

Quantitative autoradiography provides a more precise representation of the underlying glucose metabolism changes that occur as a result of MB administration, compared to MRI observations alone. Although BOLD and CBF measurements are intricately coupled with metabolism, this coupling can be perturbed, for example, by choice of anaesthetic. Therefore, it is important to corroborate these findings using a gold-standard method of quantifying glucose metabolism and comparing these results with MRI findings.

References

1. Huang et al. *Neuroimage.* 2013 2. Rodriguez et al. Radiology. 20163. Lin et al. PLoS ONE. 2012

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**Poster**

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**Program #/Poster #:** 778.10/DDD7

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Title:** What is needed to measure executive function during target stepping tasks using fNIRS?

**Authors: *S. M. VAN DER VEEN**[1,2], W. S. S. ROYLE[2], U. HAMMERBECK[3], R. A. A. BENDALL[2], K. L. HOLLANDS[2]
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**Abstract:** Adapting walking in response to the environment requires processing visual-spatial information to plan and execute foot-placement changes. Accordingly, dual task studies demonstrate that gait adaptation requires additional cognitive resources compared to steady state walking [1]. But only recently have we become able to measuring cortical activation using functional near infrared spectrometry (fNIRS) during walking to identify the networks sub serving cognitive control processes. The aim of this study was to evaluate methodology of using fNIRS to measure changes in cortical activation during target stepping.
Young,older healthy adults and stroke survivors walked on a force-instrumented treadmill (CMill, MotekForceLink, NL) at a comfortable speed wearing a 16-fNIRS (Biopac) over the prefrontal cortex (PFC) for 3 conditions: steady state walking (no targets), regular and irregular foot-fall targets. fNIRS data were processed using HOMER2 (Matlab GUI interface) with automated motion artefact and cubic spline corrections. $HbO^2$ concentration for the different walking conditions was normalized to 7s walking immediately preceding the walking condition. $HbO^2$ concentration was compared between walking conditions in an ANOVA.
No main or interaction effects on the PFC $HbO^2$ concentration was found between walking conditions or group. The high inter-subject variability (figure 1) indicate that large sample sizes, robust signal processing for motion artefacts and longer walking periods for normalization are required.
This study shows that using fNIRS to measure cortical activation during walking tasks requires careful consideration of methodology and data processing to be robust. Further development of fNIRS processing and methodology is required in order to apply this measurement tool towards addressing key questions regarding the involved neural networks supporting cognitive processes required to adapt walking.

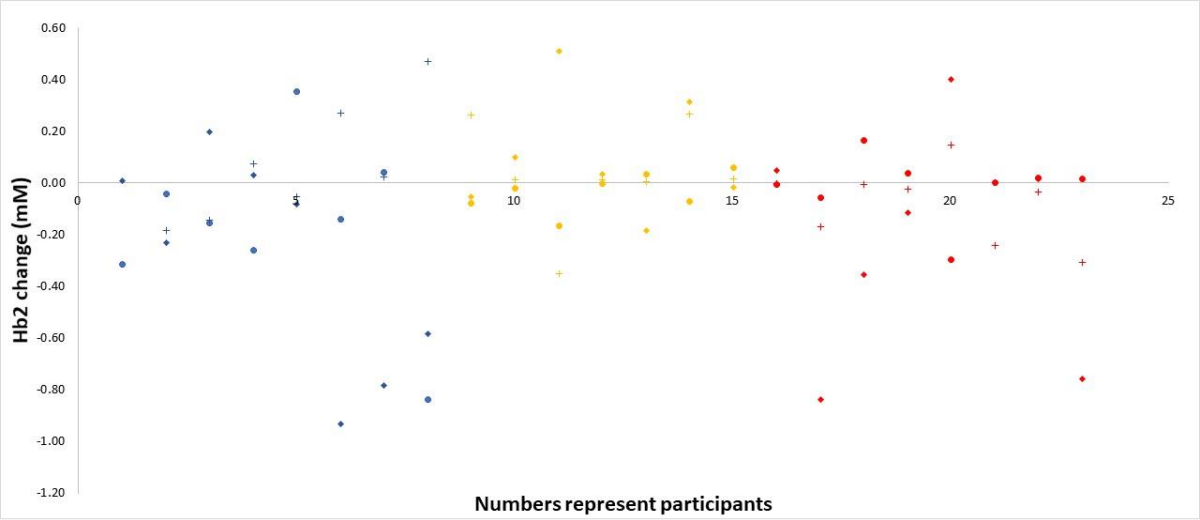


Figure 1. Data represent the mean change of $HbO_2$ for each individual participant in the three walking conditions (steady state walking: no targets, regular: targets placed at preferred foot-fall and irregular: targets eliciting foot-fall adaptation) in relation to the 7s baseline taken before each walking task. Young healthy adults (YH, N=8, 3 male, age *M±SD* 27±5 years, walking speed 1.01± 0.16ms) in blue, older healthy (OH, N=7, 4 male, age 66±9 years, walking speed 0.94± 0.23ms) in yellow and stroke survivors (SS, N=8, 6 male, age 66±9 years, Time since stroke 100± 158months, walking speed 0.52±0.26ms) in red, for each condition steady state walking (circles), regular (diamond) and irregular (+) target stepping.

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**Poster**

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**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** ESPCI
INSERM
CNRS

**Title:** Cannabinoid-induced changes in intrinsic connectivity of the rat brain depend on actomyosin contractility as assessed by functional ultrasound imaging

**Authors: *C. MORISSET**[1,2,3], M. SALERNO[4], J. FERRIER[4], C. DEMENE[1,2,3], T. DEFFIEUX[1,2,3], M. TANTER[1,2,3], Z. LENKEI[4]
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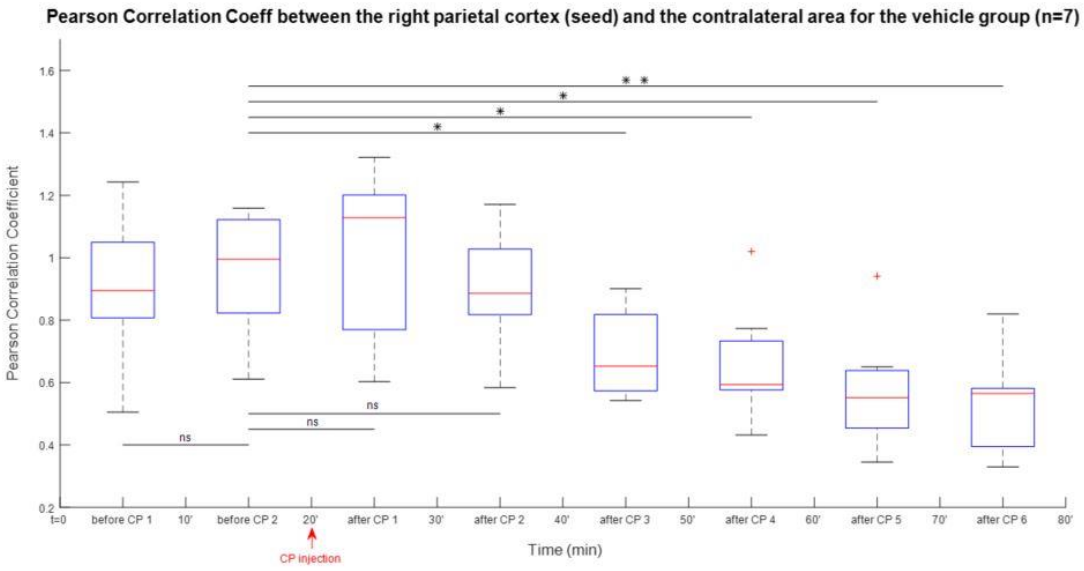
**Abstract: Aims** Exogenous cannabinoids interfere with the endocannabinoid system and modify brain connectivity. A recently identified molecular pathway, downstream of cannabinoid

receptor activation, is dependent on actomyosin contractility of the neuronal cytoskeleton, putatively inducing changes in synaptic function. Modulation of this pathway could modify resting-state functional connectivity *in vivo*. This study investigates this new mechanism by blocking neuronal actomyosin contractility with Neurelaxin-A (para-amino-blebbistatin) in the living rat brain during cannabinoid treatment (CP55,940) of adult rats. Intrinsic brain connectivity was measured by using a novel powerful brain imaging method, functional ultrasound (fUS) imaging of the neurovascular coupling. **Methods** Two experiments were performed on 24 male Dawley rats, anesthetized with an IP injection of ketamine xylasine. fUS acquisitions were performed in a coronal plane at Bregma -3.6mm. For the first experiment, animals (n=7) were recorded continuously for 90' and injected with CP after 20' of baseline. For the second one, animals were pretreated with i.c.v. injections of of either vehicle (n=9) or Neurelaxin 5mM (n=8), 30' before CP injection. Ultrasound sequences are emitted by an ultrafast ultrasound scanner. Doppler images were acquired every second from plane waves compounding. **Results** Seed-based analyses of connectivity were performed before and after cannabis treatment. Functional connectivity was significantly reduced between several cortical and subcortical regions and Neurelaxin-A pre-treatment prevented this decorrelation. **Conclusions** Our results indicate that cannabinoid-induced alterations of functional connectivity could be rescued by blocking neuronal actomyosin contractility, suggesting that actomyosin contractility is a major effector of cannabis effects on large-scale connectivity patterns.

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**Poster**

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**Title:** Age-differential relationships among dopamine d1 binding potential, fusiform bold signal, and face-recognition performance

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**Abstract:** Cortical areas involved in facial recognition exhibit thinning, lower dopamine (DA) receptor availability, and lower blood-oxygen-level-dependent (BOLD) signal during task performance with advancing adult age. These concurrent decreases are observed together with diminished facial recognition ability. However, the effects of changes in both DA and BOLD on age differences in face recognition remain unknown. Using Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI), we measured D1 receptor binding potential (BP) and BOLD signal during face-recognition performance. Twenty younger and twenty older participants performed a face-recognition task during scanning. Face recognition accuracy was lower in older ($M = 0.68$, $SEM = 0.44$) than in younger ($M = 1.25$, $SEM = 0.43$) adults as measured by d prime ($t(35) = -3.97$, $p < 0.001$), as were D1 BP ($F = 7.67$, $p < 0.001$) and BOLD signal ($F = 3.18$, $p < 0.01$) across the brain. Linear regression analyses showed significant relationships between D1 BP and BOLD in both groups. Interestingly, although the relationship was positive in younger adults (i.e., as D1 BP increased, BOLD signal increased; $r = 0.61$, $p < 0.01$), it was negative in older adults (i.e., as D1 BP decreased, BOLD signal increased; $r = -0.65$, $p < 0.01$). Ratios of BOLD:D1 BP were calculated and associations with face-recognition performance were tested. This correlation was significant for younger adults (r =

0.49, $p < 0.04$), but not for older adults ($r = 0.02$, $p > 0.05$). Opposite relationships between DA and BOLD suggest that, in younger adults, neurotransmitter (DA) and hemodynamic (BOLD) systems are synchronized, whereas in older adults, these systems are desynchronized. The relation of BOLD:D1 BP to performance suggests that neurotransmitter-hemodynamic system synchronization promotes efficient neural activity, facilitating face recognition performance. In older adults, the desynchronization between these brain systems could adversely impact task performance, contributing to reduced face recognition ability in older adults. The neurotransmitter-hemodynamic system desynchronization also supports the hypothesis of age-related reductions in the integrity of underlying neural-vascular coupling systems.

**Disclosures: M.P. Turner:** None. **H. Fischer:** None. **D. Sivakolundu:** None. **N. Hubbard:** None. **A. Rieckmann:** None. **B.P. Rypma:** None. **L. Bäckman:** None.

**Poster**

**778. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 778.13/DDD10

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** NIH Grant MH111874-01

**Title:** Electrical current changes brain function: Effects of dose and electrode montage

**Authors: *G. SCHLAUG**[1], A. B. SHINDE[2], F. MUNSCH[2], D. ALSOP[2]
[1]Dept Neurol, Harvard Med. Sch. Dept. of Neurol., Boston, MA; [2]Neurol., Harvard Med. Sch. and Beth Israel Deaconess Med. Ctr., Boston, MA

**Abstract:** Research investigating the use ofnoninvasive electrical stimulation (e.g., transcranial direct current stimulation (tDCS)) 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 the mechanisms that lead to suchchanges is limited,and the influence of variables such as *current strength*and *electrode montage*remains unexplained.Weare conducting a series of studies to characterize brain and behavioral responses to tDCS, varying dose and electrode montage. During magnetic resonance imaging (MRI), tDCS is delivered by an MRI-compatible, constant-current stimulator. Dynamic imaging using arterial spin labeling (ASL) - a non-invasive cerebral blood flow technique - and BOLD contrast MR imaging - a traditional fMRI technique - are done while tDCS is applied in the MR scanner to examine induced effects of brain activity in response to tDCS - both directly under the electrode and in remote brain regions. Our pilot data and initial analyses so far have revealed that 1) cerebral blood flow (CBF) increases in response to focal transcranial direct current stimulation, but that the increase shows a differential response comparing excitability increasing anodal tDCS; 2) the

blood flow increases during the stimulation shows a dynamic variation that differs between the different doses and montages; 3) focal stimulation of one brain region can lead to changes in CBF in functional and structural related brain regions revealing a remote network of brain regions that can be affected by focal stimulation. Our results may improve the use and application of tDCS for targeted stimulation in a broad range of brain disorders.

**Disclosures: G. Schlaug:** None. **A.B. Shinde:** None. **F. Munsch:** None. **D. Alsop:** None.

**Poster**

**778. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 778.14/DDD11

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** NIH Grant R01MH102471
NIH Grant R21NS105090
McDonnell Center for Cellular & Molecular Neurobiology 3930-26275F

**Title:** Changes in neurovascular coupling occlude oxygen-based measures of ketamine's dose-dependent effects on long-range correlations in non-human primate cortex

**Authors: *B. T. ACLAND**, L. H. SNYDER
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**Abstract:** The brains of resting humans, monkeys, and mice exhibit patterns of synchronous, low-frequency fluctuations that can be used to identify not only cortical regions, but groups of cortical regions that tend to co-activate during tasks. These "networks" can be seen most clearly in humans using functional MRI, which provides an indirect and low resolution measure of brain activity based on oxygen concentration. Mounting evidence suggests a neural basis.
To address the relationships between the low-frequency correlational structures of spiking activity, LFP, and oxygen concentration, we recorded all three signals simultaneously from four regions in parietal and cingulate cortex in resting non-human primates before, during, and after systemic injections of the non-selective NMDA antagonist ketamine. Our data demonstrate that ketamine has opposite effects on long-range correlations in both spiking activity and LFP depending on the dose administered, with low doses causing a temporary decrease in correlation, and high doses causing a temporary increase in correlation. The increased correlation after high doses of ketamine appears to arise from synchronized, low-frequency oscillations in spikes and LFP that do not occur after low doses. Intriguingly, while we would expect highly synchronized neuronal activity to induce synchronized fluctuations in oxygen concentration, this was not observed. Instead, we observe a transient decoupling of electrophysiological and oxygen correlations whose time-course appears to reflect a transient suppression of the local relationship

between spiking activity and tissue oxygenation.
Together, our findings strongly indicate that ketamine has multiple effects on long-range correlations in neural activity, and that oxygen-based measurements of these effects are confounded by ketamine-induced changes in neurovascular coupling. This highlights a broader point: that the interpretation of an intervention's effect on any signal used as a proxy for neural activity must be informed by an understanding of the intervention's effect on that proxy signal's validity.

**Disclosures: B.T. Acland:** None. **L.H. Snyder:** None.

**Poster**

**778. Brain Blood Flow, Metabolism, and Homeostasis: Functional Imaging II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 778.15/DDD12

**Topic:** F.06. Brain Blood Flow, Metabolism, and Homeostasis

**Support:** NIH Grant MH111874-01

**Title:** Establishing a dose response for transcranial direct current stimulation

**Authors: *A. B. SHINDE**
Beth Israel Deaconess Med. Ctr. and Harvard M, Boston, MA

**Abstract:** Research investigating the use of noninvasive electrical stimulation (e.g., transcranial direct current stimulation (tDCS)) 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 the mechanisms that lead to such changes is limited, and the influence of variables such as *current strength* and *electrode montage* remains unexplored. 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, 2mA and 4mA (Corresponding current densities: 0 $mA/cm^2$, 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. The anodal electrode (diameter of 4 cm) was placed over the right motor region (C4) while the cathodal electrode (diameter of 5 cm) was either placed over the left supraorbital region (unihemispheric montage) or over the left motor region (C3; bihemispheric montage). Only the 4mA condition was tested in the uni- and bihemispheric condition. Each stimulation study was of 10 min duration including an initial ramp up and final ramp down of 30 seconds. The Sham condition involved only a 30 sec ramp up to 4mA and immediately a 30 sec ramp down to 0 mA which lasted another 9 minutes. 10 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. A two factional rm-ANOVA [with conditions *Stimulation* and *Correct Sequence PostvsPre*] performed on the finger sequence task showed significant main effects of stimulation and a significant interaction between stimulation and CorrectSequencePostvsPre. Post-hoc tests confirmed a significant difference in correct finger sequences after stimulation between 2mA and 4mA vs Sham and between 2mA and 4mA (all unihemispheric). Results of ANOVA confirm the causal relationship between the anodal stimulation of the peri-rolandic region and an enhancement of the motor program consolidation phase. Further research will explore effects of electrode montage and transfer effects to the ipsilateral hand.

**Disclosures:**

**Poster**

**779. Sleep Systems**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 779.01/DDD13

**Topic:** F.08. Biological Rhythms and Sleep

**Support:** NIH Grant 1R15NS101692-01A1
Skidmore College Faculty Development Grant
Skidmore College Faculty/Student Summer Research Program
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**Title:** The contribution of circadian clock cells to the sleep-inducing effects of optogenetic activation of short neuropeptide F (sNPF) neurons in *Drosophila*

**Authors: *C. G. VECSEY**, J. M. STONEMETZ, B. A. JUNEAU, R. F. TOMA
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**Abstract:** Sleep is a complex biological process, of which many cellular mechanisms remain to be fully elucidated. One of these mechanisms is the role of neuropeptides in sleep regulation. In the fruit fly *Drosophila melanogaster*, one particularly relevant neuropeptide is sNPF. sNPF is expressed in neurons within the mushroom bodies and circadian clock circuit, but also in other locations throughout the nervous system. Mutation and thermogenetic activation studies have suggested is a sleep-promoting signal. We have examined the effects of activation of sNPF-producing neurons using optogenetic methods. By combining sNPF-GAL4 and UAS-Chrimson transgenes, exposure to red light can induce activity in sNPF neurons. Using this approach, we have found that red light stimulation increases sleep in sNPF-GAL4/UAS-Chrimson flies long-term and acutely decreased activity levels. The present study aimed to further investigate the effects of sNPF in specific neuronal populations in order to more fully explain the role of sNPF on sleep and activity levels. In order to accomplish this, a line of flies with sNPF-GAL4 and

UAS-Chrimson transgenes was crossed with flies carrying CRY-GAL80. CRY-GAL80 prevents the expression of the Chrimson transgene in neurons also expressing CRY, a molecule expressed in clock neurons. This should lead to a more selective expression of Chrimson in non-clock sNPF neurons. All flies were raised in conditions of total darkness on food containing all trans retinal, which allows them to respond to red light stimulation, and n was >20 in all groups. In flies expressing Chrimson in sNPF-positive cells but not in CRY-positive cells, a decreased effect of red light stimulation on sleep was seen in comparison to flies expressing Chrimson in all sNPF-positive cells. This shows that more than one class of sNPF-positive cells contribute to the overall effect of the molecule on sleep. Going forward, this could be further examined by restricting sNPF expression from other classes of neurons, such as those in the mushroom bodies or in a PDF-positive subset of clock neurons.

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**Poster**

**779. Sleep Systems**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 779.02/DDD14

**Topic:** F.08. Biological Rhythms and Sleep

**Support:** NIH Grant R01GM122406

**Title:** Understanding neuronal functions of circMbl in *Drosophila melanogaster*

**Authors: *A. KRISHNAMOORTHY**[1], I. PATOP[2], N. REDDY PAMUDURTI[2], J. KONAKONDLA[1], S. KADENER[1]
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**Abstract:** Circular RNA(circRNA) is a highly conserved and abundant class of RNAs of mostly unknown functions. CircRNAs are formed by circularization of specific exons by a process named backsplicing. These molecules are more stable than their linear forms and are resistant to exonucleases due to absence of free 5'or 3' ends. Circular RNAs are expressed in a tissue/ developmental stage specific manner independent of their hosting gene and regulate gene expression in *cis* by competing for the production with their hosting genes. Interestingly, proteins are produced from a subset of circRNAs. These circRNA-encoded peptides usually share a start codon with the hosting genes and might be important in synapses and muscle.
circRNAs are particularly enriched in the brain. Strikingly, this expression is highly conserved, with 80% of all circRNAs are abundant across different mammalian neuronal tissues. Synapses accumulate unusually high levels of circRNAs. Moreover, circRNA levels increase with age in

the brains of mice and flies and are affected by neuronal activity. These observations suggest important roles for circRNAs in the brain.
The protein Muscleblind, a regulator of alternative splicing, promotes circularization of its exon by binding to the flanking intronic sequences. In *Drosophila muscleblind* (*mbl*) has roles in the differentiation of photoreceptors and for development of larval and adult muscle. Until now, there is no knowledge on the function of the circular molecules of muscleblind (circMbl) despite the fact that they are the more abundant type of molecules generated from this locus.
To further investigate the role of circMbl, we generated flies expressing short-hairpin shRNAS which are specific for circMbl. Indeed, expression of this shRNA leads to a very efficient (>90%) and specific circMbl knockdown. Interestingly, ubiquitous knockdown of circMbl, using *actin-Gal4* increased the total sleep while not affecting the total activity during the day. However, upon waking up, the flies were hyperactive. Moreover, downregulation of circMbl specifically in the fly central nervous system caused abnormal synaptic function. Also, preliminary results performing single cell sequencing from control and circMbl knockdown flies results in the identification of a specific neuronal group affected by the knock down. These results indicate potential roles of circMbl in the brain. To underpin the molecular basis of these phenotypes, we are currently using tissue specific drivers to knockdown circMbl and determining the presence of these phenotypes. Simultaneously, we are performing overexpression experiments.

**Disclosures: I. Patop:** None. **N. Reddy Pamudurti:** None. **J. Konakondla:** None. **S. Kadener:** None.

**Poster**

**779. Sleep Systems**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 779.03/DDD15

**Topic:** F.08. Biological Rhythms and Sleep

**Support:** NIH Grant R15GM125073

**Title:** Dopaminergic control of sleep is independent of feeding in *Drosophila*

**Authors: *M. DRISCOLL**, V. COLEMAN, D. SITARAMAN
Univ. of San Diego, San Diego, CA

**Abstract:** Neuromodulators such as serotonin and dopamine (DA) have previously been implicated in behaviors such as sleep and feeding across vertebrates and invertebrates. The majority of the dopaminergic neurons in the fly brain project to an associative learning network called the mushroom body (MB), modulating the synaptic strength of connections within. The MB has been implicated in many motivated behaviors, including decision-making and sleep.

Approximately 2,000 kenyon cells (KCs) make up the lobes of the MB and synapse onto MB output neurons (MBONs). Transgenic activation of clusters of DA neurons have been found to result in significant sleep deficits in Drosophila melanogaster without producing a strong rebound post-deprivation. In order to ascertain whether the observed sleep deficits resulting from DA neuron activation resulted from dopaminergic regulation of sleep-homeostasis or a drive to forage we tested these neurons for feeding deficits. Further, we manipulated the levels of DopR1 and R2 in flies with increased dopamine release from specific neuronal subsets to elucidate the circuit basis of sleep-feeding regulation. These results will be presented and provide timely insights into the role of dopamine on sleep-feeding conflict.

**Disclosures: M. Driscoll:** None. **V. Coleman:** None. **D. Sitaraman:** None.

**Poster**

**779. Sleep Systems**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 779.04/DP11/DDD16

**Topic:** F.08. Biological Rhythms and Sleep

**Title:** Brain-wide activity in zebrafish during sleep and wake

**Authors: *A. ANDREEV**[1], A. NADTOCHIY[2], M. JONES[3], K. KEOMANEE-DIZON[3], P. LUU[3], S. E. FRASER[4], T. V. TRUONG[5]
[1]Translational Imaging Ctr., Los Angeles, CA; [2]Biol. Sci., [4]Mol. & Computat. Biol., [5]Translational Imaging Ctr., [3]USC, Los Angeles, CA

**Abstract:** Virtually all animals sleep, yet why and how sleep happens is still largely not understood. Sleep is a global behavior that likely involves coordination and integration across the entire brain, but up until recently it has not been possible to monitor the whole brain, at cellular resolution, to observe the global functional activity pattern of the brain in both sleep and wake states.
We present our efforts in using 2-photon light sheet microscopy to capture neuronal activity signatures of sleep and wake, in larval zebrafish (*Danio rerio*). Of key importance in the imaging platform is the effort to minimize the perturbing photo-induced effects in order to preserve the sensitive sleep/wake states of these small model organisms. We capture zebrafish brain activity continuously for periods up to 24 hours, measuring functional changes in the brain during the natural sleep/wake cycle. Using this framework, we begin to characterize the brain-wide signatures of natural sleep and wake, as well as interrogate circuits that are relevant to the behavior. We also apply this toolset to better understand effects of sleep-aiding medication such as melatonin on brain-wide neuronal activity. Insights gained from our work will contribute toward understanding the nature and function of sleep.

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**Poster**

**779. Sleep Systems**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 779.05/DDD17

**Topic:** F.08. Biological Rhythms and Sleep

**Support:** NIH Grant R15GM125073

**Title:** Octopamine regulation of sleep and arousal

**Authors: *A. NGUYEN**, R. MOGHADAM, D. SITARAMAN
Univ. of San Diego, San Diego, CA

**Abstract:** Octopamine (OA), the invertebrate homolog of norepinephrine, has been implicated in multiple behaviors in Drosophila such as feeding, sleep, and aggression. The precise circuit mechanisms by which octopamine regulates these behaviors remains largely unexplored. Using a high resolution neurogenetic screening we have identified a subset of octopamine neurons (VPM 4,5) that suppresses sleep and increases wakefulness. Neuroanatomical analysis reveals that these neurons project to the mushroom body (MB), an associative neural network analogous to the mammalian cortex. Using genetic, anatomical, and behavioral approaches we show that the OA-VPM neurons release octopamine that interacts with subsets of dopamine neurons in the MB in regulating sleep. Furthermore, calcium imaging studies show that flies that are sleep deprived display reduced activity within OA-VPM neurons as compared to sleep-replete controls. Taken together, these results reveal octopamine is important in sleep regulation through these neuronal connections. In addition to presenting this data, we will also discuss potential receptor mediated mechanisms underlying these connections.

**Disclosures: A. Nguyen:** None. **R. Moghadam:** None. **D. Sitaraman:** None.

**Poster**

**779. Sleep Systems**

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**Program #/Poster #:** 779.06/DDD18

**Topic:** F.08. Biological Rhythms and Sleep

**Support:** NSERC grant #2016-06576
NSERC grant #435843

**Title:** Hyperoxia enhances forebrain slow-wave states in urethane anaesthetized and naturally sleeping rats

**Authors: *B. E. HAUER**, B. NEGASH, K. CHAN, W. VUONG, F. COLBOURNE, S. PAGLIARDINI, C. T. DICKSON
Univ. of Alberta, Edmonton, AB, Canada

**Abstract:** Oxygen ($O_2$) is crucial for normal physiological functioning in mammals. Brain function in particular is critically reliant on a baseline amount of circulating blood $O_2$, and both immediate and lasting neural dysfunction can result from exposure to anoxic or hypoxic conditions. However, the impact of elevated levels of $O_2$ (hyperoxia) in inspired gas under atmospheric pressure on brain function remains relatively less studied. Using local field potential (EEG) recordings in spontaneously breathing urethane-anaesthetized and naturally sleeping rats, we characterized the influence of different amounts of $O_2$ in inspired gases on brain states. Under urethane anaesthesia, administration of 100% $O_2$ elicited a significant and reversible increase in time spent in the deactivated (i.e. slow-wave) state, with concomitant decreases in both heartbeart and respiration rates. This effect appeared to be mediated specifically by $O_2$, as increasing the concentration of carbon dioxide (to 5%) in inspired gas failed to produce any significant change in EEG state. Indeed, lowering the concentration of $O_2$ to 15% (by substitution with nitrogen) produced the opposite result of hyperoxia on EEG states, i.e., a decrease in time spent in the deactivated state. This suggests that it is $O_2$ itself that produces the changes in hyperoxia and not any accompanying changes in blood carbon dioxide that is responsible for the shift in forebrain state. In addition to boosting slow wave activity under urethane anesthesia, hyperoxia was also found to increase slow-wave sleep in naturally sleeping rats. Our results indicate that alterations of $O_2$ concentrations in inspired gases directly affect forebrain EEG states. This has implications for brain function, as well as for the regulation of brain states and levels of forebrain arousal during sleep in both normal and pathological conditions.

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**Poster**

**779. Sleep Systems**

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**Topic:** F.08. Biological Rhythms and Sleep

**Support:** NSERC Grant 2016-06576

Alberta Graduate Student Scholarship

**Title:** Converging on unconsciousness: Using anaesthesia to model sleep-like brain states

**Authors: *R. WARD-FLANAGAN**, A. S. LO, M. SOBEY, C. T. DICKSON
Univ. of Alberta, Edmonton, AB, Canada

**Abstract: Background:** Sleep is a dynamic process required for optimal physiological and psychological functioning, and ultimately survival. Yet, despite its fundamental significance, delineating both the function and underlying mechanisms of natural sleep has been slow to progress, likely due in part to the most common model for sleep being sleep itself. A natural choice for an alternative is anaesthesia, which has direct behavioural parallels to natural sleep, such as reversible loss of consciousness, decreased sensory awareness and reduced behavioural responsiveness. **Objective:** Our aim is to characterize how select anaesthetics promote specific electrophysiological components of natural sleep in order to help identify convergent endogenous pathways used for the induction and maintenance of unconsciousness. **Methods:** 25 male Sprague-Dawley rats were randomly assigned to one of the following anaesthetic groups for acute electrophysiological recordings: urethane (n = 10), ketamine-xylazine (n = 5), isoflurane (n = 5), pentobarbital (n = 6). All anaesthestic were delivered intravenously, except isoflurane which was delivered via nosecone continuously. Dosage was consistently monitored and adjusted to maintain a surgical plane. **Results:** Electrophysiological activity in rats anaesthetized with ketamine-xylazine exhibited a unitary state of large amplitude, slow oscillatory activity resembling NREM sleep. Isoflurane and pentobarbital evoked a burst-suppression pattern of activity, reminiscent of activity observed in coma patients. Activity under urethane resembled the activity observed in natural sleep, with cyclic and spontaneous alternations between an activated state of low-voltage fast cortical activity concomitant with theta (~ 4 Hz) in the hippocampus, and a deactivated state of large-amplitude, slow oscillations (~ 1 Hz) in both the cortex and hippocampus. **Conclusions:** Archetypical natural sleep activity consists of spontaneous alternations between activated and deactivated EEG states, known as REM and non-REM sleep, respectively. These alternations have been implicated in many critical physiological functions, such as modulation of respiratory activity during sleep, changes in heart rate, as well as higher order neural functions such as learning and memory consolidation. Currently, our data suggests that only urethane robustly exhibits the full spectrum of EEG activity observed in natural sleep in terms of components, dynamics and time frame. Subsequently, urethane is the most viable experimental anaesthetic model for natural sleep we have assessed at present.

**Disclosures: R. Ward-Flanagan:** None. **A.S. Lo:** None. **M. Sobey:** None. **C.T. Dickson:** None.

**Poster**

**779. Sleep Systems**

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**Program #/Poster #:** 779.08/DDD20

**Topic:** F.08. Biological Rhythms and Sleep

**Support:** NIH DP1MH103908
Keck Foundation I160621
Brain Research Foundation SIA grant

**Title:** Capturing general-anesthesia-activated neurons in hypothalamus

**Authors: *L. JIANGXIE**, L. YIN*, S. ZHAO, B.-X. HAN, K. DZIRASA, F. WANG
Neurobio., Duke Univ., Durham, NC

**Abstract:** * L. J & L. Y contribute equally
Each year, millions of surgical patients undergo general anesthesia (GA), a procedure that induces a brain state characterized by unconsciousness, analgesia, amnesia, and immobility while maintains vital physiological functions. However, despite the wide medical usage and the 170-year history, the underlying neurobiology of GA remains largely a mystery in neuroscience and medicine. We hypothesize that GA exerts its functions in part through neurons strongly activated by GA. Using activity markers and in vivo multi-channel extracellular recording, we discovered a specific population of neurons around the supra-optic region of hypothalamus that are persistently activated under GA. These anesthesia-activated neurons (AANs) start to fire before GA-induced loss of consciousness and cease firing before animals' emergence from anesthesia. Molecular profiling revealed that these hypothalamic AANs consist of mainly a core of pure peptidergic populations (Vasopressin and Dynorphin) and scattered inhibitory as well as excitatory cells. Utilizing the Capturing Activated Neuronal Ensemble (CANE) technology, we were able to precisely characterize and manipulate AANs. Patch-clamp recording experiemnts revealed that both volatile and injectable anesthetics, as well as sedative can all activate these AANs. We also mapped the axonal projections of AANs throughout the brain. Finally, we selectively expressed the chemogenetics actuator (hM3Dq) in AANs with CANE. Artificial activation of AANs drastically increased the total duration of slow-wave sleep (SWS), mainly through extending the duration of each sleep-bout. Detailed spectrogram analysis showed that AAN-induced sleep shared large similarities with the natural SWS. Very interestingly, we discovered that activation of the vasopressin and dynorphin neurons only within AANs also promoted SWS. Taken together, these results discovered a previously unexpected neural substrate mediating GA-induced unconscious state and natural deep sleep, and represent a transformative step toward unveiling the mystery of GA.

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**Poster**

**779. Sleep Systems**

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**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 779.09/DDD21

**Topic:** F.08. Biological Rhythms and Sleep

**Title:** Electroencephalographic analysis of the Sleepy ($sik3^{slp/+}$, $sik3^{slp/slp}$) mutant mice using the envelope characterization space

**Authors: *J. DIAZ**[1], K. E. VOGT[1], H. FUNATO[1], J.-C. LETELIER[2], M. YANAGISAWA[1]
[1]WPI-IIIS, Univ. of Tsukuba, Tsukuba, Japan; [2]Univ. of Chile, Santiago, Chile

**Abstract:** We recently reported mutant mice with significant sleep/wake abnormalities, obtained through a large-scale EEG/EMG screening of randomly mutagenenized cohort (1). One of these mutants, named *Sleepy*, bearing a splicing mutation on the *sik3* gene (with exon 13 skipping), exhibits increased daily amounts of non-REM sleep with a constitutively elevated sleep need and EEG delta power during non-REM sleep. The molecular pathway for the regulation of sleep in which *sik3* takes part is yet to be determined. The EEG envelope characterization space (analysis based on the signal envelope properties) can provide valuable information about the underlying dynamics of the neuronal ensembles contributing to EEG (2). This analysis reveals that delta waves during non-REM sleep markedly differ from the behavior of rhythmic waves, showing instead clear Gaussian properties. Considering these results, delta waves can be modeled as emerging from the superposition of EEG transients, i.e., phasic activity. In the present study, unique EEG features of *Sleepy* mutants were explored under the light of the envelope characterization space. In this parameter space, the abnormal properties of the mutant's EEG patterns are evident at a glance, either by visual inspection or automated analyses. We found that the high-amplitude non-REM delta waves characteristic of the *Sleepy* mutant are associated with an increased phasic activity in delta, theta and sigma bands. Remarkably, this augmented phasic activity is more pronounced in theta and sigma bands. These results are compatible with the hypothesis of a superposition of transient activity with broadband spectral consequences, originating from a colored spectrum as previously proposed (2), but implies different amplitudes and different temporal properties characterizing the EEG transients in the *Sleepy* mutant as compared with wildtype mice. Taken together, these results help to further characterize the sleep abnormalities induced by the *sik3* mutation. (1) doi:10.1038/nature20142 (2) doi:10.1016/j.neuroimage.2018.01.063

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**Poster**

**779. Sleep Systems**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 779.10/DDD22

**Topic:** F.08. Biological Rhythms and Sleep

**Support:** NIH Grant R01HL133847
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**Title:** The catecholaminergic innervation of hypoglossal motoneurons originating from medullary A1C1 neurons tends to be impaired in aging mice

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**Abstract:** In obstructive sleep apnea (OSA) patients, the activation of genioglossus (GG) muscle that is innervated by hypoglossal (XII) motoneurons plays a key role in the maintenance of upper airway patency. The brainstem catecholaminergic (CA) neurons provide excitatory input to XII motoneurons and contribute to the state-dependent activity of GG muscle activity across sleep-wake states. Since the prevalence of OSA is increased in elderly, we sought to investigate a possibility that the innervation of XII motoneurons by A1/C1 CA neurons may be compromised in older mice. In this exploratory study, we used transgenic middle-aged mice (age: 12 months), in which Cre-recombinase is selectively expressed in CA neurons under the dopamine-beta hydroxylase promoter. Three mice received unilateral injections (50 nl) of an adeno-associated viral (AAV) vector that delivers DNA of Cre-dependent channel rhodopsin tagged with the red fluorescent protein mCherry (AAV8-EF1a-DIOhChR2(H134R)-mCherry) into A1/C1 region at the level caudal to the obex where the ratio of A1 noradrenergic to adrenergic C1 neurons is relatively large. In 26 days, following the AAV injections, animals were perfused and brainstem sections were processed for tyrosine-hydroxylase (TH) immunohistochemistry. On average, 62% of mCherry-positive A1/C1 neurons that were transfected by the AAV injections were also TH-positive. The highest density of mCherry-positive fibers and terminals were found in the caudal medullary intermediate reticular (IRt) region, the dorsal motor nucleus of the vagus, as well as laterally and dorsally to the XII nucleus (all projections were ipsilateral to the injection site). However, only few anterogradely labeled fibers were found in both ipsi- and contralateral XII nuclei. The very sparse innervation of XII motoneurons by A1/C1 neurons found in this study contrasted with our previous findings in younger mice, in which more robust A1/C1-emanated innervation of XII motoneurons has been found (Rukhadze & Fuller, 2015). The outcomes of this exploratory study suggest that CA innervation of XII motoneurons originating from the A1/C1 neurons may be impaired in aging mice.

**Disclosures: I. Rukhadze:** None. **A. Gvritishvili:** None. **V.B. Fenik:** None.

**Poster**

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**Program #/Poster #:** 779.11/DDD23

**Topic:** F.08. Biological Rhythms and Sleep

**Title:** Neuromodulation through breathing control

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**Abstract:** It has recently been proposed that breathing can act as an organizing hierarchical principle for neuronal oscillations throughout the brain (Herrero et al, 2018; Tort et al., 2018). Here, we directly test breathing control as a natural means of neuromodulation. While brain states can influence breathing patterns (e.g. high anxiety states inducing fast breathing), the opposite possibility has attracted a great deal of interest (e.g. slow breathing inducing calm states). We test the idea that voluntary changes in breathing (e.g., deep-slow breathing) can influence neuronal excitability and rapidly induce different brain states. Simultaneous recordings of respiratory and intracranial-EEG (iEEG) signals were conducted in patients with intractable epilepsy during natural breathing (NB) and during breath-control. Breath-control conditions included deep-slow breathing (DSB), breath holding (HB), and fast breathing (FB). Electrode sampling was extensive with cortical and limbic areas, including pre-motor, frontal, insular, and cingulate cortices, as well as the hippocampus and amygdala. We used lagged-coherence measures to determine changes in synchrony between the respiratory and iEEG signals (iEEG-Breath coherence) as well as between the different brain areas (iEEG-iEEG coherence) across different breathing conditions. We found that during natural breathing, iEEG-Breath coherence was strong in ~30% of the electrodes recorded from widely distributed limbic and cortical sites. During breath-control, we found strong iEEG-Breath coherence lags (e.g., neural activity preceding the inhalation peak) in prefrontal cortical sites. These changes in oscillatory phase were accompanied by concomitant increases in iEEG-iEEG coherence between frontal-insular-cingulate networks. These results support the view that breathing can act as an organizing hierarchical principle for neuronal oscillations throughout the brain. Our results show that breath-control can be used as a natural means of neuromodulation suggesting the *breath as a powerful remote control* to the brain.

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**Poster**

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**Topic:** F.08. Biological Rhythms and Sleep

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**Title:** Is cataplexy a dissociated state of paradoxical (REM) sleep? Role of the glutamatergic neurons of the sublaterodorsal nucleus in a mouse model of narcolepsy type 1

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**Abstract:** Narcolepsy type 1 is a chronic neurologic disorder characterized by an excessive daytime sleepiness and episodes of cataplexy. Cataplexy is characterized by a bilateral loss of muscle tone during wakefulness, and triggered by a strong and generally positive emotion, without loss of conciousness. This symptom has long been described as a REM sleep dissociated state because the muscle atonia phenotype observed during cataplexy ressembles the caracteristic mucle atonia of REM sleep. This supposes that a common neuronal network underlies REM sleep and cataplexy muscle atonia, however it has never been demonstrated.
To test this hypothesis, we abolished the glutamatergic transmission in the sublaterodorsal tegmentum nucleus (SLD) -responsible for REM Sleep atonia (Garcia Valencia et al, 2016)- in narcoleptic Orex-KO mice, using short-hairpin RNA method (shRNA) directed against the vesicular transporter 2 of glutamate. Mice were injected with the experimental (shGLUT; n=9) or control (shCtrl; n=5) AAV, locally in the SLD and implanted for EEG and EMG recordings. At 8 weeks post-injection, a time necessary to ensure for an efficient blockage of the neurotransmission, mice underwent 48h of baseline recordings followed by a protocol of cataplexy induction with chocolate. As expected, blockage of the SLD glutamatergic transmission induced REM sleep without atonia in shGlut mice. However, cataplexy was not suppressed nor reduced in its total amount or bouts number, in shGLUT mice compare to shCtrl, and this during baseline condition or after cataplexy-induced protocols (Mann Whitney, p=0.82). To conclude, our data indicate that, in contrast to REM sleep, cataplexy expression does not rely on the activation of glutamate SLD neurons. The neuronal network recruted during cataplexy still needs to be discovered. Further, our data suggest that cataplexy is not a dissociated state of REM sleep into wakfulness.

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**Poster**

**779. Sleep Systems**

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**Program #/Poster #:** 779.13/EEE1

**Topic:** F.08. Biological Rhythms and Sleep

**Support:** NIH Grant R01AG047671

**Title:** Optical interrogation of arousal circuits in aged mice

**Authors: *S.-B. LI**, L. DE LECEA
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**Abstract:** Aging is associated with alteration in sleep architecture, fragmentation, which usually causes non-restorative sleep and it has been reported that the ability to sustain sleep/wake states is reduced in mice during aging. Earlier work from our lab has shown optogenetic stimulations of lateral hypothalamus hypocretinergic (LH-Hcrt) neurons and/or locus coeruleus noradrenergic (LC-NA) neurons are able to trigger sleep-to-wake transitions from either NREM or REM sleep in young adult mice. However, whether the ability of these brain nuclei in switching the brain from sleep-to-wake remains intact in aged mice was unknown. Here, we used transgenic mice combined with viral tools and optical methods to study the functional difference of LH-Hcrt neurons and LC-NA neurons in gating sleep-to-wake transitions and maintenance of wakefulness in both young (3-5 month) and aged mice (18-22 month). To determine whether intrinsic activities of these brain nuclei change during aging, we delivered viruses expressing Cre-dependent GCaMP6f to the LH and LC. We found the general patterns during sleep-to-wake transitions are similar between young and aged mice, but an overall reduction of the GCaMP6f signal amplitude in aged mice. LH-Hcrt neurons in both young and aged mice are quiescent during NREM and REM sleep. LH-Hcrt neural activity increase when the mice switch from NREM/REM sleep to sustained wakefulness or brief arousal; in contrast, activity decreases when mice switch from wakefulness to NREM sleep. LC-NA neurons have a similar pattern of neural activity compared with LH-Hcrt neurons between behavioral state transitions. To determine whether the functional ability of these brain arousal nuclei to elicit sleep-to-wake transitions is preserved during aging we delivered viruses encoding ChR2 for optogenetic manipulation of LH-Hcrt and LC-NA neurons in young and aged mice. We found that optogenetic stimulations elicit longer wake bouts in aged mice compared with young animals. We propose a lowered threshold for wakefulness promoting brain nuclei in gating sleep-to-wake transitions in aged mice, which typically have a more fragmented sleep architecture. This model may help us to better understand sleep disorders associated with aging and neurodegenerative disorders.

**Disclosures: S. Li:** None. **L. de Lecea:** None.

**Poster**

**779. Sleep Systems**

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**Topic:** F.08. Biological Rhythms and Sleep

**Support:** NS085477
HL095491

**Title:** GABAergic neurons in the median preoptic area modulate the wake-sleep cycle but not inflammatory fever

**Authors: *N. L. MACHADO**, C. B. SAPER
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**Abstract:** Background/Aims: GABAergic neurons in the median preoptic area (MnPO $^{GABA}$) are thought to be critical in the modulation of wake-sleep cycle and they have been shown to increase their neuronal activation after sleep disruption. A population of MnPO$^{GABA}$ have also been implicated in regulation of body temperature (Tc) and mediate inflammatory fever through neurons co-expressing prostaglandin receptors (EP3). However, it remains unknown if MnPO$^{GABA}$ neurons directly modulate wake-sleep homeostasis and thermoregulatory responses. In this study we investigate the effects of activation and ablation of MnPO$^{GABA}$ neurons in wake-sleep, Tc, and fever induced by lipopolysaccharide (LPS). Methods and Results: In our first series of experiments, anesthetized Vgat-IRES-cre mice (n=10) were stereotaxically injected with AAV8-hSyn-DIO-hM3D(Gq)-mCherry (DREADD) in the MnPO. Two weeks after injection, all mice were implanted with four skull screws attached to 6-pin connector for electroencephalographic (EEG) and two flexible electrodes for electromyographic (EMG) recordings. Telemetric transmitters were implanted in the peritoneal cavity to measure Tc. Following at least two weeks, we administered CNO (hM3Dq ligand), to activate MnPO$^{GABA}$ neurons, or saline as control. We found that treatment with CNO reduced time spent wake (61.9% ± 4.6 CNO vs. 87.6% ± 2.9 saline) and increased NREM sleep (37.7% ± 4.6 CNO vs. 20.7% ± 2.7 saline) but did not change REM sleep during the first hour of the dark period. Interestingly, activation of MnPO$^{GABA}$ neurons did not promote statistically significant changes in Tc of these mice (n=7). In a separate set of experiments, we injected AAV-mCherry-Flex-DTA (DTA) into MnPO of Vgat-cre (n=6) and wild type mice (WT, n=4). Following two weeks, mice were implanted with EEG, EMG and telemetric transmitters as described above. After recovery, we performed a sleep deprivation protocol (SD) using novel objects for 4 hours in the morning. Ablation of MnPO$^{GABA}$ neurons increased the latency for the first NREM episode after SD (16 ± 4.2min DTA vs 2.5 ± 1.9min WT), reduced time in NREM sleep (56.78% ± 4.9 DTA

vs. 72.1% ± 2.0 WT) and increased wakefulness (37.59% ± 5.6 DTA vs. 17.6% ± 0.8 WT) during the first three hours of sleep recovery. Following at least 48 hours, these same mice were treated with LPS (20µg/kg), and surprisingly, no difference in fever response was observed between the animals with ablated $MnPO^{GABA}$ neurons or WT. Conclusion: Our functional experiments suggest a direct role of $MnPO^{GABA}$ neurons in the modulation of wake-sleep homeostasis. However, our results also suggest that these neurons are not essential for regulation of Tc or fever induced by LPS.

**Disclosures: N.L. Machado:** None. **C.B. Saper:** None.

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**Program #/Poster #:** 779.15/EEE3

**Topic:** F.08. Biological Rhythms and Sleep

**Support:** NASA Grant NNX13AD94G

**Title:** Sleep and circadian homeostasis during long duration cephalic fluid shifts

**Authors: C. A. FULLER**[1], E. L. ROBINSON[1], T. M. HOBAN-HIGGINS[1], *P. M. FULLER[2]
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**Abstract:** Introduction: It has been proposed that at least one underlying role of sleep is to drive metabolite clearance from the adult brain via the glymphatic system. This study tested the hypothesis that changes to such metabolic clearance may alter sleep regulation or other nervous system homeostatic function. To simulate this physiological stimulus, this study used the well-established rat hind-limb suspension (HLS) model to investigate the hypothesis that a cephalic fluid shift, which results in a small chronic increase in intracranial pressure (ICP), could in turn lead to changes in sleep and circadian regulation. Methods: The HLS model was used to examine the relationship between ICP, sleep, body temperature and circadian rhythms. In this model, a tail-suspension apparatus suspends the animal in a ~30° head down orientation, producing a cephalic fluid shift mimicking that seen in the microgravity spaceflight environment. The forelimbs maintain contact with the floor and a pulley system allows the rat free access to all areas of the cage. The HLS model is the equivalent of human head down bed rest. Male Long Evans rats, 9 months of age at the start of the experiment, served as subjects for this project. Subjects were studied for 180 days, including 90 days of HLS followed by 90-days of post HLS recovery. An additional population of age-matched non-suspended animals acted as cage controls. All animals had *ad lib.* access to food and water. A 12:12 LD cycle was present. Biotelemetry (DSI) was used to record ICP, electroencephalogram (EEG), and body temperature ($T_b$). EEGs were sampled at 250 Hz, pre-filtered 0.1 to 64 Hz, and artifacts removed by detecting

peaks and troughs outside the normal EEG range. Delta EEG was obtained from 4-second FFTs binned between 0.5 and 4 Hz. Results and Conclusions: This duration of HLS was chosen to produce a chronic fluid shift. A sustained small increase in ICP was seen throughout the HLS exposure. EEG frequency domain power analysis demonstrated a reduction in delta power (0.5-4 Hz) indicating a decrease in slow wave sleep quality. Body temperature was mildly hypothermic with a 24-hr mean reduction of 0.5°C compared with baseline. Finally, the circadian rhythms of ICP, EEG and $T_b$ all exhibited reduced rhythm amplitudes, the phase of ICP rhythm was advanced and the phases of the EEG and $T_b$ rhythms delayed with respect to the LD cycle.

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**Program #/Poster #:** 779.16/EEE4

**Topic:** F.08. Biological Rhythms and Sleep

**Support:** Howard Hughes Medical Institute

**Title:** A midbrain-medullary pathway for non-rem sleep control

**Authors: *P. ZHONG**[1,2], Z. ZHANG[2], Z. BARGER[2], D. LIU[2], S. AN[2], Y. DAN[2]
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**Abstract:** The periaqueductal gray (PAG) in the midbrain is known to coordinate behavioral and autonomic responses to threat and injury through its descending projections to the brainstem. Here we show that a subpopulation of glutamatergic neurons in the ventrolateral PAG (vlPAG) powerfully promote non-REM (NREM) sleep through their projection to the caudal medulla. Optogenetic or chemogenetic activation of these vlPAG glutamatergic neurons strongly enhanced NREM sleep, whereas their inactivation increased wakefulness. Calcium imaging showed that they are preferentially active during NREM sleep. The NREM-promoting effect of these neurons is partly mediated by their projection to the caudal ventromedial medulla, where they excite GABAergic neurons. Bidirectional optogenetic and chemogenetic manipulations showed that the medullary GABAergic neurons also promote NREM sleep, likely through their innervation of multiple monoaminergic neuronal populations. Together, these findings reveal a novel pathway for NREM sleep generation, in which glutamatergic neurons drive broad GABAergic inhibition of multiple wake-promoting neuronal populations.

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**Program #/Poster #:** 779.17/EEE5

**Topic:** F.08. Biological Rhythms and Sleep

**Title:** A population of midbrain excitatory neurons control NREM sleep

**Authors: *Z. ZHANG**[1,2], P. ZHONG[1,2], F. HU[1,2], S. AN[1,2], Y. DAN[1,2]
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**Abstract:** Sleep is an essential behavioral state in all animals. The neuronal populations and circuits controlling sleep are not yet well understood. Studies in past decades have revealed a number of inhibitory neuronal populations regulating the onset and maintenance of sleep. However, a long-standing question is whether there are excitatory neurons upstream of these inhibitory circuits that regulate sleep. Here, we performed a comprehensive screening of sleep-related neurons using a Targeted Recombination in Active Populations (TRAP) mouse line combined with transcriptome analysis. We identified a novel population of excitatory neurons in the periaqueductal gray region, which are evidently activated during recovery sleep. Combining optogenetics, chemogenetics and virus-mediated circuit tracing techniques, we confirm an essential role of these neurons in promoting NREM sleep.

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University of Tsukuba Special Fellowship from Ministry of Education, Culture, Sports Science and Technology-Japan

**Title:** Cortical neuronal communication during natural slow wave sleep in mice

**Authors: *S. MATSUMOTO**[1,2], K. OHYAMA[2,3], J. DIAZ[2], K. E. VOGT[2]
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**Abstract:** One third of our life is spent sleeping. However, the precise mechanisms and physiological functions of sleep haven't been fully elucidated. The amplitude and power of slow wave activity (SWA) during slow wave sleep (SWS), recorded from electroencephalograms (EEG) is a key indicator of sleep homeostasis and therefore it likely has a central role in sleep. SWA is a consequence of synchronized activity of cortical neurons. It reflects their high participation in alternating shifts between a hyperpolarized (DOWN) and a depolarized (UP) membrane potential. Synchronization of this activity can be observed over large areas of the cortex (Destexhe et al., 1999; Vyazovskiy, et al., 2009). These phenomena raise the question of how those neurons achieve the wide spread synchronization after we fall asleep. It was reported that the SWA is a traveling wave (Massimini, et al., 2004), suggesting that SWA synchronization propagates through cortical network interactions. In addition, the modulation of the cortical connectivity is considered to be dependent on the brain state (Poulet &Petersen, 2008; Olcese et al, 2016; Massimini et al., 2017). It is also considered that cortical neurons loose reactivity compared to waking and as a result they tend to behave as isolated modules (Massimini et al., 2012; Olcese, et al., 2016). However, the precise mechanism of how the reactivity is modulated is still unclear. The studies about cortical neurons' behavior during SWA (Sachdev et al., 2004; González-Rueda et al., 2018) have been done mainly under anesthesia. There are several technical difficulties in looking at the neuronal activity in detail for a long time during natural sleep. Here we established local field potential (LFP) and multi-unit recordings coupled with cortical stimulation using optogenetics to investigate cortical communication during natural waking and sleep. Channelrhodopsin 2 expression and laser stimulation were performed unilaterally to somatosensory cortex, and the signals were recorded from primary motor cortex of both hemispheres. We found that the light-evoked potential in both ipsilateral and contralateral side to the stimulation grow stronger during SWS. This data suggest that in this state the cortical neurons are more responsive to the input. More unit activities were also recorded as a response to the stimulation during SWS suggesting that the response signals involve a higher number of neurons' activation. Moreover, this high responsiveness correlates with spontaneous delta power which is the main component of SWA, suggesting that the cortical responsiveness modulation is related to the sleep need.

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**Topic:** E.05. Brain-Machine Interface

**Support:** VA 1I01RX001640-01A1
NIH K02NS093014

**Title:** Closed-loop inhibition of spiking activity during slow oscillations and effects on spindles

**Authors: *J. K. KIM**[1,2], T. GULATI[1,2], K. GANGULY[1,2]
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**Abstract:** Previous studies have suggested that both slow-wave oscillations and spindles during sleep may mediate offline behavioral gains in motor performance. Gulati et al. (2017) previously proposed that spiking activity triggered by slow oscillations "up-state" during sleep is required for neuroprosthetic memory consolidation, by using closed-loop optogenetic methods. With these findings, we hypothesized that modulation of spiking activity during certain phases of slow oscillations could affect spindles and result in performance change of task learning, and thus spindle activity nested to slow oscillations may contribute to consolidation after learning. Here we tested this hypothesis by recording populations of neurons in the primary motor cortex of rats while they were trained on a brain machine interface (BMI) task and subsequent sleep. Using closed-loop optogenetic interventions triggered by phases of up- or down-state of slow oscillations, we investigated the effect of phase-specific inhibitions on the time coupling between slow oscillations and spindles. Although the inhibitions during up-state had significant reductions on nesting magnitude of spindles to slow oscillations, those during down-state did not have distinct effects. We also examined the time-frequency representations during the spindles nested to slow oscillations, and found the substantial reductions of power in the spindle band (9-16 Hz) near the slow oscillation up-state, only with the inhibitions during up-state. These perturbed sleep-dependent effects in the inhibitions during up-state resulted in the worsening of performance, but not in the inhibitions during down-state and in the condition of no intervention. Thus, our results suggest that closed-loop modulation of spiking activity during up states may also have effects on spindles, in general, and on nesting of spindles to slow-oscillations, in specific. This provides additional support for the notion that nesting of spindles to slow oscillations are important for memory consolidation.

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**Topic:** F.08. Biological Rhythms and Sleep

**Support:** NIH Grant NR013693
NIH Grant HL131010

**Title:** Classifying obstructive sleep apnea based on 16 chemicals in eight brain regions: Machine learning applied to 2D spectroscopy

**Authors: *P. M. MACEY**[1], M. K. SARMA[2], A. P. AGUILA[1], A. SAUCEDO[2], R. AYSOLA[3], R. M. HARPER[4], M. A. THOMAS[2]
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**Abstract: Introduction:** Sex-specific CNS structural and functional deficits accompany obstructive sleep apnea (OSA), with resulting psychophysiological symptoms that lead to morbidity and early death. Brain chemical levels, including markers of metabolic activity, neurotransmitters, and cell structure, could help reveal both structural and functional neural deficits, and potential intervention targets. In a series of studies assessing 16 or more metabolites with magnetic resonance spectroscopy (MRS), OSA patients showed a complex pattern of altered levels of chemicals, some reflective of brain function (GABA, glutamate/Glu, taurine), structure (choline/Cho, creatine, inositols), glial activation (myo-inositol/mI), neural metabolism (N-Acetylaspartic acid/NAA), and oxidative stress (ascorbic acid, glutathione), with regional variations over the insula, midbrain, thalamus and putamen. The findings of 16 chemicals in 8 or more brain regions did not clearly identify key markers of OSA-specific processes. We sought to objectively determine the pattern of 16 chemical changes in 8 specific regions that provide optimal OSA-specific markers using machine learning procedures. **Methods:** We used 2D-MRS to assess neurochemicals in the left and right insula, midbrain, putamen and thalamus of 14 OSA patients (mean age±SD:54.6±10.6years; AHI:35.0±19.4;$SAO_2$min:83±7%), and 26 healthy controls (50.7±8.5years) using an accelerated four dimensional echo-planar J-resolved spectroscopic imaging. Metabolite ratios with respect to creatine peak were calculated using a prior knowledge fitting (ProFit) algorithm. Machine learning using a combination of simple classifiers (ensemble of decision trees with maximum two splits) was applied, with cross-validation against overfitting. We identified the brain regions and chemicals most frequently used to distinguish OSA from control. **Results:** The optimum model achieved a classification accuracy of 88.1% (all controls and 10 OSA correct), with 30 trees. Ten trees used the left thalamus, 9 the left insula, right midbrain and putamen, 7, the right thalamus, 4 left midbrain,

and 3 right insula and left putamen. Glu was used in 12 trees, followed by Cho in 10, and mI and NAA in 5. Sex was only in one tree, and GABA in two. **Conclusion:** OSA patients are distinguished from healthy subjects mainly by differing levels of Glu, choline, mI, and NAA, especially in the thalamus, left insula, and right midbrain and putamen. The findings confirm OSA-specific high levels of excitatory neurotransmitters and altered structure, including glia-related changes.

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**Poster**

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**Topic:** F.08. Biological Rhythms and Sleep

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**Title:** Neural characterization of sleep-wake regulatory network via simultaneous multi-site multi-modal measurements in freely-behaving animals

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**Abstract:** Sleep-wake regulation results from complex interactions among several widely spread nuclei in midbrain, pons, and hypothalamic areas. Dorsal Raphe (DR) in midbrain and pontine structures Pedunculo-Pontine Tegmentum (PPT) and LateroDorsal Tegmentum (LDT) are thought to be involved in regulation of wakefulness and rapid-eye-movement (REM) sleep, while the Ventrolateral Preoptic nucleus (VLPO) is implicated in initiating and maintaining non-REM (NREM) sleep (Datta 2007). More recently, further midbrain structures such as ventrolateral periaqueductal gray (vlPAG) as well as cell groups in ventral medulla (Webber 2015 & 2018) are proposed to contribute to sleep-wake regulation circuitry. Identification of the causality of the interactions among these nuclei and transition patterns in and out of sleep require simultaneous measurements from the nuclei involved with sufficient spatial and temporal resolution.
We have obtained long-term experimental single- and multi-unit measurements simultaneously from multiple of the putative hypothalamic and brainstem sleep-wake regulatory nuclei, along with cortical and hippocampal activity, in freely behaving rats. All physiological measurements

are acquired continuously within multi-day recording sessions with a head-mounted digitizing amplifier that includes a 3-axis accelerometer. The hippocampal and cortical recordings, along with head acceleration, are then used to classify state of vigilance (SOV) following the methods described in Sunderam 2007.
We report the first network analysis of the sleep-wake regulatory system derived from simultaneous measurements across multiple cell groups involved in sleep-wake regulation. We found that although the coarse-grained activity of the cell groups matches the patterns presented previously in head-fixed brief recordings from individual cell groups, the firing rates with respect to cortical and behavioral markers of state transitions differ in critical ways. These suggest particular underlying cell-group interactions among those expected, and pose a fundamental question about what holds the long-term memory of the system.
Datta S. et al. J Neurosci Biobehav Rev, 2007
Sunderam S. et al. J Neurosci Meth, 2007
Webber F. et al. Nature, 2015
Webber F. et al. Nat. Comm, 2018

**Disclosures: F. Bahari:** None. **M.W. Billard:** None. **C.M. Curay:** None. **J. Kimbugwe:** None. **K.D. Alloway:** None. **B.J. Gluckman:** None.

**Poster**

**780. Recent Advances in Sleep Systems**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 780.01/EEE10

**Topic:** F.08. Biological Rhythms and Sleep

**Support:** Independent personal foundings only

**Title:** De/multiplexing waves of open probability in the corpus callosum: Approach to the hard problem of consciousness from our 1984-1986 model

**Authors: *J. F. GOMEZ-MOLINA**
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**Abstract:** INTRODUCTION. The corpus callosum (CC) communicates both hemispheres. CC could play a role in synchronizing visual perceptions (Engel 1991; Gray et al. 1989). Never contralateral regions are exactly mirrors (Gazzaniga1998). Section of these fibers create independent networks and disrupt coordinated behavior and continuity of EEG signals. Fibers of CC are functionally impaired in schizophrenia (Dehaene 2014; Gomez and Lopera 1999). In my BS-Thesis (Gomez 1984-1986; Advisor: Ignacio Escobar Mejia, Postdoc NIH and a Pioneer in Colombia) I designed neurocircuits of interhemispheric communication based on a minimalistic model of synaptic coupling (McCulloch and Pits 1943; Caianiello 1961; Escobar 1961; Del

Castillo, Escobar 1972; Clark 1984) for general interactions. This allows me to explore robust and detail-independent mechanisms of optimization and sharing of the CC (multiplexors and synchronized oscillations for routing information of unilateral specializations). This also reduces the need to conduct invasive experiments. Here I see depolarizations in CC as "waves of open channel probability" (Gomez 1986-2018). METHODS. Neurocircuit designs. Python. RESULTS. Not evidence of clear oscillations in the CC does not imply that our multiplexing hypothesis should be rejected (Fig. 1). DISCUSSION. To test if a patient is conscious hyperscanning and mutual, virtual connection of hemispheres might be necessary. CONCLUSION. The hard problem is, operationally, the "other-mind problem". There are many paradoxes of continuity in having a divided mind electrically connected by the CC (disconnected cortical graphs). Sub-threshold and truly probabilistic electrical activity can challenge our classical notions of disconnected networks.The notion of waves of open probability is a conservative approach to the more uncertain continuity conditions borrowed from particle physics.

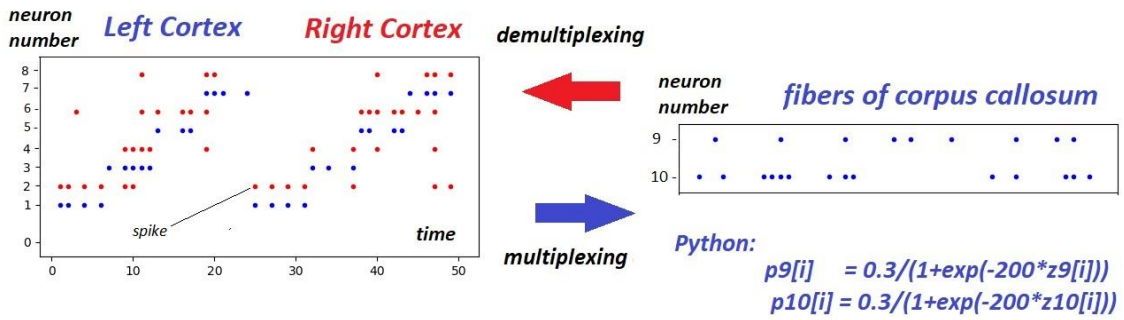


**Fig. 1.** Computer simulation using Python of a ***network of 12 neurons*** following a probabilistic design (Gomez 1986). The results are shown as raster plots of spikes of 10 neurons. The activities of 4 neurons in the left cortex (1, 3, 5, 7, blue dots) are ***multiplexed by 2 neurons (9, 10)*** that project to the right cortex. This activity is ***de-multiplexed in the right hemisphere*** for the corresponding neurons (2, 4, 6, 8, red dots). Oscillatory neurons (11, 12) at each hemisphere, synchronized between them and acting as clocks (not shown), are coordinating these processes. The simulation is implemented in Python in order to illustrate the mechanism.

**Disclosures:**

**Poster**

**780. Recent Advances in Sleep Systems**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 780.02/EEE11

**Topic:** F.08. Biological Rhythms and Sleep

**Support:** Deutsche Forschungsgemeinschaft
BCCN Munich

**Title:** Decoding spontaneous memory reprocessing during sleep in humans

**Authors: *M. SCHÖNAUER**[1], S. ALIZADEH[2], H. JAMALABADI[4], A. ABRAHAM[5], A. PAWLIZKI[5], S. GAIS[3]
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**Abstract:** Experiments in animals found that learning-related neuronal activity is replayed during sleep. This process is thought to stabilize new memories. Activity on the level of brain areas suggests similar reactivation in humans. Whether brain activity in human sleep actually reflects the specific content of previous learning episodes, however, remains unclear. To detect such material-specific memory reprocessing, we developed a multivariate pattern classification (MVPC) algorithm that can determine what type of images participants had viewed in a learning session based solely on brain activity during sleep. In our experiment, 32 subjects learned pictures of either faces or houses before an 8-h period of nighttime sleep during which brain activity was recorded with high-density EEG. We then employed MVPC methods to test whether electrical brain activity contains information specific to the previously learned material. We find significant patterns of learning-related processing in the EEG of rapid eye movement (REM) and non-REM (NREM) sleep, which are generalizable across subjects. This reprocessing occurs in a cyclic fashion during time windows congruous to critical periods of synaptic plasticity. Its spatial distribution over the scalp and frequency composition differ between NREM and REM sleep. Moreover, only the strength of reprocessing in slow-wave-sleep predicts later memory performance, speaking for at least two distinct underlying mechanisms in these states. We thus demonstrate that memory reprocessing occurs in both NREM and REM sleep in humans, and that it pertains to different aspects of memory consolidation.

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**Poster**

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**Topic:** F.08. Biological Rhythms and Sleep

**Support:** NIH Grant T90DA043219

**Title:** Excitable dynamics: A mechanism for hippocampal/neocortical function during NREM sleep

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**Abstract:** Neuronal dynamics during sleep (and thus sleep functions) rely on internally-generated events in neuronal populations. Interactions between two of these events - neocortical slow waves and hippocampal sharp wave-ripples (SWRs) - are important for the sleep-dependent consolidation of recently learned memories. Independently, each event has also been shown to perform homeostatic maintenance of the synaptic network in their respective structure. The mechanistic basis by which self-generated, self-organizing activity can perform these functions is unclear.
We report recent results showing that neocortical and hippocampal dynamics during NREM sleep are well matched by a model of excitable dynamics: each region rests in a stable state from which suprathreshold fluctuations can induce a transient population event. Specifically, the neocortex maintains a stable UP state with transitions to a transient DOWN state (slow waves) while the hippocampus is in a stable DOWN state with transitions to a transient UP state (SWRs). Each region can generate these events spontaneously (due to noisy fluctuations) or in response to an external perturbation (such as the complementary event in the other structure). Due to the predominant role of recurrent connections in maintaining activity, the dynamics of both SWR and slow waves are determined by the local network of recurrent connections. In the hippocampus, this results in the replay of recently-learned activity patterns during the SWR. In the neocortex, the result is a stereotyped activation sequence at the DOWN->UP transition following a slow wave. We outline a mechanistic framework by which spontaneous events in each region maintain the synaptic network, while their interaction acts to strengthen novel activity patterns. Together, our results indicate that the neocortex and hippocampus are in complementary excitable regimes during NREM sleep, which enable self-generated events in service of homeostatic function and effective exchange of information between the two regions in service of mnemonic function.

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**Topic:** F.08. Biological Rhythms and Sleep

**Support:** Sir Henry Dale Wellcome Fellowship
UCL Excellence Fellowship

**Title:** The temporal evolution of grid-place cell replay coordination

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**Abstract:** The hippocampus is at the centre of neural networks thought to support memory for places and events. Indeed, damage to the hippocampus is known to cause profound impairments to episodic and spatial memory. Place cells - the principal cell of the hippocampus - represent information about an animal's spatial location. Yet, during rest and awake quiescence place cells spontaneously recapitulate past trajectories ('replay'). Replay has been hypothesised to serve a variety of functions, such as spatial planning and systems consolidation - the stabilisation of a memory trace, likely through the maturation of a complementary cortical memory. An implication of the consolidation hypothesis is that hippocampal replay should lead to cortical replay - in previous work we described results consistent with this hypothesis. Namely, we showed CA1 place cells and grid cells from the deep medial entorhinal cortex (dMEC) - the main cortical output region of the hippocampus - replay coherently during periods of rest, with place cells leading grid cells[1]. Similarly, we also found robust place-grid cell replay coherence when animals were awake but had disengaged from their current task - notably such coherence was absent during periods of task engagement[2]. If grid-place cell replay coherence during offline states is a marker for consolidation, we can use it to study the dynamics of memory consolidation. For instance, the timescale of consolidation is not clear, and it is unknown whether memories ever fully de-couple from the hippocampus. We analysed grid-place cell replay coherence as animals became experienced with a simple spatial task - up to one week[1]. Preliminary data indicate after first exposure to the task, grid-place cell replay coherence was present but subtle. With increasing experience, coherence gradually increased. Thus, these results suggest consolidation may unfold over a period spanning at least a week and that the hippocampus continue to play a central role during this period.
1.Olafsdottir, H.F., Carpenter, F., and Barry, C. (2016). Coordinated grid and place cell replay during rest. Nat Neurosci 19, 792-794.2.Olafsdottir, H.F., Carpenter, F., and Barry, C. (2017). Task Demands Predict a Dynamic Switch in the Content of Awake Hippocampal Replay. Neuron 96, 925-935 e926.

**Disclosures: F. Olafsdottir:** None. **F. Carpenter:** None. **C. Barry:** None.

**Poster**

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**Topic:** F.08. Biological Rhythms and Sleep

**Support:** NIMH 60670

NIH T32 Systems Biology

**Title:** Abnormal locus coeruleus activity during sleep alters sleep signatures of memory consolidation and impairs place cell stability and spatial memory

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**Abstract:** Sleep is critical for proper memory consolidation. The locus coeruleus (LC) releases norepinephrine throughout the brain except when the LC falls silent throughout rapid eye movement (REM) sleep and prior to each sleep spindle during NREM sleep. We hypothesize that these transient LC silences allow the synaptic plasticity necessary to incorporate new information into preexisting memory circuits. We found that spontaneous LC activity within sleep spindles in the rat triggers a decrease in spindle power. By optogenetically stimulating norepinephrine-containing LC neurons during sleep at 2 Hz, we reduced CA1 spindle density and decreased REM theta power without causing arousals or changing sleep amounts. Stimulating the LC during sleep following a hippocampus-dependent food location learning task interfered with consolidation of newly learned locations, and reconsolidation of previous locations. The LC stimulation-induced reduction in sleep spindles and REM theta, and a reduced in ripple-spindle coupling all correlated with decreased hippocampus-dependent performance on the reversal task. Thus periods of LC silence in sleep are necessary for consolidation of hippocampus dependent memory that requires a change to pre-existing memory circuits.

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**Program #/Poster #:** 780.06/EEE15

**Topic:** F.08. Biological Rhythms and Sleep

**Title:** Activity-dependent downscaling of subthreshold synaptic inputs during slow-wave-sleep-like activity *in vivo*

**Authors: *A. GONZÁLEZ-RUEDA**[1,2], V. PEDROSA[3], R. FEORD[2], C. CLOPATH[3], O. PAULSEN[2]
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**Abstract:** Activity-dependent synaptic plasticity is critical for cortical circuit refinement. The synaptic homeostasis hypothesis suggests that synaptic connections are strengthened during wake and downscaled during sleep; however, it is not obvious how the same plas- ticity rules could explain both outcomes. Using whole-cell recordings and optogenetic stimulation of presynaptic input in urethane-anesthetized mice, which exhibit slow-wave-sleep (SWS)-like activity, we show that synaptic plasticity rules are gated by cortical dynamics in vivo. While Down states support conventional spike timing-dependent plasticity, Up states are biased toward depression such that pre- synaptic stimulation alone leads to synaptic depression, while connections contributing to postsynaptic spiking are protected against this synaptic weak- ening. We find that this novel activity-dependent and input-specific downscaling mechanism has two important computational advantages: (1) improved signal-to-noise ratio, and (2) preservation of previ- ously stored information. Thus, these synaptic plas- ticity rules provide an attractive mechanism for SWS-related synaptic downscaling and circuit refinement.

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**Poster**

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**Topic:** F.08. Biological Rhythms and Sleep

**Support:** NIH F31-MH100958
BCS-1461088

**Title:** Sleep spindle refractoriness segregates periods of memory reactivation

**Authors: *J. W. ANTONY**[1], L. PILOTO[1], M. WANG[1], P. PACHECO[1], K. A. NORMAN[1], K. A. PALLER[2]
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**Abstract:** Newly formed hippocampal memory traces become reactivated during sleep, suggesting sleep plays an active role in long-term memory stability. Memory reactivation can be induced during post-learning sleep by presenting stimuli that had previously been associated with learning in a method termed targeted memory reactivation (TMR). In two experiments, participants learned unique sound-picture pairs followed by unique locations for those pictures against a background grid. Next, they took a pre-nap location test and napped in the lab. During slow-wave sleep, half of the sounds were softly and repeatedly presented. At a post-nap test, cueing benefited memory. Moreover, sleep spindles — bursts of 11-16 Hz

electroencephalographic activity thought to contribute to memory processing — increased shortly after presenting TMR sound cues and predicted later memory retention. However, spindles occurring shortly before (< 2.5 s) TMR cues prevented the TMR-related spindle increase and pre-cue sigma (spindle band) power negatively predicted later memory retention. This result likely occurs because of the spindle refractoriness, which produces a rhythmicity of 3-6 seconds between successive spindles. We leveraged this rhythmicity to test the role of spindles in memory by using real-time spindle tracking to present cues within versus just after the presumptive refractory period; as predicted, cues presented just after the refractory period led to better memory. Our findings demonstrate a precise temporal link between sleep spindles and memory reactivation. Moreover, they reveal a previously undescribed neural mechanism whereby spindles may segment sleep into two distinct substates: prime opportunities for reactivation and gaps that segregate reactivation events.

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**Poster**

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VA Senior Research Career Scientist Award

**Title:** Hippocampal contributions to sleep-dependent consolidation of non-hippocampal motor sequence learning

**Authors: *A. C. SCHAPIRO**[1], A. G. REID[2], A. MORGAN[1], D. S. MANOACH[3], M. VERFAELLIE[2], R. STICKGOLD[1]
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**Abstract:** During sleep, the hippocampus plays an active role in consolidating memories that depend on the hippocampus for initial encoding. Puzzlingly, sleep spindles, which are associated with active hippocampal consolidation during sleep, correlate with the consolidation of memory in the motor sequence task (MST), a type of memory that seems unlikely to depend on the

hippocampus. Relatedly, hippocampal activity during MST performance has been found to predict overnight consolidation. This set of findings raises the possibility that hippocampal activity during MST learning, while not critical for the initial learning, sets the stage for later hippocampally dependent processing during sleep. We tested this hypothesis by evaluating learning and consolidation of the MST in 8 medial temporal lobe amnesics and 12 age-matched control participants. During the MST, participants type a 5-digit sequence (e.g. 41324) with their left hand as quickly and accurately as they can for 12 trials of 30s interspersed with 30s breaks. Participants took part in two sessions approximately 24 hours apart. Two control participants and four patients were excluded in consolidation analyses for failure to reach a learning criterion during training. The groups did not reliably differ in percent improvement over the course of the first session, with or without the excluded participants. This finding confirms that the hippocampus is not necessary for initial acquisition of the motor sequence. To assess consolidation, we compared performance on the first three trials of the second session to the last three of the first. While controls showed no change from the first to second session, patients showed a marginal deterioration and were significantly worse than controls. These results suggest that the hippocampus contributes to the consolidation of memory for a motor sequence despite not being necessary for its initial learning. Thus, the hippocampus may play a broader role in coordinating sleep-dependent memory consolidation than has previously been assumed.

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**Poster**

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**Topic:** F.08. Biological Rhythms and Sleep

**Support:** MURI N000141310672

**Title:** Hippocampal sharp-wave ripples in human NREM sleep are associated with cortical high gamma motifs and up-state sequences

**Authors: *X. JIANG**[1], I. SHAMIE[1], W. DOYLE[2], D. FRIEDMAN[2], P. DUGAN[2], O. DEVINSKY[2], E. N. ESKANDAR[3], S. S. CASH[4], J. GONZALEZ-MARTINEZ[5], E. HALGREN[1]
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**Abstract:** In NREM sleep, consolidation of declarative memory depends on the hippocampus and hippocampal sharp-wave ripples (SWRs), which allow the formation of stable cortical

representations over time. Previous studies indicate that cortical spatio-temporal activity patterns in waking may be recapitulated in NREM sleep. However, no intracranial electrophysiological evidence for replay exists in humans. Using high gamma power from human intracranial recordings as an index of neural population firing, we identified consistent sequences of neural activity peaks across widespread cortical regions during waking; these "motifs" were more similar to the high gamma activity patterns in sleeps following than sleeps preceding the waking periods where the motifs were identified. We also found that both cortical motifs and hippocampal SWRs were coupled to cortical spindles, and that widespread up-states in the cortex occurred after SWRs. We therefore hypothesized that up-state sequences following SWRs in NREM would preferentially match cortical motifs in the preceding waking period, thereby associating human cortical replay with known signatures of hippocampal replay.

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**Poster**

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**Title:** Cholinergic and nonadrenal control of memory consolidation across sleep-wake states

**Authors: *J. P. ROACH**[1,2], N. OGNJANOVSKI[3], S. J. ATON[3], L. M. SANDER[4], M. R. ZOCHOWSKI[5]
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**Abstract:** A prominent neurochemical marker of arousal state is the level of acetylcholine (ACh) and norepinephrine (NE) release within the brain. NE is released in its highest level during wakefulness and is low in both REM and NREM sleep. The highest level of ACh is seen during wakefulness, during NREM sleep ACh is at its lowest, while in REM, ACh release is at a

moderate level. Here we show that dynamic changes in both ACh and NE levels that are associated with arousal state control informational processing functions of networks though its effects on the degree of spike-frequency adaptation (SFA; an activity dependent decrease in excitability) displayed by neurons and through gating of the LTP (NE) and LTD (ACh) components of spike timing-dependent plasticity (STDP). Using a simple biophysical model which includes a slow decreases of cholinergic tone (which increases SFA) shifts the network activity from a stable high frequency pattern to a traveling wave of activity like that of SWS. The high ACh stable activity pattern can be localized to regions of the network with enhanced recurrent excitatory synapses (spatial attractors) and are highly sensitive to even slight increases in synaptic strength. The transition from stable to traveling dynamics occurs in conjunction with a decrease in sensitivity to spatial attractors. Additionally, we show that in networks with multiple encoded attractors that the changing the level of ACh allows for selective localization of network activity based on the strength of encoding synapses. During periods of wakefulness (high ACh, high NE) levels weakly encoded attractors can be stably activated and reinforced through STDP. During NREM (low ACh, low NE) traveling wave dynamics allow for connections between initially non-overlapping spatial attractors to form. During REM (high ACh, low NE) spatial attractors are destabilized. Importantly REM and NREM work in concert to form sequential ensemble memories out of multiple spatial attractors and the cyclic nature of sleep architecture is critical of this. Our model makes quantifiable predictions about how network dynamics change during sleep, notably that the both LFP oscillations and spiking patterns become more similar between REM and NREM late in sleep and that the peak frequency in the delta (0.5 - 4 Hz) oscillation will shift higher in late NREM sleep. This work provides a mechanistic insight into the role of dynamic changes in neuromodulation is sleep-dependent memory consolidation.

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**Poster**

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**Topic:** F.08. Biological Rhythms and Sleep

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DGA Doctoral Thesis

**Title:** The sleeping brain tracks informative speech in a multi-talker environment

**Authors: *M. KOROMA**[1], T. ANDRILLON[4], G. LEGENDRE[2], C. LACAUX[2], S. KOUIDER[3]
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Supérieure, Paris, France; [4]Lab. de Sci. Cognitives et Psycholinguistique (ENS, EHESS, CNRS), Ecole Normale Superieure, Paris, France

**Abstract:** Aim : Even while asleep, the brain continues to process external auditory information and this ability depends on variables such as sleep depth and the relevance of external stimuli (eg. one's own name). These results have been restricted so far to isolated stimulations and the question whether the sleeping brain can dynamically track auditory streams and select relevant information remains unexplored. To study the brain's auditory processing of a complex auditory scene during sleep, we designed a cocktail party experiment in which subjects were asked to attend to one of two auditory streams which were played simultaneously in each ear (ie dichotically).
Methods : The stream to attend was composed of French stories (« Real speech »), while the stream to ignore consisted of the same set of stories from which meaningful words were replaced by French pseudo-words (« Jabberwocky »). Subjects transitioned from wakefulness to sleep during afternoon (Experiment 1) or morning naps (Experiment 2) while listening to pairs of real stories and Jabberwocky. Participants were instructed to maintain their attention to the meaningful speaker. Novel pairs of stimuli (i.e. never heard during wake) were played during sleep. We used electroencephalography and a linear decoding model to reconstruct the stimulus envelope from brain activity and determine whether :
(i) speech is encoded during sleep and its sub-stages
(ii) meaningful speech is selectively amplified
(iii) sleep macro- and microphysiology account for the encoding and selection of auditory information.
Results : We found that both Real and Jabberwocky speech were encoded with a selective amplification of Real speech during light NREM and REM sleep. An analysis locked to micro-evenements show that the selective amplification of Real speech during light sleep were consecutive to K-complexes and disappeared following spindles. Slow-waves were concurrent with a selective suppression of Real speech while leaving the Jabberwocky stream unaffected. REM were linked to a selective suppression of Real speech as well.
Conclusions : Overall, we found evidence for the selective processing of external information during light NREM and REM sleep stages with a strong dependance on the presence of EEG hallmarks. K-complexes appeared to promote the processing of meaningful stimuli whereas slow-waves and rapid-eye movements were associated to its selective suppression.

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**Poster**

**780. Recent Advances in Sleep Systems**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 780.12/EEE21

**Topic:** F.08. Biological Rhythms and Sleep

**Title:** REM sleep deprivation alters functional brain connectivity related to amygdala and hippocampus

**Authors: *T. IWANO**, K. KAIDA, K. NIKI
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**Abstract:** It is well known that sleep deprivation, including rapid eye movement (REM) and non-rapid eye movement (non-REM) sleep, deteriorates vigilance and memory encoding in human. At the same time, functional connectivity of human brain alters after total sleep deprivation compared to the full night sleep condition. While the deterioration comes from lack of non-REM sleep, the role of REM sleep on brain function at the following day has not been made clear. In the present study, we examined the effect of selective REM sleep deprivation (REMD) on functional connectivity in the brain using functional magnetic resonance imaging (fMRI) data. Thirteen healthy males (22.1 ± 1.93 years old) participated in both the REMD and control (Cont) conditions. In the REMD condition, participants were deprived REM sleep by 80dB auditory tones during sleep at sound attenuated sleep lab. The tones were presented as soon as the experimenters detected the signals of REM sleep on polysomnography (i.e., muscle atonia, rapid eye movements, consecutive theta brain waves). This REMD treatment deprived 80.4 ± 15.0 % of REM sleep out of total 8-hour time in bed. In the control (Cont) condition, participants slept without no intervention. Following the REMD and Cont sleeps, state functional connectivity in the brain was measured by fMRI (Ingenia 3.0T, Philips, Netherlands) and compared the data of Cont condition. The fMRI data was analyzed by CONN toolbox 17.f for SPM (http://www.nitrc.org/projects/conn). Significance level was set at cluster-size-pFDR < 0.05. As a result, we found that functional connectivity between left amygdala and parietal cortex significantly increased with the REMD than the Cont condition. The functional connectivity between left hippocampus and left parietal cortex, and between left hippocampus and left temporal cortex also increased in the REMD condition. Given that, the connectivity between amygdala and hippocampus is vulnerable brain areas to REMD. On the other hand, the changes of functional connectivity in other brain areas such as parietal and temporal cortex were not found after REMD. These results suggest that REMD would affect functional connectivity in brain areas related to amygdala and hippocampus.

**Disclosures: T. Iwano:** None. **K. Kaida:** None. **K. Niki:** None.

**Poster**

**780. Recent Advances in Sleep Systems**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 780.13/EEE22

**Topic:** F.08. Biological Rhythms and Sleep

**Support:** SFN 320030_179565/1

**Title:** Neural substrates of eye movement during REM-sleep

**Authors: *C. G. HERRERA**[1], F. GIRARD[2], A. BILELLA[3], A. BABALIAN[3], D. M. ROCCARO[3], A. R. ADAMANTIDIS[1], M. R. CELIO[3]
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**Abstract:** Rapid eye movements (REM) are characteristic of the eponymous phase of sleep. Wherefrom stem the motor commands that underlie them remains an enigma. Here, we report on the existence of a cluster of calbindin-D28K-expressing neurons (Calb+) in the *Nucleus papilio (NP, part of the* dorsal paragigantocellular nucleus) that is activated during REM-sleep, and projects to the three contralateral eye-muscle nuclei. This *NP*-Calb-expressing neuron cluster is phylogenetically conserved amongst rodents, cats, monkeys and humans. Following REM-sleep rebound after REM-sleep deprivation, a large proportion of the *NP*-Calb+ neurons expressed c-Fos, which suggest that they were active during REM-sleep. To further assess the influence of the *NP* on eye movements, the Calb+ neurons were subjected to optogenetic stimulation. An adeno-associated virus (AAV) encoding floxed Channelrhodopsin-2 was injected into the *NP* of *Calb1*-Cre mice. Optogenetic activation of the *NP*-Calb+ neurons consistently induced an increase in the percentage of time-locked eye movements (EM) during REM-sleep following the onset of 1s continuous stimulation (77.2.0 ± 3.4 % vs 21.8 ± 6.1 % in controls). Activation of the same neurons during non-REM-sleep or the waking state elicited no such effect. To assess the necessity of *NP*-Calb+ to generate the EM of REM-sleep, AAV-DIO-diphtheria-receptor (DTR) was infused together with AAV-DIO-ChR2 into the NP. Three days after injecting diphtheria-toxin (DTX) all Calb+ neurons were ablated and we found that the induction of eye movements was suppressed in response to the optogenetic activation, whereas the eye movements of the waking state were not impacted. Finally, AAV-DIO-ArchT3.0-EYFP was used to specifically silence the activity of the *NP*-Calb+ neurons. A significant reduction in the total number of eye movements during REM-sleep episodes was observed (4.4 ± 1.5 vs. 18.0 ± 1.1 in the controls), whereas during the waking state or non-REM-sleep EM remained unchanged. The EM of REM-sleep are thus an expression of the activity of neurons in a NP-based brainstem pacemaker, which complements other structures implicated in the generation of voluntary EM. These differences afford further evidence that the eye movements of the states of sleep and wakefulness are controlled by distinct mechanisms.

**Disclosures: C.G. Herrera:** None. **F. Girard:** None. **A. Bilella:** None. **A. Babalian:** None. **D.M. Roccaro:** None. **A.R. Adamantidis:** None. **M.R. Celio:** None.

**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 781.01/EEE23

**Topic:** F.10. Food Intake and Energy Balance

**Support:** R01 DK09613905

**Title:** Serotonergic modulation of the central glucagon-like peptide-1 system regulates energy balance and stress

**Authors: *R. M. LEON**[1], D. J. REINER[1], L. M. STEIN[1], B. C. DE JONGHE[2], M. R. HAYES[3]
[1]Neurosci., [2]Nursing, [3]Psychiatry, Univ. of Pennsylvania, Philadelphia, PA

**Abstract:** Glucagon-like peptide-1 (GLP-1) is an anorectic hormone, known for its role in regulating energy balance, stress, and motivated behaviors. GLP-1 receptor (GLP-1R) agonists are FDA-approved for obesity and type II diabetes treatment. While the field has gained an understanding of the downstream nuclei targeted by the central GLP-1 system, little is known about the common upstream neurobiological substrates functioning as endogenous activators of this system. Recent literature implicates the serotonergic system as a potential candidate. Serotonin (5-HT) and the central GLP-1 system - both key players in energy balance and stress - interact at the cellular/molecular level, however, the physiological/behavioral effects of this interaction remains largely unknown. We hypothesized that 5-HT acts as an endogenous modulator of the central GLP-1 system and normal satiation, as well as stress/malaise-induced hypophagia is controlled, at least is part, by 5-HT- activation of the central GLP-1 system. In rats, a hindbrain administration of 5-HT (40µg, 4th ICV) reduced chow intake and body weight and increased kaolin intake. Pretreatment with the GLP-1R antagonist, exendin-(9-39) (LV ICV) attenuated the 5-HT-induced anorectic effects at 3 and 24 hours and caused a complete reversal at 1 and 6 hours. Similarly, hindbrain administration with agonists for the 5-HT2C receptor (Lorcaserin, 20µg) or the 5-HT3 receptor (SR57227, 20µg) independently suppressed food intake; effects that were also reversed by exendin-(9-39). Lorcaserin suppressed food intake acutely (1 and 3 hours) with no effects on body weight or kaolin intake, whereas SR57227 induced a more extended intake suppression (1, 3, 6, and 24 hours), reduced body weight, and increased kaolin intake. These findings suggest a temporal and possible behavioral (anorectic vs. noxious mediated hypophagia) dissociation between the intake suppressive effects induced by different 5-HT receptor populations. This is supported by preliminary data in which a pre-treatment (4V ICV) with a 5-HT3 antagonist (Ondansetron) attenuated the intake suppressive effects of a systemic LiCl treatment (20mg/kg i.p.). Collectively, these data indicate that the interaction between 5-HT and central GLP-1 is relevant for the physiological effects on food

intake regulation and that the involvement of satiating and illness-like mechanisms might be receptor dependent.

**Disclosures: R.M. Leon:** None. **D.J. Reiner:** None. **L.M. Stein:** None. **B.C. De Jonghe:** None. **M.R. Hayes:** None.

**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 781.02/EEE24

**Topic:** F.10. Food Intake and Energy Balance

**Support:** CIHR PJT-153173

**Title:** Differential contribution of $Na^+$-$K^+$ATPase activity on the resting membrane potential of MCH and orexin neurons

**Authors: *L. FANG**, V. LINEHAN, M. HIRASAWA
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**Abstract:** Melanin-concentrating hormone (MCH) neurons and orexin (ORX) neurons are two lateral hypothalamic cell populations that are important regulators of energy homeostasis, the sleep-wake cycle, and reward. These neurons have distinct electrophysiological properties, and one of the most striking differences is the resting membrane potential (RMP). MCH neurons are significantly more hyperpolarized and less excitable at rest compared to ORX neurons. However, what underlies this difference is unknown.
The $Na^+$-$K^+$ ATPase (NKA) is an electrogenic transporter that establishes the electrochemical gradient of $Na^+$ and $K^+$ across the cell membrane. The NKA activity can hyperpolarize the membrane potential; however its contribution to the RMP of hypothalamic neurons, including MCH and ORX neurons is unknown. Thus, we tested the hypothesis that NKA activity underlies the differences in the RMP of these neurons.
To investigate this, we performed *in vitro* whole-cell patch clamp on acute hypothalamic slices from male Sprague Dawley rats. When the pipette solution contained a physiological level of Na+ (10 mM), MCH neurons displayed an RMP of -84.3 ± 2.6 mV, while ORX neurons rested at -56.3 ± 1.7 mV. Ouabain (25 μM), an NKA inhibitor, induced a significant depolarization of MCH neurons, while having minimal effects on ORX neurons. In contrast, when these cells were loaded with higher Na+ (40 mM) to drive NKA activity, ouabain had similar effects on both cell types. Additionally, a low concentration of ouabain (3 μM) had little effect on either cell, suggesting that the NKA consists of mainly the α1 isozyme, and not the α3 isozyme.
Furthermore, application of prostaglandin E2 (PGE2; 0.1 nM), a known modulator of the NKA, depolarized the RMP of MCH neurons but not ORX neurons, further supporting a role of NKA

in RMP of MCH neurons.
In conclusion, our study shows that both MCH and ORX neurons express predominantly the α1 isoform of NKA. The NKA activity significantly contributes to the RMP of MCH neurons, whereas minimally contributing to that of ORX neurons. These results provide fundamental insight on the intrinsic properties of MCH and ORX neurons, while also identifying a probable molecular target for modulation of MCH neuron activity through the NKA.

**Disclosures: L. Fang:** None. **V. Linehan:** None. **M. Hirasawa:** None.

**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 781.03/EEE25

**Topic:** F.10. Food Intake and Energy Balance

**Support:** NSERC

**Title:** Genetic disruption of adipose triglycerides lipase (ATGL) in mediobasal hypothalamic neurons induces overweight and metabolic disturbances

**Authors: *R. MANCEAU**[1], A. MACHUCA-PARRA[1], K. BOUYAKDAN[1], D. RODAROS[1], A. FISETTE[1], G. MITCHELL[2], S. FULTON[1], T. ALQUIER[1]
[1]Cardiometabolic, CRCHUM, Montreal, QC, Canada; [2]CHUSJ, Montréal, QC, Canada

**Abstract: Background:** Adipose Triglyceride Lipase (ATGL) acts as the first lipase in the hydrolysis of triglycerides (TG). Recent studies show that ATGL in peripheral tissues plays major roles on energy homeostasis. We found that ATGL is expressed in the mediobasal hypothalamus (MBH) and in hypothalamic neuronal cell lines, in line with our recent study suggesting that neurons accumulate TG. ATGL expression is increased in the MBH of high fat-fed mice that maintain a healthy body weight compared to mice that become obese. In addition, ATGL expression in the MBH is increased in response to fasting. This suggests that increased ATGL may play a role in maintaining a healthy metabolic profile. We propose that hypothalamic ATGL regulates lipid metabolism in the brain that in turn contributes to energy balance.
**Materials and methods:** To test this hypothesis, synapsin-Cre or -GFP expressing AAV are stereotaxically injected in the arcuate nucleus (ARC) of male ATGL *flox* mice to KO ATGL specifically in neurons (ATGLKO).
**Results:** First, we validated that ATGL expression is reduced by 50% in ATGLKO mice. We found that ATGLKO have increased weight gain on a chow diet compared to control animals that is associated with reduced energy expenditure and increased food intake and fat mass. In addition, chow-fed ATGLKO mice have an increased fasting glycaemia and mild glucose intolerance. Finally, pharmacological inhibition of ATGL in hypothalamic neurons in vitro

increases intracellular TG content.
**Conclusion:** Together, our findings suggest that the ATGL pathway in MBH neurons beneficially regulates glucose and energy homeostasis by mechanisms that may involve regulation of TG and lipid droplets metabolism.

**Disclosures: A. Machuca-Parra:** None. **K. Bouyakdan:** None. **D. Rodaros:** None. **A. Fisette:** None. **G. Mitchell:** None. **S. Fulton:** None. **T. Alquier:** None.

**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 781.04/EEE26

**Topic:** F.10. Food Intake and Energy Balance

**Support:** Penn Arts and Sciences
NIH F32DK112561-01
NIH 2T32DK7314-36
NIH R01DK114104

**Title:** Hunger inhibits inflammatory pain through a hypothalamic-hindbrain peptidergic circuit

**Authors: *A. L. ALHADEFF**[1,2], E. HERNANDEZ[2], M. L. KLIMA[2], S. Z. PHILLIPS[2], R. A. HOLLAND[3], C. GUO[4], A. W. HANTMAN[4], B. C. DE JONGHE[3], Z. SU[2], J. BETLEY[2,1]
[1]Biol., [3]Biobehavioral Hlth. Sci., [2]Univ. of Pennsylvania, Philadelphia, PA; [4]Janelia Res. Ctr., Ashburn, VA

**Abstract:** Survival requires the ability to flexibly respond in a dynamic environment. However, the underlying neural processes that integrate competing survival needs to prioritize behavior are unknown. To gain insight into the emergence of adaptive behavior, we explored the behavioral interaction, neural circuit intersection and molecular mechanisms that mediate conflicting survival needs. Hunger and nociception are two competing signals that animals must properly resolve to ensure survival. We discovered that hunger attenuates the behavioral response and the negative affect associated with long term, inflammatory pain without altering acute nociceptive responses. Conversely, acute pain delayed feeding behavior and reduced neural activity in hunger circuits, suggesting a hierarchical and bidirectional interaction between hunger and pain that prioritizes urgent needs. Activating Agouti-Related Protein (AgRP)-expressing neurons, a hypothalamic neural population that is active during hunger, specifically abrogated inflammatory pain responses, providing a neural substrate for the interaction between hunger and pain. Systematic analysis of each major AgRP neuron projection subpopulation revealed that the neural processing of hunger and inflammatory pain converge in the hindbrain parabrachial nucleus (PBN). Strikingly, activity in AgRP-PBN neurons blocks the behavioral response to

inflammatory pain as effectively as hunger or analgesics. Furthermore, activating the ~300 AgRP neurons that project to the PBN during an ongoing pain response is sufficient to suppress nocifensive behavior. This suppression of inflammatory pain by hunger is mediated by NPY signaling, as PBN NPY Y1 receptor antagonism blocked the effects of hunger or AgRPàPBN neuron stimulation on pain. Emerging data suggest that activity in glutamatergic PBN neurons is necessary for the behavioral response to inflammatory pain. Taken together, these experiments reveal a behavioral interaction and neural circuit intersection between basic survival motives that is mediated by peptidergic signaling in the PBN.

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**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 781.05/FFF1

**Topic:** F.10. Food Intake and Energy Balance

**Support:** NIH Grant DA034009

**Title:** Endocannabinoid control of gut-brain satiation signaling

**Authors: *D. A. ARGUETA**[1], N. V. DIPATRIZIO[2]
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**Abstract:** Gut-brain signaling plays a vital role in food intake and energy balance; however, the molecular underpinnings in these processes and their dysregulation in obesity remain poorly understood. Our recent work suggests that the endocannabinoid (eCB) system in the gut controls gut-brain signaling important for food intake, and activity of the eCB system is upregulated in diet-induced obesity (DIO), which contributes to overeating. When compared to mice maintained on low-fat/low-sugar chow, mice fed a western-style diet (i.e., high fat and sucrose) for 60 days exhibited increases in daily caloric intake, meal size, and rate of feeding, which was met with a more than two-fold increase in levels of the eCBs, 2-AG and anandamide, in upper small intestinal epithelium and plasma. Pharmacological blockade of eCB signaling at cannabinoid CB1 receptors in the periphery with the peripherally-restricted neutral CB1 receptor antagonist, AM6545 (10 mg/kg), completely normalized meal patterns in western diet-fed mice to levels found in lean controls. AM6545 had no effect on food intake in lean control mice. We next tested the hypothesis that eCB signaling at CB1 receptors in the gut modulates feeding behavior by controlling nutrient-induced gut-brain satiation signaling. CB1Rs were observed to co-

localize with cells in the mouse upper small intestinal epithelium that express the gut-derived satiation peptide, cholecystokinin (CCK). Oral gavage of corn oil potently increased bioactive CCK-8 levels in plasma of lean mice, an effect blocked by pretreatment with the cannabinoid receptor agonist, WIN 55,212-2 (5mg/kg). The actions of WIN were reversed by co-administration of AM6545, highlighting the role for peripheral CB1Rs in this response. In contrast to lean mice, oral gavage of corn oil failed to affect CCK-8 levels in DIO mice, which have elevated levels of eCBs in small-intestinal epithelium; however, pretreatment with AM6545 normalized the ability for corn oil to induce CCK-8 release in DIO. Further, co-administration of AM6545 with a low dose of the CCK-A receptor antagonist, devazepide (0.1 mg/kg), completely blocked the anorexic actions of AM6545 on meal patterns in DIO mice. Collectively, our data suggest that heightened eCB signaling at small intestinal CB1Rs drives overeating in DIO by a mechanism that includes inhibiting nutrient-induced release of CCK-8, thus delaying satiation.

**Disclosures: D.A. Argueta:** None. **N.V. DiPatrizio:** None.

**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 781.06/FFF2

**Topic:** F.10. Food Intake and Energy Balance

**Support:** NSERC Discovery Grant 06248

**Title:** Two peas in a pod: Ghrelin requires functional endocannabinoid signalling in the VTA to stimulate food reward

**Authors: *A. W. EDWARDS**[1], L. M. HYLAND[1], C. FEKETE[2], M. N. HILL[3], M. J. CHEE[1], A. ABIZAID[1]
[1]Neurosci., Carleton Univ., Ottawa, ON, Canada; [2]Dept. of Endocrine Neurobio., Inst. of Exptl. Medicine, Hungarian Acad. of Sci., Budapest, Hungary; [3]Hotchkiss Brain Inst., Univ. of Calgary, Calgary, AB, Canada

**Abstract:** Ghrelin and endocannabinoids encourage feeding behaviours by activating growth hormone secretagogue receptors (GHSRs) and cannabinoid receptors (CB-1Rs) in feeding related brain regions. Their capacity to engage feeding circuits in the hypothalamus (HYP), a brain region integral to the modulation of homeostatic feeding, has been well characterized. Within the HYP, ghrelin and eCB systems interact and depend on one another to promote feeding behaviours. Interestingly, GHSRs and CB-1Rs are also expressed in the ventral tegmental area (VTA), a brain region that regulates reward and motivation. Independent stimulation of either ghrelin or endocannabinoid systems within the VTA encourages food motivation and consumption; however, the interdependence of these systems within this region

remains unclear. Accordingly, we set out to determine how ghrelin and endocannabinoid systems might interact within the VTA and the role that this putative interaction may have in regulating feeding behaviours. We predicted that if these systems depend on one another, then disruption of one system should alter the other. We examined endocannabinoid concentrations and transcript levels of important endocannabinoid system proteins between WT and GHSR KO male rats and found that the GHSR KOs indeed have a dysregulated endocannabinoid system relative to WTs. Next, we asked whether global inhibition of CB-1Rs would prevent the traditional orexigenic effect of ghrelin infused into the VTA. Peripheral injection of rimonabant (i.e. CB-1R antagonist) efficiently blocked intra-VTA ghrelin induced feeding. To clarify whether rimonabant was attenuating the orexigenic effect of ghrelin specifically within the VTA, we conducted an identical study but delivered both rimonabant and ghrelin into the VTA before we examined food intake. Again, rimonabant pre-treatment attenuated ghrelin induced feeding. Subsequent, progressive ratio operant studies have extended these findings as intra-VTA rimonabant blunts intra-VTA ghrelin's ability to enhance the motivation to feed (i.e. number of bar presses to obtain standard chow pellets) in non-fasted male rats. These data support the hypothesis that ghrelin and eCB systems collaboratively regulate feeding behaviours within the VTA

**Disclosures: A.W. Edwards:** None. **L.M. Hyland:** None. **C. Fekete:** None. **M.N. Hill:** None. **M.J. Chee:** None. **A. Abizaid:** None.

**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 781.07/FFF3

**Topic:** F.10. Food Intake and Energy Balance

**Support:** NIH grant DK 114187
ADA grant 1-18-IBS-156

**Title:** Activation of ventrolateral medullary catecholamine neurons inhibits CCK-induced satiation and c-Fos expression in the dorsomedial medulla

**Authors: *A.-J. LI**, Q. WANG, S. RITTER
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**Abstract:** Catecholamine (CA) neurons within the A1 and C1 cell groups in the ventrolateral medulla (VLM) potently increase food intake when activated by glucose deficit. In contrast, A2 CA neurons in the dorsomedial medulla are required for reduction of food intake by cholecystokinin (CCK), a peptide that promotes satiation. The goal of this experiment was to determine where these two CA populations interact to produce their opposing control of food

intake. To do this, we administered 2-deoxy-D-glucose (2DG), an antiglycolytic glucose analogue, and CCK together and separately to examine the effects on food intake and brain c-Fos expression. As reported previously, 2DG (250 mg/kg; s.c.) increased c-Fos expression in A1 and C1 neurons in VLM and CCK (5 µg/kg; i.p.) increased c-Fos expression in the caudal nucleus of the solitary tract (NTS), including a subpopulation of A2 CA neurons. However, when administered in combination with CCK, 2DG attenuated both CCK-induced satiation and c-Fos expression in A2 CA neurons. In contrast, CCK did not suppress 2DG-induced VLM c-Fos expression or food intake. To test the hypothesis that the effects we observed when 2DG was administered systemically were due to activation of VLM CA neurons, we selectively activated these neurons in Th-Cre$^{+}$ transgenic rats in which VLM CA neurons were transfected with a Cre-dependent DREADD. Selective activation of VLM CA neurons using the DREADD agonist, clozapine-N-oxide (1 mg/kg; i.p.), attenuated reduction of food intake by CCK and prevented CCK-induced c-Fos expression in A2 CA and NTS neurons, even under normoglycemic conditions. Results support the hypothesis that activation of VLM CA neurons attenuates satiety by inhibiting A2 CA neurons. These opposing hindbrain controls of food intake may also interact at in other brain sites. In initial experiments, we found that 2DG also reduced CCK-induced c-Fos expression in the lateral parabrachial nucleus.

**Disclosures: A. Li:** None. **Q. Wang:** None. **S. Ritter:** None.

**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 781.08/FFF4

**Topic:** F.10. Food Intake and Energy Balance

**Title:** Eating elicited by morphine in the lateral septum: A mu opiate receptor effect?

**Authors: *M. CALDERWOOD**, E. KUAN, B. STANLEY
Dept. of Psychology, Univ. of California Riverside, Riverside, CA

**Abstract:** Previous research suggests that stimulation of opioid receptors in the lateral septum (LS) elicits a robust but delayed feeding effect in satiated adult male rats (Stanley et al., 1988). The current study was designed to test the receptor specificity of this effect. To test whether the feeding was due to mu opioid receptor activation we attempted to replicate the feeding effect with lower doses of morphine and with a highly selective mu-opioid receptor agonist [D-Ala2, N-MePhe4, Gly-ol]-enkephalin (DAMGO) microinjected directly into the LS. In addition, we tested whether LS pretreatment with the opioid receptor antagonist naloxone would block morphine-elicited feeding. Finally, we compared food intake in response to LS mu, delta, and kappa agonist microinjections. We showed that morphine (5 µg/0.3 µl) microinjected through indwelling cannulas into the LS elicited statistically significant feeding at 2 and 4 hours post-

injection but not at 30 minutes or 1-hour post-injection. This effect was consistent and reliable across five days of repeated injections. Consistent with the hypothesis that the feeding effect is due to LS opioid receptors we found that pretreatment with naloxone (10 µg/0.3 µl) abolished morphine-elicited feeding. Finally, to test whether the feeding effect is due to mu opioid stimulation we injected highly selective mu, delta, and kappa opioid receptor agonists into the LS and found that the rats did not eat in response to any dose of the delta or kappa agonists, but did eat in response to doses of the mu agonist DAMGO. Collectively, these results suggest that mu opioid receptors in the LS may have a role in the regulation of feeding.

**Disclosures: E. Kuan:** None. **B. Stanley:** None.

**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 781.09/FFF5

**Topic:** F.10. Food Intake and Energy Balance

**Title:** Kisspeptin regulation of temperature rhythms: Impacts on metabolism

**Authors: *J. T. SMITH**, G. KAVANAGH, S. MALONEY
The Univ. of Western Australia, Perth, Australia

**Abstract:** Kisspeptin (Kiss1) is a hypothalamic neuropeptide that acts via its receptor, Kiss1r, on GnRH neurons to maintain and promote reproduction. Kisspeptin has recently identified roles in regulating metabolism as Kiss1r knockout (KO) mice exhibit increased adiposity and reduced energy expenditure. Although the mechanisms underlying these observations are currently unknown, Kiss1r is expressed in brown adipose tissue (BAT) and Kiss1r KO mice exhibit reduced Ucp1 mRNA expression in BAT indicating impaired thermogenesis and reduced energy expenditure. Moreover, 8-week old Kiss1r KO mice also exhibit reduced Ucp1 expression suggesting the changes in metabolism precede any outward changes in phenotype. As such, we hypothesised young mice with altered kisspeptin signalling would exhibit reduced core body temperatures. Core-body temperature was recorded in 15-minutes intervals over a 14-day period in 8-week old gonadectomised male and female Kiss1r KO and also Kiss1 knockdown (KD) mice, mice with a 95% reduction in Kiss1 transcription, using a temperature logger implanted into the peritoneal cavity. Additional metabolic parameters were also assessed in young mice and also in adult gonad-intact 20-week Kiss1 KD mice. Changes in metabolism were more pronounced in Kiss1r KO than Kiss1 KD animals; white adipose tissue mass and plasma leptin were elevated in female Kiss1r KOs but unchanged in female Kiss1 KDs. Unexpectedly, mean core body temperature in either the light or dark phase was unaltered in both Kiss1r KO and Kiss1 KD animals. When daily core body temperature rhythms were examined however, female Kiss1r KO and Kiss1 KD mice exhibited significantly reduced mesor indicative of a lower

temperature “set point”. Interestingly, male Kiss1 KD mice displayed reduced amplitude, indicating diminished circadian rhythm. Only male Kiss1r KOs exhibited reduced Ucp1 mRNA expression however, which suggests the effects of kisspeptin on temperature and metabolism are not wholly dependent on thermogenesis in BAT. Females also exhibited greater phenotypic changes than males supporting the previously identified sexual dimorphism in kisspeptin signalling. Given the lack of clear metabolic phenotype in Kiss1 KD mice, our study provides evidence that there is redundancy in Kiss1 expression involved in metabolic control, as has been shown for fertility. The alterations in temperature rhythms observed suggest kisspeptin may have previously unidentified roles in regulating circadian rhythm-driven pathways.

**Disclosures: J.T. Smith:** None. **G. Kavanagh:** None. **S. Maloney:** None.

**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

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**Program #/Poster #:** 781.10/FFF6

**Topic:** F.10. Food Intake and Energy Balance

**Support:** German Research Foundation (TR-SFB134)

**Title:** Nesfatin-1 negatively affects reward-related behaviors

**Authors: *R. DORE**[1], R. KROTENKO[1], J. P. REISING[1], A. DI SPIEZIO[1], H. MÜLLER-FIELITZ[1], M. SCHWANINGER[1], L. MURRU[2], M. PASSAFARO[2], O. JÖHREN[1], C. SCHULZ[1], H. LEHNERT[1]
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**Abstract:** Nesfatin-1 is a gastric- and adipose tissue-derived peptide that possesses potent anorectic properties. It is the cleavage product of nucleobindin 2 (NUCB2) and is expressed not only in the periphery but also in the central nervous system, where it is known to affect homeostatic feeding behavior by acting primarily in the hypothalamus. NUCB2/nesfatin-1 is also expressed in several reward-related areas such as tegmental nuclei and *nucleus accumbens* (*NAcc*); in addition, *in vitro* nesfatin-1 hyperpolarizes dopamine neurons and reduces their firing rate in the ventral tegmental area (VTA), a key area involved in reward processing, as well as it decreases dopamine release in the *NAcc* when administered intracerebroventricularly (i.c.v.). Thus, nesfatin-1 may reduce energy intake by modulating hedonic aspects of food intake.
To test this hypothesis, male C57BL/6J mice were tested in effort- and choice-based paradigms. Both i.c.v. (N=6) or VTA (N=8) administration of nesfatin-1 dose-dependently reduced the animals´ motivation to work for sucrose in a progressive ratio schedule of reinforcement, as demonstrated by a significant reduction in the number of sucrose rewards earned and in the

session duration. By employing an optogenetic approach in a 2-bottle choice paradigm, the reward of value of sucrose was opposed to that of a reference stimulus (sucralose + optogenetic stimulation of VTA dopamine neurons). *Ad libitum* fed mice (N=8) highly preferred sucralose + optogenetic stimulation. Fasted mice in turn showed a significant increase in the preference for sucrose. Strikingly, the preference of fasted mice administered i.c.v. with nesfatin-1 was completely reverted, indicating the capability of nesfatin-1 to fully abolish the reward value of sucrose. These effects were specific as nesfatin-1 did not affect motor activity and chow food intake, ruling out a possible locomotor impairment and anorectic effect.
Furthermore, quantification through qRT-PCR revealed significant expression of NUCB2/nesfatin-1 mRNA in laser-microdissected VTA (N=4). Finally, in *ex vivo* whole-cell patch clamp electrophysiological recordings nesfatin-1 evoked an outward current that was fully blocked by barium chloride application, suggesting that nesfatin-1 may inhibit dopamine neurons activity through the activation of G-protein-activated inwardly rectifying potassium (GIRK) channels.
Altogether, our data demonstrate for the first time that nesfatin-1 negatively modulates the brain reward system and related behaviors, and suggest that NUCB2/nesfatin-1 system participates in the complex processes of assigning the reward value of food and the effort for obtaining it.

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**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 781.11/FFF7

**Topic:** F.10. Food Intake and Energy Balance

**Support:** NIH DK113608

**Title:** Behavioral, anatomical and molecular investigation of BDNF mRNA knockdown and leptin/PACAP interactions in the rat ventromedial hypothalamus

**Authors: *C. CHEN**[1], M. M. HURLEY[1], R. MCCOY[1], Z. COOPER[1], T. DABRA[1], N. PATEL[1], I. P. GONZALES[1], W. CONLEY[1], K. BRUCKNER[1], M. GRZYBOWSKI[2], M. WONG-RILEY[2], E. ANDERSON[1], M. HEARING[1], D. A. BAKER[1], A. GEURTS[2], S. CHOI[1]
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**Abstract:** Obesity is an epidemic in the United States, impacting nearly 100 million Americans and placing an enormous socioeconomic burden on the nation. Pituitary adenylate cyclase-activating polypeptide (PACAP) and leptin, a hormone produced peripherally by adipose cells

are key signaling molecules in the regulation of feeding and metabolism. We have shown injecting PACAP or leptin into the rat VMN leads to strikingly similar behavioral and molecular changes: decreased feeding behavior, increased body weight and increased phosphorylation of STAT3 and BDNF/SOCS3 mRNA expression. Furthermore, antagonizing VMN PACAP receptors with PACAP6-38 just prior to leptin or PACAP microinjections prevented both PACAP and leptin-induced hypophagia, as well as subsequent increases in BDNF and SOCS3 mRNA expression, suggesting that endogenous PACAP receptor-dependent activity is necessary for regulating feeding behavior in the VMN. Additionally, VMN bath application of leptin resulted in increased and decreased action potential firing frequency, unlike the unimodal increase observed after PACAP administration. The apparent bimodal effect may reflect distinct intrinsic cellular physiology based on initial basal firing rates. Future experiments will examine whether discrepancies in the ability of these peptides to alter neuronal activity reflect subpopulation-specific distinctions in the expression and/or interaction of PACAP- and leptin-mediated signaling in the VMN using electrophysiology and single-cell PCR. We also hope to further characterize, in male rats, the role of BDNF in feeding behavior and body weight regulation. Specifically, we wish to determine whether BDNF is a common downstream target necessary for both PACAP and leptin to exert their hypophagic effects. To do so, we created a DOX-inducible transgene system expressing a Tet-ON transactivator that drives the transcription of a shRNA for BDNF to locally induce RNAi in the VMN and measure feeding behavior. Preliminary data suggest local DOX-induced knockdown of BDNF mRNA in the VMN trends towards an increase in feeding behavior in rats immediately following injection. Additional studies will include magnitude of RNAi expression on feeding behavior and measurements of BDNF mRNA. We believe that local DOX-injections into the VMN will significantly increase feeding behavior and weight gain in relation to the DOX- and saline-injected WT and saline-injected DOX mutants. This genetic tool will enable us to better characterize the interactions between leptin and PACAP signaling in the VMN and their dependency on BDNF expression in homeostasis and feeding behavior.

**Disclosures: C. Chen:** None. **M.M. Hurley:** None. **R. McCoy:** None. **Z. Cooper:** None. **T. Dabra:** None. **N. Patel:** None. **I.P. Gonzales:** None. **W. Conley:** None. **K. Bruckner:** None. **M. Grzybowski:** None. **M. Wong-Riley:** None. **E. Anderson:** None. **M. Hearing:** None. **D.A. Baker:** None. **A. Geurts:** None. **S. Choi:** None.

**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

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**Topic:** F.10. Food Intake and Energy Balance

**Support:** Memphis Research Consortium

Le Bonheur Children's Foundation Research Institute
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**Title:** Role of promoter I-derived brain-derived neurotrophic factor in the regulation of food intake

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**Abstract:** Brain-derived neurotrophic factor (BDNF) is an important neuropeptide in energy balance regulation. *BDNF* gene transcription is initiated from 9 different promoters upstream of individual 5' untranslated exons and spliced to a common exon that encodes the BDNF protein. We sought to assess changes in weight and feeding that result from selective disruption of BDNF production from individual promoters. Transgenic mice with selective disruption of BDNF from promoters I, II, IV or VI (Bdnf-e1, -e2, -e4 and –e6) were created by inserting an eGFP-STOP cassette upstream of the respective splice donor sites within the targeted 5' UTR. Weight trajectory of Bdnf-e1 and Bdnf-e2 mice was increased compared to wild-type (WT) littermates, whereas weight trajectory of Bdnf-e4 and Bdnf-e6 mice was similar to WT. Food intake was increased in Bdnf-e1 and Bdnf-e2 mice, and pair-feeding prevented the obesity phenotype. Mutant and wild-type littermates for each strain had similar total energy expenditure and oxygen consumption after adjusting for body composition. Therefore, the obesity observed in Bdnf-e1 and Bdnf-e2 mice is attributable to hyperphagia and not altered energy expenditure. Down-regulation of BDNF in the ventromedial hypothalamus (VMH), a region of the brain important for regulation of feeding, results in hyperphagia-induced obesity. *BDNF* exon I-containing transcripts are selectively upregulated in response to nutrient intake in the VMH, suggesting that exon I-expressing cells in the VMH (BDNF-e1 cells) may be critical for the hyperphagia phenotype observed in BDNF-e1 mutant mice. To assess whether BDNF-e1 cells are necessary to prevent hyperphagia, we used a genetic ablation strategy. To achieve selective ablation of BDNF-e1 cells, we used viral delivery to the VMH of a GFP-dependent Cre recombinase in Bdnf-e1 +/- mice to drive expression of a Cre-dependent diphtheria toxin. Mice in which BDNF-e1 cells were ablated showed elevated food intake and weight gain compared to control mice, suggesting that BDNF-e1 cells in the VMH are critical for controlling feeding behavior. Future work aims to better define the molecular and physiological properties that allow these cells to regulate feeding.

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**Poster**

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**Program #/Poster #:** 781.13/FFF9

**Topic:** F.10. Food Intake and Energy Balance

**Support:** The Department of Veterans Affairs Merit Review CP252

**Title:** Different phenotypes of feeding response to exercise in young and mature rats

**Authors: *C. WANG**[1,2,5], J. HOFMEISTER[2], M. GRACE[1], C. J. BILLINGTON[1,3,2,5], C. M. KOTZ[6,1,5,4,2]
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**Abstract:** BACKGROUND: Exercise is associated with appetite changes, and our goal is to understand the underlying BDNF-TrkB signaling involved in anorectic responses to exercise. To develop a working model, we profiled the feeding and body weight (BW) response to exercise – either by running wheel (RW) or treadmill (TM) – in rats of two different ages: < 3-month (young) and 5-month (mature). We hypothesized that both age groups would have an anorectic response to exercise, in association with BDNF-TrkB expression.
METHODS: Young (mean BW < 400 g) and mature (mean BW >600 g) SD male rats (N=46 each) were divided into 4 groups (N=10~12): sedentary (Sed), TM (45 min/d, 5d/week), RW (24/7 access), and Sed with feeding same as RW rats (pair-fed), with similar distribution of BW and fat mass. The term was 37 d for young and 33 d for mature. Feeding, weight gain and fat mass was measured. The data were analyzed with SPSS using general lineal model.
RESULTS: 1) Young RW rats initially ate the least, then ate more than pair-fed rats could, and eventually exceeded all rats. Daily feeding in mature RW rats was initially decreased, then gradual increased but to the level that pair-fed rats could reach. For cumulative feeding, mature RW rats ate less than Sed rats, while young RW rats did not. 2) Young rats with RW and TM gained about 100 g and 150 g weight, respectively, while mature rats with RW and TM gained about 20 g and 60 g, respectively. RW rats in both ages gained the least weight. Mature rats with TM had reduced weight gain vs. Sed rats while young rats with treadmills did not. 3) Young rats had a higher food efficiency than mature rats, and rats with RWs in both ages had the lowest food efficiency. Mature RW rats had negative efficiency most of the study period while young RW rats had positive efficiency at all times. 4) Young RW rats ran ~ 200 km in total (6 km as daily peak) while mature RW rats ran < 30 km as total (1.5 km as daily peak). 5) All young rats had increased adiposity (% fat mass), whereas mature RW rats had reduced adiposity.

CONCLUSIONS: RW exercise impacted the feeding and body mass profiles of young and mature rats differently, which is likely due to their differences in growth and development stages. Young rats are more active than older rats and need more energy to lay down new tissue, whereas the less active mature rats need less energy for activity and weight maintenance. In response to RW exercise, mature rats had considerable reductions in feeding, weight and fat mass gain, whereas young rats did not. Together, these findings indicate that mature rats are a good weight loss model for our future studies to understand anorectic brain pathways during exercise. BDNF and TrkB results are in process and will be presented.

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**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 781.14/FFF10

**Topic:** F.10. Food Intake and Energy Balance

**Title:** Effect of antioxidants on NPY expression in the arcuate nucleus of the hypothalamus in diabetic rats

**Authors: M. I. BARRAGAN BONILLA**[1], M. RAMIREZ[1], J. M. MENDOZA BELLO[1], B. ILLADES AGUIAR[1], *M. ESPINOZA[2]
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**Abstract:** Neuropeptide Y (NPY) is a neuropeptide expressed in the arcuate nucleus (Arc) of hypothalamus and play a key role in the control of food intake behavior by stimulating appetite. Arc integrates metabolic signals and thus regulates the glucose homeostasis. Diabetes mellitus models in rodents have shown that diabetic hyperphagia is associated with increased NPY expression level in this region. It is known that hyperphagic behavior contributes to poor glycemic control. On the other hand, it has been described that during diabetes the treatments with antioxidants can attenuate several alterations including diabetic hyperphagia, however, it is not known if that effect is associated to changes in NPY expression levels in Arc. Therefore, the objective of this study was to evaluate the effect of antioxidants on the hyperphagia and NPY expression in diabetic rats in association with blood glucose and oxidative stress markers. For this purpose, two-days-old male Wistar rats were injected with streptozotocin (70mg/kg), after weaning, they were supplemented with 10% sugared water for 4 weeks. At 10-week-old, diabetes was confirmed, and we administered the antioxidant treatments: aged garlic extract [AGE (200mg/kg)], resveratrol [RES (2.25mg/kg)] and curcumin [CUR (50mg/kg)] for 28 days orally; we also administered metformin [MET (100mg/kg)] to glycemic control and 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 perfunded transcardiacally to obtain brain and detect NPY in Arc by immunofluorescence. Diabetic rats showed hyperglycemia, weight loss, polydipsia, hyperphagia, increased GST activity ($p<0.05$), and a tendency to increase GPx activity and MDA level ($p>0.05$) in blood in comparison control group. In addition, they shown increased NPY level expression in Arc. After 28 days of treatment, MET and RES were incapable to reduce blood glucose, while AGE had anti-hyperglycemic effect, and CUR and PF caused a decreased in blood glucose of diabetic rats. On the other hand, MET, AGE, CUR and PF normalized GST activity. In relation to food intake, any antioxidant treatment was able to avoid the diabetic hyperphagia, however, NPY expression level in Arc was diminished in diabetic group with treatments MET, AGE, RSV, CUR and PF. These preliminary results suggest that a chronic treatment could attenuate diabetic hyperphagia in rats and probably it will be related to changes NPY expression in Arc.

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**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 781.15/FFF11

**Topic:** F.10. Food Intake and Energy Balance

**Support:** The Dept. of Veterans Affairs 1101BX003004-01
NIH 5R01DK100281-04

**Title:** Loss of inhibitory input to orexin neurons increases spontaneous physical activity, energy expenditure and food intake in an animal model of Parkinson's disease

**Authors: *M. STANOJLOVIC**[1], J. P. PALLAIS[1], M. LITTLE[1], C. KOTZ[1,2]
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**Abstract:** Parkinson's disease (PD) is classically associated with dopamine system deficits that affect motor function as well as cognition and mood. Energy metabolism is also altered in PD, but little is known about the underlying mechanisms that mediate these changes. Orexin (Orx) neurons are produced in the lateral hypothalamic area and play a crucial role in spontaneous physical activity (SPA), non-exercise energy expenditure (NEAT), arousal, and food intake regulation. Orexin neuron dysfunction has been observed in PD, as have changes in food intake,

SPA, and general alertness. In a PD mouse model (G2-3), mutant human alpha-synuclein (Ser129) expression is driven by mouse prion protein promoter. We hypothesized that this G2-3 mouse model shows metabolic impairments replicating that seen in PD, and that orexin dysfunction causes these metabolic disturbances. As a first step to test this idea, we profiled 3, 5 and 7 mo old wild type (wt) and G2-3 transgenic mice. Food intake (daily for 4 d), SPA, NEAT (hourly for 3 d), and body composition (prior to SPA and NEAT) were measured to investigate potential dysfunction of the Orx system. Immunohistochemistry, fluorescence, unbiased stereology and confocal microscopy were used to assess Orx neuron pathology and inhibitory synaptic inputs via GAD65 staining in the lateral hypothalamus. In alignment with our hypothesis, G2-3 animals consumed more food than their wt littermates and showed progressive increases in SPA and energy expenditure. The observed increase in SPA was predominantly during peak activity periods of both light and dark phases. While α-synuclein aggregations were detected in nuclei, the number of Orx neurons was unchanged, but there was a reduction in the number of GAD65 positive synaptic puncta. These results suggest Orx neuronal involvement in G2-3 mouse metabolic disturbances. The observed reduction in the number of GAD65 positive synapses imply loss of inhibitory input to Orx neurons, which could explain the elevated food intake, SPA, and energy expenditure. Our future research goals include examining the time course of PD metabolic impairments, as well as modulating Orx neuron activity using DREADDs (designer receptor exclusively activated by designer drugs) to alleviate the metabolic impairments in G2-3 animals.

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**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

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**Topic:** F.10. Food Intake and Energy Balance

**Support:** NIDDK Grant DK020541
NIDDK Grant DK092246

**Title:** Activation of temperature-sensitive TRPV1-like receptors in ARC POMC neurons reduces food intake

**Authors: *J. JEONG**[1], D. LEE[2], S.-M. LIU[1], S. C. CHUA, Jr[1], G. J. SCHWARTZ[1], Y.-H. JO[1]
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**Abstract:** Proopiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus (ARC) respond to numerous hormonal and neural signals, resulting in changes in food intake. Here, we demonstrate that ARC POMC neurons express capsaicin-sensitive transient receptor potential vanilloid 1 receptor (TRPV1)-like receptors. To show expression of TRPV1-like receptors in ARC POMC neurons, we use single-cell reverse transcription-polymerase chain reaction (RT-PCR), immunohistochemistry, electrophysiology, TRPV1 knock-out (KO), and TRPV1-Cre knock-in mice. A small elevation of temperature in the physiological range is enough to depolarize ARC POMC neurons. This depolarization is blocked by the TRPV1 receptor antagonist and by Trpv1 gene knockdown. Capsaicin-induced activation reduces food intake that is abolished by a melanocortin receptor antagonist. To selectively stimulate TRPV1-like receptor-expressing ARC POMC neurons in the ARC, we generate an adeno-associated virus serotype 5 (AAV5) carrying a Cre-dependent channelrhodopsin-2 (ChR2)-enhanced yellow fluorescent protein (eYFP) expression cassette under the control of the two neuronal POMC enhancers (nPEs). Optogenetic stimulation of TRPV1-like receptor-expressing POMC neurons decreases food intake. Hypothalamic temperature is rapidly elevated and reaches to approximately 39 °C during treadmill running. This elevation is associated with a reduction in food intake. Knockdown of the Trpv1 gene exclusively in ARC POMC neurons blocks the feeding inhibition produced by increased hypothalamic temperature. Taken together, our findings identify a melanocortinergic circuit that links acute elevations in hypothalamic temperature with acute reductions in food intake.

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**Poster**

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**Program #/Poster #:** 781.17/FFF13

**Topic:** F.10. Food Intake and Energy Balance

**Support:** CONACyT Grant 233918

**Title:** Accumbal thyrotropin-releasing hormone (TRH) is involved in the effect of emotional stress on hedonic food intake

**Authors: *E. ALVAREZ**, A. GONZALEZ, P. DE GORTARI
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**Abstract:** Food intake is constantly influenced by the convergence between homeostatic demands and the motivational aspects associated with food. The mesolimbic dopaminergic system with dopamine projections from the ventral tegmental area to nucleus accumbens (NAc)

is involved in processing the rewarding characteristics of food. Thyrotropin-releasing hormone (TRH) is a neuropeptide with anorectic effects; synthesized in regions involved in the homeostatic and hedonic aspects of feeding. Emotional stress alters food intake, increasing or decreasing regular chow ingestion; nevertheless when offered palatable food, most rodents increase their food intake vs. non-stressed animals. We aim to study involvement of accumbal TRH on hedonic feeding of stressed animals. Male Wistar rats had *ad libitum* access to chow (C) or chow plus chocolate milk (M) as a palatable food for 14 days, and were either group-(G) or single-housed (S), as a stressor. Animals with access to chocolate milk increased their food intake vs. rats with access to chow only. Moreover, isolation stress increased palatable food intake (MS group) but not that of chow (CS group). MS group had low corticosterone levels vs. CS., suggesting that the increase in food intake was able to reduce stress levels in single-housed animals. Given that stress seemed to be responsible of hyperphagia, in a second experiment we injected a glucocorticoid receptor antagonist (RU-486, 10µg/0.5µl/side) or vehicle directly into the NAc of isolated rats. We analyzed cumulative food intake over the 2h period following the injections. RU-486 administration reduced food intake of chocolate milk only, showing that glucocorticoids acting in NAc are able to increase palatable food ingestion. In order to evaluate a possible accumbal TRH involvement of the stress effects on palatable food intake, we injected TRH (3µg/0.5µl) intra-NAc of stressed rats. TRH administration reduced food intake regardless of the type of food offered. In conclusion, glucocorticoids' effects in NAc induce high palatable food intake but do not modify chow intake. TRH in NAc acts as an anorectic factor independently of the food offered, and recapitulates the effects on palatable food intake of rats with accumbal glucocorticoid receptor blockade. Our results suggested that TRH is not only involved in the regulation of homeostatic but also of hedonic aspects of feeding.

**Disclosures: E. Alvarez:** None. **A. Gonzalez:** None. **P. de Gortari:** None.

**Poster**

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**Program #/Poster #:** 781.18/FFF14

**Topic:** F.10. Food Intake and Energy Balance

**Support:** CONACyT Grant 233918

**Title:** Thyrotropin-releasing hormone (TRH) expression is regulated by serotonin in PVN in a dehydration-induced anorexia (DIA) model

**Authors: *J. CHAVEZ**, I. AMAYA, P. DE GORTARI
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**Abstract:** The expression of the thyrotropin-releasing hormone (TRH), considered as an anorexigenic peptide from the paraventricular hypothalamic nucleus (PVN), is down-regulated by a negative energy balance, as it happens in forced-food-restricted animals (FFR). In contrast, dehydration-induced anorexia (DIA) induces the expression of TRH in the PVN of rats despite they have a dramatic body weight loss. Serotonin (5-HT) is a neurotransmitter involved in physiological processes like thermoregulation, locomotion, learn and memory, as well as in eating behavior. Treatment with 5-HT in PVN is able to develop anorectic behaviors in rodents, suggesting that 5-HT acts as an anorectic signal. The aim of this work was to determine the role of 5-HT in the expression of TRH in the PVN of FFR and DIA female rats. We implanted a guided cannula with a stereotaxic apparatus to administrate an agonist of 5-$HT_{2A/2C}$ receptors (DOI 15 nmol) in PVN of FFR female rats (n= 7), and we found an increase in PVN TRH mRNA levels. Interestingly, the treatment with ketanserin (30 nmol), a 5-$HT_{2A/2C}$ receptor antagonist in PVN of DIA female rats, increased the TRH mRNA levels even more than DIA control group. These data suggested that 5-HT was involved in the regulation of PNV TRH expression in FFR animals through 5-$HT_{2A/2C}$ receptors, and even in DIA animals. Further studies are needed to elucidate the mechanisms and receptors involved in this regulation.

**Disclosures: J. Chavez:** None. **I. Amaya:** None. **P. de Gortari:** None.

**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 781.19/FFF15

**Topic:** F.10. Food Intake and Energy Balance

**Support:** Hungarian National Brain Research Program
Research support from Novo Nordisk A/S, Malov, Denmark

**Title:** Distribution and ultrastructural localization of the glucagon-like peptide-1 (GLP-1) receptor in the brain of rats

**Authors: *E. FARKAS**[1], C. PYKE[2], C. FEKETE[1]
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**Abstract:** In the central nervous system (CNS), glucagon-like peptide-1 (GLP-1) is synthesized by neurons of the nucleus of solitary tract (NTS). GLP-1 by acting on its receptor, the GLP-1 receptor (GLP-1R), in the CNS inhibits food intake, stimulates energy expenditure and regulates glucose homeostasis. The distribution of GLP-1R mRNA in rat brain has been investigated, but little information is available about the subcellular localization and the distribution of the GLP-1R protein in the rat brain.

To determine the localization of GLP-1R protein in the brain, a novel monoclonal antibody was used on series sections of the rat brain. The specificity of the antibody was shown by the loss of GLP-1R-immunoreactivity on sections of GLP-1R KO mice. Very dense network of GLP-1R-immunreactive (IR) perikarya and/or processes were observed in the lateral septal nucleus, median preoptic area, hypothalamic paraventricular nucleus, arcuate nucleus (ARC), median eminence (ME), amygdala, tuberomammillary nucleus, area postrema (AP) and the NTS. Ultrastructural examination of GLP-1R-immunoreactivity in energy homeostasis related regions, like the ARC, ME, AP, NTS showed GLP-1R immunoreactivity in association to the membrane of perikarya, dendrites and axonal profiles. Large number of GLP-1R-IR perikarya and dendrites were observed in the ARC. In this nucleus, numerous GLP-1R-IR axons were also observed establishing both symmetric and asymmetric type synapses. In the external zone of the ME, GLP-1R-immunoreactivity was observed on axons of hypophysiotropic neurons terminating around capillaries. In the NTS, GLP-1R-immunoreactivity was primarily observed in axons. In the AP, GLP-1R-immunoreactivity very densely labeled perikarya completely ensheeting these cells.
Double-labeling immunofluorescence demonstrated that the GLP-1R-IR structures highly outnumbered the GLP-1-IR axons in the ARC.
In conclusion, in this study we provide a detailed map of the GLP-1R-IR structures in the CNS. Our data demonstrate that in addition to the perikaryonal and dendritic distribution, GLP-1R is also present in axonal profiles suggesting the presynaptic action of GLP-1. The mismatch of GLP-1R- and GLP-1-IR profiles in the ARC, ME and AP suggest that peripheral GLP-1 may act in these brain regions.

**Disclosures: E. Farkas:** None. **C. Pyke:** A. Employment/Salary (full or part-time):; Novo Nordisk. **C. Fekete:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Novo Nordisk.

**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 781.20/FFF16

**Topic:** F.10. Food Intake and Energy Balance

**Support:** DK103335
DK105954

**Title:** TrkB-expressing neurons in the DMH are potent regulators of energy expenditure

**Authors: *J. HOUTZ**, G.-Y. LIAO, B. XU
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**Abstract:** Obesity is a pandemic affecting one-third of Americans and half a billion people world-wide. In order to maintain a healthy body weight, numerous molecular and neural pathways work to regulate a proper energy balance. Prior studies in our lab have revealed that brain-derived neurotrophic factor (BDNF) expressing neurons in the paraventricular hypothalamus (PVH) regulate several metabolic processes including feeding, locomotion, and thermogenesis. Alterations in BDNF signaling through the high-affinity BDNF receptor, TrkB, lead to a profound imbalance in energy homeostasis. Although progress has been made in defining populations of BDNF-expressing neurons that regulate energy homeostasis, the location and action of reciprocal TrkB-expressing neurons remains unknown. BDNF-expressing neurons in the preoptic area (POA) have been found to inhibit thermogenesis and promote cooling. Furthermore, both the POA and the PVH form connections with the dorsomedial hypothalamus (DMH), an integral component of established metabolic and thermoregulatory networks that contains TrkB expressing neurons,. Thus, TrkB-expressing neurons in the DMH ($DMH^{TrkB}$) represent an attractive candidate for the identification of pre- or post synaptic modulators of circuits regulating energy expenditure.

We found that $DMH^{TrkB}$ neurons are activated by both warm and cold stimuli and chemogenetic excitation of $DMH^{TrkB}$ neurons increases body temperature, locomotor activity, and energy expenditure in mice. Conversely, inhibition of $DMH^{TrkB}$ neurons decreases body temperature and energy expenditure. Together, our results strongly indicate that $DMH^{TrkB}$ neuronal activity positively regulates energy expenditure and thermogenesis. Furthermore, deletion of TrkB receptors in the DMH reduces energy expenditure and increases food intake, leading to a significant increase in body weight.

Using anterograde tracing, we revealed dense innervation of the POA and PVH by $DMH^{TrkB}$ neurons. In future studies, we will use retrograde tracing to evaluate possible anatomical connections with populations of BDNF neurons in these brain regions that are known to regulate energy expenditure. Since $DMH^{TrkB}$ neurons appear to innervate several brain regions important for the regulation of thermogenesis, we will selectively activate $DMH^{TrkB}$ neurons based on their projections in order to delineate their functional neural circuitry.

Our investigation has the potential to reveal novel pathways and neuronal populations that will be essential to understanding the mechanism through which neurotrophin signaling influences metabolism.

**Disclosures: J. Houtz:** None. **G. Liao:** None. **B. Xu:** None.

**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 781.21/FFF17

**Topic:** F.10. Food Intake and Energy Balance

**Support:** Hungarian National Brain Research Fund
Research support from Novo Nordisk A/S, Malov, Denmark

**Title:** GLP-1 regulates the POMC neurons of the arcuate nucleus both directly and indirectly via presynaptic action

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**Abstract:** GLP-1 inhibits food intake, stimulates energy expenditure and causes weight loss. Long acting GLP-1 analogues are successfully used to induce weight loss even in humans. GLP-1 exerts these effects at least partly via the POMC neurons of the arcuate nucleus (ARC). Ultrastructural examination of the localization of GLP-1 receptor (GLP-1R) in the ARC revealed that GLP-1R-immunoreactivity was present on the surface of perikarya and dendrites, but it was also associated to the surface of numerous axons suggesting that GLP-1 regulates neurons in the ARC indirectly via presynaptic effects besides its direct effect.
To determine whether GLP-1 may influence the POMC neurons via action on presynaptic terminals, patch clamp electrophysiology was performed using adult, male, POMC/Cre-floxed Rosa26/tdTomato double transgenic mice and the GLP-1R agonist Exendin-4 (Ex4; 1μM). First, in agreement with data in the literature, Ex4 markedly increased the firing rate of all examined POMC neurons (249.86±44.9%; $P<0.001$; N=20) and depolarized their membrane potential (+4.12±1.7 mV; $P<0.001$). Then, GDP-β-S (3 mM) was added to the intracellular solution to block the G-protein signaling specifically in the studied neuron. GDP-β-S prevented the Ex4-induced increase of firing rate, demonstrating that Ex4 has direct stimulatory effect on the POMC neurons.
To examine the presynaptic effects, the influence of Ex4 was studied on the miniature excitatory (mEPSC) and inhibitory postsynaptic currents (mIPSC) of POMC neurons. Ex4 increased the frequency of mEPSCs (160±20.8%; $P=0.015$) in about 50% (N=7) of the examined POMC neurons (N=15). In addition, Ex4 also increased the frequency of miniature inhibitory currents, mIPSCs (154.5±8.4%; $P=0.002$), in one-third (N=6) of the examined POMC neurons (N=19; $P=0.002$). This effect of Ex4 was not influenced by the intracellular administration of GDP-β-S indicating that GLP-1 has direct stimulatory effect on a population of the inputs of POMC neurons.
In summary, our data demonstrate that GLP-1R has both pre- and postsynaptic localization in the ARC. In addition, stimulation of GLP-1R facilitates the effects of the neuronal inputs of POMC neurons via its presynaptic GLP-1R in addition to the direct stimulatory effect of this receptor on POMC neurons.

**Disclosures: Z. Péterfi:** None. **E. Farkas:** None. **C. Pyke:** A. Employment/Salary (full or part-time):; Global Research, Novo Nordisk A/S. **C. Fekete:** 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.; Global Research, Novo Nordisk A/S, Malov, Denmark.

**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 781.22/FFF18

**Topic:** B.03. G-Protein Coupled Receptors

**Support:** 1ZIAMH002386

**Title:** Gs-coupled GPCR linkage to ERK activation in neurons and neuroendocrine cells in cellula and *in vivo*

**Authors: *S. Z. JIANG**, A. EMERY, C. GERFEN, M. EIDEN, W. XU, L. EIDEN
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**Abstract:** PACAP activates ERK in NS-1 neuroendocrine cells via the cAMP sensor/effector NCS-Rapgef2. To determine whether this coupling/signaling mode is a general feature of Gs-coupled GPCRs, we examined activation of the D1 dopamine receptor, and the beta 1 and beta 2 adrenoceptors (β1 and β2 AR), Gs-coupled GPCRs for the catecholamines dopamine, norepinephrine and epinephrine, respectively. As the β2AR has also been shown to signal to ERK via engagement of β-arrestin, we compared functionally relevant ERK activation by the D1, β1 and β2 receptors through NCS-Rapgef2, which links Gs-coupled PAC1 activation of adenylyl cyclase to ERK in NS-1 cells (Emery et al., *Sci. Signal*. , 2013; Emery et al., *J. Biol. Chem*. , 2014). In NS-1 cell lines that stably express DR1 and the β1AR (and the PAC1 receptor as a positive control), agonist treatment caused activation of all three of the major neuroendocrine cAMP-dependent signaling pathways: Epac2/p38-dependent growth arrest; PKA-dependent CREB phosphorylation; and NCS-Rapgef2 and ERK-dependent neurite elongation. In contrast, agonist stimulation of β2AR-expressing cells caused Epac2/p38-dependent growth arrest and PKA-dependent CREB phosphorylation, but did *not* result in NCS-Rapgef2/ERK-dependent neuritogenesis. To compare the desensitization profiles of the two differentially-acting beta-receptors, cells were transduced with a biosensor (split luciferase PKAR), allowing continuous real-time cAMP measurements (Emery et al., *Peptides*, 2016). In β2AR-expressing cells, the maximal effect of isoproterenol on cAMP was observed after 10 minutes of treatment and decreased rapidly thereafter. In contrast, isoproterenol-dependent β1AR activation caused persistent cAMP elevation, observed at approximately maximal levels for at least 40 minutes following agonist addition. ERK phosphorylation observed following β1AR activation (NCS-Rapgef2-dependent) results in gene transcription, including up-regulation of Egr-1, required for neuritogenesis (Ravni et al., *Mol. Pharmacol.* , 2008), while ERK activation elicited by β2AR (NCS-Rapgef2-independent) does not have this signaling property. That PAC1, DR1, and β1AR on the one hand, and β2AR on the other cause neuropeptide/catecholamine cause ERK activation, but presumably in two separate cellular compartments, may help to

explain differential stimulation of physiological events elicited by these receptors in a variety of cells and tissues. Latterly, we have shown that D1 agonist or cocaine treatment of mice in vivo causes ERK activation (Jiang et al., *eNeuro*, 2017) that is NCS-Rapgef2-dependent, supporting this interpretation of our *in cellula* results.

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**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 781.23/FFF19

**Topic:** B.03. G-Protein Coupled Receptors

**Support:** National Institute of Mental Health Intramural Research Program Z01-MH-002498

**Title:** Modulatory actions of vasopressin 1b receptor on CA2 excitability

**Authors: *N. I. CILZ**, S. K. WILLIAMS AVRAM, A. CYMERBLIT-SABBA, E. SHEPARD, S. YOUNG
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**Abstract:** We proposed (Young et al. 2006) that the dorsal CA2 region of the hippocampus is necessary for social memory and aggression because knocking out the vasopressin 1b receptor (Avpr1b), which is located almost exclusively in CA2 (Young et al. 2006), leads to deficits in those social behaviors (Wersinger et al. 2002). Optogenetic stimulation of vasopressin-expressing terminals in dorsal CA2 enhances long-term social recognition (Smith et al. 2016) and pharmacological activation of Avpr1b *in vitro* augments excitatory input onto CA2 (Pagani et al. 2015). However, whether Avpr1b activation may result in any postsynaptic changes to CA2 intrinsic excitability remains unexplored. To address this question, we developed a mouse that expresses Cre under the Avpr1b promoter (Avpr1b-Cre). We stereotactically injected a Cre-dependent virus (AAV2-hSyn-DIO-hM4D(Gi)-mCherry) carrying the Gi Designer Receptor Exclusively Activated by Designer Drugs (DREADD) into Avp1b-Cre mice to verify selective expression in CA2 neurons. As expected, principal cells in the CA2 region were positive for mCherry and strongly hyperpolarized by 10μM bath application of the DREADD agonist clozapine-n-oxide. To examine the modulatory action of Avpr1b, we used a transgenic approach by crossing Avpr1b-Cre mice with a Cre-dependent reporter line that expresses mCherry (Ai9; Madisen et al. 2010) to identify and record from Avp1b-positive CA2 neurons. We present our findings from whole-cell patch-clamp recordings made from these CA2 neurons using a bath-applied, selective Avpr1b agonist. These results expand the underlying molecular and cellular understanding of the role for Avpr1b in the CA2 region.

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**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 781.24/FFF20

**Topic:** B.03. G-Protein Coupled Receptors

**Support:** NIH Grant R01HD89147

**Title:** Impact of ligand and receptor variation in anthropoidea vasopressin 1a receptor signaling

**Authors: *M. PIERCE**, T. F. MURRAY
Dept. of Pharmacol., Creighton Univ., Omaha, NE

**Abstract:** Arginine vasopressin (AVP) and oxytocin (OT) are neuropeptides that bind to G-protein coupled receptors and influence social behaviors. In mammals, consensus mammalian AVP and OT ($Leu^8$-OT) sequences are highly conserved. In new world monkeys (NWM), six distinct OT ligand variants have recently been discovered. In marmosets, an amino acid change in the 8th position of the peptide ($Pro^8$-OT) exhibits unique structural and functional properties. The V1a receptor (V1aR) is abundantly expressed in the brain and is a member of the oxytocin/vasopressin receptor family. The exploitation of natural variation in neuropeptide ligands and receptors may provide insight into how molecular mechanism corresponds with unique social phenotypes. Chinese hamster ovary (CHO) cells expressing marmoset (mV1aR), macaque (qV1aR), or human vasopressin receptor 1 a (hV1aR) were used to assess AVP, $Leu^8$-OT and $Pro^8$-OT ligand-receptor pharmacological signatures. Calcium mobilization assays using fluo-3 AM and membrane potential assays using FLIPR Membrane Potential (FMP) blue demonstrated AVP was more potent than the OT ligands in all three V1aR-expressing cell lines. In hV1aR cells, AVP was much more efficacious than the OT analogs in calcium mobilization assays. Both AVP and OT produced concentration-dependent hyperpolarization responses. In qV1aR cells, $Leu^8$-OT and $Pro^8$-OT induced hyperpolarization was partially sensitive to pertussis toxin (PTX) suggesting a minor role for Gi/o activation, whereas in mV1aR and hV1aR cells responses to all three ligands were insensitive to PTX. Paxilline, a selective blocker of large conductance potassium (BK) channels demonstrated a small reduction in AVP-induced hyperpolarization and a moderate reduction in OT-mediated hyperpolarization in qV1aR cells, whereas responses in mV1aR and hV1aR were largely insensitive to paxilline. With Tram-34, a selective blocker of the intermediate conductance (IK) channel $K_{Ca}3.1$, the hyperpolarizing response of all three ligands was attenuated in hV1aR cells, substantially reduced in mV1aR cells, and modestly affected in qV1aR cells, demonstrating differential levels of contribution of $K_{Ca}3.1$ to the hyperpolarizing response depending on the receptor species. Taken together, these

signaling data suggest differences in receptor pharmacology that may underlie differences in social behavior. Integrative studies of behavior, genetics and ligand-receptor interaction may help elucidate the connections between receptor pharmacology and social behaviors.

**Disclosures: M. Pierce:** None. **T.F. Murray:** None.

**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

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**Topic:** B.03. G-Protein Coupled Receptors

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Consejo Nacional de Investigaciones Científicas y Técnicas
Fondo para la Convergencia Estructural del Mercosur (COF 03/11)

**Title:** G protein-coupled CRH receptors signaling in a neuronal hippocampal cellular context

**Authors: *P. A. DOS SANTOS CLARO**[1], N. G. ARMANDO[1,2], C. INDA[1,3], V. G. PIAZZA[1,4], S. SILBERSTEIN[1,3]
[1]Biomedicine Inst. of Buenos Aires (ibioba)- CO, Capital Federal, Argentina; [2]Dept. de Ciencia y Tecnología, Univ. Nacional de Quilmes, Buenos Aires, Argentina; [3]Dept. de Fisiología, Biología Mol. y Celular, Univ. de Buenos Aires, Facultad de Ciencias Exactas y Naturales, Buenos Aires, Argentina; [4]Dept. de Química Biológica, Univ. de Buenos Aires, Facultad de Farmacia y Bioquímica, Buenos Aires, Argentina

**Abstract:** The corticotropin releasing hormone (CRH) system involves GPCRs and neuropeptides (CRH and urocortins 1-3) that act as neuromodulators to develop and integrate a coordinated response to stress. Previous work has shown that icv administration of CRH in mouse brain leads to ERK1/2 activation in the hippocampus and basoamygdalar complex making these areas suitable for the study of CRH neuromodulatory capability.
The aim of our work is to characterize the signaling pathways activated by CRH receptors type 1 (CRHR1) and type 2 alpha (CRHR2α) using as a model the mouse hippocampal neuronal cell line HT22 stably expressing these receptors (HT22-CRHR1/HT22-CRHR2α). We have shown that HT22-CRHR1 cells recapitulate essential features of the cAMP response to CRH seen in primary cell cultures, making this an *in vitro* model useful to perform molecular and cellular experiments that would be more complex, difficult, and even unfeasible, *in vivo.* Furthermore, signaling mechanisms downstream CRHR1 have proven to be highly dependent on the cellular context, highlighting the importance of using neuronal derived cell lines like HT22.We use molecular and pharmacological tools to identify downstream effectors of CRHR1 and CRHR2α. The spatiotemporal features of signaling responses are assessed with Föster Resonance Energy

Transfer (FRET)-based biosensors that allow real-time observation of signaling in live cells, and flow cytometric studies for quantitation of surface receptor. ERK1/2, CREB and Akt are effectors of these GPCRs and dependent on cAMP increase in HT22-CRHR1 cells. We report that activation profiles of these effectors depended on the CRHR and the ligand tested. Besides, CRHR1 and CRHR2α exhibit distinct intracellular distribution: CRH activation promoted a fast internalization of CRHR1, whereas CRHR2α remained intracellularly located until ligand activation. We discuss these findings in terms of different structural features of these GPCRs. We analyzed whether the Gβγ complex was involved in signaling pathways downstream of CRH-activated CRHR1 with a Gβγ scavenger (Gα-transducin) or a pharmacological inhibitor (gallein) finding reduced cAMP, ERK1/2, CREB and Akt responses in absence of the complex. Our preliminary results suggest that Gβγ may also play a role in CRHR1 intracellular trafficking, as complex blockage led to a decrease in CRH-induced receptor internalization. Thus, the molecular analysis of CRHRs signaling in a neuronal cell context provide clues to understand different functional roles of CRHR1 and CRHR2α in the central nervous system.

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**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 781.26/FFF22

**Topic:** F.10. Food Intake and Energy Balance

**Support:** 2014R1A6A1029617
2016R1A2B4010398
2016R1D1A1B03932766
2017R1A5A2015385
2017R1A6A3A11029367

**Title:** Peptide hormone A suppresses food intake via melanocortin signaling in hypothalamus

**Authors: *Y. JANG**[1,2], J. HAN[3,2], S. KIM[5,2], M. LEE[3,2], I. RYU[3,2], X. JU[3], B. YOO[3,2], Y. LEE[3,2], M. RYU[4], J. HEO[5,2], G. KWEON[4,3]
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**Abstract:** Hypothalamic regulation of appetite governs whole body energy balance. Satiety is regulated by endocrine factors including leptin and impairment of its induction causes obesity. Peptide hormone A (PHA) promotes energy expenditure in periphery and systemic reconstitution

of PHA antagonized obesity. However, its role in hypothalamus to control food intake is still unknown. Here, we demonstrated that PHA is expressed in proopiomelanocortin (POMC) expressing neurons located in arcuate nucleus (ARC) of hypothalamus. PHA expression was induced by leptin- mediated STAT3 phosphorylation. Intracerebroventricular injection of PHA significantly reduced food intake via increasing phosphorylation of CREB in POMC and α-melanocyte-stimulating hormone (α-MSH) content in hypothalamus. We also found that hypothalamic injection of PHA significantly suppressed food intake and decreased body weight of high fat diet- induced obese mice which showing leptin insensitivity. We address that hypothalamic PHA provokes anorectic melanocortin pathway and mediates leptin signaling to prevent obesity (2014R1A6A1029617, 2016R1A2B4010398, 2016R1D1A1B03932766, 2017R1A5A2015385, 2017R1A6A3A1102936)

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**Poster**

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**Program #/Poster #:** 781.27/FFF23

**Topic:** F.10. Food Intake and Energy Balance

**Support:** NIH Grant R01 DK102918

**Title:** Obesogenic diet induces an increase in AgRP neuronal excitability that remains persistently elevated even after weight loss and diet intervention

**Authors: *K. GRAHAM**[1], W. WEI[1], A. KORGAN[1], K. O'CONNELL[2]
[1]Res., [2]The Jackson Lab., Bar Harbor, ME

**Abstract:** The neural processes that control appetite are key to understanding basic motivational behaviors and the mechanisms contributing to obesity. Obesity and its associated co-morbidities result from a long-term pattern of overeating and difficulty losing excess weight. However, the basic mechanisms underlying the dysregulation of food intake leading to obesity and obesity-related chronic metabolic illnesses remain unknown. Discrete appetite circuits, such as that controlled by the Agouti-related peptide (AgRP)/Neuropeptide Y (NPY)-expressing neurons in the hypothalamic arcuate nucleus (ARH), can serve as a point of entry to investigate the processes that control food intake. Under normal feeding conditions, AgRP neurons respond to peripheral cues of negative energy balance to elicit food-seeking behavior when activated and are normally rapidly suppressed once food has been presented. In contrast, our laboratory has demonstrated that an obesogenic diet in mice can rapidly remodel AgRP neuronal excitability, suggesting that diet composition itself may reinforce an obese state. Concordantly, recent

evidence from our laboratory has shown that this increase in AgRP neuron intrinsic activity does not return to baseline levels when these animals are reintroduced to chow, regardless of length of time animals were on high-fat diet (HFD) prior to change in diet. Along these lines, we are currently employing a variety of interventions, such as exercise and intermittent fasting, together with change in diet to determine if the effects of HFD on AgRP neuron activity are persistent despite common mediators for obese individuals. Taken together, these data point toward a persistent and irreversible overall change in AgRP neurons specifically due to HFD and suggest that diet intervention alone may not be sufficient to induce changes in feeding behaviors associated with obesity.

**Disclosures: K. Graham:** None. **W. Wei:** None. **A. Korgan:** None. **K. O'Connell:** None.

**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

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**Program #/Poster #:** 781.28/FFF24

**Topic:** F.10. Food Intake and Energy Balance

**Support:** NIH Grant R01 DK102918

**Title:** Divergent mechanisms regulate development and maintenance of obesity following short- and long-term high-fat diet exposure: Electrophysiological and transcriptomic evidence

**Authors: *A. KORGAN**[1], W. WEI[1], K. GRAHAM[2], C. C. KACZOROWSKI[3], K. O'CONNELL[2]
[1]Res., [3]Genomics, [2]The Jackson Lab., Bar Harbor, ME

**Abstract:** In the arcuate nucleus of the hypothalamus (ARH), neurons co-expressing the neuropeptides agouti-related peptide (AgRP) and neuropeptide Y (NPY) are essential for driving food intake. Consistent with their role in 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 diet-induced plasticity and alterations to synaptic inputs to AgRP neurons as a causal factor in obesity. Specifically, we showed that acute HFD feeding was associated with a significant increase in excitatory glutamatergic input. More recently, we have shown that both chow and acute HFD fed mice are sensitive to fasting induced hyperphagia, suggesting that similar mechanisms might underlie both fasting and diet-induced hyperphagia. However, using RNAseq, we found that *Agrp* and *Npy* gene expression does not match expression profiles following a fast, prompting further exploration of novel candidate genes underlying synaptic plasticity and the

subsequent development of obesity. In contrast, 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. Thus, obesity may result from failure of postsynaptic AgRP neurons to efficiently integrate incoming synaptic information following long-term HFD feeding. Ongoing work is aimed at probing diet-induced gene expression changes to identify underlying mechanisms potentiating aberrant signal integration as well as exploring the potential of increased synaptic excitability following acute HFD feeding in driving hyperphagic behavior and the development of obesity.

**Disclosures: W. Wei:** None. **K. Graham:** None. **C.C. Kaczorowski:** None. **K. O'Connell:** None.

**Poster**

**781. Neuropeptide Regulation of Food Intake and Energy Balance**

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**Program #/Poster #:** 781.29/GGG1

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

**Support:** NSFC Grant 61431013
NSFC Grant 81470816

**Title:** Laparoscopic sleeve gastrectomy decreased plasma ghrelin and brain reactivity to food cues

**Authors: *G. LI**[1], Y. HU[1], L. LIU[1], Q. JIN[1], M. XU[1], J. ZHAO[2], G. JI[3], Y. NIE[3], G.-J. WANG[1], Y. ZHANG[1]
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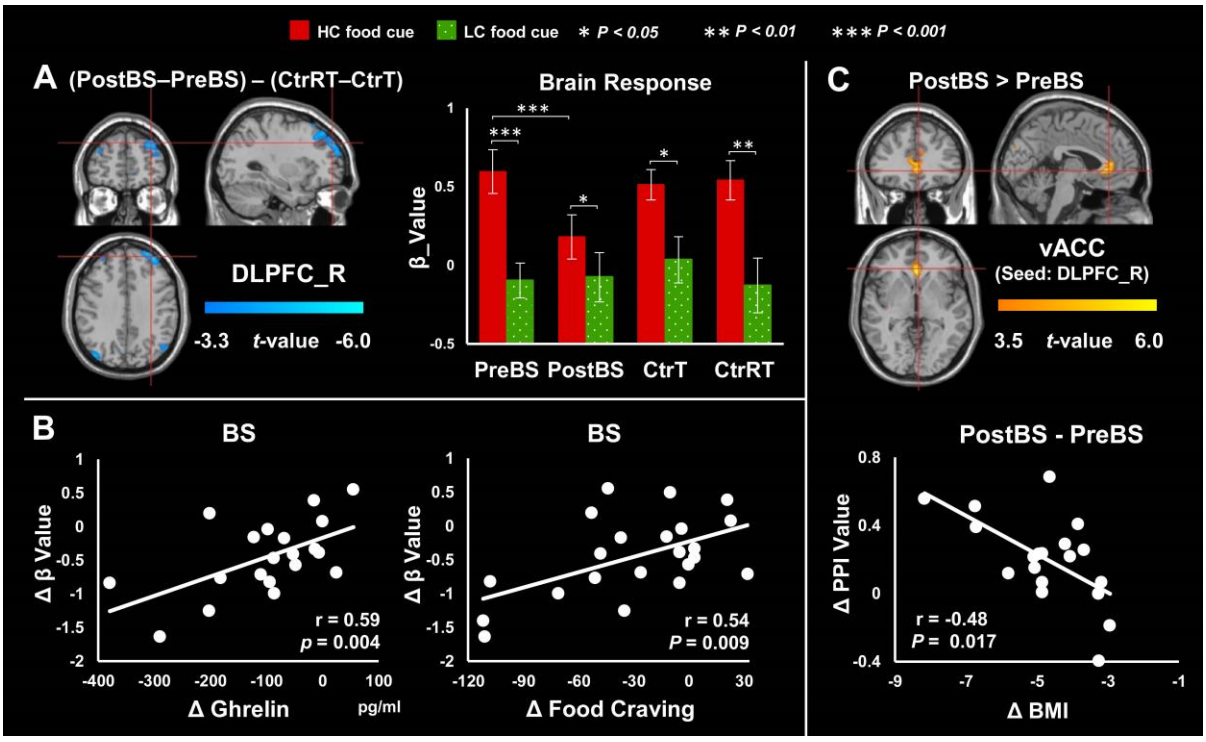
**Abstract:** Laparoscopic sleeve gastrectomy (LSG) is an effective bariatric surgery to treat obesity, and involves removal of the gastric fundus where ghrelin is mainly produced. Ghrelin regulates food-intake and preference for high-calorie (HC) foods in part through its modulation of the mesocortico-limbic dopamine pathway favoring impulsive-behaviors. We test the hypothesis that LSG-induced modulation of the prefrontal-mesolimbic neurocircuitry is associated with alterations of plasma ghrelin.Functional magnetic resonance imaging cue-reactivity task with HC versus low-calorie (LC) food cues was used to investigate brain activity in 22 obese participants (BS), both before (PreBS) and after 1 month (PostBS) of LSG, and in 19

obese controls (Ctr) without surgery that were studied at baseline (CtrT) and 1 month later (CtrRT). ANOVAs were employed to model the group, time and interactions effects on brain responses to HC vs. LC food cues. Psychophysiological interaction analyses were performed to investigate alterations in task-related functional connectivity. LSG significantly decreased fasting plasma ghrelin levels (t=-4.2, P<0.001), behavioral craving for HC food (t=-6.0, P<0.001), and there were significant interaction effects (group × time) on brain responses to HC vs. LC food-cues in the right DLPFC (PFWE<0.05) due to significant activation reduction in the BS group after surgery (t=3.7, P<0.001) (Fig 1A). The decreased DLPFC activation to food-cues post LSG was positively correlated with decreased fasting ghrelin levels and reduced craving under food-cues (Fig 1B). PPI connectivity analyses showed the right DLPFC had stronger connectivity after surgery with the ventral anterior cingulate cortex (vACC), and changes in BMI were negatively correlated with changes in connectivity between the right DLPFC and the vACC (Fig 1C). These findings suggest that LSG-induced weight-loss may be related to reductions in ghrelin, possibly leading to decreased food craving and hypothetically reducing the need for the DLPFC to respond to the HC food cues.

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**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 782.01/GGG2

**Topic:** G.02. Motivation

**Title:** The ventral hippocampus is necessary for contextual modulation of Pavlovian cue-induced reward-seeking

**Authors: *T. H. KIM**[1], P. H. JANAK[1,2]
[1]Johns Hopkins Univ., Baltimore, MD; [2]Solomon H. Snyder Dept. of Neurosci., Johns Hopkins Sch. of Med., Baltimore, MD

**Abstract:** Environmental contexts and cues associated with drugs of abuse promote craving and relapse. Contexts function as occasion setters, signaling either the CS-US relation in a previously rewarded context or the CS-no US relation in an extinction context. One brain region of interest is the ventral hippocampus, which has been shown to modulate the expression of CS-US associations in contextual fear conditioning. Here we examined if the ventral hippocampus is necessary for enhancement of cue-induced reward-seeking by reward-associated contexts. Using a ABA renewal design, rats were trained in context A to discriminate between a $CS^+$ that was followed by a 20% sucrose reward and a $CS^-$ that was followed by nothing. After rats learned to enter the port during $CS^+$ presentation and not during $CS^-$ presentation, they were placed in a different context, context B, for extinction where presentation of the $CS^+$ and $CS^-$ resulted in no sucrose delivery. The two contexts differed in scent, color of the chamber wall, and texture of the chamber floor. Once port entry responses in the extinction context reached <10% of responding on the last day of the rewarded sessions, rats were placed back into context A for renewal testing. Before test, each rat was administered an infusion of either saline or a mixture of GABA agonists, muscimol and baclofen, into the ventral hippocampus. During test, they were presented with the $CS^+$ and $CS^-$ as before but in the absence of any reward delivery. After the first test, rats were re-trained in context A, extinguished in context B, then tested a second time before which they received infusions of the opposite condition from the first test. Inactivation of the ventral hippocampus attenuated renewal of responding during the $CS^+$ in the previously rewarded context. Rats made more port entries during the inter-trial interval after muscimol/balclofen infusion than after saline infusion, indicating that the low number of port entries during the cues was not a result of some general locomotor deficit. These data support the notion that the ventral hippocampus mediates contextual modulation cue-induced reward-seeking.

**Disclosures: T.H. Kim:** None. **P.H. Janak:** None.

**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 782.02/GGG3

**Topic:** G.02. Motivation

**Support:** NIH R01 DA035943

**Title:** Disentangling neural correlates of habits and automaticity in the dorsal striatum

**Authors: *Y. VANDAELE**[1], N. R. MAHAJAN[2], J. M. RICHARD[4], H. S. PROVINCE[2], S. P. MYSORE[3], P. H. JANAK[2]
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**Abstract:** We recently developed a discrete-trials fixed-ratio 5 (DT5) procedure promoting habitual and automatic behavior in rats by providing salient stimuli - lever insertion and retraction - signaling reward availability and delivery, respectively (Vandaele et al, Front Integr Neurosci. 2017). In contrast to the DT5 procedure, rats trained under the more typical free-running fixed-ratio 5 schedule (FR5), responded less efficiently on the lever, and in a goal-directed manner. The dorsomedial (DMS) and dorsolateral (DLS) striatum are necessary for goal-directed and habitual responding, respectively, but these regions also are implicated in skill learning and automaticity. Although both habit and automaticity develop with practice and require dorsal striatum integrity, the relation between these concepts and their specific striatal neural correlates remains unclear. To address this question, we obtained simultaneous *in vivo* single unit recordings in the DMS and DLS during acquisition and after overtraining in the DT5 or FR5 procedures. We found sequence-related activity in dorsal striatum in rats trained in the DT5 procedure, but not in the FR5 procedure. Furthermore, sequence-related activity in the DT5 procedure differed with respect to region (DMS vs DLS) and training (acquisition vs overtraining). While DLS neurons were predominantly excited throughout the behavioral sequence, DMS neurons were on average excited at behavioral sequence boundaries and inhibited during lever pressing. After overtraining, activity in DMS and DLS become more similar, mainly because of a change in DLS activity. Ultimately, the comparison of sequence-related activity across training in procedures promoting behaviors differing in automaticity and expression of habits should allow disentangling the neural correlates of these two concepts in the dorsal striatum.

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**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 782.03/GGG4

**Topic:** G.02. Motivation

**Support:** NSF DGE-1746891
NIH K99 AA025384
NARSAD Young Investigator Award
NIH R01 DA035943

**Title:** Cue-outcome contingency ambiguity impacts ventral pallidum reward signaling

**Authors: *D. J. OTTENHEIMER**[1], J. M. RICHARD[3], P. H. JANAK[2]
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**Abstract:** The ventral pallidum (VP) is a basal ganglia output nucleus implicated in processing the value of rewards and mediating appropriate appetitive and consummatory responses. We recently found that, during consumption, a substantial proportion of the neural population in VP reflects the relative value of reward outcomes. Notably, in those experiments, the identity of the rewards was obscured until delivery, leaving the question of whether VP neural activity at the time of reward delivery would continue to reflect the relative value of each outcome when the identity of the rewards is fully predicted. We tested for this by training rats on a task with three cues: one predicting sucrose delivery (the preferred reward), one predicting maltodextrin (less preferred), and one ambiguous cue predicting each reward 50% of the time. We then recorded the activity of single units in VP, with special interest in reward-specific firing at the time of the cue and at the time of reward consumption. We found that cue-evoked firing of VP neurons reflected the different contingencies associated with each stimulus. The extent to which identity prediction impacted reward-specific firing following reward delivery varied across sessions. Notably, when we performed principal component analysis on the neural activity during cued and ambiguous sucrose and maltodextrin consumption, we could consistently and reliably classify an individual neuron's activity as cued or ambiguous using linear discriminant models trained on individual neurons' principal component weights, even in sessions with little evidence of an impact of cue ambiguity on mean reward firing. Our results support the existence of an expectation-dependent modulation of reward-specific firing in VP that is not necessarily a dominant feature of the population's mean activity.

**Disclosures: D.J. Ottenheimer:** None. **J.M. Richard:** None. **P.H. Janak:** None.

**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

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**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 782.04/GGG5

**Topic:** G.02. Motivation

**Support:** NIH Grant DA035943

**Title:** Dissociable contributions of ventral tegmental and substantia nigra dopamine neurons to reinforcement learning

**Authors: *R. KEIFLIN**[1], H. J. PRIBUT[3], P. H. JANAK[2]
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**Abstract:** Dopamine (DA) neurons in the ventral tegmental area (VTA) and Substantia nigra (SNc) encode reward prediction errors and contribute to reinforcement learning. Importantly, VTA and SNc DA neurons have largely dissociable projections, which suggest potentially dissociable contributions to reinforcement processes. The objective of this study was to tease apart the contribution of VTA and SNc DA neurons to reinforcement learning. To gain selective control of DA neurons, TH-Cre transgenic rats were injected with a viral vector for the expression of channelrhodopsin2 in either the VTA or SNc and optical fibers were implanted, aimed at those regions. Subjects were trained to complete an instrumental response to obtain an optical stimulation of dopamine neurons (VTA or SNc). Once reliable self-stimulation behavior was established, subjects were tested in several behavioral procedures designed to probe different components of the reinforcement process. We observed that: 1) Activation of either VTA or SNc DA neurons is strongly reinforcing but produces different patterns of responding: VTA DA self-stimulation produced regular and sustained responding throughout the session. In contrast SNc DA self-stimulation resulted in irregular bouts of active responding interrupted by long pauses. 2) Forced timeouts (periodic lever retraction) dramatically abolished responding for SNc- but not VTA- DA activation. 3) Cues paired with VTA- but not SNc- DA activation increased persistent responding in a progressive ratio schedule. 4) Activation of VTA but not SNc DA neurons supported the acquisition of a heterogeneous action sequence. Together, these results indicate that activity in VTA and SNc DA neurons recruits largely dissociable reinforcement processes. VTA-DA neurons reinforce motivated and highly organized reward seeking behaviors (hierarchical action plans). In contrast the role of SNc DA neurons appears more narrow and limited to the reinforcement of discrete actions that immediately precede DA activity (elemental motor commands).

**Disclosures: R. Keiflin:** None. **H.J. Pribut:** None. **P.H. Janak:** None.

**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 782.05/GGG6

**Topic:** G.02. Motivation

**Support:** NIH Grant DA035943

**Title:** Dynamic regulation of cue-triggered reward seeking by the basolateral amygdala and orbitofrontal cortex

**Authors: *K. M. FRASER**[1], E. KONG[1], F. PAT[1], P. H. JANAK[2]
[1]Psychological & Brain Sci., [2]Johns Hopkins Univ., Baltimore, MD

**Abstract:** While much is known about the ability of cues in the environment to serve as predictors of reward, the psychological and neurobiological mechanisms that regulate the predictive and motivational significance of reward-paired cues remains unclear. We investigated the regulation of conditioned reward seeking by discrete and phasic sensory events in the environment that inform whether a traditional conditioned stimulus will or will not be followed by reward delivery. We have demonstrated that these cues that resolve ambiguity, called occasion setters, are a unique class of Pavlovian cues that do not predict reward on their own, but are both motivationally desirable and resistant to extinction. To assess potential neural circuits underlying occasion setting we trained male Long-Evans rats in a task in which a conditioned stimulus was followed by sucrose reward only if preceded in time by the presentation of a different occasion setting cue. Presentation of either the occasion setting cue or the conditioned stimulus on their own was not followed by reward. As a result of this contingency, conditioned responding to the food cup was highest to the conditioned stimulus when preceded by the occasion setting cue. Using reversible inactivation with the GABA agonists baclofen and muscimol, we found that inactivation of either the basolateral amygdala or orbitofrontal cortex prevented rats from using occasion setters to produce adaptive conditioned reward seeking. These deficits were specific to cue-triggered behaviors as inactivation of either region did not produce locomotor impairment. These results are consistent with state value encoding theories of the basolateral amygdala and orbitofrontal cortex and suggest activity within this circuit is critical for flexibly updating the motivational significance of cues on a moment-to-moment basis.

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**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 782.06/GGG7

**Topic:** G.02. Motivation

**Support:** Mong Junior Fellowship, Cornell Neurotech
Cornell Presidential Life Sciences Fellowship
NARSAD Young Investigator Award
Robertson Neuroscience Investigator, New York Stem Cell Foundation
NIH Director's New Innovator Award
Alfred P. Sloan Fellowship
Whitehall Foundation

**Title:** The prefrontal cortex-ventral tegmental area projection modulates helplessness and locomotor activity, but not reward-seeking behavior

**Authors: *R. J. POST**[1], V. LEE[1], K. J. PELLEGRINO[1], N. W. RINGELBERG[1,3], D. A. BULKIN[1], B. J. SLEEZER[1], A. K. RECKNAGEL[1], M. R. WARDEN[1,2]
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**Abstract:** Major depressive disorder manifests as combinations of symptoms, and may include decreased engagement in effortful behavior, loss of interest in things that were once considered pleasurable (anhedonia), psychomotor agitation or retardation, weight loss or weight gain, insomnia or hypersomnia, and many others. Recent research has begun to unravel distinct neural correlates for these separable behaviors. The medial prefrontal cortex (mPFC) and its projections to downstream brain regions such as the dorsal raphe nucleus (DRN) has been shown to influence depression-related behaviors in rodents. Although the activity of dopamine neurons has been associated with depression-related behaviors, the role of mPFC control over the ventral tegmental area (VTA) has not been studied in this context. To interrogate the contribution of the mPFC-VTA projection to depression-related behaviors, male mice were injected in the mPFC with either a CaMKIIα-driven channelrhodopsin or a fluorophore-only control, and a fiber optic was implanted over the VTA. Twelve weeks following surgery, behavioral tests related to anhedonia (sucrose preference test), helplessness (tail suspension test and forced swim test), locomotion (open field test), and anxiety (elevated plus maze) were run. These tests included epochs in which the mPFC-VTA projection was stimulated. Optogenetic stimulation of mPFC axons in the VTA significantly increased struggling behavior on the tail suspension test ($t(46) = 6.51$, $p<0.001$), mobility in the forced swim test ($t(31)= 3.22$, $p<0.01$), and locomotion in the open field ($t(32)= 3.47$, $p<0.01$), but did not have a detectable effect on either sucrose preference

or anxiety-like behavior in the elevated plus maze. Unlike the stimulation of VTA dopamine neurons, the mPFC-VTA projection did not support self-stimulation or chronic place preference. These results highlight a selective role for the mPFC-VTA projection in effortful behaviors relevant to depression. Current work is focused on determining the neural dynamics of the mPFC-VTA projection during these behaviors and on characterizing the inputs to subpopulations of projection-defined mPFC cells.

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**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 782.07/GGG8

**Topic:** G.02. Motivation

**Support:** NIH Director`s New Innovator Award
a Robertson Neuroscience Investigator Award from the New York Stem Cell Foundation
a Sloan Research Fellowship
A Whitehall Research Grant
a NARSAD Young Investigator Award and Cornell University

**Title:** A corticostriatal circuit for switching between exploration and exploitation

**Authors: *Y. BAUMEL**[1], B. MONCRIEFFE[1], A. RECKNAGEL[1], J. KIM[2], M. R. WARDEN[1]
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**Abstract:** Animals living in uncertain environments must choose how to divide their time between two essential activities: gathering critical resources, such as food or water, and gathering information to enable better future decisions. In rodents, switching between exploration and exploitation is thought to require frontal cortex. Here, we report that the activity of corticostriatal projection neurons reflects switching between exploration and exploitation in rats performing a two-alternative forced choice (2AFC) task. Rats were placed in a figure-eight maze and allowed to choose between a high reward/high cost arm and a low reward/low cost arm. At first, rats alternated between arms (exploration), but then settled on a consistently preferred arm (exploitation) with occasional exploratory bouts. We recorded neuronal activity in dorsomedial striatum (DMS)-projecting anterior cingulate (ACC) neurons while rats performed this task. To target calcium indicator expression to ACC-DMS projection neurons we injected CAV2-Cre in the DMS and Cre-dependent AAV-GCaMP6m in the ACC. We then implanted a

GRIN lens over the ACC and imaged ACC-DMS neuronal activity with a head-mounted mini-microscope during task performance. In other experiments, we used a non Cre-dependent AAV to image the general ACC population. We found that activity in individual ACC-DMS neurons encoded whether the animal chose to revisit the previously visited arm (stay) or switched from the previous arm (switch), even when action (left or right) and reward size/cost were held constant. Additionally, even though general ACC and ACC-DMS recordings contained similar fractions of action- and reward-responsive neurons (ACC: 11.4% action & 20.3% reward, n=972; ACC-DMS: 11.8% action & 23.2% reward, n=332), significantly more ACC-DMS (over half) than general ACC (less than one-third) action/reward neurons were modulated by the stay/switch decision ($\chi 2$ test, $p<0.0001$). We found that we could predict future strategy with a simple drift diffusion-like behavioral model that incorporated past actions and outcomes, and discovered that ACC-DMS neurons correlated better with predicted stay/switch decisions than general ACC neurons. Our results suggest that activity in the ACC-DMS projection represents information about current and future explore/exploit decisions, potentially useful for action selection in the DMS, that is difficult to read out from the general ACC population.

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**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

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**Topic:** G.02. Motivation

**Support:** Mong Neurotech Fellowship
Robertson Neuroscience Investigator
New York Stem Cell Foundation
NIH Director's New Innovator Award
Alfred P. Sloan Fellowship
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NARSAD Young Investigator Award

**Title:** Ramping activity in midbrain dopamine neurons reflects spatial and non-spatial proximity to goals

**Authors: *A. GURU**, J. A. SCHAFFER, D. S. KULLAKANDA, A. K. RECKNAGEL, C. SEO, M. R. WARDEN
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**Abstract:** Animals are capable of engaging in sustained progress toward spatially and temporally distant goals, such as remote water sources or seasonal migration sites. How does the brain maintain behavior directed at far-off objectives? The role of midbrain dopamine (DA) neurons is of strong interest, as DA release in the ventromedial striatum (VMS) has recently been shown to increase (or 'ramp up') as rats approach rewards. Here, we sought to address some outstanding questions about this ramping activity, including whether DA neural activity also increases as animals approach goals, and what environmental and internal factors are required for the production of ramping activity. To address the first question, we used fiber photometry to record population calcium activity from ventral tegmental area (VTA) DA neurons while mice engaged in goal-directed behavior. An AAV vector encoding Cre-dependent GCaMP6m was injected into the VTA of DAT-Cre mice, and an optical fiber was implanted over the VTA. Mice were then trained to run down a linear track to collect a reward. We discovered that DA neural activity increased continuously as mice approached the reward port, and peaked at the reward. Ramping activity was sensitive to reward location, average reward value, and uncertainty ($n=6$; $p<0.05$), and there was no detectable correlation between DA activity and velocity. We then probed the environmental factors necessary to support DA cellular ramping activity. Spatial navigation provides a stream of visual and inertial information that indicates distance to reward from the current location, information that might be used to construct a continuously rising DA signal. To test for the necessity of this sensory information, mice were trained on a second task in which they ran on a wheel for a reward instead of down a linear track. Mice received a reward if they continuously ran for a fixed distance and then stopped, and were thus required to maintain an internal representation of task progress (distance to goal) to succeed. Surprisingly, this task also produced a continuously rising signal in DA neurons ($n=3$; $p<0.05$). Yoked control mice also ran on the wheel, but received rewards that were not contingent on their own behavior; in these mice DA activity did not rise but remained flat, transiently peaking during reward delivery. Together, these data demonstrate that VTA DA neural activity parallels VMS DA release, increasing as mice approach goals, and suggest that an internal representation of task progress is sufficient to support ramping DA activity.

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**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 782.09/GGG10

**Topic:** G.02. Motivation

**Support:** Wellcome Trust

**Title:** Encoding of reward-related actions across the dorsomedial-dorsolateral striatal axis: Clues from multi-site single unit recordings in the 5-choice serial reaction time task (5-CSRTT) in rats

**Authors: *T. V. GERDJIKOV**[1], J. J. HAYES[1], J. SAUND[1], D. DAUTAN[2], G. P. URCELAY[1]
[1]Neurosci. Psychology and Behaviour, Univ. of Leicester, Leicester, United Kingdom; [2]Dept. of Basic Neurosciences, Univ. of Geneva, Geneva, Switzerland

**Abstract:** The rodent striatum is involved in sensory-motor integration and reward-related learning. Lesion studies suggest functional differences between dorsomedial (DMS) and dorsolateral (DLS) striatum in relation to goal-directed and stimulus-response behaviours. Here we set out to study how reward-driven behaviour in the five-choice serial-reaction time task (5-CSRTT) is mediated by neuronal activity of these structures in the intact rat brain. We recorded single unit activity across the dorsomedial-dorsolateral striatal axis using tetrode arrays in animals pretrained in the 5-CSRTT. In the population, responding in putative striatal medium spiny neurons was more strongly pronounced in the DMS upon contact with the sucrose reward, whilst DLS neurons showed stronger modulation by response cues. These results are novel in showing neuronal activity in these regions and task, and consistent with the general notion that the DMS processes outcome related activity, whereas the DLS processes stimulus-response behaviours.

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**Poster**

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**Topic:** G.02. Motivation

**Support:** NIH Grant R01 DA033396
NIH Grant T32 EB014855

**Title:** Functional role of projection-specific subpopulations of nucleus accumbens medium spiny neurons in reward behavior

**Authors: *C. E. PEDERSEN**[1], D. C. CASTRO[2], E. ZHANG[3], M. R. BRUCHAS[4]
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**Abstract:** Nucleus accumbens (NAc) medium spiny neurons (MSN) have low intrinsic firing and require external excitatory inputs from ventral tegmental area, ventral hippocampus,

basolateral amygdala and prefrontal cortex to drive their neural activity. Although the role of distinct afferent pathways into the nucleus accumbens is being actively elucidated, the functional role of distinct NAc MSN output projections remains unknown. The emerging prevalence of endoscopic lenses has recently enabled the imaging of deep brain structures with subcellular resolution. Here, we use in vivo 2-photon microscopy, transgenic cre-driver lines and endoscopic GRIN lenses to observe the neural activity of NAc subpopulations during reward behavior in awake, behaving mice. Genetically distinct and projection-specific subpopulations of NAc MSNs engage preferentially to reward anticipation, consumption and omission. In vivo 2-photon microscopy allows for single cell discriminability but requires the head fixation of an animal during imaging. To verify our observations of reward-related activity from headfixed microscopy, fiber photometry recordings of MSN subpopulations were made in freely moving animals during reward seeking. Based on these observations of endogenous MSN activity, subsequent time-locked optogenetic experiments were performed to establish the causal role of these distinct NAc subpopulations in determining animal reward behavior. All together, these findings provide new insight into how neurons in the nucleus accumbens influence downstream targets to determine the incentive value and incentive salience of environmental stimuli.

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**Poster**

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**Topic:** G.02. Motivation

**Support:** A.P. Giannini Foundation Postdoctoral Fellowship

**Title:** Amygdalonigral salience signals shape instrumental learning

**Authors: *E. E. STEINBERG**[1], F. GORE[1], B. D. HEIFETS[1], K. T. BEIER[1], M. D. TAYLOR[1], C. FOLDY[2], T. N. LERNER[3], L. LUO[4], K. DEISSEROTH[5], R. C. MALENKA[6]
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**Abstract:** The ability to react appropriately to emotionally significant events is critical for survival. The central amygdala (CeA) is known to orchestrate adaptive responses to threatening stimuli and contribute to other cognitive processes including reward learning. While the CeA cell types and pathways that coordinate defensive behaviors have been studied in detail, the circuits

that mediate CeA-dependent reward processes and their relationship to threat responsive circuits remain poorly defined. The CeA sends a robust projection to the lateral substantia nigra (SNL) which constitutes the major direct connection from the amygdala to midbrain dopamine regions. Dopamine neurons are required for many aspects of reward learning; accordingly, we hypothesized that SNL projections could link the CeA with downstream effectors of appetitive behavior. Here, we use a multidisciplinary approach to dissect the organization and function of CeA-SNL projections in mice. Axonal arborization and single-cell gene expression analyses revealed that CeA-SNL neurons collateralize modestly and overlap with genetically-defined populations implicated in aversive learning. Consistent with our hypothesis, optogenetic activation of CeA-SNL projections reinforced instrumental though not Pavlovian associations, pointing to a selective role for this pathway in reward learning. To determine whether CeA-SNL neurons exclusively encode rewarding events, we used fiber photometry to measure population activity during natural behavior. We found that CeA-SNL neurons were activated by both appetitive and aversive stimuli in a manner that depended on their magnitude and timing, indicating that this pathway encodes salience as opposed to valence, and is well-suited to contribute to the "arousal" dimension of core affect described by contemporary theories of emotion. To assess the post-synaptic mechanism(s) through which CeA-SNL neurons modulate behavior, we used *ex vivo* slice recordings to examine their connectivity. We found that inhibitory CeA projections preferentially target SNL GABA versus dopamine neurons. Moreover, *in vivo* recordings demonstrated that SNL dopamine neurons and CeA-SNL neurons encode similar salience signals, consistent with a disinhibitory mechanism. Taken together, our data suggest that CeA-SNL neurons encode a motivational salience signal capable of profoundly shaping ongoing behavior, revealing a previously unappreciated mechanism for linking emotion, motivation and action.

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**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 782.12/GGG13

**Topic:** G.02. Motivation

**Support:** Intramural Research Program at the National Institutes of Health, National Eye Institute / EY000415-15

**Title:** Unilateral inactivation of primate amygdala causes contralateral hemineglect in emotional facial expression and defensive behaviors

**Authors: *H. LEE**, K. MAEDA, O. HIKOSAKA
Lab. of Sensorimotor Res., Natl. Eye Inst., Bethesda, MD

**Abstract:** When we face a disliked stimulus, we show not just coping behavior but our emotional state through facial expression. In parallel, visual perception could be necessary for emotional expression. Here we raised a question. How does brain modulate visually guided facial expression?
To solve this question, we observed behaviors of rhesus macaque monkey during appetitive (sweet treats) or aversive (forceps) stimuli were getting close to muzzle of head fixed monkey under each hemispheric visual field by human intruder. For appetitive stimuli, monkey opened mouth and protruded tongue out to get the treat. Against aversive stimuli, monkey showed fear related teeth-baring facial expression and defensive behaviors (blinking and defensive hand movement), even though these stimuli had no tactile stimulation and only visually threatened monkey.
After then, we unilaterally injected muscimol ($GABA_A$ receptor agonist) into amygdala, critical brain region for emotional response and visual-motor behavior, to be inactivated. As a result, unilateral inactivation of amygdala blunted fear grimace and defensive behaviors of monkey on aversive stimuli conditioned with contralateral side compared with ipsilateral conditioning. Moreover, responsivities of these behaviors were also aggravated to contralateral stimuli than those associated with ipsilateral side. However, there was no hemispheric behavioral difference in response to appetitive stimuli.
Though amygdala has been studied as a crucial brain region for coping behaviors and emotional recognition, there are lack of studies on visually guided emotional expression such as facial expression. In our additional experiments, we revealed that primate amygdala is important to eye movements to contralateral side and those in stressful environment (2017, 2018 SfN posters by Maeda and Hikosaka). Present study found that inactivated amygdala also causes contralateral hemineglect on emotional and defensive behaviors against aversive stimuli. Taken together we newly suggest that unilateral amygdala controlling contralateral hemispheric visual response may play a pivotal role to control consequent emotional expression and coping behaviors.
*H. Lee and K. Maeda contributed equally to this study.

**Disclosures: H. Lee:** None. **K. Maeda:** None. **O. Hikosaka:** None.

**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 782.13/GGG14

**Topic:** G.02. Motivation

**Support:** Anonymous Biomedical Research Foundation

**Title:** Overlapping, dissociable functional networks in the primate amygdala

**Authors: *J. MORROW**[1], K. M. GOTHARD[2], M. X. COHEN[3,4,5]
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**Abstract:** The primate amygdala is a collection of richly interconnected yet functionally and anatomically heterogeneous nuclei. Advances in multi-electrode recordings allows for more fine-grained investigations into functional networks within the amygdala, yet much of our knowledge about the functioning of the amygdala is based on single-unit recordings that are not amenable to multivariate network-based analyses. Here we show that the primate amygdala contains multiple simultaneous subnetworks that have differential responses to sensory input (visual, auditory, tactile). We applied multivariate source-separation algorithms (based on generalized eigendecomposition of temporally windowed covariance matrices) to LFP data from 16-channel V-probes that span multiple amygdala nuclei. Different recordings contained 2-6 statistically dissociable components. Components exhibited both similar and distinct temporal/spectral responses to sensory stimuli of different modalities, highlighting the complexity of the mesoscale dynamics in the amygdala. State-space analyses provided additional insights into amygdala activity, with differences in state-space trajectory speed being greatest for visual stimuli, compared to auditory and somatosensory stimuli. Taken together, these findings demonstrate the feasibility and usefulness of a multivariate approach to understanding the mesoscopic organization of the primate amygdala.

**Disclosures: J. Morrow:** None. **K.M. Gothard:** None. **M.X. Cohen:** None.

**Poster**

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**Program #/Poster #:** 782.14/GGG15

**Topic:** G.02. Motivation

**Support:** PSOMH10023

**Title:** Local field potentials in the primate amygdala during identity discrimination

**Authors: *R. C. PHILIP**[1], P. PUTNAM[2], S. LEE[1], C. P. MOSHER[3], K. GOTHARD[1]
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**Abstract:** Two adult male monkeys were trained to discriminate between previously unfamiliar conspecifics. During each session the subject monkey was shown simultaneously presented pairs

of videos depicting two of the three individuals. The subject monkeys learned by trial and error that each individual was associated with a different amount of reward (0, 3, or 8 drops of juice) by choosing one side. Both monkeys performed above criterion. We recorded local field potentials (LFP) and isolated single neurons from 32 sites (16 in each amygdala) located along the shaft of a sixteen-channel v-probe spanning the entire dorsal-ventral expanse of the amygdalae. This arrangement allowed us to compare LFP and single units in different nuclei of the amygdala. Indeed, the pattern of the LFP spectrogram varied across the main nuclear divisions of the amygdala. We found significant increases or decreases in oscillatory power at multiple frequencies that were task related. The most prominent changes in LFP dynamics were observed 200-500 ms after video-onset. These include moderate increases (>2 SD from the mean) in the 2-8 Hz and larger increases or decreases in the 10-20 Hz frequency bands. The largest and most reliable power increases (>3 SD from the mean) were observed in the 35-55 Hz frequency band. To avoid potential artifacts caused by spectral leakage from the spikes, we did not consider frequencies greater than 55 Hz. While the onset of the stimulus appears to cause the largest increases in LFP power, weaker but similar activity patterns were triggered by the presentation of a choice cue that preceded an operant behavior. We did not find large differences in the LFP dynamics associated with different reward pairings (8-3, 8-0, 3-0). Finally, we examined the relationship of spiking activity to the phase of oscillations in four frequency bands: 4-10, 10-20, 20-35, and 35-55 Hz. We found that approximately 1/3 of the neurons showed increased spiking probability at the trough or the rising phase of the two highest frequency bands (20-35 and 35-55 Hz). The subpopulation of neurons that show entrainment can be further examined for their response properties in relation to the representation of identity, reward, and task-related responsiveness.

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**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

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**Program #/Poster #:** 782.15/GGG16

**Topic:** G.02. Motivation

**Support:** NIMH-1R01MH112355-01
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**Title:** Extended amygdala-parabrachial circuits alter threat perception and encode homeostatic and hedonic feeding

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**Abstract:** In order to survive, an animal must seek and consume food while avoiding environmental threats. In mammals, food consumption is heavily influenced by the parabrachial nucleus (PBN), a pontine structure that integrates visceral information to encode metabolic needs. The PBN receives top-down input from the bed nucleus of the stria terminalis (BNST), an extended amygdala structure that encodes affective and threat information. These dense projections to the PBN enable a potential circuit that may be involved in the complex integration of environmental threat evaluation with an animal's own homeostatic or hedonic motivations for feeding. *We hypothesize that BNST-PBN circuits integrate environmental threat information to modulate food-seeking behaviors such as exploration and consumption.* Here we used complementary tracing, electrophysiological, and biochemical techniques to identify and characterize distinct excitatory and inhibitory BNST-PBN circuits. In order to assess the role of these distinct circuits, we selectively targeted GABAergic and glutamatergic BNST-PBN circuits to monitor and manipulate circuit activity during behaviors associated with affective motivation, such as hedonic and homeostatic feeding and threat perception. We found that vGAT- and vGluT2-expressing BNST-PBN circuits have divergent roles in valence-encoding, threat, and homeostatic and hedonic feeding behaviors. When activated, vGlut2+ BNST-PBN circuits cause aversion, operant negative reinforcement, anxiogenesis, and reduced feeding behavior. vGAT+ BNST-PBN circuits drive preference, operant positive reinforcement, anxiolysis/exploratory behavior, and increased feeding behavior. Using calcium imaging, we uncover divergent endogenous excitatory and inhibitory BNST-PBN circuit dynamics during feeding behavior, showing that inhibitory BNST-PBN projections are most active during feeding. We are currently evaluating excitatory BNST-PBN circuit dynamics in feeding. Additionally, rabies tracing suggests that these populations are monosynaptically connected to previously identified CGRP PBN neurons that serve as an alarm system to modulate affective motivation, as well as onto a population of dynorphin neurons in the PBN that are involved in valence-encoding and food consumption, consistent with both inhibitory and excitatory GABAergic and glutamatergic BNST input to the PBN. Together, our findings characterize distinct BNST-PBN circuits, revealing their opposing roles in threat perception and feeding behaviors to describe a mechanism by which animals evaluate environmental threat to enable feeding and promote survival.

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**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

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**Topic:** G.02. Motivation

**Support:** Anonymous biomedical research foundation

**Title:** Multisensory neurons in the primate amygdala differentiate between tactile, visual, and auditory stimuli by response polarity and response magnitude

**Authors: *K. GARCIA**[1], P. E. ZIMMERMAN[1], J. MORROW[1], C. P. MOSHER[2], K. M. GOTHARD[1]
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**Abstract:** We have previously shown that neurons in the primate amygdala differentiate between visual stimuli by variation of firing rates along three main axes: response polarity (increases or decreases of firing rate), response magnitude (departure from baseline firing rate), and duration of response (phasic or tonic changes in firing rate). In a recent set of experiments, we found that a large proportion of amygdala neurons were multisensory (i.e., responded to stimuli from multiple sensory modalities). To determine whether the same metrics differentiate between sensory modalities, we analyzed the properties of multisensory neurons recorded from the amygdalae of two adult male macaques. To avoid influences of valuation/appraisal on modality-selective neural responses, we used stimuli with no known ethological value for the monkeys. The tactile stimuli were gentle (non-aversive) air puffs delivered to 8 different locations of the face; 8 images depicting random objects or fractals; while the 8 auditory stimuli were random noises (e.g., doorbell ringing). Response polarity differentiated between sensory modalities in a majority of the multisensory neurons. In contrast, only a small fraction of neurons showed opposite response polarity to differentiate between items within a sensory modality. Item-selectivity within a sensory modality was achieved mainly by variation of response magnitude. The distribution of the item-selectivity values were similar across modalities. Differences in the temporal pattern of neural responses was both modality-specific and item-specific. For example, a neuron responded with tonic increases in firing rate to visual stimuli, phasic increases in firing rate to auditory stimuli, and phasic decreases in firing rate to tactile stimuli. Taken together these findings indicate that (1) the majority of stimulus-responsive neurons in the primate amygdala are multisensory, (2) multisensory neurons respond to stimuli devoid of social or emotional significance, and (3) different dimensions of the stimuli (modality, stimulus identity) engage differently the same neurons.

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**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

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**Topic:** G.02. Motivation

**Support:** Intramural Research Program at the National Institutes of Health, National Eye Institute / EY000415-15

**Title:** Amygdala for the saccadic eye movement in emotional contexts

**Authors: *K. MAEDA**, O. HIKOSAKA
Lab. Sensorimotor Res., Natl. Eye Inst., Bethesda, MD

**Abstract:** Goal-directed behavior is affected by various contexts on the basis of repeated experience in addition to the predicted immediate outcome of choices, but the neural mechanisms underlying such context-appropriate behavior are unclear. In our recent study, we devised a novel foraging task for macaque monkeys in which various emotional contexts (dangerous-safe, rich-poor) changed across many environments. It has shown that monkeys' eye-movement was modulated differently in these contexts independent of immediate outcome. This was associated with extremely quick saccades (express-saccades), suggesting that automatic behaviors were enhanced in this task. Also, we found that many neurons in the amygdala, especially the central nucleus (CeA), responded to the environments before any object appeared and did so selectively depending on the emotional context of the environment. The neuronal activity was tightly correlated with the reaction time of saccade across the contexts. However, it is still unknown whether these amygdala neurons actually control the initiation of saccades.
To address this question, we temporally inactivated CeA on one side by injecting a GABA agonist (muscimol, 5 μg/μl, 1 μl volume) and examined the monkey's performance of the foraging task and simple visually-guided saccade tasks.
We found that the unilateral CeA inactivation inhibited saccadic eye movements to the contralateral side. Importantly, the emotional contexts rarely affected the saccade reaction time, in contrast to the normal condition. However, the value-bias of saccadic reaction time remained and was even enhanced in simple saccade tasks. We then examined the effect of musicmol injection in surrounding areas (putamen, globus pallidus, and basolateral amygdala); the effect on saccades, especially the context-dependent effect, was weaker or absent compared with the inactivation of CeA.
These results suggest that the amygdala, especially the central nucleus (CeA), facilitates saccadic eye movement to the contralateral side when the environment is dangerous or rich.

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**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

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**Topic:** G.02. Motivation

**Support:** PHS research grant DA041674
NARSAD Young Investigator Grant, Brain & Behavior Research Foundation

**Title:** Target-specific effects of hypocretin/orexin neuron activation on seeking-taking behavior in the rat

**Authors: *C. G. PERK**[1], A. YAMANAKA[2], D. E. MOORMAN[1]
[1]Dept. of Psychological and Brain Sci., Univ. of Massachusetts Amherst, Amherst, MA; [2]Res. Inst. of Envrn. Medicine, Nagoya Univ., Nagoya, Japan

**Abstract:** Hypothalamic hypocretin/orexin (ORX) neurons are critical for the expression of reinforcement behavior requiring high motivation and are strongly implicated in substance abuse disorders. They are also involved in the regulation of arousal, fear, and stress. Exactly how orexin neurons control diverse behaviors remains undetermined but may stem from diverging projections such as to ventral tegmental area (VTA) or locus coeruleus (LC). As a first step in addressing this question, we are studying the overall role of ORX neurons, and that of ORX-VTA and ORX-LC projections in reward-motivated behaviors, using a seeking-taking task. Orexin:cre rats received AAV8 in the LH (LH-ORX rats, n = 4), or rAAV2-retro infusions in either LC (n = 4 rats) or VTA (n = 5 rats) to selectively express excitatory hM3Dq DREADDs in orexin neurons at large, or in those projecting to either target. 20 min prior to the task rats received clozapine-N-oxide (CNO, 3mg/kg, i.p.) to activate orexin neurons, or vehicle. For the seeking-taking task, rats were placed in a chamber containing two wells. The seeking well was indicated via an over-well light, which was always the left well for LH-ORX rats, but randomly chosen for other groups. Correct entry (seeking response) delivered a tone (0.1s, 2.5 kHz) and shifted the light cue to the alternate well. Entry into this well (taking response) was accompanied by a unique tone (0.1s, 3 kHz) and reward delivery (15% sucrose solution, 0.1 ml), followed by an inter-trial interval of 10-15s for LH-ORX rats, or 1s for ORX-VTA and ORX-LC animals. Analysis of preliminary data indicates LH-ORX activation increased break point on a progressive ratio (PR) seeking-FR1 taking schedule 121 ± 72% (mean ± SD) above that observed after vehicle ($p = 0.04$). In contrast, fixed ratio (FR) 1 seeking-FR1 taking was not affected after activating LH-ORX (total rewards: CNO, 144 ± 46, vehicle, 147 ± 20, $p = 1.00$; total well entries: CNO, 713 ± 221, vehicle, 718 ± 191, $p = 1.00$), VTA-ORX (total rewards: CNO, 433 ± 108, vehicle, 436 ± 92, $p = 1.00$; well entries: CNO, 1083 ± 343, vehicle, 1075 ± 347, $p = 1.00$), or ORX-LC neurons (total rewards: CNO, 428 ± 98, vehicle, 434 ± 39, $p = 1.00$; total entries:

CNO, 939 ± 342, vehicle, 1055 ± 464, p = 0.38). These data indicate orexin neurons overall selectively enhance seeking-taking behavior when a high motivational state is required, and we are currently examining how ORX-VTA or ORX-LC neuron activation effects PR seeking-FR1 taking behavior. These data will provide new insights into the roles of orexin in diverse aspects of motivated behavior for natural reinforcement and drugs of abuse.

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**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

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**Topic:** G.02. Motivation

**Support:** This work was supported by NIDA/NIH

**Title:** Elucidating the role of the supramammillary nucleus in motivational processes

**Authors: *A. KESNER**, S. IKEMOTO
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**Abstract:** Motivational capacity to interact with the environment is fundamental for everyday healthy living. Motivated behaviors ultimately manifest through reward and aversion processes, where animals must approach positive 'rewarding' stimuli and avoid negative 'aversive' stimuli to survive. The supramammillary nucleus (SuM), is a small posterior hypothalamic nucleus that provides dense projections throughout the cerebrum. Past research on SuM has focused on its role in arousal, learning, and memory. Our lab previously found that pharmacological stimulation of SuM neurons can reinforce behavior, leading us to further investigate the role the SuM and its related circuitry plays in reward and motivation. We first confirmed stimulation of SuM neurons is rewarding using a self-stimulation procedure with optogenetics involving *channelrhodopsin-2* (ChR2) in wild-type (C57/BL6) mice. Mice with ChR2 and optic fibers in SuM quickly learned to respond on a lever reinforced by photostimulation and switch responding when lever assignments are reversed. Mice do not reliably self-stimulate when optic fibers are placed in areas adjacent to SuM, ie. in the mammillary bodies or ventral tegmental area. Using a Cre-dependent ChR2 and vGlut2-Cre, Th-Cre or vGat-Cre mice, we show this rewarding effect of SuM neuron stimulation is likely mediated by glutamatergic neurons, but not dopaminergic or GABAergic neurons. Using optogenetic terminal-stimulation we dissect which glutamatergic projections from the SuM mediate self-stimulation behavior. Mice learned to respond for the stimulation of SuM glutamatergic neurons terminating in the septal area, but not terminals in other projections. In addition, mice show real-time place preference for activation of the SuM to septum circuit, and real-time place aversion for activation of the SuM to PVT circuit, indicating

bivalent affective processes driven by SuM circuitry. SuM-Septum reward is possibly mediated by dopamine, as dopamine receptor antagonism similarly decreases self-stimulation of both SuM-septum and classic dopamine mesolimbic reward circuitry. To investigate the role of SuM neurons in food taking and seeking behaviors, we conducted single-unit in-vivo electrophysiology experiments in mice seeking sucrose, a natural reward. Most SuM neurons change their firing rates as a function of sucrose seeking, taking, or both. Our results implicate the SuM and its downstream targets in motivational processes. As this circuitry is somewhat non-canonical in terms of classical reward circuits, we feel it particularly warrants future research into its role in psychiatric disorders such as depression and addiction.

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**Topic:** G.02. Motivation

**Support:** NIH R01MH11235502
FAER MTRG to AN

**Title:** Supramammillary neurons projecting to preoptic hypothalamus drive active stress responses and mediate negative valence

**Authors: *A. J. NORRIS**[1], M. M. VOTOUPAL[2], J. R. SHAKER[3], C. E. PEDERSEN[4], M. R. BRUCHAS[5]
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**Abstract:** When faced with a threat or stressor animals must decide either to respond with active (ex. fleeing exploratory, fighting) or passive (ex. freezing, submission) behavioral responses. Exposure to stressors predisposes individuals to subsequent mood and anxiety disorders. However, individuals displaying active rather than passive responses to stressors have less vulnerability to mood and anxiety disorders than those displaying passive responses. The neurocircuits underlying active responses to threat and stress remain poorly understood. One area found to mediate arousal and potentially modulate responses to threatful stress is the supramammillary nucleus (SuM). The results we report here isolate a previously uncharacterized population of glutamatergic neurons in SuM project to the preoptic area (POA). We expressed channelrhodopsin in vGLUT2+ SuM to POA projection neurons and tested for a real-time place preference. We also determined whether photo-stimulation of SuM to POA vGLUT2+ projecting

neurons was sufficient to drive preference to the light side of a light/dark arena when stimulation was provided on the dark side. Surprisingly, engagement of vGLUT2+ SuM to POA projections did not produce anxiogenic behaviors. Furthermore, our results indicate that SuM to POA vGLUT2+ projection neurons promote robust exploratory behavior, with activation of SuM neurons increasing mean distance traveled and mean rate of movement in the open field. We have also determined additional projection targets of SuM cells using retrograde viral tracing strategies and describe that here. Finally, we examined that the impact of activation of vGLUT2+ SuM to POA on the performance of a negative reinforcement operant task, whereby the animal must work to stop photo-stimulation of this circuit. Finally, we used GCaMP imaging approaches to dissect how this projection responds to various threats and stressful stimuli. In summary, these results indicate a previously unknown role for vGLUT2+ SuM to POA projections in aversive behavioral responses to threat and stressful stimuli. R01MH11235502 (MRB), NIH; Foundation for Anesthesia Education and Research MTRG to AN

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**Poster**

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Cornell Presidential Fellowship
Robertson Neuroscience Investigator, New York Stem Cell Foundation
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Alfred P. Sloan Fellowship

**Title:** Lateral habenula neurons signal the decision to stop work

**Authors: *B. J. SLEEZER**[1], D. A. BULKIN[1], R. J. POST[1], V. LEE[1], A. K. RECKNAGEL[1], M. R. WARDEN[1,2]
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**Abstract:** Lateral habenula (LHb) neurons encode negative reward prediction errors; they are excited by punishments and omission of expected rewards, and are inhibited by unexpected rewards. However, the neural dynamics of LHb in freely moving animals engaged in effortful reward-seeking behavior are less well understood. Moreover, it is unclear whether LHb exhibits

long-timescale, state-dependent activity changes. Here, we describe tonic changes in LHb activity in mice during the performance of two different reward-seeking tasks. We injected a Cre-dependent AAV encoding GCaMP6s into the LHb of klk8-Cre mice, resulting in LHb-restricted calcium indicator expression, and implanted an optical fiber over the LHb to record population calcium dynamics via fiber photometry. After recovery, mice were trained to perform a task in which a nose poke on one side of an operant chamber led to the delivery of a reward on the other side of the chamber. Mice were free to initiate, or refrain from initiating, trials during the entirety of each 30-minute session. We recorded LHb activity during a probabilistic version of this task in which each successful nose poke had a 20% chance of yielding a large reward, 60% chance of yielding a medium reward, and 20% chance of yielding no reward. As expected, we found that LHb activity increased following reward omission and decreased following delivery of medium or large rewards. When we examined mouse behavior, we found that the time between trials increased toward the end of each 30-minute session, suggestive of task disengagement. Intriguingly, we also observed a robust increase in LHb activity that correlated with task disengagement ($r = 0.1369$, $p < 0.0001$, Pearson's correlation between baseline florescence and intertrial interval). In order to probe whether the increase in LHb activity reflected the gradual development of a fatigue or satiety state, or, alternatively, a faster, reversible, and experimentally controllable motivational state change, we tested mice on a version of the task in which reward and no-reward trials were grouped into alternating 5-minute blocks. During no-reward blocks, mice usually completed several nose pokes before temporarily terminating task performance. We found that LHb activity peaked following task disengagement and decreased upon resumption of task performance in subsequent reward blocks ($p = 0.0127$; paired samples t-test between avg. fluorescence 1 min. before and 1 min. after task disengagement). These findings suggest that tonic signals in LHb reflect the decision to terminate effortful reward-seeking behavior. Ongoing studies are aimed at determining the causal impact of these signals on behavior.

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**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 782.22/GGG23

**Topic:** G.02. Motivation

**Support:** DARPA Grant HR0011-16-2-0022
NIMH Grant R01MH110594

**Title:** Tonic and phasic basal forebrain neurons distinctly signal internal and external states associated with salience, surprise, and novelty

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[1]Washington Univ. In St. Louis, Saint Louis, MO; [2]Washington Univ. In St. L, Saint Louis, MO; [3]Neurosci., Washington Univ. Sch. of Med., Saint Louis, MO

**Abstract:** Basal Forebrain (BF) is one of the principal sources of modulation and control of the neocortex. Though, BF is thought to be involved in cognitive functions such as attention, motivation, learning and memory, how BF neurons encode cognitive variables related to these functions remains a topic of active research. Previous work has identified prominent groups of BF neurons that are activated by the predictions or deliveries of salient events: phasic-activated neurons (Type 1; Lin and Nicolelis, 2008; Hangya et al., 2015), and tonic regularly-firing BF neurons (Monosov et al., 2015; Hangya et al., 2015) that ramp to the predicted time of delivery of uncertain or aversive outcomes (Type 2; Monosov et al, 2015). Here, we studied Type 1 and Type 2 neurons while monkeys participated in a series of behavioral procedures that tested whether and how BF neurons represent prediction errors, surprise, value, and novelty. We found that Type 1 neurons are highly sensitive to salient external events, but do not encode reward prediction errors (RPEs) or surprise (unsigned RPEs), per se. For example, Type 1 neurons were rapidly activated by reward predicting conditioned stimuli (CSs) and reward deliveries, and these activations were related to their value and expectancy, respectively. However, Type 1 neurons did not change their activity when rewards were unexpectedly omitted. In addition, Type 1 cells were selectively activated by the presentation of novel visual object stimuli, even when these stimuli were not associated with reward or punishment. Also, their novelty responses weakly but consistently increased if the novel object was relevant for a subsequent memory task. On the other hand, following CS presentation, Type 2 neurons signaled predictions about the timing of the outcome, particularly during reward uncertain trials, with strong ramp-like activations. Also, their trial-outcome responses were strongly modulated by both reward deliveries and omissions in a manner of "surprise". In contrast to Type 1 neurons, Type 2 neurons did not discriminate novel versus familiar objects. These data show that BF neurons are highly sensitive to rewarding and non-rewarding events in manners that may support BF's role in attention and memory. Type 1 cells signaled the occurrence of external salient events, and robustly responded to presentations of novel objects. On the other hand, on average Type 2 neurons encoded internal states, particularly the internal timing of the salient events. How the internal and external processing systems in the BF interact to affect cortical processing will be the direction of our subsequent investigations.

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**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

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**Topic:** G.02. Motivation

**Support:** F32DA043999-01A1
R01DA042499

**Title:** Mu-opioid receptors in nucleus accumbens medial shell mediate stress enhanced motivated behaviors

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**Abstract:** Mu opioid receptors (MORs) are involved in motivation for natural and drug rewards. One site for MOR action is nucleus accumbens medial shell (NAc mShell). MOR stimulation in this mesocorticolimbic hub enhances motivated behaviors. By contrast, disruption of MOR signaling has yielded ambiguous results, sometimes reducing motivation, other times being ineffective. Here, we sought to determine when MORs are recruited to mediate motivated behaviors by systematically disrupting or restoring MOR function during multiple behavior tasks. First, we show that MORs are necessary for both appetitive and aversive motivated behaviors using constitutive $MOR^{-/-}$ knockout mice (KO) in food intake and elevated zero maze tasks. Specifically, MORs were necessary for enhancing behaviors in stressful states, i.e., increased food intake after food deprivation or increased open-arm avoidance after full body restraint. Similar MOR mediated deficits were also observed with local pharmacological antagonism (CTAP) in NAc medial shell. Surprisingly, local deletion of MORs using conditional knockout mice ($Oprm1^{fl/fl}$) did not likewise prevent stress enhanced behaviors, but deletion of MORs from incoming projections to NAc medial shell did, suggesting a presynaptic mechanism. In conjunction with these studies, $Oprm1^{fl/fl}$ were crossed to dynorphin or enkephalin-cre lines to selectively delete MORs from these cell type populations. Results indicate that deletion of MORs from enkephalin, but not dynorphin, neurons disrupts stress enhanced motivation, similar to local CTAP or retro-MOR deletion. To further isolate and identify which NAc afferent population mediates stress enhanced motivation, we injected a cre-dependent retrograde fluorescent tracer in NAc medial shell in enkephalin or MOR-cre mice. Labeled sites include infralimbic cortex, ventral pallidum, dorsal midline thalamus, basal amygdala, and dorsal raphe. Future experiments will target these regions and delete or rescue MORs to disrupt or restore stress enhanced

behaviors. Next, using the anatomical information obtained from retro-tracing, we will also use caspase and optogenetic tools to experimentally delete or activate neuronal populations that may serve as the source for the MOR ligand. Lastly, to determine how MORs affect neuronal signaling while animals are in different stress states, we use cell type specific in vivo 1-photon imaging in the presence (enkephalin or dynorphin-cre) or absence (KO crossed with dynorphin or enkephalin-cre) of MORs. Collectively, these studies will isolate the and identify how MORs act in NAc to modulate motivated behaviors.

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**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

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**Topic:** G.02. Motivation

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**Title:** A parabrachial to preoptic hypothalamus opioid circuit that regulates body temperature

**Authors: *J. R. SHAKER**[1], A. J. NORRIS[1], M. VOTOUPAL[1], M. R. BRUCHAS[2]
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**Abstract:** Neurons in the preoptic hypothalamic area (POA) and in the parabrachial nucleus (PBN) are implicated in a neural circuit responsible for maintaining temperature homeostasis. Multiple lines of evidence suggest that opioid peptides act in the POA to regulate behavior and physiology. For example, agonists binding to kappa opioid receptors (KOR) and mu opioid receptors (MOR) in the POA have been shown to differentially modulate body temperature. Dynorphin (dyn) - containing neurons in the PBN have been found to show c-Fos expression after exposure to warm temperatures. Here we found that c-Fos expression is induced in the PBN by both warm and cold temperatures. c-Fos induction in both warm- and cold- exposed animals was seen in both dynorphinergic and enkephalinergic neurons. Using tracing methods, we report that dynorphinergic and enkephalinergic PBN cells project to the ventral and medial areas of the POA. Optogenetic activation of PBN dyn-positive terminals in the POA caused a robust decrease in the body temperature: After 15 minutes of stimulation, body temperature dropped

5.15±0.12°C at 20 Hz, 5.42±0.37°C at 15 Hz, 5.30±0.33°C at 10 Hz, 3.15±1.25°C at 5 Hz, and 0.32±.42°C at 2Hz. Body temperature rose to baseline in about 20 minutes post-stimulation. In real time place preference testing, activation of dyn-positive PBN terminals in POA was aversive at 22°C ambient temperature. We have also identified KOR-positive neurons present in the POA. Activation of KOR POA neurons using DREADDs likewise caused a 3°C drop in body temperature. These findings indicate that dyn-positive cells that project from PBN play important roles in maintaining homeostatic body temperature and the affective perception of temperature. The roles of enk-positive PBN to POA projections and specific opioid peptides in regulating this circuit are areas of ongoing investigation.

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**Poster**

**782. Subcortical Mechanisms in Motivated Behaviors and Physiological States**

**Location:** SDCC Halls B-H

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**Title:** Whole-brain mapping of the input-output organization of claustrum implies its functional role as a limbic-motor interface

**Authors: *J. B. SMITH**, R. KIM, J. MALLARI, A. JAUFFRET, J. WU, X. JIN
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**Abstract:** The claustrum is a forebrain, subcortical brain region whose function remains unknown due to technical difficulties in targeting this geometrically challenging structure. The majority of literature on the claustrum has focused on its role in sensorimotor processing, owing to its widespread interhemispheric projections with sensorimotor cortex. Specifically, previous anatomical tracing studies have demonstrated that the claustrum has projections to every part of cortex, yet receives the bulk of its inputs from frontal cortex. Here, using cutting-edge viral tracing, we dissect the precise input-output organization of a subset of claustrum neurons that project to secondary motor cortex (M2). By employing AAVretro.Cre injections into M2, we can precisely target claustrum output neurons with Cre-dependent AAV injections without any

contamination in the surrounding striatum or insular cortex. Furthermore, numerous immunohistochemical markers confirm our precise targeting of the claustrum. Our results indicate that claustrum neurons that target M2 have substantial branching to numerous other cortical targets including sensory cortex (somatosensory, visual and auditory areas), association cortex (cingulate and posterior parietal cortex), as well as to limbic cortices (prelimbic, orbitofrontal, entorhinal areas). However, these projections were not all even, with denser terminal fields in limbic and associative cortices. We subsequently employed a Cre-dependent, monosynaptic rabies approach to map the whole-brain inputs to these M2-projecting claustrum output neurons. We found the bulk of the inputs originate from a wide range of cortical areas across both hemispheres, primarily from limbic and associative regions of frontal cortex. The second major input was from the claustrum itself, whose population was found to consist of other claustrum output neurons as well as a wide array of claustrum interneurons that stained for different interneuron markers including PV, SOM, NPY, VIP, and others. Finally, though we did not observe projections from the claustrum to any subcortical structures, we did observe strong inputs from the basolateral amygdala, as well as parafasicular and mediodorsal nuclei of the thalamus. These anatomical results demonstrate that the claustrum is primarily driven by limbic and associative inputs from cortical and subcortical regions, which is then disseminated across almost the entire cortical mantle, particularly associative and motor cortices. Thus, we hypothesize a role for the claustrum as a node for limbic-motor interactions, whereby limbic information about emotional valence can directly alter motor-output.

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**Poster**

**783. Anxiety Disorders: Preclinical Models**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 783.01/GGG27

**Topic:** G.05. Anxiety Disorders

**Support:** MRC Programme grant MR/M023990/1

**Title:** Role of the serotonin transporter in the amygdala in trait anxiety

**Authors: *S. QUAH**[1,2], A. M. SANTANGELO[1,2], A. C. ROBERTS[1,2]
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**Abstract:** High trait anxiety, an individual's disposition to feel anxious, is associated with higher risk of developing anxiety disorders and altered activity across cortical and amygdala circuitry.

Since serotonin is implicated in the activity of these regions and is the target of first line treatment for pathological anxiety, this study determined the role of the serotonergic system within this brain circuitry in trait anxiety. First, it identified differential expression of serotonergic genes associated with anxiety and second, investigated their causal role in the high trait anxiety phenotype.
An exploratory factor analysis was conducted using data from 161 common marmosets (*Callithrix jacchus*) in an anxiety-provoking context, the human intruder test, to derive an anxiety score reflecting avoidance and vigilance behaviour. Using quantitative reverse transcription polymerase chain reaction, we then measured gene expression in a cohort of 12 animals within the medial prefrontal, orbitofrontal, and dorsal anterior cingulate cortices, amygdala, and the dorsal and median raphe nuclei, the latter where serotonergic neurons originate. We targeted serotonergic genes implicated in anxiety: the serotonin transporter (5HTT) and serotonin 1A, 2A, and 2C receptors. A correlational analysis revealed that 5HTT expression specifically within the right amygdala was positively associated with anxiety scores. Since the 5HTT downregulates serotonin signalling via reuptake of synaptic serotonin, increased 5HTT levels supports the lab's previous finding of reduced amygdala extracellular serotonin in high trait anxious marmosets (*Mikheenko et al., 2015. NPP, 40: 1395-1404*).
Based on this association, the causal role of amygdala 5HTT in 6 high trait anxious marmosets was investigated on key components of the high trait anxiety phenotype: behavioural avoidance, increased threat vigilance and impaired fear regulation. We hypothesised that inhibition of amygdala 5HTT via infusions of the selective serotonin reuptake inhibitor (SSRI), citalopram, would reduce expression of the high trait anxiety phenotype. Consistent with this hypothesis, avoidance and vigilance, as measured by the human intruder test anxiety score and conditioned fear, as measured by threat-induced cardiovascular and behavioural arousal in a fear extinction paradigm were attenuated by amygdala infusions of citalopram.
Together, these findings support the hypothesis that high amygdala 5HTT expression leads to lowered amygdala serotonin signalling which contributes to the high trait anxiety phenotype and show that an acute dose of SSRI in the amygdala has an anxiolytic effect.

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**Poster**

**783. Anxiety Disorders: Preclinical Models**

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**Topic:** G.05. Anxiety Disorders

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**Title:** A unified peak fearful tolerance score better indicates rodent anxiogenic tendency

**Authors: *W. Z. SUO**[1,2], D. W. PENG[1], P. SINGH[1]
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**Abstract:** While our knowledge for many diseases are quickly renewed with rapid progress of modern molecular biological techniques, behavioral assessment methods fall way behind. Many animal behavioral tasks are insensitive and lack of capacity for cross-study comparisons in this big data era. Because *in vivo* validation is an essential step for translating *in vitro* discoveries to next level up, the outdated behavioral tasks often become the bottle neck in the pipeline towards the clinic and pharmaceutical discoveries. With anxiety as an example, heightened anxiety causes or participates in many psychiatric disorders, such as generalized anxiety disorder, post-traumatic stress disorder, and Alzheimer's disease. Yet traditional methods assessing rodent anxiety, such as elevated plus maze (EPM), are often over-sensitive to noises leading to no or inconsistent statistical significance. Our in-depth review and analysis of previous raw data over several years revealed that even within a group that has identical genetic background, genotype, age and gender there were sometimes large individual differences in their activity levels. Some of their travel distance and/or time in a defined area could be several times more than others, which created large standard deviation. After multiple trials, here we report a revision of traditional rodent anxiety assessing tasks by changing the binary (e.g., closed versus open arms) to a range of continuously increasing fearful challenges via an elevated platform (EP) for eliciting the anxiogenic responses. This change permits to identify an individualized peak fear tolerance (PFT) that is insensitive for many noises (e.g., travel time and distance in a given zone) and the PFT can be standardized to a unified score that thus enables cross-cohort/study comparisons. Comparison of EPM and EP tasks in parallel indicated that this new EP task was highly sensitive and stable, and that the standardized scores for PFT reduced the cross-cohort variations and rendered positive statistical significance that failed to be revealed not only by EPM but also by EP that used other parameters, such as time spent in a given zone. Therefore, this revised EP using the standardized PFT score represents a much better improved method for assessing rodent fear and anxiety.

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**Poster**

**783. Anxiety Disorders: Preclinical Models**

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**Topic:** G.05. Anxiety Disorders

**Support:** NIH Grant DA038453
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**Title:** Characterization of mice lacking galanin in noradrenergic neurons

**Authors: *R. PEARCY**[1], N. SCIOLINO[2], N. PLUMMER[2], D. LUSTBERG[1], P. JENSEN[2], D. WEINSHENKER[1]
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**Abstract:** The neuropeptide galanin is expressed throughout the brain and body, with the exact pattern of expression varying between species. However, the locus coeruleus (LC), the main noradrenergic nucleus in the brain, consistently shows high galanin expression among humans and rodents, indicating that LC-derived galanin may play a conserved biological role in normal brain function. Disruptions in the galaninergic system have been widely associated with disorders such as depression, anxiety, and addiction, yet the source of the relevant galanin for these disorders has not been identified. In order to examine the functional role of LC-derived galanin, conditional knockout mice (Gal cKO) were generated by crossing mice expressing Cre recombinase under control of the noradrenergic-specific dopamine beta-hydroxylase promoter with a floxed galanin line of mice. Immunohistochemical analysis confirmed a selective loss of galanin in brain noradrenergic neurons of Gal cKO mice. Analysis of norepinephrine and metabolites with high performance liquid chromatography in LC projection regions indicates normal norepinephrine levels in the Gal cKO mice. Behavioral testing in adult males and females shows that these animals display increased anxiety-like behavior in some tasks compared to their wild-type littermates, consistent with galanin's previously reported anxiolytic properties. Future studies will work to determine the mechanisms by which LC-derived galanin may influence anxiety-like behaviors.

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**Poster**

**783. Anxiety Disorders: Preclinical Models**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 783.04/HHH3

**Topic:** G.05. Anxiety Disorders

**Title:** Effects of chemogenetic inhibition of prefrontal parvalbumin interneurons on emotional and cognitive behaviors following chronic stress exposure

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**Abstract:** Chronic stress is a major risk factor for affective disorders like anxiety and depression, which are disproportionally prevalent in women. The reasons for this sex bias are unknown, but may involve a stress-induced imbalance between excitatory and inhibitory (E/I) neurotransmission in the prefrontal cortex (PFC). Specifically, we have previously reported sex differences in the sensitivity of prefrontal GABAergic system to chronic stress. Female mice chronically stressed in adulthood showed hypoactivity in the PFC along with an increased number of PV-expressing inhibitory interneurons (PV-I). Increased PV mRNA expression also positively correlated with increased emotionality (anxiety- and depressive-related behaviors) in females. Furthermore, we have observed that chronic PV-I activation using chemogenetics is sufficient to evoke anxiety-related behaviors in unstressed females but not males. The goals of the present study are to extend these findings by testing the sex-specific therapeutic efficacy of acutely inhibiting prefrontal PV-Is after chronic stress exposure. To this end, adult male and female PV:Cre mice were injected with a Cre-dependent inhibitory DREADD receptor virus into the PFC and subjected to 4 weeks of unpredictable chronic mild stress (UCMS). Mice then underwent testing for emotional and cognitive behaviors with the DREADD ligand clozapine-N-oxide administered 30 minutes prior to each behavioral test. Preliminary results show that PV-I inhibition is ineffectual at rescuing anxiety-related behaviors in the open field test in chronically stressed male mice. However, in stressed female mice, early findings trend towards a rescue of anxiety-related behavior in the open field by PV-I inhibition. In the novel object recognition test, PV-I inhibition combined with chronic stress appears to impair cognitive performance in both sexes. Based on these preliminary findings, we conclude that targeting prefrontal PV-Is may have unique potential for treating stress-related anxiety disorders in females, though cognitive side-effects also need to be considered. These behavioral results will need to be further confirmed, and future immunohistological analyses will also be conducted to determine structural and functional changes to PV cells that may be contributing to prefrontal E/I imbalance and their possible rescue by chemogenetic inhibition. Altogether, this research contributes to our understanding of the role of the prefrontal GABAergic system in sex-specific susceptibility to stress-related disorders and potentially open the door to research in novel therapies for affective disorders.

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**Poster**

**783. Anxiety Disorders: Preclinical Models**

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**Topic:** G.05. Anxiety Disorders

**Support:** Fulbright Award (to MMP)
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**Title:** Norepinephrine and frustration: Methylphenidate and propranolol affect reward devaluation and ethanol self-administration

**Authors: *M. R. PAPINI**[1], M. PUDDINGTON[3], J. THOMPSON[2], C. TORRES[4]
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**Abstract:** Animals that learned to expect a large reward and surprisingly receive a small reward reject the devalued reward (consummatory successive negative contrast, cSNC) and increase ethanol and benzodiazepine voluntary oral consumption after the devaluation event (emotional self-medication, ESM). The ESM effect has been attributed to the anxiolytic properties of both drugs (related to GABAergic transmission) that would reduce frustration induced by reward devaluation. To test this hypothesis, the cSNC effect was modulated either by the norepinephrine/dopamine reuptake inhibitor methylphenidate (MPH, 2.5 mg/kg) or the norepinephrine/epinephrine antagonist propranolol (PRO, 10 mg/kg). Based on the anxiogenic (MPH) and anxiolytic (PRO) effects of these drugs, it was assumed that MPH would enhance and PRO would reduce the cSNC effect, therefore enhancing and reducing, respectively, the ESM effect. cSNC training included 10 5-min preshift sessions of access to 32% sucrose followed by 5 postshift sessions with access to 2% sucrose for 3 groups (downshifted groups). Three other groups received 15 sessions of access to 2% sucrose (unshifted controls). Immediately after each cSNC session, animals received access to 10% ethanol and water in a 1-h, 2-bottle, free-choice preference test. The drugs were administered ip 5-7 min before sessions 11 and 12 (first and second devaluation events). MPH enhanced the cSNC effect and led to a modest, but significant ESM effect. PRO eliminated the cSNC effect and yielded no evidence of ESM. Saline led to a significant cSNC effect, but to only a nonsignificant trend in ESM. These results are consistent with an interpretation of cSNC in terms of frustration and of ESM as dependent upon the reward derived from the reduction of frustration caused by drug intake. Future research will test the hypothesis that noradrenergic receptors in the amygdala (known to be involved in cSNC) may be responsible for the behavioral suppression triggered by reward devaluation.

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**Poster**

**783. Anxiety Disorders: Preclinical Models**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 783.06/HHH5

**Topic:** G.05. Anxiety Disorders

**Title:** Intestinal inflammation induced neurobehavioral changes is associated with altered ventral striatal function in mice

**Authors: *A. CHAKRABORTI**[1], M. SCARDUZIO[2], C. GRAHAM[1], A. HERNANDEZ[5], A. CHEN[1], R. TELANGE[1], D. EPSTEIN[1], M. NUKAYA[1], S. MUKHTAR[3], T. VANGROEN[4], L. MCMAHON[4], M. GRAY[2], S. WATTS[3], G. KENNEDY[1], J. BIBB[1]
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**Abstract:** Inflammatory Bowel Diseases (IBD) represent a major health concern with a continuously rising incidence and prevalence. Psychiatric disorders especially anxiety and depression are frequently co-morbid with IBD, thereby substantially increasing disease burden and exacerbating risk of secondary functional gastrointestinal diseases. The mechanisms mediating this comorbidity are poorly understood. Within the brain, striatum controls multiple cognitive aspects including motivation, rewarding and aversive stimuli perception, and motor and behavioral responses. Recent studies suggest a critical role for ventral striatum (nucleus accumbens, NAc) in anxiety and depression. However, the role of NAc in intestinal inflammation-induced neurobehavioral changes has not been well studied. In rodents, oral Dextran Sulphate Sodium (DSS) administration induces colonic inflammation with clinical and histological similarity to ulcerative colitis. We assessed effects of DSS-induced colitis on NAc-mediated behavior, corticostriatal plasticity, and signal integration. Male C57BL6J mice (8-9 weeks old) administered 3% DSS in drinking water developed colitis as evidenced by increased disease activity score and biomarkers of bowel inflammation including colonic myeloperoxidase activity, fecal Lipocalin-2 levels, and gene expression of proinflammatory cytokines. This was accompanied by loss of intestinal permeability and reduced expression of the tight junction protein occludin. These GI outcomes were comorbid with anxiogenic effects detected in behavioral paradigms including open field and elevated plus maze tests. In preliminary studies of synaptic excitability, whole cell patch clamp recordings of D1 or D2-expressing medium spiny neurons (MSNs) in the NAc revealed an increased intrinsic membrane excitability of D1-MSNs, accompanied by enhanced basal glutamatergic cortico-striatal synaptic transmission in the DSS treated mice.These behavioral and neurophysiological abnormalities were accompanied by attenuated PKA-dependent phosphorylation of the GluR1 subunit of the AMPA receptor and reduced activation of the ERK1/2 pathway in NAc neurons. Additional maladaptations in signal integration were detected, consistent with increased vulnerability to stress and anxiety. To our

knowledge, this is the first report that IBD-induced behavioral changes are associated with altered NAc function. Our findings provide novel insights into gut-brain communication that may ultimately lead to improved therapeutic strategies to combat neurobehavioral alterations associated with gastrointestinal disorders.

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**Poster**

**783. Anxiety Disorders: Preclinical Models**

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**Topic:** G.05. Anxiety Disorders

**Support:** NIH R01 MH114296
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**Title:** Investigating the effects of EAAT3 overexpression on OCD-relevant behaviors in mice

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**Abstract:** Obsessive Compulsive Disorder (OCD) is a debilitating psychiatric disorder characterized by intrusive obsessive thoughts and compulsive behaviors. The etiology of OCD is unknown, but twin and family studies show a significant role for genetics, with multiple studies identifying association of polymorphisms in the SLC1A1 gene with OCD. The most common of these OCD-associated polymorphisms increases expression of the encoded protein - excitatory amino acid transporter-3 (EAAT3). To directly test the effect of increased EAAT3 levels on OCD-relevant behaviors, we used the Flexible Accelerated STOP Tetracycline Operator-knockin (FAST) system, which combines cre, flippase, and tTA technology to manipulate gene expression in a cell-type and temporally specific manner. Slc1a1-overexpressing (OE) mice were created by breeding Slc1a1-tetO mice with CamKII-tTA hemizygotes. The resulting progeny show increased striatal EAAT3 expression (as measured by Western blot) that is normalized in a dose-dependent manner by doxycycline. Slc1a1-OE mice with increased EAAT3 expression throughout development show increased stereotypies compared to tTA-negative littermate controls following administration of a high dose of amphetamine (8mg/kg) (genotype main effect, $F(2,43) = 39.06$, $p < 0.0001$, n=20 WT, 25 Hemi). In addition, these mice show an

increase in anxiety-like behavior, spending significantly less time in the open arms of the elevated plus maze (unpaired t-test, p=0.02, n=20 WT, 25 Hemi) and less time in the center region of the open field (unpaired t-test, p=0.04, n=20 WT, 25 Hemi). In a second cohort, Slc1a1-OE mice were raised on doxycycline to ensure normal EAAT3 expression during development; doxycycline was then removed to increase EAAT3 expression specifically in adulthood. Adult Slc1a1-OE mice also show an increase in amphetamine-induced stereotypies compared to littermate controls (genotype main effect, $F(2,36) = 14.962$, $p < 0.0001$, n=17 WT, 17 Hemi). In contrast, adult Slc1a1-OE mice do not have increased anxiety-like behavior relative to littermate controls. This suggests EAAT3 overexpression differentially impacts anxiety-like and stereotypic behaviors through different circuit mechanisms at different developmental timepoints. Ongoing experiments are investigating this question using cFos immunohistochemistry and in vivo calcium imaging.

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**Poster**

**783. Anxiety Disorders: Preclinical Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 783.08/HHH7

**Topic:** G.05. Anxiety Disorders

**Support:** the National Natural Science Foundation of China (31600970, 81200119)
the Fundamental Research Funds for the Central Universities (2042016kf0036)

**Title:** Optogenetic LTD induction in the central nucleus of amygdala produces anxiolytic effects

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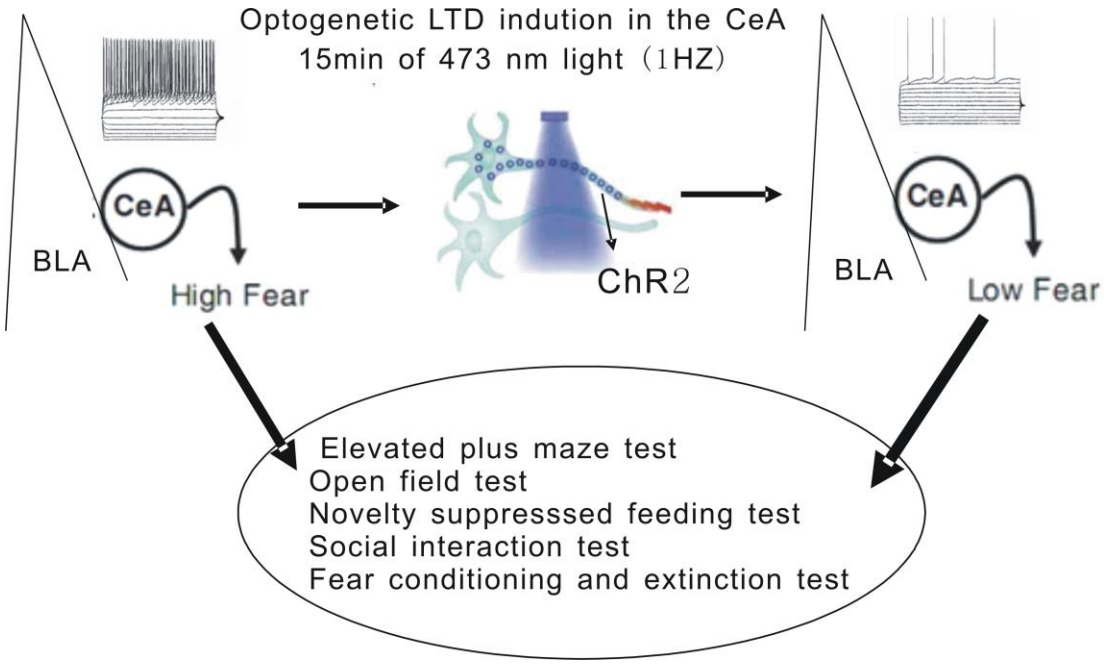
**Abstract:** Anxiety disorders are one of the most common psychiatric diseases with a lifetime prevalence of 28% and contribute to the etiologies of major depression and substance abuse. Although it has been proposed that the central nucleus of amygdala (CeA) controls fear, and its dysfunction potentially contributes to anxiety disorders, few studies have shown the effect of optogenetic activation of CeA neurons in vivo on unconditioned fear-related behaviors or the conditioned fear extinction process. Here, we explore the role of the CeA in unconditioned and conditioned fear-related behaviors by using optogenetics and anxiety assays in freely moving mice. We observed that temporally precise optogenetic stimulation of the CeA increased unconditioned fear-related behaviors on the elevated plus maze test, the open field test, the social interaction test, and the novelty-suppressed feeding test. Optogenetic activation of the CeA also increased conditioned fear expression and impaired fear extinction. We then found that

optogenetic LTD induction in the CeA effectively exerted a significant anxiolytic effect on both conditioned and unconditioned fear-related behaviors. Taking these results together, we identify the CeA as a neural subregion for the real-time optogenetic modulation of the conditioned and unconditioned expressions of anxiety. Our optogenetic LTD protocol may inspire the development of novel treatments for anxiety disorders involving deep brain stimulation to induce plasticity at relevant brain areas.




(Figure 1. The excitability of CeA neurons was inhibited by LTD induction. Optogenetic LTD induction in the CeA effectively exerted a significant anxiolytic effect on both conditioned and unconditioned fear-related behavioral tests.)

**Disclosures: L. Bi:** None.

**Poster**

**783. Anxiety Disorders: Preclinical Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 783.09/HHH8

**Topic:** G.05. Anxiety Disorders

**Title:** Early exposure to methylphenidate does not affect the anxiety-like behavior of normal or dopamine-deficient adult rats

**Authors: *G. J. KAPLAN**[1,2], A. HARDIN[2], A. TERAN[2], D. SANCHEZ[2], J. RAZZO[2], Z. HARMONY[2], R. HEDINGER[1], J. FENG[1], C. CRAWFORD[2]
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**Abstract:** Ritalin (methylphenidate) is the most commonly-prescribed stimulant medication for the treatment of ADHD. Despite high prescription rates among kindergarten-aged children, methylphenidate was not approved for use in children younger than nine, and research into its long-term consequences is lacking. Previous preclinical studies using older rats have indicated that methylphenidate treatment can alter drug responsivity, opioid sensitivity, and affective behavior. In the present study, we further examined the effects of early methylphenidate exposure on anxiety-like behaviors in adulthood in normal rats and rats with a dopaminergic dysfunction caused by neonatal 6-hydroxydopamine (6-OHDA) lesions. It is possible that this underlying dysregulation in dopaminergic functioning may cause methylphenidate to have substantially different effects in ADHD patients, when compared to control subjects. Thus, methylphenidate and other ADHD medications may restore the dopaminergic system to normalcy without causing additional alterations in neuronal functioning (i.e., long-term changes in affective behavior). To this end, on postnatal day (PD) 3, male and female rat pups were injected intracisternally with 6-OHDA (100 μg) or vehicle (sham lesion) to generate normal and dopamine-deficient groups. Both groups were given methylphenidate (0, 0.5, 2 or 5 mg/kg) once daily for ten days starting on PD 11. On PD 60, anxiety-like behavior was assessed by the light/dark box test, and on PD 65, all rats were tested on the elevated plus maze. Rats that received the neonatal 6-OHDA lesions spent less time in the light area in the light/dark box test and made fewer entries into the open arms of the elevated plus maze. Interestingly, in the present study, methylphenidate treatment did not alter affective behavior. These results imply that, in children, dopamine deficiency may lead to later-life anxiety irrespective of treatment with methylphenidate.

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**Poster**

**783. Anxiety Disorders: Preclinical Models**

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**Topic:** G.05. Anxiety Disorders

**Support:** NIH Grant T32-NS45540
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**Title:** Genetically targeted circuit mapping of the oval nucleus of the bed nucleus of the stria terminalis

**Authors: *C. A. ITOGA**[1], C. FATERI[2], P. A. ECHEVERRY[2], J. DELGADO[2], J. M. LAI[2], S. BADHON[2], H. CAI[3], X. XU[4]
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**Abstract:** The bed nucleus of the stria terminalis (BNST) has an established role in modulating anxiety behavior and coordinating cognitive, emotional, and neuroendocrine responses to stress. Despite being a relatively small structure in the basal forebrain, the BNST consists of multiple subregions, and specific targeting of one subregion such as the oval nucleus of the BNST has been technically difficult. Here we report genetic targeting of the oval BNST (ovBNST) subregion using the PKC-δ-IRES-Cre (PKCd-Cre) mouse. Our characterization of this mouse shows that strong PKCd-Cre expression occurs in the anatomically corresponding oval subregion, and there is little or no PKCd-Cre expression in the dorsomedial portion and the ventral portion of the BNST. About 50% of the ovBNST neurons are PKCd-Cre expressing cells, of which 10% are also immunopositive for corticotropin releasing hormone. This unique spatial distribution of molecular expression allows for genetically targeted circuit mapping and functional studies of the ovBNST in the intact brain. To understand how PKCd-expressing ovBNST neurons govern neural signal integrations and transformations in the putatively anxiogenic BNST subregion, we use new viral genetic tracing to map global and local circuit connections to and from PKCd+ neurons. Genetically modified monosynaptic rabies tracing shows that the majority of PKCd+ ovBNST inputs come from the central amygdala, periventricular thalamus, hippocampal CA3, and posterior lateral thalamic nuclei. In contrast, the great majority of PKCd+ ovBNST projections appear to exclusively project to ventral BNST which is also putatively anxiogenic. We further analyzed the effects of optogenetic activation of PKCd+ ovBNST neurons on anxiety-related physiological and behavioral measures. Stimulation of PKCd+ cells in ovBNST is anxiogenic, as measured behaviorally with open field and elevated plus maze tasks, and also results in elevated heart rate and breathing rate. Together, our research will shed new light on the neural circuit organization and function of this unique BNST subregion.

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**Poster**

**783. Anxiety Disorders: Preclinical Models**

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**Program #/Poster #:** 783.11/HHH10

**Topic:** G.05. Anxiety Disorders

**Title:** Characterization of stress-induced changes in glutamatergic neurotransmission in a rat model of chronic corticosterone treatment (CCT)

**Authors: R. BERGIN**, A. MAURER, M. WEILAND, S. DIEHL, *B. FERGER, I. IONESCU, K. ALLERS
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**Abstract:** Chronic stress models in rodents may emulate the dysregulated brain circuitry found in psychiatric patients and by this translatable aspect enable a higher accuracy in predicting efficacy of novel drugs. Here, male Wistar Han rats were exposed to chronic treatment (21 days) with corticosterone (CORT) in drinking water (300 µg/ml). We characterized hypothalamo-pituitary-adrenal (HPA) axis reactivity to dexamethasone suppression (DST) and stress-induced changes in glutamatergic neurotransmission measured with glutamate biosensors (Pinnacle Inc.) in two brain regions responsible for processing stressful stimuli and regulated via the glucocorticoid system, namely the prefrontal cortex (PFC) and the basolateral amygdala (BLA). Longitudinal measures of fecal CORT levels show that CCT animals exhibit constantly increased CORT levels during the treatment, which quickly revert to control levels during washout. DST, carried out 5 days after the end of the treatment, show that CCT animals are immune to DST-induced suppression of CORT. Therefore, we conclude that the CCT animals have a dysregulated HPA axis that resembles the phenotype seen in subgroups of psychiatric patients. In the PFC, CCT extends the duration of glutamate increase in response to 5 min Restraint Stress (RS) when compared to control animals; upon repeating the RS 2 hrs later, the response no longer differed between control and CCT animals. Conversely, in the BLA, the response to the first RS did not differ between groups; however, upon exposure to the second RS, control animals had a lower response, whereas CCT inhibited this habituation. Additionally, we validated, in the CCT model, the postulated mechanism of action via modulation of prefrontocortical glutamate of clinically efficacious N-methyl-D-aspartate receptor (NMDA-R) antagonists, such as S-ketamine and traxoprodil. To conclude, we have shown in the CCT model: (I) Dysregulation of the HPA axis reactivity similar to the situation in patients; (II) Hyper-reactivity of the BLA in response to repeated RS, which also bears a resemblance to the patient situation, in which psychiatric patients exhibit coping issues with stress and a hyperactive amygdala; (III) Hyper-reactivity of the PFC to novel stress, which is similar to the high alertness seen in patients suffering from anxiety disorders; and (IV) Validation of the postulated mechanism of action of clinically efficacious NMDA-R antagonists.

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**Poster**

**783. Anxiety Disorders: Preclinical Models**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 783.12/HHH11

**Topic:** G.05. Anxiety Disorders

**Support:** CNPq Fellowship
Fapitec Fellowship

**Title:** Effects of a rat model of gestational hypothyroidism on state-like anxiety and forebrain gabaergic and dopaminergic ystems

**Authors: E. MENEZES**[1], P. R. SANTOS[1], T. COSTA GOES[1], V. CIBELLE DE CARVALHO[1], F. TEIXEIRA SILVA[1], D. BADAUE-PASSOS JUNIOR[1], *H. E. STEVENS[2]
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**Abstract:** Thyroid hormones (THs) are essential for multiple processes of neurodevelopment: neurite outgrowth, synaptogenesis and myelination of neural tracts. These processes regulate important phases of cortical growth and functioning. Gestational hypothyroidism (overt and subclinical) affects 15.5% of American pregnant women and their offspring. In a rat model, we investigated the effects of maternal hypothyroidism on state anxiety-like behavior and forebrain gabaergic and dopaminergic systems in adult offspring to identify underlying neurobiological targets for treatment. Experimental gestational hypothyroidism was induced by administering 0.02% methimazole (MMI) in drinking water to pregnant Wistar rats from gestational day 9 to delivery. Exploratory behavior (hole board), contextual fear conditioning, locomotion (open field), and 30-day reserpine parkinsonian induction were assessed from postnatal day 75 to 120 (P75-P120). Neurotransmitter-related protein and gene expression by western blot and qPCR were evaluated in offspring forebrain at P120. During exploratory behavior, the frequency of *head-dip* was higher in MMI offspring (14.0 (9.0 - 17) *versus* 17.5 (15.25 - 20.5) n=13, U=38.00, $p<0.05$). In the first minute of fear conditioning, MMI offspring showed less time freezing (two-way ANOVA ($F(1, 25) = 3.835$, $p=0.0614$ with Bonferroni posttest 33.61 ± 2.46 *versus* 5.939 ± 0.982, t 2.548, $p=0.0387$). Groups did not differ in baseline locomotor activity but reserpine significantly reduced activity only in MMI offspring (ANOVA interaction: ($F 3, 80 = 6.96$, $p< 0.001$ Day7-15 / $F(3, 80) = 4.989$ $p< 0.005$ Day 7-30). GAD67 (Glutamic acid decarboxylase) and DAT (dopamine transporter) protein expression was lower in MMI offspring in prefrontal cortex (GAD67: 1.069 ± 0.1347 *versus* 0.5971 ± 0.06698, $p<0.05$ and DAT: 0.7312 ± 0.2032 *versus* 0.05695 ± 0.003477, $p<0.05$) but not in striatum. Tyrosine hydroxylase protein expression was reduced in MMI offspring in prefrontal cortex and striatum (PFC 1.264 ± 0.2312 *versus* 0.3094 ± 0.05932 and striatum 1.573 ± 0.1381 *versus* 0.9605 ± 0.08454, $p<0.01$). D4R (Dopamine Receptor) but not D1R gene expression was reduced only in prefrontal cortex in

MMI offspring (F= 4.599, p =0.0111, R square 0.365). Our results indicated that restriction of maternal thyroid hormones exclusively during intrauterine development affected anxiety-like behavior postnatally in association with reduced gabaergic and dopaminergic forebrain systems. These findings strongly support the hypothesis that adequate delivery of maternal THs to fetus are crucial to the development of structures of the central nervous system critical for emotion regulation.

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**Poster**

**783. Anxiety Disorders: Preclinical Models**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 783.13/HHH12

**Topic:** G.05. Anxiety Disorders

**Support:** CNPQ 141532/2016-5

**Title:** Effects of D1, D2 and CRF1 receptor antagonists on social investigation deficits induced by chronic social defeat stress in mice

**Authors: *C. A. FAVORETTO**, P. ARAUJO, G. C. MACEDO, I. M. H. QUADROS
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**Abstract:** Chronic exposure to stress enhances the vulnerability of individuals to neuropsychiatric disorders, such as anxiety and depression. Social defeat is an animal model suitable for investigation of social stress and its behavioral, neural and endocrine consequences, particularly in rats and mice. Repeated exposure to social defeat stress promotes deficits in social interaction and social interest, and disrupts dopaminergic signaling in the nucleus accumbens (Nacc) of rodents. D1 and D2 medium spiny neurons contained in Nacc seems to play different roles in response to relevant environmental stimuli, both aversive and appetitive, such as stressful and social stimuli. In addition, dopaminergic response to stress and social stimuli seems to be modulated by CRF1 receptors. Thus, we aimed to investigate the effect of treatment with selective D1 and D2 dopaminergic receptor antagonists (SCH-23390 and raclopride, respectively) and CRF1 receptor antagonist (CP-154,526) on the social interest of animals exposed to social defeat stress. For that, adult male Swiss albino mice were submitted to 10 days of social defeat, when they were physically and psychologically confronted by aggressive resident males. Another group of mice were housed in pairs, separated by a transparent acrylic partition, and used as control group. Ten days after the end of defeats, mice were treated (i.p. injection) with D1, D2 or CRF1 receptor antagonists, or treated with vehicle, and then tested on a

social investigation test. Considering the total time and the bout (time / entries frequency) spent investigating a social target, mice exposed to chronic social stress showed reduced social investigation. Deficits in social investigation were not altered by treatment with SCH-23390 but were reversed by treatment with raclopride. Furthermore, CP-154,526 intensified social deficits promoted by social defeat stress. This study demonstrated that the deficits on social investigation promoted by chronic social defeat stress are modulated by D2 and CRF1 receptors activity. D1 dopaminergic receptor seems to be less or not related to the assessed behavior.

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**Poster**

**783. Anxiety Disorders: Preclinical Models**

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**Program #/Poster #:** 783.14/HHH13

**Topic:** G.05. Anxiety Disorders

**Support:** NIH Grant MH091451
NIH Grant DC009910
NIH Grant MH112232

**Title:** Deconstructing infant trauma and pathology: Infant hippocampus targeted by stress but stress paired with mother targets amygdala

**Authors: C. RAINEKI**[1], M. OPENDAK[2], E. C. SARRO[3], *B. S. EAST, JR[4], D. A. WILSON[5], R. M. SULLIVAN[6]
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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**

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**Topic:** G.05. Anxiety Disorders

**Support:** VA Merit award BX002558-01

**Title:** Mechanisms of methylphenidate-induced enhancement of fear extinction and modulation by the COMTval158met polymorphism

**Authors: J. DESLAURIERS**[1,2], S. CALDWELL[1], X. ZHOU[1], *V. B. RISBROUGH[1,2]
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**Abstract:** Posttraumatic stress disorder (PTSD) affects 7-8% of the American population while rates are up to 20% in military veterans. The val158met polymorphism in the catechol-O-

methyltransferase (COMT) gene has been associated with a greater risk of neuropsychiatric disorders, including PTSD. In the Marines, Met/Met carriers with PTSD have increased fear responses to danger and safety signals. Also, a preclinical study using a “humanized” COMT mouse line showed increased cued fear and reduced extinction recall in mice homozygous for the Met allele. The val158met polymorphism is thought to affect catecholamine availability predominantly in prefrontal cortex (PFC) circuits. We hypothesized that the DAT (dopamine transporter) and NET (norepinephrine) blocker methylphenidate, known to preferentially blocks catecholamine reuptake in the PFC, enhances extinction recall. We also investigated whether DAT or NET blockade is sufficient to drive the MPD effects. To test this hypothesis we administered either vehicle, MPD (10-20 mg/kg IP), the NET blocker atomoxetine (5 mg/kg IP) or the DAT blocker GBR-12909 (20 mg/kg IP) immediately before extinction training in mice “humanized” for the COMTval158met polymorphism. We then evaluated their effects on cued fear and extinction recall. MPD reduced cued fear in all mice, regardless of genotype and sex. On extinction recall, a gene × MPD interaction was found in males, not females, with greater extinction recall in Val/Val carriers. The NET blocker atomoxetine did not affect cued fear response, but increased extinction recall in male Met/Met, not Val/Val, carriers. No effect of atomoxetine was found in female Met/Met and Val/Val mice. The DAT blocker GBR-12909 decreased cued fear and increased extinction recall in both male and female mice, regardless of genotype. Together with previous reports showing improved PTSD symptoms following MPD treatment, our findings suggest that MPD might be a therapeutic alternative for PTSD patients. DAT blockade appeared to be sufficient to enhance extinction recall and might be the primary driver of MPD effects. However, the genotype-dependent effects of MPD and atomoxetine, which preferentially targets the PFC, suggests that the COMTval158met polymorphism modulated the NET-driven effects on extinction recall. Further work is necessary to investigate the sex-dependent effects of NET and DAT blockers on fear extinction.

**Disclosures: J. Deslauriers:** None. **S. Caldwell:** None. **X. Zhou:** None. **V.B. Risbrough:** 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, DoD.

**Poster**

**783. Anxiety Disorders: Preclinical Models**

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**Topic:** G.05. Anxiety Disorders

**Support:** AHA 14SDG18300010

**Title:** MEMRI reveals that acute angiotensin II exposure in male WKY rats excites select brain regions and either normalizes or exaggerates regional differences when compared to the naive SHR

**Authors: *L. F. HAYWARD**[1], J. WATKINS[1], L. COLON-PEREZ[1], M. FEBO[2], J. ZUBCEVIC[1]
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**Abstract:** Recently, our group identified several brain regions linked to heightened anxiety and autonomic responsiveness in the normotensive WKY when compared to the SHR, a rodent model of essential hypertension and chronically elevated angiotensin II. The current study was undertaken to evaluate whether acute administration of angiotensin II in the WKY would alter the pattern of regional brain activation to more closely reflect that observed in the naïve SHR. 24 hours following an intraperitoneal co-injection of angiotensin II (0.32 microgram/kg) and manganese (i.p. 50 mg/kg), rats (n=6-11/group) were lightly anesthetized and imaged on a 4.7 Tesla MRI using a multi-slice spin echo sequence: TE=15ms, TR=350ms, 22 slices, 256x256 resolution. Manganese-enhanced MRI (MEMRI) enabled mapping of signal enhancement in the brain associated with neuronal activity marked by paramagnetic Mn2+ accumulation. Acute exposure to angiotensin II in the WKY increased indicators of neuronal activation in multiple brain regions. In the central gray, dorsal and median raphe, lateral hypothalamus, parabrachial nucleus, and ventral tegmental area, activity was elevated by angiotensin II when compared to both control WKYs and naïve SHRs. Since angiotensin II can be anxiogenic, we suggest that these regions may be more involved in neural processing associated with stress and anxiety. Conversely, angiotensin II injection significantly elevated neural activity in the anterior hypothalamus, pontine reticular nuclei, midbrain reticular nucleus, pedunculopontine tegmental nucleus, supraoptic nucleus, and subcoeruleus in the WKY and the resultant levels of activity were comparable to that observed in the naïve SHR. These findings suggest that these brain regions are more critical for the central processing of angiotensin II and its effects on cardiovascular function.

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**Poster**

**783. Anxiety Disorders: Preclinical Models**

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**Program #/Poster #:** 783.17/HHH16

**Topic:** G.05. Anxiety Disorders

**Title:** Fear processing in the SAPAP3 knockout mouse model of OCD

**Authors: *Z. LAPALOMBARA**, S. E. AHMARI
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**Abstract:** Obsessive-compulsive disorder is a debilitating mental disorder characterized by intrusive thoughts and repetitive behavior. One theory of OCD pathogenesis is that patients form maladaptive fearful associations with neutral stimuli, leading to maintenance of fear. While human behavioral and imaging studies have provided evidence for this theory, investigation of the possible underlying neural mechanisms has been limited. We therefore turned to SAPAP3 KO mice, a model that displays perseverative grooming and anxiety-like behavior. 4-6-month-old male mice were used for all experiments, and experimenters were blind to genotype during data collection. Using a 3-shock Pavlovian fear conditioning paradigm [three pairs of a 20-second tone (5kHz, 75dB), co-terminating with a 2-second shock (1mA)], we found that KOs have an enhanced fear conditioning response compared to WTs (time x genotype interaction: $F(3, 69) = 9.23$, $p < 0.0001$; n = 13 KO, 12 WT). To exclude the possibility that altered pain signaling contributed to this response, we tested for pain sensitivity using Hargreaves and von Frey tests. No differences between genotypes were observed (Hargreaves: $p = 0.19$, $t = 1.34$, $df = 48$; von Frey: $p = 0.34$, $t = 0.97$, $df = 48$), indicating that enhanced fear conditioning in KOs is not due to differences in pain sensitivity. To begin to explore the neural correlates of the elevated freezing response, we broadly examined candidate regions that might contribute to differential fear processing using the immediate early gene cFos. A second cohort (n = 10 KO, 7 WT) was perfused 60 minutes after the final fear conditioning tone, and cFos+ cell density was acquired for regions previously related to fear conditioning. No differences in cFos+ cell density were observed between KOs and WTs when using a repeated measures model. However, after correcting for multiple comparisons, within-genotype cell densities in the prelimbic cortex (PL) and basolateral amygdala (BLA) were significantly positively correlated in KO, but not WT, mice. Furthermore, cell density in the central amygdala (CeA) was significantly positively correlated with most regions (e.g. PL, BLA, periaqueductal grey, bed nucleus of the stria terminalis) in KOs, but not WTs. These data indicate that SAPAP3 KO mice display elevated cFos+ cell density correlations between fear-associated brain regions (i.e. PL, BLA, CeA) after fear conditioning compared to WT mice, suggesting a potential circuit mechanism for the elevated fear conditioning response observed in KOs. Ongoing experiments are testing this hypothesis using *in vivo* fiber photometry to measure calcium activity in the PL and BLA during fear conditioning.

**Disclosures: Z. Lapalombara:** None. **S.E. Ahmari:** None.

**Poster**

**783. Anxiety Disorders: Preclinical Models**

**Location:** SDCC Halls B-H

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**Topic:** G.05. Anxiety Disorders

**Support:** NIH grant R01 MH113007

**Title:** Oxytocin receptors in the dorsolateral bed nucleus of the stria terminalis (BNST) bias fear learning toward temporally predictable cued fear

**Authors: *J. A. DABROWSKA**[1], D. MARTINON[2], A. N. ROMAN[3], P. LIS[3], P. MACKINNON[3], S. APPLEBEY[3], G. BUECHNER[3]
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**Abstract:** Hypothalamic oxytocin (OT) neurons project to dorsolateral bed nucleus of the stria terminalis ($BNST_{dl}$), a forebrain region critically involved in the modulation of fear and anxiety. We have recently shown that blocking OT receptors (OTR) in the $BNST_{dl}$ reduces acquisition of cued fear measured in the fear-potentiated startle (FPS). AIM: The aim of the study was to investigate if OT neurons are involved in fear acquisition. METHODS and RESULTS: Using *in vivo* microdialysis in freely moving male Sprague-Dawley rats we show that in contrast to acute stress, exposure to cued fear conditioning increases OT content in $BNST_{dl}$ microdialysates. We next applied double-immunofluorescent approach combined with confocal microscopy to determine a percentage of OT neurons co-expressing cFos in the paraventricular (PVN), supraoptic (SON), and accessory nucleus of the hypothalamus (AN) in response to fear conditioning. We show that rats exposed to fear conditioning show moderate activation of OT neurons in the PVN, whereas robust activation in the SON and AN. Finally, to determine the role of OTR in fear memory formation, we infused rats with selective OTR antagonist or OT to the $BNST_{dl}$ before fear-conditioning and measured ability to learn discrimination between cued (signaled) and non-cued (unsignaled) fear using FPS. We show that application of OT into the $BNST_{dl}$ significantly increases discrimination between cued and non-cued fear and biases responses toward cued fear, whereas blocking OTR disables the discrimination. CONCLUSIONS: OTR neurotransmission in the $BNST_{dl}$ plays a pivotal role in the ability to discriminate between threat and safety.

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**Poster**

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**Topic:** G.05. Anxiety Disorders

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**Title:** Pharmacological targeting of cyclooxygenase-2 for the treatment and prevention of anxiety disorders

**Authors: *A. J. MORGAN**[1], A. GAULDEN[2], M. ALTEMUS[3], S. PATEL[3]
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**Abstract:** Acute and chronic stress can increase the risk of developing anxiety disorders and depression. Anxiety disorders are the most common psychiatric disorders, and daily stress levels among adults continue to rise. Our laboratory has previously shown that augmenting endogenous cannabinoid (eCB) signaling can reduce anxiety-like behavior, and this system is an emerging pharmacological target for a range of affective disorders. In addition to the canonical methods of augmenting eCB levels in the CNS, the immediate-early gene product. Here, we show that pretreatment with the highly selective COX-2 inhibitor, Lumiracoxib (LMX), prevents anxiety behavioral phenotypes in both acute and chronic stress models. In acute stress experiments, four groups of ICR mice were used: Vehicle NoStress (n=24), LMX NoStress (n=27), Vehicle-Stress (n=23), and LMX-Stress (n=26). For the stressed groups, mice were given LMX 5 mg/kg or Vehicle, 90 minutes prior to 30 minutes restraint stress, and then tested immediately in Elevated zero maze (EZM) and Light Dark box (LD). LMX was able to prevent the stress phenotype, indicating that LMX is able to prevent anxiety-like behavior in an acute stress model In a separate set of experiments, mice were given 25mg/mL of corticosterone or vehicle in drinking water for 4 weeks, and administered subchronic LMX for the last week of treatment (Control-Veh; n=35, Cort-Vehicle; n=23 or Cort-LMX; n=32), then ran on several anxiety measures, spread across a week of testing. Mice in the chronic stress paradigm treated with Cort-Veh had significantly reduced distance traveled in the open arm ($p$=0.0013*), of EZM and distance traveled in the light side of the LD box ($p$=0.0267*), indicating those mice showed a chronic stress phenotype. But subchronic LMX was able to prevent the chronic stress phenotype, with Cort-LMX mice no different from controls on open arm distance ($p$=0.925*), as well as distance traveled in the light side of LD ($p$=0.139*); (*By Holm-Sidak test after two-way ANOVA; male ICR mice aged 12 weeks old used in all experiments, data represent a total of 3 replications of the experiment). Despite these data, the potential pleiotropic mechanisms by which COX-2 can regulate anxiety and stress response physiology are incompletely understood. We are currently working to determine the mechanisms underlying the differences seen in these behavioral experiments, using electrophysiological and in vivo cellular imaging techniques to determine how COX-2 inhibition affects neuronal excitability and synaptic signaling in the amygdala following stress exposure.

**Disclosures: A.J. Morgan:** None. **A. Gaulden:** None. **M. Altemus:** None. **S. Patel:** None.

**Poster**

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**Topic:** G.05. Anxiety Disorders

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**Title:** Maternal care determines the male sexual performance in high-yawning rats

**Authors: *J. EGUIBAR**, M. DORANTES-NIETO, C. CORTES, A. UGARTE
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**Abstract:** The high-yawning (HY) subline from Sprague-Dawley rats was obtained through strict inbreeding process for more than 90 generations in base of their spontaneous yawning frequency. HY rats had a higher proportion of males with no copulatory activity in four test with an estrous female. Additionally, sexually experienced male rats showed higher inter-intromission intervals, more sexual bouts that significantly delay ejaculation and also longer post-ejaculatory intervals suggesting lower motivation. Maternal care of HY dams showed deficient nest building, atypical retrieving and lower arched-back nursing posture respect to Sprague-Dawley dams. The aim of this study was to analyze the male sexual behavior of HY and Sprague-Dawley rats submitted to cross- or in-fostering during the first 24h after birth and evaluate sexual behavior at 3 months of age. Female rats used as stimulus were ovariectomized under deep anesthesia induced by ketamine/xylazine and one week later induced full estrous behavior by the sequential administration of estrogen 5μg and 44 h later progesterone 2 mg through subcutaneous injection, steroids dissolved in olive oil (0.2 mL). Our results showed that Sprague-Dawley dams did not change the distribution on the proportions of ejaculations when crossfostering respect to infostering male rats with a mean between 2 to 3 ejaculations in 30 min. On the contrary, HY dams increased the proportion of sluggish subjects in male SD rats ($\chi 2$ $P \leq 0.01$); and in the case of HY male rats increase significantly the proportion of non-copulators and sluggish ejaculators. In conclusion, HY dams are capable to reduce the sexual capacities in Sprague-Dawley, as well as HY rats. In base of that we proposed HY rats as an adequate model of impotence and lower sexual motivation.

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**Poster**

**783. Anxiety Disorders: Preclinical Models**

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**Program #/Poster #:** 783.21/HHH20

WITHDRAWN

**Poster**

**783. Anxiety Disorders: Preclinical Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 783.22/HHH21

**Topic:** G.05. Anxiety Disorders

**Support:** NIH MH-97988

**Title:** Intra-BNST PACAP produces dose-dependent increases in anxiety-like behavior in female rats

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**Abstract:** Repeated exposure to stressful stimuli can result in maladaptive consequences, including increased anxiety-like behavior and altered peptide expression in anxiety-related brain structures like the bed nucleus of the stria terminalis (BNST). Moreover, stressor exposure is associated with psychopathologies that are more common in women, including anxiety disorders and trauma-related disorders. In male rodents, pituitary adenylate cyclase activating polypeptide (PACAP) has been shown to dose-dependently enhance multiple anxiety-like behaviors, including increased plasma corticosterone and elevated startle amplitude. Furthermore, PACAP is both necessary and sufficient for the enhanced anxiety-like behavior observed following chronic stress and we have recently shown that chronic variate stress (CVS) sensitizes the anxiety-like response to intra-BNST PACAP in males. Additionally, evidence suggest that PACAP may interact with ovarian hormones (i.e., estrogen) to contribute to sex differences in stress-related disorders. For instance, following chronic stress cycling female rodents show an attenuated anxiety-like response to intra-BNST PACAP that is dependent on estrus. Moreover, PACAP is associated with both the onset and severity of PTSD in women. Given this potential interaction, the current study assessed the effects of PACAP in stress naïve, intact, cycling females to determine whether intra-BNST PACAP produces similar dose-dependent effects in females and whether this effect varies across the estrus cycle. We found a dose-dependent increase in startle 30 minutes following intra-BNST PACAP infusion and this effect appeared to be independent of estrus. These results suggest that in the absence of stress, females and males show similar dose-dependent effects of PACAP on anxiety-like behavior and that the opposing effects of circulating ovarian hormones on the intra-BNST PACAP response we've previously observed likely depends on whether or not the animal has been exposed to stress.

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**Topic:** G.05. Anxiety Disorders

**Support:** NIH R15 MH104485
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**Title:** Anxious phenotypes: Prior experience and orexin 2 ($Orx_2$) receptor activation lead to social stress resilience

**Authors: *J. D. YAEGER**[1], C. D. STATON[1], K. T. KRUPP[2], T. R. SUMMERS[3], C. H. SUMMERS[3]
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**Abstract:** Treatment of affective disorders is limited by therapeutic options that may bypass specific critical neurophysiological mechanisms that generate depressive and anxious symptomology. An individual's response to fear and motivational capacity are tied to the expression of affective phenotypes, although the relationship with phenotype is clinically ignored. To understand the role of these factors in phenotypic formation, we used prior knowledge of a stressful environment and whole brain (icv) inhibition/activation of $Orx_2$ receptors. The Stress-Alternatives Model (SAM) is a four day, modified social defeat paradigm in which a smaller test mouse (male C57BL/6) is provided an opportunity to escape from a larger aggressor (CD-1), effectively separating a sampled population into two distinct phenotypes: Escape (uses active coping and is less anxious) and Stay (submissive and more anxious). As phenotype determination is unaltered by the second day of SAM interaction, treatments may be applied on day 3 in an attempt to reverse phenotypic outcome. The Social Interaction/Preference (SIP) Test compares the time mice spend near an empty container to the time they spend near a container enclosing an aggressive target, categorizing mice as Resilient or Susceptible to social stress. We demonstrate an advantage of SAM interaction, because the Escape phenotype is also Resilient, and mice that Stay are Susceptible to stress, anxiety and depression. With prior experience to the escape route in the SAM, mice exhibited a proportional shift in phenotype with the Escape outcome being favored over Stay. Furthermore, Escape mice, despite prior escape route knowledge, demonstrated Resilience in the SIP Test and Stay mice expressed Susceptibility. Inhibition of $Orx_2$ receptors (MK-1064) caused Escape mice to remain submissively in the SAM arena, while inducing Susceptibility in the SIP Test. Activation of $Orx_2$ receptors ([$Ala^{11}$,D-$Leu^{15}$]-Orexin B) minimally promoted escape behavior in Stay mice and drastically augmented Resilience in the SIP Test. Excitation of $Orx_2$ receptors also decreased

startle and freezing behaviors, while increasing attention spent on the SAM escape routes. Together, these results illustrate that phenotypic determination is partially dependent on the ability to react appropriately to fearful stimuli and an individual's motivational state. The interaction between anxiolytic behavior and $Orx_2$ stimulation is suggestive of a novel therapeutic approach to affective disorders.

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**Program #/Poster #:** 783.24/HHH23

**Topic:** G.05. Anxiety Disorders

**Title:** Central nervous system effects of soulatrolide, a coumarin isolated from calophyllum brasiliense cambess (calophyllaceae)

**Authors: K. L. ÁLVAREZ-MARTÍNEZ**[1], *C. ALBA-BETANCOURT[1], S. L. GUZMÁN-GUTIÉRREZ[2], D. GASCA-MARTÍNEZ[3], M. C. VILLAFAÑA-LIRA[1], R. REYES-CHILPA[4], M. A. DEVEZE-ÁLVAREZ[1], Á. J. ALONSO-CASTRO[1]
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**Abstract: Abstract:**
Previously, the coumarin soulatrolide was isolated from *C. brasilense* leaves. In traditional medicine, *C. brasiliense* is used for the treatment of pain. A recent report showed that an hexanic extract of *C. brasilense* bark showed central nervous system depressant effects in mice. The sedative and antidepressant effects of soulatrolide (1-50 mg/kg p.o.) were assessed with the pentobarbital-induced sleeping time test and the tail suspension test, respectively.
The effects of soulatrolide (1-50 mg/kg p.o.) on locomotor activity were evaluated using the rotarod test. The anxiolytic activity of soulatrolide (1-50 mg/kg p.o.) was assessed using the elevated plus maze test, the ligh-dark test, and the open field test. The results were compared with clonazepam (CNZ) (1.5 mg/kg p.o.). Soulatrolide showed sedative effects on the pentobarbital-induced sleeping time test and the rotarod test but lacked antidepressant activity on the tail suspension test. Soulatrolide showed anxiolytic effects with similar activity compared to 1.5 mg/kg CNZ in the open field test and the light-dark test. In conclusion, soulatrolide showed sedative, and anxiolytic activity in mice.

**Disclosures: K.L. Álvarez-Martínez:** None. **S.L. Guzmán-Gutiérrez:** None. **D. Gasca-Martínez:** None. **M.C. Villafaña-Lira:** None. **R. Reyes-Chilpa:** None. **M.A. Deveze-Álvarez:** None. **Á.J. Alonso-Castro:** None.

**Poster**

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**Program #/Poster #:** 783.25/HHH24

**Topic:** G.05. Anxiety Disorders

**Title:** The development and utility of rodent paradigms to assess the activity of the vasopressin V1a receptor antagonists, balovaptan and JNJ-17308616, *in vivo*

**Authors: *D. MISZCZUK**[1], A.-M. KÄRKKÄINEN[1], S. ROBJOHNS[2], R. HODGSON[1]
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**Abstract:** The activity of vasopressin at the V1a receptor has been implicated in psychiatric indications and V1a receptor antagonists are being evaluated as novel therapeutics. Two small molecule V1a antagonists, balovaptan and JNJ-17308616, have been reported previously to be efficacious in animal models. The intent of these studies was to evaluate the effects of these antagonists in animal paradigms associated with vasopressin activity. Previously it has been reported that central administration of vasopressin (AVP) produces a characteristic scratching behavior in mice that can be used as a surrogate behavioral measure of V1a receptor target engagement. In this study, Vasopressin (AVP) was administered intracerebroventricularly (i.c.v.) at the following coordinates: AP = +0.5 mm; ML = +1.0 mm; DV = -2.5 mm relative to bregma, and scratching behavior was assessed and quantified by a trained observer 15 min following AVP delivery. The concentration of AVP and the pre-treatment time were selected following parametric studies. Consistent with previous reports, the infused mice displayed a characteristic scratching behavior that has been linked to V1a receptor engagement. Once the optimal methodology was established, we pretreated animals with either balovaptan (100 or 300 mg/kg, po), JNJ-17308616 (30 or 100 mg/kg, po) or vehicle to assess the effect of scratching. Historically, compounds that antagonize the V1a receptor significantly reduce scratching behaviors in AVP-treated mice. Balovaptan blocked the scratching response at both doses tested, whereas JNJ-17308616 demonstrated a non-significant trend toward lowering the scratching response. In addition, we evaluated the effects of balovaptan and JNJ-17308616 in the elevated plus maze test of anxiety in rats. Although an increase in percent time and entries into the open arms was observed with diazepam indicating an anxiolytic effect, no significant increase in open arm time or entry was observed with either V1a antagonist tested. Following the behavioral assay, plasma and brain were taken from the animals to assess exposure. Balovaptan had robust

mean plasma (100 mg/kg: 1250 ng/ml; 300 mg/kg: 1449 ng/ml) and mean brain (100 mg/kg: 2344 ng/g; 300 mg/kg: 3496 ng/g) exposures. JNJ-17308616 had lower brain exposures; at 100 mg/kg the mean plasma exposure was 3023 ng/ml and the mean brain exposure was 309 ng/ml. The data from these studies demonstrate the in vivo activity of small molecule V1a antagonists following systemic administration in AVP-induced behaviors in the mouse. However, additional studies are will need to be conducted to evaluate whether these effects can be extended to animal models of anxiety.

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**Title:** Carbamoylated erythropoietin (cEPo) reduces anxiety during social interaction in the stress-alternatives model

**Authors: *K. KRUPP**[1], J. D. YAEGER[2], N. T. JONES[1], C. D. STATON[2], T. R. SUMMERS[3], S. S. NEWTON[1], C. H. SUMMERS[3]
[2]Biol., [3]Dept. of Biol., [1]Univ. of South Dakota, Vermillion, SD

**Abstract:** During socially stressful interactions, decision-making and aptitude for learning are critical components in determining the extent an individual will display anxious behavioral responses. Although both of these elements are crucial, the neural mechanisms of learning and decision-making during social stress are not well understood. Brain-derived neurotrophic factor (BDNF) and other neurotrophins are a class of neuropeptides known for their role in neuroplasticity, as well as learning and memory formation. Erythropoietin (EPo), a hormone well known for its involvement in red blood cell production, has a similar role as neurotrophins when modulating behavior and promoting neural plasticity, such as neurogenesis, in the brain. Chemically modifying EPo by *in vitro* carbamoylation produces cEPo, which shows similar neuronal effects as EPo, but does not display erythropoietic actions. We hypothesize that the neuroplastic and learning effects of cEPo may be dependent on its action in the dorsal dentate gyrus of the hippocampus, where neurogenesis occurs. The Stress Alternatives Model (SAM) is a 4-day social stress paradigm, in which a mouse is placed into an open field arena with a larger

aggressive conspecific for 5 minutes. Unlike other social defeat models, the SAM allows the smaller mouse an opportunity to escape from the aggressor. Test mice display one of two behavioral phenotypes: avoiding social aggression (Escape) or submission to the aggressor (Stay). On day 5, mice are put through a Social Interaction Preference (SIP) test to measure their susceptibility or resilience to social stress. In these studies, 7-8-week-old male C57BL/6 mice were given a single intracerebroventricular (icv; 100 ng), or single intra-dentate gyrus (iDG; 10 ng) injection of cEPo or vehicle after day 2 of the SAM. On day 3, 10% of icv cEPo treated mice and 18.75% of iDG cEPo treated mice reversed their phenotype (Stay to Escape). By day 4, 30% of icv cEPo treated mice and 37.5% of iDG cEPo treated mice reversed their phenotype; whereas, mice receiving vehicle injections did not change. Furthermore, nearly 100% of mice treated with icv cEPo exhibited resilience in the SIP test regardless of behavioral phenotype. Together, these results illustrate an anxiolytic role of cEPo during social stress and suggest a potential mechanism that influences learning in anxious situations.

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Beltran-Morgado Foundation for the Advancement and Communication of Neuroscience in Veracruz

**Title:** Anxiolytic effect of chronic intake of supplemental magnesium chloride ($MgCl_2$) in rat

**Authors: *M. MACÍAS-CARBALLO**, F. GUTIÉRREZ-MÉNDEZ, L. LÓPEZ-MERAZ, L. BELTRAN-PARRAZAL, C. MORGADO-VALLE
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**Abstract:** Anxiety-like behaviors are part of the natural repertoire of animal behavior. In humans, anxiety disorders are a prevalent psychiatric condition. There is a necessity for an anxiolytic drug that reduces the risk of developing dependence. Also, the development of non-sedative anxiolytic drugs with distinct doses for anxiolytic and sedative effects would be of considerable clinical interest. Magnesium ($Mg^{2+}$) is one of the most important elements involved in biochemical processes. In the literature, there is suggestive but inconclusive evidence for a beneficial effect of $Mg^{2+}$ supplementation in humans with mild anxiety. Here, we studied

whether $Mg^{2+}$ has an anxiolytic effect on anxiety-like behavior in rats. We used two groups (n=9 rats each): 1) Control group: drank potable water containing 0.011 g/L $MgCl_2$ for 4 months. 2) Chronic intake of supplemental $MgCl_2$ group: drank potable water containing 0.011 g/L for 3 months, and potable water containing 5 g/L for 1 month. At the end of the fourth month, we induced anxiety with a SC injection of veratrine (0.6 mg/kg), a sodium channel activator, and proceeded to behavioral tests. In the elevated plus-maze test, after injection of veratrine, the group with chronic intake of supplemental $MgCl_2$ showed a statistically significant increase in the percentage of time spent in- ($p < 0.004$ , $t = 3.351$, $df = 16$) and entries into the open arms ($p < 0.0001$, $t = 5.873$, $df = 16$), with respect to control. We also measured anxiety-like behavior using the open-field test. After injection of veratrine, rats from the group of chronic intake of supplemental $MgCl_2$ spent more time in the central zone of the arena ($p < 0.03$, $t = 2.25$, $df = 16$, respect to control group) indicating that they were less anxious. Our findings suggest that chronic $MgCl_2$ supplementation has an anxiolytic effect.

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**Poster**

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**Topic:** G.05. Anxiety Disorders

**Support:** T32 DA07288

**Title:** Oxytocin ameliorates TMT-induced anxiety and gene expression

**Authors: *R. A. REICHARD**, J. HOPKINS, J. SALAA, G. GIANOTTI, J. MCGINTY
Neurosci., Med. Univ. of South Carolina, Charleston, SC

**Abstract:** The neuropeptide oxytocin (OXT) is emerging as an efficacious treatment for anxiety and depression-related pathologies such as post-traumatic stress disorder (PTSD) and drug addiction. Our lab has previously shown that systemic administration of OXT reduces cue- and stress-induced reinstatement in rats with a history of methamphetamine self-administration that were previously exposed to the predator odor, 2,3,5-trimethyl-3-thiazoline (TMT). However, the efficacy of prophylactic OXT treatment to alter TMT-induced anxiety and the brain structure(s) mediating these effects are not known. To address these issues, female Sprague Dawley rats were injected with OXT [(1 mg/kg), i.p] or saline 30 minutes prior to 1% TMT or saline exposure on days 1-5. Immediately following exposure, open field behaviors were recorded for fifteen minutes on days one and five. To assess the anxiety state of the different groups, light/dark box and zero maze testing was performed on days 6 and 7 respectively. The brains were extracted 45

minutes after zero maze testing and processed for in situ hybridization using RNAScope™. The expression levels of *Oxt*, *Crh* and *Fos* mRNA in the paraventricular nucleus (PVN) and *Crh*, *Oxtr* and *Fos* mRNA in the dorsal and ventral lateral bed nucleus of the stria terminalis (dlBST and vlBST) were compared between treatment groups. As expected, TMT exposure produced an anxiogenic phenotype as evidenced by reduced time spent in the center of an open field, the number of entries into and time spent on the lighted side of the light/dark box, and the number of open arm entries and time spent in open arms on a zero maze. These effects were absent in rats that received OXT prior to TMT exposure. The TMT-induced anxiety state was accompanied by increased *Crh* expression in the PVN which was significantly lower in rats which received OXT pretreatment. *Oxt* mRNA levels in the PVN were not altered by TMT exposure but were significantly higher in rats that received prophylactic OXT injections. TMT exposure increased *Fos* expression in *Crh*+ and *Crh*- neurons that express *Oxtr* in the vlBST. The increases in *Fos* were not seen in rats that received OXT injections prior to TMT exposure. There were no significant differences between treatment groups in mRNA levels that were assessed in the dlBST. These results demonstrate that prophylactic OXT treatment ameliorates TMT-induced anxiety and implicate the PVN and vlBST as brain structures contributing to these effects.
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**Poster**

**783. Anxiety Disorders: Preclinical Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 783.29/HHH28

**Topic:** G.05. Anxiety Disorders

**Support:** NIMH R01 MH100068
NIMH R01 MH095790
NIMH K01 MH079130

**Title:** Extended time course of clinical change following neurofeedback

**Authors: *M. RANCE**[1], C. WALSH[2], D. G. SUKHODOLSKY[5], B. PITTMAN[3], M. QIU[2], S. KICHUK[3], P. GRUNER[3], S. WAZYLINK[3], W. KOLLER[2], M. BLOCH[3], D. SCHEINOST[2], C. PITTENGER[3,4,6], M. HAMPSON[2]
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**Abstract:** Real-time functional magnetic resonance imaging (rt-fMRI) neurofeedback is a powerful method of altering brain activation and a promising clinical tool. Induced changes are known to persist for some time after the intervention. (Amano, et al., 2016; Megumi, et al., 2015; Ramot, et al., 2017; Robineau, et al., 2017; Scheinost, et al., 2013; Subramanian, et al., 2011; Young, et al., 2017). Knowledge of the progression of the time course and persistence of induced changes are crucial for clinical applications.
To examine the effect of neurofeedback intervention, we examine the time course of clinical symptom change in two different clinical populations, combining data of preliminary analyses of two ongoing studies training the patient sample to regulate two different respective brain areas: the ventral frontal cortex in adults with obsessive compulsive disorder and the supplementary motor area in adolescents with Tourette's Syndrome. Both studies employed a "real" and a "sham" neurofeedback condition.
The data revealed a shared temporal pattern of continuing improvement for weeks after the intervention. This pattern was visible in subjects that received the "real" neurofeedback intervention that continued to improve.
Neurofeedback studies should include longer follow up periods for weeks or months to capture the effect of the intervention that might be observed later than anticipated and otherwise missed. Another implication is that temporal design of neurofeedback studies must be carefully reviewed especially in crossover designs.

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**Poster**

**783. Anxiety Disorders: Preclinical Models**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 783.30/HHH29

**Topic:** G.04. Mood Disorders: Depression and Bipolar Disorders

**Support:** National Research Foundation of Korea Grant No.2016R1A2B2006474
National Research Foundation of Korea grant No.2017R1A6A3A01005765
National Research Foundation of Korea grant, Medical Research Center No.2017R1A5A2015395

**Title:** SIRT2 contributes to chronic stress resilience by regulating synaptic plasticity

**Authors: *S.-E. WANG**[1], S. KO[2], J. SEO[2], H.-R. JO[1], H. SON[2,3]
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**Abstract:** Silent information regulator 2 proteins (Sirtuin2 or SIRT2) is an $NAD^+$-dependent deacetylase that regulates cellular oxidative stress response. It modulates transcriptional silencing and protein stability through deacetylation of target proteins including histones. Previous studies have shown that SIRT2 plays a role in mood disorders and hippocampus-dependent cognitive function, but the underlying neurobiological mechanism is poorly understood. Here, we report that chronic stress-induced down-regulation of SIRT2 reduced pre-synaptic molecules, such as *Synapsin1* and *Synaptophysin* through chromatin remodeling in the hippocampus. We observed that knockdown of SIRT2 in the dentate gyrus precipitated susceptibility to stress accompanied by impairment of synaptic plasticity. Conversely, SIRT2 overexpression showed the phenotype of resilience to stress. Together, our results indicate that SIRT2 plays an important role in the response to stress, thereby modulating depression.
This work is supported by National Research Foundation of Korea (NRF) grant (No. 2016R1A2B2006474, 2017R1A6A3A01005765) and Medical Research Center (2017R1A5A2015395) funded by the Ministry of Science and Technology (MEST), Republic of Korea.

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**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.01/HHH30

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** MINECO/FEDER PSI2016-77895-R

**Title:** Increased risk to alcohol relapse induced by inflammatory pain: Studies in non-operant rat models

**Authors: *Y. CAMPOS-JURADO**, J. CUITAVI, J. D. LORENTE, M. IGUAL-LOPEZ, E. TORRES-CAMPOS, J. L. GONZALEZ-ROMERO, L. MARTI-PRATS, L. HIPOLITO
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**Abstract:** Epidemiologic data have shown a relationship between pain and drug use disorders (DUD) especially to opioids and alcohol. Indeed, a recent clinical study showed that the correct management of pain in patients with a previous history of alcohol use disorder decreases the risk of relapse in alcohol drinking, suggesting that in this prone population, pain may increase the vulnerability to relapse in alcohol consumption. Previous data in rats revealed that inflammatory pain desensitizes mu opioid receptors (MORs) in the ventral tegmental area (VTA) and increases intake of high doses of heroine. Due to the relevant role of MORs in alcohol effects, we hypothesize that this desensitization may alter the patterns of alcohol intake and alcohol relapse.

In the present study, we further evaluated VTA MORs function under inflammatory pain condition. For that, we administered two doses (7 and 14 ng) of DAMGO (MORs agonist) directly into the VTA and performed c-Fos immunohistochemistry to analyze the result of the VTA MORs activation in the projecting areas (Nucleus Accumbens, Medial Prefrontal Cortex, Amygdala and ventral pallidum). Results showed that pain induces the dysregulation of MORs in the VTA, which had different profile depending on the projecting region. Later on, we evaluated the effect of inflammatory pain on alcohol relapse through two different non-operant paradigms. On the one hand, results from an Alcohol Deprivation Effect model (ADE) showed that inflammatory pain increases the risk of developing ADE, without affecting the magnitude of this effect. On the other hand, we used an intermittent 2-bottle choice paradigm in male and female rats. In this model male rats showed an increase of alcohol intake after an abstinence period in both pain and control groups. Surprisingly, in female rats the increment of ethanol intake during post-deprivation days was only patent in the pain group, suggesting that in female rats pain might act as an alcohol relapse factor. Our results uncover the need to understand the neural basis of the complex relation between inflammatory pain and vulnerability to suffer DUD.

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**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.02/HHH31

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** National Plan on Drug abuse, Ministerio de Sanidad of Spain (MSSSI, grant PNSD001I2015 to G.H.)
National Institutes of Health (NIAAA, INIA grant U01 AA020912 to A.W.L.)

**Title:** Targeting RPTPβ/ζ in preclinical models of alcohol use disorder: Role of ALK

**Authors: *G. HERRADON**[1], R. FERNÁNDEZ-CALLE[1], M. VICENTE-RODRÍGUEZ[1], M. PASTOR[1], E. GRAMAGE[1], B. DI GERONIMO[1], J. M. ZAPICO[1], C. CODERCH[1], C. PÉREZ-GARCÍA[1], A. W. LASEK[2], B. DE PASCUAL-TERESA[1], A. RAMOS[1]
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**Abstract:** Pleiotrophin (PTN) and Midkine (MK) are cytokines that are upregulated in the prefrontal cortex after alcohol administration and have been shown to reduce ethanol drinking and reward. Through one of their receptors, Receptor Protein Tyrosine Phosphatase (RPTP) β/ζ,

PTN and MK increase tyrosine phosphorylation of substrates that are key in alcohol signalling pathways such as Fyn kinase and Anaplastic Lymphoma Kinase (ALK). We hypothesize that RPTPβ/ζ plays a role in alcohol effects. To test this hypothesis, we treated mice with small-molecule inhibitors of RPTPβ/ζ (MY10, MY33-3) before testing them for binge-like drinking using the two-bottle drinking in the dark protocol. Mice treated with RPTPβ/ζ inhibitors, particularly with MY10, drank less ethanol than controls. Consistent with the decrease in ethanol consumed, mice treated with MY10 showed a reduced preference for the ethanol solution compared with vehicle-treated mice. Sucrose drinking was not affected by MY10 treatment. MY10 treatment blocked ethanol reward in conditioning studies. In addition, MY10 showed limited effects on ethanol-induced ataxia, and potentiated the sedative effects of ethanol. Interestingly, ethanol treatment of neuroblastoma cells increased phosphorylation of ALK and TrkA, known substrates of RPTPβ/ζ. Treatment of neuroblastoma cells with MY10 or MY33-3 also increased levels of phosphorylated ALK and TrkA. However, concomitant treatment of neuroblastoma cells with ethanol and MY10 or MY33-3 prevented the increase in pTrkA and pALK. The data support the concept that RPTPβ/ζ is a potential target for pharmacotherapy to treat excessive alcohol consumption. Our data suggest that RPTPβ/ζ inhibitors decrease drinking and reward by promoting ALK endocytosis and interfering with ethanol-induced activation of ALK. The data suggest that MY10 is a potential new compound that may be useful for the treatment of alcohol use disorder.

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**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.03/HHH32

**Topic:** G.08. Drugs of Abuse and Addiction

**Title:** Increased voluntary alcohol consumption and preference in female, but not male, oxytocin receptor knockout mice

**Authors: *K. M. RODRIGUEZ**[1], H. K. CALDWELL[2]
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**Abstract:** Oxytocin (Oxt) is a neuropeptide whose projections are distributed throughout the brain. While Oxt is most widely known for its role in the neural regulation of social behavior, it has also been found to impact alcohol dependence, appearing to offer some protection. Rodent studies have demonstrated that Oxt can reduce voluntary alcohol consumption. Similarly,

intranasal treatment with Oxt reduces cravings and helps improve withdrawal symptoms in humans diagnosed with alcohol use disorder (AUD). In addition, in human post-mortem brain studies there is evidence of a disrupted Oxt system in patients diagnosed with an AUD. Specifically, increases in Oxt mRNA in the pre-frontal cortex and decreases in Oxt peptide immunoreactivity in the supraoptic nucleus. So, too are there genetic studies linking variations in the Oxt receptor (Oxtr) gene with alcohol-facilitated aggressive behavior. Unfortunately, there the data are limited with regard to the role of Oxt in alcohol consumption. Thus, using Oxtr knockout (-/-) mice, we sought to determine if genetic disruption of the Oxtr results in increased alcohol consumption. We hypothesized that male and female Oxtr -/- mice would have increased alcohol consumption following a physical stressor compared to Oxtr wildtype (+/+). Using the two-bottle preference test, mice had continuous access to alcohol and water. Both pre- and post-stress alcohol consumption and preference were measured. In males, we found that there were no significant genotypic effects in alcohol consumption or alcohol preference. In females, we found that Oxtr -/- mice consumed significantly more alcohol pre- and post- stress. Based on these data we hypothesize that changes in the Oxt system may make females more vulnerable to developing AUDs. Currently, potential mechanisms and neuroanatomical targets of interest are being investigated. In conclusion, this study provided insight into the important role the Oxt system may play with regard to alcohol consumption in females.

**Disclosures: K.M. Rodriguez:** None. **H.K. Caldwell:** None.

**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.04/HHH33

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH Grant AA023291
NIH Grant AA015512

**Title:** Within-session and across-session patterns of oral ethanol consumption in alcohol-preferring (P) rats given intermittent access to 20% ethanol

**Authors: L. VOUTOUR**, J. BRETON, N. PINKOWSKI, J. PASCUA, E. PUESCHEL, *S. M. BRASSER
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**Abstract:** Previous data have demonstrated that alcohol-preferring (P) rats exposed to an intermittent-access drinking paradigm display reductions in ceramide levels in forebrain and heart, and decreases in liver cholesterol, indicative of beneficial effects of voluntary alcohol intake on lipid profiles in this genetic line (Godfrey et al., 2015). These findings agree with other

reports of downregulation of genes involved in cholesterol synthesis in inbred alcohol-preferring (iP) rats under conditions of moderate levels of free-choice drinking (Klein et al., 2014). Here, we examined detailed within-session and across-session patterns of drinking by P rats in a 20% ethanol intermittent-access paradigm to assess how they distribute their alcohol intake over time. Adult male P rats (n=11) were tested in intake sessions involving voluntary access to a 20% (v/v) ethanol solution vs. water, alternating with abstinence periods involving access to water only (45 ethanol drinking sessions total over 3 months). Lick responses to ethanol and water were monitored for later quantitative analysis. Across initial sessions, P rats decreased the frequency of their drinking episodes (# of bins sampled/session), which was accompanied by an increase in the amount of ethanol consumed per episode (*P*'s < 0.001). Intake stabilized during the remainder of the chronic exposure period. Analysis of drinking within session revealed that the largest drinking episode occurred during the first half hour (1.85 ± 0.06 g/kg), while ethanol intake during the remainder of each session ranged on average between 0.03-0.37 g/kg/half hour. These results indicate that aside from a larger drinking bout upon first ethanol access each session, P rats distribute their alcohol intake moderately in this paradigm, which has important relevance to favorable health-related effects observed from voluntary drinking in this lin*e.*

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**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.05/HHH34

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NHMRC Australia (Project Grant 628680)
Royal Golden Jubilee Ph.D. Program (PHD/0253/2552)
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**Title:** Blocking of α6 nicotinic acetylcholine receptors by N,N'-decane-1,10-diyl-bis-3-picolinium diiodide decreases alcohol self-administration in alcohol-preferring rats

**Authors: *J. SRISONTIYAKUL**[1], H. E. KASTMAN[2], E. V. KRSTEW[2], P. GOVITRAPONG[1,3], A. J. LAWRENCE[2,4]
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**Abstract:** Cigarette and alcohol use often co-occur implying an interaction between these drugs in our brain. Evidence is emerging that nicotinic acetylcholine receptors (nAChR) is a shared molecular component of nicotine and alcohol addiction. This is further corroborated by the capabilities of smoking cessation medications, which target nAChR, to also decrease alcohol drinking. The α6 subunit of nAChR is hypothesized to mediate the rewarding properties of alcohol and nicotine due to its exclusive distribution in the reward system. Pharmacological manipulation of this subunit leads to reduction in alcohol intake as well as nicotine. However, the traditional antagonist against the α6 subunit, α-conotoxin MII, cannot pass the blood-brain barrier. To overcome this obstacle, a novel selective α6 nAChR antagonist *N*,*N'*-decane-1,10-diyl-*bis*-3-picolinium diiodide (bPiDI) was developed. Systemic injection of bPiDI attenuates nicotine self-administration indicating bPiDI abilities to penetrate the blood-brain barrier and modulate nicotine reinforcement. Therefore, the current study aimed to determine the effects of bPiDI on alcohol dependence using self-administration paradigm. Adult male alcohol-preferring rats were trained to orally self-administer 10% (v/v) ethanol or sucrose solution until stable responses were achieved. They were subsequently injected intraperitoneally with bPiDI (1 or 3 mg/kg) prior to the self-administration session to assess the drug effects on the animal motivation to consume alcohol. Then, they underwent extinction period, in which no rewards or cues were given in the operant chambers. After their responses were extinguished, they were injected with bPiDI and tested for the drug effects on cue-induced reinstatement of reward-seeking behavior. Results showed that bPiDI (3 mg/kg) significantly reduced alcohol self-administration under fixed and progressive ratio schedules of reinforcement, without any effects on sucrose self-administration. Nevertheless, the same dose of bPiDI was unable to inhibit cue-induced reinstatement of alcohol- and sucrose-seeking behavior. Overall, the data support the role of α6 subunit of nAChR in the reinforcing effect of alcohol, but not in the relapse to alcohol-seeking behavior. These results cumulatively suggest that bPiDI might be a potential therapeutic agent to limit both alcohol and nicotine consumption with no adverse effects on responding for a natural reward.

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**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.06/HHH35

**Topic:** G.08. Drugs of Abuse and Addiction

**Title:** Neuroinflammation-induced ethanol intake in BDNF heterozygous and KMO knock-out mice

**Authors: *G. A. PORTER**[1], J. C. O'CONNOR[2]
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**Abstract:** Alcohol use disorder affects up to 15.1 million adults in the United States each year and is associated with many comorbid diseases and disorders, such as chronic inflammatory diseases and depression. Studies have shown that immune response genes mediate alcohol intake in humans and rodents, implicating a genetic component in alcohol abuse. Notably, it was found that acute inflammation by lipopolysaccharide (LPS) treatment increased ethanol intake in C57/Bl6 mice. Brain-derived neurotrophic factor (BDNF) deficiency has been implicated as a genetic vulnerability factor in the development of disorders such as depression. BDNF heterozygous mice have also been shown to have an exaggerated neuroinflammatory response and dysregulated neurometabolic response to peripheral LPS or stress, including upregulated KMO-dependent neurotoxic kynurenine metabolism. In this study, we hypothesized that neuroinflammation would promote greater ethanol intake in $BDNF^{+/-}$ mice than wild-type (WT) mice. Additionally, we hypothesize that mice lacking kynurenine monooxygenase (KMO), the rate-limiting enzyme for neurotoxic kynurenine metabolism and a known mediator of several inflammation-induced depressive-like behaviors, will have reduced ethanol intake. $BDNF^{+/-}$ and WT mice were injected i.p. with 0.83 mg/kg LPS or saline. One week later, $BDNF^{+/-}$, WT, and $KMO^{-/-}$ mice were continuously exposed to increasing concentrations of ethanol (3-21%) in a two bottle choice paradigm. Ethanol intake tended to increase in both LPS treated $BDNF^{+/-}$ and WT mice ($p=0.1$). $BDNF^{+/-}$ mice showed increased ethanol intake over WT in both treatment conditions. Interestingly, $KMO^{-/-}$ mice showed significantly reduced ethanol intake. These results suggest that BDNF deficiency may predispose individuals to alcohol use disorder, while inhibiting KMO-dependent kynurenine metabolism may be a potential therapeutic route to reducing alcohol abuse.

**Disclosures: G.A. Porter:** None. **J.C. O'Connor:** None.

**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.07/HHH36

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** AA013641
AA019431

**Title:** Extreme ethanol drinking during early post-abstinence phase in rhesus macaques

**Authors: N. P. NEWMAN**[1], N. A. R. WALTER[1], V. C. CUZON CARLSON[2], *K. GRANT[3]
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**Abstract:** The behavior of repeatedly drinking beyond binge intoxication as defined at least 80 mg/dl blood ethanol concentration (BEC) into extreme levels (BEC 2-3 times beyond binge levels) has been documented in college and alcohol use disorder treatment-seeking populations. The ability to engage in extreme alcohol drinking infers brain mechanisms that subserve drinking motor patterns while other sensory-motor and cognitive functions are impaired. Extreme drinking levels have been documented in a non-human primate (NHP) model of alcohol self-administration, but only in a subset of monkeys. However, repeated periods of forced abstinence results in relapse drinking that exceeds pre-abstinence levels. The purpose of this study was to quantify relapse drinking in terms of BEC achieved and determine if pre-abstinence drinking influenced the effects of relapse drinking. We defined low-binge, heavy and extreme drinking as average BEC less than 80 mg/dl, 80-160 mg/dl and greater than 160 mg/dl, respectively. Young adult, male rhesus macaques (n=9) underwent 14 months of voluntary ethanol (4% w/v) consumption available 22 hrs/day (i.e., open-access condition). Abstinence condition (only water available) was then imposed for 35 days, followed by reinstatement of open-access to ethanol. BECs taken 4-5 times/individual at 7 hrs after the start of the daily drinking session during the three weeks prior to and following abstinence were compared. Prior to abstinence the number of monkeys that had average BECs less than 80 mg/dl, 80-160 mg/dl and greater than 160 mg/dl were 3, 4, 2, respectively. Following abstinence, the number of monkeys that had average BECs less than 80 mg/dl, 80-160 mg/dl and greater than 160 mg/dl were 0, 4, 5, respectively. Notably, all monkeys, regardless of pre-abstinent levels of BECs, had significantly increased BECs beyond low-binge level during relapse drinking. The most extreme single-subject average BEC during relapse drinking was 253 mg/dl. Using this model, examination of thalamo-cortico-striatal pathways, as well as brainstem mechanisms, suggest that excitatory/inhibitory glutamatergic and GABAergic balance maintains motor output associated with drinking patterns beyond low-binge levels while inhibiting associative processes.

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**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.08/HHH37

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** MEXT KAKENHI, Grant Number 16K08913

**Title:** Implications of toll-like receptor signaling in the development of ethanol dependence in mice brain

**Authors: *K. MIZUO**, S. WATANABE
Dept. of Legal Med., Sapporo Med. Univ., Sapporo, Japan

**Abstract:** Alcohol is one of the most abused drug worldwide. The number of alcohol dependant is over a million in Japan. Although a lot of study suggested candidates, certain mechanism underlying the development of alcohol dependence is still unclear. It has been reported that brain-enriched miR-124 play a critical role in the dependence of abused drugs, such as cocaine. Moreover, we have reported that acute ethanol administration caused the long-lasting increase in the expression of miR-124 in mouse brain. In the present study, we investigated the expression of miRs in mouse ethanol dependence model. Mice were treated with liquid diet containing ethanol for 10 days. Using the escalating ethanol dosage schedule, the mice were fed the ethanol diet as follows: 1st day: 1 w/v%; 2nd and 3rd day: 3 w/v%; 4th to 10th day: 4 w/v% ethanol diet, respectively. The control mice were given the same volume of ethanol-free liquid diet with sucrose substituted in isocaloric quantities for ethanol. The mice chronically treated with ethanol revealed severe withdrawal signs after discontinuation of ethanol. The mice were killed by decapitation and the lower midbrain (containing ventral tegmental area) was dissected. RT-PCR analysis for detection of miRs in the brain was performed. The expression of miR-132, miR-212 and miR-146a were decreased in lower midbrain following chronic treatment of ethanol. It has been reported that miR-146a regulates toll-like receptor (TLR) 4 and TLR7 expression. TLR4 has been implicated in the development of alcohol-induced liver disease and osteonecrosis. We investigated the changes in TLR4 and TLR7 in ethanol dependence. The both expression of TLR4 and TLR7 in lower midbrain were significantly increased following chronic treatment of ethanol. We next investigated the role in TLRs signaling in the development of ethanol dependence using inhibitors of TLRs. We observed that the treatment of resatorvid, a TLR4 inhibitor, significant prevented in the development of ethanol dependence. These findings suggest our hypothesis that chronic ethanol treatment decreases in miR-146a in lower midbrain, resulting in the development of ethanol dependence via activation of TLR4 signaling.

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**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.09/HHH38

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** R01-DA009411-17
2T32MH014654-40

**Title:** The long-term effects of adolescent and adult chronic variable stress on operant self-administration of alcohol

**Authors: *D. A. CONNOR**, J. DROGIN, A. MAK, J. A. DANI
Neurosci., Univ. of Pennsylvania, Philadelphia, PA

**Abstract:** Stress is a major risk factor for alcohol use disorders, and exposure to stressors during adolescence is particularly detrimental. For example, adolescent exposure to stress positively predicts alcohol dependence in adulthood. A mechanistic account linking early-life stress to long-term changes in addiction-related behavior remains unclear. However, several pieces of evidence suggest stress-induced changes in the developing dopaminergic system are important: (1) the mesolimbic dopaminergic system undergoes maturation during adolescence, (2) adolescent individuals show greater physiological response to stressors compared with adults, and (3) stress is known to act directly on mesolimbic substrates of motivation and reward. Thus, we sought to investigate if adolescent and adult rats were differentially sensitive to long-term effects of chronic stress on operant alcohol self-administration in adulthood. Using adolescent and adult Long-Evans rats we modeled exposure to early-life and adult stress with a chronic variable stress (CVS) protocol. We selected this stress protocol because it reduces habituation to daily stress exposure by including pseudorandom daily exposure to alternating stressors: restraint, elevated platform, oscillating rocker platform, predator odor (fox urine), and overnight wet bedding. Rats were exposed to CVS for 14 days— adolescent: post-natal day (PND) 28 until PND 42, adult: PND 83 until 96. Thirty days after CVS treatment, rats were trained to lever press for saccharin solution (0.125%). Once stable responding to saccharin was achieved, alcohol was progressively faded into saccharin solution. Rats exposed to CVS during adolescence showed increased acquisition of sweetened 4% alcohol self-administration. Additionally, after saccharin fading, adolescent CVS-exposed rats showed increased self-administration of unsweetened 10% alcohol compared to littermate controls. In contrast, rats exposed to CVS during adulthood showed no long-term effect on alcohol self-administration. These findings suggest that adolescence is associated with a heightened vulnerability to long-lasting effects of chronic stress leading to increased liability for alcohol use disorders.

**Disclosures: D.A. Connor:** None. **J. Drogin:** None. **A. Mak:** None. **J.A. Dani:** None.

**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.10/HHH39

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** Butler University Holcomb Awards Committee
Indiana Academy of Sciences

**Title:** Comparing consumption and preference of combined alcohol and nicotine in male and female C57BL/6J mice

**Authors: *J. N. BERRY**, K. BENSON
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**Abstract:** Alcohol and nicotine are two of the most commonly abused substances and are also widely abused together. Smoking tobacco cigarettes containing nicotine is known to increase the number of alcoholic drinks per day and increase the chances of alcohol dependence. Both alcohol and nicotine are known to individually increase levels of dopamine in the mesocorticolimbic reward pathway. Using either a continuous access or an intermittent access two-bottle choice paradigm, we investigated the effects of the acquisition, maintenance, and withdrawal from chronic alcohol (3-20% v/v), nicotine (5-30 μg/ml), or a combination of both alcohol and nicotine in adult male and female C57BL/6J mice. Withdrawal behavior (i.e. somatic signs of withdrawal) was measured approximately 24 hours after both alcohol and/or nicotine were removed. Both male and female mice consumed more alcohol and more nicotine in the intermittent access two-bottle choice paradigm compared to the continuous access two-bottle choice paradigm. Female mice had increased consumption and preference for higher concentrations of alcohol and/or nicotine compared to male mice. Given the mechanistic overlap between the two substance and the large number of individuals who are co-dependent on both alcohol and nicotine, future studies should continue to examine the effects of combined alcohol and nicotine.

**Disclosures: J.N. Berry:** None. **K. Benson:** None.

**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.11/HHH40

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** Grant from DGAPA-UNAM to OPG (IN215218)
Grant from DGAPA-UNAM to MMD (IA205218)
Grant from DGAPA-UNAM to AERC (IN217918)
PosDoc Program from DGAPA-UNAM to EPC

**Title:** Witnessing violence during early-mid adolescence increases alcohol intake in late-adolescence in the rat

**Authors: *E. PALOMARES**[1], M. MENDEZ DIAZ[2], A. E. RUIZ-CONTRERAS[3], O. PROSPERO-GARCIA[4]

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**Abstract:** Early life stressful experiences have been widely linked to drug seeking and consumption. Hence, we have investigated the effect of witnessing aggression at early and mid-adolescence on alcohol consumption on late-adolescence male and female rats. Six adolescent (3 males/3 females) Wistar rats cohabited with an adult male Wistar rat from postnatal days (PND) 21 to PND 34. The experimental adolescent rats were exposed every other day for 25 minutes to witnessing the social defeat of their roomy, adult male Wistar rat, by an aggressive male intruder rat (Long Evans). The control group was subjected to the same procedure, but spearing the intruder, during PND 23 to 33. From PND 34 to 49 their voluntary consumption of alcohol (1 bottle with 10% v/v of alcohol and the other of water) was evaluated. Adult resident rats received 1.46 defeats in average (range, 1-1.83). Results show that adolescent female but not male rats that witnessed social defeat during early-mid adolescence exhibited an increase of alcohol consumption in late adolescence. These results suggest that witnessing intrafamily violence during early adolescence result in an increase in alcohol consumption in late adolescence. However, female rats seem to be more vulnerable to this stressor.

**Disclosures: E. Palomares:** None. **M. Mendez Diaz:** None. **A.E. Ruiz-Contreras:** None. **O. Prospero-Garcia:** None.

**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.12/HHH41

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIAAA Grant 5U01AA019967-08

**Title:** Adolescent binge-like ethanol vapor has no effect on aversion-resistant or operant ethanol intake in adulthood

**Authors: *T. B. NENTWIG**[1], E. J. GLOVER[2], E. M. STARR[2], A. H. SELCHICK[1], L. J. CHANDLER[1]
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**Abstract:** Earlier age of first alcohol use is associated with heightened risk for the development of an alcohol use disorder (AUD). However, it is unclear whether exposure to alcohol during adolescence alters the motivation to drink and promotes drinking despite negative consequences.

We assessed aversion-resistant ethanol intake in adult male Long-Evans rats exposed to ethanol vapor in a binge-like manner during adolescence. Rats were subjected to either five repeated cycles of adolescent intermittent ethanol vapor (AIE) or air (AIR) from postnatal day (PD) 28 through PD44. Using a two-bottle choice intermittent alcohol access (IAA) procedure in which animals had access to 20% ethanol and water for 24 hrs, 3 days/week, ethanol intake during adulthood was examined beginning on PD59. Ethanol consumption and preference were assessed at 30 min and 24 hr time points. Rats were tested for aversion-resistant drinking using ethanol adulterated with successively increasing concentrations of quinine (10, 30, 50, 100 mg/L), with testing at each concentration separated by one week. The first tests occurred between weeks 6 through 9, and the second between weeks 12 through 15. Subsequently, rats were tested for operant ethanol intake using fixed (FR) and progressive ratio (PR) schedules of reinforcement. Following completion of operant ethanol self-administration, the rats then underwent a home cage two bottle sucrose preference test. In the IAA procedure, both AIR- and AIE-exposed rats exhibited similar levels of ethanol intake and preference at 30 min and 24 hr time points ($p$ > 0.60). Quinine adulteration (30, 50, 100 mg/L) after 6 weeks of IAA resulted in significant suppression of 30 min and 24 hr ethanol intake and preference to a similar extent in AIR- and AIE-exposed animals ($p$'s > 0.50). Similar results were obtained during retest after 12 weeks of IAA ($p$'s >0.50). In an operant paradigm, AIR- and AIE-exposed rats responded similarly for ethanol delivered on FR1 and FR3 schedules of reinforcement ($p$ > 0.70) and exhibited similar breakpoints for ethanol under a PR schedule of reinforcement ($p$ > 0.20). In addition, no between group differences were observed in a home cage sucrose preference test ($p$ > 0.70). These results suggest that binge ethanol vapor exposure during adolescence does not induce greater voluntary ethanol consumption in adulthood or alter the motivational aspects of ethanol intake. Moreover, AIE exposure does not impart aversion-resistance following prolonged drinking. Overall, these data suggest that AIE exposure alone may not be sufficient to facilitate the development of AUD phenotypes in adulthood.

**Disclosures: T.B. Nentwig:** None. **E.J. Glover:** None. **E.M. Starr:** None. **A.H. Selchick:** None. **L.J. Chandler:** None.

**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.13/HHH42

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** University of Dayton startup funds (TB)
University of Dayton Honors Program (HP)

**Title:** An abbreviated alcohol deprivation effect model of relapse behavior in male and female Long Evans rats

**Authors: *T. R. BUTLER**, H. J. PETERSON, B. PORTER
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**Abstract:** Alcohol use disorders (AUDs) affect over 15 million people in the U.S. (SAMHSA, 2015). One major challenge to approaching treatment for AUDs is its chronic relapsing nature. Approximately 3 out of 4 people with AUDs will not remain abstinent within one year of becoming sober (Miller et al., 2001). The alcohol deprivation model has been long-studied as a preclinical model of relapse. After a baseline period of drinking followed by several periods of deprivation and re-access to ethanol, rats consume markedly more ethanol during the re-access periods compared to baseline. This is termed the alcohol deprivation effect (ADE). Models that show an ADE in rats typically require 2-12 months; however, a study by Sinclair & Tiihonen (1988) showed a robust ADE in Long Evans rats after a much shorter timeframe. Following Sinclair & Tiihonen's truncated design, we implemented a 16 day baseline followed by 3 cycles of 7 day deprivation and 7 day re-access to ethanol (10% v/v) with 8 male and 8 female Long Evans adult rats. Data were analyzed using one-way repeated measures ANOVA within sex, with Dunnett's multiple comparisons tests comparing baseline to each re-access period. The last 7 days of baseline drinking (g/kg/24h) were averaged for one baseline value and then compared with the first 24h g/kg ethanol intake of each re-access period. In male rats, a significant ADE was observed for the second and third re-access periods ($F(3, 28)=3.84$, $p<0.05$). For females, a significant ADE was observed for the first re-access period ($F(3, 24)=4.158$, $p<0.05$), but there was not a significant ADE observed for the second or third re-access period. These data indicate opposite trends for male and female adult rats in their propensity to show ADE following repeated cycles of ethanol deprivation and re-access. These data are preliminary and follow-up studies will be necessary to verify the usefulness of this design as a model of relapse-like behavior, as previous studies use a much longer timeframe Important follow-up studies will also consider the impact of age at initiation of ethanol drinking, as vulnerability for AUD development is greater if alcohol drinking is initiated in adolescence.

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**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.14/HHH43

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NHMRC grant RG170120
UNSW Tuition Fee Scholarship

**Title:** Ventral tegmental area dopamine neurons and relapse to alcohol seeking

**Authors: *Y. LIU**, P. JEAN-RICHARD-DIT-BRESSEL, J. YAU, G. GIBSON, C. W. G. CLIFFORD, G. P. MCNALLY
Univ. of New South Wales, Sydney, Australia

**Abstract:** Relapse or return to drug-seeking after a period of abstinence or extinction remains a fundamental impediment to successful treatment. Pharmacological data suggest that the actions of dopamine, especially via nucleus accumbens shell Drd1 receptors, is essential to relapse. However, when during a relapse episode dopamine neurons are important, how their activity varies during different forms of relapse, and the causal roles of these activity variations in relapse are each unknown. Here we assessed the roles of ventral tegmental area dopamine neurons ($VTA^{Th}$) during two different forms of relapse to alcohol-seeking: renewal (context-induced reinstatement) and reacquisition in freely moving male Th-Cre Sprague Dawley rats. Using fibre photometry, we show that reacquisition but not renewal of alcohol-seeking is associated with calcium transients in $VTA^{Th}$ neurons. These transients were temporally specific to seeking behaviours that earned alcohol-associated stimuli and ingestion of alcohol. They were not observed to the same behaviours in the same sessions that did not earn these stimuli or alcohol ingestion. Then, using chemogenetics (KORDs) we show that silencing $VTA^{Th}$ neurons reduces reacquisition but not renewal of alcohol seeking. Finally, we show that optogenetic inhibition of $VTA^{Th}$ neurons during the periods in which they showed increases in calcium transients reduced reacquisition but that the same silencing at equivalent times had no effect on renewal. Taken together, these findings show the role of $VTA^{Th}$ neurons can be dissociated across different forms of relapse in the same animals. Renewal proceeds largely independent of $VTA^{Th}$ neurons whereas the presence of alcohol during reacquisition restores activity (calcium transients) of $VTA^{Th}$ neurons to alcohol-seeking behaviours as well as alcohol-related stimuli and this restoration underpins a rapid return to alcohol-seeking and ingestion.

**Disclosures: Y. Liu:** None. **P. Jean-Richard-dit-Bressel:** None. **J. Yau:** None. **G. Gibson:** None. **C.W.G. Clifford:** None. **G.P. McNally:** None.

**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.15/HHH44

**Topic:** G.08. Drugs of Abuse and Addiction

**Title:** Adolescent, but prepubescent stress increases the likelihood that animals will be high alcohol consumers

**Authors: *K. A. RODRIGUEZ**[1], A. SIMMONS[2], S. M. THOMPSON[3], M. S. MCMURRAY[3]
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**Abstract:** Chronic stress during early life or adolescence can contribute to development of alcohol or drug addiction. Early life stress can also increase the likelihood of experiencing other major stressors later in life. Despite these severe consequences, the effect of stress during early life and adolescence has not been examined jointly. We developed a rodent model to determine the effects of stress during critical developmental periods on subsequent alcohol consumption. Rodents experienced either an early life stressor, an adolescent stressor, or stress during both periods of development. To induce early life stress, a modified maternal separation (MS) model was used in which rodents were separated from their dam and litter for 1 hour a day for 7 consecutive days starting on postnatal day 17. This MS model induced stress during a prepubescent period in rodents compared to previously used MS paradigms, making the stress on rodents more comparable to neglect in humans. Stress in adolescence was modeled with a social defeat (SD) paradigm, comparable to bullying in humans, and rats were subjected to defeat for 10 consecutive days starting on postnatal day 30. Voluntary consumption was measured in late adolescence (postnatal days 40-50) through a drinking in the dark paradigm in which rats were given access to alcohol in gelatin form. Our results found that rats who experienced only SD or MS + SD were more likely to be classified as a high drinker compared to the MS alone group and control. Animals completed a loss of righting reflex test in adulthood in order to determine if differences in consumption could be related to differences in alcohol sensitivity or metabolism. High drinking rodents took a longer time to lose their righting reflex and a shorter time to regain their righting reflex, demonstrating that these subjects were less sensitive to the biological effects of alcohol, but stress condition did not cause differential effects. Here, we established that social defeat in adolescence increased self-administration of alcohol, potentially contributing to alcohol addiction; however, maternal separation during this later period did not affect alcohol consumption.

**Disclosures: K.A. Rodriguez:** None. **A. Simmons:** None. **S.M. Thompson:** None. **M.S. McMurray:** None.

**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.16/HHH45

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** Lycoming College Professional Development Grant
The Arthur A. Haberberger Chairman's Endowed Student-Faculty Research Program
The George B. Gaul Endowed Student-Faculty Research Program

**Title:** Caffeine increases the reinforcing efficacy of a sweetened alcohol solution

**Authors: *S. E. HOLSTEIN**, G. BARKELL, M. MCVEETY
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**Abstract:** In recent years, caffeinated energy drinks have become increasingly popular. However, when combined with alcohol, these caffeinated beverages have been associated with increased alcohol intake and a greater desire for alcohol. Although this caffeine-induced increase in alcohol drinking has been shown in both human and animal studies, it remains unknown whether caffeine may increase alcohol drinking and desire to drink by increasing the reinforcing efficacy of alcohol. Therefore, the purpose of the current study was to investigate the relationship between caffeine and the reinforcing properties of a sweetened alcohol solution in rodents. Eight male Long Evans rats were trained to self-administer a lightly sweetened alcohol solution (10% v/v ethanol, 2% w/v sucrose) following a sucrose fading procedure. After stable responding for the sweetened alcohol solution was achieved, rats received an intraperitoneal injection of saline or caffeine (2.5, 5.0, 10.0, 20.0 mg/kg) thirty minutes prior to the operant self-administration session. Caffeine (10.0 mg/kg) significantly increased alcohol-reinforced responding compared to saline. Although there was a trend for an overall increase in responding on the inactive lever with caffeine, there was no significant increase in responding on the inactive lever at 10.0 mg/kg. These results suggest that caffeine may have increased operant responding for the sweetened alcohol solution by enhancing the reinforcing efficacy of the solution (rather than by inducing a non-specific stimulant response). In order to further evaluate this hypothesis, a separate cohort of Long Evans rats (n = 8) were trained in a progressive ratio task in order to evaluate the effect of caffeine on the motivation to self-administer a sweetened alcohol solution. Consistent with the hypothesis, caffeine (10 mg/kg) significantly increased the breaking point for alcohol. These results indicate that a moderate dose of caffeine not only enhances the reinforcing efficacy of a sweetened alcohol solution, but also increases the motivation to seek out and self-administer a sweetened alcohol solution, which may ultimately contribute to patterns of uncontrolled intake and a greater desire to drink in alcohol users.

**Disclosures: S.E. Holstein:** None. **G. Barkell:** None. **M. McVeety:** None.

**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.17/HHH46

**Topic:** G.08. Drugs of Abuse and Addiction

**Title:** Pindolol, the FDA approved drug for hypertension ameliorates emotional and neurogenic consequences of long-term binge consumption of ethanol and attenuates consumption in mice

**Authors: *O. L. PATKAR**[1], A. BELMER[2], P. M. KLENOWSKI[3], S. E. BARTLETT[1]
[1]Queensland Univ. of Technol., Brisbane, Australia; [2]QUT-IHBI-TRI, Woolloongabba, Australia; [3]Med. Sch., Univ. of Massachusetts, Worcester, MA

**Abstract:** Long-term binge alcohol consumption alters the function of neurochemical signalling molecules in the brain, particularly noradrenaline (NE) and serotonin (5-HT) which regulate emotion, mood and memory. Alcohol withdrawal has been shown to upset normal emotional behaviour leading to the development of anxiety and depression. Also, prolonged consumption of alcohol has been shown to affect hippocampal neurogenesis, which has a direct effect on the development of negative affective states. Given the lack of efficacy of current treatment options to address these neurological consequences of long-term binge consumption, there is an increased need for the development of new and better alternatives for alcohol use disorders (AUDs). Using the well-established drinking in dark paradigm in mice that facilitates high ethanol intake, symptoms of behavioural intoxication and high blood ethanol levels, we report that pindolol the FDA approved drug for hypertension having a dual pharmacological activity on noradrenergic and serotonergic receptors, reduces consumption in long-term ethanol consuming mice. Furthermore, pindolol also reduces anxiety-like behaviour following long-term ethanol intake (12-15 weeks) in mice at 24 hr withdrawal in the marble burying test (MBT) and the elevated plus maze (EPM). Additionally, electrophysiological techniques and drug microinfusion procedures have revealed that the basolateral amygdala may be the pharmacological site of action of pindolol in the brain where it exerts its effects on ethanol intake. Finally, chronic pindolol treatment (2 weeks) attenuates impairments in hippocampal neurogenesis as evidenced by an increase in number of newborn neurons co-expressing markers of cell differentiation (BRDU+, KI+ and DCX+) as compared to controls. Together, our results highlight the efficacy of pindolol to address the consequences of long-term binge consumption of alcohol on the brain. These findings support the ability of pindolol to be used as an effective treatment option for AUDs.

**Disclosures: O.L. Patkar:** None. **A. Belmer:** None. **P.M. Klenowski:** None. **S.E. Bartlett:** None.

**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

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**Topic:** G.08. Drugs of Abuse and Addiction

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**Title:** Interference between Pavlovian and instrumental stimuli is associated with alcohol consumption in young adults

**Authors: *M. N. SMOLKA**[1], H. CHEN[1], S. NEBE[1], M. GARBUSOW[2], D. J. SCHAD[3], M. A. RAPP[3], Q. J. M. HUYS[4], A. HEINZ[2]
[1]Technische Univ. Dresden, Dresden, Germany; [2]Charité, Berlin, Germany; [3]Univ. Potsdam, Potsdam, Germany; [4]Translational Neuromodeling Unit / UZH & ETHZ, Zurich, Switzerland

**Abstract:** Aims: Pavlovian-to-instrumental transfer (PIT) tasks examine the influence of Pavlovian conditioned stimuli on instrumental behavior. The importance of (conditioned) context stimuli on (instrumental) alcohol consumption is widely acknowledged, and alcohol-dependent patients show increased PIT effects compared to healthy controls. We now investigated whether PIT effects are also linked to risky alcohol use (> 60 g/occasion) in young adults. Methods: We assessed drinking behavior and PIT during fMRI in 191 healthy 18-year-old adults. PIT effects were operationalized by change of error rates (ER) when '*collecting good shells*' or '*leaving bad shells*' during presentation of positively and negatively valenced Pavlovian stimuli. Results: *Collecting good shells* and *leaving bad shells* was more difficult when Pavlolvian background stimuli were incongruent to the required instrumental behavior (negative when collecting and positive when leaving) than in congruent trials (ΔER 15.2 %; $p$=1.12x10$^{-15}$). Moreover, high risk drinking compared to low risk drinking was associated with a stronger increase of ER during incongruent PIT trials (ΔER 21.3 % vs. 9.2 %; $p$=3.47 x10$^{-3}$). At the brain level we found that in subjects with low risk drinking higher behavioral PIT effects were associated with more pronounced BOLD signals in the ventral striatum, the dorsomedial PFC and dorsolateral PFC when facing incongruent trials. Subjects with high risk drinking did not show this association. Conclusions: Our results demonstrate that individual PIT effects are related to alcohol use even in a preclinical sample. Imaging data further indicate that risky drinking is associated with a blunted response of top-down control networks when Pavlovian values and instrumental demands are incongruent.

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**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 784.19/HHH48

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** R01MH099085

**Title:** Individual differences in alcohol intake predict ketamine self-administration behaviors differentially in male and female rats

**Authors: *C. E. STRONG**, K. N. WRIGHT, M. KABBAJ
Biomed. Sci., Florida State Univ., Tallahassee, FL

**Abstract:** Alcohol use disorder (AUD) is characterized as a chronic relapsing disorder and currently, effective treatment options are lacking since 75% of people suffering from AUD relapse within one year. Recently, though, clinical studies have begun to investigate the therapeutic value of ketamine as an AUD treatment option, based on preclinical data showing that ketamine reduces alcohol intake in male rats, though this has never been examined in female rats. Furthermore, ketamine itself is addictive, and our lab previously demonstrated this in both sexes, showing that female rats were more sensitive to the reinforcing effects than males. Therefore, the present study examined the safety of ketamine as an AUD treatment by assessing the interaction between ketamine and alcohol in both sexes. To do this, we used the intermittent access to 20% alcohol in a 2-bottle choice (IA2BC20%) paradigm and intravenous ketamine self-administration (0.5 mg/kg/infusion). Male and female Sprague-Dawley rats were maintained on the IA2BC20% paradigm for ten weeks, with ketamine self-administration nested from week four to seven. Rats were split into high or low alcohol-drinkers (HAD and LAD, respectively) to assess the impact of individual differences in alcohol consumption on ketamine self-administration. Our data indicates that HAD male rats displayed attenuated ketamine self-administration under fixed ratio 1 (FR1) and progressive ratio (PR) schedules of reinforcement and reduced ketamine craving. HAD male rats that self-administered ketamine also showed reduced alcohol intake after cessation of ketamine self-administration compared to HAD male rats self-administering saline. LAD male rats produced similar ketamine self-administration behavior as male rats drinking water. In female rats, HAD enhanced motivation to self-administer ketamine, demonstrated by increased PR breakpoint compared to LAD and water-drinking female rats. Additionally, LAD female rats increased alcohol intake to the level of HAD female rats following ketamine self-administration. Together, this data demonstrates that the interaction between alcohol and ketamine may have protective effects in male rats but enhance addictive-like behavior in female rats. Further work will investigate intracellular signaling mechanisms and morphological changes in the nucleus accumbens mediating the sex differences observed in this behavior to provide some insight on the mechanism mediating the interaction between alcohol and ketamine in male and female rats.

**Disclosures: C.E. Strong:** None. **K.N. Wright:** None. **M. Kabbaj:** None.

**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** DGAPA-PAPIIT to MMD IA205218
DGAPA-PAPIIT to OPG IN215218
DGAPA-PAPIIT to AERC IN217918

**Title:** Anxiety-like behavior, pain perception and sex may predict alcohol consumption pattern: Role of cannabinoid and dopaminergic receptors

**Authors: *O. AMANCIO-BELMONT**[1], A. L. BECERRIL-MELÉNDEZ[2], M. MÉNDEZ-DÍAZ[2], A. E. RUIZ-CONTRERAS[4], O. PROSPERO-GARCIA[3]
[1]UNAM, Mexico, DF, Mexico; [2]UNAM, Mexico City, Mexico; [3]UNAM, Mexico, D. F., Mexico; [4]Lab. Neurogenomica Cognitiva, Fac. Psicologia, UNAM, D.F., Mexico

**Abstract:** Maternal care deprivation (MCD) is a reliable rodent model of early life stress that leads to behavioral alterations such as anxiety-like symptoms and a reduction in the total amount of sleep, and REM sleep; which may increase the vulnerability to alcohol consumption. The objective of this study was to evaluate pain perception, anxiety-like behaviors, sleep quality and motivation for a palatable reward to predict vulnerability to alcohol consumption. Pregnant Wistar rats were obtained at gestational day 14-17 from our facilities (Facultad de Medicina, UNAM). The day of birth was designated as PND 0. MCD was performed from PND 2 to PND 16, between 9:00 and 12:00 h daily. Rats were weaned on PND 21. From PND 22 to PND 60 rats were reared with siblings of the same sex (4-5 rats/cage). Once the rats became adults (PND 60), all groups ($n$ = 17-20 each group) were submitted to the elevated plus maze to determine anxiety-like behaviors (anxiety trait). Then, rats were trained to press a lever to obtain a palatable reinforcer (a chocolate-flavored pellet) at fixed ratio 5 (FR5) and to a progressive ratio session to determine the motivation for such palatable reinforcer. Afterwards, the subjects underwent a passive-prevention test to evaluate anxiety-like behaviors (anxiety state). Later, the pain threshold was quantified by using the Hot Plate test. Further, rats were surgically implanted with electrodes for recording EEG and EMG to evaluate sleep quality. Finally, they were submitted to a voluntary alcohol (10% v/v) protocol for 10 days, and at the end of the alcohol protocol rats were sacrificed, and PFC, NAcc and hippocampus was obtained to analyze the expression of cannabinoid (CB1R and CB2R) and dopaminergic (D1R, D2R and D3R) receptors by Western blot. Results indicate that MCD increases anxiety-like behaviors, i.e. reduces time in open arms; reduces pain threshold and increases alcohol intake in both sexes. However, the motivation for a palatable reward was not affected by MCD, but there are differences by sex. Also, female rats

consume more alcohol than male. Our results suggest that early life stress, sex, high anxiety levels and a low pain threshold is associated with a high alcohol consumption.

**Disclosures: O. Amancio-Belmont:** None. **A.L. Becerril-Meléndez:** None. **M. Méndez-Díaz:** None. **A.E. Ruiz-Contreras:** None. **O. Prospero-Garcia:** None.

**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.21/HHH50

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** CNPq
CAPES
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**Title:** Taurine enhances alcohol intake and anxiolytic-like behaviors in alcoholic rats

**Authors: R. R. PULCINELLI**, N. A. NIETIEDT, L. F. DE PAULA, C. B. GAROFALO, A. W. HANSEN, S. BANDIERA, P. E. R. BITENCOURT, *R. GOMEZ
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**Abstract: Introduction:** Alcohol is a drug of abuse that induces dependence by modulation of GABAergic and dopaminergic systems. Taurine is an amino acid that exerts positive modulatory effects on $GABA_A$ receptors and restores the exploratory behavior disturbed by alcohol withdrawal in rats. The aim of this study was to evaluate the effect of taurine treatment on alcohol voluntary consumption in rats and its effect on behaviors tests. **Methods:** Male adult Wistar rats were free to choose from a bottle containing saccharin solution or another one containing alcohol 20% w/v with saccharin for 6 weeks. Likewise, control group was allowed to choose between 2 bottles containing saccharin solution. The daily liquid consumption of both groups was monitored. On day 22 they were divided into 4 groups to receive 100 mg/kg taurine (Alcohol/Taurine and Control/Taurine groups), intraperitoneally, once a day, for 20 days, or saline (Alcohol/Saline and Control/Saline groups). On days 22 and 33, rats had their behaviors evaluated in the open field test and on day 34, in the light/dark test. (CEUA-UFRGS #32850). **Results:** Taurine treated rats drank, on average, 40% more alcohol than non-treated animals, and had a significant increase of 10% in alcohol preference. A single acute taurine dose decreased the total ambulation of control animals and increased central crossings of alcohol group. Taurine increased the latency for grooming regardless of groups in both open field tests, and on the second exposure, grooming frequency was also decreased in these animals. On the light/dark test, only in alcoholic animals, taurine increased the time spent in light compartment, the number

of transitions between compartments and the latency to enter in the dark compartment. **Conclusion:** Chronic taurine treatment increases the voluntary alcohol consumption and preference in rats, probably due to synergistic effect with alcohol that facilitates the activation of dopaminergic reward pathway. Taurine promotes an anxiolytic-like behavior only in alcohol treated rats, possibly emphasizing its synergistic effect which occurs also on the GABAergic system. Previous alcohol detoxification could be determinant for the appearance of taurine anti addictive effect.

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**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.22/HHH51

**Topic:** G.08. Drugs of Abuse and Addiction

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NIH Grant MH093650 to V.S.
Burroughs Wellcome Fund through the Transformative and Translational Program in Addiction Sciences to S.G.Q.

**Title:** Prefrontal sigma receptors in alcohol use disorder

**Authors: *S. G. QUADIR**, C. F. MOORE, S. M. TANINO, P. COTTONE, V. SABINO
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**Abstract:** Alcohol Use Disorder (AUD) is a chronic relapsing condition characterized by compulsive, uncontrolled consumption of alcohol. AUD is also characterized by impairments in decision making, driven by dysregulation of prefronto-cortical regions, including the anterior cingulate cortex (ACC) and medial prefrontal cortex. Little is known about the neurotransmitter systems involved in both the excessive, compulsive drinking and the cognitive deficits observed in alcohol addiction and whether any overlap between them exists. The Sigma 1 receptor (Sig-1R) system has been proposed as a novel target for the treatment of addictive disorders, due to its ability to modulate the rewarding and reinforcing effects of multiple drugs of abuse, including alcohol. The overall goal of this research is to examine the role of Sig-1Rs in prefronto-cortical regions in alcohol addiction-relevant behaviors, including alcohol self-administration, motivation to work to obtain alcohol, and cognitive flexibility. We have found that chronic, intermittent exposure to alcohol vapors increases Sig-1R levels in the ACC of rats during withdrawal. The objective of this specific study was, therefore, to investigate the effect of the knockdown of Sig-

1R in the ACC on alcohol intake and cognitive measures in both air- and vapor-exposed rats, using different schedules of operant ethanol self-administration and an operant protocol of attention set-shifting. For this purpose an adeno-associated viral vector (AAV) containing either a Sig-1R knockdown shRNA or GFP-Control was microinfused. Experiments, which are currently underway, will clarify the possible role of ACC Sig-1Rs in alcohol addiction and associated deficits in cognitive flexibility.

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**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.23/HHH52

**Topic:** G.08. Drugs of Abuse and Addiction

**Title:** L-DOPA decreases operant responding for alcohol in rats

**Authors: *N. HOLTZ**[1], L. C. KRUSE[1], I. O. ALLEN[1], S. J. WEBER[1], J. J. CLARK[1], P. E. PHILLIPS[2]
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**Abstract:** Dysregulation of the dopamine system is a central mechanism driving substance use disorders. Our laboratory has shown that rats that steadily increase (i.e., escalate) cocaine consumption over chronic use show decreased dopamine transmission compared to rats that maintain stable drug intake. Restoring dopamine transmission in these escalated rats through the administration of the dopamine precursor, L-DOPA, decreased their cocaine consumption. While these data do not support a role for L-DOPA in producing or maintaining abstinence, they do suggest that dopamine-replacement therapy may have utility in reducing drug consumption, especially in populations that have transitioned from casual to habitual drug use, as an adjunctive to behavioral and cognitive therapies. We suggest that such an approach could be particularly beneficial in alcohol use disorder, essentially restoring control of intake to "social-drinking" levels. Therefore, the present study sought to examine whether the effects of L-DOPA on cocaine intake generalized to ethanol (EtOH) use. Adult male rats were presented with a two-bottle choice between EtOH solution (20%) or water, either intermittently (every other day, n = 15) or continuously (daily, n = 15) for 50 days. Next, animals made nose poke responses (FR1) for 0.2 ml of EtOH solution (20%) over 1-h daily sessions for 24 days. On Days 25 and 27, rats received either L-DOPA (30 mg/kg) given with the peripheral decarboxylase inhibitor, benserazide (15 mg/kg), or vehicle, counterbalanced across days. Total EtOH consumption did not differ between the continuous- or intermittent-access groups during the two-bottle-choice period, or during subsequent operant sessions, and so these groups were combined for

subsequent analyses. L-DOPA significantly decreased operant responding for EtOH compared to vehicle treatment ($P < 0.05$). We are presently examining if giving rats extended (6-h) operant sessions will yield individual differences in the escalation of EtOH, and whether this may predict the effects of L-DOPA. In the meantime, the initial results show promise that L-DOPA treatment could be a useful clinical tool for treating individuals who are prone to heavy episodic drinking.

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**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.24/HHH53

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** FAPESP Process Number: 2013/24986-2
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FAPESP Process Number:2017/21470-6

**Title:** Cannabidiol potentiates ethanol consumption in rats exposed to ethanol vapor chamber

**Authors: *S. A. ENGI**[1], E. E. OLIVEIRA SANTOS, 04023-062[2], F. E. CRUZ, 04023-062[2]
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**Abstract:** Drug abuse reached considerable proportions in the last years. Studies have shown that cannabidiol (CBD) has anxiolytic, anti-psychotic, antidepressant and neuroprotective properties. There are also evidence that CBD can reduce drug-seeking behavior. Despite of the relevance little is known about the effects of CBD treatment on ethanol (EtoH) addiction like behaviors. This study aimed to investigate the effects of CBD treatment upon EtoH consumption in rats exposed to EtoH vapor chamber. We used 16 male Wistar rats divided into 4 groups: a) air + vehicle; b) air + CBD; c) EtoH vapor chamber + vehicle and; d) EtoH vapor chamber + CBD. Animals underwent 14 weeks of operant self-administration training followed by 13 sessions of EtoH 10% operant self-administration and simultaneous daily exposure to ethanol vapor chamber (14 hours on/10 hours off, producing blood alcohol levels of ~200 mg/dl). Controls were exposed to room air. Self-administration sessions were carried during the withdrawal period. Thirty minutes before the start of self-administration sessions, animals received CBD (10 mg/Kg, i.p.). Our results demonstrated that animals that received CBD (10 mg/Kg, i.p) (air + CBD group) showed an increased EtoH consumption (Mean: 0.64 ± 0.04) when compared to control (air + vehicle group) (Mean: 0.44 ± 0.02) and that this consumption was higher in animals that received CBD and were exposed to EtoH vapor chamber (Mean: 0.97

± 0.09). This study demonstrated that CBD at the dose of 10 mg/Kg probably cause some neuronal modification that could result in increased EtoH taking and seeking behavior. **Financial** Financial Support: FAPESP (Process Number: 2013/24986-2, 2016/18701-3 and 2017/21470-6).

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**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.25/HHH54

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH Grant P20GM113109

**Title:** Hedonic taste reactivity to ethanol between differentially reared rats

**Authors: *E. C. BRASE**, T. J. WUKITSCH, T. J. MOSER, M. S. BLOEDEL, J. K. GOMENDOZA, P. M. SMALL, M. E. CAIN
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**Abstract:** Currently, it is established that differential rearing during the post-weaning period alters the incentive salience ("wanting") for several reinforcers. Rats reared in isolation respond more in operant paradigms for psychostimulants, ethanol, and sucrose when compared to rats reared in enriched and standard laboratory conditions. However, the aspect of motivation that drives the increased responding for ethanol between differentially reared rats is unknown. Therefore, the current research project examined differentially reared rats' taste reactivity responses to ethanol to characterize differences that may exist in hedonic value between the rearing groups. Male and female Long-Evans rats arrived in the lab on postnatal day (PND) 21 and were randomly assigned to either isolated (IC), enriched (EC), or standard condition (SC) environments for a 30-day rearing period. Rats were then implanted with indwelling intraoral fistulas which were routed from the mouth to a metal connector protruding from an acrylic head cap anchored to the skull. After recovery, rats underwent taste reactivity testing for a range of ethanol, sucrose, and quinine concentrations presented in a counterbalanced order ($H_2O$; 5%, 10%, 20%, 30%, & 40% ethanol; 0.10M, 0.25M, & 0.50M sucrose; 0.0005M & 0.0001M quinine). Taste reactivity data collected via video recording was analyzed frame by frame to quantify the different orofacial responses (Grill & Norgren, 1978). Hedonic (i.e. "liking") responses included tongue protrusions and lateral tongue protrusions. We hypothesized that overall hedonic responses to ethanol between differentially reared rats will vary as a function of ethanol concentration. We also hypothesized that there would be differences in "liking" responses for sucrose as a function of concentration, as differential rearing may alter "liking" in a way that generalizes to non-drug reinforcers. Preliminary findings suggest that IC rats have

lower levels of hedonic responding for ethanol overall and that male EC rats show an increasing trend in hedonic responses as ethanol concentration increases, while female EC rats show the opposite effect. Response trends for sucrose show female IC rats with higher responding at the lowest sucrose concentration compared to female ECs, whereas males again show the opposite effect. These preliminary results suggest that differential rearing may alter sensitivity to the taste of different reinforcers, which may explain motivational differences to acquire alcohol in operant paradigms.

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**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.26/HHH55

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH Grant P20GM113109

**Title:** The effect of differential rearing on aversive taste reactivity to ethanol

**Authors: *T. MOSER**[1,2], T. J. WUKITSCH[2], M. S. BLOEDEL[2], E. C. BRASE[2], C. CUNNINGHAM[2], R. STEARNS[2], S. TAYLOR[2], M. CAIN[2]
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**Abstract:** Adolescent drinking of ethanol affects the developing brain causing deficits in neuronal microstructure which can lead to ethanol addiction earlier in adulthood and higher rates of dependency. Females are even more susceptible to these neuronal deficits as their brains develop earlier than males. Differential rearing during adolescence alters neuronal plasticity which may change the liking response to ethanol. Raising adolescent rats in an environmentally enriched condition reduces the motivation to consume ethanol in operant self-administration compared to rats in an isolated condition. Differential rearing's effect on aversive behaviors, however, has not been determined. Therefore, we sought to determine whether differential rearing and sex alters the aversive responding to ethanol. In the current study, we evaluated the differences of aversive orofacial responses between male and female rats raised in Enriched (EC), Standard (SC), and Isolated (IC) Conditions during adolescence. We hypothesized that ICs will have lower aversive behaviors (e.g. gapes, fluid expulsions) compared to both ECs and SCs across a range of ethanol concentrations. We also hypothesized that there will be no effect of sex on aversive behaviors. Male and Female Long-Evans rats arrived at the lab by postnatal day (PND) 21 and were then randomly assigned to either EC, IC, or SC with their sex cohorts for a 30-day rearing period. Rats were implanted with intraoral fistulas that were routed through the

mouth and anchored to the skull. After a week of recovery, rats underwent taste reactivity testing with a range of concentrations of ethanol, quinine, sucrose, and water presented in a counterbalanced order (H2O; 5%, 10%, 20%, 30%, & 40% ETOH; 0.10M, 0.25M, & 0.50M Sucrose; 0.0005M, & 0.0001M Quinine). Videos were scored for behaviors, with standards provided by Grill and Norgren (1978), frame by frame for sixty seconds. Preliminary results suggest a trend that EC males and IC females exhibit more aversive behavior at lower concentrations of ethanol which decreases as ethanol concentrations increase, whereas the IC males and EC females are inversed. When exposed to quinine, EC and IC males are similar across concentrations, whereas IC and EC females exhibit more aversive behaviors at higher concentrations. These results suggest that differential rearing may alter the taste response to ethanol and therefore alter motivation to acquire ethanol for drinking.

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**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 784.27/HHH56

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** INSERM
Conseil régional de Picardie (CRP)

**Title:** Epigenetic mechanisms negatively regulates long-term depression and learning in adolescent rat hippocampus after two binges of ethanol by modulating GluN2A and 2GluN2B ratio

**Authors: *I. DRISSI**, R. ALARY, C. DESCHAMPS, G. FOUQUET, I. MARCQ, V. DEBUYSSCHER, M. NAASSILA, C. VILPOUX, O. PIERREFICHE
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**Abstract:** Ethanol (EtOH) exposure leads to cognitive impairment by affecting both modes of synaptic plasticity (long-term potentiation, LTP and long term depression, LTD). We previously reported that two binges of EtOH (3g/kg i.p, 9h apart) induce a memory impairment in adolescent rat by abolishing LTD in the hippocampus 48h later (Silvestre de Ferron et al., 2015). The LTD disruption was associated with an increase in GluN2B subunit of the NMDA receptor. However the cellular mechanism responsible for these changes remains unclear. Here we tested the hypothesis that two binges of EtOH induced epigenetic modifications that abolish LTD in the CA1 area of the hippocampus. We used adolescent rats (45-55 days old) which received 2 i.p injections of EtOH ,9h apart, alone or with Sodium Butyrate (NaB, 600mg/kg/i.p) (Simon-

O'Brien et al.,2015) 30min before each EtOH administration. 48h later, we evaluated learning performance with novel object recognition test (NOR). To assess neurotransmission and synaptic plasticity, we used field recordings in CA1 area of hippocampal slices. We also determined the involvement of GluN2A and GluN2B subunit in NMDA fEPSP using specific antagonists. Further, HDAC activity and HDAC2 isoform expression were measured in isolated CA1 area. Our results showed that EtOH decreased learning performance, strongly reduced LTD, disrupted GluN2A/GluN2B ratio by increased fNMDA-EPSP sensitivity to GluN2B antagonist while sensitivity to GluN2A antagonist was decreased. EtOH increased also HDAC enzymatic activity and HDAC2 expression in CA1 area. Interestingly, NaB injection prevented all these effects induced by EtOH. In fact, in presence of NaB learning performance in NOR test was restaured, the GluN2A/GluN2B ratio was corrected and LTD reappeared. This study demonstrated that binge drinking modulates epigenome by increasing HDAC2 expression in the CA1 area and this modifications are involved in LTD disruption after 48h through a modulation of GluN2A and GluN2B subunit of the NMDA receptor.

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**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 784.28/HHH57

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH/NIDA DA033344
NIH/NIAAA AA024146
NIH/NIAAA AA006420
NIH/NIAAA AA022249

**Title:** Exploring sex differences in the prevention of ethanol drinking by naltrexone in dependent rats during abstinence

**Authors: *A. MATZEU**[1], L. Y. TERENIUS[2,3], R. MARTIN-FARDON[4]
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**Abstract:** Despite considerable efforts, there are few drugs available for treatment of alcohol (ethanol, EtOH) use disorders (AUDs). Ethanol modulates several aspects of the central nervous systems including neurotransmitter/neuromodulator systems. Relapse vulnerability is a challenge for the treatment of EtOH addiction. Among the valuable medications for AUDs, naltrexone

(NTX) is a pharmacological treatment for alcoholism. The present study's aims were to evaluate NTX effect on EtOH drinking in EtOH dependent male and female rats during abstinence. Wistar rats were first trained to orally self-administer EtOH. Half of them were then made dependent ($EtOH_D$) by chronic intermittent EtOH (CIE, 14h ON, 10h OFF) vapor exposure for 6 weeks, the other half, EtOH nondependent ($EtOH_{ND}$), were exposed to air. Rats were then tested for NTX (10 mg/kg, p.o.) effects on the resumption of EtOH drinking at three abstinence time points: acute (8h, A-Abst), late (2 weeks, L-Abst) and protracted abstinence (6 weeks, P-Abst). Male and female $EtOH_D$ showed an escalated intake of EtOH after CIE, with higher blood alcohol levels and somatic withdrawal signs compared to non-dependent rats. NTX reduced EtOH intake in male and female $EtOH_{ND}$ rats at A-Abst, L-Abst and P-Abst. In $EtOH_D$ rats NTX reduced EtOH intake in male rats only at P-Abst, while in females it reduced EtOH intake at all three abstinence time points. NTX decreased EtOH intake in $EtOH_{ND}$ subjects regardless of the time of abstinence and sex. In $EtOH_D$ subjects, the effects of NTX improved with longer abstinence time in males while it similarly reduced EtOH drinking in females at all abstinence points. The data suggest that even though NTX is an efficacious drug in decreasing EtOH drinking, its therapeutic efficacy is dependent on the time of intervention during abstinence as well as sex. The data further suggest that EtOH dependence induces different neuroadaptations in male and female reflected by a different NTX effect. A better understanding of the changes induced by EtOH is needed for the development of better pharmacotherapeutic treatment for AUD prevention.

**Disclosures: A. Matzeu:** None. **L.Y. Terenius:** None. **R. Martin-Fardon:** None.

**Poster**

**784. Drugs of Abuse and Addiction: Alcohol: Intake and Preference**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH/NIDA DA033344
NIH/NIAAA AA024146
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NIH/NIAAA AA022249

**Title:** Blockade of orexin receptors in the paraventricular nucleus of the thalamus prevents stress-induced food seeking behavior in rats with a history of ethanol dependence

**Authors: A. MATZEU**[1], *R. MARTIN-FARDON[2]
[1]Scripps Res. Inst., La Jolla, CA; [2]Neurosci., The Scripps Res. Intsitute, La Jolla, CA

**Abstract:** Neural systems that are involved in processing natural rewards and drugs of abuse overlap, and exposure to drugs of abuse induces neuroadaptations that can cause compulsive-like behavior. Recruitment of the orexin (Orx) system by drugs of abuse may induce neuroadaptations that slant its function toward drug-directed behavior. Behavioral and functional evidence suggests a role for Orx signaling in the neurobehavioral and motivational effects of ethanol (EtOH). It is known that Orx neurons projects to the paraventricular nucleus of the thalamus (PVT), a structure that plays a key role in energy homeostasis, arousal, endocrine regulation, reward and stress regulation. This study aimed to determine (1) whether stress-induced reward seeking behavior toward a highly palatable food reward changes following a history of EtOH dependence and (2) whether Orx transmission in the PVT mediates stress-induced natural reward-seeking behavior in animal that had a history of EtOH dependence. Wistar rats (males and females) were first trained to orally self-administer sweetened condensed milk (SCM), a highly palatable food reward. Half of them were then made dependent ($EtOH_D$) by chronic intermittent EtOH (CIE, 14h ON, 10h OFF) vapor exposure for 6 weeks, the other half, EtOH nondependent ($EtOH_{ND}$), were exposed to air. At the end of the 6 weeks dependence induction, at 8 h of abstinence, the rats were tested for stress-induced SCM seeking. The data show that stress triggered SCM-seeking behavior in both $EtOH_D$ and $EtOH_{ND}$ with the same efficacy. However, blockade of both Orx receptors in the PVT with TCS1102 (15µg/0.5µl) prevented stress-induced SCM seeking in $EtOH_{PD}$ rats only. The results suggest a maladaptive recruitment of PVT-Orx transmission by EtOH dependence reflected by a differential effect of TCS1102 in $EtOH_D$ *vs.* $EtOH_{ND}$ rats.

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**Poster**

**785. Opioids: Neural Mechanisms of Addiction**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 785.01/HHH59

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH Grant R00DA037279-02

**Title:** Interruption of continuous morphine administration in mice negatively impacts brain and behavior

**Authors: *E. LEFEVRE**[1], M. T. PISANSKY[2], L. BYSTROM[1], D. W. LEIPOLD[1], T. KONO[1], M. PRAVETONI[1], P. E. ROTHWELL[2]
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**Abstract:** Clinical use of opiate-based analgesics can lead to negative consequences like dependence and addiction. In contrast to immediate-release formulations, extended-release

formulations of opiate-based analgesics produce small fluctuations in plasma drug levels, which should reduce abuse liability. However, due to pharmacokinetic variability, patients often report short periods of opiate withdrawal with physical symptoms such as anxiety, vomiting and diarrhea. We propose that when otherwise continuous opioid exposure is interrupted by short periods of withdrawal, maladaptive changes in brain function occur that promote abuse liability and addiction. To test this hypothesis, male and female mice were implanted with osmotic minipumps to continuously deliver morphine (63 mg/kg/day) over a period of 6 days, and administered twice-daily naloxone injections (10 mg/kg) to interrupt opioid receptor stimulation. Following this treatment paradigm, behavioral, genetic and physiological techniques were employed to identify divergent adaptations in continuous versus interrupted morphine exposure. Continuous morphine exposure produced tolerance of psychomotor activation. In contrast, interruption of morphine exposure with naloxone caused psychomotor sensitization, an addiction-related behavior mediated by adaptations in the nucleus accumbens (NAc). We next performed RNA-seq analysis of NAc tissue, to analyze differential gene expression after continuous or interrupted morphine exposure. After controlling for false discovery rate, we found no genes that were significantly regulated by continuous morphine exposure alone, whereas interrupted morphine exposure significantly regulated 1,328 genes. Genes that were differentially regulated by continuous and interrupted morphine exposure encoded for subunits of the GABA-A receptor, as well as subunits of various voltage-gated ion channels. This data prompted further analysis of cellular properties using ex-vivo slice electrophysiology. We recorded from NAc medium spiny neurons (MSNs) identified by expression of the D1 or D2 dopamine receptor in transgenic reporter mice. Intrinsic excitability was significantly, and selectively, increased in D2 MSNs after interrupted morphine. Continuous morphine exposure increased the amplitude of spontaneous inhibitory postsynaptic currents (sIPSCs) onto D1 MSNs, whereas interrupted morphine exposure tended to increase sIPSC amplitude onto D2 MSNs. This study illustrates dramatic and divergent adaptations in cellular function that occur with different patterns of opiate administration.

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**Poster**

**785. Opioids: Neural Mechanisms of Addiction**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 785.02/HHH60

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH Grant DA07058,
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NIH Grant AA023178

**Title:** Adolescent binge drinking enhances sensitization to morphine's anti-nociception

**Authors: *S. L. CHANG**[1], W. HUANG[2], H. HAN[1], I. K. SARIYER[3]
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**Abstract:** Binge drinking can elevate the blood alcohol content (BAC) to > 80 mg/dL/17.4 mM, causing gut leakage leading to increased endotoxin in the circulation and contributing to enhancement of neuroimmune signaling pathways. Morphine abuse is frequently linked to drinking. Morphine exerts its actions mainly on the seven transmembrane G-protein-coupled mu opioid receptors (MOR). Opioid use disorders (OUD) include combination of opioids with alcohol leading to opioid overdose-related deaths. We hypothesized that binge drinking could potentiate the onset and progression of OUD. Using C57BL/6J (B6) mice as a model, we examined the possible impact of binge drinking on morphine's anti-nociception. The mice were treated with or without 3-d binge ethanol (EtOH, 5 g/kg/d, 42% v/v, i.g.), and the anti-nociceptive changes were evaluated using hot plate test at 24 h after the final EtOH injection with or without a cumulative subcutaneous dose (0, 0.1, 0.3, 1.0, and 3.0 mg/kg) of morphine at intervals of 30 min. The response curve of the mice given binge EtOH was shifted to the left, indicating enhanced sensitization to morphine's anti-nociception. We then investigated the gene expression profile of MOR at 2 min, 5 h, or 24 h after the first EtOH dose and at 24 h and 48 h after the third EtOH dose after binge EtOH in the striatum (STr). Interestingly, binge exposure to EtOH upregulated MOR expression in the striatum of the B6 mice, possibly causing the enhanced sensitization to morphine's anti-nociception. Overall, our results suggest that binge drinking may contribute to the onset and progression of OUD.

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**Poster**

**785. Opioids: Neural Mechanisms of Addiction**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 785.03/HHH61

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH Grant ZIADA000566

**Title:** Biphasic effects of opioids on brain oxygen: Implications for drug overdose

**Authors: *E. A. KIYATKIN**[1], A. AFZAL[2], E. SOLIS, JR[3]
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**Abstract:** Respiratory depression is the most dangerous effect of high-dose opioid drugs, which can result in the development of coma and lethality. To characterize this effect for different opioid drugs, we used oxygen sensors coupled with high-speed amperometry to examine the changes in oxygen levels in the nucleus accumbens (NAc) of rats induced by intravenous injections of heroin, fentanyl, and oxycodone. Both heroin and fentanyl delivered at the doses maintaining self-administration (0.1 and 0.01 mg/kg, respectively) induced rapid, but transient decreases in NAc oxygen that became stronger and more prolonged with dose increases. Fentanyl was 10-20x stronger than heroin at inducing brain hypoxia. To clarify the mechanisms underlying brain hypoxia induced by these drugs, we conducted oxygen measurements in the subcutaneous space, an area with no or minimal metabolic activity. Both drugs decreased subcutaneous oxygen levels, suggesting respiratory depression with a subsequent drop in blood oxygen levels as the primary mechanism responsible for decreases in brain oxygen. While decreases in NAc oxygen were also induced by oxycodone at a large dose (1.2 mg/kg), this drug moderately increased NAc oxygen at low and moderate doses (0.15-0.6 mg/kg). This latter effect appears to be independent of changes in respiratory activity and it could occur due to cerebral vasodilation via neurovascular coupling as confirmed by our finding that intravenous oxycodone also increases NAc glucose levels. Oxycodone is about 10-fold weaker than heroin and ~100-fold weaker than fentanyl at inducing brain hypoxia under conditions of intravenous administration. The present study demonstrates that all opioid drugs, including the dangerous illicit drug of abuse heroin, the highly potent general anesthetic fentanyl, and the widely prescribed analgesic oxycodone, induce acute brain hypoxia due to respiratory depression. For heroin and fentanyl, this effect occurs at relatively low doses and occurs rapidly (1-3 min), highlighting its prominent role in the development of coma and lethality and the critical time constraints for any pharmacological treatment of this detrimental effect.

**Disclosures: E.A. Kiyatkin:** None. **A. Afzal:** None. **E. Solis:** None.

**Poster**

**785. Opioids: Neural Mechanisms of Addiction**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 785.04/III1

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** DA044451

**Title:** Depletion of the gut microbiome composition alters oxycodone self-administration and withdrawal in rats

**Authors: *S. SIMPSON**, G. DE GUGLIELMO, M. KALLUPI, O. GEORGE
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**Abstract:** Addiction to oxycodone and other opiates represents a major health problem in the United States. Every day, 3,900 people initiate non-medical use of prescribed opiates, 78 overdose deaths occur, and 650,000 new opioid prescriptions are dispensed. The cellular mechanisms that are involved in the analgesic and reinforcing effects of oxycodone, including μ-opioid receptor activation, are relatively well known, but the mechanisms that are responsible for the vulnerability or resistance to the escalation of oxycodone use remain elusive. Increasing evidence suggests that the gut-brain axis may play a role in altering behavioral and neurological functions, and chronic opioids may alter gut microbiota. We investigated whether the disruption of a healthy microbiome alters the escalation of oxycodone self-administration in adult rats. The animals were implanted with intravenous catheters and trained to self-administer oxycodone (150 ug/kg/inj, 12 h/session) for 21 days. After the achievement of the escalation of oxycodone intake, the animals were depleted of an intact microbiome by the administration of an antibiotic cocktail in the drinking water for two weeks. In the second phase of the trial (two weeks), animals were given the antibiotic cocktail along with a cocktail of short-chain fatty acids (SCFAs), metabolites that are commonly disrupted through the reduction of microbiome fermentation in response to die-off from antibiotics. A significant increase in oxycodone self-administration was observed during the antibiotic treatment, and this escalation of intake was reversed by SCFA administration. Animals were tested for irritability-like behaviors and hyperalgesia during withdrawal. Antibiotics increased both irritability and hyperalgesia and SCFA administration blocked this effect. To follow up on SCFA signaling in the brain during withdrawal, we characterizing ensembles that are active during opioid withdrawal in several areas of the brain including the Habenula, VTA and PAG that overlap of SCFA receptor expression and cFOS activity in these regions during withdrawal. These results demonstrate that oxycodone intake and withdrawal-induced hyperalgesia and irritability like behaviour are increased after alterations of gut microbiome composition, suggesting a direct influence of the gut-brain axis on drug intake. Potential insights into the molecular mechanisms and repurposing of small molecules to mimic the effects of SCFAs may reveal new treatment strategies to limit the vulnerability to escalated opioid intake.

**Disclosures: S. Simpson:** None. **G. de Guglielmo:** None. **M. Kallupi:** None. **O. George:** None.

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**785. Opioids: Neural Mechanisms of Addiction**

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**Program #/Poster #:** 785.05/III2

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** 1F31DA044726-01A1

**Title:** Effect of noradrenergic-derived galanin on opioid addiction-related behaviors in mice

**Authors: *S. FOSTER**, D. WEINSHENKER
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**Abstract:** Background: The neuropeptide galanin attenuates several opioid addiction-related behaviors in rodents including opioid reward, withdrawal symptoms, and drug-induced reinstatement, suggesting that this neuropeptide may be a biological target for the treatment of opioid use disorder. However, galanin is co-expressed in cholinergic, serotonergic, and noradrenergic neurons in multiple brain regions, and no one has yet established whether one of these neurotransmitter and neuroanatomical systems may provide the majority of galanin's beneficial properties. The noradrenergic system is a prime candidate for investigation because the locus coeruleus expresses particularly high levels of galanin across species, and the noradrenergic system is dysregulated in opioid addiction. Hypothesis: Here, we seek to investigate whether reduction of noradrenergic-derived galanin enhances morphine conditioned place preference (CPP) and intravenous self-administration (SA) of the ultrashort-acting opioid remifentanil. Methods: Studies were performed using 3-7 month-old male and female conditional knockout mice that lack galanin specifically in noradrenergic neurons (Gal cKO) and their wild-type littermates (WT). Mice underwent an 8-day CPP paradigm where each genotype was divided into saline and morphine (5 mg/kg) treatment groups during conditioning sessions. For SA studies, a separate cohort of mice underwent operant food training prior to surgery to facilitate nosepoke responding for a reinforcer. Then, mice had the right jugular vein surgically catheterized, followed by one week of recovery. Mice from each genotype acquired intravenous SA at either a low dose (6.4 μg/kg/infusion) or a higher dose (64 μg/kg/infusion) of remifentanil during daily, 1-h operant conditioning sessions on an FR-1 schedule for at least 5 days, after which maintenance behavior was assessed. Results: Treatment with 5 mg/kg morphine supported a stronger place preference in Gal cKO as compared to WT mice. For SA studies, the 6.4 μg/kg dose of remifentanil, which supported minimal operant responding in WT mice, was sufficient to elicit acquisition of remifentanil SA in Gal cKO mice. Conclusions: The loss of galanin specifically in noradrenergic neurons enhances opioid reward and reinforcement. Future work will investigate whether overexpression of noradrenergic galanin can oppositely suppress these behaviors.

**Disclosures: S. Foster:** None. **D. Weinshenker:** None.

**Poster**

**785. Opioids: Neural Mechanisms of Addiction**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 785.06/III3

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** DA044451

**Title:** Nociceptin/orphanin FQ in the central nucleus of the amygdala selectively reduces oxycodone self-administration in rats with high addiction-like behaviors

**Authors: *G. DE GUGLIELMO**[1], M. KALLUPI[1], P. SCHWEITZER[1], L. SOLBERG WOODS[2], A. A. PALMER[3], O. GEORGE[1]
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**Abstract:** Oxycodone is one of the most widely prescribed painkillers in the United States. Over the past 15 years, oxycodone consumption has increased nearly 500%, and opioid-related overdose deaths have quadrupled, but the neurobiological mechanisms that are responsible for this escalation of oxycodone use are poorly known. Extensive work has found that the activation of μ-opioid receptors is critical for the initial euphoric and acute positive reinforcing effects of opioids. Recent work found that the dysregulation of another opioid receptor, the nociceptin/orphanin FQ (N/OFQ) receptor, may be even more important after chronic exposure to opioids. We investigated the role of N/OFQ in the escalation of oxycodone self-administration in heterogeneous stock (HS) rats,a unique outbred strain of rats that is characterized by high genetic variability that mimics genetic diversity in humans. We used oxycodone self-administration (150 ug/kg/inj, 12 h/session) combined with the behavioral characterization of compulsivity based on progressive-ratio responding and withdrawal-induced hyperalgesia. We measured robust individual differences in these three variables and established an Addiction Index as a comprehensive evaluation of addiction-like behaviors for each individual. We identified rats with high (HA) and low (LA) addiction-like behavior, based on the Addiction Index. Using electrophysiological techniques, we found that HA rats, compared with LA rats, exhibited a significant increase in spontaneous γ-aminobutyric acid (GABA)ergic transmission, reflected by isolated spontaneous inhibitory postsynaptic currents (sIPSCs), in the medial subdivision of the central nucleus of the amygdala (CeA). Superfusion of the CeA slice with N/OFQ (500 nM) decreased spontaneous GABA sIPSCs in both HA and LA rats, but the decrease was more pronounced in HA rats, suggesting that low levels of N/OFQ in the CeA may be responsible for high GABA release and the high escalation of oxycodone intake. We then tested the effect of intra-CeA N/OFQ infusions on the escalation of oxycodone self-administration in HA and LA rats. N/OFQ (1 υg/site) significantly reduced oxycodone intake in HA rats, without affecting oxycodone self-administration in LA rats. These results suggest that the downregulation of N/OFQ levels in the CeA may be responsible for hyperGABAergic tone in the CeA that is observed in dependent subjects with high oxycodone intake. The development and repurposing of small molecules that target the N/OFQ system may have therapeutic efficacy in the treatment of opioid use disorder, particularly in heavy users.

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**Poster**

**785. Opioids: Neural Mechanisms of Addiction**

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH Grant 5R01DA042499-02

**Title:** Role of hippocampal calcium-gated potassium channel SK2 in drug-paired contextual memory formation

**Authors: *D. BUREK**, S. B. WILLIAMS, W. POST, J. MORON-CONCEPCION
Washington Univ. Sch. of Med., Saint Louis, MO

**Abstract:** Long-lasting drug-paired contextual associations are one of the main drivers of relapse to drug seeking behavior. We have previously used context-dependent sensitization to morphine to model this association, in which a mouse exhibits escalating hyperactivity in response to escalating doses of morphine. We observe increases in NR2A-subunit-containing NMDA receptors and attenuation of NMDAR currents by the calcium-gated potassium channel SK2 following context-dependent sensitization. We are presently investigating the role of SK2 channels in a drug-paired memory-based paradigm, conditioned place preference (CPP). Following morphine CPP, we observe impaired hippocampal LTP mediated by AMPA and NMDA receptors, which we hypothesize strengthens the association between drug reward and context. Quantitative polymerase chain reaction assays of SK2 gene expression show no difference between animals conditioned with morphine or saline; moreover, SK2 gene expression shows no correlation to CPP score. Since SK2 channels provide negative feedback on NMDA receptor activity, we are also leveraging behavioral pharmacology by using the selective SK2 channel blocker apamin in the dorsal hippocampus during post-conditioning preference testing to probe the contribution of SK2 channel activity in retrieval of conditioned memory. Alternatively, by chronically disrupting SK2 channel activity during CPP with a viral overexpression construct of a dominant-negative SK2 channel, we can determine the role of SK2 channels in the learning phase of drug-paired conditioning. We will also investigate functional changes in SK2 channels following morphine CPP with slice electrophysiology in the dorsal hippocampus. Ultimately, we hope to elucidate the mechanism by which calcium-gated potassium channel SK2 mediates hippocampal plasticity underlying drug-paired contextual memory formation.

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**785. Opioids: Neural Mechanisms of Addiction**

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**Topic:** G.08. Drugs of Abuse and Addiction

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**Title:** The differential roles of $Ca_v1.2$ and $Ca_v1.3$ within the dorsal hippocampus in aversive responses of drug withdrawal in chronic morphine-dependent rats

**Authors: *F. SHEN**[1,2], Y. DUAN[1,2], M. ZHANG[3], S. JIN[1,2], N. SUI[1,2]
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**Abstract:** The aversive properties of withdrawal are in part dominated by L-type calcium channels (LTCCs) in chronic opiate dependent subjects. However, underlying the responses of withdrawal and aversive learning, how the discriminatory mechanisms modulated by the different subtypes of LTCCs, including $Ca_v1.2$ and $Ca_v1.3$, need to be addressed further. In the present study, we used adult male Sprague-Dawley rats. For locating the distinguish roles of $Ca_v1.2$ and $Ca_v1.3$ in the dorsal hippocampus (DH) underlie withdrawal responses and aversive learning, firstly, LTCCs antagonist verapamil was injected in morphine-dependent rats before conditioned place preference (CPA) training. Meanwhile, the intracellular free calcium in the DH was tested in vivo by the probe-based endomicroscopy, and the variation between the behavior and protein expression was also checked by the specific inactivation agents of $Ca_v1.2$ siRNA and $Ca_v1.3$ shRNA. Results showed that the intracellular free calcium in the DH was increased significantly after the injection of naloxone, and verapamil inhibited both this kind of calcium releasing, and then the acquisition of CPA. Furthermore, after the specific inactivation agents intra-DH administration, the acquisition of morphine CPA was impaired by $Ca_v1.2$ siRNA and $Ca_v1.3$ shRNA, but the somatic withdrawal responses were not. However, the variation of $Ca_v1.3$ was increased in the DH immediately when the naloxone injected into the subjects without CPA training, and that of $Ca_v1.2$ increased after CPA conditioning. These findings suggested that $Ca_v1.2$ tend to affect the associated aversive learning, whereas $Ca_v1.3$ does only the withdrawal response in the DH of morphine dependent rats.

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**Poster**

**785. Opioids: Neural Mechanisms of Addiction**

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** RO1-DA030074
T32-DA007278

**Title:** Differential pre- and post-synaptic K+ channel regulation by kappa opioid receptors affect dopamine neuron physiology

**Authors: *K. L. REICHARD**[1], P. M. SOTERO DE MENEZES[1], A. D. ABRAHAM[1], C. I. CHAVKIN[2]
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**Abstract:** Kappa opioid receptor (KOR) signaling on dopamine neurons has been implicated in behavioral responses to stress including aversion, dysphoria, and increased drug-seeking. Prior electrophysiological studies show that KOR agonists can hyperpolarize dopamine cell bodies, but the molecular mechanism of these effects have not been fully characterized. KORs are also highly expressed on dopaminergic terminals in the ventral striatum, where acute exposure to KOR agonists generates a robust inhibition of evoked dopamine release. Neither the behavioral effects of acute presynaptic inhibition of dopamine terminals, nor the mechanism of this effect have been previously demonstrated. In this study, we verify that KORs act on dopamine neurons by activating G protein-coupled inwardly rectifying potassium channels (GIRKs) and arrestin-dependent p38 MAPK signaling in the cell bodies. We found that a 4AP-sensitive, α-DTX-insensitive K+ channel contributes to KOR-mediated presynaptic inhibition of dopamine release, as recorded using fast-scan cyclic voltammetry. We also found that systemically administered KOR agonists alter striatal phosphorylation of the SNARE-associated protein, Munc18. Munc18 phosphorylation has previously been linked to CB1 and mGluR presynaptic inhibition but its regulation has not previously been linked to KOR signaling or regulation of transmitter release in dopamine neurons. These studies demonstrate a unique mechanism of presynaptic KOR signaling, which indicate there may be behavioral consequences of presynaptic KOR distinct from dysphoria and aversion. Finally, using pharmacological and genetic methods to locally inactivate KOR expressed in dopamine neurons, we also investigated the contribution of terminal inhibition of dopamine release to KOR-mediated hypolocomotion. These studies describe a novel molecular mechanism of KOR action that is functionally independent from arrestin-p38 MAPK actions of somatodendritic KOR. These findings delineate dopamine-dependent behavioral effects of KOR signaling within the VTA and the striatum and follow up studies will

determine how this functional separation enables dynorphin inputs into these regions to activate distinct behavioral repertoires within the circuit.

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**Poster**

**785. Opioids: Neural Mechanisms of Addiction**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 785.10/III7

**Topic:** G.08. Drugs of Abuse and Addiction

**Title:** Oxycodone withdrawal leads to changes in AP1 family of transcription factors in the rat dorsal striatum

**Authors: *C. A. BLACKWOOD**[1], M. LEARY[2], R. HOERLE[2], M. JOB[2], M. MCCOY[2], B. LADENHEIM[2], J. SUBRAMANIAM[2], J. L. CADET[2]
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**Abstract:** Addiction to opioid agonist, oxycodone is a pubic health menace due to it over-prescription and illicit use. Moreover, oxycodone addicts suffer from withdrawal symptoms including repeated relapses; however, very little is known about the neuroadaptive changes that occur in the brain. Self-administration studies have shown that animals given long access to opioids escalate their drug intake and exhibit compulsive drug seeking behaviors that may be secondary to neuroadaptive changes in striatum-dependent habitual behaviors. Moreover, our lab and others have shown that compulsive drug seeking behavior is associated with changes in Immediate Early Genes (IEGs). It remains unclear whether IEGs play a critical role during oxycodone withdrawal. We trained male Sprague-Dawley rats to self-administer oxycodone. We performed a cue-induced extinction test for 31 days from the last day of training. We used short access (ShA) (3 hours) and long access (LgA) (9 hours) exposure to oxycodone self-administration (SA) followed by protracted forced abstinence to measure cue-induced oxycodone seeking. After 31 days of withdrawal rats were euthanized and brains were isolated to extract RNA. q-RT-PCR was used to measure the mRNA expression of immediate early genes (IEGs) including cfos, fosB, fra1, fra2, junB, junD, cfos, Nr4A1, Nr4A2, and Nr4A3 in the dorsal striatum. Rats with LgA to oxycodone escalated their drug intake during the experiment, whereas the ShA rats did not. Cue-induced extinction tests revealed that LgA rats showed increased lever pressing after 19 days compared to ShA and saline rats. Gene expression data revealed increased fosB and JunD mRNA levels in all 3 oxycodone groups. In contrast, junB and cfos mRNA expression was upregulated only in the LgA groups. There were, however, no changes in Nr4A1-3 and Fra1-2 mRNA levels in any oxycodone group. Taken together, our findings suggest that long access to oxycodone is associated with escalation of drug intake and incubation of

oxycodone seeking. Our data also implicate potential roles of striatal IEGs in behaviors associated with oxycodone withdrawal.

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**Poster**

**785. Opioids: Neural Mechanisms of Addiction**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 785.11/III8

**Topic:** G.08. Drugs of Abuse and Addiction

**Title:** Oxycodone self-administration alters the expression of fibroblast growth factor genes in the rat striatum

**Authors: *J. L. CADET**[1], M. LEARY[2], M. JOB[1], S. JAYANTHI[1], C. BLACKWOOD[1]
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**Abstract:** Oxycodone is a semisynthetic opioid prescribed for people who suffer from various pain syndromes. Chronic abuse of oxycodone can lead to addiction. To treat oxycodone addiction, a better understanding of cellular mechanisms that maintain addiction is necessary. These mechanisms may include altered gene expression in the nucleus accumbens (NAc) and the dorsal striatum (DS), two brain regions implicated in various behavioral aspects of addiction. Some of the genes whose expression might be affected by oxycodone are fibroblast growth factors (FGFs) and their receptors (FGFRs) because drugs of abuse are known to influence the expression of trophic factors in the brain. These growth factors regulate functions involved in controlling neuronal development, cellular maturation, and memory formation. Therefore, we tested the possibility that oxycodone exposure might cause changes in mRNA levels of FGFs and FGFRs in the dorsal (DS) and ventral (VS) striatum. We allowed rats to self-administer (SA) oxycodone according to either short (ShA, 3 hours) or long (LgA, 9 hours) access schedules. These were followed by periods of a month of abstinence to measure oxycodone seeking. The long access group showed two distinct phenotypes of oxycodone self-administration, high (LgA-H) and low (LgA-H). After 31 days of withdrawal, ventral and dorsal striatal tissues were isolated and mRNA levels of FGFs and FGFRs were quantified. In the DS, oxycodone SA is associated with significant decreases in FGF3 and FGFR1 mRNA levels in all oxycodone groups compared to the control group. DS FGF2 expression was significantly increased in LgA-L and LgA-H groups, but not in the ShA group, compared to the control group. In the VS, oxycodone SA was associated with significant increases in FGF3 and FGF15/19 mRNA levels in the ShA in comparison to the LgA and control groups. These results suggest that oxycodone might significantly impact striatal molecular events that are involved in neuronal development and

memory formation. These results are consistent with previous studies that have suggested that drug addiction may involve, in part, a *rejuvenation process* that causes addicts to make decisions comparable to individuals with less mature brains.

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**785. Opioids: Neural Mechanisms of Addiction**

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**Program #/Poster #:** 785.12/III9

**Topic:** G.08. Drugs of Abuse and Addiction

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**Title:** miRNA gene regulation and Argonaut-2 in the development of oxycodone self-administration

**Authors: *F. M. VASSOLER**[1], C. M. SCHONHOFF[2], D. N. TECENO[2], T. D. PATTON[2], E. M. BYRNES[3]
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**Abstract:** Opioid addiction is a lifelong disease resulting from long-lasting molecular and behavioral changes. Micro RNAs (miRNAs) are key modulators of gene regulation and are known to be involved in addiction. Argonaut-2 is a protein that is necessary for miRNA-mediated gene silencing as it is an integral protein in the RISC complex responsible for binding short guide RNA. It is the goal of these experiments to test the hypothesis that miRNAs are necessary for the acquisition of addiction-related behaviors utilizing a rat oxycodone self-administration model. Expression of miRNAs within the nucleus accumbens were measured following oxycodone or saline. Target proteins from candidates were also examined including hnRNPU. Ongoing experiments are examining if disruption of the miRNA system within the accumbens utilizing Crispr/Cas-9 genome editing to delete the Argonaute-2 gene will disrupt acquisition of oxycodone self-administration. If miRNAs are necessary for the regulation of genes involved in the development of addiction, then knocking down Argonaute-2 may prevent miRNAs from regulating gene expression and thus the development of addiction.

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**Topic:** G.08. Drugs of Abuse and Addiction

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**Title:** Chronic opioid treatment and naltrexone-induced withdrawal alter neuropeptide Y protein levels and RNA expression in the locus coeruleus of male and female rats

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**Abstract:** The opioid epidemic is a public health crisis in the United States, with over 2.1 million people currently suffering from an opioid abuse disorder. Chronic stress is implicated as a major risk factor in opioid abuse and relapse, and treatments that increase stress resilience are currently being investigated for efficacy in opioid addiction. Recently, neuropeptide Y (NPY) has emerged as a neurochemical mediator of stress resilience. In rodent models of post-traumatic stress disorder, treatment with NPY prevents or reverses hyperarousal, anxiety, and depression-like behavior, while low levels of NPY are associated with stress vulnerability. In healthy human subjects, plasma NPY levels are correlated with feelings of dominance, confidence, and superior performance under stress. Such studies suggest NPY modulates stress resilience, and aberrant NPY activity may increase susceptibility to stress-related psychiatric illness, particularly in females. Here, we investigated adaptations in the NPY system following chronic morphine exposure and naltrexone-induced withdrawal in the locus coeruleus (LC) of male and female Sprague Dawley rats. Rats were implanted with placebo or morphine pellets (2 x 75 mg) for 6 days to induce morphine dependence. Then, rats either received saline, or naltrexone (100 mg/kg, intraperitoneally) to induce withdrawal. Rats were euthanized, and brains were harvested and dissected for Western blot analysis or high-throughput RT-qPCR. Western blot analysis indicated baseline NPY levels were comparable in males and females and chronic morphine exposure had no effect on NPY levels in the amygdala or prefrontal cortex. However, both chronic morphine and withdrawal caused significant decreases in NPY protein levels in the LC, in both males ($P < 0.01$) and females ($P < 0.01$). Further analysis of relative RNA expression in the LC across groups revealed that *NPY* was decreased in both male and female withdrawal groups, compared to placebo or morphine-treated ($P < 0.05$). Expression of the NPY receptor *Npy2R* was decreased in the LC in both chronic morphine and withdrawal groups in females only ($P < 0.05$), while expression of *Npy1R* remained unchanged in males and females. The decreased

*NPY* expression in the LC may suggest vulnerability to stress in males and females during withdrawal, while the observed decrease in *Npy2R* may represent an exaggerated effect in females. These findings demonstrate significant and sexually dimorphic adaptations in NPY signaling following chronic opioid exposure and withdrawal, and have important implications for the development of therapeutics to target the NPY system and increase resilience and resistance to relapse.

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**Poster**

**785. Opioids: Neural Mechanisms of Addiction**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 785.14/III11

**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** NIH Grany DA041809

**Title:** Mu opioid signaling in the anterior cingulate cortex regulates dopamine release in the nucleus accumbens shell

**Authors: T. A. GEE**[1], E. NAVRATILOVA[2], N. WEINTRAUB[3], B. ISAKOV[3], F. PORRECA[3], *M. L. HEIEN[2]
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**Abstract:** Opioid and dopaminergic circuits are implicated in pain processing and are both altered in response to commonly prescribed pain medications. Studies that have monitored the relationship between these neurotransmitters have made measurements on the time scale of minutes, thus missing changes that occur on the second or sub-second temporal regime. We used fast-scan cyclic voltammetry, making ten measurements per second, to study dopaminergic neurotransmission in male, S.D. rats under light isoflurane anesthesia. First, we measured the phasic dopamine (DA) response during a withdrawal from an acute noxious thermal stimulus applied to the tail of an anesthetized animal. This tail flick paradigm allowed us to ensure that the depth of anesthesia was comparable across animals through a target behavioral response (i.e., tail-flick at 6.5 sec after initiation of the radiant heat nociceptive stimulus). In the nucleus accumbens shell (NAcs) we observed a 93% inhibition of DA signaling at the point of tail flick followed by a 39% rebound above baseline signaling upon stimulus termination. The 2.3-second inhibition and subsequent 3.0-second rebound may suggest the onset of pain and the reward of pain relief, respectively. In contrast, recordings in the nucleus accumbens core showed a smaller DA decrease at the tail flick and no rebound increase, suggesting region specific processing of reward from pain relief. Our previous studies showed that pain-motivated behavior (i.e., relief) is

driven by endogenous opioid release in the rostral anterior cingulate cortex (rACC). For this reason, we hypothesized the pain-relief rebound signal was regulated by opioid actions within the rACC. We pretreated rats with intra-ACC microinjections of an irreversible MOR antagonist, β-funaltrexamine (β-FNA) (3 μg, bilaterally, 24 hr prior to testing) and measured phasic DA signals in the NAcs. β-FNA decreased the number of spontaneous dopaminergic transients observed before the stimulus by 65% (n = 6 SD rats) suggesting tonic regulation of NAc DA release by endogenous opioids within the rACC. In β-FNA pretreated rats, we did not observe a reduction of phasic DA release at the time of the tail flick, however, rACC β-FNA did not affect the rebound DA signal observed after the tail. These findings show a previously unknown regulation of tonic and phasic NAc DA release by rACC opioid signaling observable by FSCV and suggest selective modulation of pain and pain relief signals. This is an important part of elucidating a comprehensive mechanism of pain regulation by opioid medication, which will hopefully lead to the development of more effective, less addictive pain treatments.

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** Grant: DA 020129

**Title:** Chronic morphine- induced changes in the endocannabinoid system in the locus coeruleus and prefrontal cortex of male and female rats

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**Abstract:** Opioid addiction remains a serious health concern in the United States, with approximately 2.5 million people currently addicted to heroin or non-medical prescription opioids. Opioids significantly impact the noradrenergic nucleus locus coeruleus (LC), which provides the main source of norepinephrine throughout the brain. Several lines of evidence indicate that the LC is uniquely poised to be a site of convergence for opioid and cannabinoid actions. In the present study, we investigated protein expression levels of the key enzymes in the biosynthesis and degradation of endocannabinoids in the LC and prefrontal cortex (FC) of male

and female Sprague Dawley rats following chronic exposure to morphine. Rats were implanted with placebo or morphine pellets (2 x 75 mg) for 7 days. Rats were euthanized and brains were harvested. Using Western blot analysis, diacylglycerol lipase-α (DGL-α), fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL) were detected in the LC and FC. Results showed that MGL expression was significantly increased in the LC ($p < 0.05$) of male rats when compared with females following chronic morphine exposure. In contrast, FAAH expression was similar in the LC of both male and female following chronic morphine treatment. However, the male rats showed a higher expression ($p < 0.05$) regardless of treatment. In the FC, FAAH expression was higher in male and this expression was not affected by chronic morphine exposure. Female rats showed a higher expression of MGL in the FC ($p < 0.05$) but this expression was not modulated by chronic morphine treatment in either male or female subjects. Conversely, male rats showed a higher expression of DGL-α in the FC regardless of treatment. DGL- α expression in the FC was increased following chronic morphine treatment in both groups. The present results demonstrate that there is a differential expression of the main limiting enzymes of the endocannabinoids between sexes in the LC and PFC. In addition, these enzymes are differentially modulated by chronic morphine treatment in both areas. These differences could underlie sex differences in exogenous cannabinoids and morphine effects that have been demonstrated in animals and humans.

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**Title:** The role of the neuropeptide receptor system, BigLEN-GPR171, in opioid reward and withdrawal

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**Abstract:** Recently, it was identified that the neuropeptide, BigLEN, is the endogenous ligand for the orphan receptor, GPR171. BigLEN is derived from ProSAAS which is one of the most abundant peptides in the brain including areas involved in drug addiction including the medial prefrontal cortex (PFC), nucleus accumbens (NAc), basolateral amygdala (BLA), ventral tegmental area (VTA), and hippocampus (HPC). Using immunohistochemistry, we have identified that GPR171 is found within various neuronal subtypes throughout these brain areas. Our previous data has shown that inactivation of GPR171 within the BLA decreases anxiety and fear related behaviors. Given the expression pattern of the BigLEN-GPR171 system, we predict that it regulates addictive behaviors as well since these brain regions regulate memories associated with positive (i.e. drug reward) and negative (i.e. drug withdrawal) events. First, we have found that chronic morphine treatment leads to a decrease in Pcsk1n (i.e. gene that encodes BigLEN) mRNA expression in the PFC and an increase in GPR171 mRNA expression in the BLA and NAc. It is hypothesized that morphine is decreasing BigLEN expression in neurons in the PFC, which is leading to an adaptive increase in GPR171 expression in the BLA and NAc. Second, to assess the role of GPR171 in morphine induced reward, we have conducted morphine conditioned place preference with systemic administration of a GPR171 antagonist (MS21570) or vehicle 10 min prior to each morphine pairing and this lead to reduced time spent in morphine paired chamber. In addition, knockdown of GPR171 in the BLA causes a reduction in morphine conditioned place preference. Finally, to investigate the BigLEN-GPR171 system in opioid withdrawal, mice were treated with morphine and the GPR171 antagonist (or vehicle) twice daily for 5 days followed by naloxone precipitated withdrawal. Those mice pretreated with the GPR171 antagonist, showed a decrease in withdrawal symptoms compared to controls. Taken together, this data shows that this neuropeptide receptor system, BigLEN-GPR171, may be a novel target to treat opioid induced addictive behavior and withdrawal.

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**Program #/Poster #:** 785.17/III14

**Topic:** G.08. Drugs of Abuse and Addiction

**Title:** Determining the effect of cell type-specific VTA SGK1 manipulation on drug reward

**Authors: *M. A. DOYLE**[1], V. BALI[2], S. E. COOPER[1], A. R. STARK[3], M. S. MAZEI-ROBISON[2]
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**Abstract:** Drugs of abuse are known to regulate activity of the mesolimbic dopamine (DA) system. Specifically, drug-induced changes in ventral tegmental area (VTA) cellular activity and gene regulation contribute to behavioral outputs associated with addiction. Our previous work has determined that serum- and glucocorticoid-inducible kinase 1 (SGK1) catalytic activity and phosphorylation at Ser78 are increased by chronic, but not acute, administration of cocaine and morphine. Furthermore, I have shown that viral overexpression of SGK1 mutants in the VTA of adult mice produce behaviorally relevant effects on drug reward, assessed by cocaine conditioned place preference (CPP) and voluntary morphine intake using a two-bottle choice task. Specifically, intra-VTA infusion of a catalytically inactive SGK1 mutant (K127Q) significantly decreases cocaine CPP and morphine intake, suggesting that decreasing VTA SGK1 activity is sufficient to decrease drug reward. Intra-VTA infusion of SGK1 S78A, a mutant that prevents phosphorylation at Ser78, significantly decreases cocaine CPP and morphine intake, suggesting that VTA SGK1 pSer78 is necessary for drug reward and intake. To more fully understand the role of VTA SGK1 in behaviors relevant to addiction, I am now manipulating SGK1 expression in a cell type-specific manner to determine whether SGK1 activity and phosphorylation in DA or GABA neurons drives the observed behavioral effects. Utilizing novel Cre-dependent viral constructs, I am currently assessing the impact of altered SGK1 activity in VTA DA neurons on drug reward. In parallel, using a floxed-SGK1 mouse line crossed with a DAT-Cre driver line, I am determining the impact of DA SGK1 knockout on reward behavior. These studies will allow for identification of the specific cells and circuits that are critical for SGK1-mediated effects on drug reward and intake. This work will increase our understanding of the role of VTA SGK1 activity in drug-related behaviors, a necessary step in assessing the feasibility of SGK1 inhibition as a novel therapeutic avenue for addiction.

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** R21 DA044757-01

**Title:** Rna sequencing of ribotag mRNA from striatal microglia during morphine escalation and naloxone precipitated withdrawal

**Authors: *J. F. NEUMAIER**[1], K. R. COFFEY[1], A. J. LESIAK[2], B. D. DUFOUR[2], E. K. VO[3]
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**Abstract:** Many facets of opioid dependence contribute to the clinical and social crisis that we are now facing. In addition to the increasing loss of control over drug use that accompanies extensive exposure to opioids, the severity of withdrawal becomes worse over successive cycles of opioid use and discontinuation. Just the threat of withdrawal symptoms is a major barrier that stops individuals who would like to discontinue opioids from detoxing. Furthermore, these symptoms can precipitate relapse to drug taking in order to alleviate withdrawal. In this experiment we investigated the contribution of microglia-mediated inflammatory responses to withdrawal. To accomplish this we utilized RiboTag, a technique which allows for isolation and analysis of RNA that is actively undergoing translation in a specified set of cells. We used male and female transgenic CX3CR1-Cre/RiboTag mice that express HA-tagged rpl22 exclusively in resident microglia. These mice were administered a rapidly escalating, tolerance inducing, noncontingent morphine schedule (versus saline) followed by naloxone-precipitated withdrawal (versus saline), then at 4hrs we sacrificed the mice and immunopurified the ribosome-associated RNA from microglia and then analyzed the RNAs undergoing translation using RNAseq. This method yielded over 5000 genes that were enriched in microglia relative to the remaining striatal tissue. Further, several hundred genes were differentially expressed between saline animals and morphine animals, and between morphine animals and naloxone precipitated withdrawal animals. No differences were observed between saline animals and non-opioid escalated naloxone treated animals. These changes in microglia response during morphine escalation and withdrawal represent a broad exploration of translational changes that occur during a critical time in opioid use. Gene set enrichment analysis and other bioinformatic analyses of the networks of RNA translation changes are currently being performed. We are currently validating changes in gene expression using RT-qPCR and FISH. Careful analysis of these genes will give us new mechanistic information leading to a deeper understanding of how microglia respond to opioid withdrawal and should lead to the identification of novel targets for inhibiting microglial responses to opioids and withdrawal.

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**Poster**

**785. Opioids: Neural Mechanisms of Addiction**

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**Topic:** G.08. Drugs of Abuse and Addiction

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**Title:** ΔFosB: A major player in the hippocampus of human opioid overdose cases

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**Abstract:** Background: Patients with opioid use disorder have disrupted neuronal activity leading to tolerance, dependence, and cravings. At the molecular level, animal studies have given us insight into potential players implicated in this disruption. Our focus is on ΔFosB, a splice variant of transcription factor FosB. It is established that ΔFosB, normally absent in brain tissue, accumulates following prolonged exposure to drugs of abuse. It is believed that ΔFosB may be responsible for establishing events that lead to long lasting changes in gene expression following abuse.
Objective: Most opioid use disorder studies identifying ΔFosB as an important molecular switch have been on rodent models. We hypothesize that ΔFosB has a comparable role in the human brain.
Methods: Our laboratory examines human post-mortem tissue obtained at autopsy of opioid overdose. We presented evidence of ΔFosB protein expression in nucleus accumbens, amygdala and hippocampus, using the immunohistochemistry assay. Using Nanostring®, a multiplex gene expression analysis protocol that measures expression of 770 genes, we now also have quantitative evidence that ΔFosB mRNA is expressed in the hippocampus of our human cases.
Conclusion: We confirm that in our opioid cases, ΔFosB is a determining factor in the shift from normal behavior to addicted behavior in subjects with opioid use disorder.

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**Topic:** G.08. Drugs of Abuse and Addiction

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**Title:** Effects of chronic prescription opioid use on corticostriatal connectivity and gray matter volume

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**Abstract: Rationale:** Prescription opioid misuse and addiction represents the fastest growing public health crisis in the US, resulting in a 30% year over year increase in opioid overdoses and an economic burden totaling $78.5 billion per year. Elucidating the mechanisms undergirding opioid use disorder (OUD) is critical for identifying new treatments. In animal models of addiction, repeated use of opiates, nicotine and cocaine, produces glutamatergic neuroplasticity in corticostriatal circuitry that mediates reinstated drug seeking. Analogous to animal models, human fMRI studies report weaker corticostriatal resting-state functional connectivity (rsFC) in nicotine and cocaine dependent users however, the effects of chronic prescription opioid use on corticostriatal rsFC and anatomy remain unclear. **Hypothesis:** As compared to healthy controls, prescription opioid users will evidence weaker rsFC and less gray matter volume in corticostriatal circuitry. **Methods:** Long-term prescription opioid users (33) and drug-free controls (30) consented to be MRI scanned during a T1 structural and 10-min BOLD eyes-closed resting state BOLD acquisition. Structural images were preprocessed using the computational anatomy (CAT12) toolbox and SPM12 according to a standard pipeline. rsFC data were denoised using the conn toolbox (0.01 to 0.08 HPF, despiking and Motion/WM/CSF PCA regression). 3mm radius spheres around bilateral nucleus accumbens peaks served as sources in a group-level seed-to-voxel bivariate correlation analysis within an *a priori* region of interest mask, encompassing the vmPFC and ventral striatum ($p<.05$, cluster FWE). **Results:** As compared to controls, the opioid group exhibited weaker rsFC between the ventral striatum and vmPFC and less gray matter volume in the vmPFC. Overall, the strength of rsFC was positively associated with the gray matter volume in the vmPFC. **Conclusions:** Results from the current study demonstrate that chronic prescription opioid use is associated with weaker corticostriatal rsFC concomitant with structural alterations in the ventromedial prefrontal cortex. These findings conform with the preclinical and clinical neuroscience literature on addiction, implicating the corticostriatal pathway as a potential transdiagnostic, final pathway in compulsive drug use. Findings will be discussed in the context of a potential role for glutamatergic medications for treating opioid use disorder.

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**Title:** Corticostriatal connectivity strength predicts dysregulated hedonics in opioid-dependent adults

**Authors: *P. A. MCCONNELL**[1], E. GARLAND[2], J.-K. ZUBIETA[3], B. FROELIGER[1]
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**Abstract: Rationale:** Corticostriatal (CS) dysfunction may underlie dysregulated motivation and positive affect (PA) in prescription opioid use disorder (OUD).
**Hypothesis:** OUD is associated with alterations in CS connectivity and PA regulation.
**Methods:** Long term OUD (33) and drug-free controls (30), performed a PA upregulation task during an fMRI scan. Between-subjects effects in BOLD response, task-based functional connectivity (tbFC), and PA upregulation were investigated via ANCOVA. Set-level inference ($p<.05$) was used to examine functional coactivation within a CS network mask (bilateral vlPFC and ventral striatum [VS]). CS tbFC during PA trials (View, Upregulate) were assessed between coactivated VS and vlPFC nodes identified in the BOLD GLM interaction.
**Results:** During upregulation, OUD exhibited less BOLD response in the CS network (OUD = .04, Control = 0.16, $p = 0.003$). ROI-ROI tbFC analyses elaborated this finding; OUD CS tbFC strength predicted baseline PA ($r=.27$, $p=.03$) and post-upregulation PA response to positive imagery (OUD rZ = .04, Control = .08; $p = 0.04$). Post-hoc path analysis of these associations revealed evidence of significant OUD group-moderation effects in both paths: between CS tbFC strength, baseline PA ($p = .035$), and post-regulation PA ($p < .001$).
**Conclusions:** Confirming our hypothesis, OUD subjects evidenced weaker CS BOLD response and tbFC during attempted PA upregulation. Preclinical data show that increased opioid consumption produces neuroplasticity in CS circuitry involved in cognitive appraisal of affect. These maladaptations reduce motivational drive to pursue natural rewards and, in humans, are suspected to be a core endophenotype expressing hedonic deficits and blunted sensitivity to natural reward cues. Here, we show that network-level BOLD coactivation during attempted PA upregulation identified a functional CS circuit in which OUD subjects exhibit tbFC deficits that are associated with blunted hedonic tone and perceived efficacy of positive-affective upregulation. Interestingly, only OUD evidenced relationships between CS connectivity strength, hedonic tone and perceived upregulatory effectiveness. These results, together, suggest that connectivity deficits may be a unique limiting factor for successful PA upregulation in this population and that the severity of OUD-related dysfunction in hedonic processing is tied to neural circuitry function. Moving forward, CS tbFC may serve as an important biomarker of therapeutic efficacy, and also may be advantageously modulated by brain stimulation approaches (eg, TMS) during affect-regulation training (eg, MORE).

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**Topic:** G.08. Drugs of Abuse and Addiction

**Title:** Specific firing patterns of VTA GABA neurons dictate the motivational experience of acute opiate reward

**Authors: *M. A. BERGAMINI**[1], H. STEENLAND[1], G. MAAL-BARED[1], L. EL-FAYOMI[1], R. CHOY[1], D. J. VAN DER KOOY[2]
[1]Univ. of Toronto, Toronto, ON, Canada; [2]Dept Med. Genet, Univ. Toronto, Toronto, ON, Canada

**Abstract:** Opioid addiction is a debilitating and costly epidemic that claims thousands of lives every year. The potent acute rewarding effects of opiates, and the aversiveness of opiate withdrawal, are powerful motivational experiences thought to be mediated by GABAergic and dopaminergic neurons in the ventral tegmental area (VTA), respectively. Both agonizing and antagonizing GABAa receptors on VTA GABA neurons elicits rewarding behaviors in mice through distinct activation of downstream projections to the brainstem TPP versus those to local dopamine neurons projecting to the nucleus accumbens, respectively. However, mice have been shown to express aversions to optogenetic activation of these VTA GABA neurons by 20Hz pulses, findings which we have replicated. Additionally, both agonizing and antagonizing VTA dopamine (DA) receptors alleviates opiate withdrawal aversions, suggesting that opiate-associated motivational experiences are not binarily determined by the increased or decreased activity of these cells, but rather their action potential firing profiles. Therefore, we propose that specific firing patterns of VTA GABAergic neurons mediate the experience of opiate reward, and that the specific firing patterns of VTA DA neurons mediate the aversiveness of opiate withdrawal. As such, we recorded the activity of VTA GABA and DA neurons extracellularly in freely moving mice following systemic acute morphine or saline injections and during states of opiate withdrawal. In separate, drug-naïve animals, using excitatory opsins, we stimulate VTA GABA or DA neurons in the exact manner as previously recorded, and assess whether these activation patterns are experienced as rewarding or aversive. We show that stimulating VTA GABA neurons with the identical firing pattern recorded from putative VTA GABA neurons following a morphine injection produces real-time rewarding behaviors in mice, as well as conditioned place preferences for that patterned stimulation. Moreover, the average frequency of this variable rewarding pattern (18Hz) approximates the frequency of the non-patterned aversive 20Hz signal, lending support to our prediction that the motivational experience of acute opiate reward is pattern specific.

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**Topic:** G.08. Drugs of Abuse and Addiction

**Support:** Board of Governors Regenerative Medicine Institute

**Title:** The effects of opioids on dopaminergic neuron activity in a human brain-chip system

**Authors: D. WEST**, S. SANCES, A. LAPERLE, R. HO, A. MEYER, A. WOODBURY, M. WORKMAN, V. DARDOV, *V. A. MOSER, C. SVENDSEN
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**Abstract:** Opioid overdose is responsible for over 100 deaths per day in America, and the U.S. Department of Health & Human Services has declared this crisis as a public health emergency. Beyond acute overdose, there are prolonged burdens on health care and extensive costs for opioid abuse treatments. There currently exists only a small pool of FDA-approved drugs for opioid addiction that are limited in availability, possess unpredictable side-effects, and may have addictive qualities of their own. To better study the mechanisms of opioids and potentially develop pharmacological addiction intervention strategies, we developed a Brain-Chip, which is a scalable microphysiological system (MPS), also known as an Organ-Chip, that contains living human neurons from induced pluripotent stem cells (iPSCs). Single cell RNA-sequencing analysis identified a population of inhibitory interneurons that express opioid receptors. In addition, the Brain-Chips contained iPSC-derived dopaminergic neurons, the cell type involved in mediating the rewarding effects of opioids. Another feature of the Brain-Chip is the addition of a perfusable vascular compartment that contains iPSC-derived brain microvascular endothelial cells that directly interact with the neural compartment through a porous membrane, thereby recapitulating the blood brain barrier (BBB) to accurately study drug delivery through the BBB. Large-scale automated analysis of live calcium imaging data of the Brain-Chips was used to assay changes in spontaneous neuronal activity. Metabolomic and HPLC analyses are ongoing to assess the production of dopamine and additional metabolites in the Brain-Chip. To test the utility of this system in the discovery of novel therapeutics to combat opioid addiction, the effects of clinically-relevant opioid agonists and antagonists on neuronal activity, release of dopamine, and cell physiology are being evaluated. This work promises to provide a new tool to assess the addictive potential of experimental pain therapeutics by direct assessment of human neuronal dopamine release.

**Disclosures: D. West:** None. **S. Sances:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Holder. **A. Laperle:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Holder. **R. Ho:** None. **A. Meyer:** None. **A. Woodbury:** None. **M. Workman:** None. **V. Dardov:** None. **V.A. Moser:** None. **C. Svendsen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Holder.

**Poster**

**786. Cortical and Hippocampal Circuit Interactions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 786.01/III21

**Topic:** H.01. Animal Cognition and Behavior

**Support:** R01MH054671-18

**Title:** Characterization of LFP and unit activities in the primary visual cortex during sleep

**Authors: *Y. SENZAI**[1,2], A. FERNÁNDEZ-RUIZ[3], D. LEVENSTEIN[3], G. BUZSAKI[4]
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**Abstract:** The neocortex is a highly stratified brain structure. Different cell types in different cortical layers have different physiologIcal features and connectivity in the circuit. To understand the operation of the neocortical circuits, it is important to elucidate the activity patterns of the different cell types in different brain states. No reliable electrophysiological method exists to identify the anatomical layers. Furthermore, extracellular electrophysiological recordings in the neocortex failed to reveal the cell type identities of recorded units. To address these problems, we apply multisite laminar recordings from the primary visual cortex (V1) during sleep and waking behaviors. Using current source density and independent component analyses of the local field potential, we are able to reliably identify each layer with high accuracy. In addition, using optogenetic and spike-transmission probability methods, we separate the recorded neurons into excitatory and inhibitory categories layer by layer and describe their state-dependent firing characteristics, monosynaptic connectivity within and across layers. In addition, we examine how each neuron subclass contributes to the various LFP patterns in different layers. Our findings demonstrate how high-density recording can provide lamina-specific information about the firing patterns of cortical neurons.

**Disclosures: Y. Senzai:** None. **A. Fernández-Ruiz:** None. **D. Levenstein:** None. **G. Buzsaki:** None.

**Poster**

**786. Cortical and Hippocampal Circuit Interactions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 786.02/III22

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Gain control of hippocampal place fields

**Authors: *K. MCCLAIN**[1], D. TINGLEY[1], G. BUZSAKI[2]
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**Abstract:** Gain control is a canonical neurological computation by which the magnitude of a cell's response to "tuned" stimuli is modulated by some "untuned" behavioral or physiological variable. In the hippocampus, neurons are strongly tuned to the location of the animal, but show high trial-to-trial variability that obscures this spatial representation. This variability is heuristically attributed to changes in behavior, brain state or other variables. A quantitative analysis is needed to identify the effects of these untuned variables and their role in hippocampal population coding. We investigated the effects of non-spatial variables on the spatial tuning of hippocampal cells in rats performing a variety of spatial navigation tasks, such as running speed and population activity. Contrary to previous reports suggesting that speed globally increases firing rates of pyramidal cells and interneurons in the hippocampus, we found that the effect of speed is heterogeneous across populations of pyramidal cells, including strongly speed-suppressed place fields. Neurons were also heterogeneously affected by the activity of the local population, although the majority of place cells were positively modulated by the population firing rate of neighboring cells. These results suggest that gain control has multiple components which can contribute to the trial-to-trial variability in the hippocampus. These findings will be useful in constructing an adapted gain control model constrained by measured quantitative data.

**Disclosures: K. McClain:** None. **D. Tingley:** None. **G. Buzsaki:** None.

**Poster**

**786. Cortical and Hippocampal Circuit Interactions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 786.03/III23

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant R01MH107396-01
NIH Grant R01MH054671-14
NIH Grant U01NS099705
EMBO Long-Term Fellowship ALTF 1161-2017

**Title:** Hippocampal circuit connectivity revealed by simultaneous extracellular and intracellular recording in awake-behaving mice

**Authors: *M. VALERO**, D. F. ENGLISH, G. BUZSÁKI
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**Abstract:** Most computation in the brain takes place between neurons, typically through synaptic interactions. Yet, very few methods are available for studying synaptic plasticity during the course of learning and memory. Synaptic connections between neurons have been usually studied by paired intracellular recordings in vitro. Spike transmission probability measure across neurons is an indirect method but it needs verification by direct methods. To address these issues quantitatively and allow for large-scale assessment of neuronal interactions, we combine focal optogenetic stimulation with extracellular silicon probe recordings and intracellular recordings along the CA3-CA1 hippocampal axis in head-fixed behaving mice. We aim to identify true monosynaptic excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs) between our intracellular and extracellular pairs of cells *in vivo*, monitor their changes during behavior and obtain sufficient 'ground truth' data for properly interpreting spike transmission-based results. Taking advantage of the focal optogenetic stimulation, we assess the presynaptic cell identity and the direction of communication between the presynaptic action potentials and the intracellular responses. Our method allows for not only assessing synaptic effects pair by pair but to examine how population behavior of neurons affects communication across neuronal pairs and how gain control can modify the efficacy of synaptic communication in the behaving animal.

**Disclosures: M. Valero:** None. **D.F. English:** None. **G. Buzsáki:** None.

**Poster**

**786. Cortical and Hippocampal Circuit Interactions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 786.04/III24

**Topic:** H.01. Animal Cognition and Behavior

**Support:** MH107396-01
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NS099705
Sir Henry Wellcome Postdoctoral Fellowship
EMBO

FAPESP

**Title:** Optogenetic manipulation of hippocampal ripples during spatial learning

**Authors: *A. FERNÁNDEZ RUIZ**[1], A. OLIVA[2,1], E. FERMINO DE OLIVEIRA[1,3], F. ROCHA-ALMEIDA[4,1], G. BUZSAKI[5]
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**Abstract:** Hippocampal sharp-wave ripples (SPW-Rs) are highly synchronous network activity patterns. They are believed to support consolidation of recently acquired episodic memories and planning future actions by generating ordered neuronal sequences of previous or future behavioral experiences. SPW-Rs emerge when the brain is disengaged from the environment, most prominently during consummatory behaviors, periods of immobility and non-REM sleep. Previous studies found that electrical disruption of hippocampal SPW-Rs during sleep or learning lead respectively to impairments in memory consolidation or task performance. However, electrical stimulation is highly unspecific a do not allow a precise control of hippocampal network dynamics. To overcome these limitations, we developed an optogenetic approach to manipulate hippocampal activity during SPW-Rs in a closed-loop fashion. To this end, we virally expressed light-activable opsins in the dorsal hippocampi of rats and implanted multiple optic fibers and silicon probe arrays along the dorsal CA1 region. Taking advantage of simultaneous recordings in CA1 pyramidal and dendritic layers, we implemented an FPGA-based closed-loop detection system based on the concurrent detection of both the ripple and sharp-wave components. This method allowed a reliable SPW-R detection in both sleep and awake states. We then employed this system to perform close-loop optogenetic manipulations of hippocampal network dynamics in rats performing a spatial learning task. We are testing the hypothesis that the ordered reactivation of CA1 assemblies during SPW-Rs is necessary to sustain working memory during spatial learning.

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**Poster**

**786. Cortical and Hippocampal Circuit Interactions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** U01NS099705
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R01MH107396-01

**Title:** Routing of hippocampal sharp wave-ripples to subcortical structures

**Authors: *D. TINGLEY**[1], G. BUZSAKI[2]
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**Abstract:** The hippocampal sharp wave-ripple is often conceptualized as a network event that is critical for the hippocampal-neocortical dialog thought to underlie systems consolidation. However, many projections out of the hippocampus (HPC) target subcortical structures. Therefore, we investigated the impact of HPC ripples on the most densely innervated subcortical output, the lateral septum (LS). We find that a subset of HPC ripples are 'routed' to the LS in a state-dependent and content-dependent manner. Furthermore, LS ensembles of neurons were found to synchronously burst producing a local ripple event that could be decoupled from dorsal HPC activity (see figure). This interneuron network oscillation was significantly shorter that HPC ripples, therefore limiting the 'content' that such events could carry. Thus downstream neurons that receive LS inputs are likely to be modulated by a population burst in a manner that is independent from any sequence content within each event. Finally, we hypothesize that such HPC-subcortical interactions may be crucial for non-mnemonic functions related to hypothalamic activity regulation.


**Disclosures: D. Tingley:** None. **G. Buzsaki:** None.

**Poster**

**786. Cortical and Hippocampal Circuit Interactions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 786.06/III26

**Topic:** H.01. Animal Cognition and Behavior

**Support:** R01MH107396-01
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23853 - UFMG/REITORIA/PRPQ/PESQUISA E EXTENSÃO, subprojeto 361

**Title:** Improved ripple detection for real-time and closed-loop manipulation of memory in neural systems

**Authors: *E. F. OLIVEIRA**[1,2], A. FERNÁNDEZ RUIZ[3], I. J. D. BERALDO[4], G. F. BECKER[4], R. B. D. SILVA[4], D. C. SORIANO[5], G. BUZSAKI[6], C. LOPES-AGUIAR[4]
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**Abstract:** Experiments suggest that sharp-wave ripples events (SPW-R), registered as 120-200 Hz fast oscillations in the local field in the CA1 pyramidal hippocampal layer, provide effective windows of information transfer from the hippocampus and affect activity throughout the neocortex. Recent studies have employed closed-loop strategies to test the relevance of SPW-R for memory consolidation. However, they either do not provide details on the performance of the classifiers or report high false positive rates (up 60%). Despite the growing interest in this field, there is a shortage of open source tools designed to perform SPW-R detection in real time. In order to address this question, we examined different simultaneous events, such as the multi-unit activity, noise, including EMG, and gamma power band and investigated how detection of SPW-Rs can be improved, increasing true detections and decreasing false alarms. We developed an Open-Ephys GUI plug-in for SPW-R detector, based on reliable events. For the fast detection of SPW-R events for a closed-loop application, we developed a simple hardware for real-time SPW-R processing. All of our hardware is based on the Intan recording system. We anticipate that the tools we have developed can be used to investigate memory processes more effectively by online manipulation of SPW-Rs.

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**Poster**

**786. Cortical and Hippocampal Circuit Interactions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 786.07/III27

**Topic:** H.01. Animal Cognition and Behavior

**Support:** R01MH107396-01
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U01NS099705

**Title:** The role of inhibition in the normal and epileptic hippocampus

**Authors: *S. ROGERS**[1], J. GELINAS[2], D. KHODAGHOLY[2], A. FERNÁNDEZ RUIZ[3], J. DIMIDSCHSTEIN[4], G. J. FISHELL[5], G. BUZSAKI[6]
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**Abstract:** Epileptic seizures reflect a perturbation of the balanced state between excitation and inhibition, yet the exact role of inhibitory interneurons in the initiation and propagation of epileptic seizures is widely debated. Evidence has emerged suggesting that interneurons play both an anti-epileptic and pro-epileptic role in the maintenance of epileptic brain networks. Enhanced inhibition can suppress spiking of principal cells, but also assists in synchronization of neuronal populations. We revisited the role of inhibitory interneurons in the CA1 on normal and pathological brain oscillations and spiking activity in the kindling model for temporal lobe seizures in behaving rats. Using a viral construct that restricts the expression of a desired gene to interneurons, we induced expression of an excitatory designer receptor exclusively activated by designer drug (DREADD) into all subtypes of CA1 interneurons of the hippocampus and implanted silicon probes to record LFP and single unit responses. We first plan to test the effect of tonically increasing inhibitory tone by administering the ligand for the DREADD, clozapine N-oxide (CNO), intraperitoneally in non-epileptic rats to understand the local contribution of CA1 onto the generation of gamma (40-100 Hz), theta (5-8 Hz), and ripple (150-200 Hz) oscillations in behaving rats. We will also quantify the effect of activation of DREADDs by CNO by recording the cellular activity from both interneurons and pyramidal cells in the CA1 in vivo. We will then examine the role of sustained inhibition on afterdischarge and behavioral seizure duration, severity, and development of kindled seizures in animals that were treated with CNO to activate the interneurons every other day. We will compare the rate of interictal epileptiform discharges (IEDs), pathological population spikes that are hypothesized to play a role in the cognitive deficits associated with chronic epilepsy, between days when the animal was given an inert vehicle injection and CNO. Activation of interneurons across the entire hippocampus had a profound effect on the LFP patterns in the intact hippocampus and also reduced the number of IEDs, but whether or not we can isolate the effect to a single region of the hippocampus is yet to be determined. Surprisingly, tonic enhancement of inhibition exerted a relatively small effect on afterdischarge duration, despite the increased time to develop a fully kindled state. These findings suggest that afterdischarges depend on mechanisms other that disinhibition. The mechanisms underlying physiological and epileptic changes are under investigation.

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**Poster**

**786. Cortical and Hippocampal Circuit Interactions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 786.08/III28

**Topic:** H.01. Animal Cognition and Behavior

**Support:** R01MH107396-01
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U01NS099705

**Title:** Non-invasive modulation of neural activity by application of an external electric field

**Authors: *O. YAGHMAZADEH**, G. BUZSÁKI
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**Abstract:** Non-invasive neural modulation by external stimulus has always been of great interest in neuroscience, for both research purposes as well as development of potential curative methods. Because spiking activity of neurons is controlled by the membrane potential, electromagnetic fields can bias their timing and rate. Therefore, inducing changes to the extracellular potential by imposition of an electric field inside the brain can modulate the neural activity.
In the recent years transcranial Electrical Stimulation (tES) has gained increasing interest in neural modulation for both animal research and clinical studies with a variety of outcomes. However, tES requires wearable electrodes and a gel interface which deteriorates over time. Besides inconvenience, it is not practical for long-term stimulation, such as overnight sleep.
To overcome these limitations of tES, we attempt to induce an electric field inside the brain by contactless application of an external electric field. Although pioneering studies have claimed measurable impact of electromagnetic fields induced by radiofrequncy stimulation on neural activity, no direct evidence of such effect on single cell neurons has been reported. Here, we aim to demonstrate modulation of spiking activity of neurons *in vivo*, measured by extracellular silicon-probe recording, as a result of exposure to an external electric field. Using a TEM Cell antenna, uniform Electric field with intensities higher than 400V/m are applied. The animal under test, either in sleeping state or under anesthesia, is placed inside the antenna. Stimulation is applied at 3-sec intervals separated by 3-sec of no stimulation. Neural spiking rates are used as a measure of modulation induced by the stimulation compared to activity during no stimulation.

**Disclosures: O. Yaghmazadeh:** None. **G. Buzsáki:** None.

**Poster**

**786. Cortical and Hippocampal Circuit Interactions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 786.09/III29

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Large-scale intercortical interactions during sleep

**Authors: *D. KHODAGHOLY**[1], J. GELINAS[2], G. BUZSAKI[3]
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**Abstract:** Large-scale recording from neural networks and their interactions is critical for understanding how information is processed and transmitted in the brain. Coupling between specific limbic and cortical brain regions is implicated in aspects of memory acquisition, consolidation, and retrieval, but how these interactions are coordinated over topographically diverse functional networks during online task performance and in offline states is unclear. Here we demonstrate large-scale temporal coupling and pattern of oscillatory activity between primary sensory and association cortices interactions by simultaneous acquisition of local field potential (LFP) and spiking activity from a large part of the dorsal cortical surface and multiple locations in the hippocampus in rats. We investigate the spatiotemporal interactions of the hippocampus with diverse functional cortical regions, as well as the physiological interactions of these cortical regions with each other. Moreover, we define the neuronal volumes involved in generation of LFP oscillations with varied frequencies and determine their capacity for traveling and sequence of occurrence across the cortical surface. The ability to acquire and analyze LFP simultaneously from multiple functionally distinct brain regions will enhance comprehension of neural network processes and has implications for brain disorders characterized by disordered network function such as epilepsy.

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**Poster**

**786. Cortical and Hippocampal Circuit Interactions**

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**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 786.10/III30

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Maturation of communication between primary and association cortices across development

**Authors: *J. GELINAS**[1], D. KHODAGHOLY[2], C. MAYER[3], G. POUCHELON[4], S. DOMINGUEZ[1], G. J. FISHELL[5], G. BUZSAKI[6]
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**Abstract:** The brain's ability to support cognitive processes, such as perception, attention, and memory, represents a critical evolutionary advancement. Neural networks underlying cognitive processes are characterized by bidirectional communication between numerous brain regions, allowing integration and advanced processing of multimodal sensory information. Here, we examine the maturation of information transfer between primary sensory cortices and association cortices. For this purpose, we use outbred mice from postnatal day 5-14 to perform in vivo electrophysiologic recordings. We acquire neural signals with a novel advanced neural interface device, the NeuroGrid, which permits minimally invasive, high spatiotemporal resolution recording, in combination with an immunohistochemical analysis to anatomically localize the recording electrodes. Primary and association cortices display similar increases in signal continuity and power spectra peaks across development. These regions begin to synchronize intra-regional oscillatory activity on fine-time scales by the middle of the second week of life, but cross-regional coupling is established based on regional identity. These data allow us to better understand the neurophysiologic patterns that characterize normal maturation of large-scale cortical communication.

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**Poster**

**786. Cortical and Hippocampal Circuit Interactions**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 786.11/III31

**Topic:** H.01. Animal Cognition and Behavior

**Support:** R01MH107396-01

**Title:** Investigating hippocampo-cortical dialogue using wide-field calcium imaging and electrophysiology *in vivo*

**Authors: *R. A. SWANSON**[1], J. BASU[2], G. BUZSAKI[3]
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Institute, New York Univ. Sch., New York, NY; [3]New York University, Sch. of Med., New York, NY

**Abstract:** Systems consolidation is a proposed process by which recently learned information is gradually transferred from labile hippocampal (HPC) circuits to distributed networks in the neocortex (CTX). The mechanisms underlying consolidation are thought to rely on the spontaneous replay of task-related patterns of neural activity in HPC and CTX during "offline" periods of quiet wakefulness and sleep, and are facilitated by HPC sharp-wave ripple events (SPW-Rs). Recent findings suggest that SPW-Rs are temporally aligned with the transient reorganization of whole-brain dynamics: (i) in electrophysiological recordings, SWRs are coordinated with local reactivation of task-relevant patterns of spiking activity in lower- and higher-order cortical regions; (ii) in whole-brain fMRI, SPW-Rs coincide with an increase in BOLD signal across nearly all cortical regions. However, due to the spatial limitations of extracellular physiology and the temporal limitations of the BOLD signal, the regional dynamics of neocortical activity during SPW-Rs are unknown.
We developed a preparation that combines wide-field calcium imaging of the dorsal cortical hemisphere with simultaneous high-density silicon probe recordings in HPC and retrosplenial cortex (RSC). By comparing simultaneous RSC electrophysiology and wide-field fluorescence, we found that the wide-field signal was a reliable indicator of neocortical multi-unit activity during periods of behavioral quiescence. Thus, this preparation allows us to investigate the relation between HPC SPW-R and CTX local and global spiking dynamics with high spatiotemporal precision. Preliminary results revealed an average increase in activity in posterior and midline association CTX areas during SPW-Rs recorded in dorsal CA1 of the HPC, mirroring known hippocampo-cortical anatomical connectivity. Current investigation focuses on the temporal coupling of a subset of SPW-Rs to transitions from a regime of high (UP state) to low (DOWN state) spiking activity in RSC. SPW-R-locked UP->DOWN transitions are preceded by a significantly greater increase in activity in posterior midline cortices than those with no preceding SPW-R. Our results suggest that increased activity in a subset of CTX regions increases both the probability of dorsal SPW-Rs in HPC and sensitivity of these CTX regions to perturbation by SPW-Rs. Together, these findings represent progress towards understanding whole-brain dissemination of hippocampal information to associational cortical areas.

**Disclosures: R.A. Swanson:** None. **J. Basu:** None. **G. Buzsaki:** None.

**Poster**

**786. Cortical and Hippocampal Circuit Interactions**

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**Topic:** H.01. Animal Cognition and Behavior

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**Title:** Location-contingent medial septum activation causes the remapping of hippocampal CA1 place fields

**Authors: *V. VARGA**[1,2], P. C. PETERSEN[3], G. BUZSAKI[3]
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**Abstract:** Location encoding by hippocampal place cells is important for mapping the environment. How place fields emerge and change is not known. Changing synaptic weights or inducing dendritic plateau potentials in pyramidal cells has been shown to induce place fields. It is less known though how subcortical input to the hippocampus contribute to the stabilization and plasticity of the place map. We optogenetically activated all medial septum (MS) neurons at specific locations in a T-maze while recording hippocampal neurons in the dorsal CA1. We hypothesized that the combination of rhythmic disinhibition of pyramidal neurons and release of acetylcholine by activating MS GABAergic and cholinergic neurons, respectively, will affect place fields. MS stimulation resulted in the remapping of location-specific place cell firing. Both emergence of new place fields and disruption or alteration of existing fields were observed. The extent of remapping was quantified by correlating the pre-stimulation, stimulation and post-stimulation firing rate vectors of all putative pyramidal cells (n = 204 from 4 mice, to date) recorded on the maze. Place cell activity in pre- versus post-stimulation trials was significantly less correlated than stimulation-coincident and post-stimulation laps that suggesting long-lasting alteration of place-specific activity by the location-contingent activation of the MS. MS stimulation also affected locomotion in a context-dependent manner. During maze running, especially before the decision point, the movement of the animal decelerated during MS stimulation. In contrast, the same stimulation in the homecage induced head movement and locomotion. Our results suggest that the MS contributes to the maintenance and reconfiguration of the hippocampal networks.

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**Poster**

**786. Cortical and Hippocampal Circuit Interactions**

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**Topic:** H.01. Animal Cognition and Behavior

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F32 MH107159

**Title:** Focal optogenetic activation reveals heterogeneous place field plasticity rules within and between hippocampal subregions

**Authors: *S. A. MCKENZIE**[1], D. F. ENGLISH[2], G. BUZSÁKI[1]
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**Abstract:** Memory recall likely depends upon changes in synaptic strength between neurons that were active during learning. Though this link between synaptic plasticity and recall is well established, less is known about how synaptic plasticity causes the reinstatement of particular neural representations. The fundamental challenge lies in the difficulty of studying synaptic connectivity while monitoring the activity of large numbers of neurons *in vivo*. Recently, we validated a statistical model that estimates connection strength by looking at the reliability of action potential transmission from pre- to postsynaptic neuron. With this tool, and recent advances in optogenetic control of small groups of neurons, we tested how depolarization of neurons in CA1, CA3 and the dentate gyrus affects neuronal synchronization and place field tuning. As mice (CaMKII-Cre::Ai32) ran laps on a linear track, fixed-place optogenetic stimulation induced a heterogeneous pattern of remapping. Some stimulated neurons gained fields in the stimulated location or elsewhere, others lost fields, while the majority maintained their tuning despite repetitive, strong optogenetic drive. Non-light-driven CA1 neurons also showed remapping that coincided with the stimulation. Such light-induced remapping occurred to a lesser degree in CA3 and the dentate gyrus. In CA1, the light-activated neurons that showed place field remapping fired more during sharp-wave ripples, as compared to those neurons that increased firing with light but did not remap. This difference in ripple recruitment could be observed prior to optogenetic stimulation, suggesting a pre-existing bias for those neurons that will be susceptible to alterations in synaptic coupling. To explain the remapping in non-stimulated CA1 neurons, despite the lack of strong pyramidal-pyramidal recurrents, we are currently testing whether ripple-modulated, plastic pyramidal cells affect the rest of the CA1 population through changes in the pattern of feedback (lateral) inhibition. Together these experiments show a remarkable degree of heterogeneity of plasticity rules within and across hippocampal sub-regions.

**Disclosures: S.A. McKenzie:** None. **D.F. English:** None. **G. Buzsáki:** None.

**Poster**

**786. Cortical and Hippocampal Circuit Interactions**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 786.14/III34

**Topic:** H.01. Animal Cognition and Behavior

**Support:** Lundbeck Foundation Postdoctoral fellowship
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R01MH054671-14
U01NS099705
Independent Research Fund Denmark

**Title:** Theta rhythm perturbation by focal cooling of the septal pacemaker in awake rats and its effect on place cells

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**Abstract:** The theta rhythm coordinates neuronal activity in the hippocampus, entorhinal cortex and other areas involved in spatial memory. Theta oscillations are present during behaviour and sleep, and the power and frequency of theta increases with running speed (McFarland, 1974; Ravassard, 2013). Lesions and pharmacological inactivation of the medial septal area, has shown that the area is vital for theta rhythms in the hippocampus (Lawson and Bland, 1993; Vertes and Kocsis, 1997), it impairs learning and memory (Winson, 1978; Chrobak et al., 1989; Givens and Olton, 1994; McNaughton et al., 2006).Still it is not known what mechanisms generate the rhythm and what role the frequency and amplitude plays. Towards answering these questions, we have performed local thermal perturbation of the medial septum, to alter the frequency of theta. Temperature perturbation is a very powerful tool to study brain rhythms as they affect time-scales of natural occurring processes equally without applying any external dynamics.We implanted silicon probes in CA1 in hippocampus and a cooling probe in the medial septum in rats. The cooling effect was either attained using dry ice or a Peltier device, mounted in a cooling device on the head of the animal. The cooling-device was connected to a silver rod implanted in the medial septum, that was thermally isolated along the length to attain a focal effect of the cooling (Aronov and Fee, 2011). The animal performed alternating trials on a figure eight maze, with ongoing cooling sessions, for performance quantification and to allow us to study the effects on spatial neuronal activity in the hippocampus. We successfully lowered the theta frequency by 2Hz during behavior. We observed degraded performance during the cooling as the animal made more errors on the maze. We also observed increased running during the cooling, and typically also a temporary decrease in movement as the temperature reversed to normal

range. Further, we found a sharp drop in gamma power in the hippocampus as an effect of the cooling, an indicator of a lack of entorhinal input (Fernández-Ruiz et al., 2017). Finally, we recorded place cells in the hippocampus to learn how the altered theta rhythm affects phase precession.In summary, our results reveal that the theta rhythm can successfully be altered by cooling the medial septum, that it has behavioral effects and potentially leads to memory impairment.

**Disclosures: P.C. Petersen:** None. **G. Buzsaki:** None.

**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 787.01/III35

**Topic:** H.01. Animal Cognition and Behavior

**Title:** A whole brain atlas of the monosynaptic input targeting four different cell-types in the prefrontal cortex of the mouse

**Authors: *S. K. ÄHRLUND-RICHTER**, Y. XUAN, H. KIM, J. VAN LUNTEREN, M. CARLÉN
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**Abstract:** The prefrontal cortex (PFC) is pivotal to cognitive processing, and changed activity in the prefrontal network is thought to underlie symptomatology in neuropsychiatric disorders. Activity in the PFC is shaped both by the balance of inhibitory and excitatory actions in the local network and by long-range input from other brain areas. We designed a modified viral system for mapping of mono-synaptic input targeting neuronal populations of interest. We used the novel system to trace the input to three central populations of inhibitory interneurons (parvalbumin, somatostatin or vasointestinal peptide expressing) and to the excitatory (calcium/calmodulin-dependent protein kinase IIα expressing) neurons, respectively, in the medial PFC. Using the software suite developed in our earlier publications we have characterized the long range inputs to all four neuron types, and also the local inputs from the PFC network. The main input to both excitatory and inhibitory neurons in PFC is derived locally, but all four types also receive extensive long-range input from the rest of cortex and sub-cortical areas. With our new viral system we could also map local connections between cell types in the PFC to investigate the local network. To this end, we have characterized, in a whole-brain and local manner, the neuronal populations that give input to, i.e., provide information to the neurons in the PFC. This information will be used in subsequent studies for targeting and manipulation of specific identified circuitry, as to bring understanding of how different brain regions interact with the PFC to shape cognition, and our behavior.

**Disclosures: S.K. Ährlund-Richter:** None. **Y. Xuan:** None. **H. Kim:** None. **J. van Lunteren:** None. **M. Carlén:** None.

**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 787.02/III36

**Topic:** H.01. Animal Cognition and Behavior

**Support:** DARPA W911NF-14-2-0043

**Title:** Caudate stimulation modulates value coding dynamics in corticostriatal circuits

**Authors: *S. R. SANTACRUZ**[1,2], E. L. ZIPPI[2], J. M. CARMENA[1,2]
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**Abstract:** Decision-making is a critical process that allows people to achieve goals in a multitude of scenarios and is indispensable for healthy behavior. In humans, dysfunctional decision-making and reward processing are symptoms of many neuropsychiatric disorders, such as anxiety disorders, major depressive disorder, and schizophrenia. Determining the neural circuitry that drives flexible decision-making is thus extremely relevant to understanding the spectrum of healthy and pathological behaviors. To date, considerable evidence has demonstrated that the prefrontal cortex and striatum support flexible choice behavior, but the precise mechanisms responsible for integrating and updating value information remain unclear. 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 this work, we applied unilateral microstimulation in the caudate nucleus of two rhesus macaque subjects to selectively mediate decision-making during a free-choice probabilistic reward joystick task. 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 hypothesize 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. Notably, firing rate activity of these units around the time of stimulus presentation was significantly modulated post-stimulation. This modulation was stimulus-specific and value-specific, and occurred in the absence of baseline changes in firing activity. Together with behavioral data, this suggests that modulation of neural value signals underlie behavior bias induced with Cd electrical stimulation.

**Disclosures: S.R. Santacruz:** None. **E.L. Zippi:** None. **J.M. Carmena:** None.

**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 787.03/III37

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NHMRC ECF 1122221
Wellcome Trust Senior Investigator Award

**Title:** Shifting roles of the dorsal striatum in action sequence learning

**Authors: *K. TURNER**[1,3], A. SVEGBORN[2], T. W. ROBBINS[4]
[1]Dept. of Psychology, [2]Univ. of Cambridge, Cambridge, United Kingdom; [3]Sch. of Psychology, Univ. of New South Wales, Sydney, Australia; [4]Univ. Cambridge, Cambridge, United Kingdom

**Abstract:** A shift in control from the medial to the lateral regions of the dorsal striatum occurs as behaviours become more habitual or skilled. The aim of this study was to determine the role of the dorsal striatum sub-regions in the acquisition of a skilled sequence task and to examine the role of dopamine D1 and D2 receptors during expression of well-trained sequences. We have a developed a five-step sequential nose poke task in rats for measuring initiation, execution and termination of skilled action sequences. We found that lesions to the dorsolateral striatum (DLS) impaired acquisition of sequencing, however lesions to the posterior dorsomedial striatum (pDMS) enhanced learning of action sequences. These results support suggestions of parallel processing in the medial and lateral sub-regions, whereby the DLS supports rigid habit-like responding while the DMS promotes flexible response patterns, and we show that sequence learning occurs more rapidly with DMS loss of function. Furthermore, DLS lesions delayed sequence initiation without impacting on reward collection latency, suggesting a deficit in self-initiated actions rather than a motivational or motor impairment. In a separate cohort of well-trained rats, we examined the role of dopamine D1 and D2 receptors via local infusions in the pDMS and DLS on sequencing actions. Firstly, DLS inactivation produced sequencing deficits similar to that observed in lesioned rats, however there were no changes associated with pDMS inactivation. Infusions of D1 and D2 antagonists did not alter behaviour in either sub-region, however the D2/D3 receptor agonist quinpirole increased errors at a low dose and reduced sequences at the high dose when infused into the DLS. The ballistic motor response pattern observed on this task was largely untouched by these manipulations, suggesting execution of refined motor skills is not reliant on dorsal striatal circuitry. Therefore, action sequence learning is accelerated in the absence of the pDMS and impaired by DLS lesions, with expression of trained sequences also dependent on DLS and particularly D2/D3 receptor function. Using a

novel heterogeneous sequencing task, these results shed light on the dissociable role of the dorsal striatum sub-regions in sequence learning and skilled motor actions.

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**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 787.04/III38

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant EY015387

**Title:** tDCS alters neuronal activity and LFP synchrony in the primate prefrontal cortex and the frontostriatal network

**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 form of neuro-stimulation that has gained popularity as a clinical tool for the treatment of neuropsychiatric disorders. Despite growing interest in this technique, we know little about the mechanisms by which tDCS might work, and, more specifically, how it affects neurophysiology. Previous studies have suggested that tDCS can modulate cortical excitability in a polarity-dependent fashion, such that anodal stimulation is thought to increase cortical excitability, whereas cathodal stimulation may decrease it. Here, using multi-electrode intracranial recordings in awake behaving monkeys, we show that tDCS applied in the proximity of the prefrontal cortex (PFC) can enhance spiking activity (MUA) and LFP synchrony in the ipsilateral PFC and caudate nucleus (CAUD). We find that neurophysiological effects of tDCS depend on polarity (anodal/cathodal), intensity of stimulation (0.5, 1, 1.5 mA), and on the location of the return scalp electrode. Moreover, we find a transient, parameter-dependent increase in MUA in both PFC and CAUD following stimulation onset, which plateaus after the first 5 s of tDCS. Finally, we find that tDCS can enhance the frequency-dependent LFP synchrony (pairwise phase consistency) between the PFC and CAUD, primarily in the beta and lower-frequency bands. Together, these results support the effectiveness of tDCS to modulate neuronal activity and functional connectivity in the frontostriatal network.

**Disclosures: S.E. Seidl:** None. **C. Ranganath:** None. **W.M. Usrey:** None. **E.G. Antzoulatos:** None.

**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 787.05/III39

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Chronic social defeat stress enhances dorsolateral striatal-dependent response learning

**Authors: T. M. GADBERRY**[1], E. L. VIEREGG[1], O. K. SIAL[2], L. F. PARISE[2], C. A. BOLANOS-GUZMAN[1], *M. G. PACKARD[3]
[1]Psychological and Brain Sci., [2]Institure for Neurosci., Texas A&M Univ., College Station, TX; [3]Texas A&M Univ. Dept. of Psychology, College Station, TX

**Abstract:** Extensive evidence indicates that *acute* exposure to several different types of stressors including anxiogenic drugs, predator odor, and fear-conditioned stimuli enhances the acquisition of dorsolateral striatal-dependent response learning in various plus-maze tasks. However, the effects of *chronic* stress on DLS-dependent habit learning and memory is largely unknown. Therefore, the present study examined the effects of chronic social defeat stress (CSDS) on the subsequent acquisition of response learning. Adult male C57BL/6J mice (*n*=5) were exposed to CSDS over 10 days using aggressive CD1 mice, while control mice (*n*=5) were handled daily. Mice 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, mice 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 in order to mount a hidden escape platform. Relative to control mice, animals previously exposed to CSDS were significantly enhanced in task acquisition. Taken together with previous research, the findings suggest that both acute *and* chronic exposure to stress/anxiety facilitates the acquisition of DLS-dependent response learning. Increasing evidence has implicated a role for the dorsal striatal habit memory system in numerous psychopathologies (e.g. drug addiction, OCD, PTSD), and the development and expression of maladaptive habitual behaviors in these disorders can be influenced by stress/anxiety. Thus, social defeat stress may provide a useful translational paradigm for further investigation of the neurobiological mechanisms through which robust emotional arousal enhances habit learning and memory.

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**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 787.06/III40

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant 1P20GM113131-01A1

**Title:** Subregions of the prefrontal cortex differentially project to the anterior and posterior dorsomedial caudate-putamen

**Authors: *C. L. ROBISON**, T. N. KAZAN, S. CHARNTIKOV
Dept of Psychology, Univ. of New Hampshire, Durham, NH

**Abstract:** The dorsal caudate putamen (dCPu) is a subcortical structure involved in an array of Pavlovian and operant behaviors. Part of the dCPu's function derives from its extensive interaction with prefrontal cortical regions. The dorsomedial CPu (dmCPu) is especially important for goal-directed behaviors, but experimental evidence indicates that this importance varies along an anteroposterior axis. Here, we use retrograde tract tracing using traditional fluorogold and novel DREADD approaches to demonstrate that the anterior and posterior portions of the dmCPu differ in the inputs they receive from prefrontal cortex subregions. While both anterior and posterior dmCPu receive bilateral prefrontal afferents, with the majority coming from the ipsilateral side, the posterior dmCPU projects more extensively to the infralimbic and prelimbic subregions. Given the role of these cortical regions in decision-making and behavioral flexibility, our findings may provide critical information for studies investigating the role of corticostriatal projections in these behaviors.

**Disclosures: C.L. Robison:** None. **T.N. Kazan:** None. **S. Charntikov:** None.

**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 787.07/III41

**Topic:** H.01. Animal Cognition and Behavior

**Title:** *In vitro* and vivo characterization pf-8180824a novel α2/α4 subtype-selective positive allosteric modulator of nicotinic acetylcholine receptors

**Authors: *R. KOZAK**[1], P. TIERNEY[2], M. D. GRANNAN[3], M. WEBER[2], K. DIULGOLENSKI[2], G. BORA[2], E. BELOVA[2], E. GUILMETTE[1], J. LITCHFIELD[2], L. STEVENS[2], Q. YANG[2], J. T. LAZZARO[2], L. ZHANG[2], J. B. TUTTLE[2]
[1]Biogen Inc., Cambridge, MA; [2]Pfizer Inc., Cambridge, MA; [3]Aquinnah Pharmaceuticals, Cambridge, MA

**Abstract:** Nicotinic acetylcholine receptors composed of α4β2 subunits are the most widespread nicotinic receptors in the brain and are involved in sensory processing, memory, cognition, and mood regulation. Enhancing activity at these receptors by positive allosteric modulation is of therapeutic importance for a number of cognitive deficits. α4β2 PAMs theoretically permit higher receptor occupancy, more efficient channel opening, prevent short and long-term desensitization, and may therefore overcome many of the significant challenges that have historically limited their therapeutic potential. In this study, a novel class of α4β2 PAMs were identified that have good activity and selectivity and share a common pharmacophore that consists of an ionizable basic amine proximal to a hydrogen bond donor with a hydrophobic tail. The lead compound PF-06180824 produced a significant leftward shift in concentration response curves in automated planar single cell patch clamp (IonWorks Barracuda; $EC_{50}$ 1 BμM), good intrinsic activity ($E_{max}$) and no agonist activity. In addition, this compound has good metabolic stability, a clean off-target profile, and good brain penetration that warranted further in vivo characterization. PF-06180824 potentiated electrically evoked dopamine (DA) release in the ventral striatum, using ex vivo fast-scan cyclic voltammetry, but only in the presence of a GABA-B antagonist, and significantly increased hippocampal granule cell firing rate in awake, behaving mice when measured by optical calcium imaging using a genetically encoded $Ca^{2+}$ indicator for GCaMP6. Overall these results confirm PF-06180824 as a viable pharmacological tool to further investigate the full therapeutic potential of this mechanism.

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**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 787.08/III42

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Temporal information processing in the monkey striatum: Dissociable roles of projection neurons and cholinergic interneurons in interval timing performance

**Authors: *A.-C. MARTEL**, P. APICELLA
CNRS, Inst. de Neurosciences de la Timone, Marseille, France

**Abstract:** Previous theoretical and experimental studies emphasize the role of the striatum in time perception. However, we lack information about how temporal representations are achieved at the level of distinct components of the striatal circuitry which can be electrophysiologically identified, namely phasically active neurons (PANs) and tonically active neurons (TANs), thought to be GABAergic projection neurons and cholinergic interneurons, respectively. To address this issue, we examined the influence of interval timing performance on striatal activity in two macaque monkeys performing reaching movements toward a visual target under two situations: one in which animals initiated the movement when they estimated that a given time interval has elapsed (duration estimation task, DET), and the other in which the movement was triggered by an external stimulus presented at the end of the same interval (temporal prediction task, TPT). In each situation, there were two visually-cued intervals (*short* and *long* in the seconds range) which varied randomly during a trial block, the two situations being tested separately. We recorded neurons that met criteria for PANs (n=262) and TANs (n=232). We focused here on PAN activations occurring during the early 0.5 s of the interval and during 0.5 s before triggered (TPT) or self-timed movements (DET). The fractions of PANs activated during these periods were 27% and 34% in the TPT and DET, respectively. We identified PANs that showed an effect of situation (21%), interval duration (15%), and both (14%). Changes in TAN activity contrast with those of PANs, consisting mostly of brief pauses in firing in response to the cue in 35% of recorded TANs. The pause magnitude was differentially modulated by the situation or interval duration, reflecting the constraints on timing performance or the accuracy of temporal prediction. These results suggest that temporal information is processed quite differently by the two neuron types. Cholinergic TANs act essentially as detectors of a stimulus associated with a specific time interval. The TAN signal would be needed to time upcoming behavioral events and to influence output neurons (PANs) that encode information about action and other task components, including the time elapsed since the TAN signal.

**Disclosures: P. Apicella:** None.

**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** National Institutes of Health Grant (1R01NS091037)
Israel Science Foundation Grant (770/17)

**Title:** Effects of chemogenetic activation of the dorsal striatum on brain wide functional connectivity and behavior

**Authors: *J. ASLEH**, O. RECHNITZ, N. COHEN, D. DERDIKMAN, I. KAHN
Technion – Israel Inst. of Technol., Haifa, Israel

**Abstract:** In the basal ganglia circuit, the striatum is the first integrator of cortical information receiving inputs from virtually all cortical structures. Hence, it is involved in motor, emotional and cognitive behaviors. Striatal medium spiny neurons (MSNs) are divided to two subpopulations, collectively comprising the direct and indirect pathways. Imbalance in activity of these pathways has been associated with pathologies such as Parkinson's disease, Huntington's disease, and autism spectrum disorder. To better understand the effects of striatal MSN disruption in these disorders, we characterized pathway-specific striatal MSN activation in mice by targeting MSNs of the direct (Drd1-cre) or indirect (A2a-cre) pathways, and selectively expressed Gq-DREADD, using cre-dependent viral vectors. We first checked the impact on striatal activity of DREADDs activation by Clozapine N-oxide (CNO) administration. We recorded this activity extracellularly in freely moving mice, and found that CNO caused modulation of spiking activity. Behaviorally, both genotypes, related to direct and indirect pathways, exhibited impaired motor coordination: Decreased time on the rod in the Rotarod test, decreased likelihood to move, and a tendency for asymmetrical rotation in the open field. To map brain-wide responses we subsequently used functional connectivity MRI (fcMRI) in head-fixed awake animals scanned over multiple sessions. Compared to controls, both genotypes showed increased corticostriatal correlation in areas densely connected to the striatum, predominantly the motor and somatosensory regions. Finally, we intend to combine the behavioral testing data-driven approaches such as multidimensional scaling (MDS) and dynamic analysis of resting state data to profile the effects of this manipulation. We expect that the outcome of this study will increase our understanding of disorders resulting from MSN disruption.

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**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 787.10/III44

**Topic:** H.01. Animal Cognition and Behavior

**Title:** The ventral striatum's role in reinforcement learning

**Authors: *C. TASWELL**[1], V. D. COSTA[2], S. HOANG[1], K. C. SCARIM[1], E. R. MURRAY[1], B. B. AVERBECK[2]
[1]Unit on Learning and Decision Making, [2]Section on Learning and Decision Making, NIH/NIMH, Bethesda, MD

**Abstract:** The ventral striatum (VS) plays a role in reinforcement learning, as part of a broader neural system. We have examined the range of learning processes to which it contributes, and have found that it plays a specific role in learning about rewarding images. To further assess the role of the VS in RL, we tested rhesus macaques with VS lesions on deterministic and stochastic two-arm bandit learning tasks with gains and losses. Most RL studies assessing the VS focus on appetitive learning, treating lack of reward as aversive. However, aversion comes in many forms, and losing accumulated rewards may differ from not gaining additional rewards. To examine this, we conditioned tokens as reinforcers in a task where animals could both gain and lose tokens. We ran four experiments; three used deterministic reinforcement and one used stochastic reinforcement. In all experiments, novel images were introduced at the beginning of blocks of about 100 trials, and the animals had to learn the gains or losses associated with each experiment. In the first deterministic experiment we introduced four images in each block which had associated outcomes of +2, +1,-1,-2 tokens. In the second experiment we added a cue with a value of 0 to the set (+2, +1, 0, -1, -2). In the third experiment mimicked the first, except 75% of the time, the outcome was the value of the cue, and 25% of the time, the outcome was 0. In the final experiment, -4 replaced -2 as the large token loss. The animals had to learn over trials, in each block, the outcomes associated with each cue, and choose the best cue in each trial. We fit 6 different RL models that varied in the number of free parameters used to model the choice behavior. All models were built around the Rescorla-Wagner RL value update equation. For both groups in each experiment, the AIC chose the simplest model. Examination of the fits showed that the model did not always accurately predict behavior, although it did well given the complexity of the task, particularly for control animals. To examine the fit of the model, we ran an ANOVA on each group separately to assess how well the models fit the behavior. Across the four experiments, the only condition where the monkeys' behavior significantly differed from model predictions was in the 2 v 1 condition for the VS monks. In the 2 v 1 condition, VS monkeys consistently performed worse than the RL model predicted. Across the four experiments, there were no other conditions where the monkeys' choice behavior significantly

differed from the RL model predictions, for either group. Thus, the VS does not play a general role in all forms of reinforcement learning, but plays a specific role in learning to select between rewarded outcomes.

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**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 787.11/III45

**Topic:** H.01. Animal Cognition and Behavior

**Support:** F32 MH110184-03
R01DA029150

**Title:** How does activity of D1R+ and D2R+ neurons in the dorsomedial striatum influence choice following learning?

**Authors: *K. DELEVICH**, B. HOSHAL, Y. ZHANG, S. VEDULA, C. HALL, A. G. COLLINS, L. E. WILBRECHT
UC Berkeley, Berkeley, CA

**Abstract:** Medium spiny neurons (MSNs) in the dorsomedial striatum (DMS) are thought to encode the value of possible actions, and optogenetic manipulation of the activity in these neurons has been shown to influence action selection in a lateralized context (Tai et al 2012). It is thought that trial and error learning alters the activity of DMS MSNs to promote selection of high value actions, yet it is not clear what differential roles are played by D1R bearing (D1R+) and D2 bearing (D2R+) MSNs. We hypothesized that D1R+ neurons would play a role in learned action value while D2R+ neurons would play a role in suppressing choice of low value actions or in regulating the balance of exploration and exploitation. We used DREADD (Designer Receptor Exclusively Activated by Designer Drug) technology and an odor-based multiple choice foraging task to test the role of D1R+ and D2R+ neurons in learned choice. We trained mice in an odor-action-reward association in which mice freely explored an arena with four pots containing distinctly scented shavings; only one pot contained an accessible reward. Once mice chose to dig in a pot, the trial was concluded. Through trial and error, mice learned to choose the pot with the accessible reward and to avoid the other three choices (to training phase criterion of 8/10 consecutive correct choices). Twenty four hours later, we selectively manipulated D1R+ or D2R+ neurons during a test phase via DREADD activation. During the test phase, we found that mice made more choices to unrewarded odors when D1R+ neurons were inhibited (hM4Di) or D2R+ neurons were excited (hM3Dq). When D2R+ neurons were

inhibited (hM4Di), choice behavior was comparable to mCherry controls. To better understand the underlying mechanisms driving the observed changes in cue-guided action selection, we modeled task data using reinforcement learning (RL) models. While standard RL models reliably captured test phase behavior in control mice, they failed to do so for D1-hM4Di and D2-hM3Dq groups. Models that featured a decay parameter that allows odor values learned during training to revert towards their naïve values improved the ability of RL models to capture the behavior of these mice. In particular, the D1-hM4Di group exhibited significantly different decay parameters compared to controls, consistent with DREADD induced disruption of learned odor values. Our results suggest that activity in D1R+ neurons in the DMS plays a role in storage or readout of cue-action-outcome associations. Finally, our data show learned suppression of low value choices, involving action suppression or "no-go" function, can be maintained even when activity in D2+ neurons in the DMS is inhibited.

**Disclosures: K. Delevich:** None. **B. Hoshal:** None. **Y. Zhang:** None. **S. Vedula:** None. **C. Hall:** None. **A.G. Collins:** None. **L.E. Wilbrecht:** None.

**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 787.12/III46

**Topic:** H.01. Animal Cognition and Behavior

**Support:** CONICYT-PCHA Fellowship Doctorado Nacional 2017- 21171609
FONDECYT N°1141088
FONDECYT N°1151478

**Title:** Neuronal correlates in the orbitofrontal cortex, nucleus accumbens, and dorsolateral striatum during delay discounting task

**Authors: *V. AZÓCAR**[1], R. FUENTES[2], J. A. FUENTEALBA[1]
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**Abstract:** Impulsive Choice is defined as the preference for a small but immediate reward over a large reward but with delay. A procedure to measure impulsive choice is the delay discounting task (DDT). In this paradigm, the subject makes choices between large delayed or small immediate reinforcer on each trial. Different areas in the brain has been associated to impulsive choice such as lateral oribitofrontal cortex (lOFC), the nucleus accumbens core (Nacc) and the dorsolateral striatum (DLS). The local field potential (LFP) is a measure of the brain activity that reflects the highly dynamic processing information across to several network areas. LFP has been associated to different brain functions such as visual attention, recall of memory, perception

and auditory working memory. **Despite the evidence regard to role of lOFC, Nac and DLS in impulsive choice, to our knowledge, there is no evidence about neuronal correlates within or across of these areas related to impulsive choice in a delay discounting task.** We study the neural correlates underpinning impulsive decision making using the DDT paradigm and electrophysiological recordings in freely moving animals. The DDT consists in five blocks comprising 12 trials each. The trial begins when the light turns on and after of random jitter (500-1100 msec) the levers appears. The random jitter was introduced in the protocol to dissociate the motor effect from the decision-making process. One lever was designate as the immediate lever (responding with 1 pellet) and the other one as the delayed lever (responding with 3 pellets). The recording electrodes arrays were implanted in both hemispheres at the following coordinate: lOFC +3,25 AP, ±2,8 ML, -5.5 DV; Nac +2,25 AP, ±1,2 ML, -7DV; DLS +0,2 AP, ±3,8 ML, -3,5 DV. The NAc, lOFC and DLS were continuously recording during the DDT task Our results show that 150 msec after of the light turn on there is an increase in delta band (0-4 Hz), theta band (4-8 Hz) and alpha band (8-12 Hz) in the Nacc and the OFC but not in the DLS. This increase is lower when the delay in the block is large and is not present during an omission. These novelty results suggest that in the increase in the low frequencies in the lOFC and the Nacc lies the representation of the future reward during the delay discounting task.

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**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** Five-Year CUNY Graduate Center Fellowship
CUNY Doctoral Dissertation Fellowship
NIDA, NIGMS SC1DA 034995

**Title:** Investigating the role of the direct pathway in goal-directed control of action sequences

**Authors: *E. GARR**[1], A. R. DELAMATER[2]
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**Abstract:** Goal-directed behavior is defined as the ability of actions to be guided by the anticipation of future consequences. It is known that goal-directed control depends on the functioning of the dorsomedial striatum (DMS). Within the DMS, the activity of the D1 medium spiny neurons (MSNs) of the direct pathway and the D2 MSNs of the indirect pathway are implicated in opposing patterns of activation when goal-directed behavior is exhibited. Following up on our previous work in which we investigated how goal-directed control

manifests itself in action sequences, we performed an experiment in which we investigated the role of the direct pathway in action sequence performance. To transiently disrupt the direct pathway during and/or after action sequence learning, we virally expressed Gi-DREADDs in the DMS of D1 Cre rats ($n$ = 40) and then injected CNO during and/or after training. There were four training groups: DREADD+CNO, DREADD+vehicle, mCherry+CNO, and mCherry+vehicle. The DREADD+CNO group performed fewer sequences early in training ($Fs(1,155) > 6.66$, $p < .05$) and were also slower to initiate ($Fs(1,82) > 5.98$, $p < .05$) and complete ($Fs(1,110) > 4.61$, $p < .05$) sequences compared to the control groups. However, the relative proportion of correct sequences did not differ between groups ($Fs(1,85) < 1.49$, $p > .05$). Follow-up extinction tests conducted after training showed that injecting the DREADD+CNO group with vehicle and the DREADD+vehicle group with CNO did not result in changes in performance, indicating that D1 MSNs in the DMS participate in action sequence performance only early in acquisition. Selective-satiation tests were then conducted. D1 MSN inhibition during training and/or test did not interfere with rats being able to suppress sequence performance during reward devaluation ($Fs(1,18) > 5.52$, $p < .05$; $Fs(1,37) > 7.87$, $p < .05$). However, unlike controls, rats for which D1 MSNs were functional during training but disrupted during test were not able to slow sequence initiation times when rewards were devalued (post-hoc contrast, $p > .05$). In other words, D1 MSNs contributed to goal-directed control of sequence initiation when they functioned normally during training. In addition, while controls failed to display devaluation effects on completion times, the slowing of sequence completion times during reward devaluation was spared in rats for which D1 MSNs were inhibited during training and test (post-hoc contrast, $p < .05$). This suggests that suppressing D1 MSNs during training preserves the expression of goal-directed sequence completion. The poster will also include data from a similar experiment using viral infusions in the dorsolateral striatum.

**Disclosures: E. Garr:** None. **A.R. Delamater:** None.

**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant MH081843
NIH Grant MH102211
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**Title:** Prefrontal corticotropin-releasing factor (CRF) neurons impair frontostriatal neural function via local receptor signaling

**Authors: *S. HUPALO**[1], A. J. MARTIN[1], D. M. DEVILBISS[2], R. L. JENISON[1], C. W. BERRIDGE[1]
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**Abstract:** The dorsomedial frontostriatal circuit supports higher cognitive processes that guide goal-directed behavior. We recently demonstrated that corticotropin-releasing factor (CRF) receptor activation in the caudal dorsomedial prefrontal cortex (dmPFC) impairs, while CRF receptor blockade improves frontostriatal-dependent working memory in rats. To address whether local CRF neurons are a source of CRF to the caudal dmPFC, we expressed hM3Dq- or hM4Di-coupled designer receptors (DREADDs) selectively in CRF neurons within this region. Chemogenetic activation of PFC CRF neurons using the DREADD ligand, clozapine-N-oxide (CNO; 0.3, 3 mg/kg) dose-dependently impaired performance in a delayed alternation test of spatial working memory. In contrast, chemogenetic suppression of this neuronal population improved working memory. The cognition-impairing actions of PFC CRF neuronal activation were prevented with intra-PFC infusion of a CRF antagonist (D-Phe-CRF; 100 ng) or a protein kinase A (PKA) inhibitor (Rp-cAMPs; 20 nM). Therefore, the cognitive actions of PFC CRF neurons are dependent on local CRF release and subsequent activation of CRF receptors in a PKA-dependent manner.
Additional studies examined the effects of PFC CRF neuronal activation on task-related activity of neuronal ensembles and local field potentials across the dorsomedial frontostriatal circuit in cognitively-tested animals. Animals were implanted with chronic recording electrodes in layer V of the dmPFC and the dorsomedial striatum (dmSTR). Chemogenetic activation of PFC CRF neurons (3 mg/kg CNO) suppressed task-related activity of putative dmPFC pyramidal neurons strongly tuned to delay and reward task events. Meanwhile, dmPFC neurons displaying no task selectivity (e.g. untuned neurons) were unaffected, indicating PFC CRF neuronal activation does not increase inhibitory tone non-specifically. Downstream in the dmSTR, we observed weaker inhibitory effects on delay and reward-related activity of putative medium spiny neurons. Lastly, these electrophysiological effects were associated with frequency-specific changes in delay- and reward-related oscillatory activity and functional connectivity within the frontostriatal circuit. Collectively, these results demonstrate that PFC CRF neuronal activity impairs higher cognitive function, an action associated with a robust suppression of PFC neuronal encoding of working memory and alterations in functional connectivity across the dorsomedial frontostriatal circuit.

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**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 787.15/III49

**Topic:** H.01. Animal Cognition and Behavior

**Support:** R01-DA029613

**Title:** Androgen receptor responsive afferents to the nucleus accumbens

**Authors: *L. B. DOKOVNA**[1], R. I. WOOD[2]
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**Abstract:** The nucleus accumbens (Acb) is an important structure in the mesolimbic dopamine (DA) pathway for decision-making, and reward and reinforcement learning. Androgens are rewarding (Sato et al., 2008), and supraphysiologic levels can modify decision-making involving DA activity in Acb (Wallin et al. 2015; Wallin-Miller et al., 2018). Androgens may alter behavior though their activation of the androgen receptor (AR), a classical genomic receptor. However, how androgens directly access Acb to alter decision-making remains poorly understood. The present study utilized enhanced immunohistochemistry to determine if ARs are found in Acb, and to evaluate the distribution of AR-positive afferents to Acb. Rats received iontophoretic injections of cholera toxin beta (CTB; 0.5% solution in 0.1M PBS) into Acb core or shell under stereotaxic guidance. One week later, rats were sacrificed, perfused, and their brains were sectioned on a freezing microtome at 40 μm in a series of 12. One series was stained for AR using a monoclonal anti-AR antibody [EPR1535(2)] raised in rabbit (1:200; ab133273; Abcam). To enhance AR immunoreactivity in brain regions with low AR density (e.g. medial prefrontal cortex, mPFC; Low et al.,2017), we performed antigen retrieval with sodium citrate buffer and 1% sodium borohydride, plus tyramide signal amplification. After initial incubation in the avidin-biotin complex (ABC), sections were exposed to 0.5% biotinylated tyramide for 10 min, followed by further ABC incubation. We found improved AR staining throughout the brain, including in Acb, particularly in the shell subregion. Additional AR staining was visible in CA1 of dorsal and ventral hippocampus, and in layers II/III of cortex, including the mPFC. Additional sections were stained for CTB (goat anti-CTB; 1:10,000, List Biological Laboratories) to identify Acb afferents. Inputs to the Acb shell were observed in CA1 of ventral hippocampus, the ventral tegmental area, the bed nucleus of the stria terminalis (BST), and mPFC, particularly in infralimbic cortex. Lastly, sections were double-labelled for AR and CTB. A small number of AR-positive afferents to Acb shell were found in infralimbic cortex. Abundant double-labeling was present in the CA1 region of ventral hippocampus and the BST. TSA-enhanced staining for AR revealed AR-positive neurons in Acb and demonstrated widespread AR-sensitive afferents to

Acb from cortical and subcortical regions. These findings suggest potential mechanisms through which androgens may modulate decision-making. Supported by NIH R01-DA029613 to RIW.

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**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 787.16/III50

**Topic:** H.01. Animal Cognition and Behavior

**Title:** Microinjection of histone deacetylase inhibitors into the striatum, but not the frontal cortex, facilitates the acquisition of timed performance

**Authors: S. A. YOUSEFZADEH**[1], P. V. AGOSTINO[2], *W. H. MECK[1]
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**Abstract:** Timed performance in the peak-interval (PI) procedure requires that mice learn a target duration (e.g., 20 s) and then set 'Start' and 'Stop' response thresholds centered around the target duration in order to maximize reinforcement and minimize energy expenditure. In the peak-interval procedure (PI), mice are presented with fixed-interval (FI) trials during which the onset of a tone reliably predicts the time at which reinforcement will be made available. In order to characterize the accuracy and precision of timing, un-reinforced probe trials are randomly intermixed within a session. Under these conditions, mice readily learn to start responding when they are "close enough" to the target duration and to stop responding when they are "far enough" away from the target duration. At present, there is little understanding about the molecular mechanisms underlying the acquisition of these 'Start' and 'Stop' response thresholds. Numerous studies have demonstrated a pivotal role for histone acetyltransferase CREB-binding protein in the epigenetic modification of memory and synaptic plasticity. Histone deacetylase (HDAC) inhibitors block the activity of histone deacetylases and thus increase histone acetylation, thereby facilitating learning and memory for a variety of behavioral tasks. As a consequence, the current experiment was designed to investigate whether microinjection of the HDAC inhibitors sodium butyrate (NaB) or Trichostatin A (TSA) into the cortex or striatum would facilitate the acquisition of the 'Start' and 'Stop' response thresholds in a 20-s PI procedure. Mice began training on a modified PI procedure in which different groups of mice (n=8) received microinjections of either NaB, TSA, or vehicle into the dorsal striatum (DS), ventral striatum (VS), or the frontal cortex (FC) for 6 consecutive daily sessions. Following a 5-day recovery period, mice were retrained to determine whether there were any long-lasting effects of treatment. The results indicated a significant enhancement of the acquisition of the 'Start' response threshold for the mice receiving injections of NaB or TSA into the DS and significant enhancement of the 'Stop' response threshold for mice receiving injections of NaB or

TS into the VS. In contrast, no significant effects were observed for NaB or TSA injected into the FC. The enhancements observed in timed performance will be discussed in terms of the regulation of gene expression through acetylation and deacetylation of histone proteins in the striatum as well as the potential role of microtubule dynamics and cytoskeletal signaling.

**Disclosures: S.A. Yousefzadeh:** None. **P.V. Agostino:** None. **W.H. Meck:** None.

**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 787.17/III51

**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH intramural

**Title:** A novel device to measure effort, vigor, and persistence in rodents

**Authors: *B. A. MATIKAINEN-ANKNEY**[1], A. V. KRAVITZ[2,3]
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**Abstract:** Physical activity is one of the greatest indicators of health. Nuanced aspects of physical activity, such as effortful behaviors, have typically been studied in rodents through lever presses or nosepokes to obtain a reward. While these assays provide valuable information about the persistence exhibited by a rodent (i.e. how many lever presses an animal will execute in order to obtain a reward), they do not reveal information about the direct effort (force) or vigor (speed) of an animal's behavior. Yet motivation is associated with alterations in effort and vigor: rodents increase the force they will exert on a lever to obtain larger rewards (effort), and will increase their speed of responding to obtain increasingly palatable rewards (vigor). As such, there is a need for behavioral testing apparatuses that elucidate these additional parameters of physical activity. We developed a novel device to measure force, speed, and frequency of lever pressing movements, thus providing information about effort, vigor, and persistence, respectively. Going forward we hope to use this device in concert with accumbal neural data (photometry, electrophysiology) collected from obese and lean mice to understand how obesity affects both physical activity and underlying neural circuits, and to develop a more informed model of the persistent effects of obesity.

**Disclosures: B.A. Matikainen-Ankney:** None. **A.V. Kravitz:** None.

**Poster**

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**Program #/Poster #:** 787.18/III52

**Topic:** H.01. Animal Cognition and Behavior

**Support:** National Institute of Healthgrants R21 HD HD070611
R01 MH104603-01

**Title:** Examining the role of 5a-reductase in depression and antidepressant effects of exercise

**Authors: *A. L. GOIN**[1], S. SCHEGGI[1,2], M. FAGAN[3], P. THOMPSON[4], M. BORTOLATO[1]
[1]Univ. of Utah, Salt Lake City, UT; [2]Mol. and Developmental Med., Univ. of Siena, Siena, Italy; [3]Psychiatry, Texas Tech. Univ., Lubbock, TX; [4]Psychiatry, Southwest Brain Bank Mood Disorder, San Antonio, TX

**Abstract:** Neuroactive steroids have been shown to participate in the regulation of mood, yet the specific involvement of these mediators in the pathophysiology of depression remains unclear. Our lab has specifically investigated the potential implication of 5α-reductase (5αR), a key rate-limiting enzyme of neurosteroid and androgen synthesis, in depression. Building on preliminary evidence that 5αR inhibition has been associated with depressive symptoms in vulnerable patients, we first examined the expression of its two major isoenzymes in post-mortem brain samples from depressed subjects. Our initial results show that 5αR expression is significantly reduced in the prefrontal cortex and nucleus accumbens of depressed subjects, as compared with non-affected controls. Strikingly, we also documented that 5αR expression was reduced in the same regions of rodents subjected to chronically stressful manipulations aimed at reproducing depression-like manifestations. Building on these premises, we hypothesized that the well-documented mood-enhancing and antidepressant effects of physical exercise may reflect the involvement of 5αR. Accordingly, previous work has shown that exercise increases 5αR2 levels and its key product dihydrotestosterone (DHT), the main androgenic metabolite of testosterone; notably, DHT may facilitate adult neurogenesis, one of the core mechanisms whereby physical exercise is thought to exert antidepressant effects. Ongoing studies in the lab are testing the effects of voluntary wheel running in 5α-reductase 1 and 2 knockout mice, and analyzing the differential impact of this exercise on their behavioral responses, as well as neurogenesis.

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**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** NIH Grant R01 EY-022411
Penn Medicine Neuroscience Center Pilot Program
Hearst Foundation Fellowship

**Title:** Caudate neurons represent a confidence-like signal in a reward-biased perceptual decision-making task

**Authors: *Y. FAN**[1], T. DOI[2], J. I. GOLD[1,3], L. DING[1,3]
[1]Neurosci. Grad. Group, Univ. of Pennsylvania, [2]Neurosci. Dept., [3]Neurosci. department, Univ. of Pennsylvania, Philadelphia, PA

**Abstract:** The brain often combines sensory and reward information when making decisions. One possible site of this combination is the caudate nucleus, which encodes a diversity of relevant signals. For example, caudate neurons encode information about stimulus identity and strength in tasks with stimulus manipulations and information about reward context and expectation in tasks with reward manipulations. Our goal is to identify how individual caudate neurons may contribute to combining sensory and reward information in the context of decisions that depend on both. We recorded single-unit activity of 121 caudate neurons in two monkeys performing an asymmetric-reward motion discrimination saccade task. The monkeys' decisions and reaction times (RT) reflected both motion strength and reward asymmetry. Using multiple linear regressions, we identified "combination" neurons whose average firing rates were jointly modulated by reward and motion strength (33, 40 and 56 neurons during motion-viewing, peri-saccade and post-saccade epochs, respectively). We examined how activity of these neurons relates to choice confidence, a key computational quantity for decision formation and evaluation, which is estimated as the reward-dependent probability of the chosen option being correct, given the observed RT. Using a separate linear regression with confidence and choice as regressors, we found that firing rates were modulated by confidence in a majority of the "combination" neurons (17, 28 and 33 neurons, respectively). In theory, decision formation-related confidence differentiates between choices such that increasing confidence for one choice means decreasing confidence for the other. In contrast, evaluation-related confidence reflects a general prediction of receiving reward later on, regardless of choice identity. During the motion-viewing epoch, 65% of confidence-modulated neurons showed opposite signs of confidence modulation for the two choices, consistent with decision formation-related confidence. During the peri-saccade and post-saccade epochs, the majority of neurons showed the same sign for both choices, consistent

with evaluation (68% and 61%, respectively). Such post-decision activity is often associated with choice bias in the next trial. Only four neurons showed confidence modulation both before and after a decision. These results suggest that, on the single-neuron level, many caudate neurons encode reward, motion strength, and time-dependent confidence; on the population level, contributions of confidence-encoding caudate neurons may transition from formation of current decision to evaluation that influences future decisions.

**Disclosures: Y. Fan:** None. **T. Doi:** None. **J.I. Gold:** None. **L. Ding:** None.

**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 787.20/III54

**Topic:** H.01. Animal Cognition and Behavior

**Support:** Canadian Institutes of Health Research (T.W.). CIHR Grant MOP_102482

**Title:** Distinguishing putative interneuron classes in macaque fronto-striatal circuit during goal-directed behavior

**Authors: *K. BANAIE BOROUJENI**[1], T. WOMELSDORF[1], S.-A. HASSANI[1], M. OEMISCH[2]
[1]Vanderbilt Univ., Nashville, TN; [2]Yale Univ., New Haven, CT

**Abstract:** Neural information flow through the striatum depends on the functional specialization of distinct interneuron classes. A large majority of interneurons is believed to realize pathway specific routing for Go- versus No-Go decisions, while other classes of interneurons are implicated to gate inputs (fast spiking interneurons), or modulate local circuit activity in yet unknown ways (e.g. cholinergic interneurons, persistent and low threshold spiking interneurons, fast adapting interneurons, and neurogliaform cells). So far, there is no technology available to study the specific functional contributions of these neurochemically defined interneurons in the awake behaving nonhuman primate brain. Here, we set-out to overcome this limitation and propose an approach to define striatal interneurons not by their neurochemical profile, but by their activity dynamics and spike waveform characteristics during actual reward-based learning. We hypothesized that we can distinguish multiple cell classes based on their unique activity dynamics that were previously reported for striatal interneurons in the slice and in the rodent model. To test this hypothesis, we measured in vivo extracellular activity of >800 single cells in frontal and striatal areas of the nonhuman primate and identified how cells differ in those directly observable, which are cells' action potential shape, their firing rate, their global variability of firing, as well as their temporally local patterning of firing. Using these cell features in a data driven cluster analysis, we distinguish seven different cell classes in the striatum. We reliably

extract a subclass of regular firing interneurons with higher firing rates and repetitive, stuttering spiking, a subclass of regular firing interneurons with a moderately high sustained rate, as well as subclasses with bursty and irregular firing patterns. These findings demarcate the boundaries of functionally distinct cells that may partly map onto cells labeled neurochemically and may allow identifying unique functional specializations of cells during reward-based learning and action selection. We validate our approach by clustering eight cell classes in the frontal cortex and reproducing reliable cell class boundaries in our new dataset compared with an independent earlier dataset recorded during a feature-based attention task. In summary, we show that extracellular recordings can be used to distinguish cell classes based on their firing patterns and action potential dynamic. We propose these clusters could be putative representors of the main interneuron types in the striatum, based on known cell type specific dynamics from in-vitro work.

**Disclosures: K. Banaie Boroujeni:** None. **T. Womelsdorf:** None. **S. Hassani:** None. **M. Oemisch:** None.

**Poster**

**787. Animal Cognition and Behavior: Cortical and Striatal Circuits**

**Location:** SDCC Halls B-H

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**Topic:** H.01. Animal Cognition and Behavior

**Support:** Australian Postgraduate Award
Australian Research Council/Discovery Projects

**Title:** Direct pathway spiny projection neurons in the posterior dorsomedial striatum are necessary for goal-directed learning

**Authors: *J. PEAK**, G. HART, B. BALLEINE
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**Abstract:** It is now well accepted that the posterior region of dorsomedial striatum (pDMS) is necessary for learning goal-directed instrumental actions, however the role of pDMS spiny projection neurons (SPN), which project either directly (dSPNs) or indirectly (iSPNs) to basal ganglia output structures, in such learning remains largely unknown. In a series of experiments, we aimed to examine the role of dSPNs and iSPNs in the acquisition of goal-directed instrumental actions in rats. Our first experiment used double retrograde labelling in combination with an activity marker (zif-268/EGR1) to measure activity of dSPNs and iSPNs following instrumental or yoked, non-contingent training. Immunofluorescence quantification revealed significantly higher zif-268 expression in the pDMS following instrumental relative to yoked training in dSPNs but not iSPNs. Our second experiment examined whether dSPNs are

functionally required for goal-directed learning. We used a two-virus approach; retrograde AAV-Cre was infused bilaterally into the substantia nigra, and Cre-dependent hM4Di DREADDs was infused bilaterally into the pDMS to specifically express hM4D-DREADDs on dSPNs. Rats were trained on an instrumental lever press task, and prior to each training session, dSPNs were silenced with a systemic injection of clozapine-n-oxide (CNO; control rats received vehicle). We then conducted a drug-free test of goal-directed learning using an outcome devaluation test with specific satiety. We found that rats that had dSPNs in the pDMS silenced during training failed to show sensitivity to outcome devaluation despite restoration of that pathway on test. Our final experiment assessed whether we could replicate these effects by increasing iSPN activity, thereby shifting the balance of direct and indirect striatal output in the same direction. We used the same two-virus approach and instead infused AAV-cre bilaterally into the globus pallidus and Cre-dependent hM3Dq DREADDs bilaterally into the pDMS to express hM3D-DREADDs on iSPNs. We found that increasing iSPN activity during instrumental training, did not affect rats' sensitivity to outcome devaluation at test. Together, these results suggest that activity in dSPNs in the pDMS is necessary for learning goal-directed instrumental actions, and that disruption of goal-directed learning via inhibition of dSPNs is not simply due to a change in the balance of dorsal striatal output. Results will be discussed in terms of the relative involvement of direct and indirect pathway neurons in learning and performance of instrumental actions.

**Disclosures: J. Peak:** None. **G. Hart:** None. **B. Balleine:** None.

**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 788.01/III56

**Topic:** H.02. Human Cognition and Behavior

**Support:** NSF Award 0726113
NSF Award 0852636
NSF Award 1523614

**Title:** Perception and awareness of backward visual masking in a patient with bilateral frontal leucotomy

**Authors: *J. CHANOVAS**[1], H. RIEIRO[2], S. MARTINEZ-CONDE[1], E. GALLEGO[3], F. VALLE-INCLÁN[3], S. L. MACKNIK[1]
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**Abstract:** Visual illusions dissociate the observer's perception of a stimulus from its physical reality and are powerful devices in the search for the neural correlates of visibility. The reduction

or elimination of visibility of one stimulus (target), visible when presented alone, can be achieved by the presentation of another stimulus (mask) without changing the physical properties of the target. This illusion is known as visual masking and has been used extensively as a primary tool to isolate the neural circuits of visibility. Our visual masking studies have shown that transient neuronal responses in V1 associated with the onset and termination of the target are important in its visibility. Yet, imaging studies in humans show that circuits that maintain the visibility of simple targets are found in the occipital lobe beyond V1/V2. Some theories of conscious perception, moreover, suggest a role of parietal or frontal lobe processing. Despite the historically powerful role of brain-damaged patients in brain mapping, relatively few studies of consciousness have investigated brain damaged human patients. We assessed the contribution of frontal areas in the visibility of visual targets with one of the few remaining frontal leucotomy patients in the western world. J.R., a 73-year-old male who had most of his prefrontal cortex disconnected from the rest of the brain, after receiving a bilateral frontal leucotomy at the age of 22, was tested for his perception of visual masking stimuli and compared to a cohort of age-matched controls (n=30). Visual stimuli were presented on a computer screen and consisted of vertical bars, where the central bar (target) was abutted by two flanking bars (masks). The participants conducted multiple sessions of a two-alternative forced choice (2-AFC) task, in which they indicated the longest of two targets by either pointing at (J.R.) or touching (age-matched controls) the corresponding side of the screen. A key feature of this study was that, after making their choice for each trial, participants reported verbally whether the left versus right targets were ‘different’ or ‘equal’. Because the targets were never truly equal, targets that were reported ‘different’ were coded as visible to the participants, whereas targets that were reported as ‘equal’ must have been perceived as invisible. Whereas 2-AFC performance was equivalent for J.R. and the age-matched controls, J.R.’s verbal reports suggest that he may have never truly seen the targets in any condition. This suggests that frontal lobe damage results in a type of blindsight in which the patient can perform tasks based on visual inputs, despite not truly experiencing visual awareness of the targets.

**Disclosures: J. Chanovas:** None. **H. Rieiro:** None. **S. Martinez-Conde:** None. **E. Gallego:** None. **F. Valle-Inclán:** None. **S.L. Macknik:** None.

**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 788.02/III57

**Topic:** H.02. Human Cognition and Behavior

**Support:** ERC-2013-ADG “Perceptual Awareness”

**Title:** Neural basis of unconscious visual motion perception in hemianopia

**Authors: C. A. PEDERSINI**[1], A. LINGNAU[2], N. CARDOBI[1], J. SANCHEZ LOPEZ[1], S. SAVAZZI[1], *C. MARZI[3,1]
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**Abstract:** Hemianopia is a visual field defect characterized by impaired vision in one hemifield due to a lesion along the contralateral post-chiasmatic visual pathway. Despite loss of vision, some unconscious visual abilities ("blindsight") could be preserved, especially with moving stimuli that can activate extrastriate area V5 even in the absence of area V1. The main aim of this study is to detect existence and source of the neural activation observed following stimulus presentation to the blind hemifield and to assess its relationship with behavioral performance and perceptual awareness. In an fMRI study we tested a group of 9 hemianopic patients (3 females; mean age= 56.55, sd= 9.25) with different lesion sites and extents and a group of age-matched healthy participants during the execution of an orientation discrimination task with either moving or static stimuli. An awareness scale was used to collect information on the level of awareness in dynamic and static blocks. In the contrast of interest (dynamic - static) we carried out both a whole brain general linear model analysis, including age and sex as nuisance factors, and a region of interest analysis within functionally localized area V5. A correlation analysis was performed between brain activity and behavioral performance. Finally, both modulation of area V1 and integrity of white matter fibers were assessed to locate the main sources of activation of area V5. Fractional Anisotropy (FA) and Mean Diffusivity (MD) were extracted from the intact and damaged hemisphere from Optic Radiations, Lateral Geniculate Nucleus (LGN) - V5 tracts and Superior Colliculus (SC) - V5 tracts. Following blind hemifield stimulus presentations healthy participants showed an activation involving only bilateral area V5 whilst patients showed a widespread bilateral activation involving area V5, extrastriate areas and the posterior parietal cortex (PPC) along the dorsal stream. Interestingly, the bilateral activation of areas V5 was observed only in those patients who reported a higher level of awareness in the dynamic condition and was positively correlated with performance in the same condition. The negative BOLD signal observed in bilateral area V1 and the significant differences found in FA and MD between damaged and intact hemispheres in optic radiations and LGN - V5 fibers, demonstrated that the SC - V5 connection is likely to be the source of V5 activation in patients. Furthermore, we believe that the bilateral activation associated with a higher level of awareness in the dynamic condition and positively correlated with behavioral performance, is probably subserved by the pathway connecting the SC with V5 and PPC through the pulvinar.

**Disclosures: C.A. Pedersini:** None. **A. Lingnau:** None. **N. Cardobi:** None. **J. Sanchez Lopez:** None. **S. Savazzi:** None. **C. Marzi:** None.

**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 788.03/III58

**Topic:** H.02. Human Cognition and Behavior

**Support:** Grant-in-Aid for Scientific Research(B) 16H02839

**Title:** Back projection of visual stimulation onto heart rate during cardio-visual rubber hand illusion

**Authors: *A. YUMOTO**[1], S. SHIMADA[2]
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**Abstract:** The sense of self-body ownership relies on the representation of both interoceptive and exteroceptive inputs coming from our own body. The rubber hand illusion (RHI) can be induced by synchronous cardio-visual feedback on the self and a rubber hand. A previous study have reported that witnessing unexpected movement of the illusory embodied rubber hand is inversely influenced (back projected onto) the real hand, which is called back projection. In this study, we examined whether the heart rate could be influenced by changing the frequency of light flushing during cardio-visual rubber hand illusion. Ten healthy right-handed students (2 females; aged 22 ± 1.2 years) participated in this experiment. Each sessions involved the RHI phase and the subsequent back projection (BP) phase. During RHI phase (180 s), the participant watched the rubber hand which was flashed synchronously with the heart rate in the synchronous condition. In the asynchronous condition, the rubber hand was flashed by altering the heart rate to be faster (130%). The proprioceptive drift difference (PDD) was defined as the lateral difference in the reached positions before and after the RHI phase. During the BP phase (90 s), the participant watched the rubber hand flushed synchronously with the subject's pulse (similar to synchronous condition) for 30 s, and then the flush frequency was changed to be faster (130%) or slower (70%) in the successive 60 s. We measured the heart rate change between the first baseline period (0-30 s) and the BP period (60-90 s) in the BP phase. We found that RHI was induced in the synchronous condition in terms of PDDs (greater than zero) ($t(19) = 2.7$, $p < .01$). There was also weak but significant PDDs in the asynchronous condition ($t(19) = 1.9$, $p < .05$). For BP phase, the heart rate was significantly decreased in the sync_slow condition (smaller than zero) ($t(9) = 3.6$, $p < .01$), but not in other conditions ($p > 0.1$). There was a significant difference in the heart rate change between sync_fast and sync_slow conditions ($t(9) = 3.2$, $p < .01$). These findings indicate that participant's heart rate was decreased under the influence of the change in the frequency of light flushing on the rubber hand after having illusory body ownership. These results suggest that the back projection of visual stimulation onto heart rate can be induced by utilizing the rubber hand illusion.

**Disclosures: A. Yumoto:** None. **S. Shimada:** None.

**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 788.04/III59

**Topic:** H.02. Human Cognition and Behavior

**Support:** R01 DC007603
R01 DC014510

**Title:** Formant frequency discrimination in adults who stutter

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**Abstract:** Current theories of stuttering suggest that this disorder of speech fluency is associated with deficits in sensorimotor processes underlying speech movement production and active modulation of sensory systems. In this study, we examined whether deficits in the sensorimotor system of people who stutter also lead to differences in the perception of speech sounds. We recruited 14 adults who stutter and 14 age-, sex-, and handedness- matched nonstuttering adults. The experiment consisted of two conditions: real-time perception of self-produced sounds and perception of pre-recorded (but also self-produced) sounds. Each participant completed 4 blocks of each of the conditions. We used a two-interval forced choice paradigm to examine participants' sensitivity to auditory perturbation during active speech production and passive listening. In each trial of the active condition, participants were cued to produce two repetitions of a word presented on a computer monitor. In the passive condition, participants passively listened to two repetitions of a pre-recorded of their own speech. In both conditions, during one of the stimuli an auditory feedback perturbation with varying magnitude (0, 62.5, 83.3, 104.2, 125, 187.5 cents increase in formant frequencies) was applied. After completion of each trial, participants were asked to indicate whether the two stimuli were different (by pressing a button). In each of the conditions and for each participant, we calculated proportion of correct responses. Psychometric functions were then fitted to individual responses, using a Maximum Likelihood criterion. We used the fitted psychometric functions to calculate point of subjective equality (PSE) at 50% correct response—as a measure of perceptual sensitivity. From each psychometric function, we also extracted its slope value—as a measure of perceptual uncertainty. We found that PSE values of the stuttering group were higher than PSE values of the nonstuttering group ($p = .019$). We also found that slope values in the passive condition were greater than slope values in the active condition ($p < .001$). In addition, slope values of the stuttering group were lower than slope values of the nonstuttering group ($p = .012$). Overall, these results suggest that a)

perceptual uncertainty increases in the active condition for both groups, and b) stuttering participants have both higher perceptual thresholds and greater perceptual uncertainty in detecting formant perturbations. Together, these results provide evidence for deficits in integration and interaction of neural mechanisms of speech production and perception in adults who stutter.

**Disclosures: A. Daliri:** None. **L. Max:** None.

**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 788.05/III60

**Topic:** H.02. Human Cognition and Behavior

**Support:** Esther Hyatt Wender Summer Research Fellowship

**Title:** EEG differences between perceiving speech versus noise in physically identical sine-wave speech stimuli

**Authors: *M. A. PITTS**[1], A. R. DYKSTRA[3], J. GLASS[2], C. HENDRY[2], E. CANSECO-GONZALEZ[1]
[1]Psychology, [2]Reed Col., Portland, OR; [3]The Brain and Mind Inst., Univ. of Western Ontario, London, ON, Canada

**Abstract:** Sine-wave speech (SWS) is composed of time-varying sinusoids that approximate the first three formants in speech. SWS is initially perceived as noise in naïve listeners. After a brief training, however, SWS is perceived as intelligible speech, providing a unique opportunity to measure neural activity associated with conscious speech perception. To dissociate neural activity linked with perception from activity linked with performing the task, we varied perception and task independently. In all three phases of the experiment, participants listened to SWS, control versions of SWS (which were acoustically similar but unintelligible), and pure tones while performing a one-back task on either tones (phases 1 and 2) or SWS (phase 3). Participants perceived SWS as noise in phase 1 and as speech (due to intervening training) in phases 2 and 3. Thus, perception differed between phases 1 and 2/3, while the task differed between phases 1/2 and 3. EEG measures showed early (~200-300 ms), fronto-central negative-going differences between SWS and control stimuli only when SWS was perceived as speech (phases 2/3). When SWS was relevant to the task (phase 3), additional EEG differences, including the P3b (300-500 ms) and a sustained frontal negative wave (300-800 ms), were evident. These results challenge theories that posit a long-latency cortical ignition associated with conscious perception, as the perceptual differences observed here occurred relatively early in time, and regardless of the task.

**Disclosures: M.A. Pitts:** None. **A.R. Dykstra:** None. **J. Glass:** None. **C. Hendry:** None. **E. Canseco-Gonzalez:** None.

**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 788.06/III61

**Topic:** H.02. Human Cognition and Behavior

**Support:** NSF GRFP

**Title:** Rivalry and fusion can coexist in a tristable dynamic state

**Authors: *G. RIESEN**[1], A. M. NORCIA[2], J. L. GARDNER[3]
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**Abstract:** Dichoptic inputs are either 'fused' together or engage in binocular rivalry - outcomes considered separately in most of the literature. Experiments and models have typically treated them as mutually exclusive, with fusion not reportable in most rivalry paradigms. We find a dynamic "tristable" state in which fused, left- or right-eye dominant percepts can result from static stimuli. Statistical analysis indicates that this is not simply the result of a parallel fusional process intermittently halting or interrupting rivalry; rather both should be considered part of a single process.

We parametrically varied the fusability of dichoptic stimuli and had observers report their appearance over time. 19 participants were shown dichoptic Gabor patches (carrier spatial frequency: 5 cpd, SD=0.7) with orientation disparities of [0 10 20 25 30 35 40 50 90] degs about the vertical using a pellicle beam splitter. Observers reported the apparent orientations of the patches (clockwise, counter-clockwise, vertical or unsure) relative to reference points for two one-minute periods each. For non-zero disparities, rotated appearances signified left- or right-eye views while verticality indicated fusion. To elicit fusion without stereopsis, a second set of stimuli were shown with everything rotated 90 degs to produce vertical disparities.

Perception was tristable between fusion and rivalry for patches ~30 degs apart. 7 participants were excluded due to slow rivalry (mean durations >25s at 90 degs) or non-fused percepts at zero disparity. The rest reported exclusive rivalry for disparities >~35 degs and exclusive fusion at <~20 degs. At ~20-35 degs, subjects reported periods of both. The same was observed for vertical disparities, but with exclusive rivalry from ~30 degs on.

We reject two basic models where a separate fusion process interrupts rivalry to produce tristability. The 'storage' model has rivalry paused during fusion, as seen when attention is removed from rivalry. The dominant eye before and after fusion would then usually be the same. The 'interruption' model has rivalry continue underneath fusion. This would cause differences in

the durations of rivalry periods flanking fusion (which are ‘cut short’ by it). Bootstrapped simulations of these models do not match our data.
We have demonstrated that certain static stimuli can be seen as fused and rivalrous over time, revealing a novel temporal aspect of fusion as it alternates with rivalry. Statistical analysis rules out simple combinations of rivalry and fusion processes and presents the need for a dynamic model capable of generating all three outcomes.

**Disclosures: G. Riesen:** None. **A.M. Norcia:** None. **J.L. Gardner:** None.

**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 788.07/III62

**Topic:** H.02. Human Cognition and Behavior

**Title:** Early identity recognition of familiar faces is not dependent on holistic processing

**Authors: S. MOHR**[1], A. WANG[2], *A. D. ENGELL[3]
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**Abstract:** It is widely accepted that holistic processing is critical for early face recognition, but recent work has suggested a larger role for feature-based processing. Indeed, there is some indication that as familiarity increases, recognition becomes less dependent on holistic processing and more dependent on facial features. Regardless of the nature of the mechanism, the earliest step in familiar face recognition is the matching of a perceptual representation of the familiar face to a stored representation of that same face; a process thought to be indexed by the N250r event-related potential. In the current face priming event-related potential studies, we investigated whether this perceptual representation can be effectively activated by faces that are manipulated to emphasize feature-based processing and to disrupt holistic processing. To emphasize feature-based processing of primes, we utilized isolated face parts in the first experiment and face inversion in the second experiment. In the first experiment, we observed the well-documented N250r modulation when a familiar whole face prime was followed by a face of the same identity. Critically, we also observed this effect for familiar isolated eye primes (though not for mouth primes) when followed by a whole face of the same identity. In the second experiment, prime images were familiar whole faces presented in either an upright or inverted orientation. Face inversion is known to disrupt holistic processing. However, the inverted face primes were no less effective than the upright face primes in modulating the N250r. Together, the results of these studies indicate that activation of the earliest face identity recognition processes is not dependent on holistic processing of a typically configured face (though this does not preclude a role of holistic processing in natural viewing). Rather, feature-based processing

can effectively activate the perceptual memory of a familiar face. Of note, we found that isolated eyes, but not isolated mouths, activated early recognition processes.

**Disclosures: S. Mohr:** None. **A. Wang:** None. **A.D. Engell:** None.

**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 788.08/III63

**Topic:** H.02. Human Cognition and Behavior

**Support:** NSERC Discovery Grant RGPIN-2014-05248

**Title:** Clarifying theta's role in the brightness enhancement of a flickering stimulus

**Authors: *J. K. BERTRAND**[1], A. A. OUELLETTE ZUK[2], N. J. WISPINSKI[3], K. E. MATHEWSON[3], C. S. CHAPMAN[1]
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**Abstract:** In 1938 Bartley reported that 10 Hz flickering-stimuli were perceived to be twice as bright as constant stimuli. Recently, we attempted to replicate Bartley's results, but found instead that 4 Hz flickering-stimuli were perceived as brightest (Bertrand et al., 2018). Both groups suggest that brightness enhancement is a result of entraining endogenous neural rhythms (alpha (~10 Hz) for Bartley, and theta (~4 Hz) for Bertrand et al.). The current study explores two questions which arise from these apparently contradictory results: 1) Could task differences between Bertrand et al. and Bartley cause recruitment of distinct oscillatory processes? 2) Could the reported theta-enhancement just be an aliasing of the alpha rhythm being divided across two locations (~10 Hz / 2 = ~5 Hz)? Experiment 1 altered our task (discrimination) to more closely mirror Bartley's task (matching). Participants (n = 29) adjusted the brightness of a flickering stimulus (2 - 12 Hz) until it was perceived as equal to that of a constant stimulus. We hypothesized that the need to almost exclusively focus on the flickering stimulus might recruit alpha rhythms and thus ~10 Hz stimuli would appear brightest. Contrary to this hypothesis, our results show that 2 and 4 Hz stimuli elicit the greatest brightness enhancement. Experiment 2 tested whether our behavioural and EEG findings in theta were a by-product of divided attention between two locations (Crouzet & VanRullen, 2017). Here, participants (n = 28) were presented stimuli in isolation. On half the trials, only a single test stimulus appeared (Constant, 4 Hz or 9 Hz) and participants indicated its perceived brightness by adjusting a non-flickering reference stimulus. On the other half of the trials, two stimuli appeared in sequence and participants judged if the first or second was brighter. Preliminary results show 4 Hz stimuli are perceived as brightest, providing additional support that brightness enhancement arises from entrainment of

the theta rhythm. Thus, we can now conclusively rule out alpha related effects as inducing the brightest percepts (either from Bartley or via aliasing) and plan to pursue the neural cause of theta-related brightness enhancement.

**Disclosures: J.K. Bertrand:** None. **A.A. Ouellette Zuk:** None. **N.J. Wispinski:** None. **K.E. Mathewson:** None. **C.S. Chapman:** None.

**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 788.09/III64

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIMH Intramural Program Grant ZIAMH002588
NSERC

**Title:** Category-specialized brain regions respond preferentially to both pictures and words

**Authors: *N. A. KHAN**[1], S. W. GORLICK[1], W. D. STEVENS[1], A. MARTIN[2]
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**Abstract:** A central, defining feature of brain regions involved in representing object concepts is that they should respond in a category-specific manner, regardless of input modality or format (e.g., pictures or written words). To investigate this issue, we used functional MRI to scan healthy young adult participants (n = 26,12 female, mean age = 24) as they performed a semantic classification task ("man-made" or "natural" judgments) while viewing randomly intermixed trials containing either pictures or words denoting different object categories (scenes, tools, animals, bodies). Consistent with previous studies, viewing scenes (relative to viewing animals, bodies, and tools) activated multiple brain regions bilaterally, including parahippocampal cortex (PPA), and the so-called retrosplenial complex (RSC) and occipital place area (OPA). Viewing bodies (relative to viewing scenes, animals, and tools) activated the extrastriate body area (EBA). Viewing words denoting scenes (e.g., farm, skyline, lake, courtyard) or body parts (e.g., ankle, arm, shoulder, knee), relative to words from every other category, differentially elicited distributed patterns of activity that overlapped with the category-related activations associated with viewing pictures from these two categories. This activity was stronger in the left than right hemisphere, and located in the more anterior regions of the processing streams associated with viewing pictures. These results are consistent with a property-specific, rather than a modality-specific, model of object category representation.

**Disclosures: N.A. Khan:** None. **S.W. Gorlick:** None. **W.D. Stevens:** None. **A. Martin:** None.

**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

**Location:** SDCC Halls B-H

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**Topic:** H.02. Human Cognition and Behavior

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Key Science Project of the Department of Education, Yunnan Province, China (2016Z010)

**Title:** Are there different contributions of cortical and subcortical visual pathways to the processing of closure: A tdcs study

**Authors: *W. ZHU**[1], J. DREWES[2]
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**Abstract:** The specific nature of closure is important for the computation of an object representation (Donnelly et al., 1991; Pomerantz et al., 1977; Treisman and Paterson, 1984). And it has been proven that the discrimination of closure is typically faster and easier than that of other geometrical features. However, the neural substrate underlying this perceptual advantage is yet unclear. Neuroimaging studies found that topological perception (e.g. discriminating if a figure is closed or open) mainly activated the anterior temporal lobe (ATL), which lies in the late destination of ventral visual pathway.(Zhou, Zhang et al. 2008). Thus we hypothesized that closed figures may be processed via a rapid subcortical shortcut to ATL bypassing V1. In order to test this prediction, we applied transcranial direct current stimulation (tDCS) in an odd quadrant task. In our experiment, participants received sham and active cathodal-inhibitory tDCS over the occipital cortex (V1). In the odd quadrant task, all four quadrants each contained a figure, and participants were asked to report whether a quadrant differs from the other three. The disparate quadrant differs from the rest either in geometric properties (e.g. orientation) or in topological properties (closed vs. open figure). After suppressing activity in V1, a decrease of performance was found in the geometric discrimination but not in topological discrimination. Thus, the results provided direct evidence that the discrimination of closure does not necessarily depend on the initial processing at V1 and may be mediated via a rapid subcortical pathway to ATL bypassing V1.

**Disclosures: J. Drewes:** None.

**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 788.11/III66

**Topic:** H.02. Human Cognition and Behavior

**Title:** Feedback in contour perception: Short and long time courses

**Authors: *J. DREWES**[1], W. ZHU[2]
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**Abstract:** The human visual system is able to extract information from visual input very quickly. Previously, we found evidence of recurrent processing in a contour discrimination task using a rapid stimulus repetition paradigm, with performance peaking at about 60ms between two stimulus presentations. Here, we extend the scope of our investigation towards longer durations and higher temporal resolution. We successfully reproduced our previous finding of a fast performance peak around 60ms ISI, but we found an additional performance trend superimposed to the shorter effect, peaking at about 80-90ms but lasting more than 300ms. Noise tolerance increase for a double stimulus presentation compared to a single stimulus ranges from 35% at 25ms ISI to just more than 80% at 125ms, then slowly declining to converge against 35-40% at 400ms. We present an analysis of inter-individual differences within the above time windows. These results add further behavioral proof for rapid information feedback in the formation of shape percepts, however the information appears to be buffered for longer periods than previously reported.

**Disclosures: W. Zhu:** None.

**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 788.12/III67

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH Grant R01HD079106

**Title:** Automatic and task related encoding of number in the dorsal visual stream

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**Abstract:** Previous functional imaging studies and single neuron recording studies have demonstrated that number is automatically encoded in the dorsal visual stream including in intraparietal sulcus. These studies suggest that parietal cortex provides a veridical sensory readout of the number of items in the visual field. Another line of work suggests that intraparietal areas are highly plastic association cortex, potentially representing multiple stimulus features depending on the task at hand. Here we used a function imaging paradigm to directly compare the encoding of number when it was task relevant and irrelevant. We found that number could be decoded from brain activity throughout the dorsal visual stream, including in early visual cortex, during both tasks, but that the decoding was stronger when participants were attending to number. When number was held constant the task condition could be decoded in parietal cortex but not early visual cortex. Our findings demonstrate that number is automatically encoded throughout the dorsal visual stream, but that the intraparietal areas may represent a critical confluence of visual encoding and task dependent processing.

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**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 788.13/III68

**Topic:** H.02. Human Cognition and Behavior

**Support:** NSERC Discovery Grant (RGPIN-2015-06696)
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Sony Faculty Research Award
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**Title:** Decoding of thermal sensations from human brain activity

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**Abstract:** Sensing temperature is a supramodal experience; when we touch a warm coffee mug, we can feel not only ‘warm’ sensation of its temperature but also emotional comfort and pleasantness. Previous research has shown that this thermal perception includes physical,

physiological and psychological process, accompanying various aspects of affective components, from pain (Yarnitsky, & Ochoa, 1990) to pleasantness (Rolls, Grabenhorst, & Parris, 2008). What are the neural mechanisms underlying the perceptual processing of physical temperature information? In the last decades, several studies have investigated how the brain represents thermal sensations using fMRI with univariate analysis. Although it has been suggested that the posterior insula is the primary region for processing thermal information (Craig, Chen, Brandy, & Reiman, 2000; Peltz et al., 2011), the empirical evidence has been inconclusive. First, it is not clear whether this area is exclusively related to warm (Rolls, Grabenhorst, & Parris, 2008) or cold stimuli (Hua, Strigo, Baxter, Johnson, & Craig, 2005; Oi et al., 2017). Moreover, it is possible that other brain areas, such as the postcentral gyrus or prefrontal regions, are also involved in processing thermal information, but that the information is encoded in distributed patterns of brain activity that are inaccessible with univariate analysis of fMRI data. In the present study, we aim to extend the previous findings by using multi-voxel pattern analysis (MVPA) to investigate where and how the brain represents the experience of thermal sensation. In the experiment, warm (42°C) and cold stimuli (11°C) were handed to participants one at a time while their brain activity was measured with fMRI. A linear support vector machine classifier was trained and tested to decode thermal sensation from patterns of brain activity. We found that thermal sensation can be decoded not only from the insula and the postcentral gyrus, which have been identified to be engaged in thermal and tactile perception, but also from the medial frontal gyrus, the inferior parietal lobule as well as the occipital cortex. These findings suggest that processing thermal information includes a distributed network of brain regions, which all contribute to the supramodal nature of thermal perception.

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**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

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**Program #/Poster #:** 788.14/JJJ1

**Topic:** H.02. Human Cognition and Behavior

**Support:** ERC Starting Grant 640448

**Title:** The speed of light - and darkness - through the human visual system

**Authors: S. S. DALAL**[1], B. U. WESTNER[1], M. J. DIETZ[1], C. J. BAILEY[1], *T. POPOV[2]
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**Abstract:** The speed at which visual information propagates down the visual pathway remains surprisingly unclear. Furthermore, some studies suggest that the processing of dark stimuli may

occur more quickly by taking advantage of greater neural resources in the visual system. We aimed to characterize the timing of impulses down the visual pathway with a combination of ERG (electroretinography) and MEG.
In the first experiment, healthy participants (N=10) viewed 200 light flashes of 1 ms duration. ERG responses were examined with respect to the corresponding responses of thalamus and visual cortex, as reconstructed with MEG. We implemented a novel neuroimaging strategy, combining beamforming with the Hilbert transform to yield analytic amplitude and phase across the whole brain for several high gamma bands (55-75 Hz, 75-95 Hz, 105-120 Hz, and 120-145 Hz) as the basis for nonparametric statistical mapping based on variability across trials. Intertrial phase coherence was also calculated from these results per voxel and frequency band. The first cortical responses appear at 27 ms at ~115 Hz, lagging the corresponding retinal oscillatory potential by 8 ms.
In a second experiment, we recorded retinal and cortical responses to 480 ms light flashes using a similar strategy (N=10). High frequency responses for flash offsets occurred earlier than flash onsets in the cortex but not in the retina. Interestingly, while onset responses involved a wide range of frequencies (55-195 Hz in the retina, and 55-145 Hz in the cortex), offset responses were restricted to the 75-95 Hz frequency band in both retina and cortex.
Our results provide evidence that high-frequency modulations reflect the precise timing of information handling in both cortex as well as its afferents: the timing of the ERG oscillatory potential indeed suggests that it arises from the output stages of the retina and after a short delay, a massive cortical response appears in several structures in primary and higher-order visual cortex. These high gamma band responses occurred much earlier than the classic visual evoked response. Furthermore, faster propagation times but not earlier retinal processing for darks than lights were observed, implicating a thalamic role. Furthermore, the outcomes add to the ongoing discussion about the function of narrowband oscillations in the human visual system.
Measuring ERG together with MEG may therefore provide a more informative measure of information processing at each stage of the visual pathway. It may furthermore provide a potential strategy to discover disturbances of the visual pathway in disease, including neurological and psychiatric disorders.

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**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 788.15/JJJ2

**Topic:** H.02. Human Cognition and Behavior

**Title:** Recruitment of the motor system during music listening: An ALE meta-analysis

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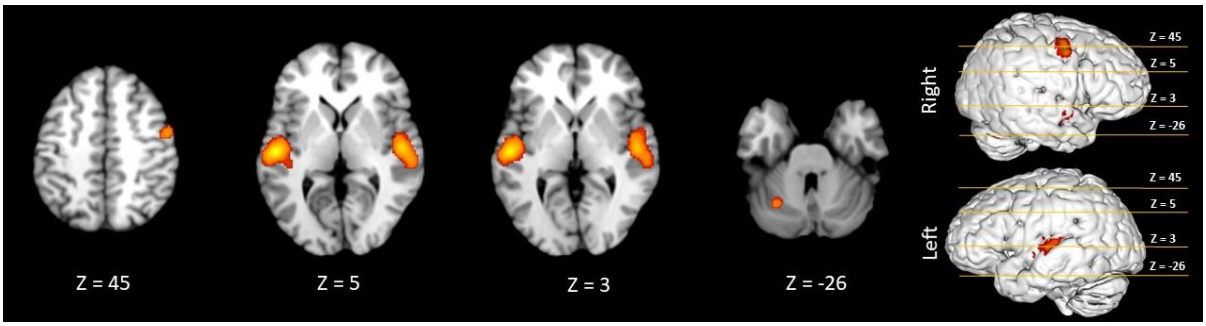
**Abstract:** Passively listening to music has been reported to activate regions of the brain involved in motor execution and motor planning (e.g., Baumann et al., 2007; Meister et al., 2004; Bengtsson et al., 2009). However, the numerous studies that report this motor involvement differ in terms of precisely which parts of the motor system are found active. Thus, which motor regions are automatically recruited for music perception are yet unknown. Knowing the regions that are involved in this can help to determine what the functional significance of motor activation is: for example, ventral pre-motor cortex (vPMC) activity would indicate recruitment of the action observation network. In this study, we used activation likelihood estimation (ALE) to conduct a meta-analysis of neuroimaging literature on passive music listening, to determine which motor regions are consistently active across experimental designs. 41 studies were analyzed, resulting in a total of 524 subjects contributing 781 activation foci in total. Activations were found in the bilateral superior temporal gyrus, transverse temporal gyrus, insula, pyramis, bilateral precentral gyrus, and bilateral medial frontal gyrus. As predicted, activation was also seen in the motor system including the left premotor cortex, left primary motor cortex, and the right cerebellum. Surprisingly, we did not see activation of the supplementary motor area (SMA), though several existing theories propose that we should, and several individual studies have found such activations. These results support theories of shared neural circuits for action and perception and also identify which motor neural substrates are activated during passive music perception. We further discuss the likely functional role that each of the observed neural activation sites play in passive music perception, and how SMA recruitment for music listening may be highly context-modulated.




**Disclosures: C. Gordon:** None. **P. Cobb:** None. **R. Balasubramaniam:** None.

**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 788.16/JJJ3

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH NEI EY022454
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**Title:** Discovering brain representations across multiple feature spaces using brain activity recorded during naturalistic viewing of short films

**Authors: *A. O. NUNEZ-ELIZALDE**, F. DENIZ, J. S. GAO, J. L. GALLANT
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**Abstract:** The human cerebral cortex comprises many functionally distinct areas that represent different information about the world. It has been challenging to map these areas efficiently. Here we present a new approach that addresses this problem. Subjects watch 30 interesting short films while their brain activity is measured with fMRI. The short films contain speech, video, music, environmental sounds, emotions, human interaction and narrative structure. Each film was labeled using more than a dozen different high-dimensional feature spaces reflecting the visual, auditory and conceptual content of the films. In effect each feature space constitutes a different hypothesis about how visual, auditory and conceptual information might be represented in the brain. Brain activity elicited by the films is then modeled using a novel voxelwise encoding model based on simultaneous Tikhonov regularization of the labeled feature spaces using a multivariate normal prior. The resulting encoding model reveals which specific feature spaces are represented in each voxel, and how each voxel is tuned with respect to those features. To validate the approach we examined voxelwise model predictions using 27 minutes of novel short films not used for model estimation. We find that the voxelwise encoding model significantly predicts activity of voxels distributed broadly across the cerebral cortex. Model prediction accuracy is highest ($R^2 > 0.2$) for voxels located in sensory regions such as early visual cortex, primary auditory cortex and regions related to language processing (Brocas, superior premotor ventral, and superior temporal gyrus). Significant predictions are also found for voxels located in association regions in prefrontal cortex (superior and inferior frontal gyri) and lateral parietal cortex, though these predictions are poorer than those for sensory and language regions. Furthermore, we find that the pattern of feature selectivity across cortex is highly consistent across all five individual subjects. Finally, we show that motion energy and spectrogram feature spaces recover known visual retinotopic and auditory tonotopic maps. The recovered feature spaces can capture novel functional subdivisions, even within well-studied regions such as middle temporal cortex.

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**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** Reed College Summer Research Fellowship

**Title:** Neural activity linked with visual awareness and task-relevance in a novel 2x2 design

**Authors: *A. KYROUDIS**[1], M. A. COHEN[2], M. A. PITTS[1]
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**Abstract:** This experiment was aimed at critically informing current empirical theories of perceptual awareness. The general design was based on Dehaene et al.'s (2001) visual masking study. Dehaene et al. (2001) used a sandwich masking technique to render visual stimuli clearly seen or unseen on different trials while controlling for overlapping brain activity elicited by the masks (subtracting blank control trials from target-present trials). While this design was clever, elegant, and the results were intriguing, the stimuli were always task-relevant such that neural activity linked with conscious perception may have been confounded with neural activity associated with performing the task. In the current study, we used this same sandwich masking technique to manipulate perceptual awareness, but we also manipulated task-relevance, resulting in a 2x2 design. The critical stimuli were line drawings of animals and objects that always appeared for 33ms. In the unseen condition, 100ms masks immediately preceded and followed the stimuli, while in the seen condition, these same masks were separated from the stimuli by 200ms blank periods. On 20% of trials, a red oval was presented instead of a critical stimulus. During task-relevant blocks, subjects made trial-by-trial reports as to whether they saw an animal, an object, or nothing; in task-irrelevant blocks, subjects responded whenever they saw a red oval, but otherwise did not respond. We compared event-related potentials (ERPs) elicited by the critical stimuli in seen versus unseen trials, separately for the two task conditions. The results from the task-relevant condition replicated the findings of Dehaene et al. (2001), while the results from the task-irrelevant condition differed, particularly at time-points beyond 300ms. Specifically, the P3b wave, which has been proposed as a neural marker of perceptual awareness, was absent in the task-irrelevant condition. These results suggest that long-latency ERP differences between seen and unseen stimuli are more related to the reporting task than to perception per se.

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**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** Intramural research program of the NIH/NINDS
Leon Levy Foundation
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**Title:** Neural signatures of perceptual content and memory trace during bistable perception

**Authors: *R. HARDSTONE**, M. W. FLOUNDERS, M. ZHU, B. J. HE
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**Abstract:** When presented with an image that can be interpreted in multiple ways, our perception of the image switches spontaneously between the different interpretations as we try to resolve the ambiguity. Here we show that subjective perception while viewing ambiguous or unambiguous images can be decoded from ongoing MEG activity. We also provide a novel view of how percepts gain and lose stability while viewing ambiguous images by analyzing trajectories through behaviorally defined neural state-spaces.

Eighteen subjects (8 Female, Age: mean 24.6, s.d. 3.9 years) were recorded with MEG (CTF, 275 axial gradiometers) performing three visual perception tasks. During each task the subject pressed buttons to indicate their current percept of the image. In task 1, subjects viewed ambiguous images for 60 seconds at a time. In task 2, they viewed modified versions of these images for 5 seconds at a time, which enhance one of the possible interpretations (unambiguous images) and do not cause perceptual switching. In task 3, we presented the same ambiguous images with interleaving blank periods, which increased the likelihood that the current percept of the image persisted.

Applying linear support vector machines (SVM), we could decode perceptual content using activity in the slow cortical potential (SCP, <5 Hz) range throughout the percept's duration, but not by using alpha or beta-band amplitude envelope. The SCP decoders generalized across the majority of the duration of the percept, and also between the ambiguous images and their unambiguous counterparts. To further investigate mechanisms of perceptual switching, we applied multi-linear regression to MEG activity using behavioral variables as regressors. Using the regression weights we defined a low-dimensional neural state-space with each dimension corresponding to a behavioral variable. Analyzing trajectories through this state-space showed that higher occipital alpha and beta-band amplitudes led to increased duration of a percept, and that signatures of a perceptual switch occur in SCP activity, along with alpha and beta amplitude.

When ambiguous images were presented with interleaving blank periods we found that lower alpha and beta amplitude led to an increased likelihood of a perceptual memory trace.
The nature of ambiguous perception has long been debated and has important implications for disorders (such as autism) which show altered perceptual switching dynamics. We have shown that while perceptual content information is found predominantly in the slow cortical potential range, the mechanisms of perceptual maintenance and switching are functionally distributed across frequency bands.

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**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

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**Program #/Poster #:** 788.19/JJJ6

**Topic:** H.02. Human Cognition and Behavior

**Support:** National Eye Institute (NEI R01EY026042 to SP)

**Title:** Neural substrate of visual navigation cue integration

**Authors: *S. LI**[1], Z. LU[2], S. PARK[3]
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**Abstract:** At every moment of navigation, the visual system needs to quickly determine whether to go forward or not in the immediate environment. To make such decision, the visual system incorporates multiple levels of information available in the scene. In this study, we aim to understand how different types of cues that influences navigation is represented in the visual system. Past studies suggest that a scene-selective visual cortex, the occipital place area (OPA), codes for the navigational affordance provided by paths. The presence of a path in a scene is one of the salient visual navigation cues. Here, we aimed to build a hierarchical structure in navigational cues available in a scene by adding signs that instructs a viewer to proceed or not; and a spatial layout based on visual openness of a scene. We rendered artificial images of natural environments based on combinations of signs (go or stop) x path (path or no path) and spatial layout (open or closed). 168 different images were presented in a fast event-related design during fMRI scans (N=12). We used representational similarity analysis (RSA) to ask how the different navigation cues are represented across the ventral visual cortex. Four hypothetical models were built to represent the dissimilarity between each pair of stimuli: spatial layout model, path model, sign model, and a combined model that integrates all three types of navigation cues. We hypothesized that if a brain region is involved in the navigability computation of scenes, the neural pattern of this area will be best predicted by the combined model that integrates multiple

available cues for navigation. We first calculated the neural activation pattern dissimilarity of each pair of stimuli, which was then used to calculate the correlation with the models. This analysis revealed that the OPA activation pattern dissimilarity was not correlated with neither of the three individual models (spatial layout, path and sign), but showed a significant correlation with the combined model only (tau= 0.18, $p<0.05$). This contrasted with another scene-selective region, the parahippocampal place area (PPA), which showed significant correlation with all of spatial layout, path and the combined model. This selective correlation observed in the OPA with the combined model suggests that OPA is the region involved in computation of the visual navigability in scene. In addition, the fact that neither of individual models significantly correlated with OPA pattern suggest that the integration of multiple visual navigation cues in the OPA might be based on an automatic global analysis about the navigability rather than based on serial augmenting of individual navigation cues.

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**Poster**

**788. Human Cognition and Behavior: Perception and Imagery I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 788.20/JJJ7

**Topic:** H.02. Human Cognition and Behavior

**Title:** The precision and stability of imagination: Reconstructing colors from oscillatory neural activity

**Authors: *P. PANDEY**[1], J. M. VETTEL[2], A. J. COHEN[1], A. PAUL[1], E. B. FALK[1], J. O. GARCIA[2]
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**Abstract:** Across a diverse set of domains, neuroscientists have investigated whether imagined mental events rely on direct analogs for how the brain processes sensory input from the external world. For instance, research on hand movements has shown similar activation in motor cortices for imagined and prepared movements compared to actual movements (Michelon et al., 2006). Similarities have also been shown for perceptual domains, including visual perception (Pearson et al., 2015) and somatosensation (Blakemore et al., 2005), but the precision, variability, and state-dependency of these representations is not well understood.
Here, we show longitudinal data (semi-weekly sessions) from two tasks: (i) color imagination task, and (ii) passive face viewing task while EEG was measured. The color imagination task

consisted of forty 12-second trials per session. Each trial consisted of a single full-field hue chosen from an HSV color space uniformly sampled distribution, displayed for 4 seconds. Immediately after this viewing period, the participant is asked to imagine the shown color for 8 seconds. Following the imagination task, each session also included a face task, consisting of variety of faces (sampled from the AT&T face dataset) that were passively viewed for 4 seconds each. Prior to both tasks, we administered questionnaires on sleep behavior (Pittsburgh Sleep Diary; Monk et al., 1994, Karolinski sleepiness scale; Åkerstedt & Gillberg, 1990) and affect (Positive and Negative Affect Schedule; Watson et al., 1988, modified Differential Emotions Scale; Fredrickson et al., 2003).
Using an encoding framework, previous reconstruction of perceived color has showed specific differences across the visual hierarchy (Brouwer & Heeger, 2009) in fMRI BOLD responses. We have extended this research to imagined color from EEG oscillatory activity building upon previous research that explored EEG-based reconstructions of perceived orientation (Garcia et al., 2013). Using a cross-validated leave-one-out procedure, we show that color response profiles (CRPs) may be successfully reconstructed while imagining color. Variability in bandwidth and temporal dynamics of these CRPs further suggest the susceptibility of these representational units to a variety of state variables, both internally and externally generated.

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**Title:** Visual network modularity in patients with central vision loss

**Authors: *L. L. FLEMING**[1], W. K. BURGE[2], D. DECARLO[3], K. M. VISSCHER[1]
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Alabama at Birmingham, Birmingham, AL; [3]Ophthalmology, Univ. of Alabama at Birmingham, BIRMINGHAM, AL

**Abstract:** Several lines of evidence have shown that the adult brain has the ability to change itself in response to changes in sensory experience. Central vision loss is one major change in sensory experience that has been shown to have some impact on both brain structure and function. Here we ask how this loss influences the networks involved in processing vision. Given that the brain functions as a collection of networks, understanding how vision loss influences these networks is crucial to understanding the plasticity of the brain during altered sensory experience in adulthood. Here, we examine the visual network changes associated with macular degeneration (MD), a disease that results in loss of high resolution central vision, requiring individuals to rely on the much lower resolution of peripheral vision to perform everyday tasks. Specifically, we examined how the community structure of the visual network is different in individuals with central vision loss compared to those with healthy vision. We performed eyes-open, resting state fMRI in nine MD patients and nine matched controls in order to examine whether central vision loss is associated with changes in a measure of network structure called modularity. Modularity is defined as the extent to which a given network can be broken down into smaller clusters, known as “modules”, and the degree to which these modules possess more within- vs. between-module connections. In healthy vision, studies suggest that the modularity of visual cortex reflects the functionally distinct, hierarchical organization of the brain’s visual system. Here we examined whether loss of central vision in macular degeneration disrupts this modularity in the visual network. Standard preprocessing procedures were performed, including motion scrubbing, and assessment of motion parameters between groups, confirming movement was not significantly different between the two groups. Overall, we found that macular degeneration is associated with decreased visual network modularity compared to healthy controls. This finding suggests that there is less segregation of the visual network in participants with macular degeneration, possibly due to an overall decrease in retinal inputs to the visual system. However, future studies need to further explore the extent to which this change in modularity reflects overall vision loss vs. a compensatory mechanism to more effectively process deprived vision. Nevertheless, our findings show that the structure of the visual network may be related to long term differences in the type of visual input being processed.

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**788. Human Cognition and Behavior: Perception and Imagery I**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 788.22/JJJ9

**Topic:** H.02. Human Cognition and Behavior

**Support:** Advanced ERC n. 323606

**Title:** Specialization of cortical areas for hand and tool motion

**Authors: *P. AVANZINI**[1], P. CARDELLICCHIO[2], V. PELLICCIA[5], F. CARUANA[3], G. LO RUSSO[5], G. RIZZOLATTI[3], G. A. ORBAN[4]
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**Abstract:** The use of fMRI and random-dot patterns for localizing motion-responsive regions has prevented so far a time-resolved mapping of the cortical regions sensitive to human motion, as well as of those regions which may have developed during evolution a sensitivity to specific types of motion such as that proper to tool actions, whose kinematics differ considerably from those of hand actions. To overcome this issue, here we recorded the stereo-EEG activity in 49 drug-resistant epileptic patients (24M, 25F), implanted with intracerebral electrodes for presurgical monitoring, while they passively observed hand and tool action videos. Taking advantage of the high temporal resolution of stereo-EEG, we tested for each lead the cross-correlation between high gamma power (50-150 Hz) and motion speed extracted from hand and tool videos, and mapped results to a brain template according to the procedure described in Avanzini et al (2016). By using a trial-based cross-correlation for hand videos, we not only localized 17 human-motion sensitive regions, but also estimated for each of them the degree of speed selectivity (as the R coefficient) and sorted them temporally (according to the lag shift between the two signals).The two variables were inversely related (the higher R, the lower lag), except for retroinsular cortex, which exhibited both low R and lag. The direct comparison of the leads correlating with speed with those active following action onset (Caruana et al 2017) showed a dissociation between action observation and speed processing at the fronto-parietal level. Only parts of the fronto-parietal regions encode motion, the rostral portion of the dorso-ventral stream being completely insensitive to it. For each lead sensitive to hand and/or tool motion, we computed a tool-hand (TH) index comparing the correlation strength for tool (T) and hand (H) motion: (T-H)/ (T+H), whose distribution indicated that more leads correlated more strongly with tool than with hand motion. Five regions preferring tool motion were detected outside V1-3, four in the left, one in the right hemisphere. The four left hemisphere regions were located in pOTS (TH=0.92) and pMTG (TH=0.74), both in occipito-temporal cortex, in the caudal part of PFt (TH=0.76), and in dorsal precentral sulcus (TH=0.95). These results underscore the importance of the high time resolution of intracerebral recordings, reveal a dynamic modulation within the cortical network responsive to human motion, and suggest that specific tool-motion sensitive regions may have developed on top of a human motion sensitive network.

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**Program #/Poster #:** 788.23/JJJ10

**Topic:** H.02. Human Cognition and Behavior

**Title:** The time course of context-induced distortions of the egocentric reference frame for perceptual judgments and saccade guidance

**Authors: *J. M. PETERSON**, P. R. DASSONVILLE
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**Abstract:** Orientation judgments are made within a reference frame that is greatly dependent on the vestibular system, but the visual system is also able to extract contextual cues from a viewed scene (e.g., vertical door frames, horizontal desktops). This becomes dramatically apparent when prominent cues are misleading, as in the case of the rod-and-frame illusion (RFI, Asch & Witkin, 1948), where, in otherwise complete darkness, a large tilted frame causes a distortion of the egocentric reference frame, such that perceived vertical becomes biased in the direction of the frame's tilt. Consequently, the perceived orientation of an enclosed line (the rod) is rotated in the direction opposite the frame's tilt. Past studies of the RFI have documented the manner in which contextual cues are incorporated into an observer's reference frame, but the time course of this effect remains unclear. To characterize this time course, we employed two variations of the RFI. In Experiment 1, participants were instructed to make a short vertical eye movement to the topmost point on a response circle that surrounded the fixation point, with saccade onset timed to occur sometime before or after the onset of a tilted (±15°) frame; such eye movements have been demonstrated to be susceptible to distortions of the egocentric reference frame (Dassonville & Reed, 2015; Morgan et al., 2015). In Experiment 2, participants indicated the perceived orientation of a briefly flashed rod (~8 ms duration) presented before or after the onset of a tilted frame. The tilted frame had no effect on saccades initiated or rods presented well before (200 ms) frame onset, whereas those occurring well after (200 ms) frame onset demonstrated the predicted biasing effect of the tilted frame. In between these extremes, eye movements first began to show an influence of the frame ~120 ms after its appearance. Given the typically-cited 30 ms oculomotor delay, these results suggest that it takes ~90 ms for the tilted frame to begin to affect perceived vertical. For perceptual judgments, the effect of the frame was significant for rods presented 133 ms *before* frame onset and reached a maximum plateau for rods presented simultaneous with frame onset. An effect of the frame that precedes the frame's actual onset can be explained by a difference in the processing delays for 1) the orientation judgment task and 2) the context-driven distortion of the egocentric reference frame. The pattern of findings reported here indicate that the orientation judgment takes at least 133 ms longer than the delay in the frame's distortion of the egocentric reference frame.

**Disclosures: J.M. Peterson:** None. **P.R. Dassonville:** None.

**Poster**

**789. Human Cognition and Behavior: Perception and Imagery II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 789.01/JJJ11

**Topic:** H.02. Human Cognition and Behavior

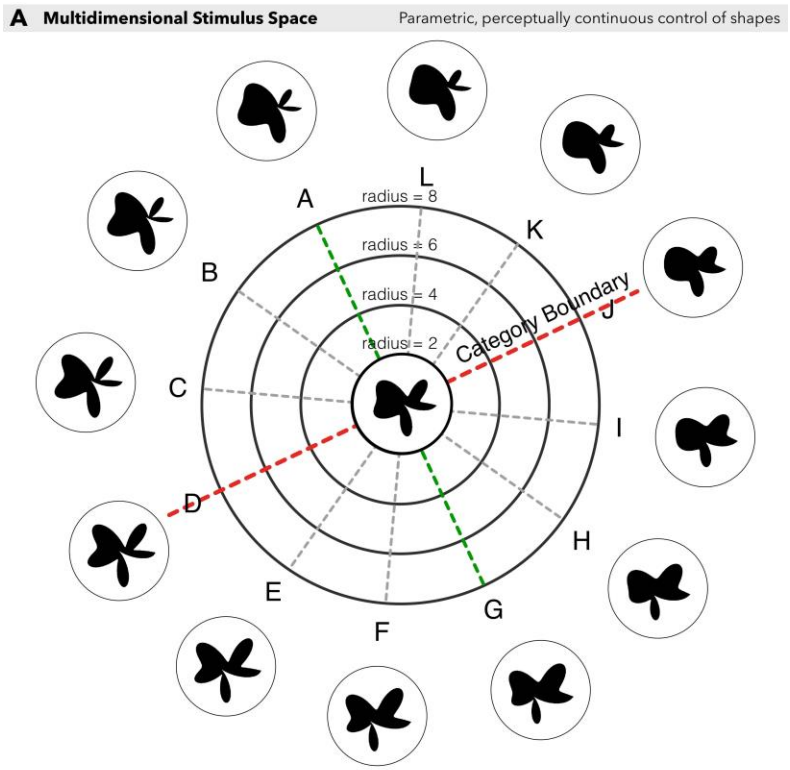
**Support:** NIH Grant R01 MH069456
Intel Corporation

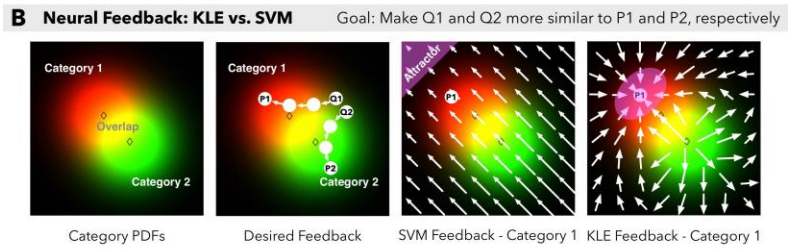
**Title:** Using closed loop real-time fMRI neurofeedback to induce neural plasticity and influence perceptual similarity

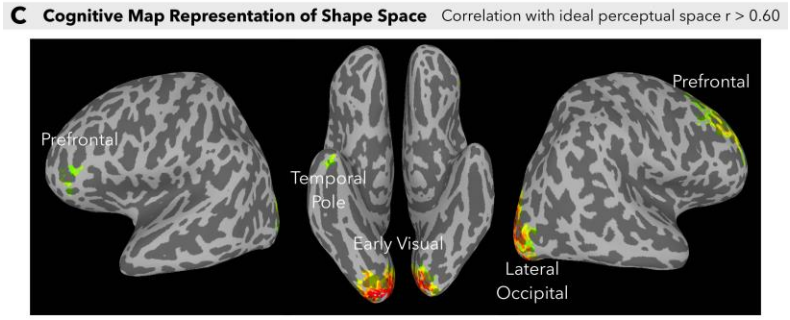
**Authors: *M. IORDAN**[1], V. J. RITVO[1], K. A. NORMAN[1], N. B. TURK-BROWNE[2], J. D. COHEN[1]
[1]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [2]Psychology, Yale Univ., New Haven, CT

**Abstract:** Neural representations of visual categories are modulated by both explicit learning (Folstein et al. 2015) and implicit neurofeedback training (Jackson-Hanen et al. SfN 2014). However, the causal link between the neural representation of categories and their perception remains unclear. To address this question, we seek to induce neural plasticity of visual representations via closed-loop real-time fMRI neurofeedback (deBettencourt et al. 2015) and test whether this drives categorical perception. To this end, we constructed a stimulus space of complex artificial shapes that vary along multiple dimensions independently (Op de Beeck et al. 2001). Behavioral norming (n=750) confirmed that each stimulus dimension was perceived in an equivalently graded manner and, neurally, multiple brain regions represented this space as a putative cognitive map, mirroring perception (n=9; EVC, LOC, PFC, temporal pole). Within this space, we hypothesized that using neurofeedback to strengthen non-overlapping (unique) features and suppress overlapping (shared) features of novel abstract visual categories should also differentiate the categories perceptually. Additionally, we developed a novel computational approach (KL-Evidence) for computing the neurofeedback provided to differentiate categories, based on mutual information between the distributions of neural responses they elicit. Extensive simulations showed that our method outperforms traditional methods (e.g., SVM) in pinpointing non-overlapping features, especially for subtly intertwined neural representations. We'll present preliminary results from an fMRI study in which we employ this feedback method to induce plasticity in neural representations elicited by arbitrary categories from the stimulus space. By collecting perceptual similarity ratings pre- and post-feedback, we examine a potential causal role for induced neural plasticity in categorical perception. More generally, the approaches we

develop may open up a new platform to investigate, understand, and potentially improve human learning with fMRI.




**Disclosures: M. Iordan:** None. **V.J. Ritvo:** None. **K.A. Norman:** None. **N.B. Turk-Browne:** None. **J.D. Cohen:** None.

**Poster**

**789. Human Cognition and Behavior: Perception and Imagery II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 789.02/JJJ12

**Topic:** H.02. Human Cognition and Behavior

**Support:** James S. McDonnell Foundation scholar award (220020284)
European Research Council grant (310809)

**Title:** Neural correlates and population receptive field mapping for perception and mental imagery of touch in the human brain

**Authors: *Z. TAL**[1], S. HOFSTETTER[2], R. GEVA[3], W. ZUIDERBAAN[4], S. O. DUMOULIN[5], A. AMEDI[6]
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**Abstract:** Mental imagery was mostly investigated in the visual and motor domains. It is generally accepted that mental imagery processing relies on similar regional networks as in visual perception and motor execution, including the primary cortices, though to a lesser extent. Tactile mental imagery studies are sparse, and whether similar phenomenon of shared neural correlates also characterize tactile imagery and tactile perception is still under debate. Moreover, whether full-body tactile imagery follows somatotopic organizational principles (i.e. topography) has yet to be shown. Here we applied phase-locked fMRI experimental design and population receptive field (pRF) modeling to map and characterize the neural correlates of passive tactile perception and imagery tasks. During tactile perception condition, the participants' right body side was stimulated sequentially from lips to toes. In the imagery condition, the participants were instructed to imagine the same tactile sensation of the body. Both pRF and cross-correlation analyses methods revealed the somatotopic organization of the primary somatosensory cortex (S1, Fig1A). Interestingly, S1 was not recruited by mental imagery of tactile perception (Fig 1B). However, mental imagery activation was found to increase along the anterior-posterior axis of the parietal cortex, peaking at the superior parietal lobule/precuneus as shown by the higher variance explained of the pRF model (Fig. 1C). Importantly, within this area, mental imagery activation was topographically organized, revealing a full-body tactile mental imagery homunculus (Fig 1D). To conclude, our results show for the first time the power of pRF modeling in studying both somatotopic organization and higher body-related topographic representations, such as tactile mental imagery. Crucially, we found a novel organized representation of full-body tactile imagery in a region known to be involved in self-centered

processing. This result further demonstrates that topography is a key principle of brain organization that also encompass high cognitive functions.

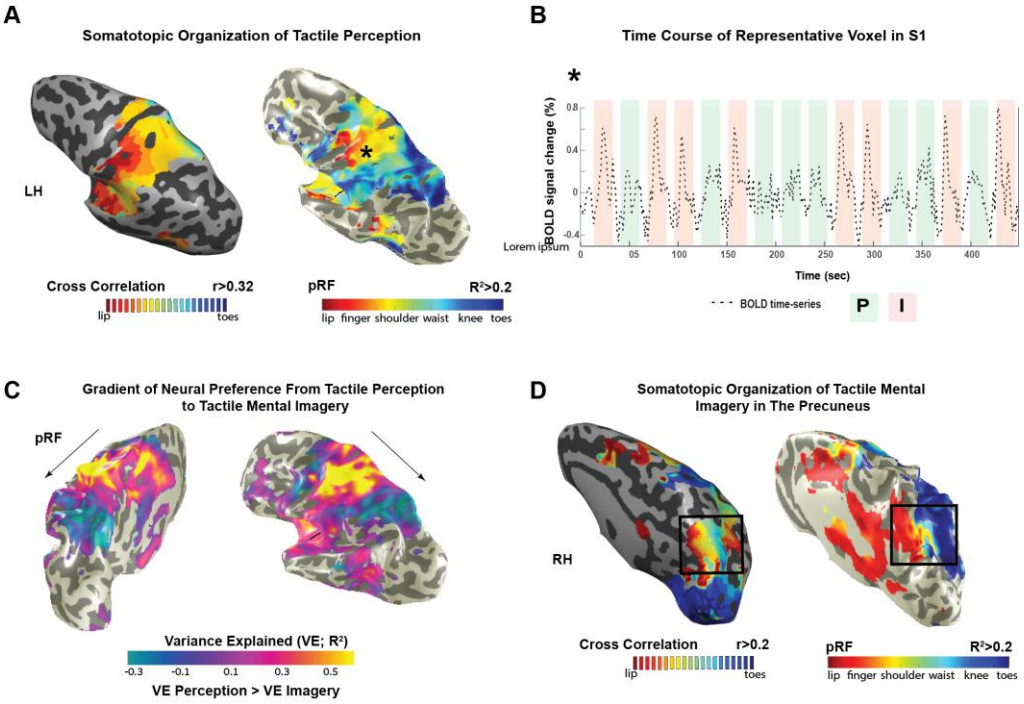


**Figure Legend:**

**A.** Topographic somatotopic maps of tactile perception is S1 found with cross correlation (left) and population receptive field (pRF) analyses (right). n=15;
**B.** Example of the BOLD time series from a voxel in left S1 (marked by *). P indicates trials of tactile perception. I indicates trials of tactile imagery.
**C.** Maps of the difference between the variance explained (VE) of the pRF model for tactile perception and tactile mental imagery.
**D.** Topographic maps of body tactile mental imagery in the right posterior parietal/precuneus shown with cross correlation (left) and population receptive field (pRF) analyses (right).

**Disclosures: Z. Tal:** None. **S. Hofstetter:** None. **R. Geva:** None. **W. Zuiderbaan:** None. **S.O. Dumoulin:** None. **A. Amedi:** None.

**Poster**

**789. Human Cognition and Behavior: Perception and Imagery II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 789.03/JJJ13

**Topic:** H.02. Human Cognition and Behavior

**Support:** UCSD Academic Senate Research Grant
UCSD FISP Postdoctoral Grant
UCDS Contextual Robotics Institute Seed Grant

**Title:** Identifying the shape and texture features underlying the perception of social traits from strangers' faces, such as attractiveness, trustworthiness, and intelligence, using a computational framework

**Authors: *A. J. YU**[1], J. GUAN[1], C. K. RYALI[2]
[1]Cognitive Sci., [2]Computer Sci. and Engin., Univ. of California San Diego, La Jolla, CA

**Abstract:** Face processing plays a central role in everyday life: humans readily infer personality traits such as attractiveness, trustworthiness, and intelligence, from a glance of a stranger's face. While the veracity of these social trait impressions is under debate, they exert a significant influence on real-life decisions, e.g. choosing a mate, interpreting witness testimony, interviewing a potential hire, or deciding whom to befriend in a crowd of strangers. Previous attempts to characterize the facial (physiognomic) features underlying personality trait judgments have lacked either systematicity or interpretability. In this work, we utilize a novel computational framework to tackle this problem, by combining a latent face representation and a linear mapping between this face space and human social trait judgments. Specifically, we represent the space of all faces using the Active Appearance Model, which has recently been shown to have latent features encoded by face patch cells in the macaque monkey, and use linear regression to finding linear combinations of facial features that maximally account for human perception of 20 social traits in a large dataset of faces and social judgments. In terms of systematicity, our model achieves state-of-the-art prediction on trait judgments -- competitive with the best convolutional neural network so far. To tackle interpretability, we present a novel dual space analysis to characterize the linear combination of features that drives the perception of each trait. We find that facial features important for social perception are largely distinct from those underlying demographic and emotion perception, contrary to previous suggestions that personality impressions are driven by demographic perception or are over-generalizations of the emotion perception system. We also use synthetically generated faces to visualize the constituent facial features underlying the perception of different social traits, and interpret these features in terms of a large repertoire of geometric features. Finally, we present a novel correlation decomposition analysis that parses trait judgment correlations (e.g. attractiveness and dominance) into the distinct roles played by (1) facial features that drive the perception of multiple social traits and (2) correlations in the distribution of facial features in the human population - this analysis yields novel and surprising insights into human face perception.

**Disclosures: A.J. Yu:** None. **J. Guan:** None. **C.K. Ryali:** None.

**Poster**

**789. Human Cognition and Behavior: Perception and Imagery II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 789.04/JJJ14

**Topic:** H.02. Human Cognition and Behavior

**Support:** Intramural Research Program for NIMH

**Title:** Domain specificity within human medial parietal cortex during memory recall

**Authors: *E. H. SILSON**[1], A. D. STEEL[2,4], A. KIDDER[5], C. I. BAKER[3]
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**Abstract:** Human medial parietal cortex, is commonly considered a component of the default mode network and implicated consistently in both memory encoding and retrieval. Within medial parietal cortex the parietal-occipital sulcus (POS) provides an anatomical landmark that separates regions more involved in visual scene processing (posterior-ventral) from those more involved in scene construction from memory (anterior-dorsal). Functional connectivity with scene- and face-selective regions of ventral temporal cortex reveals an alternating pattern of regions within medial parietal cortex – scene, face, scene – along an axis largely orthogonal to the POS. Such a pattern suggests domain-specific subdivisions for memory within medial parietal cortex.

Here, we tested this domain-specific prediction using task-based fMRI. Participants (n=20) completed a memory task in which they were cued via word stimuli to recall famous people (e.g. Brad Pitt), famous places (e.g. Statue of Liberty), personally familiar people (e.g. participants' own mother) or personally familiar places (participants' own home).

We identified three medial parietal regions of interest (ROIs) using independently acquired resting-state functional connectivity data. Traversing anteriorly along the axis orthogonal to POS, BOLD activity evoked by recollection of either places or people exhibited an alternating pattern of response that corresponded with the functional connectivity preferences. These regions showed strong preference for both category and familiarity, exhibiting greater activity during recall of personally familiar items

compared to famous items within the preferred category defined by the functional connectivity. These results demonstrate alternating domain-specific regions in medial parietal cortex during memory recall and suggest a more heterogeneous organization of mnemonic representations in medial parietal cortex than previously thought. The organizational principles that define the perceptual network in ventral temporal cortex appear to be recapitulated for memory in the medial parietal portion of the 'default mode' network.

**Disclosures: E.H. Silson:** None. **A.D. Steel:** None. **A. Kidder:** None. **C.I. Baker:** None.

**Poster**

**789. Human Cognition and Behavior: Perception and Imagery II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 789.05/JJJ15

**Topic:** H.02. Human Cognition and Behavior

**Title:** Distinct subdivisions of medial parietal cortex revealed by functional connectivity with category-selective ventral temporal cortex

**Authors: *A. D. STEEL**[1], E. H. SILSON[3], C. I. BAKER[2]
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**Abstract:** Domain-specificity is a core organizing principle of human ventral temporal cortex (vTC), with, for example, regions selectively responses to scenes and faces, in the parahippocampal place area (PPA) and fusiform face area (FFA), respectively. For PPA, it has been suggested that information evolves from concrete to more abstract representations along the posterior to anterior axis. Consistent with this hypothesis, contrasting functional connectivity of posterior and anterior PPA reveals a region in medial parietal cortex anterior to parietal occipital sulcus that is active during mental imagery of scenes and mental navigation. However, the extent that other category-selective regions in vTC are functionally connected to regions of medial parietal cortex is unclear. Here, we investigated the functional topology of medial parietal cortex based on its resting state functional connectivity with vTC. Functional connectivity of anterior FFA and PPA was calculated for each participant (n = 68) revealing interdigitated PPA- and FFA- preferring regions that alternated their preferred connectivity (PPA, FFA, PPA) along an axis orthogonal to the parietal occipital sulcus. Further, these regions exhibited corresponding face- and scene-selectivity in independent functional localizer data. Further exploration of the individual regions revealed category-specific decreases in BOLD, such that the BOLD decrease was largest for non-preferred categories. These results suggest that medial parietal cortex may be subdivided based on differential functional connectivity to vTC, and that these divisions show characteristic responses to high-level visual categories. Further, given the high-degree of overlap with regions implicated in episodic memory recall, these data suggest that domain-specificity, which is a hallmark of vTC organization, may also be a defining feature of medial parietal cortex in the context of memory.

**Disclosures: A.D. Steel:** None. **E.H. Silson:** None. **C.I. Baker:** None.

**Poster**

**789. Human Cognition and Behavior: Perception and Imagery II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 789.06/JJJ16

**Topic:** H.02. Human Cognition and Behavior

**Support:** National Institute of Mental Health Intramural Research Program (ZIAMH002920)

**Title:** Separating scene perception and scene construction in human medial parietal cortex

**Authors: *A. W. GILMORE**, E. H. SILSON, S. E. KALINOWSKI, A. STEEL, A. KIDDER, C. I. BAKER, A. MARTIN
Lab. of Brain and Cognition, NIMH/NIH, Bethesda, MD

**Abstract:** The retrosplenial complex (RSC) has been associated with multiple scene-related cognitive functions, including visual scene perception, spatial navigation, autobiographical memory retrieval and episodic future thought. Located in medial parietal cortex, RSC encompasses retrosplenial cortex proper, but also extends into the parieto-occipital sulcus (POS) posteriorly and to the precuneus and posterior cingulate cortex dorsally. Recently, a distinction was proposed between anterior and posterior aspects of the RSC, such that posterior aspects preferentially process visual information and are organized retinotopically (constituting a "medial place area;" MPA), whereas anterior aspects process information retrieved from memory to construct vivid scenes and scenarios (Silson, Steel, and Baker, 2016). Here, we tested this proposed separation of processes within RSC within a single group of participants using fMRI. After completing a resting-state scan, participants performed a memory task in which they covertly recalled episodes from their past and imagined hypothetical future scenarios, and then completed a scene/face localizer task. Anterior and posterior regions within RSC were identified based on different patterns of resting-state functional connectivity, a division consistent with results from the memory and localizer tasks. A double dissociation was observed, such that anterior RSC was more strongly associated with remembering or imagining events than was MPA, whereas MPA was more scene-selective than the anterior RSC region. In examining effects within subjects, peak responses from the (constructive) memory task were anterior to peaks identified in the (perceptual) scene localizer task in all but one hemisphere of one participant. Subsequent analyses identified the fundus of the POS as a potential cross-over point between cortex that preferentially relates to scene perception and scene construction. These results highlight functional heterogeneity within medial parietal cortex and RSC and suggest that alternative, more specific cortical labels are desirable in future work.

**Disclosures: A.W. Gilmore:** None. **E.H. Silson:** None. **S.E. Kalinowski:** None. **A. Steel:** None. **A. Kidder:** None. **C.I. Baker:** None. **A. Martin:** None.

**Poster**

**789. Human Cognition and Behavior: Perception and Imagery II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 789.07/JJJ17

**Topic:** H.02. Human Cognition and Behavior

**Title:** Investigating auditory conscious perception with a threshold task and intracranial EEG

**Authors: *K. L. CHRISTISON-LAGAY**[1], C. MICEK[1], S. I. KRONEMER[1], S. FORMAN[1], M. AKSEN[1], A. ABDEL-ATY[2], F. VAN DUYNE[4], M. BOLY[5], E. JUAN[6], T. BUGNON[6], E. M. YEAGLE[7], J. L. HERRERO[7], S. BICKEL[8], A. D. MEHTA[9], L. J. HIRSCH[1], J. L. GERRARD[3], D. D. SPENCER[3], H. BLUMENFELD[1]
[1]Dept. of Neurol., [3]Dept. of Neurosurg., [2]Yale Univ. Sch. of Med., New Haven, CT; [4]Yale Univ., New Haven, CT; [5]Departments of Neurol. and Psychiatry, [6]Univ. of Wisconsin-Madison, Madison, WI; [7]Feinstein Inst. For Med. Res., Manhasset, NY; [8]Neurosurg. / Neurol., Hofstra Northwell Sch. of Med., Manhasset, NY; [9]Neurosurg., Hofstra North Shore LIJ Sch. of Med., Great Neck, NY

**Abstract:** Recent work has made significant headway in understanding the temporal and spatial dynamics of the neural mechanisms of consciousness. Our lab previously developed a perceptual threshold task that used a face stimulus calibrated to a participant's 50% detection rate (Herman et al. 2018, Cerebral Cortex). Participants were subsequently prompted to report whether they perceived the stimulus, and the stimulus' location (to validate perception). We have used this visual paradigm in conjunction with intracranial electroencephalography (icEEG) in patients with intractable epilepsy and found initial activation of early visual cortex for both perceived and not perceived stimuli. In perceived trials only, this was followed by a decrease in both the early visual areas and the default mode network and a wave of activity that swept through the cerebral cortex, followed by a late reactivation of the early visual areas. We call this pattern of activity the "switch-and-wave." In the current study, we expand our investigation of conscious perception to the auditory domain to establish whether similar "switch-and-wave" activity accompanies conscious auditory perception. We have developed an auditory counterpart to our visual task, in which three target sounds are calibrated to a participant's 50% detection threshold and embedded in auditory white noise. A target sound (a whistle, a 'laser', or a waterdrop) is presented for 75ms, and participants are prompted to report whether they perceived the sound, and the sound's identity (to validate perception); for trials in which participants indicate they do not hear a sound, they are asked to randomly guess on the forced-choice question about sound identity. In behavioral studies (n=25), we found that the stimulus perception rate was 57.5% (2.7% SEM) when the target was present whereas the false positive rate was 10.9% (2.9% SEM) for blank trials. When participants indicated they heard a target sound, they correctly indicated the sound's identity in 89.5% (2.3% SEM) of trials; when they indicated they had not heard a

sound, sound identification accuracy was 36.7% (2.2% SEM) (chance is 33%). Therefore, this represents a robust behavioral paradigm for testing conscious auditory perception. We have begun testing this auditory paradigm in epilepsy patients with icEEG at multiple centers. Early analyses of broadband gamma power suggest there are similarities in the conscious perception of auditory and visual stimuli. Analyses of broadband gamma power in relation to this task are ongoing.

**Disclosures: K.L. Christison-Lagay:** None. **C. Micek:** None. **S.I. Kronemer:** None. **S. Forman:** None. **M. Aksen:** None. **A. Abdel-Aty:** None. **F. van Duyne:** None. **M. Boly:** None. **E. Juan:** None. **T. Bugnon:** None. **E.M. Yeagle:** None. **J.L. Herrero:** None. **S. Bickel:** None. **A.D. Mehta:** None. **L.J. Hirsch:** None. **J.L. Gerrard:** None. **D.D. Spencer:** None. **H. Blumenfeld:** None.

**Poster**

**789. Human Cognition and Behavior: Perception and Imagery II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 789.08/JJJ18

**Topic:** H.02. Human Cognition and Behavior

**Title:** Intracranial EEG topography of neural networks with transient and sustained shifts in attention

**Authors: *J. LI**[1,4], S. KRONEMER[1,2], H. KWON[1], C. MICEK[1], J. RYU[1], M. AKSEN[1], W. HERMAN[1,2], Y. WU[4], J. GERRARD[3], D. D. SPENCER[3], H. BLUMENFELD[1,2,3]
[1]Neurol., [2]Neurosci., [3]Neurosurg., Yale Univ., New Haven, CT; [4]State Key Lab. for Strength and Vibration of Mechanical Structures, Xi'an Jiaotong Univ., Xi'an, China

**Abstract:** Daily activities require frequent updating of attentional states to guide behavior towards salient stimuli and ignore distractors. Task-specific transient and sustained changes in attention networks are commonly studied utilizing attention paradigms that focus on either event (e.g., individual stimuli) or state-related (e.g., active vs. rest phases) designs. The mechanisms that drive state versus event-related attention network changes may be shared. The current study aims to investigate the spatiotemporal dynamics for state and event-related attention network demands utilizing intracranial EEG (icEEG). Adult, intractable epilepsy patients (n = 11; females = 6) undergoing icEEG implantation (100-300 subdural electrodes; sampling frequency = 1024 Hz) were recruited from the Yale Epilepsy Surgery Program. While in-patient seizure monitoring was underway, patients were asked to complete a computerized task with two main task phases: rest and active phases. During the rest phase (32 seconds) the patients were asked to fixate on a cross. The active phase (32 seconds) required participants to make a button press for a target stimulus (“X”) in a stream of English letters. Thus, this paradigm combines state (rest versus active phases) and event (letter stimuli) attention network demands. Broadband gamma (40-115

Hz) power change to task phases and stimuli were analyzed because this frequency of electrophysiological activity has been previously shown to correspond to population neuronal firing. In addition, data-driven k-means clustering was utilized to correlate gamma power time courses among brain regions. Results show gamma power increases in the SMA, primary visual cortex, precentral gyrus, and anterior insula at the junction between rest (fixation) and task onset, and again with task offset and rest onset. Sustained signal increases during the task phase were observed among motor regions (e.g., primary motor cortex) and decreases in the default mode network (e.g., the precuneus and ventral medial prefrontal cortex). Target and non-target stimuli revealed transient increases of gamma power in the visual primary and association cortex. Target stimuli k-means clustering of gamma power change indicated discrete spatial clusters, including a visual cortex cluster, a primary motor cortex cluster, and multiple association cortex clusters. These results suggest that attention networks are modulated at state and event-specific levels to optimize performance when attention is required and to disengage during rest. Deficits to the neural mechanisms that drive these attention network dynamics may result in diminished behavioral performance.

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**Poster**

**789. Human Cognition and Behavior: Perception and Imagery II**

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**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 789.09/JJJ19

**Topic:** H.02. Human Cognition and Behavior

**Title:** Relationship between stimulus opacity and intracranial broadband gamma power in a conscious visual perception task

**Authors: *C. MICEK**[1], K. L. CHRISTISON-LAGAY[1], M. WILLIAMS[1], S. I. KRONEMER[1,2], W. X. HERMAN[1], J. LI[1], L. J. HIRSCH[1], J. L. GERRARD[3], D. D. SPENCER[3], H. BLUMENFELD[1,2,3]
[1]Neurol., [2]Neurosci., [3]Neurosurg., Yale Univ. Sch. of Med., New Haven, CT

**Abstract:** The precise neural mechanisms of conscious perception are not well understood, but are of fundamental importance in understanding normal brain function as well as cognitive disorders. Previous work from our lab assessed normal conscious perception in 9 subjects using broadband gamma (40 - 115 Hz) intracranial EEG (icEEG) recording while performing a threshold visual perception task with a constant face image presented at each subject's 50% perceptual threshold (Herman et al., 2018, Cerebral Cortex). We described a widespread "switch and wave" of cortical activity occurring with consciously perceived stimuli, whereas not-

perceived stimuli only elicited transient activity confined mainly to visual cortex. One unanswered question was the possible effect of stimulus strength on the cortical switch and wave activity. In addition to the constant stimulus phase of the study we also performed a calibration phase in which the faces were presented at 25 different opacities. This provided an opportunity for us to investigate relationships between stimulus opacity and cortical broadband gamma activity. Analysis of data from the calibration phase shows results similar to the constant stimulus phase. On average the perceived stimuli elicited a widespread wave of increased broadband gamma activity in the frontoparietal association cortex extending to the medial temporal lobes, as well as a switch off of activity in visual cortex and the default mode network. In addition, the not-perceived stimuli elicited transient broadband gamma activity increases mainly confined to visual cortex. For perceived stimuli, we analyzed the relationship between stimulus opacity and broadband gamma activity in the visual cortical regions identified in our prior study and found a significant positive correlation ($p < 0.05$). Ongoing analyses will further investigate the relationship between stimulus opacity and gamma activity in other brain regions to determine if linear or non-linear transitions occur which may account for differences between consciously perceived vs. not-perceived stimuli.

**Disclosures: C. Micek:** None. **K.L. Christison-Lagay:** None. **M. Williams:** None. **S.I. Kronemer:** None. **W.X. Herman:** None. **J. Li:** None. **L.J. Hirsch:** None. **J.L. Gerrard:** None. **D.D. Spencer:** None. **H. Blumenfeld:** None.

**Poster**

**789. Human Cognition and Behavior: Perception and Imagery II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 789.10/JJJ20

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH Grant R01NS055829

**Title:** Early and late electrophysiological changes to visual conscious perception

**Authors: *S. I. KRONEMER**[1,2], M. AKSEN[1], H. KWON[1], C. MICEK[1], K. L. CHRISTISON-LAGAY[1], S. FORMAN[1], J. S. PRINCE[1], J. DING[1], J. RYU[1], M. KHOSLA[1], E. SABERSKI[1], U. AYDIN[6], C. GROVA[6], J. WU[3], M. CROWLEY[3], R. T. CONSTABLE[4], H. BLUMENFELD[1,2,5]
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**Abstract:** Recent neuroimaging findings show that consciousness involves multiple, spatially discrete brain regions, including subcortical (e.g., brainstem, thalamus, and striatum) and cortical networks (e.g., association cortex, default mode network, and sensory cortex). The precise temporal dynamics that define the sequence of activity among these regions remain unknown.

Previous electrophysiological recordings suggest both early (<200ms) and late (>300ms) temporal dynamics facilitate the ignition of consciousness and the perceptual and post-perceptual processing of a conscious event, respectively. The current investigation interrogates the spatiotemporal dynamics for conscious-linked activity with a specific emphasis on the detection or ignition mechanisms that may drive the non-linear propagation of activity from sensory to association cortices. In addition, this study examines how precursor fluctuations in brain state influence subsequent activity among detection and perceptual processing networks. We hypothesize that the networks that drive stimulus detection, including primary and higher association cortices may engage approximately 100-300ms post-stimulus. Healthy, adult participants (N = 57, females = 37) were recruited to record simultaneous electrophysiological signals with 256-channel high-density scalp EEG (Electrical Geodesics, Inc.) and binocular pupillometry (SR Research) while completing an at-threshold visual perception task. Individual T1-weighted, whole-brain anatomical MRI (Siemens Medical Systems, Germany) and photogrammetry were collected to model scalp sensor three-dimensional locations and estimate the cortical surface source of scalp broadband gamma (40-115Hz) activity. Preliminary event-related potential findings comparing perceived versus not perceived stimuli replicate previous findings of a sustained potential from 300ms post-stimulus onset (P300). Source localization of broadband gamma activity reveals activity among cortical networks corresponding with previous intracranial EEG and fMRI findings, including visual cortex signal 100-200ms post-stimulus onset for both perceived and not-perceived stimuli, and association cortex signal >300ms for perceived stimuli only. These results indicate source localization of scalp EEG data can be an ideal method aimed to resolve inquiries on the spatiotemporal characteristics of conscious-linked activity. In addition, pupillometry recordings establish pupil dilation, microsaccade, and blink rate as distinguishing physiological measures of perceived and not perceived visual stimuli.

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**Poster**

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**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 789.11/JJJ21

**Topic:** H.02. Human Cognition and Behavior

**Title:** Potential novel mechanism for the attentional blink in a conscious perception task

**Authors: *S. FORMAN**[1], K. L. CHRISTISON-LAGAY[1], C. MICEK[1], S. I. KRONEMER[1,2], M. AKSEN[1], M. M. CHUN[4,2], H. BLUMENFELD[1,2,3]

[1]Dept. of Neurol., [2]Neurosci., [3]Neurosurg., Yale Univ. Sch. of Med., New Haven, CT; [4]Psychology, Yale Univ., New Haven, CT

**Abstract:** The attentional blink is a robust behavioral phenomenon in which individuals fail to see a second stimulus when it is presented at a specific delay relative to a first stimulus. While this phenomenon has been studied for decades, the exact mechanisms involved in the attentional blink remain somewhat unclear. In a recent intracranial EEG study in our lab, it was revealed that when a person consciously perceives a stimulus (a face titrated to a person's 50% detection threshold), a small initial increase in gamma power in the visual cortex is observed followed by a robust decrease in gamma power in the visual cortex with a nadir at around 350ms (Herman et al., 2018, *Cerebral Cortex*). This activation and subsequent deactivation in the visual cortex corresponds well with the timing of the attentional blink, and therefore, presents a possible mechanism for the phenomenon. To investigate whether an attentional blink occurs during this decrease in activity in V1, we modified our original task to include a second stimulus (X) that was presented after the face. In the present study, participants were instructed to fixate on a stream of block letters presented in the center of the screen for the duration of each trial. After a delay, a face stimulus (T1), that was calibrated to the participant's 50% detection threshold, was presented for 50ms in one quadrant of a computer screen. The X (T2) was embedded in the stream of the letters and presented for 50ms either 200ms, 300ms, or 600ms after the face presentation. On 12% of trials no face was presented and on 20% of trials no X was presented (blanks). Following each trial participants were asked three questions: 1) Did you see a face? 2) Where was it located? 3) Did you see an X? When participants reported that they had not seen the face (no perception of T1), they had a high rate of T2 report regardless of the T2 delay. However, when participants accurately reported T1, their ability to report T2 was significantly reduced at delays of 200ms and 300ms ($p<0.05$, corrected for multiple comparisons); but their ability to report T2 was preserved at a delay of 600ms. These behavioral results suggest there is a "blink" in our current paradigm, which aligns with the timing of the observed decrease in activity in the visual cortex in our previous study. We are currently further investigating the relationship between the behavioral "blink" and decrease in gamma power in V1 via scalp EEG.

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**Poster**

**789. Human Cognition and Behavior: Perception and Imagery II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 789.12/JJJ22

**Topic:** H.02. Human Cognition and Behavior

**Title:** Pupil dynamics as a covert measure of conscious perception in a visual no report paradigm

**Authors: *M. AKSEN**[1], S. I. KRONEMER[1,2], J. S. PRINCE[1], Z. DING[1], A. AGARWAL[1], G. WOLF[3], B. PEARLMUTTER[6], R. COIFMAN[3,4], M. PITTS[7], H. BLUMENFELD[1,2,5]
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**Abstract:** Despite competing models for the neural mechanisms of conscious perception, neuroimaging and electrophysiological studies have found that perception involves broad signal propagation from sensory to association cortex over hundreds of milliseconds following the onset of a detected stimulus. A primary challenge for the neuroscience of consciousness is that parallel cognitive functions co-occur with perception (e.g., working memory) and may partially account for signal that is interpreted as being consciousness-linked. Most studies of consciousness in humans facilitate this limitation by requiring recall of perceptual experiences. Perceptual reports are critical for the experimenter to determine whether stimuli were perceived, yet the neural networks required for report may confound the activity specific to perception. In particular, it is speculated that at least a portion of signal from previous investigations, particularly late activity (>500ms post-stimulus), may be specific to perceptual report. To address the confound of perceptual report, a no-report paradigm is necessary to covertly monitor the percepts of a participant without overt report instead utilizing a physiological measure that acts as a proxy for perceptual report. Previous work from our lab and others shows that in a report paradigm pupil size, blink, and microsaccade rate discriminate between perceived and not perceived stimuli. Importantly, utilizing pupil size alone, a linear-kernel support vector machine (SVM) classifier predicts perception of *individual* trials at 75% accuracy on average for all trials and up to 90% accuracy when sampling the most confident third of trials. However, it is unclear if these pupillary, microsaccade, and blink responses are specific to a report paradigm. To test this, we recruited healthy, adult participants to complete a novel no-report paradigm with simultaneous 1000 Hz binocular pupillometry (EyeLink 1000 Plus, SR Research) to determine if pupil size, eye movements, and blinks offer predictive value of percepts in a no-report setting. The no-report paradigm involves task-relevant (reported) and task-irrelevant stimuli (not reported), either of which may or may not be perceived. Preliminary findings show that perceptually-linked pupil changes in the no-report paradigm are similar to those of our report paradigm. Moreover, these trials can be confidently classified utilizing the SVM parameters trained on report paradigm data. These results suggest that pupillometry may be used in conjunction with a neuroimaging and/or neurophysiology approaches and a no-report paradigm to isolate the neural mechanisms of consciousness.

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**Poster**

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**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 789.13/JJJ23

**Topic:** H.02. Human Cognition and Behavior

**Support:** NSF

**Title:** Studying auditory processing in group contexts with low-density wireless eeg

**Authors: A. K. KHALIL**[1], *Y. WU[2], J. R. IVERSEN[1]
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**Abstract:** This study examines the feasibility of studying auditory perception in multi-participant, free-field contexts using customized, research-grade low density (four to eight channels), wireless, dry EEG headsets. Large numbers of such easy to use headsets open many possibilities for data collection efficiency, as well as group brain dynamic studies. Research goals in this proof-of-concept were twofold. First, it was investigated if classic ERP components, such as N1, P2, mismatch negativity (MMN), and P300 complex, could be measured using this novel approach, and if well-documented effects associated with target detection can be replicated in a less-controlled, ecological setting. Second, it was explored if varying instructions to co-present participants can lead to task-related differences in observed effects. 39 healthy adults engaged in an auditory oddball detection task in groups of two to five. Stimuli were three types of 339 ms sinusoid pulses (250Hz, 650Hz, and 150Hz) presented over a powered speaker. Standards were presented pseudo-randomly at an 80% probability. The two types of oddball pulses occurred pseudo-randomly at a 10% probability, yielding an interchangeable set of targets and distractors. Participants were assigned to count one of the two types of oddball stimuli and ignore the other in a counterbalanced manner. In keeping with existing work, grand averaged ERPs revealed that stimulus probability modulated the amplitude of ERP components within the time window of the N1 ($F(2,68) = 6.4$, $p < 0.01$) and P300 ($F(2,68) = 37.6$, $p < 0.01$), while attention modulated the amplitude of the MMN ($F(1,34) = 6$, $p < 0.01$), as well as ERP responses to oddball targets within the window of the P2 ($F(2, 68) = 7.2$, $p < 0.01$), P300 ($F(2,68) = 37.6$, $p < 0.01$), and the late positive component ($F(6,204) = 44$, $p < 0.01$). Outcomes offer proof of concept that fine-grained measures of auditory processing and attention can be easily obtained in more naturalistic contexts, opening new possibilities for studying cognition and social dynamics outside of traditional laboratory settings.

**Disclosures: A.K. Khalil:** None. **Y. Wu:** None. **J.R. Iversen:** None.

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**789. Human Cognition and Behavior: Perception and Imagery II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 789.14/JJJ24

**Topic:** H.02. Human Cognition and Behavior

**Title:** Mapping modality invariance across visual and auditory narratives with between-brain spatial pattern methods

**Authors: *P. S. JOHNSON**[1], M. REGEV[3], U. HASSON[4], J. CHEN[2]
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**Abstract:** Spoken and written language, while different in their sensory properties, often seem to be interchangeable in terms of the meaning we ultimately receive from them. How does the brain support this convergence despite the separation of visual and auditory processing pathways? What brain regions are biased toward modality-specific processing, and which are modality-invariant? Prior work has mapped modality specificity and invariance in the brain using temporal inter-subject correlation (ISC) methods (Hasson 2004), which measure stimulus-driven response via time-aligned activity across subjects. Modality specificity is reflected in greater alignment among subjects exposed to a given sensory input type (e.g., visual or auditory) than between subjects exposed to different input types; modality invariance is indicated by significant alignment regardless of input type. In Regev et al. (2013), two groups were presented with the same story either spoken or written. Modality invariance was found in high-level cognitive areas, largely overlapping with language regions and the default mode network (DMN). The primary goal of the current work is to use a similar paradigm to Regev (2013) - subjects listening or reading the same story - to ask how specificity and invariance manifest across the cortical hierarchy, using spatial pattern correlation across subjects (Chen et al., 2017) rather than temporal alignment, and using a new narrative stimulus. 18 subjects participated in the text reading condition (Regev et al., submitted) and 18 subjects in the speech listening condition. The two stimuli were not time-aligned, having been brought together from two different sources. As the inter-subject analyses are based in the idea of temporally aligned stimuli, we performed a piecewise interpolation to transform the Listening condition BOLD responses (~13.5 minutes) to temporally match the Reading condition BOLD responses (~15 minutes). Preliminary results show that spatial pattern methods broadly replicate the results of the prior temporal alignment study: low pattern similarity was observed between groups in sensory areas (auditory and visual cortices), while high pattern similarity was observed between groups in DMN and language regions. Applying dimensionality reduction methods to spatial patterns suggests that dynamics of similarity across the narrative are robust across different reduction methods. Future analyses will

explore how semantic and structural linguistic features of the narrative contribute to moment-by-moment differences between the reading and listening brain responses.

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**Poster**

**789. Human Cognition and Behavior: Perception and Imagery II**

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**Topic:** H.02. Human Cognition and Behavior

**Support:** Research Council of Norway - grant number 240389/F20
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**Title:** Human insula response to auditory deviants: Evidence from intracranial EEG recordings

**Authors: *A. O. BLENKMANN**[1], J. LUBELL[1], A. LLORENS[2], I. FUNDERUD[1], S. COLLAVINI[3], P. G. LARSON[2], J. IVANOVIC[2], T. R. MELING[2], T. BEKINSCHTEIN[4], S. KOCHEN[3], T. ENDESTAD[1], R. T. KNIGHT[5], A.-K. SOLBAKK[1]
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**Abstract:** The insular cortex is involved in multiple functions, including speech production, experience of emotions, interoceptive awareness, and salience processing. Neuroimaging and lesion studies have demonstrated that the insula is also involved in auditory processing (Bamiou et al., 2003). However, little is known about the electrophysiological basis of the insula underlying auditory deviance detection (i.e. the mismatch between standard and deviant tones).To address this we recorded intracranial EEG from 16 adult patients with drug resistant epilepsy undergoing presurgical monitoring who had depth electrodes implanted in subregions of the insula. Patients passively listened to a stream of bilaterally presented tones while reading. The paradigm consisted of 300 standard tones interleaved with 300 deviant tones per block. Patients completed between 3 to 10 blocks of passive listening. Deviant tones differed from standard tones in: 1) intensity (louder or softer), 2) frequency (higher or lower), 3) sound source location (right or left), or 4) timing (a shorter duration, or a silent gap in the middle of the tone) (Näätänen et al., 2004). Electrode coordinates were obtained from coregistered MRI and CT images using iElectrodes toolbox (Blenkmann et al., 2017). Intracranial EEG data was manually cleaned to remove artifacts, filtered, downsampled and epoched. Channels were bipolar referenced and high frequency band activity (HFA) analytic amplitude signal was obtained using the Hilbert transform (75-145 Hz). There were a total of 90 channels in the insula across the

sixteen patients. Forty-four percent of the channels showed significant HFA activations to tones when compared to the baseline period. Notably, sixty-eight percent of these channels showed significantly different HFA activations to deviant tones compared to standard ones. Some channels showed deviant-specific activations to one particular deviance condition, while others showed activations to a combination of two or more deviants. The channels showing auditory responses and auditory deviancy effects were more prevalent in the posterior relative to the anterior insula. Our results reveal that the human insula is involved in auditory sound processing and deviance detection, thereby providing evidence for a key role of the insula in the predictive processing of the auditory environment.

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**Poster**

**789. Human Cognition and Behavior: Perception and Imagery II**

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**Program #/Poster #:** 789.16/JJJ26

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH Grant EY022350

**Title:** How are the statistics of object co-occurrence represented in cortex?

**Authors: *M. F. BONNER**[1], R. A. EPSTEIN[2]
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**Abstract:** Many objects have a natural place in the world—a location or context where they can typically be found. For example, tea kettles and stoves are often found in kitchens, while fire hydrants and traffic lights are found on city sidewalks. This type of contextual knowledge can help people identify where they are in the world (e.g., “I’m in the kitchen”) and what other objects they might encounter. A key issue for characterizing how contextual knowledge is represented in the human brain is understanding the statistical structure of object co-occurrence in the natural environment. Here we used a technique adapted from computational linguistics to identify the latent statistical structure of object co-occurrence in a set of 22,000 natural images in which every object was manually labeled. This quantitative model generates a set of multidimensional embeddings that capture information about the contexts in which objects typically occur. We used these embeddings in an fMRI experiment to examine the cortical representation of contextual knowledge during natural object perception. In the scanner, subjects viewed a large set of objects, shown individually with no scene background. Using voxelwise

encoding models, we identified linear mappings between the contextual embeddings of objects and their associated cortical responses, and we assessed whether these models could predict the fMRI responses to a held-out set of objects. Our preliminary findings suggest that high-level visual cortex routinely encodes contextual associations when viewing individual, isolated objects, even when this information is not present in the immediate perceptual scene. These representations were most prominent in scene-selective regions, which have previously been implicated in the processing of spatial environments and navigational landmarks. These findings suggest that a key function of scene-selective cortex is to link the local perceptual scene with statistical representations of object co-occurrence in the natural environment.

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**Poster**

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**Title:** The role of local symmetry in the neural representations of scene categories

**Authors: *J. WILDER**[1], M. REZANEJAD[2], S. DICKINSON[1], K. SIDDIQI[2], A. JEPSON[1], D. B. WALTHER[1]
[1]Univ. of Toronto, Toronto, ON, Canada; [2]McGill Univ., Montreal, QC, Canada

**Abstract:** Humans have the ability to categorize briefly flashed images of real-world scenes, even when simplified to line drawings. It is still unknown which image features underlie this ability. This feat requires rapidly processing local information in an image to come to a global assessment. In the 1900s, the Gestalt psychologists proposed grouping rules that give a qualitative account for how edge segments or shape parts in an image are grouped into larger structures. One such principle is symmetry. We recently proposed an algorithm for analyzing the local ribbon symmetry content of line drawings of complex real-world scenes (Rezanejad et al., MODVIS 2017). This method gives contour pixels a high score when that contour has a slowly changing distance to another nearby contour (i.e. is roughly parallel), while a low score is given to a contour that undulates independently of nearby contours. We used these scores to partition

the contour pixels in a line drawing into two disjoint sets, the most ribbon symmetric and the least ribbon symmetric. Each set yields an image, either symmetric or asymmetric, containing exactly half of the contour pixels. In a rapid categorization experiment, observers were better at classifying the symmetric images than the asymmetric ones (Wilder et al., VSS 2017). In order to understand how the visual system makes use of local symmetry information, we conducted an fMRI study. Using a block design, we showed human observers these same scenes; either the full intact images, the most ribbon symmetric half-images, or the least ribbon symmetric half-images. Scene categories were decoded from neural activity patterns in several regions of interest (ROIs), namely, V1, V2, V3, V4, the fusiform face area (FFA), the lateral occipital complex (LOC), the retrosplenial cortex (RSC), and the parahippocampal place area (PPA). Decoding accuracy was above chance for early visual areas (V1-V4), but did not systematically vary between image conditions. Overall, decoding accuracy in higher-level visual areas was higher than in V1-V4. Importantly, we found an advantage for decoding scene category from neural activity when participants viewed symmetric scenes over when participants viewed asymmetric scenes. Furthermore, decoding accuracy in the high-level ROIs was the same in the symmetric as in the intact condition but lower in the asymmetric condition. Our results show that the symmetric condition preserves essential information about scene content that is lost in the asymmetric condition. One intriguing possibility is that local ribbon symmetry is incorporated into the visual system's representation of real-world scenes at a relatively high level of processing.

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**Topic:** H.02. Human Cognition and Behavior

**Support:** NEI R01EY026042

**Title:** T

**Authors: *J. PARK**[1], S. PARK[1,2]
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**Abstract:** Detecting local boundaries that impose limits to locomotion is crucial for navigation. In a series of fMRI experiments, we investigated whether there is a coding of navigational distance provided by a local boundary, if it is sensitive to different amount of navigational distance, and how the functional constraint of a boundary plays a role. We used a Virtual Reality

software to render indoor environments with different types of a boundary and to systematically manipulate distance to such boundaries. In Experiment 1 (N=15), we asked whether scene-selective regions code for navigational distance to the boundary. Stimuli had 3 levels of distance to the back wall (Near, Middle, Far) with a local boundary factor (Glass-Wall, No-Glass-Wall). In Glass-Wall condition, a transparent glass-wall restricted the navigational distance while keeping the visibility of the back wall the same as No-Glass-Wall condition. Critically, the distance to the glass-wall was always kept the same. If a brain region represents the navigational distance, neural patterns of such region will distinguish Near, Middle and Far in No-Glass-Wall condition but not in Glass-Wall condition. Using a multivoxel pattern classification employing a linear support vector machine, we found such results in the Occipital Place Area (OPA) suggesting its sensitivity to the navigational distance restricted by the glass-wall. If OPA truly codes for the navigational distance, then it should distinguish different amount of distance restricted by the glass wall. Experiment 2 (N=14) addressed this question by varying the position of a glass-wall while keeping the visible distance the same. As predicted, the OPA showed a significant classification for Glass-Wall condition where navigational distance varied, but not for No-Glass-Wall condition. These results show that the OPA is sensitive to changes of navigational distance restricted by the local boundary. In Experiment 3 (N=15), we tested whether the functional constraint of a boundary matters for coding the navigational distance. In Curtain condition, a crossable boundary (a transparent curtain) was placed instead of the glass-wall. The OPA's classification of distance in Curtain condition resembled that of No-Glass-Wall condition but differed from Glass-Wall condition, implying an importance of the functional constraint of a boundary. Together, this study provides a series of evidence that OPA is sensitive to boundaries that limit movements and represents the distance to those boundaries, suggesting that human scene-selective cortex may act as a perceptual source of critical information for navigation.

**Disclosures: J. Park:** None. **S. Park:** None.

**Poster**

**789. Human Cognition and Behavior: Perception and Imagery II**

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**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 789.19/JJJ29

**Topic:** H.02. Human Cognition and Behavior

**Title:** Uncovering the temporal dynamics of scene understanding using event-related potentials

**Authors: *A. HAREL**
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**Abstract:** Humans show remarkable abilities in recognizing scenes. These abilities are especially impressive considering how many dimensions scenes vary on, ranging from low-level

image-statistics to high-level semantics and action affordances. It has recently been suggested that the visual system overcomes this computational complexity by extracting the scene's global scene properties (GSPs) (Greene and Oliva, 2009). GSPs are intermediate-level scene primitives describing the structure and function of real-world scenes (e.g. naturalness, openness, navigability), thereby capturing key aspects of scene understanding. GSPs are considered to be extracted rapidly and automatically, but the temporal dynamics underlying their processing is currently unknown, particularly how early they are extracted, and how much their extraction is influenced by top-down factors, such as task relevance. The present work describes a series of Event-Related Potential (ERP) experiments aimed at establishing the neural time signatures of GSPs processing and their functional significance for scene perception and categorization. We report that early sensory-evoked ERP components carry significant information about GSPs: the amplitudes of P1, N1, and particularly the P2 components vary as a function of the scene's spatial expanse (open /closed) and naturalness (manmade/natural) and these effects are evident across a variety of image presentation conditions, including both naturalistic and highly-constrained computer-generated scenes. Notably, the early neural responses to GSPs are very little modulated by the recognition goals of the observer, suggesting pre-attentive, mandatory processing of global scene information. Further, in line with the idea that open and closed scenes can be thought as two ends on a navigability continuum, we found that the P2 component is also sensitive to the number of pathways that afford movement in the local environment, consistent with fMRI research showing that the occipital place area (OPA) automatically encodes the structure of navigable spaces (Bonner & Epstein, 2017). Together, our findings suggest that GSPs are processed robustly and automatically within the first 250 milliseconds of processing. We propose that GSPs may bridge across low-level and high-level scene representations and that due to their ecological validity they may be utilized to assess the scene's action and navigability affordances.

**Disclosures: A. Harel:** None.

**Poster**

**789. Human Cognition and Behavior: Perception and Imagery II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 789.20/JJJ30

**Topic:** H.02. Human Cognition and Behavior

**Support:** a Louisiana Board of Regents Research Competitiveness Subprogram award to S.G.G.

**Title:** Fear in the theatre of the brain: Elucidating the neural mechanisms of fear generalization from imagined to viewed percepts

**Authors: *L. M. BURLEIGH**, J. OWENS-FRENCH, F. CHAISSON, A. MADDEN, L. RAGGIO, S. G. GREENING
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**Abstract:** Mental images can provoke intense emotional states (Holmes & Matthews, 2010). Imagery and perception have common neural and physiological mechanisms, including activation of the early visual areas (Albers et al., 2013). We tested the prediction that individuals can acquire fear to imagined percepts and if this fear transfers to viewing percepts. To date, 22 participants completed our experiment involving fMRI and self-reported measures to determine participants' fear. The participants completed a task in which they viewed and imagined two stimuli, and were fear conditioned when imagining the CS+. Participants are only told that mild electrical stimulation will be paired with one of the stimuli, but not which stimulus, viewed or imagined. Participants completed 6 runs of each task after completing 6 runs of a habituation form of each task. The habituation runs were identical to the task, however there was no fear conditioning (mild electrical stimulation) included. Behaviorally, participants report greater fear when imagining the CS+ than imagining the CS-. When acquiring fear to an imagined stimulus, we found significant activation in the right hippocampus, left insula, and bilaterally in the caudate. These findings are consistent with previous literature indicating that these regions are involved in processes related to emotional memory, autonomic arousal, and emotion-related motivation. Behaviorally, participants also report greater fear when viewing the CS+ than when viewing the CS-, though neither is ever paired with shock. When fear is generalized from an imagined precept to a viewed one (i.e., CS+ view > CS- view), we found significant activation in the left hippocampus, the right caudate, visual cortex, and right dorsal lateral prefrontal cortex. We can conclude that participants generalize the fear acquired when imagining the stimulus to viewing the stimulus, and this process is associated with the mechanisms of fear learning and memory, and selective attention. These preliminary results indicate that humans can fear condition to imagined percepts, that this fear generalizes to instances of viewing the conditioned percept, and that the mechanisms involved in each relate to those of fear learning and mental imagery more generally.

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**Poster**

**789. Human Cognition and Behavior: Perception and Imagery II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 789.21/JJJ31

**Topic:** E.04. Voluntary Movements

**Title:** Are neural mechanisms underlying hypnotic susceptibility shared with motor imagery?

**Authors: *J. CIRILLO**[1,2], A. J. SRZICH[1,2], W. D. BYBLOW[1,2], J. W. STINEAR[1,2], G. ANSON[1,2]
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**Abstract:** Inter-individual variability in hypnotic susceptibility is poorly understood. We hypothesised that hypnotic susceptibility may share neural mechanisms with kinaesthetic motor imagery (KMI). To test this, we obtained electromyographic recordings from the right first dorsal interosseous muscle of 11 neurologically healthy participants (8 female; 19-37 years). Motor evoked potentials (MEPs) were elicited by transcranial magnetic stimulation (TMS) over left primary motor cortex in hypnotized and non-hypnotized states during active and rest phases of a KMI and an "observe" task. Hypnotic susceptibility was classified as "high" (Stanford Hypnotic Susceptibility Scale Form C (SHSS:C) score ≥7; n=5) or "low" (SHSS:C score ≤6; n=6). For the active phase of the KMI task, participants imagined a phasic squeeze and release of their index finger and thumb in time with a LED flash (1 Hz). TMS was delivered during the imagined squeeze ("on" state) and imagined release ("off" state) throughout each trial. For the "observe" task participants did not imagine the index finger and thumb movement during the LED flash although the on-off schedule was retained. A rest phase for each task was included in which TMS was delivered while participants fixated on the unlit LED array. To investigate the modulation of corticomotor excitability the ratio of "on" relative to "off" MEP amplitude was calculated for both active and rest phases. There was a Task x Susceptibility interaction ($F_{(1,9)}$= 10.6, $p = 0.01$, $\eta_p^2 = 0.54$). Modulation of corticomotor excitability was greater for KMI than "observe" for both the "low" (KMI: 1.24 ± 0.22, Observe: 1.03 ± 0.14; $p = 0.038$, $\eta_p^2 = 0.283$) and "high" (KMI: 1.79 ± 0.53, Observe: 1.08 ± 0.30; $p = 0.008$, $\eta_p^2 = 0.461$) hypnotic susceptibility groups. In addition, corticomotor excitability was greater during KMI trials in the "high" hypnotic susceptibility group than "low" ($p = 0.043$, $\eta_p^2 = 0.380$). One interpretation is that corticomotor excitability differences between groups during the KMI task may be associated with increased attentional focus in the high hypnotic susceptibility group. This modulation of corticomotor excitability was not affected by hypnosis.

**Disclosures: J. Cirillo:** None. **A.J. Srzich:** None. **W.D. Byblow:** None. **J.W. Stinear:** None. **G. Anson:** None.

**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 790.01/JJJ32

**Topic:** H.02. Human Cognition and Behavior

**Support:** JSPS KAKENHI JP16J01822
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JSPS KAKENHI JP16H03755
JSPS KAKENHI JP18H04935
JSPS KAKENHI JP16H05862

**Title:** Two streams of feedback signals from parietal cortex to visual areas subserve visual awareness

**Authors: *K. YUASA**[1,2,3], H. TAKEMURA[1,2], I. MOTOYOSHI[4], K. AMANO[1,2]
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**Abstract:** Visual information is hierarchically processed in the cortico-cortical feedforward and feedback loops. Previous studies have reported a role of feedback signals to the primary visual cortex for establishing visual awareness (Lamme, 2001; Kok et al., 2016). Here, we aimed to clarify the temporal properties of the signal transmission relevant for visual awareness, by analyzing inter-regional causalities of MEG responses to visual stimuli. Forty-one healthy volunteers participated in our study. Gabor patches with 100%, 0%, and threshold-level contrasts were pseudo-randomly presented for 100 ms at the peripheral visual fields over 630-1,155 trials, and participants judged the presence or absence of the stimuli. Sixteen regions-of-interest (ROIs) were identified via surface-based fitting of the retinotopy atlas (Wang et al., 2015), and the response time courses of each ROI were estimated by eLORETA (Pascual-Marqui, 2007). For every pair of ROIs, a non-parametric Granger causality analysis in the time-frequency domain estimated the inter-regional neural signals. We identified the cortical responses relevant for visual awareness by comparing the strength of the inter-regional signals for threshold-level contrast stimuli between “Seen” and “Unseen” trials. Two major components were identified; modulatory signals from the parietal cortex to the primary visual cortex, and modulatory signals from the parietal to the ventral visual cortex. Both components were observed at the broadband frequency (5-100 Hz), and significant differences occurred from 220 and 260 ms after stimulus onset ($p<0.05$), respectively. Our results suggest that the modulation of not only the primary visual cortex but also the ventral visual cortex by the parietal visual cortex may be relevant for establishing visual awareness. Consistent with our finding, recent studies have demonstrated that visual awareness can be induced by TMS at the IPS even in patients lacking V1 (Mazzi et al., 2014), suggesting the existence of the neural loop for visual awareness independent of the primary visual cortex. In addition, the modulatory signals from the IPS to the ventral visual streams underlying visual processing were demonstrated by a recent fMRI study (Kay & Yeatman, 2017). Modulation of the ventral visual cortex by the parietal visual cortex in our study may reflect a neural loop distinct from the feedback loop from higher visual cortices to the primary visual cortex reported in previous studies. Thus, we identified two major neural loops essential for visual awareness: the signals from parietal visual cortex to the primary and ventral visual cortices.

**Disclosures: K. Yuasa:** None. **H. Takemura:** None. **I. Motoyoshi:** None. **K. Amano:** None.

**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 790.02/JJJ33

**Topic:** H.02. Human Cognition and Behavior

**Title:** Fertility status in visual processing of men's attractiveness

**Authors: *R. GARZA**[1], R. R. HEREDIA[2], A. B. CIESLICKA[2], J. BYRD-CRAVEN[1]
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**Abstract:** Abstract
Physical characteristics are visually salient information that display an insight into a potential mate's immunocompetence, status, and reproductive potential (Djikstra & Bunk, 2001; Dixson, Grimshaw, Ornsby, & Dixson, 2014; Lasek & Gaulin, 2009; Singh, 1994). In men, characteristics such as a v-shaped torso and body hair are often a desired characteristic by women because it displays men's upper body strength and hormonal levels. Recently, the use of eye tracking in attraction research has demonstrated that visual patterns are behavioral indices of interest to a potential mate. The current study examined visual perception through eye movements of fertile and non-fertile Hispanic women of Mexican-American descent ($N$ = 92) viewing images of men with different waist to chest ratios and body hair distribution. Using eye tracking technology, women viewed men with full body hair distribution longer in all waist to chest ratios and focused most of their visual attention towards the upper region of the body (i.e., midriff, chest, & face). Interestingly, non-fertile women viewed men longer in all waist to chest ratios indicating that there are differences in behavioral accounts of attraction across the menstrual cycle. These findings suggest that women have an attentional bias to regions associated with strength, dominance, and immunocompetence, supporting an evolutionary framework in explaining physical attraction, and they also suggest that attraction is not solely constrained to a timeframe of the menstrual cycle.

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**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 790.03/JJJ34

**Topic:** H.02. Human Cognition and Behavior

**Support:** R01EY025978
SIRE program, Emory University

**Title:** Measuring the strength of synesthetic associations using an individualized implicit association test

**Authors: *S. A. LACEY**[1], M. MARTINEZ[2], L. C. NYGAARD[3], K. SATHIAN[1]
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**Abstract:** Synesthesia is a phenomenon in which experiences in one sensory or cognitive domain are associated with automatic, involuntary experiences in a second domain. The most common form is grapheme-color synesthesia in which a specific color is experienced when seeing a particular letter or number. These synesthetic associations are both arbitrary (there is no obvious connection between the letters and colors) and idiosyncratic (different synesthetes may experience different colors for the same letter). Individuals can be tested for a range of synesthesias using the Synesthesia Battery (SB: Eagleman et al., J Neurosci Meth, 2007); this measures the consistency with which individuals choose the same color for the same grapheme and returns a standardized score which distinguishes genuine synesthetes from non-synesthetes. However, while the SB measures consistency, it does not measure the strength of synesthetic associations. To address this, we used the Implicit Association Test (IAT: Greenwald et al., J Pers Soc Psychol, 1998) which we have previously used to show that synesthetes have greater sensitivity to some crossmodal correspondences than non-synesthetes (Lacey et al., Eur J Neurosci, 2016). In the IAT, participants associate two stimuli with the same response key. A single stimulus is presented on each trial and participants make speeded responses, which are faster when the key associations are congruent and slower when incongruent, i.e., there is a congruency effect (Parise & Spence, Exp Brain Res 2012). Here, grapheme-color synesthetes completed the SB and an individualized IAT in which two response keys were paired with their two most consistent SB associations in either congruent (each key is associated with a grapheme and its correct synesthetic color, e.g., A + red, B + green) or incongruent (i.e., A + green, B + red) conditions. Non-synesthetic controls also performed the IAT, using the grapheme-color associations for the synesthete to whom they were matched for age and gender. We expected that synesthetes would have greater IAT congruency magnitudes than non-synesthetes and, to the extent that strong associations should also be consistent, a positive correlation between SB scores and congruency magnitudes in the synesthetes. As predicted, synesthetes showed larger congruency magnitudes than non-synesthetes, regardless of whether a grapheme or a color was presented; interestingly, consistency (SB) and strength (IAT) appeared to be unrelated. To our knowledge, this is the first use of the IAT paradigm to test the strength of synesthetic associations and offers a new method of testing for synesthesia itself.

**Disclosures: S.A. Lacey:** None. **M. Martinez:** None. **L.C. Nygaard:** None. **K. Sathian:** None.

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**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 790.04/JJJ35

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIMH DIRP
NSF STC award CCF-1231216

**Title:** Exploring predictive information in action with psychophysics and machine learning

**Authors: *E. G. MCMAHON**[1], R. GONZALEZ[2], K. NAKAYAMA[2], L. G. UNGERLEIDER[1], M. VAZIRI-PASHKAM[1]
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**Abstract:** Predicting the actions of others is relevant in many social situations from extending a handshake to elaborate waltzes. To study the preparatory information in movements and how people are able to interpret these preparatory cues, we designed a partnered reaching task. One partner (Attacker) wore headphones and was instructed to tap on one of two targets on a Plexiglas screen with their index finger. The other partner (Blocker) was instructed to tap the same target in two conditions. In the competitive condition, the Blocker had to beat the Attacker to the target (Vaziri-Pashkam, Cormiea, & Nakayama, 2017), and in the cooperative condition, both participants were asked to tap the same target at the same time. The Attackers were recorded throughout the session. We used the recorded videos to determine when preparatory information becomes available in the movement and whether it varies depending on the social context. To do this, in a psychophysical paradigm, subjects viewed short clips that contained movements from the beginning of the trial to various time points relative to the Attacker's finger lift off from the table and were asked to predict whether the Attacker was going to point to the left or right target. Subjects were able to predict the direction of movement with 75% accuracy ~20 ms before finger lift off for the competitive condition and ~40 ms in the cooperative condition. This 75% threshold was available significantly earlier and showed significantly larger variance across Attackers in the cooperative condition. Next, using a linear support vector machine on frames of the motion energy trained to decode the direction of movement, we confirmed that preparatory information is available earlier in the cooperative condition than the competitive condition. A follow-up searchlight analysis revealed that all body parts contained informative predictive cues with the head showing predictive information earlier in the movement for both conditions, but especially for the cooperative condition. Together, these results reveal that subjects are able to use preparatory cues in the movements of others to predict

action goals before the start of the movement and that these cues are exaggerated in the cooperative context to communicate the goal of actions.

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**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 790.05/JJJ36

**Topic:** H.02. Human Cognition and Behavior

**Title:** Neural signatures of perceptual reversals of bistable visual and linguistic stimuli

**Authors: *K. M. ORTEGO, JR**, M. PITTS, E. CANSECO-GONZALEZ
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**Abstract:** The study of ambiguous visual stimuli has provided a wealth of information about how the visual system creates coherent representations of the world from inherently noisy and overwhelmingly dense sensory inputs. The Reversal Negativity (RN) is an event-related potential (ERP) elicited when one's subjective perception of a bistable ambiguous figure, such as the Necker Cube or Rat-Man drawing, switches from one of its possible interpretations to the other. The RN is thought to reflect a change in the perceptual configuration of a stimulus' current representation in the brain, and has been observed in response to other forms of perceptual switching, such as that which occurs in binocular rivalry. The current study investigates whether ambiguous sentences having two valid interpretations (e.g. "The chicken is ready to eat") are represented in a similar bistable fashion as these ambiguous figures.
To investigate this question, we recorded participants' brain activity using EEG while presenting them with ambiguous figures followed by disambiguated variants, and ambiguous sentences followed by line drawings depicting one of the sentence's two possible meanings. On each trial, participants indicated whether or not the disambiguating stimulus matched their subjective interpretation of the previously seen ambiguous figure or sentence. We then compared ERPs elicited by these disambiguating stimuli in mismatching (reversal) reports vs. matching (stable) reports. Replicating previous findings, we observed the typical occipito-parietal RN associated with reversals of bistable visual figures. In response to reversals of our "bistable" ambiguous sentences, we identified a large, frontally-distributed negativity effect occurring over a nearly identical time-course as the visual RN. We interpret this finding as evidence that the brain may engage in similar types of processing and perceptual switching across different types of bistable ambiguities, in this case for more abstract "conceptual" ambiguities such as those present when forming representations of sentences.

**Disclosures: K.M. Ortego:** None. **M. Pitts:** None. **E. Canseco-Gonzalez:** None.

**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 790.06/JJJ37

**Topic:** H.02. Human Cognition and Behavior

**Title:** Robotics to investigate hallucinations in healthy and early psychosis patients

**Authors: *F. BERNASCONI**[1], G. ROGNINI[2], M. SOLCÀ[1], M. M. MURRAY[3], K. Q. DO[4], P. CONOUS[4], P. PROGIN[4], O. BLANKE[5]
[1]Lab. of Cognitive Neurosci. (LNCO), Ecole Polytechnique Fédérale De Lausanne (EPFL), Genève, Switzerland; [2]Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland; [3]Radiology, Univ. Hosp. Ctr. and Univ. of Lausa, Lausanne, Switzerland; [4]Ctr. for Psychiatric Neurosci., Prilly-Lausanne, Switzerland; [5]Bâtiment H4, EPFL - SV - CNP - LNCO, Geneve, Switzerland

**Abstract:** Auditory hallucinations, delusion of control and delusion of thought interference are among the Schneider's first-rank symptoms (FRS) for schizophrenia. Those aberrant perceptions are often associated with an external agent, the presence hallucination (PH). Recent findings demonstrated that sensorimotor conflicts between upper limb movements and somatosensory feedback on the back can induce the PH in healthy subjects, suggesting that PH is caused by misperceiving the source and identity of sensorimotor signals of one's own body. Despite this new insight into the PH, very little is known about its neural basis. Here we applied the same sensorimotor conflict in healthy volunteers, while brain activity was measured with EEG. Behaviourally, we replicated previous findings, showing that strong sensorimotor conflict can induce the PH. Electrophysiologically, our results show that strong sensorimotor conflict results in a modulation of the alpha band power, and a functional dysconnection within the right fronto-temporal network, specific for the gamma band. In addition, this modulation of functional connectivity was associated with the subjective experience of PH. Interestingly, the dysconnection within the same right fronto-temporal network and frequency, allowed us to distinguish between first-episode psychosis patients with vs. without FRS, with a fully data-driven approach. These results are consistent with the evidence that PH can be caused by lesions in three distinct brain regions: temporo-parietal, insular, but especially into the frontoparietal cortex, and provide new insights into the neural basis underpinning the PH and more generally the FRS, showing that gamma oscillations and the fronto-temporal network as critically associated with it.

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**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 790.07/JJJ38

**Topic:** H.02. Human Cognition and Behavior

**Title:** How absolute is absolute pitch?

**Authors: H. LI**[1], W. CAI[2], H. ZHOU[2], X. WANG[3], *J. HUANG[4]
[1]Tsinghua Univ., Tsinghua Laboratory of Brain and Intelligence, China; [2]Central Conservatory of Music, Beijing, China; [3]Dept. of Biomed. Engin., [4]Zanvyl Krieger Mind/Brain Inst. and Dept. of Biomed. Engin., Johns Hopkins Univ., Baltimore, MD

**Abstract:** Absolute pitch (AP) is a musical terminology referred to the ability to name a musical note without the benefit of a reference tone. While AP has been extensively studied, there are no definitive criteria to determine if an individual has AP. In the present study, we used a set of quantitative psychophysical methods to measure listeners' ability in naming musical notes and tones at finer frequency intervals, with or without a reference tone in three native Chinese-speaking groups: professional musicians, amateur musicians, and non-musicians. Our results revealed a discrete population distribution of the participants in naming musical notes with professional musicians being separated from non-musicians and most of amateur musicians. Based on their musical notes naming performance, the participants were further categorized as low (L), medium (M) and high (H) performance groups. Participants in both L and M groups exhibited significantly better performance when tested with a reference note than without. The H group performed equally well with or without a reference note. In addition, decreasing the error tolerance level from 100 to 0 cents did not significantly reduce the percentage correct in naming musical notes for the H group, but it resulted in lower percentage correct for the L and M groups. Moreover, the performance of the L and M groups was significantly better with music notes corresponding to white piano keys than with black piano keys, whereas H group showed no such a difference. We further tested the ability of naming tones with 20-cent frequency resolution for participants in M and H groups. Some musicians in both groups were found to possess reliable tone naming ability with frequency resolution smaller than one semitone.

**Disclosures: H. Li:** None. **W. Cai:** None. **H. Zhou:** None. **X. Wang:** None. **J. Huang:** None.

**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

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**Topic:** H.02. Human Cognition and Behavior

**Support:** UAB Center for Clinical And Translational Science UL1 TR000165
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NIH NEI 1 U01 EY025858-01A1

**Title:** Relating the cortical projection of retinal lesions to the projection of preferred retinal locus in participants with macular degeneration

**Authors: *P. DEMIRAYAK**[1], M. K. DEFENDERFER[2], M.-E. WINSLETT[3], P. D. STEWART[1], D. K. DECARLO[1], K. M. VISSCHER[2]
[2]Neurobio., [1]Univ. of Alabama at Birmingham, Birmingham, AL; [3]Univ. of Alabama at Birmingham, Alabama, AL

**Abstract:** Macular Degeneration (MD) is characterized by loss of central vision due to a scotomain the retina. Rather than using the fovea for viewing fine-scale stimuli, patients often use a new eccentric fixation area that includes a spared peripheral portion of retina (preferred retinal locus-PRL). In order to study the cortical changes associated with vision loss, it is essential to map the regions associated with the scotoma as well as the PRL. We sought to characterize the cortical projection of the scotoma and compare it to the projection of the PRL in MD participants and controls.Here we take an individual participant approach, as we have extensive MRI and behavioral information for each MD participant and control. To measure the extent of an individual's cortical projection of the scotoma, we visually stimulated the entirety of the spared retina, and examined areas not active (to a threshold level) in response to stimulation. Full visual field was stimulated with flickering light stimuli, through a tissue to diffuse light throughout the visual field, in a blocked fMRI design. PRL stimulation followed the same blocked design, but here, flickering checkerboards were presented at a location to which the participants were instructed to aim their PRL (or, in the case of controls, their fovea). Retinal sensitivities of all participants were measured by using a Macular Integrity Assessment (MAIA) system.Our results showed that full field stimulation in controls led, as expected, to activity throughout visual cortical regions. However, in MD participants, this stimulation was strong in classically peripheral cortical regions but weak in centrally-representing regions, consistent with

the patients' central vision loss. The extent of the inactive portion of visual cortex varied by individual. These individual differences in BOLD responses may be associated with the magnitude of the visual loss in the central scotoma in patients with MD. Interestingly, the relationship between the location of the scotoma projection and neural activity associated with the PRL task differed from participant to participant. These two locations sometimes overlapped, meaning 'scotoma' locations sometimes were also 'PRL' locations. The differences may relate to individual differences in compensatory neural mechanisms. Overall our results may guide our understanding of the functional outcome of neural plasticity in adult vision loss.

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**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 790.09/JJJ40

**Topic:** H.02. Human Cognition and Behavior

**Title:** Different patterns of visual processing activity in females and males during visual encoding

**Authors: *D. SPETS**, S. SLOTNICK
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**Abstract:** There has been little research on sex differences in the human brain during visual encoding. We reanalyzed fMRI data from four experiments to investigate the similarities and differences in visual processing between female and male participants during the encoding phase of a long-term memory task. In all the experiments, during encoding, participants maintained central fixation while viewing abstract shapes in the left or right visual field. During retrieval, old shapes were presented at fixation and participants classified each shape as previously in the "left" or "right" visual field. Across all experiments, there were eighteen male participants and forty-three female participants. For each experiment, female participants were selected such that they were equal in number and approximate spatial memory performance to male participants (total N = 36). There was no significant difference between spatial memory accuracy for females and males (74% correct, $p > .5$). For the fMRI analysis, a random-effect general linear modal analysis was conducted. All contrasts were thresholded at $p < .001$, false discovery rate and cluster [S1] extent corrected to $p < .05$. As expected, the contrast of shapes in the left visual field and shapes in the right visual field produced retinotopic activity in the contralateral occipital cortex for both females and males. The contrast of shapes in the left visual field and right visual field for females versus males produced largely different patterns of activations. For shapes presented in the left visual field, females had greater activity in contralateral occipital cortex,

bilateral sensorimotor regions, and bilateral intraparietal sulci, while males had greater activity in the inferior parietal cortex, dorsolateral prefrontal cortex, ventromedial prefrontal cortex, hippocampus and Broca's area. For shapes presented in the right visual field, females had greater activity in contralateral occipital cortex, while males had greater activity in the perirhinal cortex, ventromedial prefrontal cortex, superior temporal gyrus, and inferior parietal cortex. Both males and females activated different areas of the posterior language processing cortex. Regardless of visual field, females had greater activity in contralateral occipital cortex than males, and females and males activated different areas of contralateral and ipsilateral occipital cortex. The present findings suggest different patterns of visual processing activity for males and females during visual encoding.

**Disclosures: D. Spets:** None. **S. Slotnick:** None.

**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 790.10/JJJ41

**Topic:** H.02. Human Cognition and Behavior

**Support:** Esther Hyatt Wender Summer Research Fellowship

**Title:** Synesthesia, visual search and the n2pc

**Authors: *C. A. HENDRY**, A. HOUGH, O. CHESLEY, C. GRAULTY, M. A. PITTS, E. CANSECO-GONZALEZ
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**Abstract:** Grapheme-color synesthetes experience consistent and automatic associations between graphemes (letters or numbers) and colors. The current study investigates whether synesthetic color perception provides an advantage in a visual search task. Electrophysiological and behavioral data were collected across three experiments. In experiment 1, synesthetes and matched controls performed a visual search task to find a target letter amongst 7 distracter letters positioned in a circular array. For each synesthete, 2 letters with the same color association (e.g. both red) were designated as targets while the distracter letters were all different (e.g. non-red) colors. The stimuli (black letters) and task (find a target letter and report it) were identical for both groups. Comparing event-related potentials (ERPs) recorded on electrode sites contralateral vs. ipsilateral to the target, allowed us to measure the "N2pc" component, a well-studied marker of selective attention ~200-300 ms post-target stimulus. We found faster reaction times, along with a larger and earlier N2pc for synesthetes vs. controls, suggesting that their synesthetic perception of color may have speeded their attention toward the target. In experiment 2, non-synesthetes were tested with the same paradigm as exp. 1, but with an added colored-letter

condition, where every letter was presented in a unique color on the screen. The colored grapheme condition was intended to simulate the synesthetic color perception of synesthetes in exp. 1. When color was available as a search cue, non-synesthetes had faster reaction times along with larger and earlier N2pcs than when they were presented with uncolored (black) letters. The magnitude of these behavioral and neural differences was very similar to that observed for synesthetes in exp. 1. Experiment 3 served to replicate the results of exp 1 with a new population, and to investigate visual search performance with stimuli that do not elicit synesthetic percepts. The procedure was the same as exp. 1 with the addition of two conditions: an unfamiliar graphemic condition (Georgian alphabet) and a non-grapheme condition (stick figures). We found faster reaction times, along with larger and earlier N2pc for synesthetes vs. controls across all three conditions, suggesting that their synesthetic perception of color may not be the main factor speeding their attention toward the targets. Synesthetes may possess a generic advantage in visual search tasks due to enhanced early processing of visual stimuli in general.

**Disclosures: C.A. Hendry:** None. **A. Hough:** None. **O. Chesley:** None. **C. Graulty:** None. **M.A. Pitts:** None. **E. Canseco-Gonzalez:** None.

**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 790.11/JJJ42

**Topic:** H.02. Human Cognition and Behavior

**Support:** NHMRC grant 1055084

**Title:** How does attention affect perceived finger location and ownership in the grasp illusion?

**Authors: *M. E. HEROUX**[1], L. S. FLETCHER[2], A. A. BUTLER[1], A. P. WANG[2], S. C. GANDEVIA[1]
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**Abstract:** Passively grasping an unseen artificial finger causes the index fingers to feel ~5 cm closer (from 12 cm) and induces a sense of ownership over the finger (Héroux et al. 2013, J Physiol). This study determined how interoceptive awareness (IA) and attention influence this grasp illusion. In Experiment 1, the grasp illusion and IA were measured in 30 subjects (18 males; mean age: 34.0 years [range: 20-57]). Each condition (grasp and no-grasp) lasted 3 min, followed by measures of perceived index finger spacing and perceived ownership over the artificial finger (7 point Likert scale); IA was measured by heartbeat tracking (over 40s) and an interoception questionnaire (0=high interoception, 5=no interoception). Experiment 2 also involved 30 subjects (17 males; mean age 33.7 years [20-57]) and determined the effect of

attentional focus on the grasp illusion with three conditions: (1) auditory-guided cueing to increase upper limb awareness, (2) touch-guided cueing to increase upper limb awareness, and (3) watching a silent film (control). Experiment 1 replicated our previous results, with the grasp illusion reducing perceived spacing by 4.5 cm [2.8 to 6.2] (mean [95%CI]) and inducing ownership of 4.2 [3.4 to 4.9] (between 'neither agree or disagree' and 'somewhat agree'). Ordinary least-square models did not retain either measure of IA as explaining part of the variance of perceived spacing or ownership measures. In Experiment 2, compared to the control condition, auditory- and touch-guided cueing did not influence index finger spacing or perceived ownership. However, the models showed IA explained a scientifically meaningful (and statistically significant) portion of the variance of the effect of auditory cueing on index finger spacing (heart rate tracking: -0.12 [-0.19 to -0.04]; each 10 bpm error caused a 1.2cm reduction in perceived spacing) and perceived ownership (interoceptive questionnaire: 1.0 [0.2 to 1.8]; an increase of 1 point on the questionnaire increases perceived ownership by 1). Overall, attention modulates the strength of the grasp illusion when individual differences in IA are considered.

**Disclosures: M.E. Heroux:** None. **L.S. Fletcher:** None. **A.A. Butler:** None. **A.P. Wang:** None. **S.C. Gandevia:** None.

**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 790.12/JJJ43

**Topic:** H.02. Human Cognition and Behavior

**Support:** ANR-16-CE28-0015 Developmental Tool Mastery
IHU CeSaMe ANR-10-IBHU-0003

**Title:** Cortical dynamics of tool-extended sensing

**Authors: *L. E. MILLER**[1], C. FABIO[1], R. SALEMME[1], V. HAYWARD[2], A. FARNÈ[1]
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**Abstract:** The ability to use tools plays a fundamental role in the daily lives of humans and is a defining feature of our species. It is no surprise that decades of neuroscience research have been dedicated to understanding how tools are controlled by the sensorimotor system. The majority of this research to date has focused almost exclusively on the motor side of tool use, even though tools convey sensory information whenever they contact a surface. We recently investigated whether tools can extend sensory processing beyond the body (Miller et al., under review), a phenomenon we termed tool-extended sensing. In a series of behavioral experiments, we demonstrated that users can localise impacts on the surface of a hand-held rod with remarkably high accuracy. The present study sought to investigate the cortical dynamics of this phenomenon.

We used electroencephalography to measure neural oscillations while participants localized impacts on a hand-held rod. The experiment consisted of a sensory working memory task, where participants determined whether the two impacts (separated by 2000-2500 ms) occurred at the same or different location. Our initial analysis was focused on the first impact and the information maintenance period. Contact on the rod led to an initial desynchronization in both the beta band (18-30 Hz; 200-400 ms post contact) and the alpha band (8-13 Hz; 300-600 ms). In both bands, the desynchronization was most prominent in channels over the somato-motor cortices of both hemispheres. Only the alpha band, however, showed evidence of maintaining information about the specific location contacted. We observed a sustained synchronization of alpha activity (800-1700 ms) over bilateral frontal and contralateral sensorimotor channels. Alpha power in these channels was significantly different between both locations, suggesting that this activity plays a critical role in maintaining the specific location of contact in working memory. These results represent an initial step towards understanding how tool-extended sensing emerges from the functional coupling between technological, biomechanical, and neural levels of information processing.

**Disclosures: L.E. Miller:** None. **C. Fabio:** None. **R. Salemme:** None. **V. Hayward:** None. **A. Farnè:** None.

**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 790.13/JJJ44

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH Grant R01-NS074980
APDA grant #20082501

**Title:** Isolation and characterization of the medial temporal lobe-basal ganglia circuit using diffusion magnetic resonance imaging

**Authors: *C. N. MCKEE**[1], A. PERUGINI[1], V. THAKUR[2], B. J. KNOWLTON[2], M. IACOBONI[3], M. A. BASSO[4], D. W. SHATTUCK[5]
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**Abstract:** We recently discovered a dopamine-independent impairment in memory-based decision-making in people with Parkinson's disease (PD) (Perugini et al., 2016; Perugini & Basso, 2018). Although the neural circuitry responsible for this deficit is unknown, it is widely accepted that the medial temporal lobe (MTL) and the basal ganglia (BG) play significant roles in processing memory information and decision making, respectively (Shohamy et al., 2007). We

hypothesize that an interaction between MTL and BG is necessary for combining memory and sensory information to make perceptual decisions and that alterations in this pathway may impair this ability in PD patients. An MTL-BG pathway appears in non-human primates, but this pathway is not well-studied in humans. To establish normative data on the existence and details of the MTL-BG circuit in healthy humans, we analyzed T1-weighted (T1w) and diffusion-weighted magnetic resonance imaging (DMRI) data from 848 subjects (Age=28.75y±3.67; 476F/372M) from the Human Connectome Project 900 Subjects Release. We implemented a fully automated workflow using BrainSuite. Cortical surface models were extracted from T1w MRI and mapped to a labeled brain atlas using surface-constrained volumetric registration. Structural ROI labels and 3 custom spherical ROIs in atlas space were mapped to each subject's T1w space. A single shell (b=2000 s/mm2) of the DMRI data was used to fit diffusion tensors and orientation distribution functions (ODFs) using the Funk Radon and Cosine Transform (FRACT). Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AxD), and radial diffusivity (RD) were calculated from the tensor data. Whole-brain deterministic streamline tractography was computed from the ODF data and filtered using a combination of the hippocampus and parahippocampal gyrus label ROIs and the remapped spherical ROIs, which isolate tracks running through the tail of the caudate nucleus. Our automated approach successfully isolated this fiber bundle bilaterally in 835 of the 848 subjects; we isolated the bundle in the remaining 13 subjects after minor manual adjustment of the ROI spheres. Diffusion index means were computed across all voxels intersecting the tracks. Cross-subject average values were (mean±s.d.): FA, 0.268±0.021; RD, 0.000669±0.000034 mm2/s; AxD, 0.00101±0.00004 mm2/s; and MD, 0.000783±0.000035 mm2/s. Next, we will assess whether properties of the MTL-BG circuit correlate with integration of memory and sensory information for decision-making, and uncover whether this circuit is dysfunctional in PD, which may in turn lead to novel diagnostic tools and targets for deep brain stimulation.

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**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

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**Topic:** H.02. Human Cognition and Behavior

**Support:** NRF-2016R1C1B2016039
NRF-2016R1E1A2A01939949

**Title:** Combining local visual structures into global objects causes new afterimage illusion

**Authors: *C. JUNG**[1], W. CHOI[1,2], G. KIM[3], S.-B. PAIK[1,2]
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**Abstract:** One of the most important tasks of our visual system is to separate object from the background so that we can extract meaningful information from visual input. In particular, our visual system combines local visual structure into global object to distinguish object from background. Here we report a new type of illusion that reveals how local visual components are combined to form perception of global object. We observed that when observers adapt to a stimulus with few colored concentric rings, afterimage of the stimulus does not simply exhibit opposite colored concentric rings (negative afterimage) but changes over time to form a solid filled circle (merged afterimage). We hypothesized this merging afterimage illusion emerges when our visual system interprets multiple spatially separated visual inputs (concentric rings) into single object (solid circle). To test our hypothesis, we performed a series of human psychophysical experiments. First, we compared the amount of spatial propagation in afterimage of multi-segment object that can form global structure and a single-segment object which can we perceived as an object by itself. As expected, we observed that multi-segment object with global structure cause significantly greater spatial propagation than the single-segment object, which thereby cause merging afterimage illusion. This result shows that merging afterimage illusion is not merely a byproduct of general characteristics of afterimage, such as fuzzy edges or blurring, and suggests that perceptually combining multiple items are necessary to produce this new merging afterimage. Next, we designed two stimuli with identical physical segments, one that can be grouped into a global object and the other that cannot be, by changing the organization of segments. Although the two stimuli have same set of physical segments, a stimulus that can be grouped into a global object showed significantly longer perception of merged afterimage than the stimulus that cannot be, showing that global interpretation of given stimulus is necessary to cause merging. Additionally, we found that merged afterimage of stimulus with high chromaticity lasts significantly longer compared to that of achromatic stimulus. This is in accordance with previous studies, which showed that chromaticity can affect the perceptual separation of object and background (e.g. watercolor illusion (Pinna et. al., 2001), neon-color spreading (van Tuijl & Leeuwenberg, 1979)). Our results show that perception of afterimage can be affected by the mechanism of identifying objects, and suggest that such mechanism might occur in a distinct color-specific pathway, or in cell-type specific manners.

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**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 790.15/JJJ46

**Topic:** H.02. Human Cognition and Behavior

**Title:** Preference and intake of salty, sweet and fatty foods and self-reported abnormall smell and taste perception in pregnant women from Ciudad Guzman, Jalisco,Mexico

**Authors: *A. CASTAÑEDA DÍAZ DE LEÓN**[1], A. G. MARTÍNEZ MORENO[1], C. M. HUNOT ALEXANDER[2], M. NAVARRO MEZA[1]
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**Abstract:** Highr intake of sugars, lipids and sodium in pregnant women have been related with complications during this physiological state. Behaviors like changes in food preferences could promote the intake of these nutrients, at the same time, food preferences modifications may be related with abnormall smell and taste perception. The present study aims were identify preference and intake of salty, sweet and fatty food as well as self-reported abnormall smell and taste perception in pregnant women from Ciudad Guzman, Jalisco, Mexico. In this cross sectional study participated 66 pregnant women (26 first trimester, 24 second trimester and 16 third trimester, with age 23.7 ± 4.7) and 36 non-pregnant women (controls, with age 20.9 ± .41). Data were gathered from PrefQuest (Cronbach's alpha = 0.8) and the Multi-Center Smell and Taste Questionnaire. We obtained 31 (pregnant women) and 39 (non-pregnant) intake records. Weight, height and pre-pregnancy weight were registered The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Coast of Jalisco University Center, University of Guadalajara. Data were tested for normality test. Pregnant and non-pregnant groups were compared using Student-T test or Mann Whitney U-test. Pregnant group divided into trimesters was compared with control group using ANOVA or Kruskall-Wallis. $Chi^2$ test was used for categorical variables. The results indicated, first trimester prefered less foods with sugars mixed with lipids (*p=0.034*) and third trimester prefered more foods with sugar (*p=0.038*) compared with control group. Pregnant women had a higher carbohydrates (*p=0.027*) and fruits intake (*p=0.022*) than control group. Besides, first trimester group registered higher carbohydrates (*p=0.013*) and fruits (*p=0.026*) consumption than control group and same results were reported for sugary drinks in the second trimester group (*p=0.019*). Pregnancy women reported more smell (*p=0.000*) and taste changes (*p=0.001*) than non-pregnant group. In comparison with control group, the trimesters groups refered more abnormall smell sensitivity (*p=0.000*) and, also the first trimester group reported more abnormal taste sensitivity (*p=0.023*). These results suggest that pregnant women could be at risk of high sweet foods intake during second and third trimester. In addition, this group reported abnormal smell and taste perception during pregnancy. Further research is needed to analyze the relation between chemosensory changes, preference and intake of salty, sweet and fatty foods in this physiological state with molecular tests.

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**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 790.16/JJJ47

**Topic:** H.02. Human Cognition and Behavior

**Support:** MRC New Investigator Grant

**Title:** Action comprehension in disorders of consciousness

**Authors: *R. SOKOLIUK**[1], S. CALZOLARI[1,2], D. CRUSE[1]
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**Abstract:** Patients with disorders of consciousness (DOC) such as coma or vegetative state are unable to follow commands to move (e.g. “Kick your leg”), although it has been shown that a significant proportion of those patients (~20%) is conscious but unable to show it behaviourally. Hence, it is important to develop measures of awareness that are independent of the patient’s behaviour. Theories of semantic embodiment propose that the same brain regions (pre- and primary motor cortices) that are required to execute a movement (i.e. to follow commands) are also required to comprehend speech describing that movement (e.g. the verb ‘to kick’). These theories provide an interesting link to DOC research as it follows that a patient must comprehend an action in order to execute it, and thereby demonstrate their awareness. Embodiment of action meaning can be identified in single subjects with electroencephalography (EEG). Here, we visually presented motor and non-motor words to 24 healthy participants. To maintain participants’ attention, a word definition was displayed in 25% of the trials, and participants had to judge whether it matched with the previously presented word. We found differences in the event-related potentials (ERPs) elicited by motor and non-motor verbs (e.g. ‘kick’ versus ‘hope’) from 164-203ms poststimulus, showing a frontal positive and a posterior negative cluster. Moreover, a Global Dissimilarity Analysis in this time window revealed evidence for different neural generators underlying motor and non-motor verb comprehension. The sensorimotor mu rhythm (8-12Hz), known to be modulated by a range of motor tasks, was significantly more attenuated from 555-785ms poststimulus over central electrodes in response to motor verbs. To our knowledge, this study is the first to show an early difference in the ERP on the sensor level between words of the same category (i.e. verbs). This early dissociation between motor and non-motor word processing supports the theory that sensorimotor cortices are necessary for semantic access of an action concept. This EEG task is thus well suited as a bedside measure of semantic embodiment and action comprehension in DOC patients. We are currently conducting a longitudinal study of patients with DOC to test the link between action comprehension and the ability to demonstrate awareness by following verbal commands to move. We hypothesise that

DOC patients who show similar EEG results to the ones obtained from healthy participants are more likely to recover from their DOC due to preserved cortical regions necessary to follow commands to move. If successful, this EEG method may thus improve accuracy of prognoses and diagnoses in DOC patients.

**Disclosures: R. Sokoliuk:** None. **S. Calzolari:** None. **D. Cruse:** None.

**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 790.17/JJJ48

**Topic:** H.02. Human Cognition and Behavior

**Support:** DFG Grant EXC307
Max Planck Society
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Barbara-Wengeler Foundation

**Title:** Parietal theta burst TMS does not modulate dominance durations of bistable perception: Evidence from three experiments across multiple stimuli

**Authors: *G. SCHAUER**[1], A. BARTELS[1,2,3]
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**Abstract:** When a stimulus has two competing interpretations, perception tends to alternate over time: bistable perception. A special case hereof occurs when the two eyes receive differing information in the same retinal space, perception also alternates: binocular rivalry (BR). Functional magnetic resonance imaging (fMRI) studies have shown the right anterior intraparietal sulcus (IPS) as well as posterior superior parietal lobule (SPL) activated during perceptual transitions. However, the causal role of these regions remains unclear, as distinct transcranial magnetic stimulation (TMS) studies have reported either shortening or lengthening TMS effects on perceptual dominance durations. Reasons for these divergent results may lie in the use of different stimuli or of distinct TMS protocols. Here we tested effects of a single, inhibitory TMS protocol, continuous theta burst stimulation (cTBS), applied to the IPS, SPL, and vertex control on distinct classes of bistable perception in three separate samples of participants (total N = 52). In sample one we used structure from motion (SFM) bistable perception, in sample two BR between random dots that was either reported, unreported or unreportable, and in sample three both of the above stimuli as well as BR between flickering checkerboards. Contrary to our expectation, cTBS neither consistently affected dominance durations across the stimuli,

test sites, nor samples. This null effect was supported by Bayes factors. In a last experiment we correlated participants' cTBS induced change in BR dominance with the change in motor-evoked potentials (MEP) following cTBS to primary motor cortex. While MEP amplitude was reduced, corroborating the inhibitory effect of cTBS, we observed no correlation with the cTBS effect on BR. Given the comparably large N used in the present study, the replication of our null-finding across several classes of bi-stable stimuli, and the lack of correlation of cTBS effects between motor and parietal cortex, the present findings cast doubt on the efficacy of the cTBS protocol over parietal cortex and the generalisation of cTBS effects from motor to parietal cortex.

**Disclosures: A. Bartels:** None.

**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 790.18/JJJ49

**Topic:** H.02. Human Cognition and Behavior

**Title:** Active inference and global brain free energy minimization during visual categorization in humans

**Authors: *L. T. TRUJILLO**
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**Abstract:** According to the theory of active inference, the brain predicts sensations and infers their causes via a generative model of the world. Active inference is achieved when the brain minimizes its free energy, an information-theoretic upper bound on the difference between the brain's current and predicted states. Perception and action correspond to two ways a brain can minimize free energy: i) changing its beliefs about the world (i.e. its generative model), or ii) acting on the world in order to change sensory input in accordance with its beliefs. The free energy principle may provide a general explanation for how the brain realizes perception and action; however, empirical confirmations of this principle are currently limited. This presentation reports the empirical quantification of the free energy of global states of the human brain during the active inference of visual category structure. Seventy-two channels of scalp electroencephalographic (EEG) signals were recorded while 22 young adults categorized Gabor stimuli into two categories defined by an implicit integration of stimulus orientation and spatial frequency (1 s stimulus presentation followed by 0.5 s performance feedback, 1.2 - 1.5 s ITIs). Brain free energy is a function of two probability densities estimated from the behavior and EEG data. The first density describes the joint probability of sensations and their causes given an individual's generative model; it was computed by assessing participant categorization performance relative to the true category structure of the stimuli. The second density describes the probability of sensory causes given the activation of the neural representation of those

causes; it was computed after using support vector machine learning algorithms to classify stimulus-locked EEG trials into one of two sets predictive of a visual stimulus category. Each set of classified trials was associated with spatiotemporal EEG patterns that characterized the large-scale neural representation of a visual category. Global brain free energy was significantly lower for correct versus incorrect visual categorizations ($p < .001$), as expected if correct categorizations were based on a relatively accurate generative model of the true visual category structure. Also, total global brain free energy correlated with the free energy ($r = 0.65$; $p < .001$) and decision uncertainty parameter ($r = 0.96$; $p < .001$) of a computational model of the categorization task (a partially observable Markov decision process implementing approximately Bayes-optimal decisions). These findings are evidence for a relationship between categorization, active inference, and brain free energy minimization.

**Disclosures: L.T. Trujillo:** None.

**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 790.19/JJJ50

**Topic:** H.02. Human Cognition and Behavior

**Title:** Neurophysiological responses to glare: An event-related potential study

**Authors: *D. YOSHIOKA**[1], Y. TAKAGI[2], T. MIYAGI[1], K. KANNAGA[1], S. AKAIKE[4], K. ONDA[4], H. HORITA[4], S. TAKEUCHI[3,5], M. MIYAZAKI[1,2,3]
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**Abstract:** Glare is a phenomenon caused by strong bright light, which induces discomfort and visual disabilities. To prevent this problem, many methods quantifying glare have been suggested so far (e.g., Unified Glare Rating). These conventional methods calculate the glare indexes using only physical parameters, but a subjective phenomenon of glare is considered to include neurophysiological factors also. In this study, we used electroencephalography (EEG) to reveal the neurophysiological responses to glare. Sixteen subjects participated in this study. During EEG recordings (63 electrodes, placed according to the 10-10 system), the participants performed glare judgement. In each trial, a white flash stimulus (duration: 500 ms) was presented to the participants. The brightness of the flash stimulus varied between trials by 5 degrees around the participants' point of subjective equalities (PSEs) of glare, which were identified before the EEG recordings. After presentation of the flash, the participants judged whether they felt "glare" or "no glare" with the flash. For analysis, we focused on the EEG data obtained under the

condition of the flash brightness corresponding to the participants' PSEs. In this condition, the judgment ratios of "glare" and "no glare" were approximately even. By comparing event-related potentials (ERPs) between the trials of the "glare" and "no glare" judgments under the equivalent brightness condition, we identified neurophysiological responses specific to glare. The ERPs in the left frontal areas exhibited larger positive activity (latency: 170-190 ms) when the participants judged the flash as a "glare" than when they judged the flash as "no glare." Particularly, the ERP at F1 exhibited a significantly larger positive peak when the participants judged the flash as a "glare" ($p = 0.037$). This result indicates that the ERP component at F1 reflects subjective glare. It was previously suggested that frontal EEG asymmetry could be related to emotional conditions (e.g., Coan & Allen, 2003). The ERP component at F1 might, therefore, be associated with the emotional discomfort caused by glare.

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**Poster**

**790. Human Cognition and Behavior: Perception and Imagery III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 790.20/JJJ51

**Topic:** H.02. Human Cognition and Behavior

**Support:** UBACyT 20020130100861BA
USAL VRID: 1812

**Title:** The influence of semantic relatedness on the subliminal processing of words and pictures. a masked priming paradigm study

**Authors: *J. M. ANDREAU**[1,2], N. M. BRUNO[1], S. TORRES BATÁN[1,2], A. A. IORIO[1,2], M. N. DÍAZ RIVERA[3], I. EMBÓN[4], L. J. JIMENEZ[5]
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**Abstract:** Research with masked priming paradigm has shown the presence of unconscious semantic processing of words and pictures. In this paradigm, the masked priming effect consists in the subliminal processing of a cue stimulus (prime) at a semantic level, which in turn, accelerates the conscious recognition of a subsequent stimulus (target). The behavioral correlate of this semantic masked priming effect is a decrease of the RT in a categorization task (e.g., recognizing animals vs tools), when the prime is semantically related to the target (e.g., the pair cat-dog). Previous studies suggested that the speed of subliminal semantic processing is stimulus dependent, being faster for pictures as compared to words. Moreover, it has been hypothesised

that the semantic relatedness of pictorial stimulus would lead to a stronger priming effect as compared to words. The present study, therefore, tested the semantic masked priming effect between words and pictures and also analyzed the semantic relatedness between the prime-target pair for each stimuli format. Participants performed a masked priming task with words or pictures as prime-target stimuli pairs. They were instructed to perform a semantic categorization task, deciding whether the target stimulus was an animal or an object. Trials consisted of three different conditions for each stimulus format: strongly-related (SR), weakly-related (WR) and non-related (NR). The first two corresponding to the congruent condition (CC) and the last one belonging to the incongruent condition (IC). We found significant differences in RT between CC vs IC, for both pictures and words, being the responses faster for pictures over words suggesting a difference in the speed of information processing. Nevertheless, contrary to what the literature predicted, no interaction were found between the presentation format (pictures/words) and the semantic relatedness. This could suggest that even though semantic processing are faster for pictures, this doesn't mean a stronger priming effect. These results are important in the context of recent theories regarding subliminal semantic processing and should be acknowledge in future semantic masked priming research.

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**Poster**

**791. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 791.01/JJJ52

**Topic:** H.02. Human Cognition and Behavior

**Support:** Volkswagen AZ 86 507-3
DFG SFB 1089

**Title:** Visually selective single unit activity in the human medial temporal lobe during dissociation of conscious perception and memory

**Authors: *S. MACKAY**[1], T. P. REBER[1,4], M. SOEHLE[2], J. BOSTRÖM[3], C. E. ELGER[1], F. MORMANN[1]
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**Abstract:** Semantic cells in the human medial temporal lobe (MTL) are cells that have been reported to respond to specific concepts in a selective and semantically invariant manner. Their

response latencies with respect to stimulus onset exceed the duration of object recognition, which suggests involvement in higher cognitive processes. Since the MTL is essential for declarative memory formation, the observed semantic selectivity in this region may be related to, or even facilitate, mnemonic processes. The aim of this study was to investigate the behavior of stimulus-selective cells in a spatial memory task during the dissociation of memory encoding and conscious perception. Memory formation was inhibited by a small dose of propofol, a pharmacological agent which causes anterograde amnesia while conscious perception is preserved. In up to now 4 patients we were able to induce anterograde amnesia while leaving conscious perception of the stimuli intact. Recording from 404 neurons, we analyzed selective increases in firing rates to the preferred stimuli. We found that under propofol, response magnitudes significantly decreased while response latencies significantly increased in amygdala ($p < .01$), hippocampus ($p < .05$) and parahippocampal cortex ($p < .01$). These findings indicate that pharmaceutical disruption of basic response properties such as magnitude and latency in visually selective cells does not affect conscious perception but does appear to be a neural correlate of impaired memory formation.

**Disclosures: S. Mackay:** None. **T.P. Reber:** None. **M. Soehle:** None. **J. Boström:** None. **C.E. Elger:** None. **F. Mormann:** None.

**Poster**

**791. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 791.02/JJJ53

**Topic:** H.02. Human Cognition and Behavior

**Support:** Volkswagen AZ 86 507-3
DFG SFB 1089

**Title:** Frequency-selective single units in the human primary auditory cortex during different stages of vigilance

**Authors: *M. S. KEHL**[1], T. P. REBER[1,3], J. BOSTRÖM[2], C. E. ELGER[1], F. MORMANN[1]
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**Abstract:** It is still poorly understood how the activity of neurons in the human primary sensory areas is modified by different stages of vigilance such as wakefulness and sleep. Imaging studies have indicated that the activity of the primary auditory cortex is not significantly different during sound presentation in sleep and wakefulness (Portas et al., 2000). However, only very few cases of single neuron recordings in the human primary auditory cortex have been reported until today

(Bitterman et al., 2008; Ossmy et al., 2015). Here we report the results from single unit recordings in both transverse gyri of Heschl in an epilepsy patient undergoing pre-surgical monitoring. We recorded the neural activity of 105 units (53 SU/ 52 MU) in response to a synthetic random-chord auditory stimulus composed of frequencies covering the audible spectrum with 18 tones per octave (Bitterman et al., 2008). We presented this random-chord stimulus continuously during 3 full nights of sleep, and recorded the neural activity in parallel. The overnight recordings allowed up to 10,000 presentations per frequency, and numerous presentations during each sleep stage.
Our recordings during wakefulness confirmed the ultra-fine frequency tuning of single neurons in the human primary auditory cortex previously described (Bitterman et al., 2008). Using a customized spike sorting software (Niediek et al., 2016) we were able to track single neurons through the course of an entire night. We found that frequency-selective neurons in the primary auditory cortex were firing throughout the night (including SWS) in response to tones of their preferred frequency. Frequency-selective neurons tended to exhibit a stronger response to their preferred tones during wakefulness than during non-REM sleep, which in turn was stronger than during REM sleep. Comparing the average normalized tuning curve for different sleep stages showed that the ultra-fine frequency tuning observed in awake humans is conserved during sleep (even in SWS).
Our data provide the first direct evidence that cellular functions in the human auditory cortex are largely independent of the current state of vigilance. This suggests that the principle gateway to conscious auditory perception lies downstream from the primary auditory cortex.

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**Poster**

**791. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 791.03/JJJ54

**Topic:** H.02. Human Cognition and Behavior

**Support:** Volkswagen AZ 86 507-3
DFG SFB 1089

**Title:** Decision confidence is represented at the single-unit level in the human medial temporal lobe

**Authors: *A. UNRUH-PINHEIRO**[1], M. R. HILL[1], B. WEBER[2], J. BOSTRÖM[3], C. ELGER[1], F. MORMANN[1]

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**Abstract:** Several studies have suggested that the human medial temporal lobe (MTL) is involved in decision making. Subjective value correlates of food stimuli have been reported at the single-unit level. However, the literature lacks attempts to decorrelate potential confounding signals to determine if it is truly value that is being encoded in the firing rates. An important effect often confused with value is salience, defined as the unsigned value. Other possible confounds are static properties of the stimuli, such as salt or sugar content. On the other hand, to our knowledge, no human intracranial electrophysiological study has so far investigated the representation of decision variables such as confidence during binary decisions in the MTL.
In this study, we recorded single-neuron activity from neurosurgical patients implanted with intracranial microelectrodes in the MTL while they performed two decision-making tasks. First, in a Rating task, patients were presented with 20 food stimuli and asked to report a rating, allowing for both positive and negative values, thus controlling for salience. Subsequently, a Two-Alternative Forced-Choice task was performed, consisting in the sequential presentation of two stimuli. The patients were asked to report their preferred stimulus and how much they preferred this stimulus over the other one, as a graded measure of decision confidence. During a break, the product chosen most often was consumed to satiation. After this, a second round of the tasks was performed, to control if changes in behavioral variables were also reflected in the neuronal activity.
We found that single neurons in the human MTL appeared to encode in their firing rates the reported decision confidence and that this signal was modulated by the food intake. Therefore, we provide the first evidence that suggests processing of decision confidence by single neurons in the MTL. We could also replicate previously reported findings of value-modulated neurons. However, these cells did not reflect the change in the value of the stimuli. Therefore, our results call into question whether the human MTL really represents subjective value, and suggest that other confounding variables might be encoded instead.

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**Poster**

**791. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 791.04/JJJ55

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH F31-AG057109

NIH R01-MH111790

**Title:** Recollection precision enhancement by active retrieval: Testing the role of the hippocampal-cortical network using noninvasive brain stimulation

**Authors: *A. NILAKANTAN**[1], M. GUNLOGSON[1], V. MANDOSKE[1], B. DURR[1], S. VANHAERENTS[2], D. BRIDGE[1], J. VOSS[1]
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**Abstract:** Active retrieval enhances episodic memory, which is thought to involve increased hippocampal activity. Here, we used network-targeted noninvasive brain stimulation to test the causal role of the hippocampal-cortical network as it supports active retrieval and influences later memory. Sixteen participants went through five consecutive daily sessions of network-targeted continuous theta-burst stimulation (cTBS) at a parietal cortex location selected based on its high fMRI connectivity with the hippocampus. The impact of active retrieval on recollection memory was assessed before and ~24 hours after stimulation using an associative object-location memory test. Critically, we used distance error to segregate the effects of active retrieval on recollection precision versus recollection success, and hypothesized that network targeted stimulation would specifically modulate recollection precision, the memory process dependent on the hippocampus. Stimulation significantly increased the influence of active retrieval on recollection precision relative to sham ($p<0.005$). In contrast, stimulation had a marginal effect on recollection precision in a passive control condition that did not involve active retrieval ($p=0.05$). There were no effects of stimulation on recollection success in either condition ($p>0.1$). These findings provide behavioral evidence that the hippocampal-cortical network causally contributes to the influence of active retrieval on recollection memory precision. Interestingly, five-days of cTBS selectively modulated hippocampal-dependent memory, as stimulation had the greatest influence on the active retrieval condition (versus control) and only on recollection precision (versus success). fMRI correlates of memory performance will also be discussed in order to identify the locus of the neural activity changes responsible for the selective effects due to stimulation.

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**Poster**

**791. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 791.05/JJJ56

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIA R01-AG049002
NIMH R01-MH106512

**Title:** Effects of noninvasive stimulation targeting the hippocampal-cortical network on forgetting of verbal paired associates differ by age

**Authors: *E. KARP**[1], A. NILAKANTAN[1], M. GUNLOGSON[1], R. PALUMBO[1], S. VANHAERENTS[2], J. VOSS[1]
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**Abstract:** Multiple-session non-invasive stimulation targeting the hippocampal-cortical network can improve new learning. However, previous studies have not investigated whether stimulation also affects retention of material learned previously. Effects of stimulation on retention could offer clues as to the mechanisms by which stimulation affects memory. For instance, improved new learning at the expense of more rapid forgetting could implicate effects of stimulation on neurogenesis, whereas improvements in both new learning and reduced forgetting would suggest heightened capacity for plasticity. In a counter-balanced design, younger adults ($N$=15, mean=26.51 years, range 19-35 years) and older adults ($N$=15, mean=72.79, age-range, 65-80) received five consecutive daily sessions of network-targeted stimulation versus sham stimulation. Both groups showed improvements of new learning in a source memory task. To test effects of stimulation on retention of information over the week of stimulation, we developed a verbal paired associates task (VPA). Before stimulation, participants were given three opportunities to learn a set of 28 word pairs, using a testing-effect design to increase learning. Following stimulation, cued recall was tested and forgetting was calculated relative to the performance level achieved prior to stimulation. Older adults forgot more words than younger adults ($p<0.01$), and the effects of stimulation were opposite for these groups. Whereas older adults tended to forget less due to stimulation (relative to sham), younger adults tended to forget more due to stimulation ($p=0.03$). These findings of opposite effects of stimulation on forgetting rates in older versus younger adults suggest that stimulation targeting the hippocampal-cortical network might achieve new learning enhancements via different fundamental mechanisms in these age groups.

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**Poster**

**791. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 791.06/JJJ57

**Topic:** H.02. Human Cognition and Behavior

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

**Title:** Optimizing hippocampal-cortical network modulation via repetitive transcranial magnetic stimulation: A dose-finding study

**Authors: *M. V. FREEDBERG**[1], J. A. REEVES[2], D. HAUBENBERGER[3], Y. K. CHEUNG[4], J. L. VOSS[5], E. M. WASSERMANN[6]
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**Abstract:** Recently, it has been shown that repetitive transcranial magnetic stimulation (rTMS) of the parietal lobe can enhance functional connectivity (FC) of the hippocampal-cortical network (Wang et al., 2014). This is associated with improvement in associative memory, suggesting that parietal rTMS may help patients with memory disorders. Wang et al. arbitrarily chose a 5-day stimulation regimen. However, the number of consecutive daily stimulation sessions required to produce this change is unknown and systematic dose-finding is new to noninvasive brain stimulation. To determine the number of days needed for a clinically meaningful increase in hippocampal network FC, we adapted a procedure used to determine the maximum tolerable dosage in drug trials, the Continual Reassessment Model (CRM; Garret-Mayer, 2006). The CRM, an adaptive Bayesian procedure, iteratively recommends dosages based on previous data until it converges on a recommendation. We performed rTMS on five cohorts of 3 participants while adjusting the number of sessions per the CRM. Values for hippocampal network FC were determined from resting-state fMRI before and after multi-day stimulation. To set our criterion for a clinically meaningful FC change, we used the data from Wang et al. (2014). In their data set, the left precuneus and left medial occipital cortex showed significant group-level increases in FC with the left hippocampus due to stimulation. Using these data, we set the threshold FC change at 0.028 by maximizing Youden's index (sensitivity + specificity - 1) and performing a receiver-operator curve analysis. Preliminary CRM recommendations using data from N=15 subjects indicate that 4 days of stimulation is needed to yield meaningful FC change, although data collection is ongoing. This trial represents the first systematic attempt to determine the dose of rTMS required to produce network FC changes.

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**Poster**

**791. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 791.07/JJJ58

**Topic:** H.02. Human Cognition and Behavior

**Support:** BRAIN Initiative R01-MH111790
Training Program in the Neuroscience of Human Cognition T32-NS047987

**Title:** Optimizing simultaneous TMS/fMRI methods to target the hippocampal-cortical network with configurable stimulation trains varying in frequency, pattern, and duration

**Authors: *M. S. HERMILLER**[1], R. A. YOUNG[1], Z.-D. DENG[3], Y. CHEN[1], T. B. PARRISH[1], J. L. VOSS[2]
[2]Med. Social Sci., [1]Northwestern Univ., Chicago, IL; [3]Natl. Inst. of Mental Hlth., Bethesda, MD

**Abstract:** The hippocampus and distributed brain regions interact as a hippocampal-cortical network (HCN). Neural activity from regions comprising this network synchronize at theta frequencies, providing a possible mechanism of interregional communication. Transcranial magnetic stimulation (TMS) can modulate network connectivity to causally test brain networks and their functional roles. We have previously shown stimulation-induced changes in HCN fMRI connectivity, especially within core network regions such as the hippocampus, was greatest following TMS delivered in a theta-burst pattern rather than a beta-frequency (20-Hz). However, no previous studies have measured immediate impacts of patterned TMS such as theta-burst on neural correlates of cognitive processing. Therefore, our current experiment uses concurrent TMS/fMRI to measure activity in the hippocampus and surrounding regions during memory processing while theta-burst stimulation is delivered, relative to other stimulation patterns. Here, we describe our optimized method to obtain fMRI signals of hippocampal memory processing for desired configurations of TMS frequencies, patterns, and durations. Notably, we optimized parameters such that theta-burst (50-Hz triplets every 200ms) could be used during concurrent fMRI, rather than repetitive trains (i.e., 1-Hz) or single pulses. To our knowledge, this is the first report of theta-burst stimulation used in concurrent TMS/fMRI. Here, we report quality control metrics obtained using three primary methods, including direct pulse-slice interference, temporal gap stimulation, and interleaved-slice TMS/fMRI. Direct pulse-slice interference revealed irreparable and long-lasting artifact. Stimulation during temporal gaps between each image volume yielded artifact-free data, but this technique imposed limitations on stimulation duration. This is problematic because lower frequency stimulation, such as theta-burst, require durations longer than can be accommodated by this method before signal loss (i.e., 0.6-40s). Finally, interleaved-slice TMS/fMRI was free of artifact, and customization of scan parameters allowed

for stimulation trains with any duration of theta-burst stimulation able to be accommodated. These findings indicate that it is possible to deliver TMS of a wide range of frequencies, patterns, and durations without loss of fMRI signal quality, which can be used to test hypotheses regarding the role of theta-burst activity patterns in human HCN function. Optimized methods for stimulation localization during scanning and for modeling of induced electrical fields based on this localization will also be discussed.

**Disclosures: M.S. Hermiller:** None. **R.A. Young:** None. **Z. Deng:** None. **Y. Chen:** None. **T.B. Parrish:** None. **J.L. Voss:** None.

**Poster**

**791. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe III**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 791.08/JJJ59

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIMH R01-MH106512

**Title:** State-dependent expression of hippocampal-cortical fMRI connectivity changes due to noninvasive stimulation

**Authors: *K. N. WARREN**[1], M. S. HERMILLER[1], S. VANHAERENTS[2], J. L. VOSS[1]
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**Abstract:** Episodic memory is supported by the hippocampus and a distributed network of interacting cortical regions. We have previously shown that noninvasive brain stimulation targeting this hippocampal-cortical network (HCN) increases resting-state fMRI correlations among network regions and influences episodic memory. However, the relevance of resting-state fMRI connectivity to cognitive processing is uncertain. Therefore, we investigated the effects of network-targeted brain stimulation on fMRI connectivity measured during a specific memory demand: autobiographical retrieval. Furthermore, we compared these effects of stimulation on memory-related fMRI connectivity to those observed via resting-state fMRI in the same subjects. Subjects (N=16) underwent resting-state and autobiographical-retrieval fMRI scans followed by five consecutive days of high-frequency (20 Hz) repetitive transcranial magnetic stimulation to left lateral parietal cortex. Follow-up fMRI occurred 24 hours and 1 week after the last day of stimulation. Initial analyses identified changes in whole-brain fMRI connectivity 24 hours after stimulation in both resting-state and autobiographical retrieval-state scans. Relative to sham, stimulation had a greater effect on fMRI connectivity measured during the autobiographical retrieval state, with increased fMRI connectivity in this state relative to the resting state. Additional results in the 1-week follow-up will be discussed to determine whether this state-

dependency persists following stimulation. These findings indicate that the expression of fMRI connectivity changes following network-targeted stimulation are state-dependent, with increased effects of stimulation fMRI connectivity observed when subjects are engaged in a network-relevant memory retrieval demand. This result supports the utility of noninvasive stimulation for the modulation of cognition, as the effects of stimulation on the targeted network persisted long after stimulation but primarily in the circumstance when the network was engaged by relevant cognitive processing.

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**Poster**

**791. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 791.09/JJJ60

**Topic:** H.02. Human Cognition and Behavior

**Support:** ONR N00014-15-1-0033

**Title:** Relationships between individual electroencephalography and resting state signatures of memory for items and contexts

**Authors: *H. R. DIMSDALE-ZUCKER**[1], K. KIM[2], A. J. BARNETT[2], L.-T. HSIEH[3], Z. M. REAGH[2], C. RANGANATH, Ph.D.[2]
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**Abstract:** Successful memory for item and context information is a core feature of episodic memory and has been tied to various behavioral, electrophysiological, and hemodynamic signatures. Although these different methods are thought to measure the same underlying cognitive operations, little is known about direct links between them. Both electroencephalography (EEG) and resting state functional magnetic resonance imaging (rsfMRI) are believed to reflect activity in large-scale cortical networks, and these measures are sensitive to memory for items and contexts. However, the relationships between these variables and individual differences in memory remains unclear. To tackle this outstanding question, 40 healthy younger adults (18-35 years old) completed an item and source recognition memory task while undergoing EEG recording to enable measurement of item- (LPC and FN400 ERPs) and source-based (frontal-midline theta power) memory signatures. In a separate session, we additionally acquired rsfMRI and individual computed cortico-hippocampal networks based on an existing model (Ranganath and Ritchey, 2012) of preferential item (anterior temporal) and

source (posterior medial) networks. We find that ERP magnitudes are sensitive to recollection and that behavioral performance for item and source responses is also related to connectivity profiles. Further analyses will determine the relationship between individual differences in ERP, functional connectivity, and behavioral measures of recollection, familiarity, and source memory. This data provides a missing link between EEG and resting state networks related to memory for items and contexts.

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**Poster**

**791. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 791.10/JJJ61

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH Training Grant T32 AG 50061-2
Office of Naval Research Grant N00014-15-1-0033
Office of Naval Research/Department of Defense Grant N00014-17-1-2961

**Title:** Scaffolding of event representations in cortico-hippocampal networks

**Authors: *Z. M. REAGH**, R. BUGSCH, J. MACALUSO, C. RANGANATH, Ph.D.
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**Abstract:** Our experiences consist of complex events involving people, places, things, and situations. However, most laboratory studies of event representation and memory use static images such as objects and scenes, which may limit our understanding of how information is extracted from real-world events and scaffolded into neural representations. In this experiment, we created eight brief video clips in which a central character interacts with a dynamic environment. Clips included one of two characters (“Lisa” or “Tommy”) in one of four contexts. Importantly, the four contexts included two perceptually-unique exemplars of two distinct locations - coffee shops and grocery stores. There were high-level similarities (e.g., presence of coffee cups) across related contexts, which are thought to tap into a common event schema despite low-level differences (e.g., red ceramic cups versus glass mugs). While in the MRI scanner, participants viewed each clip three times and performed cued recall. In addition, outside of the scanner, they performed a recognition memory task. We predicted that representations of central characters would persist across distinct contexts (e.g, Lisa across all contexts) in an anterior-temporal cortico-hippocampal network (AT; including perirhinal cortex and temporal poles). Conversely, we predicted stable representations of specific contexts across central

characters (e.g., a particular coffee shop across both characters) in a posterior-medial network (PM; including parahippocampal cortex and precuneus). We also predicted that some regions in the PM network - notably medial prefrontal cortex - would generalize across related contexts (e.g., the two coffee shops). Behavioral results revealed highly accurate recall and recognition of details about characters and contexts, with no significant memory biases. We analyzed the similarity of voxel pattern information from fMRI data collected during multiple viewings and recall of each video clip. Preliminary analyses reveal that activity in PM and AT networks are sensitive to video content. Ongoing analyses will test for differential representation of character and context information, as well as gradients of specificity and cross-regional correlations during viewing and recall of video clips.

**Disclosures: Z.M. Reagh:** None. **R. Bugsch:** None. **J. Macaluso:** None. **C. Ranganath:** None.

**Poster**

**791. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 791.11/JJJ62

**Topic:** H.02. Human Cognition and Behavior

**Support:** ONR/DoD N00014-17-1-2961 (MURI)

**Title:** Consolidation promotes retention of events that form a coherent narrative: Evidence for higher-order structure in episodic memory

**Authors: *B. I. COHN-SHEEHY**[1,2,3], C. RANGANATH[1,2,4]
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**Abstract:** Many studies have shown that people break up continuous experiences into discrete events. Although researchers often focus on how events are segregated in memory, people can link information across multiple events. For instance, if a friend tells you they forgot to turn off the stove, and if they later mention the fire department rescued their house, information from these separate events may become linked in memory. Some theories of memory consolidation suggest that memories for related events can be linked into a higher-order structure through offline interactions between the hippocampus and neocortex. We hypothesized that delay-dependent consolidation can promote retention of events that can be linked through a coherent narrative, even if these events are encoded at separate times. To investigate how coherence relates to recall, we created a new paradigm in which participants encoded four fictional stories, presented as continuous audio clips. Coherence was operationalized in terms of four side-characters, each appearing in the context of two separate story clips centered on one of two main

protagonists. Critically, the events involving the side-characters were unrelated to the surrounding main stories (i.e. "sideplots"). For two side-characters, the sideplot events could be linked into a larger narrative ("coherent sideplot events"), whereas sideplot events for the other two side-characters were unrelated to each other ("incoherent"). Half of the participants recalled the stories immediately after story presentation, and half recalled the stories after a 24-hour delay. Blinded scoring revealed that the 24-hour delay group recalled more information from coherent than from incoherent sideplot events ($t(35)=3.79$, $p<0.001$), whereas the immediate recall group showed no significant differences in recall between coherent and incoherent sideplot events ($t(35)<1$). Comparison between groups revealed a significant Delay X Coherence interaction ($F(1,70)=6.32$, $p<0.014$), indicating that the effect of sideplot coherence was significantly larger after a 24 delay. Crucially, events involving main protagonists (i.e. not sideplots) were not recalled differently between the 24-hour and immediate recall groups. The results are consistent with the idea that coherent events are preferentially consolidated in memory. We hypothesize that this consolidation effect may be supported by interactions between the hippocampus and a posterior medial neocortical network, that enables the organization of events into higher-level representations. We will present preliminary results from functional magnetic resonance imaging (fMRI) testing this hypothesis.

**Disclosures: B.I. Cohn-Sheehy:** None. **C. Ranganath:** None.

**Poster**

**791. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 791.12/JJJ63

**Topic:** H.02. Human Cognition and Behavior

**Support:** Vannevar Bush Faculty Fellowship (Office of Naval Research Grant) N00014-15- 1-0033

**Title:** Hippocampal low frequency oscillations in prediction of temporal regularity

**Authors: *K. KIM**[1], L.-T. HSIEH[2], J. CRIVELLI-DECKER[1], J. PARVIZI[3], C. RANGANATH[1]
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**Abstract:** By learning statistical regularities, people can use past experiences to predict upcoming events. Hippocampal theta oscillations are increased following events that violate predictions (i.e., prediction error (PE); Axmacher et al., 2010; Chen et al., 2013). Little is known about whether or how such hippocampal "novelty" responses are related to learning or prediction. In the present study, using intracranial electroencephalography, we investigated the

electrophysiological characteristics of hippocampal processing during exposure to novel and repeated sequences of items. Hippocampal activity was recorded as patients made semantic judgements on a series of items (i.e., Is this living?; Can you ride on it?). The continuous stream of items consisted of 'fixed' sequences, in which four objects were repeatedly shown in the same temporal order, 'random' sequences, in which four objects were repeatedly shown in an unpredictable order, and 'novel' sequences consisting of four novel items. Data from hippocampal electrodes were analyzed in a time window starting from 300 ms preceding stimulus onset to 1200ms after onset. Time-frequency analysis was conducted using the Hilbert transformation, and a permutation test was used to test the statistical significance of conditional differences. We find that hippocampal regions that exhibited significant theta power increases during processing of novel items also exhibited theta power increases preceding onset of unpredictable items in random sequences. Conversely, these regions showed increases in alpha power prior to onset of predicted items in fixed sequences. This result converges with recent scalp EEG work (Crivelli-Decker et al., in press) suggesting a role for theta oscillations in prediction-error driven learning and for alpha oscillations in sequence-based prediction.

**Disclosures: K. Kim:** None. **L. Hsieh:** None. **J. Crivelli-Decker:** None. **J. Parvizi:** None. **C. Ranganath:** None.

**Poster**

**791. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 791.13/JJJ64

**Topic:** H.02. Human Cognition and Behavior

**Support:** ONR N00014-15-1-0033

**Title:** Individual differences in source memory are related to white matter microstructure in healthy young adults

**Authors: *A. J. BARNETT**[1], H. R. DIMSDALE-ZUCKER[2], Z. M. REAGH[3], C. RANGANATH, Ph.D.[1]
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**Abstract:** Retrieval of the context in which an item was encountered is thought to rely upon the coordinated action of the hippocampus and the posterior medial (PM) network—a group of regions including the parahippocampal, retrosplenial, and posterior cingulate cortices. The cingulum bundle is a white matter tract that connects these regions together, and, as such, is a candidate tract that may support source memory—memory for the context in which an item was

encoded. The uncinate fasciculus, on the other hand, connects regions of an anterior temporal (AT) network such as the temporal pole and the orbitofrontal cortex which are thought to play more of a role in semantic memory and familiarity, rather than source memory. In this study, we examined whether the individual variability in microstructure of these white matter tracts could explain differences in source memory ability and item recognition across subjects. We hypothesized that higher integrity of the cingulum bundle, measured by fractional anisotropy (FA), would be related to better source memory performance, and that higher FA in the uncinate fasciculus would be related to recognition performance. To that end, subjects encoded pictures of objects in the context of one of four questions and, following a delay, were instructed to perform a recognition test with source judgements. Subjects later underwent a diffusion MRI scan using a multishell high angular resolution diffusion-weighted imaging protocol. Deterministic tractography was performed on each subject to extract the cingulum and uncinate tracts, and mean FA was extracted from the resulting streamlines. We found that individuals who had higher mean FA in the cingulum bundle also had higher source memory accuracy, but this was not true for the uncinate fasciculus. These results provide evidence that the cingulum bundle may serve as a structural foundation for detailed source memory by connecting regions of the PM network. Future analysis will examine whether item recognition is related to uncinate fasciculus microstructure.

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**Poster**

**791. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe III**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 791.14/JJJ65

**Topic:** H.02. Human Cognition and Behavior

**Support:** ONR N00014-15-1-0033
NSF 1650042

**Title:** Characterizing the neural representation of verbal sequence knowledge

**Authors: *W. B. REILLY**[1], C. RANGANATH[2]
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**Abstract:** Humans have a remarkable ability to use event schemas—structured knowledge about typical sequences of events—in order to predict spatial, temporal, and causal relationships in novel contexts. Although event schemas play a fundamental role in high-level cognition, little is known about the neural mechanisms that support representation of this form of structured

knowledge. The hippocampus is known to support memory for specific event sequences, but Ranganath and Ritchey (2012) proposed that the Posterior Medial (PM) Network represents abstract knowledge about sequences that correspond to event schemas. To probe the specificity of event schema representations in cortico-hippocampal networks, we used fMRI to examine brain activity magnitude and activity patterns as participants made semantic judgments on a continuous stream of sequentially-presented verbs. Three types of sequences were constructed by systematically manipulating the order in which the verbs were presented and whether that order was fixed on each repetition. In the 'intact' condition, verbs were presented in an order that, as determined by a norming study, corresponded to an expected sequence of events based on a well-learned schema. In the 'scrambled-fixed' condition, five verbs were presented in an order that did not correspond to an event schema, and this order was identical on each repetition. Finally, in the 'scrambled-random' condition, the verbs were presented in a new, random order on each repetition. Crucially, across participants the stimuli were counterbalanced such that the same stimuli were used for each condition, with the only difference being the order in which the items were presented. Participants' reaction times were faster for intact than for scrambled-fixed and scrambled-random sequences, suggesting that they used their pre-existing schema knowledge to facilitate their semantic decisions. Ongoing univariate fMRI analyses were designed to detect regions sensitive to the manipulation of event schema content, and pattern similarity analysis was leveraged in order to test whether PM regions represent specific event schema content. A whole-brain cortical parcellation was employed in exploratory region of interest pattern analyses in order to characterize the extent of schema representations throughout cortex.

**Disclosures: W.B. Reilly:** None. **C. Ranganath:** None.

**Poster**

**791. Human Cognition and Behavior: Human Long-Term Memory: Medial Temporal Lobe III**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 791.15/JJJ66

**Topic:** H.02. Human Cognition and Behavior

**Support:** SNSF - P300P1_161178
MO930/4-1, SFB1089
Volkswagen Foundation

**Title:** Representation of abstract semantic knowledge in populations of human single neurons in the medial temporal lobe

**Authors: *T. P. REBER**[1,3], M. BAUSCH[1], S. MACKAY[1], J. BOSTRÖM[2], C. E. ELGER[1], F. MORMANN[1]

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**Abstract:** Abstract classification of constituents of the external world is a vital ingredient of human cognition. It is known that distinct macroscopic areas of the neocortex encode distinct semantic features of sensory input. Projections from supramodal neocortical regions converge onto the medial temporal lobe, where sparse representations of neocortical firing patterns are encoded into episodic memory. It remains poorly understood how neurons in the medial temporal lobe (MTL) achieve the feat of efficiently encoding the vast amounts of information represented in activity patterns distributed over large portions of the neocortex. We show that information is encoded in high levels of semantic abstraction, which may be key to solve this problem. We recorded single unit activity from human subjects implanted with depth electrodes for chronic seizure monitoring in the MTL (4917 units, 25 patients). Subjects repeatedly viewed 100 images that can be subdivided in 10 categories of 10 exemplars each. Highly abstract, semantic representations of the stimuli emerged on the level of population activity of MTL neurons. This is remarkable as individual units were driven by only few effective stimuli. Representational similarity analyses indicated that superordinate semantic features govern population activity especially in the hippocampus and amygdala as compared to entorhinal and parahippocampal cortex. Furthermore, pattern classification algorithms trained to decode superordinate category generalize successfully to unseen exemplars, and classifiers trained to decode exemplar identity more often confuse exemplars of the same versus different superordinate category. While high abstraction is efficient and may facilitate generalization of knowledge to novel situations, it also comes at the cost of loss of detail and may even be central to false memory generation.

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**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 792.01/JJJ67

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH F32 NS09757
NIH R01 MH063901

**Title:** The human intraparietal sulcus modulates task-evoked functional connectivity for cognitive control

**Authors: *K. HWANG**[1], J. M. SHINE[2], M. D'ESPOSITO[1]
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**Abstract:** It is proposed that cognitive control can be achieved by establishing the optimal routing of information flow along neural pathways (Miller & Cohen, 2001). In our previous human fMRI study (Hwang et al., 2018 Cerebral Cortex), we found that activity in the lateral prefrontal cortex and the intraparietal sulcus (IPS) co-varied with task-related changes in functional connectivity strength between occipito-temporal regions while subjects performed distinct tasks on the same visual stimuli. This result suggests that frontal and parietal regions may provide top-down biasing signals to establish task-specific functional connectivity patterns. However, this result only provides correlational evidence, and it is possible that instead of casually influencing connectivity patterns, fronto-parietal regions read out stimuli information from occipito-temporal regions to perform the task. The goal of the current study is to use theta-burst transcranial magnetic stimulation (TMS) to causally test the relationship between fronto-parietal activity and task-evoked functional connectivity patterns. Thirteen human participants participated in a multi-session TMS-fMRI study. During all fMRI sessions, subjects viewed sequences of images of faces and buildings, and were required to detect n-back repetitions (2-bk and 1-bk) of a target category (faces or buildings). Replicating our previous finding, we found that functional connectivity between ventral temporal and early visual regions (V1-V4) selectively increased during the processing of task-relevant information. In separate TMS-fMRI sessions, we used theta-burst TMS to disrupt IPS and a control region (S1) prior to fMRI scanning. We found that causally disrupt IPS function decreased the overall functional connectivity strength between occipito-temporal regions, and specifically weakened the connectivity strength between task-relevant regions, which further correlated with behavioral decrements in reaction time. In contrast, control TMS had no effect on task-evoked functional connectivity strength and behavioral performance. These findings provide causal evidence indicating that human IPS exerts top-down biasing signals to modulate task-evoked functional connectivity for cognitive control.

**Disclosures: K. Hwang:** None. **J.M. Shine:** None. **M. D'Esposito:** None.

**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 792.02/JJJ68

**Topic:** H.02. Human Cognition and Behavior

**Support:** British Academy pf130059
National Institute for Health Research (NIHR) Oxford Biomedical Research Centre

NIHR National BioResource (Oxford Biobank)

**Title:** Dissociative catecholaminergic effects on visual attention: Catechol-O-methyltransferase (COMT) and dopamine beta-hydroxylase (DBH) genes differentially modulate visual attention

**Authors: *M. CHECHLACZ**[1], N. SHALEV[2], S. VANGKILDE[5], M. J. NEVILLE[3], E. M. TUNBRIDGE[4], A. NOBRE[2]
[1]Sch. of Psychology & Ctr. for Human Brain Hlth., Univ. of Birmingham, Birmingham, United Kingdom; [2]Exptl. Psychology, [3]Oxford Ctr. for Diabetes,Endocrinology and Metabolism, [4]Psychiatry, Univ. of Oxford, Oxford, United Kingdom; [5]Univ. of Copenhagen, Copenhagen, Denmark

**Abstract:** Genetic variability influencing neurotransmitter signalling has the potential to explain the origins of individual differences in cognition. The cognitive processes enabling to selectively prioritize behaviourally relevant visual information while ignoring distraction are collectively known as visual attention. Visual attention entails a set of complex cognitive mechanisms underlying either the way attention is maintained over time or oriented towards specific objects. The neural networks supporting attention are modulated by several neurotransmitters including dopamine and noradrenaline. The current study investigated the effects of a single nucleotide polymorphism in two catecholaminergic genes COMT ($Val^{158}Met$) and DBH (444 G/A) on individual differences in attention functions. 125 male participants (age range 34-51) were recruited from the Oxford Biobank by genotype-based recall to ensure comparable genotype frequencies. Participants were tested on a continuous performance task measuring sustained attention, a Go/No-Go task measuring response inhibition and a task assessing attentional selection in accordance with Bundesen's theory of visual attention (TVA). Eight independent measures representing discrete attentional functions were calculated and entered into statistical analyses: target sensitivity and response bias (response inhibition); standard deviation of reaction time and percentage change in target sensitivity (sustained attention); processing speed, working memory capacity, threshold of perception and distractibility (attentional selection). ANOVA with DBH genotype (AA, n=42; GG, n=47; GA, n=36) as between subject factor revealed a significant group difference in the extent to which target sensitivity had changed ($F(2,122)=6.115$; $p=.003$; Partial $\eta^2=.091$) with a striking increase in performance over time in DBH heterozygotes. No other group differences in attentional function were found with respect to the DBH genotype. ANOVA with COMT genotype (Val/Val, n=42; Met/Met, n=43 Val/Met, n=40) as between subject factor revealed a significant effect of the genotype on perceptual threshold ($F(2,122)=4.069$; $p=.019$; Partial $\eta^2 = .063$) with perceptual threshold significantly decreased with increased Val allele dosage. No other group differences in attentional function were found with respect to the COMT genotype. In conclusion, our findings provide experimental evidence that: (i) dopaminergic and noradrenergic genotypes have dissociative cognitive effects on visual attention; (ii) too little or too much catecholamines may have equally detrimental effects on sustained attention.

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**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 792.03/JJJ69

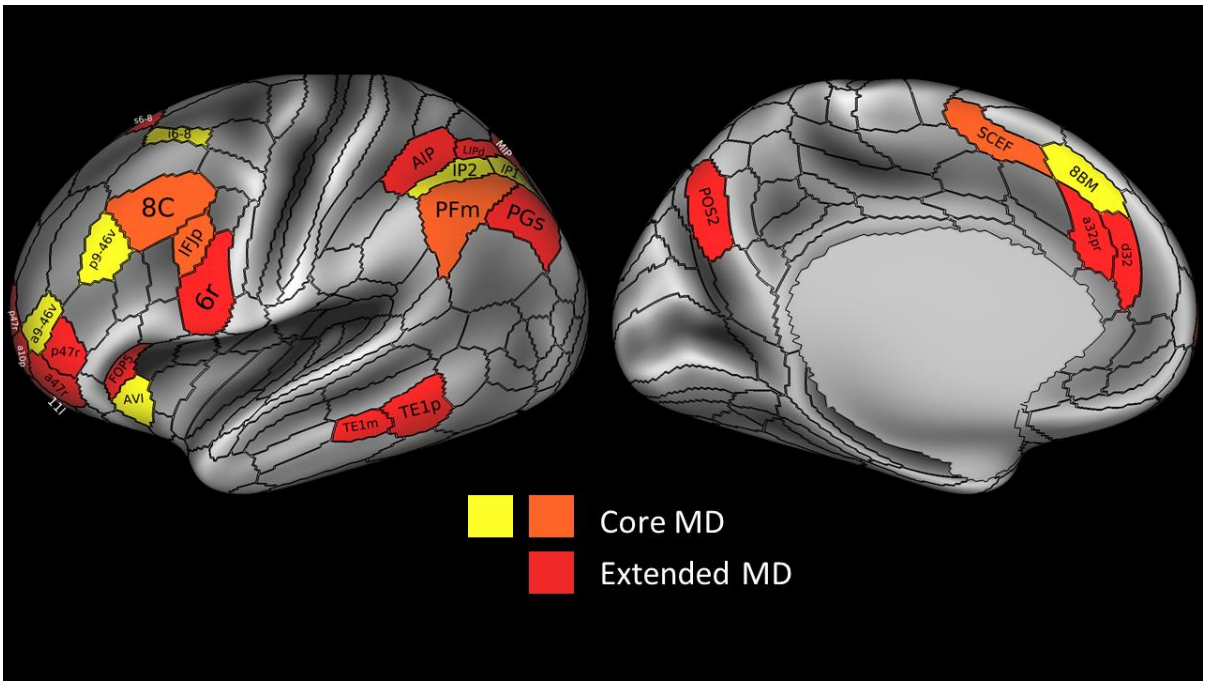
**Topic:** H.02. Human Cognition and Behavior

**Support:** MRC grant SUAG/002/RG91365 (JD)
RO1 MH-60974 (DCVE)
Cambridge Trust - Yousef Jameel Scholarship (MA)

**Title:** The fronto-parietal multiple demand system in multimodally parcellated cortex

**Authors: *M. ASSEM**[1], M. F. GLASSER[2,3], D. C. VAN ESSEN[2], J. DUNCAN[1]
[1]MRC Cognition and Brain Sci. Unit, Univ. of Cambridge, Cambridge, United Kingdom; [2]Dept. of Neurosci., Washington Univ. in St. Louis, Saint Louis, MO; [3]St. Luke's Hosp., Saint Louis, MO

**Abstract:** In complex behavior, multiple task steps combine to achieve a goal. Each step or cognitive episode requires a rich control structure, binding and relating relevant stimuli, goals, actions, rules, rewards etc. The multiple demand (MD) system refers to a set of fronto-parietal regions that are preferentially active across a diverse range of cognitively demanding tasks. We have proposed a core role for MD regions in the assembly of cognitive episodes (Duncan J., 2013, Neuron). Here we investigated the neuroanatomical organization of the MD system within the multi-modal cortical parcellation of the Human Connectome Project (HCP) (Glasser et al, 2016, Nature). We analyzed data from 449 HCP subjects, each with a defined individual-specific cortical parcellation. Data averaged across hemispheres identified a set of 27 parcels (extended MD) using the conjunction of significant modulation in 3 task contrasts: Working Memory 2bk>0bk, Math>Story, and Hard>Easy Reasoning. Most active were a subset of 11 core MD parcels. Core MD parcels are widely distributed, including 4 areas (a9-46v,p9-46v, IFJp and 8C) in lateral prefrontal cortex; area i6-8 immediately anterior to the frontal eye field; area AVI in the anterior insula; areas 8BM and SCEF in dorsomedial frontal cortex; and areas IP1, IP2, and PFM in lateral parietal cortex. Using resting state connectivity analysis, we found that core MD parcels, despite their wide spatial separation, form a strongly connected network. For our 3 task contrasts, the activation profile across the extended MD system was broadly similar, though some task preferences were evident in non-core regions. Subcortically, we found tightly localised MD regions in the dorso-medial thalamus, antero-dorsal striatum, and cerebellum. These results characterise a highly specific cortical-subcortical network recruited by diverse cognitive demands. Access to many kinds of cognitive content, coupled with strong connectivity and information exchange, may equip this system with the flexibility needed to assemble diverse, novel and rapidly changing cognitive episodes.

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**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 792.04/JJJ70

**Topic:** H.02. Human Cognition and Behavior

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NSF SMA-0835976
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NIH F31-NS103306
NSF DGE-1247312
NIH F31-MH101969

**Title:** Functional subdivisions of superior parietal lobule revealed by memory, attention, and connectivity

**Authors: *R. W. LEFCO**[1], S. W. MICHALKA[3], S. M. TOBYNE[1], J. A. BRISSENDEN[2], A. L. NOYCE[2], D. C. SOMERS[2]
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**Abstract:** Superior parietal lobule (SPL) and intraparietal sulcus (IPS) are part of a frontoparietal network that is recruited in a broad range of attentionally demanding visual tasks. Within SPL/IPS, retinotopic mapping has identified functionally distinct regions (IPS0-4) along the medial bank of the intraparietal sulcus, extending into SPL. These regions are flanked, dorsally and ventrally, by non-retinotopic regions that also participate in attentional processes. Here, we used task, resting-state, and retinotopic fMRI scans to reveal functional distinctions between these dorsal and ventral subdivisions of SPL/IPS. First, by contrasting a 2-back visual working memory task (VWM-2b) with an auditory 2-back task, we identified two bilateral frontal cortical regions of interest (ROIs), superior and inferior precentral sulcus (sPCS and iPCS, respectively), in individual subjects. Using those frontal ROIs as seeds, we examined resting-state functional connectivity throughout SPL/IPS. Although both seeds were strongly connected to retinotopic IPS0-4, we identified differences in other SPL/IPS subregions. Dorsal SPL was more strongly connected to sPCS than to iPCS, while the fundus & lateral bank of IPS was more strongly connected to iPCS than to sPCS. In order to examine the functional significance of these network differences, we assessed recruitment of these structures during a multiple object tracking task (MOT) and a change detection visual working memory task (VWM-cd). The task recruitment mirrored the functional connectivity results. MOT more strongly recruited both sPCS and dorsal SPL, while VWM-cd more strongly recruited both iPCS and ventrolateral IPS. The two tasks robustly recruited the intervening retinotopic IPS0-4. The dorsal vs. ventral distinctions do not appear to reflect visual attention vs. visual working memory differences, per se. Parametric analysis of load in both tasks revealed that ventral, but not dorsal, SPL was differentially sensitive to the attentional or working memory load, independent of task. In contrast, ventrolateral IPS was differentially sensitive to the tasks, independent of load, perhaps reflecting the spatial updating of attention required in the MOT task. Taken together, these findings reveal dorsal-ventral functional gradients within the frontoparietal dorsal attention network.

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**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 792.05/LLL1

**Topic:** H.02. Human Cognition and Behavior

**Support:** NSF Grant BCS-1439188

**Title:** A frontal network controlling feature attention revealed by combining functional connectivity and machine learning

**Authors: *S. MEYYAPPAN**[1], A. RAJAN[1], H. WALKER[1], Y. LIU[2], G. R. MANGUN[2], M. DING[1]
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**Abstract:** Past work suggests that the right inferior frontal junction (rIFJ) plays an important role in the control of feature attention. In this study, we further examined this problem, with additional emphasis placed on whether rIFJ acts alone or as part of a feature attention control network. Functional MRI data were recorded from subjects performing a cued visual spatial and feature attention task. At the beginning of each trial, an auditory cue instructed the subject to either attend one of two spatial locations (left versus right visual field), referred to as spatial trials, or one of two colors (red versus green), referred to as feature trials. Following a random delay, two rectangular stimuli appeared, one in each visual field, and the subjects reported the orientation of the rectangle in either the attended location (spatial trials) or the attended color (feature trials). Analyzing single-trial cue-evoked fMRI responses using multi-voxel pattern analysis and functional connectivity analysis we report the following results. First, for feature trials, the decoding accuracy between attend-red and attend-green conditions was significantly above chance level in the right IFJ, whereas for spatial trials, the decoding accuracy between attend-left and attend-right conditions in the same region of interest was at the chance level. Second, a whole-brain searchlight analysis identified additional frontal regions, including dorsolateral prefrontal cortex and inferior frontal gyrus, where the decoding accuracy between attend-red and attend-green is significantly above chance level. Third, functional connectivity between these three frontal regions was significantly higher for feature trials compared to spatial trials, and predicted behavioral performance. These results lend additional support to the hypothesis that rIFJ plays an important role in the control of feature attention, and suggest that dorsolateral prefrontal cortex and inferior frontal gyrus, along with rIFJ, comprise the brain's network of feature attention control.

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**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 792.06/LLL2

**Topic:** H.02. Human Cognition and Behavior

**Title:** 'Silence' following direct electrical stimulation of the human default mode and limbic networks: Linking subjective experience, cortical responsiveness to applied electric currents, and the topographical organization of intrinsic brain networks

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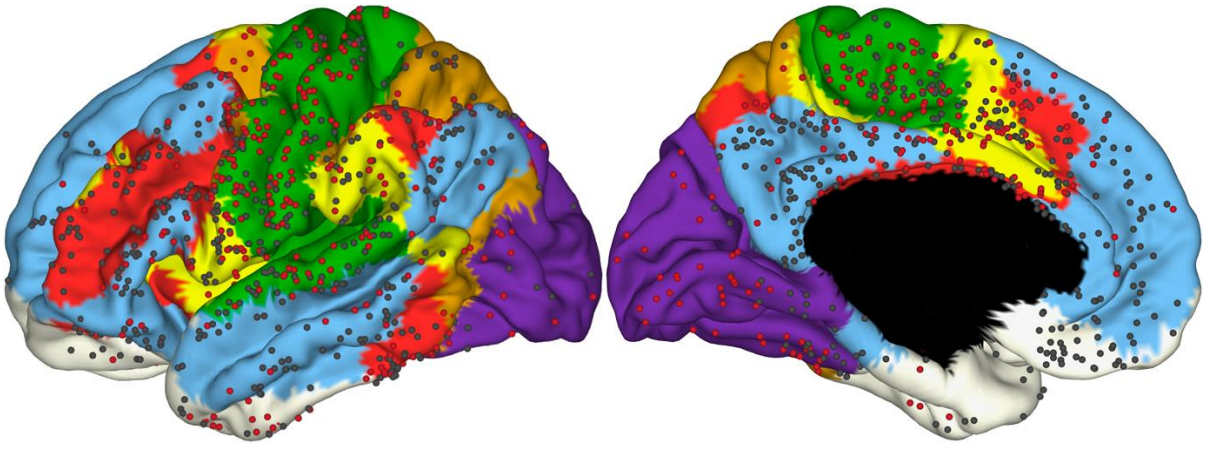
**Abstract:** For more than a century, direct cortical stimulation (DCS) of the human brain has been known to elicit a remarkable variety of effects, including somatomotor experiences, visual distortions and hallucinations, emotions, and memories. Our recent work, however, has revealed that DCS within the default network does not lead to changes in subjective experience (Foster & Parvizi, 2017, Neurology 88). To extend our prior work, we aimed to map the global patterns of DCS effects throughout the entire cortical surface of the human brain. We administered DCS (typical parameters: 50 Hz, 2-10 mA current, 200-300 us pulse width) during task-free, passive rest states at over 1500 unique electrode sites implanted in 75 patients with focal epilepsy undergoing pre-surgical intracranial EEG monitoring. We found striking evidence that the rate at which DCS induced experiential effects mapped closely onto intrinsic brain network boundaries: default and limbic networks, consisting largely of transmodal brain regions, were almost invariably silent in response to DCS (<10% elicitation rate; black circles = null effects), whereas stimulation in the somatomotor, visual, and salience networks exhibited much higher (>40%) elicitation rates (typically yielding somatomotor, visual, or complex physiological/emotional effects, respectively; red circles). Other networks (frontoparietal, dorsal attention) showed intermediate levels of elicitation. This overall pattern aligns closely with a model of a principal gradient hierarchy of macroscale cortical organization derived from functional connectivity data (Margulies et al., 2016, PNAS 113). Our study is the first comprehensive investigation of DCS across the entire human cortical surface, suggesting that the pattern of effects elicited by focal brain stimulation follows a striking topographical organization that closely parallels the hierarchical sensorimotor-to-transmodal gradient of intrinsic brain networks.



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**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 792.07/LLL3

**Topic:** H.02. Human Cognition and Behavior

**Support:** P50-MH109429

**Title:** Fixation-related neural dynamics during free viewing of static and dynamic images

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**Abstract:** In natural vision, we gather information by actively scanning a scene and fixating on points of interest. Generally, humans perform 3-5 fixations/second separated by rapid "saccadic" eye movements. At each fixation, a volley of visual input is initiated in the retina and this "sample" of information is then processed by a succession of neural ensembles in areas staged along the brain's visual pathways. Using simultaneously recorded eye movements and electrocorticographic (ECoG) signals in human surgical epilepsy patients, we investigated the influence of natural visual exploration on neural dynamics. We used saccade and fixation onsets during free viewing of static and dynamic images (i.e. pictures and movies) to sample eye movement-related activity. Broadband high-frequency activity (BHA; 70-150Hz - AKA - "high gamma") exhibited a brief amplitude increase immediately prior to the onset of eye movements across a distributed fronto-temporal network. This activity was most prominent about 30ms before the onset of a saccade and terminated with the initiation of the eye movement. In contrast, we observed that the phase of low frequency activity was concentrated after the saccade offset. This later effect was specific to the frequency of saccadic exploration (i.e. 2-7Hz), suggesting that saccadic activity is important in reseting the phase during active vision. Altogether, the current results supports an "Active Sensing" model in which the sensory input entering the brain is acquired by motor sampling routines. This motor-related signal predictively resets and aligns the high-excitability phases of ongoing neural oscillations at fixation onsets (i.e. when visual information will propagate through the brain). The ongoing analyses aim to reveal the role of this phase concentration in supporting information processing (e.g. by boosting sensory input and stabilizing sensory representation).

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**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 792.08/LLL4

**Topic:** H.02. Human Cognition and Behavior

**Title:** Posterior-contralateral theta oscillations and N170 amplitudes in attentional bias to fearful faces

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**Abstract:** Fearful faces can inform an observer that there is a potential threat in the environment. This attentional bias towards fearful faces consists of three steps, orienting, engagement, and disengagement. Attentional bias can be measured using event-related potentials (ERPs). The N170 ERP component is a negative peak around 170 ms after stimulus onset and is associated with facial processing and processing the emotional expression. The N170 is maximal at occipitotemporal electrode sites and is thought to reflect activation of the occipital face area (OFA), fusiform face area (FFA), and the superior temporal sulcus (STS). N170 has been found to be enhanced posterior-contralateral to fearful faces indicating enhanced processing of the salient stimuli. However, ERP removes the frequency domain from the data, which can provide additional information about brain activity. Theta oscillations (5-7 Hz) are related to the basal forebrain and sensory cortices becoming synchronized. The purpose of this study was to examine the posterior-contralateral N170 and the posterior-contralateral theta oscillations in the attentional bias to fearful faces. Twenty-four participants performed a dot-probe task that horizontally displayed either fearful and neutral faces (fear left or fear right) or two neutral faces (neutral trial). The faces were displayed for 50 ms and there was a 500 ms delay from face offset to dot onset. EEG data was collected using 33 electrodes from the SynAmps2 64-channel QuickCap. The data was rereferenced to an average reference and a bandpass filter of 0.1 to 40 Hz was used in EEGLAB. Data was epoched from -200 to 1000 ms (0 ms being face onset). The ERPLAB blink detect and simple voltage threshold (-100 to 100 μV) functions were used to remove artifacts. Electrodes P7 and P8 were used for ERP and time-frequency analyses. The N170 mean amplitude was within 150 to 190 ms. Time-frequency analysis used a Morlet wavelet wavenumber 3 and a time window of 50 to 210 ms for mean power. Both N170 and theta oscillations were enhanced for contralateral compared to ipsilateral and neutral, *p*s < .05 (no

differences between ipsilateral and neutral in either). The N170 difference (contralateral - ipsilateral) correlated with the theta difference, $R^2 = .23$, $p = .025$. That is, as contralateral N170 amplitude decreased compared to ipsilateral (i.e., was enhanced), theta power increased. The results suggest that that the basal forebrain and OFA, FFA, and STS might be more synchronized for the enhanced processing of fearful faces.

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**Poster**

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**Location:** SDCC Halls B-H

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**Program #/Poster #:** 792.09/LLL5

**Topic:** H.02. Human Cognition and Behavior

**Support:** Supported by the James S. McDonnell Foundation

**Title:** Spatial selectivity and temporal dynamics of alpha-beta oscillations across the human visual system in a spatial attention task: An ECoG study

**Authors: *X. YANG**[1,2], A. MARTIN[2], J. PARVIZI[3], J. LIN[4], R. T. KNIGHT[5], S. KASTNER[1,2]
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**Abstract:** Across the visual attention network, classical effects of selective attention on low frequency suppression have been characterized in human EEG and MEG studies, as well as in monkey local field potential studies. However, direct cortical measurements of the spatial selectivity and temporal dynamics of the alpha-beta frequency activities in the human brain, and more interestingly, how they are modulated by attention, have not been reported. We recorded electrocorticographic (ECoG) signals in eight patients implanted with intracranial electrodes while they were performing a variant of the Eriksen flanker task. Following a spatial cue and a variable delay interval, subjects differentiated between two shapes at the cued location in an array of distracters, allowing us to measure spatial selectivity within 25 degrees of visual angle. Using our probabilistic atlas of the human visual system (Wang et al., 2015), we localized electrodes to visual topographic areas and identified those with spatially-selective power suppression in the alpha-beta frequency domain. We found that low frequency suppression elicited by the cue was spatially selective and showed differential temporal dynamics with decreasingly shorter onset latencies across visual topographic areas. Specifically, spatial tuning widths of cue-evoked low frequency activity increased systematically across the dorsal visual processing pathway, similar to observations of spatial tuning widths related to high-frequency

broadband signals. The onset latencies of this suppressive effect (i.e. the time at which the low frequency activity evoked by the cue became significantly more suppressed in the response field center than the opposite location) were faster in the intraparietal sulcus (IPS) as compared to early visual areas. This temporal profile was opposite to what we observed in the cue-evoked enhancement related to high-frequency broadband power, where response onset latencies increased along the dorsal pathway from early visual areas to dorsal extrastriate areas and IPS regions. These results suggest a parallel yet distinctive representation of spatial information in low and high frequency bands, facilitating a coordinated processing of visual space that may integrate feedforward and feedback information across the visual hierarchy.

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**Poster**

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**Location:** SDCC Halls B-H

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**Program #/Poster #:** 792.10/LLL6

**Topic:** H.02. Human Cognition and Behavior

**Support:** KAKEN 15K16565

**Title:** Daily fluctuation of attention in relation to sleepiness

**Authors: *M. MATSUO**
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**Abstract:** Attention fluctuations are one of the primary concerns not only in the clinical settings but also in the commercial society. In addition, attention is now regarded as a complex of at least three major functions. However, it is not well established if the attention fluctuation occurs uniformly among these three major functions.In this study, we examined the daily fluctuation of attention using attention network test (ANT).Thirty volunteers (M= 19, F=11, mean=29.7, SD=11.8 years old) were recruited from patients suffering from daytime sleepiness. All participants took ANT every 2 hours for 4 times in a day, following a training and first time ANT session in the previous night. Using 5 times ANT data, we examined stability of each attention function using correlation analysis.The correlation analysis found that orienting and executive functions were less prone to fluctuations, as signifiant correlations between all 10 combinations were found in both orienting and executive function (Pearson's correlation analysis, $P<0.05$ in all combinations).However, analysis of alerting functions showed only one combination out of 10 was correlated (1st vs 2nd session combination: $P<0.05$ in Pearson's correlation analysis). Current results showed that among three domains of attention network, individual preference of executive and orienting functions remained similar in all 5 sessions. The

results of these two attention functions contrasted the fluctuated nature of alerting function. The current results suggested uneven effect of time on attention networks.

**Disclosures: M. Matsuo:** None.

**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 792.11/LLL7

**Topic:** H.02. Human Cognition and Behavior

**Title:** Gaze variables to food imagen reveal modulation of attention by deprivation conditions while response latencies did not

**Authors: *A. TOSCANO ZAPIEN**[1], D. N. VELÁZQUEZ MARTÍNEZ[2]
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**Abstract:** Some studies has found that when food deprived, subjects decrease their latency to find a dot that appear after a food-related word or after a food-related image, compared to the latency to the dot after a non-food word or image (Dot Probe Task). We recorded gaze variables as a more direct evaluation of attention to food stimulus. Subjects were instructed to fixate their gaze to a central point in a screen before being presented a pair of images followed by a colored dot; our task required more attention that matched the dot color. Images used were stationery items or images of light, high-carbohydrates or high-fat content food. Images were presented in pairs of all possible combination-location. In accordance to some studies that found no effect of food-related image or word in dot probe task,we observed no difference in total gaze time to each stimulus; however,even in this situation pupil size increased following high-carbohydrate or high-fat food, subjects preferred to gaze at the dessert or high-fat food and pupil dilation increased as a direct funtion of fixation time.

**Disclosures: A. Toscano Zapien:** None. **D.N. Velázquez Martínez:** None.

**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 792.12/LLL8

**Topic:** H.02. Human Cognition and Behavior

**Support:** National Science Foundation (BCS-1534823)

**Title:** Prismatic adaptation modulates visual field coverage and resting state functional connectivity

**Authors: *S. SCHINTU**[1,2], M. V. FREEDBERG[1], E. H. SILSON[3], S. GOTTS[3], S. SHOMSTEIN[2], E. M. WASSERMANN[1]
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**Abstract:** Sensorimotor adaptation to right-deviating prisms (rPA) ameliorates neglect symptoms in patients; while left prisms (lPA) produce neglect-like behavior in healthy individuals. Prism adaptation (PA) likely modulates attention by inhibiting the posterior parietal cortex (PPC) contralateral to the deviation and altering interhemispheric balance. Changes in spatial attention are associated with changes in visual population receptive fields (pRFs) in the PPC. We hypothesized that lPA, a model of neglect, would increase right visual field (VF) coverage while rPA would decrease it. We also examined whether changes in pRF were associated with altered resting-state functional connectivity (FC). Forty healthy participants took part in a multi-session experiment. First, sensorimotor and visuospatial performance were measured behaviorally with pointing and line bisection tasks. Next, participants had a baseline resting-state (10 minutes) and pRF scans (30 minutes). During pRF scans, scene stimuli were presented through a bar aperture that moved across the VF. Activity was measured during: (i) fixation, and (ii) attention conditions. Next, participants were randomized to lPA or rPA and were adapted with 150 pointing movements. Participants were then scanned the same resting-state and pRF procedure as before adaptation. Effects of sensorimotor adaptation were assessed immediately after PA and then again before the end of the experiment along with the visuospatial performance. Both PA groups exhibited significant and comparable sensorimotor after-effects for the duration of the experiment. pRF analysis showed that VF representation in both hemispheres is primarily contralateral and that contralateral VF coverage increased with higher attentional demand (attention vs. fixation). Importantly, lPA increased right, while rPA increase left, VF coverage. Importantly, in the attention condition, we observed that (i) lPA increased right, and decreased left, VF coverage, possibly mimicking neglect-like attentional imbalance, and (ii) rPA increased both right and left VF coverage. There was a greater decrease in FC between areas implicated in visuospatial adaptation after rPA than after lPA. Our results provide evidence that prism adaptation affects visuospatial attention by dynamically reorganizing response profiles in PPC, as measured by pRF, and the corresponding decrease in FC. These results are important as they have implications for our understanding of dynamic changes in PPC as a function of attentional demands as well as in response to rapid sensory-motor adaptation.

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**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 792.13/LLL9

**Topic:** H.02. Human Cognition and Behavior

**Support:** Australian Research Council (ARC) Centre of Excellence for Integrative Brain Function (ARC Centre Grant CE140100007)
ARC Australian Laureate Fellowship FL110100103
ARC Discovery Project (DP170100908).

**Title:** Decoding orientation selectivity during rapid serial visual presentation reveals the neural dynamics of the attentional blink

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**Abstract:** Despite the tremendous information processing capacity of the human brain, there is a tight bottleneck in observers' ability to identify multiple visual targets such as letters or digits presented in rapid succession. In the attentional blink (AB), observers often fail to identify the second of two targets within a rapid serial visual presentation (RSVP) stream if this second stimulus occurs within 500 ms of the first. To date it has been difficult to determine the neural mechanisms responsible for the AB, because conventional approaches to imaging techniques such as fMRI and EEG do not have the temporal resolution to isolate activity evoked by individual items within an RSVP stream. We overcame this limitation by combining EEG with a new RSVP task in which stimuli were randomly-oriented gratings (Gabors). In each RSVP stream observers looked for high spatial frequency targets amongst lower spatial frequency distractors. The orientations of the stimuli were uncorrelated, which allowed us to implement a regression-based encoding approach to separately extract orientation-selective information evoked by each item in the stream without contamination from neighboring items. In an initial experiment we validated our novel behavioral task. Observers showed a classic AB effect, and minimal influence of distractors on target reports. In a second experiment, we recorded neural activity using EEG as observers performed the same RSVP task. We used a multivariate forward encoding approach to measure orientation-selective responses to gratings within the RSVP stream. This analysis revealed independent orientation-selective representations for all items, including both targets and distractors. Critically, on trials in which the second target was not identified (i.e., AB trials), the gain of the neural representation of the second target (but not its

tuning sharpness) was reliably diminished. Conversely, when there was a strong orientation-selective response for the second target, and the immediately preceding distractor, participants could report the second target more precisely. Furthermore, orientation-selectivity for distractor items remained consistent throughout the trial regardless of behavioral performance, suggesting that distractor processing does not contribute to the AB in this task. Our findings offer a novel account of the neural processes underlying the temporal limits of visual attention in human observers.

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**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 792.14/LLL10

**Topic:** H.02. Human Cognition and Behavior

**Title:** Structural integrity and intrinsic connectivity of the salience network reflect executive dysfunction in alcohol use disorders

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**Abstract:** The neural bases of cognitive impairment(s) in alcohol use disorders have been explained either with a global brain damage underlying different neuro-cognitive alterations, of with the specific involvement of frontal regions mostly affected by alcohol neurotoxic effects. Although available evidence highlighted morphometric and functional alterations in fronto-limbic and cerebellar structures in alcoholic patients, the lack of a comprehensive neuro-cognitive assessment prevents previous studies from drawing robust inferences on the specificity of the association between neurological and cognitive impairments.
To fill this gap, we addressed the neuro-structural and functional bases of cognitive impairment in 23 alcoholic patients and 18 healthy controls, by coupling Voxel-Based-Morphometry (VBM) and resting-state *f*MRI with an in-depth neuropsychological assessment of the most relevant cognitive domains.
Multivariate analyses of neuropsychological data unveiled a defective executive/attentional cognitive domain in alcoholic patients, reflecting altered structural and functional neural metrics. VBM highlighted a diffuse pattern of grey-matter (GM) reduction in patients, involving the key-

nodes of both the meso-cortico-limbic (striatum, hippocampus, mPFC) and salience attentional (insular cortex and dACC) networks. GM density in the anterior insular and cingulate sectors of the salience network, significantly decreased in patients, explained almost half of variability in their defective executive performance. Abnormal coherence and intensity of intrinsic activity, tracking the degree of executive impairment, were observed within brain networks underlying the switch from "default-mode" rest to effortful cognitive activity based on the salience of external stimuli with respect to behavioral goals.
The significant atrophy observed, in patients, in most of the relevant resting-state networks confirms that intrinsic brain activity represents an intermediate level of analysis between neuro-structural and cognitive impairments, highlighting the neural bases of specific deficits, or possible compensatory mechanisms. The cognitive and neurological impairments observed in AUD might thus reflect a specific executive deficit due to the selective damage of a well-established brain "salience" network enhancing access to cognitive resources required for attention and working-memory processes.
These results provide a comprehensive picture of the abnormal neural architecture underlying cognitive impairment in AUDs, paving the way for future basic and translational research in this field.

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**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

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**Topic:** H.02. Human Cognition and Behavior

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VA Clinical Science R&D Career Development Award to M.E. (1IK2CX000706-01A2)

**Title:** Connectome-based predictions of attentional performance reduce to simply network interactions

**Authors: *S. LAGANIERE**[1], W. CHEONG[1], M. ESTERMAN[2], M. A. HALKO[3]
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**Abstract:** Recent computational advances allow for utilizing machine learning methods to reduce the inherent complexity of human brain networks into highly predictive models. One such method, termed connectome predictive modelling, combines many region-to-region features

('edges') from seemingly disparate brain regions to create highly reproducible predictions of attentional performance. Alternatively, decades of visual attention studies suggest that attentional performance is governed by the straightforward interaction between neuroanatomically-circumscribed fronto-parietal networks and the default network. An informed hypothesis- driven analysis would therefore suggest that attentional performance is linked to the between-network connectivity of the default network and dorsal attention network. Here, in n=71 sessions, we show that hypothesis-driven (between default network and dorsal attention network) connectivity values are statistically indistinguishable from connectome-based predictions (r= 0.539 vs r= -0.467, respectively). We replicate this finding in a separate n=149 cohort. We find that across these two datasets, using the connectome predictive modelling method, it is possible to produce similar edges ("positive network" n=661 and n=675) to the original models (n=680), but that these edges are not shared in pairwise comparisons (max: 68, min:9), and no edge is found in all models. All models identify greater numbers of edges outside of the *default-dorsal attention network* complex than within. When we examine the across-subject functional connectivity of each edge, we find that the relationship with behavior is highly correlated with across-subject variance in the hypothesis-driven network (r= -0.652, $p<0.01$). We conclude that while machine learning techniques may produce highly predictive models that translate to novel datasets, these models are limited in that they do not readily identify the underlying neuroanatomical origin of attention and do not necessarily offer more robust predictions than those derived from simple previously-identified network interactions. We believe connectome-based methods likely over-sample the same source of information, leading to an overestimation of the degrees of freedom within the models. Novel connections derived from connectome methods are likely highly correlated with true source connectivity.

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**Topic:** H.02. Human Cognition and Behavior

**Support:** ANR-14-CE13-0020-01

**Title:** Task and feature influences on numerosity representation across the human dorsal visual stream

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**Abstract:** Number represents a highly relevant source of information in our everyday life. Based on earlier neuroscientific findings, a key role in numerical processing was uniquely attributed to intra-parietal cortex, yet recent studies demonstrated that numerical information is already present at earlier stages independently from some other quantitative dimensions. Nevertheless, some debates persist on the possible role of non-numerical features in numerical judgements and brain responses to numerical stimuli, and the relative importance of earlier versus later cortical stages in the explicit manipulation of numerical quantities remains to be determined. Here we used high resolution fMRI at 7 Tesla and multivariate pattern analyses to address these questions. Twenty healthy adult subjects were scanned while being presented with arrays of dots orthogonally varying in numerosity (6, 10, or 17 items) and average item size, with the perceptual discriminability of these two dimensions matched based on prior psychophysical experiments. Participants performed one of two tasks in different blocks: during the *number task* they had to direct attention to the numerosity of each array and keep it in memory for comparison with an occasionally following target stimulus, while in the *size task* instead they performed the equivalent comparison on the average dot size of the arrays. We analyzed multi-voxel pattern responses to non-target stimuli across several early and dorsal visual stream ROIs as defined by probabilistic atlases. When merging data from the two tasks, pattern classification showed reliable decoding of numerosity in early (V1-3), intermediate (V3AB/V7) and parietal areas (IPS1-5) with similar accuracy. However, when analyzing activation patterns separated by task, numerosity decoding was enhanced in intermediate and parietal areas, but no task-driven modulation of decoding accuracy was detected in the earlier visual areas. Overall these results suggest that while information related to numerosity starts to be analyzed at a very early stage of the visual system, only later stages of processing are involved in the explicit manipulation of numerical quantities. In further analyses, we use representational similarity to investigate the extent to which pattern information is modulated by numerical distance as opposed to distance along several other dimensions (item size, total surface area, density, field area) across the different regions.

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**Program #/Poster #:** 792.17/LLL13

**Topic:** H.02. Human Cognition and Behavior

**Support:** This work was supported by Institute for Information & communications Technology Promotion(IITP) grant funded by the Korea government(MSIT) (No. 2017-0-00432)

**Title:** Frontoparietal phase synchronization of the p300 ERP component in an oddball task

**Authors: *M. KIM**, J. PARK, S.-P. KIM
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**Abstract:** P300, also known as P3, is a component of event-related potential (ERP), a positive peak appearing 300ms after target stimulus onset. P300 consists of two sub-components, P3a and P3b, where P3a is an early component and pronounced in the frontal area and P3b is induced following P3a and pronounced in the parietal area. This time difference between P3a and P3b can be evaluated by a phase difference. Hence, it seems plausible that a phase difference between frontal and parietal areas would remain consistent during the P300 period in response to a target stimulus. To address this conjecture, the present study analyzed phase locking value (PLV) of P300 between frontal and parietal areas and examined differences between the target and non-target ERPs. The oddball paradigm was used to elicit P300, in which a target to non-target ratio was 1:3. Thirty subjects participated in the experiment and each subject completed 50 blocks. 12-channel EEG on frontal area as well as 11-channel EEG on parietal area were collected for the analysis. PLV was estimated within the time interval from 150 ms to 500 ms after stimulus onset. The PLV analysis revealed significantly higher PLVs between frontal and parietal channels in the target ERP than in the non-target ERP ($p < 0.05$). It suggests that the recognition of a target stimulus may enhance long-range connections of P300-related brain responses between frontal and parietal areas.

**Disclosures: M. Kim:** None. **J. Park:** None. **S. Kim:** None.

**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 792.18/LLL14

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH R01 NS102201

**Title:** Effects of incompatible action outcomes on cortico-spinal excitability

**Authors: *B. RANGEL**[1], J. R. WESSEL[2], M. JANCZYK[3]
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**Abstract:** Effect monitoring is crucial for detecting behaviorally relevant deviations between expected and actual action outcomes. Ideomotor theory holds that actions are inextricably bound to their intended outcomes. In line with this, responses are usually given faster when the action outcomes appear on the same side of the response (compatible) than on the other side

(incompatible). Additionally, incompatible action outcomes (e.g., a right-hand action causing effects in the left visual hemifield) lead to a slowing of subsequent motor responses , suggesting motor changes associated with such incongruent action outcomes. Past studies have shown that after surprising, infrequent action outcomes, cortico-spinal excitability (CSE) is indeed reduced, moreover in global fashion (e.g., a surprising, rare outcomes of a leg-movement lead to reduced CSE of the hand). Here, we aimed to test whether the same is true for action outcomes that are neither surprising nor rare, yet are incompatible to the response. 20 healthy adult volunteers responded freely with a left or right foot pedal press to the presentation of a puzzle piece with left and right connecting knobs (S). Subjects were informed that action-outcomes (O) would be either compatible (e.g., a press of the right foot pedal lead to a puzzle piece connecting to right side of S) or incompatible (e.g., right foot -> left puzzle piece). Compatible and incompatible Os were presented with equal probability following the response (360 trials). Transcranial magnetic stimulation (TMS) pulses over the left motor cortex elicited Motor Evoked Potentials (MEPs) in the EMG of the first dorsal interosseous muscle of the right hand following each O (at 50ms intervals ranging from 100 to 350ms) and were used to measure CSE. Mean MEPs were normalized to resting baseline within subjects and were compared using repeated-measures ANOVA. Outcome compatibility had no effect on CSE ($p \geq .5$), while pulse time did ($p < .005$): earlier pulse times (100-150ms) yielded normalized amplitudes below baseline, while later pulse times (250-350ms) were above baseline. In line with this, earlier pulse times (100-150ms) and later pulse times (250-350ms) were significantly different ($p < .05$). These results imply that while compatibility did not affect CSE, global inhibition may take place at earlier pulse times following O. Such inhibition may be due to both compatible and incompatible outcomes being equally likely (and independent of performance), potentially leading participants to incorrectly predict their presentation in both conditions. Future studies will aim to test this conclusion to further elucidate changes in CSE in accordance with ideomotor theory.

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**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 792.19/LLL15

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH R01AG049424

**Title:** Closed-loop, digital, meditation training program improves sustained attention

**Authors: *D. A. ZIEGLER**[1], A. SIMON[2], C. ROLLE[3], S. N. SKINNER[4], C. L. GALLEN[2], A. GAZZALEY[5]
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**Abstract:** Attention is a fundamental cognitive process that is critical for essentially all aspects of higher-order cognition and real-world activities. While improving sustained selective attention would be beneficial, enhancing this ability has proven notoriously difficult in healthy young adults. To overcome this obstacle, we designed a mobile meditation-inspired closed-loop training app (MediTrain) that draws from focused-attention meditation practices. We hypothesized that MediTrain would improve participants' attention and working memory abilities. We conducted a double-blind, randomized, placebo-controlled trial of MediTrain aimed at improving sustained attention in meditation-naïve healthy young adults (20-32 years of age). Participants were randomly assigned to receive either MediTrain or an expectancy-matched control regimen. They completed 6 weeks of the assigned intervention with 25min of training per day, 5 days per week. Before and immediately after completing their interventions, participants underwent an extensive laboratory assessment of attention and working memory abilities, completing one primary outcome, a Sustained Attention Task (SAT) and two secondary outcomes, a distraction-filtering task and a working memory task. We also collected electroencephalography (EEG) data from each participant using a 64-channel Biosemi system. As our primary measure and test of interest, we evaluated within-participant variability in response time across trials (RTVar). We found a significant difference in RTVar on the SAT: following treatment with MediTrain participants showing a significant decrease in RTVar ($\Delta$ = -7.98 ms), while control participants did not significantly change ($\Delta$ = 1.1 ms). MediTrain treatment also resulted in decreased RTVar on an attentional filtering task ($\Delta$ = -91.1ms; p), while the placebo group did not change significantly ($\Delta$ = -9.1ms). On a test of working memory, we found a significant increase in capacity following treatment with MediTrain ($\Delta$ = 0.17), but not in control group ($\Delta$ = -0.02). These improvements are associated with positive changes in key neural signatures of attentional control (frontal theta inter-trial coherence and parietal P3b magnitude and latency), as measured by EEG. Our findings demonstrate the utility of delivering aspects of the ancient practice of concentrative meditation in a modern, technology-based approach and its benefit on enhancing cognitive control abilities.

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**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 792.20/LLL16

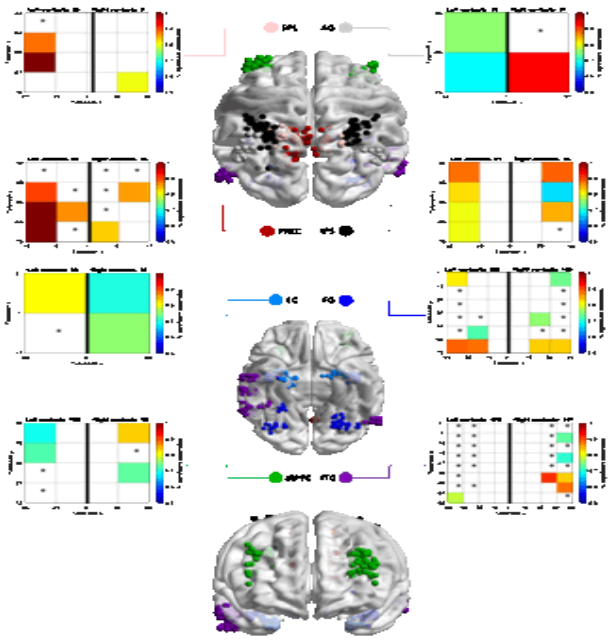
**Topic:** H.02. Human Cognition and Behavior

**Support:** DARPA Restoring Active Memory Program
THR Clinical Scholars Program

**Title:** Math cognition across space and time

**Authors: *G. UMBACH**[1], B. C. LEGA[2]
[2]Neurosurg., [1]UT Southwestern Med. Ctr., Dallas, TX

**Abstract:** Arithmetic is ubiquitous in both everyday life and the neurocognitive literature. Historically, many studies have focused on isolated steps within arithmetic such as numeral recognition or the retrieval of an arithmetic fact. We instead sought to characterize the spatial and temporal evolution of the electrophysiological activity across all steps of arithmetical computation. To achieve this, 279 adult neurosurgical patients with refractory epilepsy implanted with intracranial electrodes for localization of epileptogenic foci participated in the study. Subjects completed an episodic memory task that contained numerous two-step addition problems in between encoding and retrieval periods. EEG data corresponding to the time during which the subjects completed the task were extracted from the clinical system and analyzed in MATLAB. We identified eight brain regions that demonstrated statically significant preferential activation (as deemed by greater oscillatory power in the high gamma frequency band, 64-128 Hz) during the math period compared to the encoding period of the memory task—intraparietal sulcus (IPS), superior parietal lobule (SPL), Precuneus, angular gyrus (AG), entorhinal cortex (EC), fusiform gyrus (FG), inferior temporal gyrus (ITG), and dorsolateral prefrontal cortex (dlPFC). Using the Talairach coordinates of all electrodes within each of these regions batched across all subjects, we additionally identified cortical subpopulations that most clearly demonstrated this math effect. In the ITG, a region associated with Arabic numeral processing, math-selective neuronal populations were identified in both the posterior (Talairach y range of -36 to -54) and anterior ITG (Talairach y range of -1 to -10). The anterior focus in particular has important clinical implications due to its close proximity to deep brain parenchyma commonly resected during mesial temporal lobe epilepsy surgery. As a whole, our data confirm the importance of regions commonly implicated in numerical reasoning (e.g. ITG, SPL, AG) and of novel regions to explore further (e.g. EC).



**Disclosures: G. Umbach:** None. **B.C. Lega:** None.

**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 792.21/LLL17

**Topic:** H.02. Human Cognition and Behavior

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**Title:** Convergent functional network connectivity changes in attention capture and awareness

**Authors: H. SUN**, J. SY, D. GODWIN, H. EATON, P. RAGHAVAN, *R. MAROIS
Vanderbilt Univ., Nashville, TN

**Abstract:** Salient, unexpected events are known to powerfully capture attention and give rise to a broad cascade of systemic effects for evaluating and adaptively responding to the event. Using graph theory analysis combined with fMRI, here we tested the hypothesis that the extensive psychophysiological and cognitive changes associated with such attention capture are related to large-scale, distributed changes in the brain's functional connectivity. Recent work has shown

that perceptual awareness of a task-relevant target is associated with an increase in functional connectivity across diverse neuronal networks of the cerebral cortex (Godwin et al., *PNAS*, 2014). Given the intricate relationship between awareness and attention, we hypothesized that the exogenous capture of attention by unexpected 'oddball' stimuli may require large-scale changes in functional connectivity that are similar to the changes seen with perceptual awareness.
FMRI data was collected as 30 participants monitored a rapid serial visual presentation of letters for a target. The presentation of task-irrelevant oddballs (faces) in a small proportion of trials (6 out of 40) captured attention and disrupted target detection, more so with the first two oddball presentations than the last four oddball presentations. Using graph-theoretic analysis, we found that, like with awareness, the brain's connectivity across functional networks – as measured by the modularity and participation coefficient metrics – increased with the presentation of the first two oddballs relative to subsequent oddball presentations or during target search alone. These results suggest that the capture of attention by an unexpected event is associated with an increase in functional integration of the brain's networks. Moreover, together with the findings in Godwin et al (2014), these results suggest that awareness and attention capture are associated with similar integrative, global changes in the brain's functional connectivity.

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**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 792.22/LLL18

**Topic:** H.02. Human Cognition and Behavior

**Support:** NSF EPSCoR Award Number 1632738

**Title:** Volitional attention modulates memory encoding and retrieval

**Authors: *K. ZIMAN**, J. R. MANNING
Psychological and Brain Sci., Dartmouth Col., Hanover, NH

**Abstract:** The basic role of our attentional systems is to prioritize which aspects of incoming information we should process further. This prioritization may happen automatically (e.g. attending to the texture of the ground while walking and talking to a friend) or volitionally (e.g. searching for the same friend's face in a crowd). We designed a simple variant of the Posner cuing task to study how the volitional modulation of attention affects how we later remember the attended and unattended aspects of our experiences. We asked participants to attend to composite images, each comprising a blend of one photograph of a face and one photograph of a scene. In

each trial, the participant viewed a pair of composite images (on the left and right side of the screen) while keeping their gaze fixed on a central point. In different blocks of trials, we asked the participants to attend (without moving their eyes) to the face or the scene component of the composite image on either the left or the right side of the screen. For example, in a given block of trials we might have asked participants to attend to the face component of the images on the right side of the screen. In this way, we preserved participants' overall visual experience from trial to trial while manipulating their focus of volitional attention.
After studying a series of such images, we then asked participants to perform a recognition memory experiment. For this task, we presented a series of (non-composite) face and scene images—i.e. in each trial the participant saw a single face or a single scene image, and judged on a 1—4 scale how "familiar" the image looked. In addition to novel images, participants judged unattended and attended-to stimuli that they had seen in the previous presentation trial. We found that fully attended images (cued category on cued side) were rated most familiar. We also found that unattended stimuli that shared either a category or location with the attended stimuli were also remembered (though to a lesser extent). Unattended stimuli that shared neither the location nor category with the attended image were rated as being no more familiar than novel images. We also use neuroimaging data collected as participants performed this task to examine the full-brain network dynamics that underlie these interactions between attention and memory.

**Disclosures: K. Ziman:** None. **J.R. Manning:** None.

**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 792.23/LLL19

**Topic:** H.02. Human Cognition and Behavior

**Title:** Claustrum activation from cognitive load is modulated by pain

**Authors: *S. KRIMMEL**[1], B. N. MATHUR[2], D. A. SEMINOWICZ[3]
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**Abstract:** The claustrum is a thin structure located between the insula and putamen and is the most connected structure of the brain per unit volume, with extensive connections to sensory cortices and regions involved in cognitive control. Consistent with this pattern of connectivity, recent work suggests that the claustrum encodes top-down attention signals arising from the anterior cingulate cortex, and facilitates their transfer to the parietal cortex. Given the role the claustrum plays in cognitive processes, we sought to identify how sensory stimuli, like pain, that capture attention and disrupt cognition would modulate the claustrum's response to cognitive

tasks. We used recently developed techniques to isolate the claustrum in fMRI from two studies. In the first study (n=33), we evoked thermal pain applied to the left arm in the absence of any additional task and examined the claustrum's activation to the onset of pain and to sustained pain. In a second study (n=17), we used similar methods to isolate the claustrum in fMRI and examined how the claustrum's activation during the attention network task (ANT), a well studied task that produces extensive cognitive activation, was modulated by pain applied to the left arm. In the first study evoking pain in isolation, we found the onset of pain resulted in a significant deactivation of the right claustrum (contralateral to the painful stimulus) and produced a moderate size effect in deactivating the right claustrum during the painful block. In the second study, evoking pain on the left arm during the ANT reduced right claustrum activation from the cognitive task. Together, these data suggest that pain deactivates the claustrum and that this can reduce the claustrum activation from cognitive tasks. Coupled with existing literature showing claustrum involvement in top-down attention, these results suggest a possible mechanism whereby pain inhibits the ability of claustrum to encode and transmit top-down attention signals, inhibiting cognitive performance in the process.

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**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 792.24/LLL20

**Topic:** H.02. Human Cognition and Behavior

**Title:** Attention and engagement with marketing videos are modulated by shot duration

**Authors: *J. A. SOLYST**
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**Abstract:** Movie trailers, television commercials and other marketing content are a multi-billion-dollar industry, but the success of that content is limited by our knowledge of what features in these complex media keep viewers engaged. One of the fundamental units by which video content is organized is the shot. Filmmakers and editors have long known that shot duration can have a significant impact on the perception of its contents and the pace of the narrative. While it is known that the average shot length (ASL) has decreased significantly over the last century, our understanding of how viewers perceive shots of different durations is limited by a lack of biometric data.
Previous studies have linked decreased eyeblink rate and variance of fixation location while watching video to increased attention and engagement, respectively. To determine if these measures of attention and visual engagement with marketing videos are affected by shot duration, we used infrared eye-tracking and a webcam to monitor eyeblinks and point of gaze

while participants (n = 69) viewed television commercials (n = 11) and longer narrative-driven documentaries (n = 2). An analysis of responses to 473 unique shots (ASL = 2.2s) found that both attention ($r = 0.14$, $p = .0017$) and engagement ($r = 0.22$, $p < 0.0001$) were significantly negatively correlated with shot duration. Analysis of biometrics aligned to the start of each shot reveals that the increase in attention and engagement peaks ~750ms after onset and resolves after ~2s. These findings provide valuable insight into how one of the most important aspects of editing affects viewer attention and engagement and help inform the development and testing of engaging video content.

**Disclosures: J.A. Solyst:** A. Employment/Salary (full or part-time):; HomeAway.

**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 792.25/DP14/LLL21

**Topic:** H.02. Human Cognition and Behavior

**Title:** Frontoparietal reorganization during symbolic and nonsymbolic number processing

**Authors: *B. N. CONRAD**, E. D. WILKEY, G. R. PRICE
Vanderbilt Univ., Nashville, TN

**Abstract:** There is a longstanding debate regarding the extent to which symbolic (S, e.g. Arabic digits) and nonsymbolic (NS, e.g. dot arrays) numbers engage shared versus distinct neural mechanisms. Previous fMRI studies have largely taken a localization approach by assessing regional activation to different stimuli. Network analysis employing graph theoretical measures of task-related functional connectivity (FC) data provides a methodological framework for describing brain network topologies subserving cognition, with potential to shed new light on the S/NS number debate. Here, we use this framework to assess networks engaged during S and NS number processing. We conducted an event-related 7T fMRI study with healthy subjects (n=40, 19.5 ± 0.9 years). Participants performed a number comparison task in which they judged whether Arabic digits (S) or dot arrays (NS) were more/less than five. To assess task-related FC, we conducted beta series correlations. Trial-wise regressors were included in the subject-level general linear model, yielding a beta (activation) map for each trial. Average beta series were extracted from a whole-brain, 246 region atlas and separated based on condition. Beta series correlations were computed to construct connectivity matrices for each subject/condition. Regions were partitioned into functional modules first at the subject-level and then across the group using the community Louvain algorithm and consensus clustering. Subsequent analyses were conducted on community allegiance matrices, which indicate the percentage of subjects in which two regions were assigned to the same module. Our results indicate that 1) networks were significantly modular at the subject and group levels, 2) across a range of topological scales, six

modules were consistently detected including a frontoparietal (FP), default mode, visual, sensorimotor, temporal and subcortical module, 3) the NS condition demonstrated a larger, more distributed FP module compared to S and this reorganization was significant over pair permutations, 4) intra-module integration of the FP module was greater in the NS compared to S condition, 5) differences in a region-level metric of modular diversity were detected between conditions in several regions, including right inferior temporal gyrus, in line with work showing this region is involved in the processing of visual symbols. Our findings suggest organizational differences in the FP system during number comparison based on number format, while functional topology was otherwise largely shared between conditions. These findings complement prior work suggesting the FP network flexibly reorganizes based on task demands.

**Disclosures: B.N. Conrad:** None. **E.D. Wilkey:** None. **G.R. Price:** None.

**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 792.26/LLL22

**Topic:** H.02. Human Cognition and Behavior

**Support:** Collaborative for Teaching Innovation, Santa Clara University

**Title:** Does virtual reality improve student learning of brain anatomy? Investigation of learning gains and sustained attention with simultaneous EEG

**Authors: P. PAVLOV**[1], H. BHUGRA[1], N. LIBERTY[1], M. SCHIFFMAN[1], R. GOEBEL[3], G. GREENBERG[4], P. SIMONE[1], *J. A. SCOTT[2]
[2]Bioengineering, [1]Santa Clara Univ., Santa Clara, CA; [3]Fac. of Psychology and Neurosci., Maastricht, Netherlands; [4]Arbor Scientia Group, Carlsbad, CA

**Abstract:** OBJECTIVE: The present study aims to determine whether learning condition—interactive virtual reality (VR) or screen displays—affected learning gains in neuroanatomy, and whether level of sustained attention, measured by EEG, modulates potential effects. RATIONALE: Students are faced with a challenging task in learning brain anatomy, which has a complex 3D geometry. Learning from realistic models of 3D physical structures, such as the brain, can improve learning. Studies show that visuospatial learning by computer-based interactive, 3D learning environments improve learning outcomes compared to 2D representations. In parallel, active learning environments in VR can improve test scores. Collectively, these studies suggest that while a 3D model is superior to 2D, 3D visualizations in VR may further improve learning gains. Though this hypothesis appears intuitive, it has not been extensively tested quantitatively and empirically. To address this gap, we have implemented the following study in which learning gains are tested and brain activity, as correlate of attention, is

measured during the same task in different learning conditions. METHODS: Participants (8 male, 21 female; 18-22 years) studied brain structures using Brain Innovation's "Brain Tutor" app under one of three conditions: (a) 2D MRI slices, (b) 3D renderings, and (c) 3D VR renderings (Brain Tutor VR on Gear VR). EEG recordings were conducted during the learning phase with Emotiv Insight headset. Learning gains were measured by change in number of correct responses given before and after the learning phase. Sustained attention was measured by the ratio of alpha:beta power averaged over channels AF3 and AF4. A general linear model will be tested for the independent effects of and interaction between learning condition and sustained attention on change in test score. RESULTS: Preliminary analyses did not detect an effect of learning condition on learning gains (median=3, all conditions). Learning phase duration was correlated with learning gains, independent of condition (CC=0.37). Usability rating for Brain Tutor was 3 out of 5 or above. EEG data passing quality control included 4 2D, 5 3D, 5 VR trials. CONCLUSIONS: Engagement, measured by learning phase duration, was the best predictor of learning gains. Further analyses are required to detect potential independent or interacting effects of sustained attention and learning condition on learning gains.

**Disclosures: P. Pavlov:** None. **H. Bhugra:** None. **N. Liberty:** None. **M. Schiffman:** None. **R. Goebel:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Brain Innovation. **G. Greenberg:** None. **P. Simone:** None. **J.A. Scott:** None.

**Poster**

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**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 792.27/LLL23

**Topic:** H.02. Human Cognition and Behavior

**Title:** Parameter characterization of neural activity in the locus coeruleus to non-invasive trigeminal nerve stimulation

**Authors: *J. C. TANNER**, S. I. HELMS TILLERY
SBHSE, Arizona State Univ., Tempe, AZ

**Abstract:** Neural activity in the midbrain structure locus coeruleus (LC) modulates attention, arousal, working memory, and stress. The structure consists of noradrenergic (NA) cells with widespread projections throughout cortex, cerebellum, and brainstem. Activation of NA modulates synaptic signal transmission for attention and/or sensory stimuli. Using direct (fMRI or PET) and indirect (pupillometry) measures, literature provides evidence that tasks requiring increased exploration/attention correlate with locus coeruleus activity. Being able to affect LC activity could provide access to modulate plasticity, arousal, or working memory. Modulating LC activity is possible through invasive vagus nerve stimulation, and parameters have been

characterized for optimal effect. Both the vagus nerve and the trigeminal nerve have common direct projections and respectively project to the LC through the nucleus tractus solitarius and trigeminal nucleus caudalis. In this study, we aim to produce similar neuromodulation and characterize stimulation parameters for noninvasive transcutaneous stimulation of the ophthalmic and maxillary branches of the trigeminal nerve. Locus coeruleus activity is recorded with single unit electrodes via a custom chamber designed with MRI/CT imaging for each Macaca mulatta. Using Plexon acquisition tools and custom MATLAB paradigms, isolated LC spike activity and local field potentials are recorded alongside pupillometry during stimulation. Initial stimulation parameters are chosen from literature, delivered via a Digitimer DS8R stimulator to surface electrodes placed to stimulate the ophthalmic trigeminal nerve branch. Firing rate, LFP magnitudes, and comparative pupillometry will be used to identify stimulation parameters with maximum effect on LC activity. Using these results, behavioral and cognitive results can began to be assessed.

**Disclosures: J.C. Tanner:** None. **S.I. Helms Tillery:** None.

**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 792.28/LLL24

**Topic:** H.02. Human Cognition and Behavior

**Title:** The underlying neural mechanism of dynamic attentional bias: A voxel-based morphometry analysis

**Authors: *L. FANG**, J. M. CARLSON
Northern Michigan Univ., Marquette, MI

**Abstract:** Selective attention to threat in the environment is considered crucial for people's adaptation. According to cognitive models of attention to threat, attention will be rapidly and unconsciously shifted toward the presented threat information. The empirical evidence of the attentional bias to threat stimuli has been found in a great number of behavioral tasks, such as the visual probe task. Typically, the allocation of attention to threat is indicated by an attentional bias index, which is formulized by the differences between the averaging reaction time of different kinds of trials (congruent vs. incongruent) across sessions. The anterior cingulate cortex (ACC) network has been shown to be related with the attentional bias process. Recently, a dynamic perspective of attentional bias has been proposed, which conceptualizes attentional bias based on trial level data instead of the traditional average estimations. It was found to be more reliable across sessions than traditional attentional bias and has been shown to provide critical new information about how attentional bias changes over time. However, whether the dynamic form of attentional bias shares the same underlying neural mechanisms with traditional

attentional bias has never been addressed. Therefore, in the current study we tried to explore the brain morphometry of dynamic attentional bias. Healthy participants first were asked to complete a dot-probe task with backward masked fearful faces and then their whole-brain structural magnetic resonance images were collected via a 3 Tesla Siemens Trio whole body scanner. Trial-level bias scores (TL-BS) was calculated, based on which several parameters were further examined to detect the temporal dynamics of attentional bias: mean TL-BS, peak TL-BS, variability of TL-BS. Voxel based morphology (VBM) was used for the voxel-wise measurement of gray matter volume. The results showed that the mean TL-BS and peak TL-BS measures were significantly correlated with the ACC gray matter volume in the right hemisphere. Our findings suggest that the ACC network may serve as the neural substrate for both traditional attentional bias and the dynamic trial-based attentional bias.

**Disclosures: L. Fang:** None. **J.M. Carlson:** None.

**Poster**

**792. Human Cognition and Behavior: Attentional Networks I**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 792.29/LLL25

**Topic:** H.02. Human Cognition and Behavior

**Support:** DSO Grant DSOCL17063

**Title:** Connectome-based predictive models account for individual differences in the attentional blink

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**Abstract:** When two targets are presented close to each other in a rapid serial visual presentation stream, the second target is often missed. This effect of selective attention, known as the attentional blink (AB), varies considerably in size across individuals. Here, we investigated whether such differences could be accounted for with fMRI-based functional connectivity. These measures of network strength have previously been used to account for individual differences in sustained attention (Rosenberg et al., 2015), fluid intelligence (Finn et al., 2015), and spatial attention (Rosenberg et al., 2018). FMRI data were collected during resting state (32 minutes) and as participants (n=73) performed the AB task (36 minutes). On the following day, participants also completed a sustained attention task (GradCPT), fluid intelligence task (Raven's progressive matrices), and the attention network task (ANT) outside the scanner. Functional

connectivity was calculated for resting state (rs-fcMRI) and the AB task (task-fcMRI) across 419 cortical and subcortical regions (Schaefer et al., 2017), and used in the connectome-based predictive model (Shen et al., 2017) to account for behavioral performance on each of the tasks. We found that task-fcMRI accounted for blink size in the AB task, even when stimulus presentation information was removed through regression. In contrast, rs-fcMRI did not account for AB task performance. For the other three tasks, the reverse pattern was found, with rs-fcMRI accounting for performance while task-fcMRI did not. Our study demonstrates that multiple predictive patterns can be found in resting state fMRI, whereas many of these patterns are disrupted during task performance. Task performance itself, however, induces task-specific predictive patterns.

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**Poster**

**793. Human Cognition and Behavior: Attentional Networks II**

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**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 793.01/LLL26

**Topic:** H.02. Human Cognition and Behavior

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**Title:** Fiber cluster topography analysis of frontostriatal connectivity in healthy subjects: A diffusion mri tractography study

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**Abstract: Background:** Alterations in brain connectivity may underlie conditions such as schizophrenia or autism. We here assess the pattern of long range axonal structural connectivity between the prefrontal cortex (PFC) and striatum in 100 healthy subjects (HSs) from the Human Connectome Project (HCP); age: 22 to 35; sex: 46 females and 54 males. We propose a novel method using fiber clustering of dMRI tractography to assess the pattern of frontostriatal brain wiring which allows us to measure the degree of pattern deviation from a strictly topographic arrangement. **Methods:** To enable the identification of fiber tract parcels from the prefrontal cortex (C) and the striatum (S), we used a well-established data-driven fiber clustering pipeline (O'Donnell, 2007, 2012). This allows for a whole brain tractography parcellation according to the white matter (WM) anatomy (i.e. fiber geometric trajectory). Then, fiber clusters of interest

(i.e. from C to S) from the whole brain WM were identified according to their connected anatomical brain regions. We studied multiple Freesurfer PFC regions including all orbital, lateral and medial PFC regions and the caudate. We identified 17 fiber clusters that connect C and S. To quantify the topographical relationship of these fiber clusters, we measured the mean distances between the endpoints of the fiber clusters within the prefrontal cortex (i.e. cortical distance) and the mean distances between the endpoints of the corresponding fiber clusters terminating in the striatum (i.e., striatal distance). **Results:** We generated a plot (not shown) based on the 17 fiber clusters (with 136 pairs of fiber clusters, yielding 136 data points), showing the relationship between the cortical distances and the corresponding striatal distances of the obtained fiber clusters that connect the prefrontal cortex and the caudate. A 2-term exponential model was fit to the data points which was superior to a linear model. We showed that the PFC-striatal WM streamline projection pattern was non-linear and differed as a function of cortical distance between cluster pairs such that cluster pairs with smaller cortical distances had larger striatal distances (i.e., diverged), cluster pairs with intermediate cortical distances had similar striatal distances (i.e., were parallel), and cluster pairs with larger cortical distances had smaller striatal distances (i., converged). **Conclusions:** Using dMRI fiber cluster topography analysis in HSs, we show the PFC projection wiring pattern to the striatum is not strictly topographically organized. This approach allows us to test for variation in frontostriatal wiring patterns in other conditions such as schizophrenia.

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**Title:** Mesoscopic functional interactions in the human cortex

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**Abstract:** Functional interactions between brain regions play a central role in cognitive computations. Evaluating such functional interactions in the human brain has been challenging due to the difficulties inherent to interrogating human brain activity at adequate spatiotemporal

resolutions and with sufficient signal-to-noise ratio. Here we investigated pairwise interactions at a mesoscopic scale by quantifying the degree of coherence in intracranial field potential recordings from 4432 electrodes in 51 patients with pharmacologically intractable epilepsy over the course of 6360 hours. After correcting for artifacts and removing seizure events, we defined putative interactions by computing the coherence in different frequency bands between electrode pairs within each patient. We observed functional interactions that are consistent with known anatomical connectivity in the human brain, with macaque anatomical connections, and with neurophysiological interactions documented in macaque monkeys. These interactions showed strong stability across days. The interactions were also were also consistent across subjects. These results provide the first mesoscopic functional interactome of the human brain and constitute an important database to study modulations by state, by cognitive function, as well as by impairments due to neurological disorder.

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**Title:** Electrophysiological evidence for spontaneous and task-related anticorrelated activity between human anterior insula and posteromedial cortex

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**Abstract:** Over the past decade, the neuroimaging-based discovery of intrinsically anticorrelated activity between the default network and so-called “task-positive” networks has been a major influence in cognitive and clinical neuroscience. However, the existence and potential behavioral significance of such anticorrelated activity in the human brain remains a subject of debate. Here we studied a unique cohort of neurosurgical patients who had depth electrodes implanted in both a core “task-positive” region (dorsal anterior insula; daINS) and a core default network region (posteromedial cortex; PMC). Three patients with epilepsy, each with depth electrode contacts in the PMC and daINS simultaneously, performed 4-8 six-minute sessions of an attention-demanding gradual continuous performance task (gradCPT). In the task, distinct visual scenes

faded into one another with a new scene appearing every 800 msec, and patients were instructed to respond to (frequent) city scenes but to withhold responses to (infrequent) mountain scenes. Patients also performed 2-4 sessions (5-10 minutes each) of wakeful rest with visual fixation on a cross-hair. Our analysis focused on high-frequency broadband (HFB; 70-170 Hz) power, a reliable marker of neuronal population engagement. In each patient, we identified an electrode in the daINS that showed significantly increased HFB power, and an electrode in the PMC that showed significantly decreased HFB, during the presentation of mountain relative to city scenes. The daINS activations preceded the PMC deactivations by ~200 msec. Within each patient, over the course of entire task sessions, the daINS and PMC consistently showed anticorrelation (mean $r$ =-0.36) of infraslow (<0.1 Hz) HFB power with one another. This anticorrelated activity was also observed during wakeful rest but was weaker (p=0.02). These results provide a systematic neurophysiological validation for inter-network, intrinsic anticorrelated activity between functionally localized regions in the human brain. At the same time, our work points toward state-dependence of this anticorrelated activity as well the existence of a previously unrecognized, organized temporal order of inter-network activity during task engagement.

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**Title:** Developmental pathways to distinct neural systems and generalizable representations of children's attention networks

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Peking Univ., Beijing, China; [7]Psychiatry Res. Ctr., Hui-Long-Guan Hosp., Beijing, China; [8]Peking Univ. Huilongguan Clin. Sch., Beijing, China

**Abstract:** A core function of human attention system is to efficiently and accurately extract useful information from ever-changing environment and stay focus, which is essential to our survival and learning. There are three core features about attention networks including the maintenance of alert state, the orientation of sensory input, and the resolution of attention conflict.Understanding the distinct maturationalmechanismsof core attentioncomponents and related neural circuitry are of great importance to promote children's attention and cognitive functions. Although widely studied in adults, little is known the neurodevelopmental bases underlying these distinct attention components from childhood to adulthood. Previous studies only reported differences in behavioral performance of attention networks between children and adults. Here we conducted an event-related fMRI study to investigate cognitive, neural systems and representation patterns between children and adults regarding to attention network test (ANT) in a large sample of 219 children (7-12 year-old, 171 and 48 subjectsfrom two independent cohorts) and 136 young adults (19-25 year-old, 56 and 80 subjects from two independent cohorts). Behaviorally, children's orientation and conflict resolution abilities were significantly lower than adults, but their alerting ability reaching adult-like level. Using general additive model (GAM), weobserveddistinct non-linear developmental trajectories of alert, orient and conflict abilities from 7 to 12 years old. Analysis of fMRI data revealed three distinct brain systems, including superior parietal lobe (SPL), frontal eye field (FEF) and dorsal anterior cingulate cortex (dACC), involved in altering, orienting and conflicting respectively in both children and adults. Critically, adults showed neural activation patterns that are more specific to relevant component than children in these systems. Furthermore, we implemented an innovative analytic approach with hierarchical structure model to reveal maturational changes in neural generalization with age. Results indicated that children showed significantly less stable neural representation patterns across age within these systems than adults, with most prominent effect in dACC that is critical for conflict network. Together, our findings delineate that immature developmental profiles of distinct brain systems and generalizable representations involved in children's attention networks.

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**Poster**

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Learning: Brains, Machines, Children

**Title:** A dorso-ventral endogenous attention network in the human brain

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**Abstract:** The cerebral cortex comprises many areas involved in visual attention processing. Classical studies identify the parietal and frontal cortices as two major sources of attentional signals. Recent results in the non-human primate brain highlighted the existence of an area in the temporal cortex that plays a crucial role in guidance of spatial visual attention, and that forms an attentional control network through direct connections with the fronto-parietal attention network (Stemmann et al., 2016; Sani et al., *submitted*). The discovery of this ventral attentional-control area posits new important questions about the network organization of the primate attention system and about the degree of homology between human and monkeys in the cognitive domain. In the present study, we ask (i) whether a ventral area may exist and play a homologous role in endogenous attention in humans, and (ii) whether it communicates via direct white matter pathways with dorsal attention areas. We combined areas localization using functional MRI with white matter tracts mapping using diffusion MRI. We used probabilistic tractography to estimate the trajectories of different temporo-parietal pathways. We analysed the data using constrained spherical deconvolution and an ensemble of tractography methods (Takemura et al., 2016). We successfully identified an area within the human ventral visual stream related to endogenous attention. This area is directly connected to the dorsal attention areas in the parietal cortex within the intraparietal sulcus. These results provide a functional and structural substrate for a role of ventral human cortex in attentional control and the integration of information necessary for cognition and behavior.

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**Topic:** H.02. Human Cognition and Behavior

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**Title:** A novel neuroimaging measure of the allocation of neural resource for quantifying attentional behavior

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**Abstract:** The strategy of brain overcomes the limited capacity is to actively make a flexible control of resource allocation. Attentional behavior has been considered as the evidence of the neural resource allocation in the brain. But, the evidence connecting them is almost merely interpretations rather than direct measures. The goal of this study is to provide the neuroimaging measure of the neural resource allocation that can quantify directly attentional behavior. In this study, the neural resource allocation (NRA) is defined as the neural process which controls the amount of neural resource usage in each brain region according to their needs. It enables the spatial disproportion of neural resource usage in the whole brain. Thus, the parameter to quantify the level of NRA was acquired by calculating the spatial standard deviation of pattern of whole brain activation change from baseline (default mode). We used resting and task fMRI from three datasets, in-house data (KAIST data), Human Connectome Project (HCP data) and UCLA Neuropsychiatric Consortium (UCLA data). Many cognitive tasks including spatial working memory task with various attentional demand were performed. We further applied our approach to the data of patients with attention deficit hyperactivity disorder (ADHD). The results showed that the level of NRA showed significant linear relationship with the experimentally induced attentional demand and 'U-shape' relationships with reaction time. The NRA level was also significantly correlated with the physiological factor, pupil dilation, of attentional behavior. The neural gain of spatial attention was also significantly correlated with the NRA level. Finally, brain regions that showed NRA correlated BOLD activation was spatially correlated significantly with conventional attention network. The results were robust regardless of sensory modalities and tasks. Interestingly, the level of NRA did not reflect the attentional demand in ADHD patients and there was no significantly correlated region in the patients. Further, the functional connectivity between NRA-correlated regions well explained the level of total

symptoms of ADHD patients. In conclusion, we propose a novel measure of neural resource allocation for quantifying attentional behavior using fMRI. The measure was well correlated with behavioral and physiological parameters for attentional behavior. We also demonstrated disruption of the measure in ADHD patients. These results indicate that the process of neural resource allocation may be the underlying neural mechanism for attentional behavior. And the NRA parameter can be used for a task-free neuro-marker for attentional behavior.

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**Poster**

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**Title:** Dynamic cognitive remediation for traumatic brain injuries significantly improves attention, working memory, processing speed, and reading fluency

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**Abstract:** This study determines whether cognitive remediation to discriminate a moving test pattern relative to a stationary background (figure-ground movement-discrimination) improves vision and cognitive functioning in people with Traumatic Brain Injuries (TBI), representing a paradigm shift in treatment methods. Movement-discrimination neurotraining was used to remediate low-level visual timing deficits in the dorsal stream to determine whether it improved high-level cognitive functions, such as processing speed, reading fluency, and the executive control functions of attention and working memory in four men with TBIs between the ages of 15-68. Standardized tests, as well as MEG brain imaging, were administered at the beginning and end of 8-16 weeks of intervention training to evaluate improvements in cognitive skills. Movement-discrimination cognitive neurotraining remediated both low-level visual timing deficits and high-level cognitive functioning, including selective and sustained attention, reading fluency, processing speed, and working memory for all TBI patients we studied. High resolution MEG brain imaging, using the Fast-VESTAL procedure, showed that this movement-discrimination training improved time-locked activity in the dorsal stream, attention, and executive control networks. Remediating visual timing deficits in the dorsal stream revealed the causal role of visual movement discrimination training in improving high-level cognitive functions such as focusing and switching attention, working memory, processing speed, and

reading. This study found that movement-discrimination training was very rapid and effective in remediating cognitive deficits, providing a new approach that is very beneficial for treating mild TBIs. **Significance:** Rapid brain training exercises to improve cognitive function after a mild TBI are needed. Only when low-level visual timing deficits are remediated in those with TBIs are the improvements in high-level cognitive functions, such as reading fluency, attention, and memory, commonly found after a mild TBI, improved quickly, these improvements being sustained over time. This is the first time that a study has found that improving low-level movement discrimination in the dorsal stream improves high-level cognitive functioning, both behaviorally and using MEG brain imaging, improving both the attention and executive control networks in those with TBIs. Since movement-discrimination (PATH to Insight) neurotraining is so rapid and effective, it offers a new approach that is very beneficial for treating mild TBIs.

**Disclosures: T.A. Lawton:** A. Employment/Salary (full or part-time):; The first author TL has a potential conflict of interest, since she is the developer of PATH to Insight (PATH), and was employed by Perception Dynamics Institute.. **M. Huang:** None.

**Poster**

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**Title:** Attentional processes in typically developing children as revealed with brain event-related potentials and their source localization

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**Abstract:** Attention can be conceptualized as three functional components: alerting, orienting, and inhibition. Here we investigated these components using EEG-based event-related brain potentials (ERPs) and their neuronal source activations during Attention Network Test (ANT) in typically developing school-aged children. The task was to detect the swimming direction of the middle fish out of a group of five fishes. The target was either preceded by a cue (center, double or spatial) or no cue. EEG was recorded with 128 electrodes with simultaneous measurement of eye-tracking data from 83 12-13-year-old children. The underlying ERP components and neuronal sources of ERP activity were modelled using the CLARA distributed source analysis

method. The attention network effects were behaviorally studied using reaction times. The shortest reaction time was observed for the congruent targets and the longest reaction time was observed for the incongruent targets. The ERP results showed that the amplitude of the target N1 response at 140 - 200 ms, typically reflecting the basic visual processing, was modulated during alerting and orienting, whereas later P3 response at 480 - 700 ms, typically reflecting the attentional processes, was modulated during inhibition of irrelevant visual information. The grand-averaged-ERPs were collapsed across all the conditions to identify the neuronal sources related to target N1 period and target P3 period. Source level statistics were calculated based on the individual level source waveforms associated with the neuronal sources obtained from these target N1 and target P3 periods. Neuronal source activation for alerting was localized in the right superior temporal gyrus and bilateral lingual gyrus, for orienting bilaterally in the lingual gyrus, and for inhibition in the anterior cingulate and left superior temporal gyrus. These high-density EEG/ERP brain response effects and their sources can be used in the future to study attention and its sub-components for example in children with attentional problems.

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**Title:** Role of superior longitudinal fasciculus in visuospatial attention

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**Abstract:** Superior longitudinal fasciculus (SLF) is a major white matter tract connecting frontal and parietal cortices. Past work has shown that hemispheric differences in SLF mediate the behavioral biases in a spatial bisection task. The goal of this study was to further investigate the role of SLF in visual spatial attention by examining the relation (1) between SLF and the behavioral benefit of attentional cuing and (2) between SLF and the neural representations of attended information in posterior parietal cortex. Diffusion MRI data were recorded from 20 subjects. In addition, functional MRI (fMRI) data were recorded from the same subjects performing a cued visual spatial attention task. In the task, each trial started with an auditory cue, which directed subjects to attend to a spatial location (left or right visual field). For valid cued trials, following a random time delay, two rectangles were displayed in the right and left visual

field, and the subjects were required to discriminate the orientation (vertical or horizontal) of the rectangle in the cued location. For invalid cued trials, only one rectangle appeared in the uncued location, and the subjects were required to discriminate the orientation of the rectangle. The cue validity effect was defined as invalid cued reaction time - valid cued reaction time. From diffusion MRI SFL fiber count (i.e., numbers of SLF fibers) was extracted for each subject. From fMRI cue-evoked BOLD response was estimated on each trial and subjected to multivoxel pattern analysis. The following results were found. First, SLF track count had a significant positive correlation with the cue validity effect, and this effect is specific to SLF -- no such relation was found for other frontal-posterior fiber tracts including inferior longitudinal fasciculus (ILF) and inferior fronto-occipital fasciculus (IFOF). Second, higher SLF track count was associated with more distinct neural representations of attended location in superior parietal lobule (SPL), indexed by higher multivoxel decoding accuracy between attend-left vs attend-right conditions. This relation was again specific to SLF. Third, a statistical mediation analysis showed that SLF track count mediates the relationship between neural representations in SPL and the cue validity effect. Taken together, these results suggest that SLF plays important roles in visual spatial attention by (1) enabling the behavioral benefits of attentional cuing and (2) underlying the neural representations of attended information in posterior parietal cortex.

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**Topic:** H.02. Human Cognition and Behavior

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**Title:** Intra-individual consistency in brain responses to video clips predicts population preferences

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**Abstract:** In general, popular video clips that get so many views draw the attention of the viewers. When we repeatedly watch such engaging video clips, the neural activity could show highly consistent spatiotemporal patterns across views within each individual in an individual-dependent and stimulus-dependent manner. Moreover, such consistency nature could be a predictor of population preferences. To test the hypothesis, we assessed the degree of intra-

individual "consistency" in human electroencephalography (EEG) responses to repeatedly presented television commercials. Here "consistency" is defined as the reproducibility of waveforms across trials. Thirty-two subjects participated in this study after giving informed consent. We measured 63-ch EEG signals at a sampling rate of 1000 Hz while subjects were watching television commercials. Subjects were randomly presented with ten different commercials for 15 seconds, and ten trials were given for each stimulus. To estimate the degree of consistency of EEG responses, we applied a canonical correlation analysis (CCA)-based method between pairwise EEG trials within individuals. Then we calculated the canonical loadings, which are the correlation coefficient vectors between the canonical variates and EEG signals. We extracted the canonical loadings of the most popular commercial within the stimulus set and used as a preference template to predict population preferences. For measuring the degree of similarity of the brain responses, we used the cosine-similarity score between the preference template and canonical loadings averaged across individuals. We found a strong and statistically significant correlation between the cosine-similarity score averaged for commercials and the population preference ratings obtained from a large population. Interestingly, the subject-averaged ratings obtained from the subject group were less correlated with the population ratings compared to the cosine-similarity score. We conclude that EEG consistency within individuals elicited by repeatedly presented television commercials has a specific spatiotemporal pattern in an individual-dependent and stimulus-dependent manner, and the group-averaged patterns are associated with preferences of a large population. These findings suggest that spatiotemporal consistency in EEG responses can be an index to predict population-level human behaviors.

**Disclosures:** **A. Hoshi:** A. Employment/Salary (full or part-time):; Kirin Co., Ltd. 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.; Kirin Co., Ltd. **F. Saito:** None. **Y. Hirayama:** None. **T. Ishiguro:** A. Employment/Salary (full or part-time):; Kirin Co., Ltd. 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.; Kirin Co., Ltd. **H. Suetani:** 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.; Kirin Co., Ltd. **K. Kitajo:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Kirin Co., Ltd.

**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.01/LLL36

**Topic:** H.02. Human Cognition and Behavior

**Title:** Neural processing of social interaction: A neuroimaging coordinate-based meta-analysis

**Authors: *N. CANESSA**, M. ARIOLI
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**Abstract:** Understanding others' goals and intentions is a crucial ability for adaptive behavior in everyday social life, often impaired in several neuro-psychiatric disorders (Henry et al., 2016). While the mirror and mentalizing networks are considered to play complementary roles in this ability, i.e. decoding the actors' action goals vs. mental states (van Overwalle and Baetens, 2009), both networks seem to be recruited when processing social interactions (Arioli et al., 2018). We thus aimed to test this hypothesis, and to unveil their common and specific contributions to the neural processing of social interactions, via a coordinate-based quantitative meta-analytic approach. We performed three activation-likelihood-estimation meta-analyses of neuroimaging studies reporting brain structures involved in a) processing social interactions , b) "action representation" by the mirror network, and c) "mental state representation" by the mentalizing network. Conjunction analyses and direct comparisons unveiled, respectively, overlapping and specific regions among the resulting brain maps. We report the first evidence for a "social interaction network" in the human brain, including key-nodes of both the mirror (right premotor cortex and posterior middle/superior temporal cortex bilaterally) and mentalizing (medial prefrontal cortex, superior temporal cortex and TPJ bilaterally) networks, with the additional involvement of the amygdala. This result fits with recent evidence on a dedicated network for social interaction processing in the primate brain (Silwa and Freiwald, 2017). A mirror-social-mentalizing gradient of activity along the posterior temporal cortex appears to underpin a hierarchical neural processing of social interactions, from visuomotor analyses underlying the decoding of shared motor intentions (i.e. "what" and "how" of the interaction) to in-depth inferences on the social actors' intentional states (i.e. "why" of the interaction). The amygdala might enrich this processing with information concerning the affective valence of the observed interaction (e.g. affiliation or aversion). This evidence allows to fractionate the brain architecture underlying the processing of social interactions in different sub-components grounded in, but not limited to, the joint involvement of the mirror and mentalizing networks. These results pave the way for future studies assessing the status of the social interaction network as a neural marker of impaired social cognition, or the effects of cognitive remediation procedures (Kurtz and Richardson, 2011), in different pathological conditions (Henry et al., 2016).

**Disclosures: N. Canessa:** None. **M. Arioli:** None.

**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.02/LLL37

**Topic:** H.02. Human Cognition and Behavior

**Title:** Dark chocolate increases brain EEG gamma frequency 25-40 Hz: Associated with neuroplasticity, enhanced cognitive processing, memory and recall for brain health benefits

**Authors: *L. S. BERK**[1,2], K. DEVORE[3], N. MEHTA[4], O. OGUNYE[5], H.-G. YEO[5], E. LOHMAN[5], G. BAINS[6]
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**Abstract:** Cacao or dark chocolate is a major source of flavonoids. Flavonoids are extremely potent antioxidants and anti-inflammatory agents, with known mechanisms beneficial for cardiovascular health. However, the correlates of neuroelectric activity that initiate cacao effects on the brain health EEG gamma frequency are not known. Studies have shown that absorbed cacao flavonoids penetrate and accumulate in brain hippocampal regions involved in learning and memory. However, long term effects to acute cacao consumption on power spectral density $uV^2$ (PSD) of brain EEG and specifically, to associated beneficial gamma frequency (25-40 Hz), has not been studied. **Purpose:** This study assessed the EEG response on modulating brain frequencies 0-40 Hz but specifically to gamma frequency (25-40 Hz), after acute consuming of 48 g dark chocolate (70% cacao), at time periods (30 mins) and (120 mins), **Methods:** The dark chocolate (Tanzania organic cocoa beans) used in this study consists of only two ingredients, 70% cacao and 30% organic cane sugar (Parliament Chocolate, Redlands, CA). EEG bandwidth activity was recorded from 9 cerebral cortical scalp locations F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4 using the EEG B-Alert 10X System™ (Advanced Brain Monitoring, Carlsbad, CA). Twenty healthy subjects, age 22-40, consumed 48 g of the dark chocolate after a baseline EEG acquisition. EEG was then acquired at time periods (30 mins) and (120 mins) for two mins each. EEG data from the 20 subjects was summated for the respective time points. PSD was z-scored using the EEG baseline.. **Results:** Z-scores were generated for the time periods across 0-40 Hz. Most significant finding was PSD was quantitatively greatest for γBA over all other frequencies ($p<0.01$). Using “heatmap” graphics, we show qualitative responses greatest for γBA on the cerebral cortical brain for both time periods (30 mins and 120 mins post consumption). The 30 min time period shows the entire cortical region modulated to varying degrees of increases in

γBA, with the largest PSD increase in regions C4/P4/PZ/P3, while 120 min shows the frontal left side returning to baseline, but residual γBA in C4/P4/Pz remains. **Conclusion:** This study provides strong quantitative and qualitative evidence that EEG γBA is enhanced by consumption of 48 g 70% cacao and shows a significant effect at 30 mins to all cerebral cortical regions, and a continued γBA response at 120 mins. We suggest that cacao consumption of antioxidant concentration of 52,000 umoles /100g, is associated with subsequent γBA increase in the cerebral cortical brain. We suggest cacao antioxidant superfood can enhance neuroplasticity for behavioral and brain health benefits.

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**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.03/LLL38

**Topic:** H.02. Human Cognition and Behavior

**Support:** NSF CAREER Award PHY-1554488
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NIH Grant 1R01HD086888-01
NIH Grant R01-MH107235
NIH Grant R01-MH107703

**Title:** Functional brain network architecture supporting the learning of social versus non-social networks

**Authors: *S. H. TOMPSON**[1], A. E. KAHN[2], E. B. FALK[3], J. M. VETTEL[5], D. S. BASSETT[4]
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**Abstract:** How do people acquire knowledge about which individuals belong to different cliques or communities? Does this learning process depend on the fact that individuals are perceived in a social context? Or does it generalize to the learning of clique and community structure in non-social associative systems? Previous studies have reported that activation in and connectivity between hippocampus and medial prefrontal cortex (mPFC) is associated with the learning of non-social network structure (Schapiro et al., 2013, 2016). Our prior work expands on this observation by demonstrating that people learn the community structure of both social and non-social networks, but social traits, including social orientation (self- versus other-focused) and

perspective-taking, uniquely predict the learning of social (but not non-social) community structure (Tompson et al., in press). Here we used fMRI to measure participants' brain activity while they completed a basic perceptual task in which the order of stimulus presentation is defined by a random walk on a graph composed of clusters or communities. The resultant stream naturally forms temporal associations between stimuli. We manipulated social context by emphasizing that the stimuli represented people; to study non-social network learning, we emphasized that the stimuli represented rock formations. Importantly, we used the same visual representations across both social and non-social tasks, and only changed the meaning ascribed to the stimuli. We observed that hippocampus operates as a functional hub in both social and non-social network learning and exhibits greater global connectivity on trials where the stream moves from one community of stimuli to another. By contrast, temporoparietal junction (TPJ) operates as a hub in social but not non-social network learning, and only shows greater global connectivity on trials where the stream moves from one community of social stimuli to another. Furthermore, connectivity between hippocampus and TPJ was significantly greater for social network learning than for non-social network learning. Broadly, our study provides a promising approach to identify neurophysiological drivers of social versus non-social network learning, extending our knowledge about the impact of functional brain networks and social context on these learning processes. We conclude by discussing implications for how people adapt to new social contexts that require integration into a new social network.

**Disclosures: S.H. Tompson:** None. **A.E. Kahn:** None. **E.B. Falk:** None. **J.M. Vettel:** None. **D.S. Bassett:** None.

**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.04/LLL39

**Topic:** H.02. Human Cognition and Behavior

**Support:** JSPS KAKENHI JP17K16410

**Title:** The behavior of drinking alcohol may be associated with severe alcohol use disorder (AUD) patients may have strong and prolonged responses when they see someone drinking alcohol: A functional MRI study in Japan

**Authors: *S. FUKUSHIMA**[1,2,3], H. KUGA[4,2], N. ORIBE[2], T. MUTOU[2], T. YUZURIHA[2], H. OZAWA[3], T. UENO[2]
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**Abstract: Introduction:** Alcohol use disorder (AUD) is a pattern of alcohol use that involves problems controlling their drinking. Craving appears to play an important role in compulsive use across addictive substances, predicting negative outcomes such as increased use and earlier relapse in AUD. A few years ago, we started a functional MRI (fMRI) study to investigate the difference between AUD patients and healthy people with visual tasks. **Methods**: 24 patients with severe AUD and 15 healthy controls (HC) participated in this study. Blood Oxygen Level Dependent (BOLD) functional activation was measured with 1.5T magnetic resonance imaging (MRI). We presented visual cues using four images (image of orange juice, image of someone drinking orange juice, image of alcohol, and image of someone drinking alcohol. Participants had eight blocks of 15s of rest (viewing a mosaic image) and eight blocks of 15s of stimulus (viewing cue-image). Each block was made up of one picture. Those cue-images were presented on valence, and each cue-image was presented twice. In total, we presented eight stimuli for four minutes in each fMRI session. We used SPM12 software to analyze BOLD signals of fMRI data within each subject, as well as a group. Subject BOLD signals were compared between groups using repeated measures ANOVA. **Results:** We had a group analysis between AUD patients and HC. We detected an interaction effect between brain activation of AUD patients and HC at left precuneus, right precuneus and left posterior cingulate cortex (PCC). With a multiple comparison, AUD had significantly lower responses to the image of someone drinking juice than HC in left precuneus and left PCC ($p = 0.036$, $p = 0.044$). We revealed the time course of BOLD responses in left precuneus and left PCC. To the image of drinking juice, AUD group had significantly weaker BOLD responses than HC in the 16-18 sec ($p = 0.020$), 19-21 sec ($p = 0.001$), and 22-24sec ($p = 0.022$) in left precuneus. To the image of drinking alcohol, AUD group had a significantly stronger BOLD response than HC in the 19-21 sec ($p = 0.001$) in left PCC. In left PCC, AUD patients had more prolonged responses to the image of drinking alcohol than in the left precuneus. **Conclusions:** These results suggest that severe AUD patients had different responses in left precuneus and left PCC to the image of drinking juice and drinking alcohol, compared to the HC. The responses to the behavior of drinking alcohol may be prolonged in left PCC, and it may be associated with drug craving in patients. Severe AUD patients may have strong and prolonged responses when they see someone drinking alcohol.

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**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.05/LLL40

**Topic:** H.02. Human Cognition and Behavior

**Support:** DFG Grant

**Title:** Unraveling genetic predisposition to familial prosopagnosia using whole-exome sequencing

**Authors: *L. ARNING**[1], B. SUCHAN[2]
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**Abstract:** Congenital prosopagnosia (CP), also known as developmental prosopagnosia or face blindness, describes the inability to recognize faces. Cognitive functions such as intelligence as well as the sensory visual capabilities are usually not impaired but people with CP are negatively affected in their social life because individuals with the disorder have difficulty in recognizing family members, close friends or colleagues.
The underlying pathophysiology and the specific genetic susceptibility of CP are poorly understood. We hypothesize that rare highly penetrant genetic variants with big effect size may be involved in the disease. Since CP has a tendency to cluster in families, a family approach might be the way to find these variants.
The technology of next-generation sequencing (NGS) now provides an affordable tool to investigate the genetic variation in the entire exome or genome. As part of a larger genetic study of patients with CP, we performed family based whole-exome sequencing and targeted re-analyzing on four individuals from two families with multiple affected members. After applying different filter mechanisms we were able to downsize possible candidate SNPs to 788 and 618 SNPs for each family (coverage, mutation type, etc.) Under self-defined strict selection criteria a total of 30 SNPs was selected for further examination in other family members (affected vs. non-affected) and the extended CP cohort. Current results provide first evidence for genetic marker of congenital prosopagnosia.

**Disclosures: L. Arning:** None. **B. Suchan:** None.

**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.06/LLL41

**Topic:** H.02. Human Cognition and Behavior

**Support:** Internal funds to Center for Biobehavioral Health, Nationwide Children's Hospital
Fonds de recherche du Québec – Nature et technologies [grant number 207776]

**Title:** Developmental changes in neural activation during facial and vocal emotion recognition are disrupted in temporal lobe epilepsy

**Authors: *M. MORNINGSTAR**[1,2], W. I. MATTSON[1], S. SINGER, Jr.[1], J. VENTICINQUE[1], B. A. FULLER[1], S. GEDELA[2,3], E. E. NELSON[1,2]
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**Abstract:** Youth with temporal lobe epilepsy often experience social difficulties that may stem from deficits in the interpretation of social and emotional cues from others. Lesion studies have demonstrated that insults to brain areas relevant to emotional processing were associated with poorer emotion recognition (ER) abilities in epilepsy patients. However, less is known about the functional patterns of neural activity underlying ER deficits in this group, and how epilepsy may disrupt the development of normative processing of emotional nonverbal cues. The current study examined neural activation during a facial and vocal emotion recognition task, in 8- to 18-year-old typically-developing adolescents and youth with intractable temporal lobe epilepsy (TLE). Groups did not differ in age or gender distribution. Participants were asked to identify the intended emotion (anger, fear, happiness, sadness, neutral) in pictures of emotional faces and auditory recordings of emotional voices, while undergoing functional magnetic resonance imaging. Multivariate analyses were conducted to examine the effect of diagnosis and age on neural activation during the tasks compared to baseline. Compared to controls, youth with TLE were less accurate in recognizing emotions in voices, but not faces. At a neural level, TLE patients showed less widespread activation in areas typically involved in the perception of visual and auditory stimuli, such as the occipital fusiform face area and superior temporal gyrus. Further, TLE youth showed atypical patterns of activation in the right amygdala during both tasks, compared to control youth. Both groups showed similar age-related changes in activation across the brain, though the TLE group's growth was delayed compared to controls. These preliminary results suggest that emotional information contained in facial expressions and vocal prosody may be processed differently by typically-developing and TLE youth. Specifically, aberrant activation in the primary sensory areas and the amygdala, a brain area thought to encode the emotional salience of environmental stimuli, may impair the recognition of emotional intent in nonverbal cues. Further, the normative development of ER, at a behavioural and neural level, may be disrupted or potentially delayed in youth with epilepsy. These findings suggest that the timing of medical interventions to reduce seizures may have implications for socio-emotional processing in children and adolescents with epilepsy.

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**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.07/LLL42

**Topic:** H.02. Human Cognition and Behavior

**Title:** Relationship between pre-pulse inhibition (PPI), habituation, and medication in patients with schizophrenia and bipolar disorder

**Authors: *D. NGUYEN**
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**Abstract:** Psychiatrists can experience difficulties determining a clear diagnosis for patients with bipolar I disorder (BPI), schizoaffective disorder (SAD), and chronic schizophrenic paranoid type (SCPT) due to overlapping symptoms. Prepulse inhibition (PPI) and habituation have been demonstrated as powerful neurophysiological biomarkers for distinguishing patients with these mental disorders due to sensory gating deficits in patients. These markers may also be used to study medication effects on these measures. This study explored PPI and habituation differences in patients with BPI, SAD, and SCPT as well as the effects of medication. The effects of patient medication on PPI and habituation are also examined in this study. Patient PPI and habituation measurements were extracted from patient electromyography recordings and subsequently analyzed. Habituation was calculated for each single trial rather than calculating from averaged trials. Results from this study found significantly decreased PPI levels in SCPT patients compared to SAD patients. Within subtype groups, PPI was significantly increased in SAD patients compared to BPI depressed, SAD bipolar type, and SCPT patients. Habituation was found to significantly decrease as a function of single trials. Medication had variable effects on patients. Medicated SAD patients exhibited significantly decreased PPI levels. When separated by psychosis, BPI patients exhibited significantly increased PPI levels. Findings from this study demonstrate the prospective function of PPI as a biomarker for future clinical diagnoses along with additional studies to confirm habituation as a possible biomarker. This study also encourages future studies to observe the effects of medication on patient PPI and habituation.

**Disclosures: D. Nguyen:** None.

**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.08/LLL43

**Topic:** H.02. Human Cognition and Behavior

**Support:** JSPS KAKENHI Grant Number JP25118009
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**Title:** Comparison of fMRI activity between dog experts and non-experts observing dog training scenes

**Authors: R. OUCHI, 6300192**[1], *T. KUBO[1], E. NAKAHARA[1], K. SAMEJIMA[2], M. NAGASAWA[3], T. KIKUSUI[3], K. IKEDA[1]
[1]Nara Inst. of Sci. and Technol., Ikoma-Shi, Japan; [2]Tamagawa Univ. Brain Sci. Inst., Tokyo, Japan; [3]Azabu Univ., Sagamihara, Japan

**Abstract:** Dog experts such as dog trainers have a unique expertise to interact with dogs appropriately. It has been shown that there is a significant difference between the brain activities of them and those of non-experts in posterior superior temporal sulcus (pSTS) during watching still images showing social interaction between pairs of humans or between those of dogs. Apart from dog-related expertise, another study shows that pSTS in experts of classical ballet and capoeira showed higher activities during watching the scene of movements in their own expertise. From these studies, we hypothesized that pSTS of dog experts is activated stronger than that in non-experts when they observe human-dog interaction by a different dog expert. To investigate this point, we measured brain activity during watching human-dog interaction, and compared their brain activities with those of novices. We recruited eleven subjects who had sufficient experience and knowledge about dogs' behavior as the expert group, and fourteen subjects who did not as the non-expert group. In the experiment, twenty four videos showing dog training were presented as stimuli to the subjects. Three factors were included in the video: human demonstrators (a professional trainer or a non-expert), dog demonstrators (two well-trained guide dogs), and the training methods of the dog (with or without a toy). Three videos were prepared for each possible combination of factors under the cooperation of Japan Guide Dog General Center. The length of each video was one minute. By using these videos, we instructed each subject to complete 24 trials in the fMRI scanner. Each trial consisted of stages of Rest (10 s), Fixation (2 s), Video (60 s), Rest (4 s), Questionnaire 1 (10 s), and Questionnaire 2 (10s). The subjects rated goodness (Questionnaire 1) and generality (Questionnaire 2) of human-dog interaction of the video. fMRI data were collected during the experiment with 3T fMRI scanner, and analyzed with the general linear model using SPM and MarsBaR. After the standard preprocessing, region of interest (ROI) analysis for pSTS was conducted focusing on the difference of the human demonstrator, or difference with respect to expertise. As a result of group comparison, the expert group showed significantly higher activation in pSTS than that of novice group with respect to the difference of demonstrators. The result of the ROI analysis indicates that activities in pSTS of experts may reflect the difference of expertise. This result is consistent with the previous studies, and may imply that these activities in pSTS of dog experts contribute to their expertise for understanding human-dog interaction.

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**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.09/LLL44

**Topic:** H.02. Human Cognition and Behavior

**Support:** CSUSB Faculty-Student Grant
CSUSB Mini-Grant
CSUSB Student Research Fellowship
CSUSB Faculty Assigned Time

**Title:** An electrophysiological exploration of metacognitive errors in recognition memory

**Authors: *R. J. ADDANTE**[1], A. A. MULLER[1], L. SIRIANNI[1], C. GONZALEZ[1], R. DEKOCK[1,2]
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**Abstract:** The Dunning-Kruger effect is a metacognitive phenomenon in which individuals who perform poorly on a task believe they performed well, whereas individuals who performed very well believe their performance was only average. To date, this effect has only been investigated in the context of performance on mathematical, logical, or lexical tasks, but has yet to be explored for its generalizability and manifestation in episodic memory task performance. We used a novel method to elicit the Dunning-Kruger effect in CSUSB students via a memory test of item recognition confidence. Participants studied lists of words and were later tested on their episodic memory of the words using a five-point recognition confidence scale. After the test, participants were asked to estimate the percentile in which they performed compared to other students. Participants were separated into four groups based on their performance percentile. Results showed that participants in all four groups gave the same estimated percentile for their estimated performance. Participants in the bottom 25th percentile overestimated their percentile the most, while participants in the top 75th percentile slightly underestimated their percentile. Analyses assessed the role that episodic memory processes of recollection and familiarity play in influencing this metacognitive phenomenon of illusory superiority. Findings support Dunning and Kruger's account for both low performers and high performers, in which low performers suffer from double ignorance and high performers suffer from the false consensus effect, extending this account to a novel paradigm of episodic memory.

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**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.10/LLL45

**Topic:** H.02. Human Cognition and Behavior

**Title:** Intra and inter-subject brain activity during musical improvisation using dual-MEG

**Authors: *J. BOASEN**, H. WATANABE, H. ONISHI, A. SHIMOJO, H. SHIRAISHI, T. SAITO, K. YOKOSAWA
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**Abstract: Intro:** Phenomenological research indicates that musical improvisation therapy or training could potentially be used to combat cognitive decline, and increase social and creative ability in people of all ages. To clarify this, neurophysiological studies are needed to characterize the brain activity associated with conversational forms of musical improvisation that are presently employed in therapies. We have developed such a paradigm using magnetoencephalography (MEG). Here we present our adaptation of this paradigm for use in our unique dual-MEG system, which will permit simultaneous brain activity recording of two subjects engaged in realistic, conversational, musical improvisation.
**Materials/Methods:** Two musicians, take turns playing to a fixed metric structure on 5-key MIDI keyboards programmed to a major pentatonic scale. One musician improvises. The other either copies the rhythm of the first's performance, or improvises a response. Both musicians perform via mental imagery prior to physical performance. Sound is presented via an electrostatic speaker. The dual-MEG system comprises a 76ch. Elekta Neuromag custom device and a 306ch. Elekta Neuromag Vectorview device directly connected via fiber optic cable over a distance of 500m (Fig.1). One-way transmission latency is 4μs. One-way keyboard processing latency is 16ms. Analyses of brain activity focus on intra and inter-subject spontaneous spectral-spatial activity during periods of mental imagery, comparing activity between improvisation and copy performances. Behavioral analyses focus on characteristics of physical performance output such as note count.
**Results/Conclusion:** The overall latency of our dual-MEG system is negligible, and permits natural music performance. Although further results are forthcoming, we expect this novel paradigm to offer indispensable insight into improvisation-related neurophysiology, and lay a foundation for future dual-MEG experiments investigating the effects of musical improvisation training.

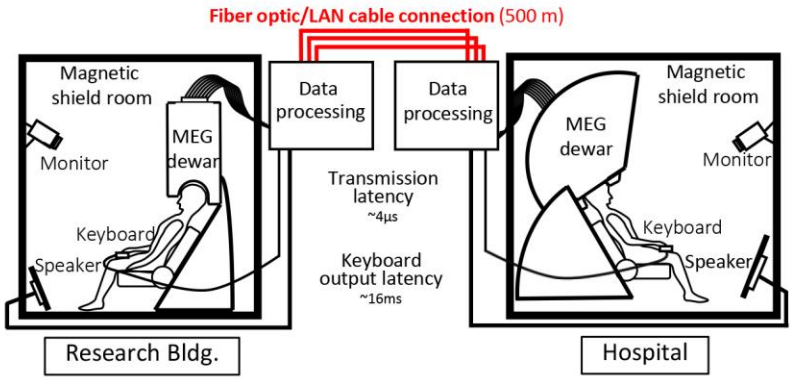


**Figure 1. Dual-MEG setup**. Simplified diagram showing how our two MEG devices at Hokkaido University are connected via fiber optic cable.

**Disclosures: J. Boasen:** None. **H. Watanabe:** None. **H. Onishi:** None. **A. Shimojo:** None. **H. Shiraishi:** None. **T. Saito:** None. **K. Yokosawa:** None.

**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.11/LLL46

**Topic:** H.02. Human Cognition and Behavior

**Title:** Neural mechanisms underlying anti-conformity in social behavior

**Authors: *J. FUJIWARA**[1], P. N. TOBLER[2], K.-I. TSUTSUI[3], M. TAIRA[4], Y. UGAWA[5], S. EIFUKU[1]
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**Abstract:** The desire to be consistent influences behavior in such a profound way that humans conform not only with the behavior of a group of others but even with the behavior of themselves. Yet, although humans have a general disposition to follow others, they sometimes refrain from conforming and go against the norm (anti-conformity). In this study, we used a sequential facial attractiveness-rating task and functional magnetic resonance imaging to investigate the neural mechanisms underlying anti-conformity both with regard to the group and oneself. In the scanner, participants rated 360 female faces for facial attractiveness one by one (pre-rating). One week after pre-rating, participants rated the same faces again, while being provided with the pre-rating of either the "group average" or "yourself". We manipulated each participant's pre-ratings by splitting them into two conditions; true (same rating as their previous rating) or false (shift above or below their previous rating), both for group and individual ratings.

Group conformity and self-conformity were measured as change in ratings from pre-rating to second rating. Behaviorally, participants on average adjusted their judgments at the second rating to conform to both group and previous own rating. Individual tendencies to conform with the group correlated positively with tendencies to conform with oneself. To analyze brain activity, we grouped trials according to degree of conformity into trials where participants rated a given face even more extremely than the indicated group or previous self rating (over-conformity), trials in which they rated it in the direction of the indicated rating (under-conformity) and trials in which they rated it in the opposite direction of the indicated rating (anti-conformity). Compared to over-conformity, anti-conformity elicited enhanced parametric activity related to rating change in medial prefrontal cortex and hippocampus. By contrast, over-conformity elicited more ventrolateral prefrontal cortex activity than anti-conformity. Thus, anti-conformity and over-conformity appear to be associated with distinct neural processes, both when considering the opinion of a group and oneself.

**Disclosures: J. Fujiwara:** None. **P.N. Tobler:** None. **K. Tsutsui:** None. **M. Taira:** None. **Y. Ugawa:** None. **S. Eifuku:** None.

**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.12/LLL47

**Topic:** H.02. Human Cognition and Behavior

**Title:** The neural correlates of the influence of social cues on food preferences

**Authors: *A. MADIPAKKAM**[1], G. BELLUCCI[1], M. ROTHKIRCH[2], F. MOLTER[3], S. PARK[1]
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**Abstract:** Eye gaze is a potent communication signal. People tend to follow the gaze of another person as it provides them with information about stimuli in their environment. Such gaze-evoked shifts in attention have been shown to increase the affective value of objects that are looked at by others in comparison to objects that do not receive any attention. Here, we investigated the neural correlates of this increase in value from gaze cues on participants' willingness to pay (WTP) for unfamiliar snack products. Snack items, previously unfamiliar to the participants, were divided into three conditions in a cueing paradigm where the eye gaze of a central face acted as an orientation cue. In the congruent condition, the snack item appeared in the same hemifield as the gaze of the central cue. That is, the item was always looked at. In the incongruent condition, the item appeared in the hemifield opposite to the gaze shift and was thus never looked at, and in the neutral condition, the central face stimulus looked straight ahead and

there was no gaze shift. Twenty-seven participants rated their WTP for the snack items before and after the gaze-cueing paradigm. Replicating our previous behavioural study, we found an increase in the WTP for items in the congruent condition ($F(2,52) = 5.37$, $p = 0.008$). Neurally, when contrasting the activation in the post-rating session to pre-rating session, there was an increase in activity in the midbrain dopaminergic regions, ventral striatum, putamen, caudate ($p_{svc} < 0.05$) and medial prefrontal cortex for congruent compared to incongruent and neutral items. Furthermore, there was a positive correlation between the neural activity in the inferior orbitofrontal cortex to congruent vs. incongruent items in the gaze cueing phase and the behavioural change in WTP ratings, suggesting that the change in value encoded by the OFC during the manipulation phase is reflected in participants' behaviour. These results show that joint attention to a snack item increases the rewarding value of the item but also that the OFC, in addition to encoding the WTP for items, also encodes the change in value. Together, the current findings highlight the influence of social information on human choice behaviour.

**Disclosures: A. Madipakkam:** None. **G. Bellucci:** None. **M. Rothkirch:** None. **F. Molter:** None. **S. Park:** None.

**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.13/LLL48

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIDA R01BA026932

**Title:** Gender differences in resting-state markers of antisociality

**Authors: *I. SIMARD**[1], M. S. SHANE[2,3]
[1]Dept. of Humanities and Social Sci., [2]Univ. of Ontario Inst. of Technol., Oshawa, ON, Canada; [3]The Mind Res. Network, Albuquerque, NM

**Abstract:** We have recently demonstrated that male offenders with psychopathic traits present a distinct resting-state activity profile marked by increased high-frequency (0.15 - 0.25 Hz) power spectra across all Resting-State Networks (RSNs) and pervasive power spectra disruptions across all frequencies in the DMN, Executive Control Network (ECN), Sensorimotor (SMN), and auditory networks in comparison to non-offenders. Interestingly, female offenders with psychopathic traits are known to present different neuronal and behavioural profiles in comparison to males of the same population. Yet, studies specifically looking into the particularities of the neuronal underpinnings of offending in females remain sparse. To fill this gap, we aimed to identify markers of resting-state activity that are unique to Female Offenders (FO; N= 38) by comparing their spectral activity to that of Female Non-Offenders (FNO; N=11).

ICA analysis was performed to identify data-driven RSNs and power spectra was computed for each 8 identified RSN. Moreover, power spectra was separated into low- (< 0.10 Hz), mid- (0.10 - 0.149 HZ) and high-frequency (0.15 - 0.25 Hz) categories and ANOVAs were conducted to assess between group spectral power differences between FO and FNO. During overall resting-state activity, FO presented significantly increased spectral power in the low-frequency bin, as well as decreased spectral power in the mid-frequency bin in comparison to FNO. Additionally, FO showed increased power spectra during low-frequency activity in the SMN and visual networks, as well as decreased power spectra during mid-frequency activity in the Basal Ganglia (BG), visual and auditory networks. Hence, female offenders displayed a very different activity amplitude profile during rest
as opposed to previous reports in male offenders, leaving resting state activity in the high-frequency band mostly preserved. Additionally, ANOVA analysis only showed significant differences between FO and FNO in the visual, auditory and BG and SMN networks, suggesting a disruption of lower-level RSNs, while RSNs involved in more cognitively demanding processes seem to be preserved. These results reflect two distinct patterns of spectral activity during rest in male and female offenders with psychopathic traits in comparison to control participants of the same gender.

**Disclosures: I. Simard:** None. **M.S. Shane:** None.

**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.14/LLL49

**Topic:** H.02. Human Cognition and Behavior

**Support:** NRF-2017M3C7A1031976

**Title:** Individual difference in action understanding and perspective-taking: A functional MRI study

**Authors: *Y. LEE**, D.-J. YI
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**Abstract:** People often try to be objective by distancing themselves from their own position when making decisions in a social context (especially about “how” to carry on the decision). They also try to construe the intention of others by thinking from their perspective (especially about “why” someone is taking the action). This suggests that the ability to switch viewpoints can be crucial to the planning and understanding of social actions. However, individuals frequently apply double standards in explaining the causes of behavior and fail to predict how others will act. By using functional magnetic resonance imaging, we investigated the relationship

between the individual's perspective-taking tendency and the neural representations underlying the action understanding. We scanned 16 participants while presenting 48 phrases describing familiar actions (e.g., drink coffee, do laundry) across four conditions: In the 'Self' and 'Other' conditions, participants were asked to imagine either themselves or an unknown person performing each action. In the 'How' and 'Why' conditions, they were instructed to think of either how or why each action is typically performed (Spunt, Falk, & Lieberman, 2010). Participants also completed the perspective-taking subscale in interpersonal reactivity index (Davis, 1983). A whole brain analysis revealed overlapping activations between the Self and How conditions in the mirror neuron system including rostral inferior parietal lobule, posterior middle temporal cortex, and middle occipital cortex in the left hemisphere. In contrast, overlapping activations between the Other and Why conditions were found in the mentalizing system encompassing posterior cingulate cortex, left temporoparietal junction and left temporal pole. To understand individual differences, we further calculated multivoxel similarity between the Self and Other conditions for each individual, and then correlated individuals' similarity measure with their perspective-taking tendency scores. We found a general pattern that neural similarity between the Self vs. Other conditions is negatively correlated with perspective-taking tendency. Such patterns were statistically significant in dorsomedial prefrontal cortex, right rostral inferior parietal lobule, and bilateral middle occipital cortices. These findings suggest that individuals with greater perspective-taking tendency represent actions more dissimilarly depending on who performs the actions.

**Disclosures: Y. Lee:** None. **D. Yi:** None.

**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.15/LLL50

**Topic:** H.02. Human Cognition and Behavior

**Title:** Neural responses to outcomes are modulated by others' trustworthiness

**Authors: *G. BELLUCCI**[1], F. MOLTER[2], S. Q. PARK[3]
[1]Inst. for Psychology I, Lübeck, Germany; [2]Sch. of Business & Econ., Freie Univ. Berlin, Berlin, Germany; [3]Dept. of Psychology, Univ. of Luebeck, 1, Germany

**Abstract:** Previous economic studies have suggested that people engage in trusting behavior as long as trust benefits them. However, another hypothesis posits that trust is a social behavior adopted irrespectively of individual rewards. Here, 31 participants (20 females, age: mean=24.3, SD=3.8) were investigated in an fMRI experiment while performing a novel paradigm (the take advice game, TAG), in which trusting behavior was disentangled from subjective rewards. In the TAG, participants played a card game with reliable and unreliable advisers who shared with the

participants accurate and inaccurate information, respectively. Participants tried to win money by trusting the advisers on the basis of their reliability in information sharing. Importantly, winnings probabilities were independent of advisers' reliability. Replicating our own previous behavioral results, participants trusted reliable advisers more than unreliable advisers and participants' trusting behavior was predicted by adviser's reliability but not by reward outcomes. This suggests that participants trusted others based on the other's reliability and not on their own monetary benefits. Applying multivariate voxel pattern analysis to fMRI data, we found that parietal and prefrontal regions involved in value signaling (intraparietal sulcus) and social cognition (lateral prefrontal cortex) encoded reliability-based trustworthiness. On the contrary, striatum and medial prefrontal cortex encoded feedback outcome. Importantly, neural responses to outcomes in the striatum and ventromedial prefrontal cortex were mediated by others' trustworthiness, indicating stronger neural activity in these regions for outcomes received during interactions with more trustworthy others. Our results suggest that positive and negative outcomes do not impact trusting behavior, which relies on cognitive processes underlying considerations of others' reliability. On the contrary, reliability-based trustworthiness modulates outcome value, impacting neural responses to outcomes in reward-related brain regions. These findings unearth the underlying neural mechanisms of trust and its effects on outcome evaluation, advancing our understanding of a central human social behavior.
*Keywords: Neuroscience, fMRI, Cognition*

**Disclosures: G. Bellucci:** None. **F. Molter:** None. **S.Q. Park:** None.

**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.16/LLL51

**Topic:** H.02. Human Cognition and Behavior

**Support:** FNS Grant PP0001_157424/1

**Title:** Beyond unpleasantness. Social exclusion affects the experience of pain, but not of comparably-unpleasant disgust

**Authors: *L. ANTICO**, C. REGUIDIERE, A. BARANDA, E. CATALDO, C. CORRADI-DELL'ACQUA
Univ. of Geneva, Geneva, Switzerland

**Abstract:** Social exclusion might elicit suffering and distress. Supposedly, social rejection and physical pain share cognitive processes and neural substrates, including secondary somatosensory cortex (S2), dorsal cingulate cortex (dACC) and anterior insula (AI), held to process the sensory and affective properties of the painful experience. Furthermore, social

rejection can influence the subjective experience and physiological response of subsequent painful stimuli. Recently, it has been suggested that social exclusion does not recruit a component of pain that is modality-specific, but rather a supra-modal representation reflecting common properties across different kinds of unpleasant experiences, even painless. Across multiple experiments, we investigated whether the effect played by social exclusion on subjective experience of pain is specific, or generalizes also to other unpleasant events that are painless, such as disgust. Neurotypical volunteers were engaged in a virtual ball-tossing game with two inclusive (inclusion condition), and two exclusive (exclusion condition) players. After each game interaction, they were subjected to comparably-unpleasant painful temperatures and disgusting liquids/odours, preselected on individual basis. We found converging evidence of reduced sensitivity to pain following exclusion (as opposed to inclusion), as revealed by the analysis of both subjective ratings and physiological responses. In addition, this effect was more pronounced in the first-half of the paradigm, and became less systematic in the remaining trials. More importantly, this effect was more pronounced in those participants who declared to feel more affected by the gaming manipulation, as measured in post-experimental ratings. Crucially, these effects were not observed for disgusting stimuli, neither of gustative or olfactory origin. Neuroimaging data underline differential interplays between social exclusion and experiences of pain and disgust. Overall, these findings indicate that the relationship between social exclusion and physical pain does not generalize to physical disgust. Therefore, it seems that social exclusion triggers a component of physical pain that is modality-specific.

**Disclosures: C. Reguidiere:** None. **A. Baranda:** None. **E. Cataldo:** None. **C. Corradi-Dell'Acqua:** None.

**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.17/LLL52

**Topic:** H.02. Human Cognition and Behavior

**Title:** Perception of laughter related to different laughables in spontaneous conversation: A fNIRS study

**Authors: *C. MAZZOCCONI**[1], Q. CAI[2], G. JIN[2], J. GINZBURG[1], S. K. SCOTT[2]
[1]Univ. Paris Diderot, Paris, France; [2]Univ. Col. London, London, United Kingdom

**Abstract:** Laughter is a non-verbal social vocalization ubiquitous in our daily interactions, able to serve different functions and to modify the meaning of the messages conveyed. Many scholars have investigated neuro-correlates of laughter in very controlled conditions, looking at activations in response to tickling, perception of humour (e.g. jokes) or while listening to laughs pre-recorded (spontaneously produced while watching a funny video or volitionally produced on

demand) presented in isolation. In our study
we explore the neurocorrelates of laughter perception when embedded in natural dialogue. Using functional Near-Infrared Spectroscopy (fNIRS), we investigate whether laughs serving different functions trigger different cortical activations by reason of entailing different mentalising processes about others' intentional and emotional states. 15 neuro-typical Chinese adults will be asked to passively watch video-clips of natural dialogic interactions extracted from the Chinese DUEL corpus (Hough et al. 2016), annotated following the framework proposed in Mazzocconi et al. (2016). According to this framework the first step for laughter function classification is the analysis and categorization of the event the laughter relates to, i.e. the laughable. We will focus on the laughable classes that occur most frequently: "pleasant/humourous incongruity" and "social incongruity" (i.e. a moment of social discomfort: embarrassment, asking a favour, criticising, etc.). 80 extracts of conversation containing laughs related to the 2 classes will be presented. 40 extracts containing conversations where no laughter occurs will be used as controls. After the fNIRS data collection, participants will be asked to listen to each stimulus again and classify the laughable after a brief explanation of the taxonomy. Acknowledging the subjective differences in laughter perception, we opt for an individual approach. Comparisons between conditions will be carried out firstly according to the experimenters classification and then according to the post-hoc behavioural individual categorisation. Based on McGettigan et al. (2013) and Szameitat et al. (2010), where the laughable is constituted by a "social incongruity", we expect to see greater activation of the amPFC, arPFC and of the Anterior Cingulate Cortex, areas proven to be related to mentalising and social reasoning. We believe that our study could provide important insights about laughter functions in dialogue, constituting an important basis for further research on clinical populations where pragmatic reasoning is affected.

**Disclosures: Q. Cai:** None. **G. Jin:** None. **J. Ginzburg:** None. **S.K. Scott:** None.

**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.18/LLL53

**Topic:** H.02. Human Cognition and Behavior

**Support:** Kakenhi 26540074
Kakenhi 17K20020

**Title:** Inter-individual EEG coherence during cooperative/ competitive task performance

**Authors: *S. IWAKI**
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**Abstract:** Although cooperative (or competitive) behavior between individuals is a crucial part of our daily life, little is known about how their brains interact while they engage in a common task either cooperatively or competitively. We use EEG hyper-scanning technique to elucidate the changes in neural interaction between the two individuals during performance of a common cognitive task either cooperatively or competitively. Sixteen pairs of male subjects (23.0 +- 2.8 years of age, all right-handed) participated in the study. Written informed consent was obtained from all subjects prior to the experiment complying with the regulation of the institutional review board. We used simultaneous recordings of EEG signals on a pair of directly facing subjects to measure changes in the spontaneous brain activities while the subjects performed a set of mental rotation task sessions. Nineteen EEG electrodes were located on both subjects' scalp according to the standard international 10-20 system. During the experiment, the pair was required to complete 10 "cooperation" task sessions and 10 "competitive" task sessions presented in a randomly intermixed order. In each session, the pair was given a sheet of paper on which 50 Shepard & Metzler type mental rotation task trials were printed. In "cooperation" session, the pair was instructed to complete the entire tasksets cooperatively as fast as possible, while in "competitive" session each subject was instructed to maximize the number of completed trials in competition with his peer. The magnitude squared coherence in alpha-, beta-, and lower gamma-band frequencies between every pair of EEG signals across the subjects were calculated for each task sessions separately. The inter-subject amplitude coherence in alpha-band (8 - 13 Hz) activities recorded in both subjects' parietal areas was significantly decreased during the period when the two subjects were engaging in the cognitive task cooperatively compared to those when they perform the same task competitively. On the other hand, the coherence in lower gamma-band (25 - 45 Hz) activities recorded in their frontal and parietal areas was increased when they perform the same task cooperatively. The results suggest that intersubject EEG coherence in alpha- and lower gamma-band spontaneous activities plays important role in both cooperative and competitive social interaction.

**Disclosures: S. Iwaki:** None.

**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.19/LLL54

**Topic:** H.02. Human Cognition and Behavior

**Support:** DARPA W31P4Q12C0166
Illinois Neurological Institute
JUMP Foundation

**Title:** Neurodynamics of team member interactions during healthcare teamwork

**Authors: *R. STEVENS**[1], T. GALLOWAY[2], A. WILLEMSEN-DUNALP[3]
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**Abstract:** Team processes are often described as taskwork and teamwork with taskwork including working on a specific duty of one's job and the relevant behaviors directly leading to the successful accomplishment of collective goals. The interdependent interactions that team members use to achieve a shared goal is teamwork. Team and task processes are intertwined and have been difficult to separate as there is a lack of quantitative measures that can directly compare the dynamics of each team member with those of the whole team using the same scale. Measures of neurodyamic organization may provide the quantitative means for distinguishing individual, shared and team processes. Second-by-second symbolic representations were created of each team member's electroencephalographic (EEG) power, and quantitative estimates of their neurodynamic organizations were calculated from the Shannon entropy of the symbolic data streams. The information in the neurodynamic data streams of healthcare ($n$ = 22), submarine navigation ($n$ = 26) and high school problem-solving ($n$ = 11) dyads was separated into the information of each team member, the information shared by two or more team members, and overall team information. Most of the team information consisted of the sum of each individual's neurodynamic information. The information of the team missing from the individual data was recovered as shared information. The shared information averaged ~7% of individual information with a range of 1 - 30%. The shared information was not uniformly distributed during three-person anesthesiology simulations, but showed peaks clustered near periods of increased team attention or uncertainty. We conclude that continuous quantitative estimates can be made from the shared, individual, and team neurodynamic information about 1) the contributions of different team members to the overall neurodynamic organization of a team, and 2) the neurodynamic interdependencies among the team members. Neurodynamic information models therefore provide generalizable measures for quantitatively tracking team member interactions during complex task performance and for identifying periods of increased information sharing between team members.

**Disclosures: R. Stevens:** None. **T. Galloway:** None. **A. Willemsen-Dunalp:** None.

**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.20/LLL55

**Topic:** H.02. Human Cognition and Behavior

**Title:** The "seductive allure" of neuroscience is not sufficient to influence social categorization

**Authors: C. MUSTIN**, P. R. NICKLAS, K. ZIMMER, M. T. STEWART, M. L. GROFT, N. J. PISTORY, *P. J. MCLAUGHLIN
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**Abstract:** The "seductive allure" of neuroscience refers to the phenomenon of judging psychological or health information to be of higher quality when it contains a neuroscientific explanation, even if irrelevant. However, it is not known whether this type of persuasion extends beyond believability ratings, to an influence on behavior change. Moreover, many popular media reports reference what we refer to as the DOSE neurotransmitters: dopamine, oxytocin, serotonin, and the endorphins, while the literature on the seductive allure effect primarily focuses on brain structure, not neurotransmission. In an early study on the influence of neurotransmitter information on social behavior, we found that discussing the social benefits of oxytocin did not affect how participants categorized other people into in- or out-groups. In the present work, a larger sample (N = 173) was recruited, ostensibly to read a news report touting benefits of either larger or smaller in-groups, supported by either a psychological or oxytocin-related explanation. Participants then saw faces and read information about fictitious stimuli presented as both fellow university students (Part 1), and later as nonstudents (Part 2). In both parts, similarity to the stimuli guided social categorization; however, oxytocin information did not affect choices. The lack of effect also contrasted with manipulation checks indicating participants processed the presented information. As a secondary hypothesis, it was proposed that reading that greater inclusion releases oxytocin would reduce the cross-race effect (CRE); the CRE is often manifested as an impairment in recognition memory of those of other races, mediated by altered viewing behavior. While our data reveal a CRE even in the absence of an explicit memory task, we again found no "seductive allure"-like effect on viewing those of different races. Similarly, neuroscience information did not affect physiological arousal to other races, as measured by pupillary dilation (curiously, there was an effect among white liberal Christians suggesting uncertainty about similarity with fellow Christians). In conclusion, while neuroscience information may be positively regarded by the lay public, it is of limited influence in social judgments made by university students.

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**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.21/LLL56

**Topic:** H.02. Human Cognition and Behavior

**Title:** The processing of non-verbal emotional vocalisation (laughter) in people with autism

**Authors: *Q. CAI**, S. CHEN, S. WHITE, S. SCOTT
UCL Inst. of Cognitive Neurosci., London, United Kingdom

**Abstract:** Laughter is a universal non-verbal emotional vocalisation, and it carries various social functions in establishing and maintaining social relations. For example, laughter often serves as a social signal to show agreement and affiliation in conversations. As a form of social emotion, understanding the meaning and intention behind laughter in social contexts is crucial for our social life well-beings. Previous study found greater engagement of brain mentalising area (amPFC and ACC) during passive listening to social laughter than spontaneous laughter in neurotypical population. However, there is insufficient evidence of laughter processing difference in individuals with deficits in mentalising ability, such as people with autism. To investigate this question would extend our knowledge of the role laughter plays in establishing and maintaining social bonds. Moreover, it is essential for the characterisation of the relationship between cognitive and affective mentalising and social interactions in autism. In this study, we use two behavioural tasks and a questionnaire to investigate the processing of laughter in a group of 25 adults with high-functioning autism and matched groups of neuro-typical controls. Firstly, we use an implicit task to determine the implicit processing of the laughter. In this study participants will be asked to rate how funny jokes are. The jokes are read aloud by a professional comedian, and paired with either spontaneous or social laughter samples. Across participants the presentation will be balanced, such that we can determine the effects of the laughter type on the perception of humour in the joke. Followed by a task uses a series of behavioural ratings to determine whether there is any perceptual difference of laughter between groups and how these perceptual differences are modulated by the authenticity of laughter, and by cognitive factors (contagion, valence and arousal). Finally, a 30 items questionnaire is used to investigate laughter behavioural on four principal components (frequency, understanding, usage, and liking). We predict that autistic individuals have difficulties in processing laughter relative to neuro-typical people, suggesting that a high level of cognitive skill such as mentalising ability is crucial in social emotion perception. Future research will investigate the role the mentalising system and orofacial mirror system plays in the processing of laughter in people with autism using neuroimaging techniques (e.g. fMRI).

**Disclosures: Q. Cai:** None. **S. Chen:** None. **S. White:** None. **S. Scott:** None.

**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.22/LLL57

**Topic:** H.02. Human Cognition and Behavior

**Support:** ESRC Studentship ES/J500173/1

**Title:** Heart rate changes in response to people living or dying show evidence of cognitive biases

**Authors: *J. CUTLER**, J. J. MILES-WILSON, D. CAMPBELL-MEIKLEJOHN
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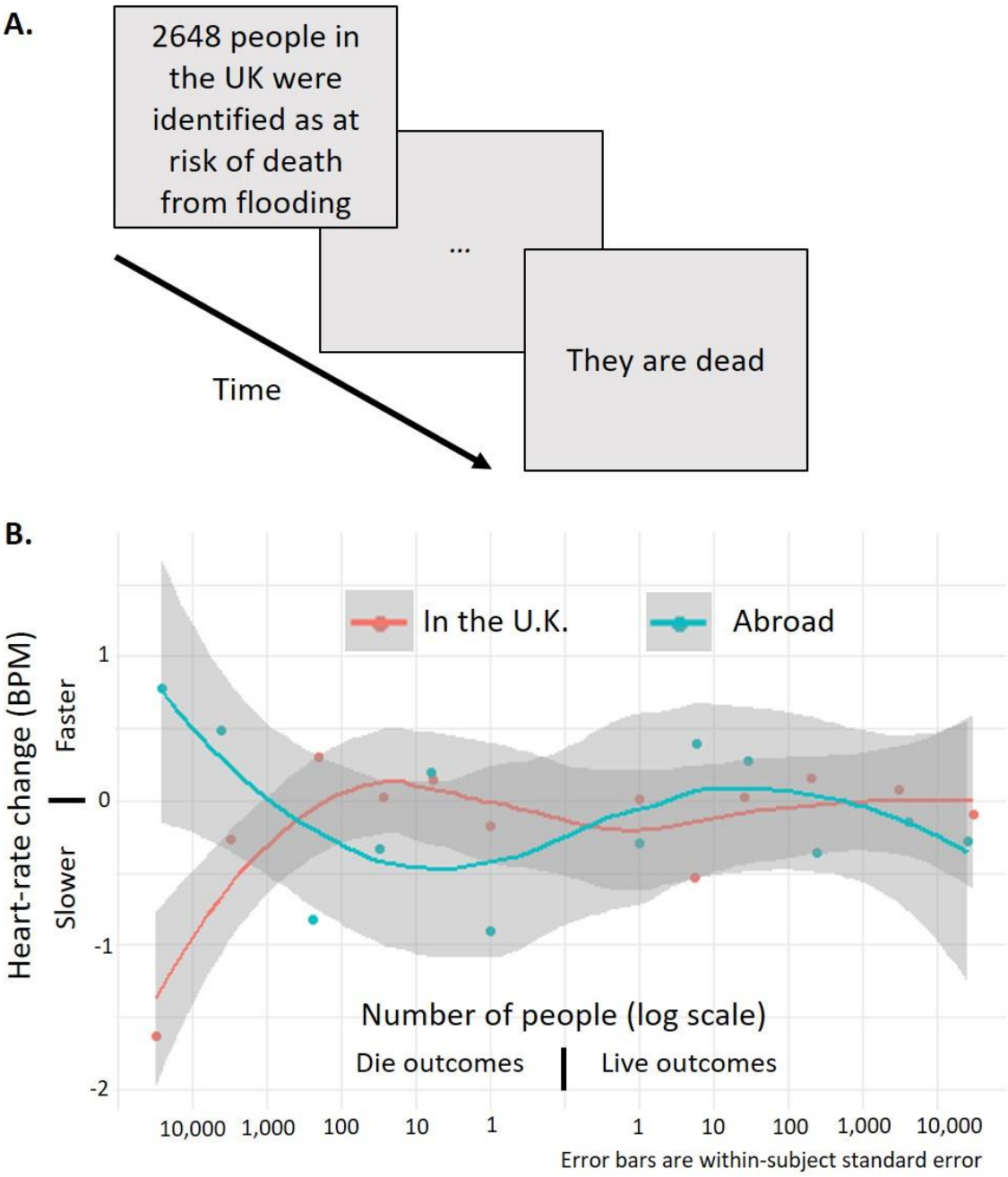
**Abstract:** Emotional responses and prosocial acts are often different toward single victims than to mass suffering. Behavioural experiments also show that factors of identity such as nationality can change our social responses. One theory of numerical biases is that our physiology has not evolved to scale its reactions from individuals to thousands, and thus the influence of arousal-dependent cognition becomes progressively non-linear for large numbers. If such a theory is plausible, biases in valuing lives of others will be reflected in human physiology. We tested how the human heart reacts to learning people in different locations and numbers have survived an ordeal or died.
189 UK residents (138 female, 50 male, 1 other; 122 UK nationality, 65 non-UK, 2 non-disclosed) read about 120 events taken from real news stories in which varying numbers of people were at risk of dying (60 in the UK, 60 abroad). The presentation described the nationality and number at risk, followed by an anticipation period and outcome revealing whether the people lived or died (Figure 1A). Heart rate data were collected using a pulse oximeter. We calculated the change in heart rate ($\Delta$HR) as the difference in beats per minute between the beat before the trial started and the second beat after the outcome.




Mixed models showed that overall ΔHR did not depend on the location of the story or participant nationality. However, the effect of the number of people on ΔHR did differ depending on location and outcome (Figure 1B). The effect of people dying was quadratic in the UK, t(180) = -2.4, p = .016 and linear abroad, t = 2.4, p = .016, while live outcomes were unresponsive to the number of people (3-way interaction $t$ = -2.8, $p$ = .005). Individual differences in these patterns show associations with personality traits. Participants numbed (reduced ΔHR) to abroad deaths over the course of the experiment, but not the UK deaths. Biases in how we value the lives of

others can be detected in heart rate changes within seconds of learning about their fate, supporting the idea that factors affecting the valuation of others are reflected in our physiology.

**Disclosures: J. Cutler:** None. **J.J. Miles-Wilson:** None. **D. Campbell-Meiklejohn:** None.

**Poster**

**794. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders I**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 794.23/LLL58

**Topic:** H.02. Human Cognition and Behavior

**Title:** Eyebrow furrowing: Beyond confusion

**Authors: *P. D. MCGEOCH**[1], A. E. OTI[2], R. L. CROFT[2], J. K. ZHANG[2], V. S. RAMACHANDRAN[2]
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**Abstract:** It is evident that humans furrow their eyebrows when trying to read small text. In this study, we confirmed this observation and demonstrated that humans furrow their eyebrows when presented with a cognitively confusing task, consistent with prior evidence from Rozin and Cohen (2003). In addition, we showed that this facial expression could be reproduced by a visually confusing task (mirror-image text). Finally, we asked whether the furrowing response could be induced by stimuli that were neither cognitively nor visually confusing. Intriguingly, we found that participants furrowed their brows when presented with a cognitively difficult task (mathematics question).

In order to arrive at these preliminary results, we presented eight undergraduate students with cognitive, visual, and auditory stimuli. Each participant was positioned with their chin on a rest and asked to perform three tasks for each condition. These included visually easy tasks (reading large text) as our control for visually confusing (mirror image text) and visually difficult (small text). We also included cognitively easy (demonstrable questions - “What is your name?”) as our control for cognitively difficult (mathematics questions) and cognitively confusing (riddles/nonsensical) questions. We then analysed their facial response when listening to audible (high volume) and nearly-inaudible (low volume) sentences. Each session was video recorded for later facial expression analysis.

Our results show that participants furrowed their eyebrows significantly more during visually confusing and cognitively difficult tasks when compared to their respective controls. This suggests that eyebrow furrowing may have a broader significance than the previous literature demonstrates. In the future, we plan to expand our subject pool and introduce parameters to test the potentially undiscovered reasons for eyebrow furrowing. Specifically, we will ask whether eyebrow furrowing serves as an act of nonverbal communication or even aids in cognition, opening a discussion into the highly contested theory of embodied cognition.

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**Poster**

**795. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 795.01/LLL59

**Topic:** H.02. Human Cognition and Behavior

**Support:** MH094681 and MH101188
IDDRC; U54 HD079125
Shriners Hospitals and the Pathology Department at UCD

**Title:** Chandelier cells contribute to altered gabaergic system in the human cerebral cortex in autism

**Authors: *S. AMINA**[1,2,3], T. HONG[2], V. MARTÍNEZ-CERDEÑO[2,3]
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**Abstract:** To unravel the pathology of the cerebral cortex in patients with autism, we asked whether there is any specific cellular alteration, and if so, which cell type/s are altered. Interestingly, we discovered a decrease in the number of Chandelier (Ch) cells in the human prefrontal cortex in autism. The Ch cell is the only GABAergic interneuron in the cortex whose axon synapses directly on the axonal initial segment (AIS) of pyramidal neurons. Axonal cartridges of Ch cells make multiple synapses on pyramidal cells, consequently Ch cells are the main interneuron subtype that regulates the final output of excitatory projection neurons. This in turn implies that the loss of a single Ch cell may critically impair proper function of projection neurons and of the cerebral cortex as a whole. Therefore, we asked whether there is a decrease in the number of Ch cell cartridges and in the number of synaptic boutons per cartridge in autism. We found that in cortical Brodmann Area 46, there is a significant decrease in the number of GAT1 GABAergic cartridges in autistic cases compared to the controls. Currently, we are analyzing the amount of GAT1, GAD67 and VGAT proteins in Ch cartridges in Broadmann Areas 9, 47, 45 and 44, in autism and control cases. These areas are reported to show cognitive impairment in autism. This study will allow us to explore the hypothesis that Ch cell pathophysiology contributes to the alterations in function of the GABAergic system that have been reported in the autistic brain.

**Disclosures: S. Amina:** None. **T. Hong:** None. **V. Martínez-Cerdeño:** None.

**Poster**

**795. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 795.02/LLL60

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIMH Grant MH094681 and MH101188
The MIND Institute IDDRC; U54 HD079125
The Shriners Hospitals
The Pathology Department at UCD

**Title:** Chandelier cells and an altered GABAergic synaptic system in the human prefrontal cortex in autism

**Authors: *T. HONG**[1], S. AMINA[2], J. REGALADO[3], V. MARTINEZ-CERDENO[1]
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**Abstract:** Autism has been correlated with a dysregulation of the excitation/inhibition balance in the cerebral cortex. Recently, we found a significant decrease in an inhibitory interneuron subtype called the chandelier cell (Ch) in the human prefrontal cortex in autism. The Ch cell is the only subtype whose axons synapse on the axon initial segment (AIS) of excitatory pyramidal cells, thus directly regulating the pyramidal excitatory output. In addition, a single Ch cell forms axo-axonic synapses on hundreds of different pyramidal cells, playing a synchronizing role in brain activity. Therefore, examining alterations to the synapses between the Ch cell axon terminal boutons and the pyramidal cell AIS can uncover changes leading to imbalanced brain activity in autism. We hypothesized that in autism, Ch cells have a decreased number of terminal boutons; we also hypothesized that the postsynaptic pyramidal cell contains fewer $GABA_A$ receptors in its AIS. In prefrontal cortex tissue of human cases with autism, we used immunohistochemistry to label Ch cell terminal boutons as well as $GABA_A$ receptors in the pyramidal cell AIS, and we used ImageJ (NIH) to quantify the amount of protein. We found a decreased amount of $GABA_A$ receptor subunit α2 protein in the pyramidal cell AIS, in Brodmann Area (BA) 46. We are currently examining BA9, BA46, and BA47 in control cases and cases with autism, as these are areas associated with the cognitive abnormalities in autism. Through this study, we will help illuminate the link between changes to the axo-axonic inhibitory synapse in the human prefrontal cortex and the neuropathology of autism.

**Disclosures: T. Hong:** None. **S. Amina:** None. **J. Regalado:** None. **V. Martinez-Cerdeno:** None.

**Poster**

**795. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 795.03/LLL61

**Topic:** H.02. Human Cognition and Behavior

**Support:** CIHR NET-54014, 200810MOP-203919
Canadian Foundation for Fetal Alcohol Research
University of Toronto

**Title:** Social problem solving in youth with fetal alcohol spectrum disorder and the role of autobiographical memory

**Authors: *S. AGNIHOTRI**[1], J. ROVET[3], S. SUBRAMANIAPILLAI[4], C. RASMUSSEN[5], D. CAMERON[2], J. RYAN[6], M. KEIGHTLEY[1]
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**Abstract: Background/Rationale:** Numerous studies have found that adolescents with Fetal Alcohol Spectrum Disorder (FASD) struggle with social cognition. An underlying issue in the development of autobiographical memory (AM) may explain why these youth encounter such difficulties. However, it has not yet been determined whether AM is impaired in youth with FASD**.** Thus, the specific objectives of the current study were to: (1) compare AM recall between adolescents living with a diagnosis of FASD and a group of typically developing control (TDC) participants and; 2) determine whether AM recall could predict performance on tasks designed to measure social skills. **Methods:** A two-group comparison study was conducted with 18 adolescents with FASD and 18 age- and sex-matched TDC participants (range = 13 - 18 years, 56% male). To address objective (1), the groups were compared on the number and types of AM details that they recalled using the Children's Autobiographical Memory Interview. To address objective (2), theory of mind and social problem solving were investigated using clinical and experimental measures. Regression analyses were completed to understand whether the number and type of AM details recalled could predict social skills performance. **Results:** Adolescents with FASD exhibited weaknesses with AM, including the recollection of event details (e.g. who was there, sequencing of events) and perceptual/sensory details from past experiences. Moreover, AM recall was found to significantly predict social problem solving performance. **Conclusions:** Deficits in AM recall in youth with FASD limit the variety and specificity of details available for them to draw upon from past social experiences. In turn, social development is impeded when these youth attempt to apply past experiences to novel situations

or to experiences with perceived similarity to previously experienced events. Understanding the function of AM in youth with FASD will enable researchers to identify mechanisms that may affect social cognition in this population. We also hope to inform the development of new interventions that are unique to the needs of adolescents with FASD and can adapt effective interventions from other populations relating to AM.

**Disclosures: J. Rovet:** None. **S. Subramaniapillai:** None. **C. Rasmussen:** None. **D. Cameron:** None. **J. Ryan:** None. **M. Keightley:** None.

**Poster**

**795. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 795.04/MMM1

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH NIMH R01MH107513
NIH R01MH11629
NIH R37HD090153

**Title:** Dynamic cross-brain neural coupling of face processes reflects the transfer of shared face information

**Authors: *J. HIRSCH**[1,2,3,6], J. NOAH[1], X. ZHANG[1], S. DRAVIDA[4], A. NAPLES[5], Y. ONO[1,7], J. MCPARTLAND[5]
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**Abstract:** Understanding the neural basis of cross-brain dynamic coupling during interpersonal interactions is an emerging theoretical frontier in social neuroscience. This coupling occurs when the neural patterns of a sender match the neural patterns of a receiver, and it has been proposed that these matched patterns represent shared neural processes including dynamic exchanges of information (Hasson, et al, 2004). This model predicts that coupling of a specific neural system (such as face processing) will increase with shared information (such as in mutual live face viewing). A two-person neuroimaging paradigm using functional near infrared spectroscopy (fNIRS) was used to acquire whole-brain hemodynamic signals on 15 dyads during real face-to-face contact and during viewing of a dynamic video-face also wearing fNIRS optodes. Although both conditions included gaze at a naturally moving face, only the real face-to-face condition included reciprocal and socially informative face and eye movements. Comparison of neural coupling for the two conditions provides a test of the “shared information for face processing”

hypothesis. Standard general linear model, GLM, comparisons were performed prior to the neural coupling analyses. Neural coupling was determined by wavelet analyses that compared cross-brain correlations with wavelet kernels for signals originating from 12 brain regions representing anatomically similar clusters of detector channels as previously described for studies of eye-to-eye contact (Hirsch, et al, 2017). Consistent with the known functional sensitivity of the right temporal-parietal junction for social processing (Carter & Huettel, 2013), the right temporal-parietal junction including the angular gyrus was more active during the real face than the video face ($p < 0.05$, FDR corrected) condition. As predicted, neural coupling for the real face-to-face condition compared to the video face condition was increased between angular gyrus and fusiform gyrus ($p < 0.002$), a recognized component of the dynamic face processing system (Pitcher,et al, 2011). There was no evidence for a difference in neural synchrony between the two conditions for any other pairs of brain regions. These findings advance a systems-specific dynamic neural coupling model for live face processing in which signals from canonical face and social processing systems are synchronized across brains during face-related interactions.
References: Hasson, et al, Science, 2004; Hirsch, et al, Neuroimage, 2017; Carter and Huettel, Trends in Cognitive Sciences, 2013; Pitcher, et al, Experimental Brain Research, 2011.

**Disclosures: J. Hirsch:** None. **J. Noah:** None. **X. Zhang:** None. **S. Dravida:** None. **A. Naples:** None. **Y. Ono:** None. **J. McPartland:** None.

**Poster**

**795. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 795.05/MMM2

**Topic:** H.02. Human Cognition and Behavior

**Support:** John Templeton Foundation's Positive Psychology and Neuroscience

**Title:** Brain models of empathy and compassion in a randomized trial of compassion meditation

**Authors: *J. ASHAR**[1], J. R. ANDREWS-HANNA[2], S. DIMIDJIAN[3], T. D. WAGER[4]
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**Abstract:** What thoughts and feelings motivate compassion behavior, and can they be predicted from brain activity? And how does compassion training affect these processes? We conducted three behavioral and brain investigations addressing these questions. In Study 1 ($N = 200$), we developed a model predicting compassionate behavior, operationalized as real-money charitable donation, from a linear combination of six self-reported *feelings* and *attributions* with high cross-

validated accuracy, $r = .67$, $p = .0001$. In Study 2 ($N = 67$), we used fMRI coupled with machine learning analyses to develop whole-brain models predicting two of these feelings—empathic care and personal distress—with high cross-validated accuracy ($r$s = .59 and .63, respectively, $p$s < .00001). Empathic care (the warm desire to affiliate) was preferentially associated with nucleus accumbens and medial orbitofrontal cortex (mOFC) activity, while distress was preferentially associated with premotor and somatosensory cortices. Both the care and distress models predicted later trial-by-trial charitable donations. In Study 3 ($N = 58$), a randomized controlled trial, we tested the effects of a compassion meditation (CM) training program on the behavioral and brain models of compassion developed in Studies 1 and 2. We compared a smartphone-based CM program to 2 conditions—placebo oxytocin and a familiarity intervention—to control for the expectancy effects, demand characteristics, and familiarity effects intrinsic to CM. Relative to control conditions, CM increased charitable donations, and changes in the Study 1 model of feelings and attributions mediated this effect ($p_{ab} = .002$). CM also led to increased activity in the subgenual cingulate cortex, relative to controls. Overall, this work contributes novel predictive models of compassion at the psychological and brain levels of analysis, and informs our understanding of the change processes and active ingredients of CM.

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**Poster**

**795. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 795.06/MMM3

**Topic:** H.02. Human Cognition and Behavior

**Title:** Neural substrates and economic costs of social avoidance

**Authors: *J. W. SCHULTZ**[1], T. WILLEMS[1], M. GÄDECKE[1], G. CHAKKOUR[1], A. FRANKE[1], B. WEBER[2], R. HURLEMANN[1]
[1]Psychiatry, [2]Ctr. for Econ. and Neurosci., Univ. of Bonn, Bonn, Germany

**Abstract:** Interacting with other people is a major source of happiness for most people. While many people spend money to seek human social interactions, people with social anxiety avoid them, at great cost to their private and professional life. To quantify social avoidance, we determined the value (certainty equivalent) of a simple game with uncertain outcome and social-emotional feedback, as a proxy for a simple social interaction. For more socially anxious participants, playing the game against a person was worth 10% less than playing the game against a computer (control condition), while the reverse was true for more sociable participants. These findings were (i) not due to general risk aversion differences as the value of the game against the computer did not vary with anxiety; (ii) specific to social anxiety and not general

anxiety, depression or autistic traits; and (iii) not attributable to differences in the valuation of the feedback as subjective valence ratings did not vary with anxiety. Activation in the left amygdala of more anxious participants was higher when considering whether to play against a human compared to a computer opponent; this difference was absent in sociable participants. Decision to play or not could be decoded from the BOLD response pattern in the right amygdala. At the outcome stage of the game, right nucleus accumbens response to wins against human opponents was higher in sociable compared to anxious participants; no such difference was found for wins against the computer. Effective connectivity between nucleus accumbens and both anterior cingulate and bilateral amygdalae during the decision was affected by anxiety - again only in trials with human opponents. Based on these results, we propose a neural substrate of social approach and avoidance behavior.

**Disclosures: J.W. Schultz:** None. **T. Willems:** None. **M. Gädecke:** None. **G. Chakkour:** None. **A. Franke:** None. **B. Weber:** None. **R. Hurlemann:** None.

**Poster**

**795. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 795.07/MMM4

**Topic:** H.02. Human Cognition and Behavior

**Support:** Russian Science Foundation Grant no. 18-11-00336

**Title:** Using brain imaging techniques to develop and validate a cognitive-architecture model, capable of producing human-like socially-emotional behavior in virtual environments

**Authors: *A. V. SAMSONOVICH**[1], V. L. USHAKOV[2]
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**Abstract:** The end-goal of this study is to develop and validate empirically a computational model based on the emotional Biologically Inspired Cognitive Architecture (eBICA: Samsonovich, 2013), describing socially-emotional cognition. Of particular interest are those cognitive processes and variables that underlie human behavior and decision making in a rich social environment, such as interactive videogames. The model variables responsible for such functionality include emotional appraisals of actions and actors, relationships of trust, leadership and competition. Comparing these variables together with model parameters against physiological measures that characterize cognition during game playing is the key to the design and validation of the model. In order to be able to do such comparison, one needs first to map physiological brain activity states to psychological states described by the model. This semantic mapping of brain activity is developed through statistical analysis of recorded brain activity

evoked by emotional stimuli, such as emotional images and behavioral acts. Having the map available, one can test model predictions not only at the behavioral level, but also at the level of internal variables of the model. The eBICA model can be validated based on this approach via comparison of the computed model dynamics and the recorded human brain dynamics, along with model and participant behavior and other measures. Employed brain imaging methods include fMRI, EEG, and eye-tracking. Methods of data processing involve the dynamic connectivity calculation and the use of regressors based on EEG and eye-tracking data. In an fMRI study, effective connectivity can be measured using Structural Equation Modeling, Granger Causality Analysis, Transfer Entropy and Dynamic Causal Modeling. The recording and analysis of eye movements provides access to the rapid unconcscious information processing. This approach has been applied to fMRI data collected in our study, using 16 subjects. Overall, results obtained here using different methods of semantic mapping appear to be compatible with each other, and support the eBICA model. Comparative strengths and weaknesses of alternative approaches are discussed. The obtained semantic map provides an insight into the interpretation of brain activity recorded via fMRI, and will be further used for evaluation of models of human emotional cognition. This work was supported by a Russian Science Foundation Grant no. 18-11-00336.

**Disclosures: A.V. Samsonovich:** None. **V.L. Ushakov:** None.

**Poster**

**795. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 795.08/MMM5

**Topic:** H.02. Human Cognition and Behavior

**Title:** Brain electrical activity during joint action. Effects of feedback

**Authors: *A. Q. ANGULO-CHAVIRA**[1], J. RAMOS-LOYO[1], M. MÜELLER[2], A. A. GONZÁLEZ-GARRIDO[3]
[1]Univ. de Guadalajara, Guadalajara, Mexico; [2]Univ. Autónoma del Estado de Morelos, Morelos, Mexico; [3]Univ. de Guadalajara., Guadalajara, Mexico

**Abstract:** When people act alone, they can coordinate their action by internal mechanisms; however, when acting together in a group, they need to know how others are doing. Information about others actions allow adjusting joint behaviors simultaneously. The aim of the present research was to identify the effects of joint action and feedback in motor coordination and brain activity. Twenty male dyads performed a visual detection task during EEG recording. They were instructed to press a button in response to visual stimuli in four conditions: individual without feedback (IN), individual with personal and interpersonal feedback (IF), joint without feedback (JN), joint with personal and interpersonal feedback (JF). In individual conditions, participants

should press the button as quickly as their previous answer. In joint condition, participants must press the button as quickly as their partner. Feedback indicated response time in a color code and, it was presented after participants' response. Event related spectral perturbation was computed in response interval. Non-parametric permutation test was applied to behavioral and electrophysiological data. As expected, results showed that information about the other person improved behavioral performance in the joint conditions, in terms of correct responses and synchronization between participants. Furthermore, participants presented higher power spectrum in posterior bilateral theta/alpha band at 300 ms in the JF than JN conditions. Also, participants presented higher power spectrum in posterior right theta/alpha band at 300 ms in IF than IN conditions. Results demonstrated that interpersonal feedback modulated individuals´ information processing and goal-directed action. These findings suggest that posterior theta/alpha oscillations index information processing about others during joint action.

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**Poster**

**795. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 795.09/MMM6

**Topic:** H.02. Human Cognition and Behavior

**Title:** Depression and the mirror neuron system: A correlative study on mirror neuron functioning and the social impairments observed in depression

**Authors: *M. WIDDOWSON**[1], C. KIM[1], Y. TONG[1], C. INACAY[1], J. PINEDA[1], F. SINGH[2]
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**Abstract:** The discovery of the mirror neurons in primates and the mirror neuron system (MNS) in humans has provided hypotheses on how biological agents understand others' emotions by integrating action and perceptual networks in the brain. In particular, social "mirroring" has been shown to be abnormal in certain psychiatric disorders, including autism and schizophrenia. While few studies exist, there is evidence to suggest that MNS abnormalities exist in depressive disorders. In our pilot study, we explored the relationship between social functioning (empathy, theory of mind, and emotion recognition) and MNS activity, as indexed by the suppression of mu rhythms (MS), in subjects with depressive symptoms. We hypothesized that symptom severity would correlate with reduced social functioning, and decreased MS, implying reduced MNS function. Thirty-two subjects, 18-25 years old, from the University of California, San Diego were recruited using an online screening system. Subjects completed Beck's Depression Inventory (BDI) online and were assigned to two groups, non-depressed (ND, BDI score: 0-13)

or mild to moderately depressed (D, BDI score 14-28) using the depressive symptom scale. Subjects completed self-report questionnaires (STAI, IRI, ECR-R), tasks (Dot Probe, TASIT), and performed a modified version of the Reading the Mind in the Eyes Test (RMET). Scalp EEG was recorded during RMET and resting state (RS).Mild to moderately depressed subjects showed significantly reduced social cognition (TASIT: $p<0.05$) compared to non-depressed subjects. Additionally, depressive symptoms were negatively correlated with social cognition (TASIT: $R=-0.51$; $p<0.01$), empathy (IRI EC: $R=-0.37$; $p<0.05$) and perspective taking (IRI PT: $R=-0.37$; $p<0.05$). There was no correlation between symptoms and negative attention bias on the Dot Probe task. On EEG, the D group showed greater variability in alpha/mu asymmetry during RS. During eyes open condition, D group showed more right frontal alpha/mu asymmetry; in eyes closed condition, D group showed more posterior alpha/mu asymmetry, reduced left frontal alpha/mu asymmetry, and interhemispheric alpha/mu hypo-coherence. These preliminary results imply that depressive symptoms correlate with decreases in social functioning and impaired MNS function as measured by EEG mu suppression.

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**Poster**

**795. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 795.10/MMM7

**Topic:** H.02. Human Cognition and Behavior

**Support:** Incubators Award, Duke Institute for Brain Sciences

**Title:** Neural activity during episodic counterfactual thinking in anxious and non-anxious individuals

**Authors: N. PARIKH**[1], K. S. LABAR[2], M. Z. ROSENTHAL[3], J. DEROSA[4], G. W. STEWART[5], *F. DE BRIGARD[6]
[1]Psychology & Neurosci., [2]Ctr. for Cognitive Neurosci., [3]Psychiatry and Behavioral Sci., [5]Duke Inst. for Brain Sci., [6]Psychology, [4]Duke Univ., Durham, NC

**Abstract:** When people mentally revisit past regretful decisions they often can't help but imagine alternative ways in which such events could have occurred instead. Normally, these episodic counterfactual thoughts (eCFT) are momentary and fleeting. However, for individuals with anxiety, eCFT about past regretful decisions tend to be persistent and repetitive. Yet, little is known about neural differences between anxious and non-anxious individuals during eCFT. Moreover, less is known about the neural effects of generating eCFT on the autobiographical memories (AM) they are derived from. The current study explores these issues. 34 individuals

(15 anxious) participated in this 3-session study. In session 1, participants reported 45 AM of past regretful decisions. A week later, in session 2, participants first remembered their AM. Then, their AM were assigned to one of three conditions, with 15 AM per condition. In the *upward* eCFT condition, participants imagined alternative better ways in which the cued memory could have occurred instead. In the *downward* eCFT condition, participants imagined alternative worse ways in which the cued memory could have occurred. And in the *remember*condition, participants simply moved on to the next trial after remembering the memory. During this session participants undergo fMRI. Finally, in session 3, participants are asked to re-simulate all 45 AM and to recall the condition in which each memory was presented during session 2. This session also occurred while participants underwent fMRI. Additionally, online ratings of valence, arousal and detail were collected. The fMRI data from sessions 2 and 3 were analyzed within a multivariate framework employing a hypothesis-free mean-centered spatiotemporal partial least squares analysis. This approach revealed two significant latent variables reflecting two distinct patterns of brain activation. The first pattern identified activity associated with the generation of eCFT common between individuals with and without anxiety, including anterior cingulate, and inferior temporal and frontal gyri. The second pattern identified differences in brain regions engaged during AM as a function of having been previously reactivated either in an upward or a downward eCFT. Importantly, this pattern also shows that precuneus and middle frontal gyrus, associated with AM reactivated in the downward eCFT condition, are more active for highly anxious individuals relative to controls. Together, these results suggest that despite strong commonalities in brain activation during eCFT in individuals with and without anxiety, the neural effects of these reactivations on the original AM differ.

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**Poster**

**795. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 795.11/MMM8

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH R37NS21135 (RTK)

**Title:** Feeling comfortable: Amygdala and orbitofrontal cortex contributions to regulating interpersonal distance - an intracranial EEG study

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**Abstract:** Humans are a social species. We universally modulate our interpersonal distance (IPD) from one another to regulate feelings of threat or safety. In return, this behavior powerfully communicates pro- and anti-social signals to others. Lesion studies and fMRI data have highlighted the amygdala and orbitofrontal cortex (OFC) as key structures involved in the regulation and perception of IPD. However, the underlying neural mechanisms remain unknown. Here, we used intracranial electroencephalography (iEEG) to examine the spectrotemporal dynamics within and between the OFC and amygdala while subjects (n = 9) watched separate short videos of either humans or objects approaching and subsequently rated their level of discomfort. In a separate set of trials, subjects were allowed to stop the approaching stimuli when they began to feel uncomfortable, and this data was used to estimate subjects' individual distance thresholds for comfort (comfort distance) during iEEG recording. Time-frequency analysis revealed a significant increase in high frequency band (HFB; 70-150 Hz) power in OFC electrodes after the approaching human surpassed the comfort distance. Indicative of a neural signal warning of conspecific approach, HFB activity in OFC increased as the human approached . Consistent with early threat-detection models, a burst of HFB activity was observed bilaterally in the amygdala that preceded OFC activation. Critically, none of these effects were consistently observed in trials where subjects viewed objects approaching. These findings establish that the amygdala and OFC are critical nodes in the signaling of human social approach. Moreover, the temporal profile of activity further suggests that the amygdala first registers when someone's personal space is violated by another person, and subsequent, higher-order processing in OFC dictates the decision of social distance separation.

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**Poster**

**795. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 795.12/MMM9

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIMH MH080838

**Title:** Insights from the social virtual brain: Right hemisphere lateralization of EEG power spectra may indicate stability of social coordination

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**Abstract:** Studies of virtual partner interactions (VPI) in which humans coordinated their finger movements with an avatar indicate that when the two partners have opposite intentions new behavioral patterns may emerge spontaneously to stabilize social coordination. Although such interactions are known to elicit a significant emotional response and mediate attribution of agency or intentionality to the virtual partner, little is known about the neural mechanisms supporting these behaviors. Here, we use the Virtual Brain, a computational platform for multiscale simulations of whole brain dynamics, to investigate features of neural activity when a virtual subject engages in coordination patterns similar to those found in VPI experiments. The virtual brain consisted of 76 cortical regions governed by the Stefanescu-Jirsa 3D neural mass model with intrinsic and large scale connectivity parameters chosen to secure a standard EEG alpha pattern at rest and elevated EEG power over the motor cortex in response to sustained movement inputs. Visual observation of the social partner's movement was represented by a sinusoidal forcing signal to bilateral primary visual cortices while the self-movement was accounted for by a similar signal of identical frequency applied to the (contralateral) left motor cortex. We found that when the amplitude of in-phase coordination decreases by more than 50%, the lateralization of the EEG power spectra (in the 10Hz frequency range) changes from right to left hemisphere and becomes unstable for lower coordination amplitudes leading to a switch to anti-phase coordination . Such modifications are associated with a significant re-organization of the correlated and anti-correlated neural network activity. New patterns of coordination consistent with the emergent strategies observed in VPI experiments restore the EEG power in the right hemisphere suggesting that this might be a signature of stable social coordination. We further explored how this signature might be altered when the large scale brain connectivity undergoes degradation consistent with neurodegenerative diseases such as multiple sclerosis or Alzheimer disease. We found that changes larger than 33% in either the speed of conduction or the scaling of global coupling led to loss of EEG power in the right hemisphere in favor of a more bi-lateral distributed pattern. Such signatures may be further used for the development of new diagnosis and treatment strategies to detect pathological conditions and improve social coordination.

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**Poster**

**795. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 795.13/MMM10

**Topic:** H.02. Human Cognition and Behavior

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**Title:** A dissociable, distributed network estimated within individuals linked to theory-of-mind

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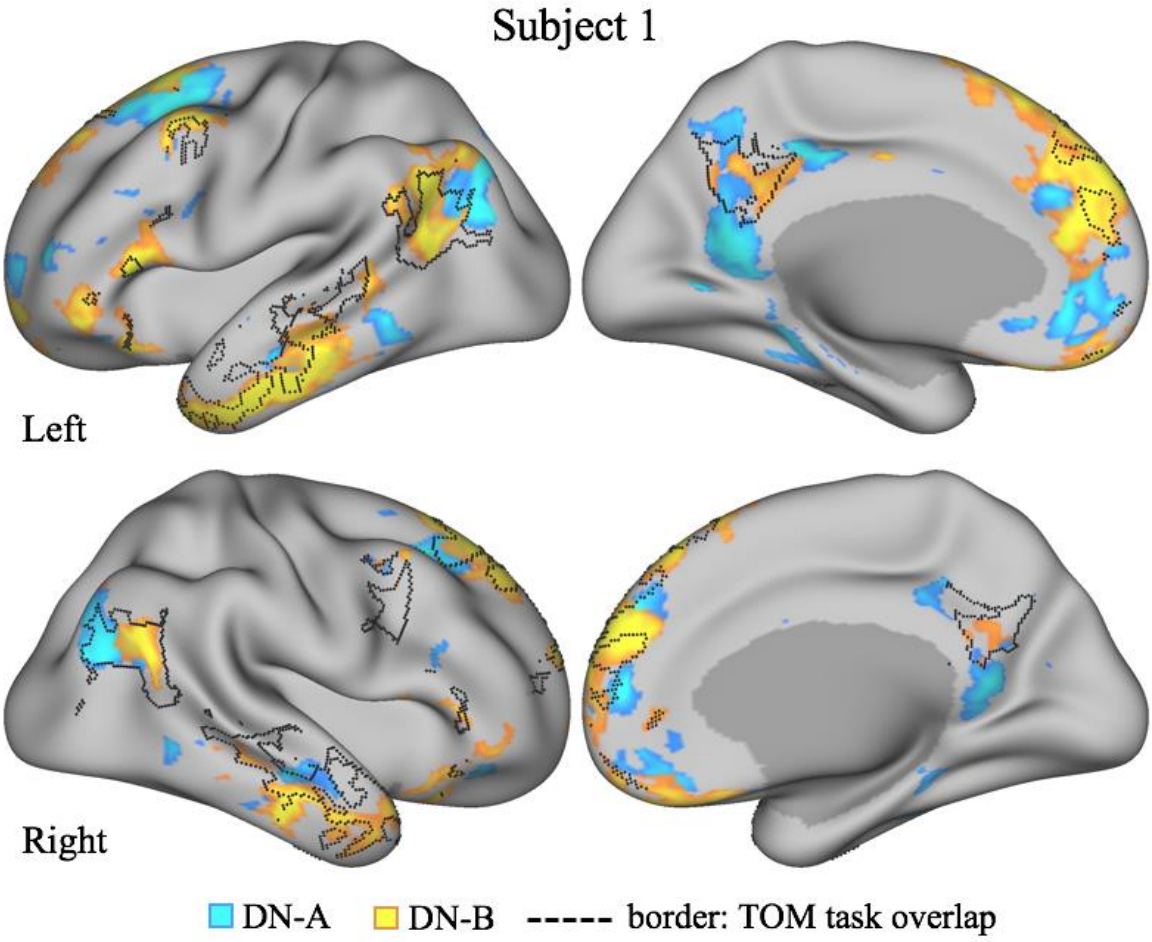
**Abstract:** The human association cortex is organized into multiple large-scale, distributed networks. Intrinsic functional connectivity (FC) analysis of repeatedly scanned individuals recently revealed a pair of interwoven, distributed networks within the boundaries of the canonical group-defined default network (DN; Braga & Bucker, 2017). Whether these newly dissociated networks, called DN-A and DN-B for convenience, preferentially subserve distinct functions remains unclear. We leveraged distinctions between DN-A and DN-B to probe whether theory of mind (TOM) and episodic retrieval tasks differentially recruit these networks. Activation of a posterior region of the inferior parietal lobule (IPL), seen in the hippocampal-coupled DN-A, has been associated with retrieval of episodic memories; whereas recruitment of an anterior portion of the IPL that extends into the temporoparietal junction (TPJ), seen in DN-B, has been linked to TOM. Six adults ($M_{age}$ = 22.2 years; 2 male) were each scanned across 4 days at high resolution (2.4mm) in sessions designed to chart individualized network organization (via FC analysis) and task-based activation. Two retrieval tasks (118min total) and two TOM localizer tasks (40min total; Dodell-Feder et al., 2011; Jacoby et al., 2016) were administered across sessions to define regions recruited for episodic retrieval and mentalizing. More than 56min of resting-state data were collected per subject and averaged for FC analysis; functional data from all sessions were registered and resampled to 1mm isotropic resolution and smoothed at 2mm FWHM. DN-A and DN-B were reliably identified using seed vertices placed in the prefrontal cortex, replicating the network organization discovered previously. Initial analysis of the TOM tasks reveals evidence of overlap with DN-B across multiple widely distributed zones of association cortex (see Figure). Ongoing analyses seek to determine whether dissociable networks underlie different forms of internally-constructed mentation.

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**Poster**

**795. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders II**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 795.14/MMM11

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIMH MH080838

**Title:** Transaction of agency between self and other: An fMRI study of social coordination

**Authors: *R. A. STEFANESCU**[1], M. ZHANG[1], A. FUCHS[1,2], F. L. STEINBERG[1,3], E. TOGNOLI[1], J. A. S. KELSO[1,4]
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**Abstract:** The virtual partner interaction (VPI) paradigm, in which a human subject interacts in real time with a virtual avatar controlled by the Haken-Kelso-Bunz model of coordination, is a principled approach that allows for parametric exploration of human social behavior. Previous studies suggest that when the two partners coordinate behavior with opposite intentions (e.g. their movements are phase-locked but one intends in-phase, the other antiphase), asymmetry in coupling strength plays an important role in the behavioral outcome and the subjective perception of agency. To better understand the neural mechanisms supporting this transaction of agency between self and other, we use fMRI to monitor brain activities in healthy subjects as they perform a finger movement coordination task with a virtual partner. A parameter controlling the virtual partner's coupling strength was varied from low (-0.13), medium (-0.25) to high values (-3). We collected fMRI recordings from 19 subjects using a block design protocol (TR=2s; TE = 35ms, Flip Angle=$90^0$, FOV=24, Number of Slices=36, Slice Thickness=4, Spacing=0) and analyzed the data in AFNI and Matlab. As expected, several clusters from visual associative and secondary visual cortices (especially right) were modulated in all coupling conditions. Additional areas in these regions as well as in supplementary motor area (SMA) were recruited during coordination with medium and strong coupling strengths. Interestingly, medium coupling uniquely activated the left thalamus. When different conditions were directly contrasted, left and right SMA was significantly activated for low/high and medium/high differences. In addition, for low/high coupling contrast, activation was significant in the inferior frontal gyrus, inferior parietal lobe, left cerebellum and right thalamus. Together, these results suggest that SMA may encode various levels of coupling from the virtual partner while stronger social coordination may recruit the functional contribution of additional brain areas known to be involved in higher cognitive functions including executive control of behavior, working memory and emotion processing. This study shines new light on the brain activity mediating the sense of agency and distinguishing between self and others and may open new opportunities for treating pathologies in which such brain functions are impaired or dysregulated.

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**Poster**

**795. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 795.15/MMM12

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIH grant MH113134

**Title:** Cerebral responses to self-agency during social inclusion and exclusion in a cyberball game

**Authors: *W. WANG**, C.-S. R. LI
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**Abstract:** Social interaction is central to emotional well-being. Many studies have employed a Cyberball task to investigate brain responses to social inclusion and exclusion and the findings highlighted regional activities in association with positive and negative social emotions. Social interaction involves self-agency, or a sense of control that engages subjective awareness of initiating, executing, and controlling one's own volitional actions. Self-agency is critical to social interaction and individuals with social anxiety find it particularly hard to initiate social interactions. On the other hand, extant imaging studies have not specifically addressed cerebral responses to self-agency during social interaction. We studied 21 adults in a mixed block design and contrasted events of observing, receiving, and initiating ball boss during three different scenarios of a Cyberball task: observation (OB), where participants observed two fellows playing; fair game (FG), where participants were involved in 3-way ball tossing with equal odds of participation; and exclusion (EX), where participants were excluded from the game following a few missed catches. In both FG and EX in contrast with OB, receiving and tossing a ball engaged a wide swatch of fronto-parietal and subcortical structures. In particular, receiving as compared to tossing a ball involved activation of the ventral striatum (VS), medial orbitofrontal cortex (mOFC) and the supplementary motor area, and the activities in the VS and mOFC appeared to be stronger during FG than during EX. These findings support distinct regional processes of self-agency during social interaction and may help identify neural markers of social anxiety.

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**Poster**

**795. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders II**

**Location:** SDCC Halls B-H

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**Topic:** H.02. Human Cognition and Behavior

**Support:** Consejo Nacional de Ciencia y Tecnología, Fronteras de la Ciencia 2015 No. 225
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Consejo Nacional de Ciencia y Tecnología (CVU: 779254)

**Title:** Theory of mind and its structural neural correlate

**Authors: *M. GIORDANO**[1], F. LIZCANO-CORTÉS[1], G. L. LICEA-HAQUET[1], M. MONTALÀ-FLAQUER[2], J. GUÀRDIA-OLMOS[2]
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**Abstract:** The theory of mind (ToM) is defined as the ability to attribute mental states to others as well as to understand that these may differ from ours and can be divided in two components, an affective component, that involves the comprehension of emotions, feelings or affective states and a cognitive component that implies the understanding of beliefs, thoughts or intentions. Among the different tests that have been used to test the affective component of ToM, the Reading the Mind in the Eyes Test (RMET) designed by Baron-Cohen (2001) is one of the most widely used. A newly developed test by Dodell-Feder et al. (2013), the Short Story Task (SST), uses naturalistic narrative stimuli to evaluate the cognitive component of ToM. Previous studies by Sato et al., (2016) have analyzed structural magnetic resonance images and obtained gray matter volume using voxel-based morphometry. They correlated performance on the RMET with gray matter volume and found a positive correlation in the dorsomedial prefrontal cortex, the inferior parietal lobe (temporoparietal junction), and the precuneus of the left hemisphere, in agreement with previous functional neuroimaging studies. In the present study, we evaluated the correlation between cortical thickness (Freesurfer©, Matlab©), and the affective and cognitive components of ToM, and calculated the connectivity density between regions of interest (ROIs) using this structural measure. We obtained structural magnetic resonance images from a sample of Mexican college students (n=24, 12 men; age =23.13±2.88 years old), and correlated their performance on the RMET and mental state reasoning scores of the SST with cortical thickness. For the right hemisphere we found a significant positive correlation between RMET and cortical thickens in the pericallosal sulcus, negative correlations with the inferior temporal gyrus, and the temporal pole. Significant positive correlations were found between the SST and cortical thickness in the inferior precentral sulcus, and inferior frontal gyrus; and a significant negative correlation with the lateral temporal-occipital gyrus. For the left hemisphere, we found significant positive correlations with cortical thickness in the transverse temporal sulcus, the rectus gyrus, and the suborbital sulcus, and significant negative correlations with the anterior cingulate gyrus and sulcus. A density of connectivity analysis was calculated for the 148 obtained ROIs from the extraction of cortical thickness. We found significant differences in the connectivity density between high and low performance individuals selected according to their scores on the ToM tests.

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**Poster**

**795. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 795.17/MMM14

**Topic:** H.02. Human Cognition and Behavior

**Support:** the MEXT-Supported program for the Strategic Research Foundation at Private Universities, 2014–2018

**Title:** Occupational abilities and functional networks estimated through resting state fMRI

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**Abstract:** (**Introduction**) The successful human life in modern society requires proper choice of occupation. Therefore, it is very important for people to know their abilities and develop career plans that best suit their abilities. Traditional test batteries have been used for evaluating occupational abilities but it is not known about what brain functions are related to the evaluated abilities by the test batteries. In this study, we attempted to identify functional networks related to occupational traits by resting state fMRI. (**Method**) The experiments consisted of a psychometric experiment and fMRI experiment. In psychometric experiment, we used a General Aptitude Test Battery (GATB) for measuring occupational abilities. The psychometric experiment and fMRI experiment were performed in separate days. For MRI experiment all subjects were scanned by 3T MRI (Siemens) in two sessions that included structural (T1) and functional imaging (resting-state fMRI). Structural images were acquired by MPRAGE sequence. Resting-state fMRI data were acquired by a multiband EPI sequence (TR 1s, 64x64 matrix, 3.4x3.4x3.4 resolution and 34 slices, acquisition time 480s). (**Results**) We chose 19 occupational abilities from GATB and attempted to identify functional networks for those abilities. For identification of functional networks, we made 272 functional ROIs on the basis of previously reported two templates (Dosenbach and Harvard templates). ROI-based network analysis, including network-based statistics, was performed and revealed 19 functional networks ($p = 0.005$; corrected), each of which reflected an occupational ability. (**Discussion and Conclusion**) We could identify functional networks reflecting 19 occupational abilities. These networks can be used for objective evaluation of occupational abilities. These functional networks also can be used to examine how the brain is organized for realizing each occupational abilities or to know what brain function is needed to develop needed an occupation ability. In addition, the measurement of the occupational abilities by fMRI takes only less than 15 minutes including acquisition times of anatomical and functional images. These show a possibility that

we can effectively evaluate occupational abilities and develop some programs for development of occupational abilities through brain function measurements.

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**Poster**

**795. Human Cognition and Behavior: Social Cognition: Neural Processes and Disorders II**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 795.18/MMM15

**Topic:** H.02. Human Cognition and Behavior

**Support:** NIHR UCLH BRC 174745

**Title:** Increased learning from self-negative information underlies biased social inference in individuals with high fear of negative evaluation

**Authors: *A. HOPKINS**[1,2,3], R. J. DOLAN[2,3], K. BUTTON[4], M. MOUTOUSSIS[3,2]
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**Abstract:** Fear of negative evaluation (FNE) is a core feature of social anxiety disorder. People who are highly fearful of negative evaluation display biased processing of social-evaluative information when related to the self. For example, they select fewer positive words when asked to predict how another agent would evaluate them, but display no bias when making predictions about an unknown other agent. However, it is unclear whether this effect arises from a reduced ability to learn from positive information or from an enhanced learning from negative information, a distinction that has important therapeutical implications. We aimed to investigate the mechanism underlying the negative self-bias in high FNE individuals using computational modelling. Data from a probabilistic social learning task (n=100), completed by participants that varied along a continuum of low to high FNE, was modelled using adapted Rescorla-Wagner reinforcement learning models. In the task, participants had to make predictions about whether a computer persona would describe them, and an unknown other agent, using a positive or negative word. Feedback was probabilistic, with 3 possible contingencies for the personas (80% positive, 50% positive and 20% positive words correct). Parameters were estimated using Markov Chain Monte Carlo methods, following a hierarchical framework with group-level parameters acting as priors for subject-level parameters. Bayesian model comparison revealed that the best and most parsimonious model for all individuals contained separate learning rates for self-negative and self-positive information but a single learning rate for other information. This suggests that the updating of information for the self is valence specific, whereas for others it is the same across valences. Learning rates were higher overall for self-positive information,

indicative of an optimism bias. Crucially, high and low FNE individuals show the same ability to learn from self-positive information, but higher FNE individuals had higher learning rates for self-negative information specifically. Therapeutical targets for social anxiety might therefore focus on reducing this bias towards negative information and might make use of the fact that the ability to accurately evaluate others is not impaired.

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**Poster**

**796. Physiological Methods: Optical Methodology: Application**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 796.01/MMM16

**Topic:** I.04. Physiological Methods

**Support:** DMR1254637
DMR1420709
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FA95501410175
FA95501510285

**Title:** Optically controlled multiscale neuromodulation tools based on silicon material

**Authors: *X. LI**[1], B. LIU[2], Y. JIANG[3], G. M. SHEPHERD[1], B. TIAN[3]
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**Abstract:** Beyond the limitation of traditional electrode-based neural system intervention tools, light controlled neuromodulation methods are developed, aiming for specificity, localization, and noninvasiveness. Optogenetics as a remarkable tool for neuroscience research, is genetically encoded photosensitive ion channels delivered to the neural targets via virus. However transgenic technologies have a big challenge in translational aspect, and non-transgenic approaches with high biocompatiblity are still desirable. Here, we developed a set of silicon based multiscale (from nano to centimeter) neuromodulation tools, which is characterized with photo-thermal and photo-voltaic effects. We demonstrated the utility of these tools by showing the glia-specific modulation in cultured cells, neural circuit mapping in slice, evoked cortical neural activity in vivo, and forelimb movement of mice with the photo-stimulated silicon neural interfaces.

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**Poster**

**796. Physiological Methods: Optical Methodology: Application**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 796.02/MMM17

**Topic:** I.04. Physiological Methods

**Support:** NIH BRAIN Initiative Grant R01MH111359
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NIH Grant NS057198
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720270 [Human Brain Project (HBP) SGA1]

**Title:** Evidence of a preferred direction of light propagation along apical dendrites in mouse cortex

**Authors: *T. V. NESS**[1], M. THUNEMANN[2], K. KıLıÇ[3,5], N. PERKINS[5], C. G. FERRI[3], S. SAKADZIC[6], A. M. DALE[3,2], Y. FAINMAN[4], D. A. BOAS[5], G. T. EINEVOLL[1,7], A. DEVOR[3,2,6]
[1]Norwegian Univ. of Life Sci., Ås, Norway; [2]Radiology, [3]Neurosciences, [4]Jacobs Sch. of Engin., UCSD, La Jolla, CA; [5]Biomed. Engin., Boston Univ., Boston, MA; [6]Martinos Ctr. for Biomed. Imaging, Harvard Med. Sch., Charlestown, MA; [7]Dept. of Physics, Univ. of Oslo, Oslo, Norway

**Abstract:** Optogenetics has become an important tool in neuroscience, because it allows targeted control of neuronal activity with high temporal precision. Understanding the optical properties of neural tissue is of key importance, because these properties will determine the volume of tissue affected by the light causing optogenetic stimulation or inhibition. Light propagation in cortex is often assumed to be homogeneous and isotropic, and typical measurements of light propagation are only in the direction perpendicular to the pyramidal apical dendrites. Here, we performed direct measurement of light propagation in vivo and ex vivo, both along, and perpendicular to, the axis of the apical dendrites in mouse cortex and found significant anisotropy.
We used a tapered optical fiber with an aperture diameter of 200 μm to deliver light from a 450-nm laser to the somatosensory cortex of adult wild-type mice. Light intensities were obtained from images of the cortical surface acquired by a CCD camera. To estimate light intensity as a function of distance in the direction along the pyramidal apical dendrites, the fiber tip was placed at gradually increasing depths below the surface of the cortex. To estimate light intensity as a function of distance in the direction perpendicular to the pyramidal apical dendrites, a right-angled prism was inserted into the cortex. The optic fiber was inserted almost parallel to the cortical surface while facing the front of the prism at different distances. We found light decay with distance to be exponential, with a two-fold lower decay constant in the direction of the

apical dendrites. The spatial light profiles were also elongated in this direction.
We also performed ex vivo measurements, with the optical fiber inserted into acutely isolated coronal brain slices. Images from a CCD camera of the slice surface were used to estimate spatial light intensity profiles. We observed that the preferred direction of light propagation was along the pyramidal apical dendrites for all tested orientations of the optical fiber relative to the depth axis of the cortex. Moreover, we noticed profound changes of light distribution in proximity to the white matter boundary when light was introduced in deeper cortical layers, most likely due to strong scattering by myelinated axons within the white matter.
In conclusion, our measurements suggest that light scattering in mouse cortex is highly anisotropic. We expect that our data will help to refine current simulation models of light propagation in neural tissue, leading to improved prediction of the spatial extent of optogenetic stimulation or inhibition.

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**Poster**

**796. Physiological Methods: Optical Methodology: Application**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 796.03/MMM18

**Topic:** I.04. Physiological Methods

**Support:** NIH Grant UO1 NS103516
NSF Grant DBI-1707312

**Title:** *In vivo* 3-photon imaging in intact adult zebrafish

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**Abstract:** Understanding brain function will depend on the ability to monitor the structure and activity of individual neurons throughout the brain of an individual, preferably intact, living animal. The ability to monitor activity and structure is already available using optical methods in transparent larval zebrafish, but the ability to image declines rapidly with age as the skull and scales develop. Here we show that three-photon (3P) imaging allows visualizing of neuronal structure and function through the head, into and through the telencephalon, as well as deep into the optic tectum and cerebellum of intact living adult zebrafish (at least 3 months old). This offers access to the neural substrates of adult behaviors such as spatial and contextual learning

and social interactions such as dominance, schooling, and mating.
3P fluorescence microscopy at excitation wavelengths of 1300 nm and 1700 nm offers several advantages when imaging deep tissue by comparison to 2P imaging, in which signal-to-background ratio declines more precipitously with increasing tissue depth and opacity. With 3P imaging, the relatively longer wavelengths of light penetrate tissue more efficiently than those of shorter 2P excitation wavelengths and the higher-order drop-off in excitation from the focal point reduces background excitation. Using excitation wavelengths of 1300 (GFP and GCamP6s and f) and 1700 (RFP and tdTomato) nm, we imaged through the scales, skin and skull of living fish. We achieved imaging at depths of up to 1000 um in the telencephalon, 800 um in the tectal and cerebellar regions *in vivo*. In addition, we were able to image one half of an entire telencephalon through to the bottom of the brain. Further improvements may allow imaging anywhere throughout the depth of the adult brain, with rapid switching between regions. Zebrafish will likely be the first vertebrate animal model in which neurons throughout the brain of an intact individual animal could be studies *in vivo* at cellular and subcellular resolution from embryo to adult, until death.

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**Poster**

**796. Physiological Methods: Optical Methodology: Application**

**Location:** SDCC Halls B-H

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**Title:** Measurement of partial pressure of oxygen in retinal capillary in mice using two-photon microscopy

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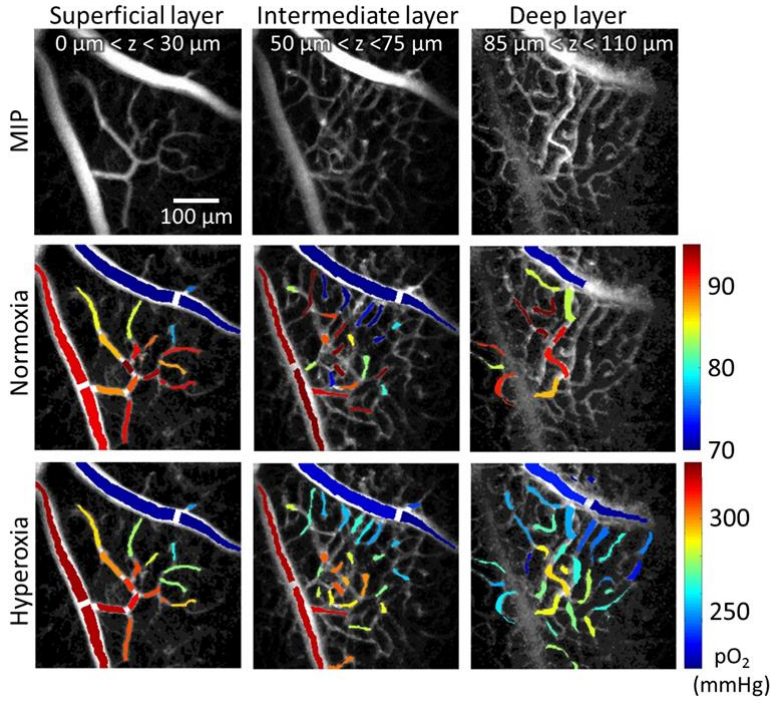
**Abstract:** Understanding oxygen delivery and consumption in retina is a key to better understand progression of important retinal diseases. However, we are still lacking the tools to measure absolute oxygen concentration in retinal capillaries, which are essential to understand oxygen transport to retina tissue. In this work, we show that two-photon microscopy imaging of oxygen partial pressure ($pO_2$) based on oxygen quenching of phosphorescence can be used to map absolute $pO_2$ in all types of retinal microvascular segments, including arterioles, venules, and capillaries. The measurement was performed in anesthetized mice (C57BL/6, n=3, female), at various retina depths, under normoxic and hyperoxic conditions. We utilized an advanced oxygen-sensitive nanoprobe and off the shelf objective with a long working distance, without additional optical correction mechanisms. The transverse and axial distances within the measured tissue volume were calibrated with the help of a model of the eye optical structure. To our knowledge, this is the first demonstration of absolute $pO_2$ imaging in retina capillaries *in vivo*. This method will lead to improved understanding of oxygen delivery at the microvascular scales and mechanisms that are driving development of various eye disorders.

Figure 1. Absolute $pO_2$ distribution in retina microvasculature during normoxia and hyperoxia. Top, middle, and bottom rows represent survey images and $pO_2$ measurements during normoxia and hyperoxia, respectively. Columns represent different microvascular layers: superficial (1st column), intermediate (middle column), and deep layer (3rd column). Vascular segment colors in 2nd and 3rd rows represent average of all $pO_2$ point measurements within the vascular segment (color bar in mmHg). Color-coded masks were overlaid on the gray-scaled maximum intensity projection (MIP) survey scan images.

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**Poster**

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**Topic:** I.04. Physiological Methods

**Title:** Novel fluoropolymer PEO-CYTOP nanosheets advancing open skull method for *in vivo* two-photon imaging of living mouse brain

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**Abstract:** In the field of biological and medical sciences, *in vivo* two-photon microscopy has become widely used for deep tissue imaging. Compared to visible lights, near-infrared laser light pulses for inducing two-photon excitations of conventional dyes are rarely scattered or absorbed in living tissue. For long-term imaging of the deeper regions in living mouse brains, “open skull method” is usually employed. In this method, such surgical operations as digging a hole in the skull and sealing it with a glass cover slip are required in order to make a chronical cranial window. However, these surgical operations are generally so tricky and require several high-level skills. On the other hand, nanosheets, polymer thin films in the order of 10-100 nm thickness, have been recently expected as novel materials for medical applications because of their high flexibility, adhesion strength, and transparency. Noticeably, it has been clarified that nanosheets which thickness is 200 nm or less have strong adhesiveness because of van der Waals interaction.
In this study, we utilized a newly-developed nanosheet, PEO-CYTOP nanosheet, as a sealing material for the hole of the chronical cranial window. By a spin-coating method, a 130-nm thickness nanosheet was made from a solution of amorphous fluoropolymer CYTOP (Asahi Glass Co., Ltd.). It exhibited an excellent water-retention. Subsequently, one side of the surfaces was laminated by spin-coating with polydimethylsiloxane (PDMS) of 5 nm thickness and then the PDMS layer surface was hydrophilized by attaching poly ethylene oxide (PEO). This hydrophilic surface showed a higher adhesion strength than the hydrophobic one. As the result, this PEO-CYTOP nanosheets showed strong adhesiveness to the brain surface and suppressed bleeding at the surface. Next, by utilizing the higher flexibility, we successfully made a large curved cranial window tightly sealed by the nanosheet that coved almost the upper side of the brain surface. Moreover, the nanosheet did not produce such aberrations those caused by differences in the refractive index of the conventional cover slip in the optical path, because the thickness of the nanosheet was quite smaller than the wavelength of light. Thus, the aberrations

were considerably compensated just by adjusting the refractive index of the immersion solution. By such optimizations, we successfully achieved *in vivo* deep-imaging of the mouse prefrontal cortex consisting of complicated layer-like structures at the depth of about 1.6 mm. In future, the combination of nanosheets with adaptive optics will improve the long-term *in vivo* imaging of living organs including living brains.

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**Poster**

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**Title:** Two-photon imaging of neuronal activity in motor cortex of common marmosets during upper-limb behavioral tasks

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**Abstract:** Two-photon imaging has revealed neural activities underlying a variety of brain functions in rodents and other small animals. However, no study has succeeded in the imaging of common marmosets participating in upper-limb movements. Here we report the two-photon imaging of neural activity in motor cortex of marmosets during the tasks. Because marmosets have posed a challenge due to limited success in training on motor tasks, we first developed the protocol to train marmosets to perform upper-limb movement tasks. The marmosets learned to control a manipulandum to move a cursor to a target on a screen after 2-5 months of training sessions. We succeeded in the two-photon calcium imaging of layer 2/3 neurons in the motor cortex during this motor task performance and the detection of task-relevant activity from

multiple neurons, dendrites and axonal boutons. In a two-target reaching task, some neurons showed movement direction-selective activity over the training days. In a short-term force-field adaptation task, some neurons dynamically changed their activity when the force field is on. Two-photon calcium imaging in behaving marmosets may become a fundamental technique for analyzing the spatial organization of the cortical neurons and dynamics of the neuronal activity underlying action and cognition.

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**Topic:** I.04. Physiological Methods

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**Title:** Automated region of interest detection method for calcium imaging with stimulation related task

**Authors: *K. KIM**[1], S. KANG[1], Y.-E. HAN[2], J.-C. RAH[2], J.-W. CHOI[1]
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**Abstract:** Calcium imaging is a widely used neuronal imaging method. By applying it to in vitro and in vivo experiment, tens to hundreds of neuronal activities can be measured simultaneously. This benefit of calcium imaging allows us to study neuronal circuits. On the other hand, too many neuronal activity is a distraction to observe activities from a small population of neurons within hundreds of neurons. There have been signal processing studies to improve signal quality in a calcium imaging data by demixing spatially overlapped neuronal activities into each individual neuronal activity. These signal processing method is useful to observe small population of neurons better. However, there still is an issue on selecting target neurons which has important information. Even if few target neurons are located among hundreds of neurons, it is difficult and time consuming to search the target neurons since it has been performed manually in conventional methods.In this study, we introduce a novel method to search region of interest (ROI) of target neurons automatically in a calcium imaging data with stimulation condition. Once a stimulation is onset, it is expectable that the ROIs related to the stimulation show an exponentially decaying signal in time domain. This distinct feature can be modeled with exponential function and considered as a matched filter. By applying this matched filter to the calcium imaging data containing hundreds of neurons, the level of matching result, that is the inner product between calcium imaging data and the matched filter, is calculated for each of neurons. Under the repeated stimulation condition, the level of matching results are accumulated

enough to have a probability density function (PDF). By applying statistical calculation such as t-test, it is possible to select the target ROIs that have specific significant level. Once the significant level is set, these whole processes can be performed automatically.The result shows that the proposed automatic ROI search method detected a small population of target neurons that is related to the stimulation. The target dendrites and small spines were detected even though they are located next to non-target cell body which has relatively high level of fluorescent activity.This novel method can be useful for understanding neuronal circuit especially in a complex region that contains many neurons with dynamic activities. In the current studies, calcium imaging techniques aim to measure larger number of neurons (i.e., thousands of neurons) in a window, so that we claim that the proposed method can be an essential method in the future.

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**Poster**

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**Topic:** I.04. Physiological Methods

**Support:** JST, CREST
KAKENHI

**Title:** Visualizing neural activities at the regions of the GCaMP6 expressed mouse brain in the neural circuit related to feeding behavior, including lateral hypothalamus, under freely moving using an implantable micro imaging device

**Authors: *M. S. GUINTO**, Y. OHTA, M. KAWAHARA, M. HARUTA, T. NODA, K. SASAGAWA, T. TOKUDA, J. OHTA
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**Abstract:** Feeding behavior arises from a complex interplay of multiple control systems in which food-related cues (orosensory, olfactory, and visual inputs) from the prefrontal cortex (PFC) are conveyed to neural circuits implicated in the cognitive processing of reward and pleasure. Uncovering the dynamics between the major regions of so-called reward circuits, namely, the lateral hypothalamus (LH), ventral tegmental area (VTA) and nucleus accumbens (NAc), will provide valuable insight to motivational behavior and neurobiological processes modulating macro levels.
We have developed a lightweight (~0.02 g), compact (~450-μm width) and needle-shaped implantable CMOS fluorescence imaging device which has an LED for exciting fluorescent protein and an imaging sensor that can detect fluorescence. Our device allows simultaneous

visualization of network related areas to examine this complex reward system network, and it will hardly stress the mouse almost without restricting the behavior of the mouse. This demonstrates that our device is optimal for experiments under the free movement of mice. In addition, we confirmed by immunostaining that damage to brain tissue due to implantation is extremely small by reducing the size and weight of the in-house device. We succeeded in visualizing dopamine neuronal activity in VTA by administering alcohol in the mesolimbic system of the reward system using transgenic mouse with GFP tag.
In the present study, we report the observation of high level, sustained neural activity in the LH, a key region in the feeding behavior, in which cell bodies projecting to VTA exist. Different nerve activities were clearly observed in various conditions in the feeding process such as fasting, desperate feeding after hunger, sleeping after satiety, and lightly touching food after awakening.
From now on, through the use of the miniature imaging devices, this study clarifies the direct involvement of specific regions in the limbic system such as LH, VTA, amygdala, NAc and identifies the modalities by which these neuronal subsets operate.

**Disclosures: M.S. Guinto:** None. **Y. Ohta:** None. **M. Kawahara:** None. **M. Haruta:** None. **T. Noda:** None. **K. Sasagawa:** None. **T. Tokuda:** None. **J. Ohta:** None.

**Poster**

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**Title:** *In vivo* three-photon excited fluorescence imaging in the spinal cord of awake, locomoting mice

**Authors: *Y.-T. CHENG**[1,2], S. L. DENOTTA[3,2], J. S. JONES[2], D. A. RIVERA[2], S. HU[2], J. RAIKIN[2], D. G. OUZOUNOV[4], T. WANG[4], X. LI[2], J. C. CRUZ HERNANDEZ[2], I. M. BASTILLE[2], N. NISHIMURA[2], J. R. FETCHO[1], C. XU[4], C. B. SCHAFFER[2]
[1]Neurobio. and Behavior, [2]Meinig Sch. of Biomed. Engin., [3]Col. of Vet. Med., [4]Sch. of Applied and Engin. Physics, Cornell Univ., Ithaca, NY

**Abstract:** Nonlinear optical microscopy is a powerful technology for non-invasively recording the firing activity of a large population of neurons using calcium sensitive fluorescent reporters. Spinal cord neurons in central pattern generator (CPG) circuits control rhythmic locomotor behaviors but sit below the highly optically scattering white matter, making imaging of these

cells challenging, even with two-photon microscopy. Recent work has shown that utilizing higher order nonlinear optical processes, such as three-photon excited fluorescence (3PEF), enables deeper penetration into scattering tissue. Here, we explore the use of 3PEF imaging using a 1.3-μm excitation source to image cellular structure and function in the mouse spinal cord. We first imaged the topology of the microvascular network and measured blood flow speed throughout the vascular hierarchy, from the lateral arterioles, through the capillary bed, and to the dorsal spinal vein. Next, we examined the response of microglia (GFP) and dorsal ascending axons (YFP) to occlusion in the venules (QDot 655) that drain the spinal cord. The surgical preparation we use to gain optical access to the spinal cord enables us to spine fix the mice, while awake, under the microscope. Mice can then "run" on a spinning disk while we image their spinal cord. Once trained, mice exhibited a normal running gait and grooming behaviors while spine fixed atop the disk. We then used 3EPF imaging of the genetically-encoded calcium sensor GCaMP6s to measure neural activity in spinal cord neurons. In mice expressing GCaMP in sensory neurons (CaMKIItTA-GCaMP6s), we observed stimulus-locked neural responses (dF/F > 50%) in response to electric shocks to the hind paw. When these animals were awake under the microscope, the neural firing frequency, as well as the amplitude of the calcium response, increased as the mouse went from a resting state to continuously running on the disk. In efforts to image activity in some of the CPG neurons that control limb motion, we delivered AAV9-LoxP-GCaMP6s virus into the spinal cord of Chx10-Cre animals. This led to GCaMP6s expression in V2a cells, which reside ~500 μm underneath the cord surface. When combined with quantitative tracking of limb kinematics, this capability for 3PEF imaging of cell-resolved neural activity could enable detailed studies of how activity patterns in CPG circuits coordinate rhythmic locomotion.

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**Poster**

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**Topic:** I.04. Physiological Methods

**Support:** McKnight Foundation
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NIH 1R01MH101297
NSF 1516235

**Title:** Considerations for applying information theoretic approaches to calcium imaging datasets

**Authors: *J. R. CLIMER**, D. A. DOMBECK
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**Abstract:** Information theoretic approaches are useful for quantifying the information action potentials contain about various behavioral states and environmental stimuli. For example, during navigation action potential trains from extracellularly recorded hippocampal neurons can be analyzed to measure the information contained about the animal's spatial position, commonly using the "information rate[1]". This estimates the mutual information between position and the action potential train using a rate map and the corresponding normalized occupancy map and is measured in bits per second or (more commonly) bits per action potential. Information rate can also be applied to measuring information about other variables, like heading direction, speed, and time. However, it depends on assuming a short-timescale counting process where events are independent, such as in spike trains. These assumptions are violated for fluorescence traces collected via calcium imaging, which are nonstationary and can take on non-integer values. For example, the genetically encoded calcium indicator GCaMP6f reports an action potential via a transient lasting ~200-300ms. At a running speed of 25 cm/sec, a single action potential transient will not return to 10% of the peak until the animal has traveled ~10 cm. This results in a broadening of the spatial fields and a difficulty in quantifying the spatial information contained in the transient. These problems are exacerbated when firing is modulated by multiple variables that share information (e.g. speed and position). To investigate the effects of indicator dynamics on the information rate, we first acquired behavioral datasets (locomotion speed and track position vs. time) from mice navigating in virtual linear tracks. To these we added simulated spike trains containing varying amounts of spatial and speed information. The spike trains were convolved with different calcium transient shaped kernels, and noise was added. This dataset provided the opportunity to examine the correspondence between information rates estimated from calcium traces vs spike trains over a large parameter space. We also compared these information rates to those calculated from de-convolved traces and to alternative measures based on contemporary estimators of mutual information applied to un-binned data. Our results may also prove useful for estimating information contained in fluorescence traces from other functional indicators.

1. William E. Skaggs and Bruce L. McNaughton and Katalin M. Gothard and Etan J. Markus. An Information-Theoretic Approach to Deciphering the Hippocampal Code. Proc. IEEE 1030--1037 (1993). doi:10.1109/PROC.1977.10559

**Disclosures: J.R. Climer:** None. **D.A. Dombeck:** None.

**Poster**

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**Topic:** I.04. Physiological Methods

**Support:** NS090473
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**Title:** Imaging neuronal responses through all cortical layers and subplate of visual cortex in awake mice with optimized three photon microscopy

**Authors: *M. YILDIRIM**[1], H. SUGIHARA[2], P. SO[3], M. SUR[4]
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**Abstract:** In sensory cortices, information arrives from primary nuclei of the thalamus into multiple cortical layers, but most densely into layers 4 and 6, and is subsequently transformed by inter-laminar circuits to enable cortical information processing. Two-photon microscopy has been used to measure neuronal activity mainly in superficial cortical layers, but has severe limitations for imaging deeper layers. Thus, response features of identified neurons in deeper cortical layers have remained unclear. Here, we demonstrate the optical design of a custom-made three-photon microscope to image a vertical column of the cerebral cortex >1 mm in depth in awake mice with low (<20 mW) average laser power. In order to optimize microscope design for minimal imaging power requirement, we designed a scan and tube lens integrated with the objective lens to reduce the aberration in the microscope, and we designed the collection optics to maximize the collection efficiency. We demonstrate functionality of the microscope by imaging the cross-laminar dendritic structure of layer 5 neurons in GFP-M mice, and functional visual responses of neurons expressing GCaMP6s across all layers of the primary visual cortex (V1) as well as in the subplate in awake mice. These recordings of identified deep layer neurons reveal that layer 5 neurons are more broadly tuned to visual stimuli whereas layer 6 neurons are more sharply tuned compared to neurons in other layers. Subplate neurons, located in the white matter below cortical layer 6 and also characterized here for the first time, are less visually responsive, and their orientation selectivity is broader compared to those of neurons in the cortical layers. These results demonstrate the design and utility of a custom-made three-photon microscope in revealing fundamental differences between neurons in different cortical layers, and between cortical and subplate neurons - which have been implicated in the pathogenesis of developmental brain disorders including autism and schizophrenia. Also, we determined the pulse energies required for different damage mechanisms such as optical breakdown and bulk

heating of visual cortex for three photon microscopy with varying several laser parameters. This characterization can help to map different damage mechanisms for in vivo brain imaging with corresponding laser parameters. Furthermore, the principles we describe can guide the development of damage-free three-photon microscopy for live functional imaging with subcellular resolution in other complex tissues.

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**Support:** NIH

**Title:** Two-photon microscopy imaging of capillary red blood cell flux in mouse brain reveals vulnerability of white matter to hypoperfusion

**Authors: *B. LI**[1], R. OHTOMO[2], M. THUNEMANN[3], J. YANG[2], B. FU[2], C. RAN[2], J. POLIMENI[2], D. A. BOAS[4], A. DEVOR[5], E. LO[2], K. ARAI[2], S. SAKADZIC[2]
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**Abstract:** Brain cerebral gray matter (GM) and white matter (WM) differ greatly in capillary density, blood flow, and oxygen metabolism. Regulation of cerebral capillary blood flow in GM of healthy brains and its alteration in brain disorders have been extensively investigated in animal models. However, no data about capillary blood flow in WM has been reported. To address this under-investigated topic, we employed two-photon fluorescence microscopy to measure capillary red blood cell (RBC) flux in both GW and WM, in isoflurane-anesthetized C57BL/6 mice, through a sealed cranial window. Our deep capillary RBC flux measurements (up to 1.2 mm under brain surface) were enabled by a far-red fluorophore Alexa 680, and photon-counting detection. Our results show that in control animals, the mean capillary RBC flux at baseline in cerebral WM (67±6 RBC/s) was significantly higher than that in GM (48±4 RBC/s). However, under cerebral hypoperfusion in a mouse model of bilateral carotid artery stenosis, the WM capillary RBC flux was significantly reduced (43±8 RBC/s), while the GM capillary RBC flux (45±8 RBC/s) remained comparable with the control values. The GM and WM RBC flux also exhibited different responses to mild hypercapnia. Under mild hypercapnia in healthy control mice, the RBC flux in the GM capillaries increased significantly (63±5 RBC/s), while the RBC flux in the WM capillaries exhibited a smaller fractional increase (72±7

RBC/s). We hypothesize that the observed variations in the GM vs. WM capillary RBC flux values are related to the topology of arteriolar blood supply where WM is supplied downstream with respect to the GM. Specifically, a decrease in blood pressure in the upstream GM arterioles may cause a disproportional pressure drops in downstream arterioles supplying the WM. This may result in an increased vulnerability of WM to the global cerebral hypoperfusion compared to the GM. This work demonstrates that the WM capillary RBC flow could be measured using standard two-photon microscopy setup, which may be available to many investigators in this research field. Our results indicate significant differences between the WM and GM RBC flux, both at baseline, and in response to hypoperfusion and mild hypercapnia. Our results also show that capillary blood flow in WM might be disproportionally more susceptible to hypoperfusion than that in GM, suggesting a possible mechanism for the WM deterioration in brain diseases involving global cerebral hypoperfusion.

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**Poster**

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**Title:** Optical deep brain stimulation of the central auditory pathway

**Authors: *B. S. COVENTRY**[1,2,3], E. L. BARTLETT[2,4,3,1]
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**Abstract:** Neurological and sensory neuroprostheses based on electrical stimulation have proven effective in treating maladies such as Parkinson's disease and Tourette's syndrome with deep brain stimulation (DBS), as well as restoration of auditory and visual percepts with cochlear and retinal implants. However, deficits in modern devices, such as current spillover and inability to selectively target local circuits, results in undesirable auditory and visual percepts in sensory prostheses and undesirable side effects in central nervous system implants. Infrared neural stimulation (INS) is an optical technique which has been shown to selectively stimulate nerves and neurons using long wavelength (> 1450 nm) infrared light. INS is a promising stimulation modality because it does not require genetic modification of the target, allowing translation to

human patients without additional genetic manipulations. Furthermore, previous studies in nerve have suggested that INS is more spatially specific than conventional electrical stimulation. Preliminary studies in the central nervous system have suggested INS can elicit responses in cortical structures. However the efficacy of INS in generating biophysical responses in thalamocortical networks is unexplored. Demonstration of effective thalamocortical recruitment would establish INS a potential stimulation therapeutic. In this study, Sprague-Dawley rats of both sexes were implanted with optrodes in the medial geniculate body (MGB) in the auditory thalamus and 16 channel microwire arrays in the primary auditory cortex (A1). After recovery, auditory and infrared stimuli were presented to awake, restrained animals. Auditory stimuli consisted of click trains at sound levels between 60 and 90 dB, random spectrum stimuli with spectral contrasts of 5, 10, and 15 dB, and amplitude modulated broadband noise. Infrared stimuli operated in quasi-continuous wave with singular pulses of 0-600 mW power with varying pulse widths between 5-100 ms duration. At conclusion of stimulation, animals were presented with a final stimulation day of 600mW 50 ms pulses for one hour for c-FOS immunohistochemistry. Brains were stained with anti-cFOS and anti-NeuN to determine spatial spread of activation in the MGB and anti-GFAP for analysis of immunoreactivity of implanted optrodes and electrodes. Initial results show that infrared stimulation of MGB gives rise to repeatable and short-latency action potentials and local field potentials in the auditory cortex. Furthermore, in comparison to auditory click stimuli, responses exist on limited number of channels, suggesting INS acts in a spatially specific manner.

**Disclosures: B.S. Coventry:** None. **E.L. Bartlett:** None.

**Poster**

**796. Physiological Methods: Optical Methodology: Application**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 796.14/MMM29

**Topic:** I.04. Physiological Methods

**Title:** Mapping auditory activity throughout the central brain of *Drosophila* males and females

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**Abstract:** In the *Drosophila melanogaster* courtship ritual, males chase females while producing a dynamic courtship song via unilateral wing vibration. While this acoustic signal is comprised of two syllables (sine and pulse), it nonetheless contains patterns that vary over multiple timescales. Flies sense acoustic signals through the antenna, which houses auditory receptor neurons - these neurons project to particular domains of the AMMC in the central brain. While

the detailed organization of cell types in the AMMC is being worked out and a functional map of the AMMC and wedge neuropil has been described, we still know almost nothing beyond these two early mechanosensory centers. We therefore lack information to address how male or female fly brains represent the complex patterns that comprise courtship song and extract salient features to inform behavioral choices. To improve our understanding of the computations performed by each layer of the auditory pathway we require a thorough description of acoustic representations across all stages of the auditory circuit. Here we developed a pipeline for *in vivo* volumetric calcium imaging of the *Drosophila* central brain at cellular resolution during auditory stimulation and across-fly registration of activity maps for both males and females. We used a structural marker for alignment within a fly brain, and for across-fly brain registration to an intersex *in-vivo* atlas. We monitored neural activity pan-neuronally using the calcium sensor GCaMP6s, and volumetric data was segmented into regions of interest (ROIs) using a constrained non-negative matrix factorization algorithm, extracting thousands of neuropil-shaped and soma-shaped ROIs per fly. Using this approach, we discovered auditory ROIs spanning known early mechanosensory neuropils such as the AMMC, sadle and wedge, but also higher order neuropils, namely, the AVLP, PVLP, PLP and LH, previously understudied in the context of audition. Auditory ROIs have a broad spectrum of stimuli tuning, and they segregate spatially depending on their preference to pulse vs sine stimuli. We will present analyses of auditory response stereotypy across flies and how auditory responses through the auditory pathway change to give rise to tuning for behaviorally relevant song features.

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**Poster**

**796. Physiological Methods: Optical Methodology: Application**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 796.15/MMM30

**Topic:** I.04. Physiological Methods

**Support:** NIH R21DA042581
NIH R01DA042499

**Title:** Development of a virtual reality paradigm for *in vivo* hippocampal imaging during drug-induced contextual learning

**Authors: *S. B. WILLIAMS**[1], M. W. ARRIAGA[2], W. POST[3], E. B. HAN[2], J. MORON-CONCEPCION[3]
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**Abstract:** Opioids, like other drugs of abuse, result in structural and functional changes in the hippocampus, leading to long-lasting associations between the opioid-induced reward and the environment; possibly mediating relapse of drug-taking behavior. Using *ex vivo* approaches, our lab has shown that morphine conditioned place preference (mor CPP) decreases the number of dendritic spines of hippocampal CA1 neurons, mediated by NR2B containing NMDA receptors, yet the timing and dynamics of these events and their potential relationship to the association between drug reward and context are unknown. To observe neural networks in real time as mor CPP and reinstatement take place, we have designed a virtual reality conditioned place preference (VR-CPP) paradigm that can be paired with two-photon imaging. The three chamber VR-CPP apparatus contains a neutral middle chamber and two conditioning chambers containing distinct visual cues. Mice are head fixed in the VR environment and allowed to freely run on a Styrofoam ball suspended by air pressure. Movement of the ball is tracked, converted to forward and yaw velocities by custom written software in LabView, and then fed to a virtual reality engine written in Matlab, which updates the visual scene permitting the animal to navigate through the VR environment. Mice are trained to control their position in the VR by operant conditioning using H2O rewards, then are submitted to a biased mor CPP paradigm. After 8 days of mor-paired contextual conditioning, mice demonstrate a significant shift in place preference for the VR mor-paired. When combined with two-photon *in vivo* imaging, this novel behavioral paradigm allows unprecedented spatio-temporal resolution in following the structural and plasticity changes that underlie mor CPP.

**Disclosures: S.B. Williams:** None. **M.W. Arriaga:** None. **W. Post:** None. **E.B. Han:** None. **J. Moron-Concepcion:** None.

**Poster**

**796. Physiological Methods: Optical Methodology: Application**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 796.16/MMM31

**Topic:** I.04. Physiological Methods

**Support:** Grant-in-Aid for Research Activity start-up 17H06866

**Title:** GCaMP and GFP imaging in VTA by an implantable imaging device

**Authors: *Y. SUNAGA**[1], Y. OHTA[1], M. HARUTA[1], T. NODA[1], K. SASAGAWA[1], T. TOKUDA[1], Y. AKAY[2], M. AKAY[2], J. OHTA[1]
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**Abstract:** Extracellular recordings have been widely performed to study neural activity in the brain using multi electrode arrays. Although this approach has been found useful in many applications, it has limited access to observe neural activities in VTA for a longer duration.

Therefore, we recently introduced the fluorescence imaging approach to understand the dynamics of VTA neurons using GCaMP series since their fluorescent intensities have been influenced by neural activities [1]. However, it has been a challenge to access and image VTA area and observe fluorescence reactions of animals under freely moving condition. In order to overcome these challenges and especially to observe fluorescence reaction associated with animal behavior, we have developed implantable fluorescence imaging devices based on a CMOS image sensor [2, 3]. Our device size is $0.5 \times 3.0$ mm$^2$ with the thickness of 0.15 mm, and its weight is less than 0.05 g. The device consists of a dedicated CMOS image sensor, LEDs for excitation and a filter to divide fluorescence and excitation light, both of which are chosen for measurement targets. The sensor and LEDs can be driven by using only six wires. The imaging device was inserted in the deep brain, and was fixed with the skull by a dental cement or a super bond. The wires are removable and are connected only while imaging experiments are performed. In this work, we performed *in vivo* fluorescence imaging in VTA area and assessed the fluorescence detection performance. The CMOS imaging implant was inserted in the ventral tegmental area (VTA) of a mouse, and GFP and GCaMP fluorescence intensity changes associated with nicotine intake were tried to observe. Our preliminary studies suggested that fluorescence intensity of GFP and GCaMP changes in response to nicotine intake can be observed and quantified. We are currently focusing on the use of our imaging implant based on GCaMP fluorescence to study neural activities of VTA neurons in rats. [1] T. Chen *et al*. nature. 499, 7458, 2013. [2] Y. Sunaga *et al.*, IEEE BioCAS 2014, Lausanne, Swiss. [3] Y. Sunaga *et al.*, Jpn. J. Appl. Phys., 55, 3S2, 2016.

**Disclosures: Y. Sunaga:** None. **Y. Ohta:** None. **M. Haruta:** None. **T. Noda:** None. **K. Sasagawa:** None. **T. Tokuda:** None. **Y. Akay:** None. **M. Akay:** None. **J. Ohta:** None.

**Poster**

**796. Physiological Methods: Optical Methodology: Application**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

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**Topic:** I.04. Physiological Methods

**Support:** 5U01NS094296
F30 HL128023
R01 NS063226
MURI, W911NF-12-1-0594

**Title:** Analysis of real-time 3D vascular network dynamics in the cortex during whisker stimulus using SCAPE microscopy

**Authors: *Y. CHEN**, M. A. SHAIK, K. B. PATEL, C. KIM, S. E. BENEZRA, V. VOLETI, E. M. C. HILLMAN
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**Abstract: Introduction:** Local increases in brain blood flow accompany neural activity and form the basis of the BOLD signal detected in functional magnetic resonance imaging (fMRI). Analysis of how vasodilation initiates in *in-vivo* brain can improve our interpretation of fMRI data and the mechanisms of neurovascular coupling. Prior studies using two-photon microscopy line-scanning to monitor vessel diameter have concluded that first-order capillaries dilate over one second earlier than penetrating arteries[1]. However, such measurements are limited by their ability to capture only a small region of interest in a single plane at high enough speeds to observe responses. No study to date has captured the 3D vascular dynamics within an intact vascular network in response to a single stimulus. Here we utilize swept, confocally-aligned planar excitation (SCAPE) microscopy[2], which can image in 3D images at high speeds, to analyze the spatiotemporal pattern of *in-vivo* cortical vasodilation in response to whisker stimuli in awake, behaving mice.
**Methods:** After recovery from placement of a chronic glass cranial window over somatosensory cortex, mice were injected with intravenous dextran-conjugated fluorophores, head-fixed and imaged awake using SCAPE microscopy. A field of view of around 350 x 1100 x 200 microns (x-y-z) was imaged at over 10 volumes per second for 30 second trials in which 1 or 5 second tactile whisker stimuli were presented.
**Analysis and Results:** A range of analysis methods have been applied to the resulting data, including quantification of dilation dynamics and plasma volume changes throughout the vascular network, from pial arterioles, to diving arterioles, capillaries, ascending venules and veins. Dilation in regions all along the vessel trees can be monitored simultaneously. The resulting data is now being incorporated into models of vascular flow and resistance as well as propagated vasodilation to determine how all areas of the vascular network coordinate to yield functional hyperemia.

**Reference**

1. Hall CN, Reynell C, Gesslein B, et al. Capillary pericytes regulate cerebral blood flow in health and disease. *Nature*. 2014;508(7494):55-60. doi:10.1038/nature13165.
2. Bouchard MB, Voleti V, Mendes CS, et al. Swept confocally-aligned planar excitation (SCAPE) microscopy for high-speed volumetric imaging of behaving organisms. *Nat Photonics*. 2015;9(2):113-119. doi:10.1038/nphoton.2014.323.

**Disclosures: Y. Chen:** None. **M.A. Shaik:** None. **K.B. Patel:** None. **C. Kim:** None. **S.E. Benezra:** None. **V. Voleti:** None. **E.M.C. Hillman:** None.

**Poster**

**796. Physiological Methods: Optical Methodology: Application**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 796.18/MMM33

**Topic:** I.04. Physiological Methods

**Support:** NIH Grant R01 NS099122

**Title:** Improvements in simultaneous sodium and calcium imaging from dendrites and spines

**Authors: K. MIYAZAKI**, *W. N. ROSS
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**Abstract:** Calcium imaging has been an important tool in examining electrical events in CNS neurons. However, this approach only indirectly reports data about membrane potential changes. In principle, an analysis of intracellular sodium dynamics more directly reveals this kind of information because membrane currents are mostly due to sodium influx. Unfortunately, there are only a few studies using sodium imaging in single neurons. This is due primarily to the challenge of detecting sodium signals in small dendritic compartments. Another issue is that most calcium imaging from spines has been performed by two-photon laser systems, which needs line scanning to achieve high speed; imaging extended fields requires slower scanning. In order to improve these kinds of measurements we developed a system for simultaneous sodium and calcium imaging using a high-speed CCD camera. The original system used high power multiplexed LEDs for fluorescence excitation. Recently, we enhanced this system using lasers instead of LEDs and a new set of indicators.To achieve high speed and sensitivity we used a microscope with an Olympus 60X, 1.1 NA lens and a RedShirtImaging NeuroCCD 80x80 camera operated at 500 Hz. To detect sodium and calcium changes we injected cells with combinations of indicators that have separated excitation bands (either SBFI and OGB-1, or, more recently, Calbryte-630 and ANG-2). In the new system CW lasers (375, 473, 514, and 561 nm) illuminated optical fibers (50 or 200 µm diam) and the ends of these fibers were focused to 2.5-10 µm diam spots on hippocampal slices. Custom designed dichroic and emission filters allowed alternate detection of fluorescence from the two indicators when the laser source was switched. Quasi-simultaneous illumination was achieved by switching between the LEDs or the lasers every 2 ms. Effective intensity was changed by varying the laser pulse duration. Alternate camera frames, synchronized with the switching of the lasers, detected emission separately from each indicator. Software then separated the signals into two streams that were displayed along with simultaneously recorded membrane potential from the patch electrode.The high intensity focused laser spots gave good S/N for the sodium and calcium signals compared to LED illumination, in part because there was less background fluorescence. The sensitivity of the system was limited by photodynamic damage from the laser illumination. Using ANG-2 and

Calbryte-630 as the indicators (instead of SBFI and OGB-1) generated less photodynamic damage because of the redshift of the excitation wavelengths. In addition, by eliminating excitation at 375 nm we could add laser uncaging to the system.

**Disclosures: K. miyazaki:** None. **W.N. Ross:** None.

**Poster**

**796. Physiological Methods: Optical Methodology: Application**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 796.19/MMM34

**Topic:** I.04. Physiological Methods

**Support:** NIH-DC03180

**Title:** Removable cranial window for chronic multi-scale and multi-modal optical imaging in marmosets

**Authors: *Y. GUO**[1], X. SONG[2], X. WANG[3]
[1]Johns Hopkins Univ., Baltimore, MD; [2]Johns Hopkins Univ. Dept. of Biomed. Engin., Baltimore, MD; [3]Dept Biomed Engin, Johns Hopkins Univ. Sch. Med., Baltimore, MD

**Abstract:** The common marmoset (Callithrix jacchus), a highly vocal New World monkey species, has garnered considerable interest in recent years as a promising primate model in neuroscience studies. The smooth cortical surface of the marmoset brain provides a special advantage for studying cortical functions using optical imaging methods. In this study, we developed procedures to perform multi-scale and multi-modal optical imaging in the auditory cortex of awake marmosets. The major goals of our procedures are: 1) targeted neuron labeling with virus-mediated methods, based on data obtained with intrinsic imaging; 2) a removable imaging window design, allowing us to remove and replace the window for different imaging modalities. To perform intrinsic imaging and virus injection, we designed an artificial dura (AD) based cranial window. Since the dura of marmosets is opaque and must be removed for optical imaging, an AD is necessary for protecting the cortex, preventing the dura growing back and thus keeping the window clear. The optically flat AD is made of silicone (Shin-Etsu, ET-1300T), with a diameter of a quarter inch, and thickness of 150~200um. An additional 1.3mm wall structure along with a 3mm wide flange that was inserted under the surrounding dura, prevent the dura growing back into the imaging window. A customized rubber chamber structure was used to cover and protect the window when the animal is back to its cage. After obtaining a functional map with intrinsic imaging through the chronically-implanted window, we were able to achieve targeted GCaMP-carrying virus injection, which allowed us to perform calcium fluorescence imaging afterward. The virus was mixed with the dye (Fast Green) to visualize the diffusion pattern and possible back-flow when injecting the virus. The mixture was loaded into glass

micropipettes, which were pulled and ground so that the tip has a ~30um outer diameter and a ~20° angle. We were able to penetrate the silicone AD easily and achieve consistent injection speeds by manually pushing a syringe air-coupled with the micropipette. To achieve higher brain stability during two-photon imaging in awake marmosets, the original silicone based cranial window was removed and replaced by a modified AD, which has a coverslip in the middle. Through this modified window we were able to record calcium signals from individual neurons with a customized two-photon microscope. The removable cranial window was safe and relatively easy to maintain. It enabled chronic optical imaging in marmosets over several months.

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**Poster**

**796. Physiological Methods: Optical Methodology: Application**

**Location:** SDCC Halls B-H

**Time:** Wednesday, November 7, 2018, 1:00 PM - 5:00 PM

**Program #/Poster #:** 796.20/MMM35

**Topic:** I.04. Physiological Methods

**Title:** Separation of hemodynamic signals from GCaMP fluorescence measured with widefield imaging

**Authors: *M. VALLEY**[1], M. G. MOORE[2], J. ZHUANG[1], N. MESA[3], M. REIMERS[2], J. WATERS[1]
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**Abstract:** Over the last few years there has been a dramatic increase in the number of mouse lines with GCaMP expression throughout much of neocortex offering the opportunity to image cortical activity using calcium indicators with high signal-to-noise and genetically-targeted expression. Widefield calcium imaging has emerged as a valuable tool to measure meso-scale brain calcium dynamics using these new indicators. Its strengths, a large field-of-view with a high sampling rate, permit experiments that simultaneously image activity from the entirety of dorsal cortex, revealing a dynamic systems-level representation of cortical interactions during mouse behavior. However, the interpretation of these widefield data is complicated by the substantial mixing of calcium signals with hemodynamics. Here, we present a new approach to demixing hemodynamic signals from calcium activity using the strategy that signals observed in GFP mice should be removed from GCaMP mice. We motivate this approach by showing that a linearization of the Beer-Lambert equation - where in our system four pathlength parameters would typically be estimated using simulations - can be exactly captured by a linear model with two variables. Using this insight, we gather data from awake mice expressing GFP or GCaMP using a multi-spectral widefield macroscope that alternates two backscatter measurements (575nm and 630nm) simultaneously with a fluorescence measurement. With two backscatter

channels, we train spatially-detailed regression models to find what amount of fluorescent variance in GFP mice can be explained by the backscatter data at each pixel. We generalize these primary models across mice using a meta-model trained on shared features of the data to estimate spatial detail unique to each animal. We quantify the success of this approach demixing hemodynamic variance in several commonly used Cre driver lines with different cortical laminar expression patterns and show in what conditions this approach offers advantages over non-spatially-detailed demixing. We also demix GCaMP data and show that we can remove stereotyped hemodynamic responses to visually-evoked activity. This method offers a means to quantify and demix hemodynamic contamination at every pixel in a widefield movie, and is an essential step towards converting fluorescence measurements to calcium activity.

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**Poster**

**796. Physiological Methods: Optical Methodology: Application**

**Location:** SDCC Halls B-H

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**Program #/Poster #:** 796.21/MMM36

**Topic:** I.04. Physiological Methods

**Support:** NIH Grant T32EB007509
NIH Grant 1OT2OD025307

**Title:** Calcium imaging of neural activity in the periphery

**Authors: *M. MCPHEETERS**[1], J. ZHUO[1], G. COFFEE[2], A. M. ROLLINS[1], S. J. LEWIS[3], M. W. JENKINS[3]
[1]Biomed. Engin., [2]Pediatric Pulmonology, [3]Pediatrics, Case Western Reserve Univ., Cleveland, OH

**Abstract:** Neuromodulation has shown great potential for treating a myriad of diseases (e.g., obesity, heart failure, rheumatoid arthritis). To realize this potential, there is a need to better understand how peripheral signaling controls organ function and how neuromodulation could harness the body's intrinsic control mechanisms to treat disease. We are interested in developing tools to study the functional organization of the peripheral nervous system and in particular, peripheral ganglia, in order to understand and alter the character of physiological responses. To this end, we are combining calcium imaging and infrared neuromodulation to allow real-time imaging and control of nerves and ganglia. We have previously shown that infrared neuromodulation both excites and inhibits peripheral activity with unique selectivity. However, nerves and ganglia are highly scattering, leading to significant challenges for both imaging and

applying target stimulation with light. Here, we show our initial work and discuss future steps to address these challenges.

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**Poster**

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**Location:** SDCC Halls B-H

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**Topic:** I.04. Physiological Methods

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NSF CBET1605679
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NSF IGERT Competitive Innovation Fund

**Title:** Long-term hydrogel immobilization for light sheet imaging of optogenetically-stimulated organisms

**Authors: *K. BURNETT**[1], E. EDSINGER[2], D. R. ALBRECHT[1]
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**Abstract:** Long-term imaging of *C. elegans* at high spatial resolution requires effective and innocuous immobilization of the organism. Light sheet microscopy is capable of fast, long-term 3D imaging with minimal photobleaching and phototoxicity, but requires that light passes through refractive index-matched materials. To meet these physical and optical demands, we recently developed a rapid hydrogel encapsulation method suitable for light sheet imaging of living, immobilized *C. elegans* of all developmental stages. We identified a range of suitable hydrogel and crosslinking conditions, including some providing paralytic-free restraint, and characterized worm immobilization for high-resolution single-cell imaging. We determined that the hydrogel has similar light scattering properties and autofluorescence compared to low melt agarose, a material standardly used for light sheet imaging. Additionally, we recorded volumetric images of GCaMP responses in sensory neurons expressing the Chrimson red-light-activated ion channel in the same animal for over 14 hours, and observed distinct responses in dendrite and soma compartments. We also demonstrated the versatility of our technique by immobilizing soft marine organisms, such as jellyfish and pigmy squid. Overall, we envision the combination of long-term 3D volumetric imaging with spectrally-separated optical excitation and monitoring of neural circuits will be useful for numerous functional neuroscience experiments in *C. elegans* and other small organisms (e.g., *Drosophila* and zebrafish).

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**Poster**

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**Topic:** I.04. Physiological Methods

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ANR-10-INSB-04-01 (France Bioimaging)
NIH Grant 1U01NS103464-01 (Brain Initiative)

**Title:** Fast sampling of calcium transients by 3d-random-adress scanningof neurons in V1 cortex across multiple layers in awake mice

**Authors: *W. AKEMANN**[1], J.-F. LÉGER[2], V. VILLETTE[2], B. MATHIEU[2], C. VENTALON[2], S. DIEUDONNÉ[2], L. BOURDIEU[2]
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**Abstract:** Fast optical sampling of in-vivo neuronal activity by 2photon excitation microscopy of activity indicators usually remains limited to cell bodies and dendrites in the objective focal plane. We developed a new type of 2-photon microscope which is capable of sampling electrical activity from 3D cortical networks of neurons in head-fixed animals up to kilohertz rate. The microscope operates in a non-imaging mode where individual laser pulses are spatially modulated with tilt and defocus to sample the data from individual cell bodies within a 400x400x400 $\mu m^3$ volume of cortical sheet by random-address rather than scan of the entire volume. Single pulse modulation is achieved by a two-axis, large-aperture acousto-optic spatial light modulator synchronized to a 40 kHz regenerative and parametric laser amplifier. Individual pulses are further modulated in phase and amplitude to pattern the beam into a square array of up to 25 focal spots targeting the bodies of individual cells, interleaved with a pattern of 10 spots targeting the surrounding neuropil. The spatial patterning of the beam helped to raise the single pulse photon yield and to dampen significantly motion-induced signaling artefacts during locomotion and posture change of the animal. We validated the microscope by recording single unit activity from neurons in primary visual cortex after viral expression of the calcium indicator GCaMP6f in principal cells and interneurons of layer 2/3 and 5A while the animal was free to move on a treadmill. In agreement with published data we find a significantly higher level of spontaneous activity of layer 5 cells, including a higher incidence of large amplitude burst

discharge, while layer 2/3 cells were more sensitive to the orientation of a moving contrast grating when presented as visual stimulus.

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**Poster**

**796. Physiological Methods: Optical Methodology: Application**

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**Program #/Poster #:** 796.24/MMM39

**Topic:** I.04. Physiological Methods

**Support:** Keck Foundation

**Title:** Ultrasound neuromodulation via spatially confined miniaturized fiber-optoacoustic converter

**Authors: *Y. JIANG**[1], H.-A. TSENG[1], L. LAN[2], S. S. CHA[2], H. MAN[3], C. YANG[4], X. HAN[2], J.-X. CHENG[2]
[2]Dept. of Biomed. Engin., [3]Biol. Sci., [4]Chem., [1]Boston Univ., Boston, MA

**Abstract:** Ultrasound has been recently explored as a new modality for neural modulation. It has the unique advantages of noninvasiveness However, the bulky size of commercially available transducers prevents the integration of ultrasound modulation with freely behaving animal, and the focal size of the commercially available transducer is several millimeters in diameter, comparable to the size of a mouse brain. Here, we developed a miniaturized Fiber-Optoacoustic Converter (FOC), which has a diameter of 600 μm, and can convert nano-second laser pulses into acoustic waves. The generated acoustic energy is estimated to be 0.4 MPa, with a center frequency of 2 MHz and a variable repetition rate from 100 Hz to 10 kHz. Using this FOC system, we show that ultrasound can directly activate individual neurons, generating intracellular Ca2+ changes both in vitro and in vivo. Neurons closer to the FOC will more likely to be activated than neurons further away. We also provide evidence of transient membrane poration as the mechanism for ultrasound neural modulation. Finally, we demonstrate that the motor behavior can be altered when acoustic stimulation is delivered to the motor cortex by the FOC in live behaving mouse.

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