TRIANGLE CHAPTER
SOCIETY FOR NEUROSCIENCE

4th Annual Spring Neuroscience Meeting

2018

Program and Abstracts

May 24th, 2018

Embassy Suites, RTP

Triangle_SfN

TriangleSfN

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Neuroscience and Neurosurgery Research

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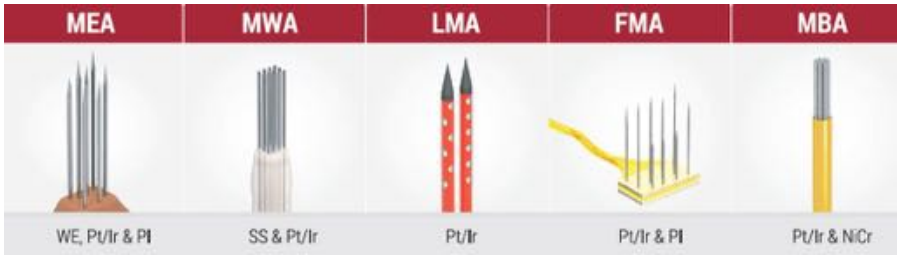

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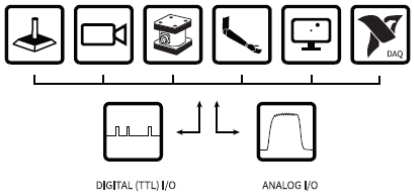

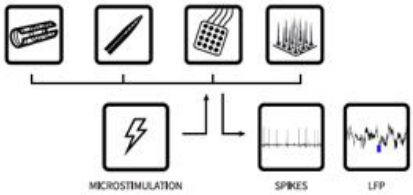

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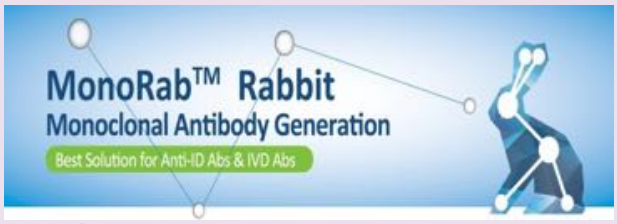

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Congressional Letter

RICHARD BURR
NORTH CAROLINA

United States Senate
WASHINGTON, D.C. 20510

May 24, 2018

North Carolina Triangle Chapter
of the Society for Neuroscience

Dear Friends:

I send my best wishes as you meet today for the 4th Annual Spring Neuroscience Conference. The research being done in North Carolina on a variety of health issues is imperative in the search for treatments and hopefully for cures.

Events such as you are hosting today are great opportunities for the participants to learn more about current advances and possibilities in the field of neuroscience. I hope each of you will be able to share from your experiences as well as find information which will open new doors in your research field.

North Carolina is proud to be home to such wonderful research facilities and the work you are all doing. Thank you for your continued efforts, and best wishes for a great day.

Sincerely,

Richard Burr
United States Senator

Congressional Letter

Senator Thom Tillis
North Carolina

U.S. Senate
Washington D.C. 20510

May 24, 2018

Dear Friends,

I am pleased to extend my best wishes to everyone gathered at the North Carolina Triangle Chapter of the Society for Neuroscience's 4th Annual Spring Neuroscience Conference. While my Senate schedule prevents me from attending today's event, I would like to acknowledge keynote speaker Dr. Patricia Janak as well as our distinguished local speakers for their hard work and innovative research within this field.

This conference is a unique opportunity for attendees to learn about the critical concerns that are faced by our communities and nation. I applaud the efforts of the Society to support local scientists and physicians in furthering neuroscience research. It is an honor to represent a state that is home to our nation's premier research institutions, and I commend the important work that you are doing.

Please feel free to contact my office if I can ever be of assistance to you. I wish you all the best for a successful and informative event.

Sincerely,

Thom Tillis
U.S. Senator

Website

TRIANGLE CHAPTER
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Program

10:00 A.M. **Presidential Welcome**

Local Speaker Presentations:

10:10 A.M. **Dr. Alison Adcock**

Associate Professor of Psychiatry and Behavioral Sciences, Duke University

"Motivations to Learn: Neural Contexts and Plastic Systems"

10:45 A.M. **Dr. Heather Patisaul**

Professor of Biological Sciences, NC State University

"Endocrine disruption of neuroendocrine pathways and behaviors"

11:20 A.M. **Dr. Ben Philpot**

Professor of Cell Biology & Physiology, UNC Chapel Hill

"Angelman syndrome treatment opportunities and clinical biomarkers"

Poster Sessions, Lunch, & Networking

12:00 P.M. Poster Session I and Vendor Exhibits
1:00 P.M. Lunch / Networking Topic Tables
2:00 P.M. Poster Session II and Vendor Exhibits

Keynote Address & Awards Ceremony

3:10 P.M. **Dr. Patricia Janak**

Bloomberg Distinguished Professor
Krieger School of Arts & Sciences, Department of Psychological and Brain Sciences
School of Medicine, Department of Neuroscience

"How does dopamine mold your behavior? Behavioral neuroscience studies of dopamine, learning, and motivation"

4:15 P.M. Poster Awards & Reception

Speakers

Patricia Janak, PhD

"How does dopamine mold your behavior? Behavioral neuroscience studies of dopamine, learning, and motivation"

Dr. Patricia Janak joined the Hopkins faculty in 2014 as a Bloomberg Distinguished Professor with appointments in the Department of Psychological and Brain Sciences in the Krieger School and the Department of Neuroscience in the School of Medicine. Dr. Janak earned her bachelor's degree in psychology and biology from Rutgers University and her PhD in biopsychology from the University of California, Berkeley, and conducted postdoctoral research at the Wake Forest School of Medicine and the National Institute on Drug Abuse, National Institutes of Health. From 1999 to 2014, Dr. Janak was faculty at the University of California, San Francisco where she was the Howard J. Weinberger, M.D., Endowed Chair in Addiction Research at the University of California, San Francisco.

Dr. Janak is an internationally-recognized leader in behavioral and systems neuroscience of learning and addiction. She has made critical contributions that have enhanced our understanding of the neurobiology of reward learning, both under normal conditions, and in pathological conditions, such as addiction. Dr. Janak's work seeks to combine psychology's animal models of learning with neuroscientific approaches for measuring and manipulating neural activity to delineate biological mechanisms of reward learning. At Hopkins, she is applying this approach to understanding the role of amygdala-prefrontal circuitry in emotional learning, and to defining the contribution of dopamine neuronal activity in natural and drug reward seeking.

Dr. Janak serves on the executive and steering committees for the Kavli Neuroscience Discovery Institute, as well as the steering committee for the Science of Learning Institute, a cross-disciplinary effort to accelerate science-to-practice translation along the continuum of learning, from basic research in molecules and genes to the creation of effective public school policy. She has been the recent Chair of the NIDA Board of Scientific Counselors, and will Chair the Program Committee for the annual Society for Neuroscience meeting in 2019.

Alison Adcock, MD, PhD

Heather Patisaul, PhD

Ben Philpot, PhD

Presidential Remarks

Welcome message from the President:

Dear Colleagues and Friends,

It is an honor to welcome you to our 4th Annual Triangle SfN Spring Meeting. Over the past few years, our annual conference has provided a venue to highlight the outstanding research of our diverse neuroscience community. We are pleased by your continued interest and support, and are happy that we can again offer a full day of new and exciting research presentations.

This year, we have invited four distinguished neuroscientists to speak at our meeting. It is with great pleasure that we welcome Drs. Alison Adcock of Duke University, Heather Patisaul of NC State University, Ben Philpot of UNC Chapel Hill, and our keynote speaker Dr. Patricia Janak of Johns Hopkins. We are also pleased to offer two poster sessions and a special lunch networking session to allow students and trainees to explore a variety of career opportunities with prominent neuroscientists in the area.

This meeting depends on the hard work of our talented councilors, and committee members. I would like to personally thank our many graduate students and postdoctoral fellows who are the driving force of our chapter. Through their hard work and commitment, we have made great strides in our outreach and advocacy programs. As our membership continues to grow, I would encourage all members, at all stages of your career, to commit to service to our chapter. Please be sure to visit our committee interest tables throughout the day to explore opportunities in outreach and policy within our chapter.

I want to thank all of our members and sponsors for joining us today. I look forward to your continued participation in our neuroscience communities' vibrant, scientific exchange.

Patricia Jensen, Ph.D.
Triangle SfN Chapter President
Investigator
Developmental Neurobiology Group
National Institute of Environmental Health Sciences

SESSION 1; ABSTRACT NO. 1

Role of CA2 Neuronal Activity Level in Conditioned Fear Learning

GM Alexander, NV Riddick, D Lustberg, SS Moy, SM Dudek
Laboratory of Neurobiology, NIEHS, Research Triangle Park, NC 27709

Hippocampal pyramidal cells (PCs) are critical for certain forms of learning and memory, and work from our lab and others has shown that PCs in CA2 are required for social cognition and behavior. Permanently silencing CA2 PCs in mice impairs social memory, and we found that chemogenetically increasing or decreasing CA2 PC activity increases or decreases sociability, respectively. Further, mice lacking Regulator of G-Protein Signaling 14 (RGS14), a protein that is highly enriched in and restricted to CA2 PCs, learn faster than wild-types (WTs) in the Morris water maze spatial memory test. CA2 PCs in these RGS14 knock-out (KO) mice have increased excitability and a capacity for LTP at CA3 CA2 synapses in stratum radiatum, where LTP normally does not occur. Although the enhanced spatial learning abilities of the RGS14 KO mice suggest a role for CA2 PCs in at least one hippocampus-dependent behavior, the role of CA2 PCs in fear conditioning is unknown. Fear conditioning, a form of associative learning, involves the hippocampus and extrahippocampal brain structures such as the prefrontal cortex and amygdala. Because we found that chemogenetic modification of CA2 PC excitability altered prefrontal cortical activity, we asked how modifying CA2 PC activity would affect fear conditioning. We expressed Gq- or Gi-coupled DREADDs in CA2 PCs and administered CNO before the shock-tone-context pairing. On subsequent days, we measured freezing behavior in the same context but without the tone (contextual fear) or in a new context but in the presence of the tone cue (cued fear). We found that activation of CA2 PCs during the shock pairing resulted in increased freezing behavior in male and female mice upon cue presentation. Because both Gq DREADD expression and RGS14 deletion increases CA2 PCs activity, we also measured conditioned fear responses in RGS14 KO mice. We predicted that, similar to Gq-DREADD-expressing mice, RGS14 KO mice would show enhanced freezing behavior. Indeed, RGS14 KO mice had increased freezing upon cue presentation relative to WTs. Interestingly this effect was only seen in female KO mice. Emerging evidence from our lab suggests that sex differences arise following manipulations of CA2 activity; for instance, chemogenetic inhibition of CA2 PCs during the shock pairing resulted in increased freezing in the associated context in female, but not male, mice. These findings support the conclusion that CA2 PC activity plays a functional role in the corticolimbic circuitry that includes prefrontal cortex and amygdala. Given the behavioral sex differences in the Gi-DREADD and RGS14KO mice, we propose that the function of CA2 PCs in this circuitry may be sexually dimorphic.

SESSION 1; ABSTRACT NO. 2

Beta Adrenergic Blockade Impairs Performance on an Emotional Learning Task

E Armstrong-Carter, KL Humphreys, JK MacCormack, S Meltzer-Brody, KA Lindquist, KA Muscatell
Department of Psychology and Neuroscience, University of North Carolina at Chapel Hill, 27514

Emotional learning, the fundamental process by which a once neutral object acquires value or valence because of its capacity to predict a rewarding or threatening outcome, is complex and dynamic. Research suggests that emotional learning is influenced in part by underlying peripheral physiology, specifically the sympathetic nervous system. However, no known studies have manipulated sympathetic arousal to examine its causal role in emotional learning

outcomes. Thus, in the present study, we administered a beta adrenergic receptor blocking medication propranolol, which attenuates sympathetic activation, in a randomized, double-blind, placebo-controlled study to determine if blunting of sympathetic arousal impairs individuals' adaptive emotional learning. Eighty-five young adults (55% male, average age 21) were randomly assigned to take either 40 mg of propranolol or a placebo. Three hours later, participants completed the Balloon Emotional Learning Task (BELT), a computerized exploration-based instrumental emotional learning task that presents a series of balloons which are pumped up for points. Critically, balloons explode after either a short, long, or variable number of pumps, and thus participants must learn the association between the color of the balloon and the number of pumps after which it explodes. Results indicated that participants who received propranolol performed worse, ie. scored fewer points, on the BELT ($M = 336$, $SD = 72$) compared to those on placebo ($M = 380$, $SD = 78$), $t(87)=2.70$, $p = .008$. Thus, participants on the beta-blocker appeared to have compromised emotional learning when compared to those on the placebo. These results suggest that the sympathetic adrenergic response is a critical component to effective emotional learning. These findings contribute to an understanding of the specific physiological processes that impact the neuroscience of learning and cognition.

SESSION 1; ABSTRACT NO. 3

Loss of Diacylglycerol Kinases Eta and Iota Disrupts Maternal Care and Neuropsychological Behavior in Female Mice

V Bartsch, M Zylka
University of North Carolina Department of Cell Biology and Physiology

Diacylglycerol kinases (DGK) regulate neuronal activity by phosphorylating diacylglycerol (DAG) and monoacylglycerol (MAG), two important lipid signaling molecules. Disrupting DGK function or DAG and MAG balance alters neuronal function and mouse behavior. Of the ten mammalian DGK genes, each has a unique tissue expression pattern and affects different biological processes. Both DGK eta (DGKη) and iota (DGKι) are expressed throughout the brain and have been linked to mental and cognitive disorders, including schizophrenia, bipolar disorder, depression, and ADHD. To determine the role of these genes in mouse behavior, we generated mice lacking expression of both DGKη and DGKι (double knockout, dKO). We quickly discovered a striking phenotype: fewer than 30% of dKO mothers' offspring survive to weaning, compared to 85% survival of wild type litters. Interestingly, pups born from dKO dams survive comparable to wild type pups when cross-fostered by wild type dams, suggesting the low survival rate is due to deficiencies with dKO mothers. Whereas dKO mothers make decent nests and retrieve stray pups properly, they fail to nurse sufficiently, as demonstrated by the diminished presence of milk spots in newborns. Additionally, dKO females show erratic, panicked responses to cage disturbances. To understand the behavioral basis for the maternal defect in the dKO mice, we tested for neuropsychological phenotypes. The dKO females show anxiety and mania, which are not seen in mice lacking DGKη or DGKι alone. To test the hypothesis that anxious and manic behavior contributes to poor maternal care, we treated dKO dams with sertraline, a drug used to treat anxiety and panic disorder—conditions whose symptoms match dKO female behavior. Indeed, peripartum sertraline treatment more than doubled the survival rate of pups mothered by dKO mice. Our research reveals the important contributions of DGKη and DGKι to psychological disorders and provides potential targets for future therapies.

SESSION 1; ABSTRACT NO. 4

Substantia Nigra Tyrosine Hydroxylase+ Neuronal Degeneration in HIV-1 TG Rats: Association with Neuroinflammation

C Bowen, W Rosenblatt, C McPherson, G Harry
DNTP, NIEHS, Durham, NC 27709

Despite the introduction of combined antiretroviral therapy (cART), human immunodeficiency virus-1 (HIV) remains present and active in the central nervous system (CNS) contributing to cognitive and motor impairment termed HIV-associated neurocognitive disorders (HAND). Animal models have suggested a role for altered synaptic connections, axonal transport, dopaminergic function, and inflammation in the process. The HIV-tg rat expresses all of the HIV viral genes except the gag-pol replication genes and exhibit features seen in HIV including behavior deficits and synaptic-dendritic alterations. Using this rat, we examined the age-related association between motor function, learning and memory, dopaminergic neurons, inflammation, and microglia reactivity. Male HIV-1 Tg rats showed diminish performance but demonstrated learning in an active avoidance paradigm at 6 and 12 weeks-of-age. The hippocampus showed no evidence of neurodegeneration or glial response as late as 5-months of age. Motor performance on an accelerating rota-rod was observed at 6 and 12 weeks-of-age, suggestive of an alteration in the dopaminergic system. An age-dependent decrease in the number of tyrosine hydroxylase (TH)+ neurons in the substantia nigra (SN) was observed by 8 months-of-age. At 5-months of age, TH+ neuronal number was not altered with no evidence of a early reactive change in astrocytes or microglia. In the striatum, Iba-1+ microglia displayed thicken apical processes yet, with no differentiation to an amoeboid phenotype. mRNA levels for Iba-1 were elevated with no change observed for Gfap, Tnfa, Il1b. A decrease in Il1a, Cxcr3, Icam mRNA levels may represents a dysregulated microglia response similar to that previously identified in human HIV patients (DeVaughn et al., 2015). Overall, the data supports an alteration in the dopaminergic system in the HIV-1 Tg rat. The progressive loss in TH+ neurons is accompanied by a slight response of microglia in the terminal field of the striatum.

SESSION 1; ABSTRACT NO. 5

The Brain-Enriched E3 Ligase TRIM67 Regulates the Growth Cone Cytoskeleton in Axon Guidance

N Boyer, C Monkiewicz, S Gupton
University of North Carolina at Chapel Hill; Chapel Hill, NC 27599

During development, neurons extend axons across long distances to find postsynaptic partners and create neuronal networks. Additionally, axons branch upon reaching their target regions to increase network complexity. At the distal end of an extending axon, the dynamic filopodia-rich growth cone senses extracellular guidance cues and facilitates directional extension of the axon. This requires tight spatial and temporal modulation of the F-actin cytoskeleton, which is reorganized rapidly in response to extracellular guidance cues. We found that at lower concentrations, the extracellular guidance cue netrin-1 increases growth cone filopodial stability and density and induces attractive axon turning, whereas higher netrin concentrations collapse and repulse the growth cone. The mechanisms by which netrin and its receptor DCC alter cytoskeletal machinery in these distinct responses however have not been fully elucidated. Here we show that TRIM67, a member of the tripartite motif protein family of E3 ubiquitin ligases, interacts with DCC and is integral to both the attractive and repulsive responses to netrin. Using murine embryonic cortical neurons, we find that the growth cones of Trim67-/- axons do not increase in size or number of filopodia in response to a low concentration of netrin as do wild-type growth cones, and do not collapse in response to a high concentration

of netrin. However, Trim67-/- axons respond appropriately to other cues. We find that TRIM67 regulates filopodia stability and localizes to the tips of filopodia, where it colocalizes and cotransports with the barbed end actin polymerase VASP. We show that TRIM67 and VASP interact and that TRIM67 regulates the dynamics of VASP at filopodial tips in response to netrin-1. We also find that TRIM67 regulates the ubiquitination of VASP, which we have previously shown to be required for proper filopodial and growth cone responses to netrin-1. These results suggest that TRIM67 mediates cytoskeletal reorganization in response to netrin downstream of DCC, as a member of the filopodial tip complex. This regulation is likely critical to appropriate neuronal morphogenesis, as we find that netrin-dependent axon branching is absent in Trim67-/- neurons in vitro, and in vivo the cortical corpus callosum projection is thinner in the absence of Trim67.

SESSION 1; ABSTRACT NO. 6

Characterization of The Temporal and Spatial Dynamics of Electrically-Evoked H2O2 in the Extracellular Space of Rat Tissue

K Butler, C Lee, L Wilson, T Rashid, S Panda, C Meunier, L Sombers
Chemistry Department; North Carolina State University; Raleigh, NC 27607

Hydrogen peroxide is a reactive oxygen species that is implicated in many neurodegenerative diseases. It participates in normal modulation of cell function; however, it can also contribute to oxidative stress, neuronal dysfunction, and cell death. Hydrogen peroxide is membrane permeable, allowing for it to diffuse through cells and into the extracellular space following its formation. There is a critical gap in understanding the unique role hydrogen peroxide plays within the brain, as dynamic changes in concentrations of extracellular hydrogen peroxide in living tissue are not well known. Previous attempts to understand this have been hindered by insufficient detection sensitivity and selectivity with conventional analytical techniques. However, fast-scan cyclic voltammetry (FSCV) allows for reliable detection of rapid fluctuations in hydrogen peroxide on a sub-second timescale. This experiment utilizes FSCV coupled with carbon-fiber microelectrodes in intact brain tissue to investigate striatal hydrogen peroxide fluctuations with changes in dopaminergic pathway activity, elicited by electrical stimulation. A novel double waveform has been developed to facilitate removal of interference from sources that generate background subtracted current at potentials near the peak oxidation potential of hydrogen peroxide, such as shifts in pH. Striatal hydrogen peroxide oxidation was monitored following electrical stimulation of dopaminergic fibers that innervate the recording region. Stimulations were delivered at varying frequencies (30 and 60 Hz) using increasing pulse numbers. The data demonstrate that changes in the hydrogen peroxide signal correspond with the duration of the stimulation. The results will elucidate the dynamic relationship between hydrogen peroxide and dopamine in the striatum in response to neuronal activation.

SESSION 1; ABSTRACT NO. 7

Monitoring Real-Time Opioid Peptide Fluctuations with Multiple Scan Rate Voltammetry

SE Calhoun, CJ Meunier, CA Lee, SK Smith, GS McCarty, LA Sombers
Chemistry Department, North Carolina State University, Raleigh, NC, 27695

Opioid signaling in dopaminergic circuits is critically implicated in natural and drug reward-seeking behaviour, as well as in motor control. However, the precise modulatory action of opioids remains ambiguous. Although several methods exist for monitoring dopamine in reward-related brain nuclei, few tools are available for selectively monitoring dynamic fluctuations of endogenous opioid neuropeptides. We are characterizing a novel fast-scan cyclic voltammetric (FSCV) waveform for monitoring

dynamic fluctuations of endogenous opioid peptides, such as methionine-enkephalin (M-ENK), in real time. This approach utilizes two scan rates and an amperometric hold in every voltammetric sweep to afford reproducible, sensitive, and selective measurements. Importantly, our electrochemical approach enables simultaneous detection of multiple chemical species in each scan, including dopamine. Thus, we have simultaneously measured rapid fluctuations of dopamine and M-ENK in the dorsal striatum of an adult, male rat, and investigated chemical dynamics during consumption of unexpected, palatable food reward. Collectively, this new approach with enable measurements that could elucidate a modulatory role for dynamic, striatal M-ENK fluctuations in endogenous opioids and prove invaluable for developing improved strategies to treat a variety of disorders including pain and drug abuse.

SESSION 1; ABSTRACT NO. 8

Characterization of a Novel Rat Monoclonal Antibody Against Murine P2RY12 for Specific Detection and Isolation of Microglia

A Cartier, L Dissing-Olesen, J Moyron-Quiroz, H Zhang, K Cohane, M Tam, B Stevens, P Taylor
BioLegend, San Diego, CA

Introduction: Microglia are the brain and spinal cord-resident macrophages that function as sentinels in maintaining CNS homeostasis. Dysregulation of these sentinels has been associated with neuropsychiatric and neurodegenerative disorders. A major limitation in understanding microglial contribution to cellular processes and their role in disease has been the lack of tools to specifically distinguish these cells from the other myeloid cells. In an effort to produce a novel, microglia-specific tool, we have generated a rat monoclonal antibody (clone S16007D) against murine Purinergic Receptor P2Y12 (P2RY12), a highly selective marker for microglial cells that enables immunostaining in histological sections as well as isolation of these cells by Flow Cytometry (FC) and magnetic nanobeads.

Methods: The specificity of the P2RY12 antibody was validated using IHC and FC in murine brain tissue sections and a stable cell line overexpressing murine P2RY12, respectively. Using FC, the phenotype of corresponding tissue resident macrophages was confirmed by their CD45 and CX3CR1 expression in single cell suspensions from mouse brain, spleen liver, and lungs. In addition, we assessed LPS-induced alterations in P2RY12 expression, an inflammatory stimulus known to downregulate P2RY12 and to induce amoeboid morphology in microglia. We also validated the utility of the P2RY12 antibody to isolate microglia with high purity and yield with BioLegend's Mojosort™ magnetic cell separation system. Single cell suspensions were prepared from C57BL/6 mouse brains using trypsin digestion followed by a 70/37/30% percoll gradient to remove myelin. Microglia were then isolated using biotinylated P2RY12 antibody, followed by incubation with streptavidin nanobeads. Isolated cells were co-stained with CX3CR1 and CD11b as general markers for microglia, and FC quantification demonstrated the purity of microglia above 99%.

SESSION 1; ABSTRACT NO. 9

Neurogenetic Analysis of CYFIP2's Role in Establishing the Acoustic Startle Threshold

J Deslauriers, D Burton, K Marsden
Department of Biological Sciences, North Carolina State University, Raleigh, NC, 27607

Animals experience a constant stream of sensory stimuli, and to effectively navigate their environments they must filter out irrelevant stimuli and respond to important ones. For example, a sudden loud sound triggers a highly conserved startle response that enables animals to escape from danger. An appropriate threshold for this behavior must be established such that threats are detected but innocuous stimuli are ignored. Startle threshold dysregulation

can produce hypersensitivity associated with autism and anxiety-related disorders, yet the genetic regulation of this threshold is poorly understood. Previously, a forward genetic screen using an unbiased, high-throughput system to analyze larval zebrafish responses to acoustic stimuli isolated five hypersensitive mutant lines. A causal nonsense mutation was identified in one line in Cytoplasmic Fragile X Mental Retardation Protein Interacting Protein (FMRP) 2 (cyfip2), but the principle pathways by which cyfip2 regulates the startle threshold remain unknown. Cyfip2 binds Rac1 to promote actin polymerization and may regulate local RNA translation through its interaction with FMRP. To determine whether the Rac1 or FMRP pathways are engaged by cyfip2 to regulate the startle threshold, we will create stable transgenic lines expressing mutant cyfip2 in which critical residues for Rac1 or FMRP binding are altered. Failure of these transgenes to rescue startle sensitivity in cyfip2 mutants would indicate that cyfip2 interaction with Rac1 or FMRP is required to regulate the acoustic startle threshold. To identify where cyfip2 is required, previous work used in vivo Ca2+ imaging to reveal that spiral fiber neurons (SFNs), hindbrain excitatory interneurons that contact the startle command-like neurons, the Mauthner cells, are hyperactive in cyfip2 mutants. We will transgenically express cyfip2 in SFNs or their upstream inputs, the auditory nerve neurons, to determine whether cyfip2 expression in these cells is sufficient to restore normal startle sensitivity. Finally, we are working to identify additional genetic regulators of the startle threshold using two approaches. First, candidate mutations identified in 2 hypersensitive mutant lines will be validated using CRISPR-Cas9. Second, we have observed significant differences in startle sensitivity between laboratory zebrafish strains and will use eQTL mapping to locate potentially associated genetic variants. In summation, these experiments will identify molecular and cellular mechanisms that regulate the acoustic startle threshold, thereby revealing direct links between genes, neural circuits, and a critical survival behavior.

SESSION 1; ABSTRACT NO. 10

Reversal of AIE-Induced Neuronal Death and Diminished Neurogenesis by Donepezil (Aricept)

K Dubester, W Liu, KL Healey, FT Crews, HS Swartzwelder
Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham NC 27705

Binge drinking is prevalent in adolescents and is likely to have lasting effects on brain function and behavior. However it is difficult to untangle the mechanisms that may underlie these effects in humans due to the interacting effects of genetic and environmental factors. Thus, studies in animal models are essential for better understanding the long term changes caused by alcohol exposure during this critical period of brain development. Adolescent intermittent ethanol (AIE) exposure is an animal model of underage drinking that induces persistent hippocampal changes including deficiencies in cholinergic inputs, alterations of synaptic and glial function, decreases in neurogenesis, and increases in neuronal death. Assessing the reversibility these AIE-induced changes is an important first step toward developing pharmacological interventions to treat the enduring effects of adolescent alcohol exposure. Donepezil (Aricept) is a selective, reversible cholinesterase inhibitor that is clinically used to ameliorate memory-related cognitive deficits. It also acts as a neuroprotective agent in the hippocampus, and we have found that it can reverse some AIE effects, including diminished dendritic spine density and aberrant Fmr1 gene expression. Therefore we hypothesized that pharmacological upregulation of cholinergic function with donepezil would reverse AIE-induced hippocampal deficits related to neurogenesis and cell survival.

SESSION 1; ABSTRACT NO. 11

Region Specific Differences in Morphometric Features and Synaptic Contact of Astrocytes During Development

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Adolescence is a critical period of CNS development and maturation. Among the distinctive behavioral characteristics of adolescence is increased risk taking, which may be driven by immature circuit formation in the prefrontal cortex that is not fully developed until late adolescence or early adulthood. Adolescence is increasingly found to be a vulnerable period for the development of substance use disorders, including alcohol abuse. Importantly, many adults who meet criteria for alcohol abuse disorder are found to have initiated drinking in early adolescence. In animal models, adolescent intermittent ethanol (AIE) exposure induces enduring neurobiological effects including a 'lock-in' of adolescent behavioral and cognitive phenotypes, as well as alterations of synaptic transmission and plasticity, that persist into adulthood. In addition to the enduring neural and behavioral sequelae of adolescent alcohol exposure, thrombospondins and astrocyte reactivity are increased in adult hippocampi, three weeks after AIE. Astrocytes are highly branched glia with perisynaptic processes (PAPs) that tightly hug the synapse. They aid in neuronal synapse formation and maturation during development and modulate synaptic transmission throughout the lifespan. The ability of PAPs to enshealthe the synapse makes them an ideal candidate to regulate the initiation, formation, maturation and maintenance of synapses that are highly regulated during adolescence. Despite this substantive role of astrocytes during brain development, relatively little is known about the development of astrocytes themselves. Thus, we investigated the morphometric trajectory of astrocytic development and PAP colocalization with synapses through adolescence and early adulthood.

SESSION 1; ABSTRACT NO. 12

Exposure to PFOS, PFHxS, or PFHxA, but not GenX, ADONA, PFOA, or Nafion BP1 Elicits Developmental Neurotoxicity in Larval Zebrafish

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Exposure to per- and poly-fluoroalkyl substances (PFAS) like perfluorooctane sulfonic acid (PFOS) or perfluorooctanoic acid (PFOA) are associated with developmental toxicity, neurotoxicity, and carcinogenesis. Legacy PFAS have therefore been replaced with shorter carbon chain and polyfluoroether compounds. The replacement PFAS GenX was recently discovered in NC drinking water sources; however, little is known about its toxicity. To address this, zebrafish were exposed to 0.044-80.0 μM of PFOA, PFOS, GenX, 4,8-dioxa-3H-perfluorononanoate (ADONA), perfluorohexanoic acid (PFHxA), potassium perfluorohexane-1-sulfonate (PFHxS), perfluoro-3,6-dioxa-4-methyl-7-octene-1-sulfonic acid (Nafion BP1), or 0.4% DMSO with daily renewal on 0-5 days post fertilization (dpf). At 6 dpf, larvae were assessed for developmental toxicity (DevTox). Locomotor activity was also assessed as a functional readout of developmental neurotoxicity (DNT) over a 40 min testing period consisting of two consecutive 10 min light periods (20 lux; L1 and L2) and two consecutive 10 min dark periods (0 lux; D1 and D2). In the DevTox assay, exposure to PFOS and PFHxS resulted in failed swim bladder inflation and ventroflexion of the tail. Exposure to GenX,

ADONA, Nafion BP1, PFHxA and PFOA failed to produce DevTox. In the DNT assay, exposure to non-teratogenic concentrations of PFOS (0.1-3.1 µM) or PFHxS (4.4-44.8 µM) triggered locomotor hyperactivity in the L1, L2, and D1 periods; exposure to 14.0 µM PFHxA produced hyperactivity in both dark phases. No significant locomotor changes were observed following exposure to GenX, ADONA, Nafion BP1, or PFOA. In summary, we identified developmental toxicity in zebrafish exposed to PFOS or PFHxS and DNT in zebrafish exposed to non-teratogenic concentrations of PFOS, PFHxS, or PFHxA. These data demonstrate the utility of using multiple zebrafish assays to rapidly assess the toxicity of replacement PFAS. This abstract does not necessarily reflect EPA policy.

SESSION 1; ABSTRACT NO. 13

The Functional Connectivity of the Resting Brain in Children with Attention Deficit Hyperactivity Disorder

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Attention deficit hyperactivity disorder (ADHD) is a prevalent and detrimental psychiatric disorder that is recently being examined with a distributed network perspective using functional magnetic resonance imaging (fMRI). Specific disruptions in connectivities both within and between intrinsic connectivity networks during a resting state have been considered as a way to characterize various psychiatric disorders including ADHD. Disruptions within the default mode network (DMN) and between the DMN and salience network (SAL) have been implicated in the pathophysiology of ADHD. The current study examined these relationships using independent component analyses on the resting state fMRI scans of 13 children with ADHD and 13 age and gender matched controls. SAL activations were compared between groups to determine whether the SAL was being adequately attenuated in children with ADHD. Our results indicate that the left prefrontal cortical region of the SAL was improperly attenuated, while the left posterior parietal region was overly attenuated during a resting state in children with ADHD compared to controls. Intrinsic connectivity of the DMN was examined using group correlation matrices. Results from this analysis show that some of the connectivities within the DMN exhibited previously determined developmentally delayed trends that highlighted a failure for circuitry to integrate. However, several other connectivities that were found to be disrupted in the current study in children with ADHD were not connectivities that had been identified by previous literature to be developmentally dynamic. Therefore, these findings provide mixed results that do not unanimously support the maturational delay hypothesis of ADHD. Overall, this study's findings provide preliminary evidence that state-inappropriate SAL activations and connectivity disruptions within the DMN are present during the resting state in children with ADHD.

SESSION 1; ABSTRACT NO. 14

Sex Differences in Neurotoxic Effects and Neurotoxic Effects on Sex Differences

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The most common genetic polymorphism is sex. The most obvious sex differences are in reproduction but other sex differences exist. As with factors like height, sex differences in non-reproductive behaviors are not dichotomous but have overlapping continuous distributions. Many studies including our own have shown that neurotoxicants can have differential effects in females and males. In some cases, these effects diminish or reverse normal sex differences in neurobehavioral function. In rats, we have found that exposure to the organophosphate insecticide chlorpyrifos (CPF) significantly reduces normal sex

differences in radial-arm maze spatial working memory, where males typically have fewer working memory errors than females. Low-dose neonatal CPF exposure (1 mg/kg/day, postnatal days 1-4) to rats reduces errors in females and increases them in males, eliminating this normal sex difference. Neurotoxic diminution of normal sex differences is not limited to insecticides. Developmental exposure of rats to a low dose (0.03 mg/kg/day throughout gestation) of the polyaromatic hydrocarbon (PAH), benzo-a-pyrene (BaP) causes a significant reversal of a normal sex difference in locomotor activity in which female rats are normally more active than male rats. Prenatal BaP exposure causes hyperactivity in males but not females, eliminating the normal sex difference in locomotor behavior. Sex-selective effects are also seen with nicotine and BaP exposures in emotional and cognitive tests. Low dose developmental exposure to BaP can have diverse, persistent effects on behavior that impact typical sex differences. The present data will be used to support efforts to educate policy makers and the public on the importance of genetic factors like biological sex in the risk presented by contaminants such as PAHs and pesticides.

SESSION 1; ABSTRACT NO. 15

The Role of Sphingosine-1-Phosphate in Pain and Itch Sensations

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Somatosensations, such as pain, itch, touch and temperature, are essential to detect environmental stimuli to escape, communicate and adapt. These stimuli can be detected by primary sensory neurons whose nerve endings are located in the skin. Although physical, chemical and biological stimulants were well investigated, the mechanisms of endogenous stimulants to the primary sensory neurons, especially lipids, are still largely unknown. In this study, we focus on one of the endogenous lipids, sphingosine-1-phosphate (S1P) and investigate the physiological roles of S1P. First, we examined whether S1P directly induces neuronal responses in primary cultured mouse dorsal root ganglion (DRG) neurons, primary sensory neurons, by using a calcium imaging method. S1P application to DRG neurons increased intracellular calcium concentrations of DRG neurons. In order to distinguish whether the increased cytosolic calcium comes from extracellular space or from cytosolic organelles such as endoplasmic reticulum, we assessed the effect of calcium removal on the responses in DRG neurons and found that the calcium derives from the extracellular side of the DRG neurons. This suggests the involvement of calcium-permeable molecules expressed in the plasma membrane. Transient receptor vanilloid 1 (TRPV1) and ankyrin 1 (TRPA1) are non-selective calcium-permeable cation channels, which are well known to be involved in pain and itch. We asked whether these two ion channels are involved in S1P-induced responses in DRG neurons by using the antagonists and DRG neurons lacking the function of each ion channel. The responding neurons to S1P are reduced by both the antagonists and in both the knockout DRG neurons, suggesting that TRPV1 and TRPA1 mediate S1P-induced DRG responses.
Next, we examined the effect of S1P on pain and itch sensations. We injected S1P into the hind paw to measure acute pain and pain induced by heat, cold and mechanical stimuli and into the nape of the neck to ask whether it induces itch. S1P induced pain and itch and experiments using TRPV1 and TRPA1 knockout mice indicated the involvement of TRPV1.
Together with these data, we found that S1P induced sensory neuron responses dependent on TRPV1 and TRPA1 and that S1P induced pain and itch behaviors, depending on TRPV1.

SESSION 1; ABSTRACT NO. 16

Developmental and Sex Differences of GPER1 And ER α Expression in the Striatum of Male and Female Rats

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The striatum comprises multiple subregions instrumental for behaviors and neurological disorders that show sex differences in incidence and function. It has been suggested that estrogens are primarily driving these sex differences. In adult female rodents, striatal regions express nonnuclear estrogen receptors. However, little is known whether estrogen receptor expression varies across the life span of both females and males. This is a critical gap in knowledge because sex-specific estrogen action varies according to developmental stage. We determined how protein expression of two estrogen receptors, GPER1 which is expressed on membranes, and ERα which can be expressed both in the nucleus and in the membrane, changes between males and females at several developmental time points. We collected brains from males and females at ages P3, P20, and adulthood (>P60; N=18) and stained for GPER1 and ERα using immunofluorescence. We used a confocal microscope to take multiple scans throughout the tissue slices in three major regions of the striatum: dorsal striatum, nucleus accumbens core, and nucleus accumbens shell. We also imaged the cingulate cortex and arcuate nucleus of the hypothalamus as positive controls for GPER1 and ERα expression, respectively. We found that GPER1 expression decreased in the dorsal striatum and increased in accumbens core and shell with age, indicating that GPER1 may be regulated differently between the dorsal and ventral subregions before puberty begins. We did not detect robust sex differences in GPER1 expression. For ERα, although expression was very low, we did observe nuclear staining patterns, especially in P3 females. This expression disappeared as animals aged and seemed more pronounced in females compared to males. This study has provided developmental time windows in which to explore changes in estradiol sensitivity across the striatum. Future directions will determine what is driving the differential regulation between region and sex.

SESSION 1; ABSTRACT NO. 17

Zebrafish Larvae Require Specific Strains of Bacteria for Neurobehavioral Development

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There is an increasing appreciation of the relationship between gut microbiota and nervous system development and function. We previously showed that axenic (microbe-free) larvae are hyperactive at 10 days post fertilization (dpf) relative to colonized zebrafish larvae. Interestingly, while exposure to heat-killed bacteria or microbe-associated molecular patterns failed to block hyperactivity in axenic larvae, colonization of axenic larvae with Aeromonas veronii or Vibrio cholerae produced locomotor hypoactivity relative to colonized controls. These data suggest that there is a developmental requirement for certain types of microbes to modulate host behavior. To address this hypothesis, eight bacterial isolates were obtained from 10 dpf conventionally colonized zebrafish larvae. 16S rRNA gene sequencing identified four unique EPA gram-negative isolates: Acinetobacter, Vibrio, Comamonas, and Comamonadaceae. Colonization of axenic embryos at 1 dpf with 100 cells/mL of Acinetobacter, Comamonas, or Comamonadaceae resulted in behavioral profiles that were identical to colonized control larvae at 8 dpf. In comparison, axenic embryos colonized with EPA Vibrio bacteria were hypoactive relative to control larvae. EPA Vibrio-related hypoactivity was prevented in axenic larvae colonized with 25 cells/mL each of Actinetobacter, Vibrio, Comamonas, and Comamonadaceae at 1 dpf. Finally, EPA Vibrio-related hypoactivity

was found to persist in 10 dpf larvae. These data suggest that specific bacterial taxa are needed to drive neurobehavioral development while colonization with other strains may result in behavioral hypoactivity. This raises the possibility that environmental chemicals may disrupt neurobehavioral development by selecting for specific classes of host-associated microbes. This abstract does not represent EPA policy.

SESSION 1; ABSTRACT NO. 18

Role of the Hippocampus in Context-Heroin Conditioned Immune Suppression

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Through Pavlovian conditioning, heroin-associated environments can produce peripheral immune suppression. A basolateral amygdala-nucleus accumbens (BLA-NAc) circuit is critical for the expression of this conditioned effect. Functional integrity of the dorsal hippocampus (DH) is also required for conditioned immune suppression, yet it is unclear if and how it interacts with this BLA-NAc circuit. To begin to answer this question, we chemogenetically manipulated two major outputs of the hippocampus, the dorsal and ventral subiculum. DREADD-mediated dorsal subiculum (DSub) inhibition in context-heroin conditioned rats, prior to testing, partially attenuated the conditioned suppression of LPS-induced indicators of nitric oxide production. This same manipulation of the ventral subiculum (VSub) prior to testing, however, did not attenuate these conditioned immune measures. These results suggest a role for the DSub, but not the VSub, and DH interactions with other brain regions via the DSub, in heroin-conditioned immune suppression.

SESSION 1; ABSTRACT NO. 19

In Situ Detection of Neuroenergetic Molecules in the Rat Striatum with Fast-Scan Cyclic Voltammetry: Extracellular Availability of Lactate and Glucose Scales with Electrical Simulation of the Dopaminergic Midbrain

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Considerable research has implicated glucose as the principal energy source of the brain. However, several recent studies have challenged this view with the demonstration that lactate is also an essential molecule for energy metabolism and memory formation. The simultaneous, real-time detection of glucose and lactate dynamics in the extracellular space at a single location is imperative to understand brain energy availability and the roles that these molecules play in fueling neuronal function. Our lab previously developed and characterized an enzyme-modified, carbon-fiber microelectrode that enabled the electrochemical detection of real-time glucose fluctuations (Lugo-Morales et al, 2013), along with simultaneous measusrements of dopamine (DA; Smith et al 2017), in the striatum of adult, male rats. However, to date, dynamic measurements of lactate concentrations in the brain have been limited. We have addressed this need by adapting the fast-scan cyclic voltammetry microbiosensor technology to monitor lactate. The modified carbon-fiber microelectrode has a sensitivity and LOD for lactate of 22 ± 1 nA·mM-1 and 7.0 ± 0.7 μM, respectively. Rapid lactate fluctuations are detected with unprecedented spatiotemporal resolution as well as excellent stability, selectivity, and sensitivity. Microbiosensors were used to simultaneously monitor glucose and lactate at discrete recording sites in the rat striatum. Our preliminary results indicate the availability of both energetic substrates increases in the extracellular space in response to dopamine release in the dorsal striatum of an anesthetized rat. Importantly,

the temporal dynamics of striatal lactate were distinct from those of glucose. Extracellular glucose and lactate concentrations in the striatum scale with the intensity and duration of midbrain stimulation, which correlates well with the concentration of DA released. Quantitative investigation of subsecond fluctuations of these key neuroenergetic substrates in both normal as well as disease states and should advance the development of appropriate therapeutic strategies for a variety of disorders.

SESSION 1; ABSTRACT NO. 20

Resting State Coupling Between Salience Network and Central Executive Network Among Cocaine Users Predicts Substance Use Frequency at 30-Day Follow-Up

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Aims: Among individuals with substance use disorders (SUD), cocaine users have one of the highest rates of continued use and prevalence rates in the US. Substance use has been found to be associated with neural dysfunction in regions encompassed by three large-scale networks, the salience network (SN), central executive network (CEN), and the default mode network (DMN). The triple-network model suggests that aberrant connectivity between these three networks may contribute to continued use. The aim of the current study was to test if internetwork connectivity among these three networks predict substance use frequency over a 30-day follow-up period.

Method: Resting-state functional magnetic resonance imaging data was collected from 26 cocaine users (M age =41.2±8.2; 77.8% AA; 7.4% female). Between-network connectivity estimates between the SN, CEN, and DMN were calculated using a dual regression approach resulting in subject-specific time series data and spatial maps corresponding to each network. Time series data was then entered into FSLNets to yield a matrix of partial Pearson correlation coefficients representing direct connection strength of SN, CEN, and DMN network pairs. Resource allocation index (RAI) was calculated to assess the strength of SN-DMN interconnectivity relative to SN-CEN connectivity. Self-reported substance use frequency was collected using the Timeline Followback at a 30-day follow-up visit.

Results: A linear regression revealed a significant effect of RAI on substance use frequency such that greater SN-CEN coupling was associated with less frequent substance use, as measured by fewer days used ($F(1,24) = 5.511$, $p < 0.05$). This model accounted for 18.7% of total variance in 30-day substance use frequency.

Conclusions: Findings suggest that SN-CEN connectivity may be a critical neural mechanism contributing to continued substance use, in line with theoretical conceptualizations of substance use disorders that highlight the role of executive control and emotion regulation processes. More specifically, substance users who allocate resources towards regions associated with these processes (i.e., the CEN) may be better able to engage in goal-directed behavior, such as engaging in less substance use. Future studies may build upon these findings to validate the use of the RAI as a biomarker of substance use outcomes and a potential target for treatment.

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SESSION 2; ABSTRACT NO. 1

Neural correlates of inhibitory control over reward

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The interaction of reward-response and inhibitory control regions has been implicated in adolescent (e.g. Somerville & Casey, 2010) and adult (e.g. Zamir &

Robbins, 2015) risky behaviors; however, the mechanisms through which reward disrupts inhibitory control are not yet well understood. This study aimed to directly test inhibitory control in competition with reward response in typical adults. Participants (N=41, 18y-25y) completed the conditioned appetitive response inhibition task (CARIT) while undergoing fMRI scanning. The CARIT consisted of two stages. First, reward was manipulated in a monetary incentive delay(MID) task. Participants received money for responses to rewarded but not neutral stimuli. Second, the previously rewarded(PR) and previously neutral(PN) MID stimuli served as no-go stimuli in a go/no-go task. fMRI data were pre-processed and analyzed using FSL v5.0. Behaviorally, participants committed significantly more false alarms to PR than to PN stimuli ($p<.05$), reflecting a reward-related disruption in inhibitory control. A full-volume comparison of correctly withheld PR trials to correctly withheld PN trials revealed significantly more activity in bilateral insula, frontal orbital cortex, and putamen for PR than for PN stimuli, FWE corrected $p<.05$. Region of interest analyses were conducted by extracting activity within 6mm radius spheres within bilateral insula, thalamus, ACC, and nucleus accumbens. Results demonstrate that while controlling for neural activity to PN trials, (a) reward-biasing during training in the MID predicts neural activity to PR stimuli during the go/no-go task, (b) neural activity to PR stimuli during the go/no-go task predicts false alarm rate on PR trials relative to PN trials, and (c) neural activity on PR trials mediates the effect of reward-biasing during training on PR false alarm rate relative to PN false alarm rate.

SESSION 2; ABSTRACT NO. 2

Reverse Translation to Discover Relevant Targets for Chronic Pain: GFRA3/Artemin

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Introduction: Chronic pain is a major health problem posing an enormous economic burden to our society. The lack of therapeutic options is driving the current opioid epidemic in humans. One of the limitations in developing potential therapeutics is a lack of understanding of the precise mechanisms in the target disease condition. To overcome this problem, we used naturally occurring osteoarthritis in pet dogs that are highly phenotyped using validated measures of pain. Analyzing tissues from these subjects, we can identify novel targets.

Objectives: To identify novel targets for pain treatment using samples from pet dogs with naturally occurring osteoarthritis.

Methods: From mouse RNA-sequencing data we determined the GDNF family receptor alpha 3 (GFRA3) is highly colocalized with the TRPV1-ion channel and thus possibly connected with pain hypersensitivity. Canine samples collected from highly phenotyped dogs (subjective assessment; ground reaction forces; quantitative sensory testing) were subjected to qRT-PCR (dorsal root ganglia [DRG]) and ELISA (serum).

Results: We found expression of GFRA3-receptor significantly increased in dorsal root ganglia (DRG) serving osteoarthritic (OA) joints (n=12) compared to normal ($p<0.01$) (n=12). Additionally, using samples from highly phenotyped normal (n=22) and OA dogs (n=54) serum artemin (GFRA3 ligand) was significantly elevated in OA dogs ($p<0.05$). Our results strongly implicate a role for GFRA3 and its ligand artemin in OA pain. These results show that samples from well-characterized (phenotyped) canine patients can be used to uncover potential novel mechanisms involved in pain states.

SESSION 2; ABSTRACT NO. 3

Single Nucleotide Variants in Zebrafish After Crispr-Cas9 Editing in Vivo

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CRISPR-Cas9 genome editing offers a promising technological advance toward correcting genetic disorders. However, this optimism has been tempered with caution regarding the specificity of the approach and uncertainty of the possible extent and nature of off-target effects. To investigate whether CRISPR-Cas9 genome-editing in vivo produces a higher occurrence of point mutations than expected from the baseline mutation rate, we performed whole exome sequencing (WES) on 54 individuals from a parent-offspring paradigm in the presence or absence of guide RNA and/or Cas9 protein. We obtained DNA from 52 zebrafish embryos from the same clutch; these individuals were subjected to CRISPR/Cas9 injection at the single-cell stage with 6 independent single guide RNAs (sgRNAs) targeting three different genes in the presence or absence of Cas9 protein. After excluding variants overserved in the parents, filtering out variants reported at the on-target CRISPR-Cas9 editing sites, and exclusion of naturally occurring variants reported in SNPFisher, we observed an aggregate of 274 variants unique to control conditions, 735 variants unique to sample conditions, and 83 variants in both conditions. Next, we asked whether our variant counts differed between control and CRISPR/Cas9-edited samples, and found a marginally significant difference ($p=.055$). This difference aligned with the presence or absence of Cas9 ($p=.065$), regardless of the sgRNA guide. Furthermore, we asked whether any observed variants occurred in predicted off-target regions reported by the CRISPRdirect engine for each sgRNA and found no variants occurring at any of the 5,994 predicted off-target sites. These data suggest that the potential for CRISPR-Cas9 editing at off-target sites is modest, at least in zebrafish, and that the trend for off-target point mutations is more likely mediated by Cas9 activity than insufficient guide-specificity. In addition, because the reported variants are in coding sequence, we are currently investigating the potential for heritability and deleterious phenotypic effects.

SESSION 2; ABSTRACT NO. 4

Highly Selective and Mechanically Robust Sensors for Electrochemical Measurements of Real-Time Hydrogen Peroxide Dynamics in vivo

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The role of hydrogen peroxide in the complex environment of the brain is not well understood. Hydrogen peroxide plays several important roles – for instance, it serves as a key chemical player in normal physiological processes such as cellular respiration, a modulator of dopaminergic signaling, and its presence can indicate the upstream production of more aggressive and short-lived reactive oxygen species (ROS). As such, hydrogen peroxide has been implicated in several neurodegenerative diseases, including the slow destruction of dopaminergic neurons in Parkinson's disease (PD). This creates a critical need to identify the mechanisms by which hydrogen peroxide modulates cellular processes in general, and how it affects dopamine (DA) neurons in the nigrostriatal DA pathway, in particular. Hydrogen peroxide dynamics can be detected in real time using fast-scan cyclic voltammetry (FSCV) at carbon-fiber electrodes. However, selective identification of hydrogen peroxide is a critical issue when working in the presence of endogenous interferents with similar voltammograms, such as adenosine and histamine. Furthermore, chemical agents used to pharmacologically verify the presence of hydrogen peroxide in the brain, such as mercaptosuccinic acid (MCS), are electroactive and can convolute the characterization of hydrogen peroxide

dynamics. We have addressed this problem by fabricating a mechanically robust, hydrogen peroxide-selective electrode. 1,3-phenylenediamine (mPD) was electrodeposited on the surface of a carbon-fiber microelectrode to create a size-exclusion membrane, rendering the electrode sensitive to hydrogen peroxide fluctuations and pH shifts, but not other commonly studied neurochemicals. These electrodes are described and characterized herein. The data demonstrate that this technology can be used to ensure the selective detection of hydrogen peroxide in the brain, enabling confident characterization of the role it plays in normal physiological function, as well as in the progression of PD and other neuropathies involving oxidative stress.

SESSION 2; ABSTRACT NO. 5

Determining the Role of Schizophrenia-Linked Protein TSNARE1B in the Endolysosomal System of Developing Neurons

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Schizophrenia is a severe neuropsychiatric disorder characterized by delusions and hallucinations, which lacks effective, targeted therapies, likely due in part to its polygenic etiology. Recently, the largest genome wide association study on schizophrenia to date identified 108 loci associated with the occurrence of schizophrenia. The fifth most significant hit mapped to a locus containing the gene TSNARE1, which encodes the previously unstudied protein t-SNARE domain containing 1 (tSNARE1). tSNARE1 contains a N-terminal c-Myb DNA binding domain and a C-terminal Qa SNARE domain that shares closest homology to Syntaxin 12 (Stx12), an endosomal SNARE protein. Rare variant mutations identified from patients with either schizophrenia or autism spectrum disorder suggest that the SNARE domain is critical to tSNARE1 function. Unlike canonical Qa SNARE proteins, the primary neuronal isoform of tSNARE1, tSNARE1b, lacks a transmembrane domain as well as any other predicted site for membrane attachment, which is thought to be necessary for membrane fusion. Therefore, our central hypothesis is that tSNARE1b acts as an inhibitory SNARE (i-SNARE) of specific membrane trafficking events. This hypothesis is supported by biochemical pull-down assays with recombinant proteins and embryonic brain lysates, which demonstrate that GST-tSNARE1 can replace Stx12 and assemble with the endosomal SNARE proteins Vti1a, Stx6, and VAMP4 into SNARE complexes. Because tSNARE1 shares its closest homology with Stx12, we hypothesized that tSNARE1 functions within the endosomal pathway. High resolution, live-cell confocal microscopy of tSNARE1b-GFP and a battery of spectrally distinct organelle markers in embryonic murine cortical neurons determined to which endocytic compartments tSNARE1b localizes. Colocalization of tSNARE1b and each marker was quantified using a semi-automated, quantitative image-analysis pipeline that robustly identifies colocalization based on two different measurements. Preliminary evidence suggests that tSNARE1 colocalizes the strongest with late endosome marker Rab7 and lysosome marker LAMP1, suggesting tSNARE1b may regulate trafficking between these organelles. Ongoing studies are exploring how tSNARE1b functions at the membrane trafficking between late endosomes, lysosomes, and autophagosomes with three-color, live-cell imaging.

SESSION 2; ABSTRACT NO. 6

Sex and Estrous Cycle Induced Differences in Medium Spiny Neuron Electrophysiological Properties in Adult Rat Nucleus Accumbens Core

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Naturally occurring hormone cycles in adult female humans and rodents create a dynamic neuroendocrine environment. These cycles include the menstrual cycle in humans, and its counterpart in rodents, the estrous cycle. These hormone fluctuations, along with other influences, induce sex differences in the phenotypes of many behaviors, including those related to reward, motivation, and associated disorders such as depression and addiction. This suggests that the neural substrate instrumental for these behaviors, including the nucleus accumbens core (AcbC), likewise differs between estrous cycle phases. It is unknown if the electrophysiological properties of AcbC output neurons, medium spiny neurons (MSNs), change between estrous cycles phases. This is a critical knowledge gap given that MSN electrophysiological properties determine what information is communicated to AcbC efferent targets. Here we test whether the intrinsic electrophysiological and excitatory synaptic input properties of adult rat AcbC MSNs differs across female estrous cycle and to males. We recorded MSNs using whole cell patch-clamp technique in two experiments: the first using gonad-intact adult males and females in differing phases of the estrous cycle, and the second using gonadectomized males and females wherein estrous cycle was eliminated. MSN intrinsic electrophysiological and excitatory synaptic input properties robustly changed between female estrous cycle phases and males. Differences in MSN electrophysiology disappeared when the estrous cycle was eliminated. These novel findings indicate that AcbC MSN electrophysiological properties change across the estrous cycle, providing a new framework for understanding how biological sex and hormone cyclicity regulate motivated behaviors and other AcbC functions and disorders.

SESSION 2; ABSTRACT NO. 7

Neuroendocrine Disruption of Placental and Brain Function by the Flame Retardant Mixture Firemaster® 550

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Firemaster® 550 (FM 550) is a flame retardant mixture applied to foam-based furniture and baby products and has become a ubiquitous contaminant in the home. FM 550 contains two brominated compounds and a mix of organophosphates. We previously showed that FM 550 may have endocrine disrupting properties, and perinatal exposure can alter anxiety-like behavior in rats. To follow up on this initial finding, here Wistar rat dams were orally exposed to 100, 300, or 1,000 µg/day from GD9 through PND21 to assess effects on juvenile and adult behaviors related to anxiety and activity. Male offspring showed alterations in anxiety-like behavior as they took significantly longer to investigate the center of the open field arena as juveniles and significantly fewer entries into the open arms of the elevated plus maze as adults. Significant changes in activity levels were also observed in adult females exposed to 100 µg FM 550. These results confirm our previous findings that perinatal exposure to FM 550 can lead to heightened anxiety and hyperactivity. Next we specifically focused on fetal exposure. We exposed Wistar rat dams to 0, 300 and 1,000 µg/day from GD9 through GD18. Fetal and placental tissues were analyzed for FM 550 components. The two brominated compounds showed dose-dependent deposition in placenta and, to a lesser degree, fetuses demonstrating fetal transfer. There was no evidence of organophosphate accumulation in fetal tissue but one dose-dependently accumulated in placenta with levels higher in males than females. Placentas from litters exposed to 1,000 µg FM 550, showed perturbations in metabolites related to serotonin (5-HT) metabolism. Additionally, TDO2 expression

was significantly up-regulated, further indicating that prenatal exposure could be altering placental 5-HT synthesis. Future work will test the hypothesis that alteration of placental neurotransmitter production could be a mechanism by which FM550 alters neural development and behavior.

SESSION 2; ABSTRACT NO. 8

Identifying Functional Regulatory Units Controlling Dopamine Neuron Subthreshold Oscillation Properties Using Population-Based Parameter Optimization

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Dopaminergic neurons of the substantia nigra pars compacta can display large amplitude subthreshold oscillations ex vivo under blockade of spike-generating mechanisms. These oscillations result from the interplay of several low-voltage activated ion channels. However, electrophysiological experiments have demonstrated substantial variability in currents produced by these channels as well as the gating properties of the channels themselves (Amendola et al., 2012), suggesting multiple ways that these membrane characteristics are produced. We used a novel, population-based evolutionary algorithm to simultaneously tune 22 parameters from 7 subthreshold ion channels and the intracellular calcium mechanism, generating many candidate models covering the range of observed subthreshold oscillation behaviors. Through dimensionality-reducing analytical techniques, we identified linear combinations of parameters, which we term functional regulatory units, that are capable of independently controlling subthreshold oscillation amplitude and frequency. We simulated application of apamin, blocking the calcium-dependent potassium channel, and found that models with parameter sets in line with the functional regulatory units produce consistent and reliable responses to the drug, whereas models generating their behavior using parameter combinations that are inconsistent with the functional regulatory units produce less predictable responses to the drug. These new techniques have broad implications for simulating populations of neurons, understanding ion channel combinations controlling neural behavior, drug discovery, and neurodegenerative disease.

SESSION 2; ABSTRACT NO. 9

A Locus Coeruleus to Lateral Hypothalamus Circuit for Suppression of Feeding

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Clinical evidence implicates altered norepinephrine (NE) signaling in overeating and excessive weight gain. Although modulators of NE signaling are currently the most effective drugs for weight loss, they result in adverse side-effects due to their broad actions throughout the nervous system. Thus, there is a critical need to identify specific NE circuits that suppress feeding without other effects. Towards this goal, we used chemogenetics in combination with fiber photometry to reveal that activation of NE-locus coeruleus (LC) neurons results in suppressed feeding and weight loss. This key finding, along with evidence that feeding is also suppressed by delivery of NE agonists into the lateral hypothalamus (LHA), suggests that increased NE-LC activity suppresses feeding through select inputs to the LHA. To test this hypothesis, we used optogenetics to activate the LC-LHA circuit in our knock-in mouse line that expresses cre recombinase under control of the noradrenergic dopamine beta-hydroxylase (Dbh) promoter. We injected the LC of Dbhcre mice with a cre-responsive virus expressing channelrhodopsin-2 (ChR2) or eYFP control, and then implanted optical probes over the LHA. We found that photostimulation (10 Hz)

of the LC-LHA circuit rapidly suppressed feeding in ChR2 mice relative to controls. To rule out the possibility that this effect was due to changes in anxiety, mice were tested in the elevated plus maze and real-time place aversion test. In both tests, photostimulation had no effect on anxiety-like behavior in ChR2 mice relative to eYFP controls, demonstrating the LC-LHA circuit regulates feeding independent of anxiety. To ascertain if NE signaling from LC neurons is required to suppress feeding, we used our Dbh conditional knockout allele in combination with En1cre (LC-Dbh mutants) to disrupt NE synthesis selectively in LC neurons. LC-Dbh mutants and littermate controls were pretreated with vehicle or the alpha-2 adrenoceptor antagonist yohimbine (3 mg/kg i.p.), which is known to activate LC neurons. We found that yohimbine suppressed feeding in littermate controls but had no effect in LC-Dbh mutants. Collectively, these findings reveal a novel role for LC neurons in the suppression of feeding that is mediated by release of NE in the LHA. The findings suggest that targeting specific NE neural pathways may yield improved weight loss therapies without anxiety side-effects.

SESSION 2; ABSTRACT NO. 10

Optical Flow Perturbations to Detect Preclinical Balance Impairment in People with Multiple Sclerosis

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Prior to self-reporting even moderate disability, people with multiple sclerosis (PwMS) already have twice the risk of falling than the general population. Additionally, PwMS have are more reliant on visual feedback for balance control than healthy individuals of the same age. Accordingly, optical flow perturbations that induce the perception of falling may be an effective means to detect preclinical balance impairment in PwMS. As an important first step, we tested the effects of optical flow perturbations on static and dynamic balance control in PwMS. We hypothesized that, compared to age-matched controls, PwMS would increase step length variability and step width variability more in response to optical flow perturbations in walking. We also hypothesized that these perturbations would have a larger, more pervasive effect on dynamic balance control in walking than on static balance control in standing, the latter quantified using center of pressure variability.

Six PwMS (1 male, 34.7±7.7 years old) and six age-matched control subjects participated in this IRB-approved study. Subjects walked at their preferred speed on an instrumented treadmill in a virtual reality hallway. The virtual hallway was perturbed continuously in medial-lateral (ML) or anterior-posterior (AP) directions during standing and preferred speed walking. Subjects also completed walking and standing control trials, in which the hallway was not perturbed. Lastly, control subjects completed an unperturbed trial at their corresponding PwMS gait speed. We calculated standard deviations of step length, step width and center of pressure to assess variability.

Differences between control subjects and PwMS were negligible for unperturbed standing and walking. In contrast, both groups increased step width variability and step length variability in the presence of ML perturbations. However, consistent with our first hypothesis, these effects on step length variability were much larger for PwMS than age-matched controls. ML visual perturbations caused step length variability to increase by 24.1% for PwMS but only 9.8% for controls. Consistent with our second hypothesis, center of pressure variability was similar between groups during standing, even when perturbations were present. Thus far, these results suggest that perturbations that elicit the visual perception of falling during walking may identify preclinical balance deficits in PwMS that may otherwise go undetected during standing.

SESSION 2; ABSTRACT NO. 11

Novel Role for Mineralocorticoid Receptors in Development and Maintenance of Hippocampal Area Ca2 Plasticity and Molecular Phenotype

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Exposure to chronic stress is a well-known risk factor for the development of neuropsychiatric disorders, including depression, schizophrenia, and post-traumatic stress disorder. In the brain, the response to stress is mediated by hypothalamic-pituitary-adrenal axis activation and the subsequent release of glucocorticoids that bind to either glucocorticoid receptors (GRs) or mineralocorticoid receptors (MRs). GRs are expressed in neurons throughout the brain, while the higher-affinity MRs are restricted to neurons in the limbic system. In the hippocampus, the distribution of GRs and MRs is subregion and species specific. In mice, CA1 and CA3 neurons express high levels of GR and low-to-moderate levels of MR. Area CA2, however, has high levels of MRs and low levels of GRs. This striking MR:GR ratio in CA2 has been reported in both mice and humans. In this study, we investigated the functional role of MR using the Cre-lox system to delete MRs from the whole brain or site-specifically in CA2. We found that MR is required for the development and maintenance of the unique CA2 protein and mRNA expression profile, including NECAB2 and RGS14. Moreover, following the deletion of MR there is an increase in GR and WFS1, a known CA1 marker, in the CA2 region neurons. These effects were found in animals that had MR knocked out embryonically, perinatally, or postnatally. Furthermore, CA2 is typically resistant to long term potentiation, a measure of synaptic plasticity. In animals with a global knockout of MR, however, CA2 displayed LTP, indicating the unique protein expression of CA2 is required for repression of synaptic plasticity. Together, these data indicate that MR has a unique role in distinguishing CA2 from its neighboring subregions and suggest that CA2 has an important role in behavioral and physiological responses to stress.

SESSION 2; ABSTRACT NO. 12

Anterior Cingulate Cortex Encodes Visual Input and Adapts to Visual Experience

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Mouse primary visual cortex (V1) is capable of encoding visual stimuli and undergoing bidirectional plasticity coincident with patterned visual experience. The prefrontal anterior cingulate cortex (ACC) receives input from visual cortex, but mechanisms of visual encoding and experience-dependent plasticity in ACC are not well-understood. We implanted electrodes into ACC in mice and recorded visually evoked potentials and isolated unit activity while tighly controlling visual experience. We report that salient stimuli preferentially drive activity in ACC, describe mechanisms by which ACC adapts to visual experience, and find an ACC-specific failure in plasticity in a mouse model of autism.

SESSION 2; ABSTRACT NO. 13

Characterization of Sex Differences in Neurobehavioral Assessments of Hippocampus-dependent Learning and Memory

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Basic neuroscience research currently has a deficit in awareness of sex differences in neurobehavioral function; stifling translation to the human population. The current project is intended to characterize sex differences in hippocampus-dependent behavioral tasks and examine the

underlying mechanisms. We assessed spatial, contextual and temporal learning using a battery of tests in two-month-old C57Bl6Tac mice: spontaneous alternation, novel context recognition (exploratory habituation), object recognition and tone and contextual fear conditioning. There were no sex differences in percent alternation, indicating similar spatial working memory, however females showed an overall increase in the number of arm entries. Males and females showed similar levels of exploratory behavior over two days of exposure to the same open field environment, including the typical reduction in exploratory behavior on the second day (referred to as exploratory habituation or novel context recognition). Novel object recognition was similar in males and females, with both showing a preference for investigating the novel object 24 hours after the familiarization phase. In the object location task males showed increased exploration of the displaced object after a 24 hour delay, whereas females did not. For tone fear conditioning we assessed hippocampus-independent delay, hippocampus-dependent trace and two non-associative controls: explicitly unpaired and sensitization (no tone present during training). Delay conditioning was similar; however, trace fear conditioning was enhanced in males. Females showed increased freezing in the sensitization group, responding fearfully to a novel tone after fear conditioning. Overall these findings show task-specific sex differences indicative of a relative enhancement in hippocampus-dependent spatial and temporal learning in males. The enhanced non-associative sensitization learning has important implications as non-associative controls are rarely used, thus differences could be erroneously assumed to be due to altered associative learning when they are in fact due to non-associative changes. In addition, this finding could serve as a basis for modelling increased anxiety disorders in women. These findings are not only informative about general sex differences, to be studied in their own right, but they also set the baseline for interpreting data in sophisticated transgenic models.

SESSION 2; ABSTRACT NO. 14

Multiplication of SNCA Locus Exacerbates Neuronal Nuclear Aging

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Human induced Pluripotent Stem Cell (hiPSC)-derived models have advanced the study of neurodegenerative diseases, including Parkinson's Disease (PD). While age is the strongest risk factor for these disorders, hiPSC-derived models represent rejuvenated neurons, lacking of the aging signature of the cells from which they are derived. Thus, there is a concern that hiPSC-derived models are not fully suitable for the study of age-related conditions. Therefore, we developed a novel method to induce aging in hiPSC-derived dopaminergic and cholinergic neurons to model PD and related synucleinopathies. Our new method induces aging through a 'semi-natural' process, by applying multiple passaging at the Neural Precursor Cell stage prior final differentiation. Juvenile and Aged hiPSC-derived neurons were characterized using heterochromatin and nuclear envelope markers, as well as DNA damage and global DNA methylation, thus validating our age-inducing method. We next compared these phenotypes between hiPSC-derived neurons obtained from a patient with SNCA-triplication (SNCA-Tri) and a Control. The SNCA-Tri neurons displayed exacerbated nuclear aging, showing advanced-aging signatures already at the Juvenile stage. Noteworthy, the Aged SNCA-Tri neurons showed more α-synuclein aggregates per-cell versus the Juvenile. For the first time, we described interplay between the overexpression of SNCA, neuronal nuclear phenotypes, and aging.

SESSION 2; ABSTRACT NO. 15

Chronic Exposure to Bisphenol F and Body Weight, Food Intake, Glucose, and Behavior in Male Mice

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Bisphenol F (BPF) is a widely used substitute of bisphenol A (BPA) that has already been found in packaged food, river sediments, and even in human plasma. Emerging in vitro data show that BPF may not be a safe alternative to BPA, pointing to similar, or even more potent endocrine disruptive abilities. The BPF has similar hormonal potency as the BPA, however, the BPF also exhibits higher steroidogenic activity with an increase of progesterone and 17α-hydroxyprogesterone, which points to additional disruptive effects of BPF. Available data on effects of rodent exposure of BPF focuses on high doses or prenatal exposure. Given the human exposure to relatively low levels of BPF, we focused on chronic, low dose BPF exposure in adult CD1 male mice and explored its effects on activity, anxiety, body weight, food intake, and glucose tolerance. We selected an oral route of administration and doses that reflect likely human exposure to BPF (0mg, 0.5mg 5mg and 50mg BPF/kg food). After 7 weeks of exposure animals were tested in the Open field test, the Elevated plus maze test, and the Glucose tolerance test. Based on toxicity studies with much higher doses of BPF we hypothesized that the chronic exposure to all 3 of the low doses of BPF would decrease activity, increase anxiety-like behavior, decrease plasma glucose as well as decrease body weight and food intake in male mice. Our data so far show no differences in activity between the groups. Additionally, contrary to our expectations the animals exposed to BPF are less anxious as reflected by lower amount of defecation in the Open field. Animals in all groups did not differ in the amount of baseline fasting glucose in plasma or in glucose tolerance. Additionally, we did not see a weight loss or decrease in food intake. However, animals in all treatment groups gained weight more slowly compared to the control group while consuming the same amount of food. We will discuss the results further in relation to direct versus parental exposure to BPF. This work is supported by NIH grant ES022759.

SESSION 2; ABSTRACT NO. 16

Functional Connectivity Between VTA and Hippocampus During Neurofeedback Training Predicts Learning to Volitionally Activate the VTA

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Activation of the Ventral Tegmental Area (VTA) and mesolimbic networks is essential to motivation and learning, however current interventions to target these regions can come with unmanageable financial and physical costs. Neurofeedback has been shown to be an effective, non-invasive therapy in a variety of contexts, however the ability to learn from and properly use neurofeedback is highly variable across subjects. In a recent study, MacInnes & Dickerson et al. (2016) showed that participants could learn to volitionally sustain their VTA activation through fMRI neurofeedback training, and that this feedback was accompanied by increased functional connectivity between the VTA and other mesolimbic areas, namely the hippocampus (HPC). However, the mechanism through which this training impacts learning is not yet known. Here, we test a mechanistic model of how mesolimbic functional connectivity drives learning from neurofeedback to self-activate the VTA. The activation task itself was divided into 5 runs: a pre-test without neurofeedback, three training runs with neurofeedback, and a post-test without neurofeedback. Connectivity was calculated for each run from the VTA to the HPC, due to the HPC's overall role in learning as well as mental imagery - a common strategy for VTA activation. A

repeated measures ANOVA was then run with connectivity during each of the three training runs as within-subject measures, and overall change in VTA activation from pre-test to post-test as a between-subject measure. Results show a trend ($F = 3.131$, $p = 0.056$) that higher VTA-HPC functional connectivity over the course of the training period leads to greater VTA activation change from pre-test to post-test, an initial demonstration that prompts further interrogation. This approach is necessary to understand the mechanisms of learning from neurofeedback, and therefore the propagation of volitional brain activation for basic science and development of new interventions.

SESSION 2; ABSTRACT NO. 17

InSyn1 Regulates Dendritic Postsynaptic Inhibition and Cognitive Behaviors.

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Previously we have developed an in vivo chemico-genetic approach for the discovery of local proteomes of neuronal substructures. Using this technique, termed in vivo BioID or iBioID, we uncovered the molecular framework of the inhibitory postsynaptic complex (iPSD), with over 140 novel trafficking, transmembrane, and signaling proteins enriched at this structure. We also found several previously uncharacterized proteins, one of which we named Inhibitory Synaptic protein 1 (InSyn1) that was tightly associated with the iPSD. We report here InSyn1 is a novel regulator of the dystroglycan complex (DGC) in neurons. DGC is composed of several proteins and we found InSyn1 interacts with one of these to target it to inhibitory synapses. Furthermore, CRISPR-based depletion further confirmed dystroglycan is critical for InSyn1 iPSD localization. To better understand the physiological relevance of InSyn1 in the nervous system, we generated InSyn1 KO mice. Interestingly, InSyn1 null hippocampal neurons show defects in the spatial distribution of the DGC, which was further supported by electrophysiological recordings. Because genetic mutations in the DGC not only display severe muscular dystrophy but also exhibit cognitive dysfunctions, we performed a battery of hippocampal dependent behavioral tests and found InSyn1 null mice exhibit complex cognitive abnormalities. These data indicate that InSyn1 is critical for the function of a distinct subset of inhibitory synapses and is important for hippocampal-dependent cognitive behaviors.

SESSION 2; ABSTRACT NO. 18

Skin Innervation Patterns of ITCH Neurons

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Decoding somatosensory information begins at the skin. One sensory input, itch, has only recently begun to be understood. Typically, one of two methods are widely used to study itch: intradermal injection into the nape of the neck and cheek injections. Despite giving the same basic information, the number of scratching bouts for a given compound in cheek assays is usually about one-fifth of the number of scratching bouts from nape injections. Additionally, itch compounds injected into the cheek also cause wiping, which is assumed to be a nocifensive response. In this study, we explored the discrepancy of itch response in the nape of the neck and in the cheek by examining the skin tissues derived from the mice, which express tdTomato in somatostatin (SST) neurons. At the periphery in the dorsal root ganglia, SST is a marker for itch sensory neurons. These SST labeled mice were perfused and skin from the cheek and the nape of the neck were sectioned and imaged with confocal microscopy and the density of somatostatin neurons (in neurons/μm^2) for the nape and cheek regions were determined. Additionally, it has been reported that female mice injected in

the nape of the neck with chloroquine have a higher number of scratching bouts than males injected with chloroquine in the nape of the neck. Therefore, we used these mice to compare the skin innervation density of somatostatin neurons for the cheek and nape between male and female mice. Finally, we compared the changes in innervation patterns of somatostatin neurons by developing an atopic dermatitis mouse-model using compound MC 903 (a vitamin D analog). Overall, our findings will help us understand the differences in itch behavior in mice due to the distribution of primary afferent innervation in the skin.

SESSION 2; ABSTRACT NO. 19

Estrous Cycle-Dependent Sex Differences in Rat Dorsal Striatal Msn Excitability

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The neuroendocrine environment in which the brain operates is both dynamic and differs by sex. How this unstable neuroendocrine state affects neuron properties has been significantly neglected in neuroscience research. Behavioral data across humans and rodents indicate that natural changes in steroid sex hormone exposure affect sensorimotor and cognitive function in both normal and pathological contexts. These behaviors are critically mediated by the dorsal striatum: a well-conserved constituent of the basal ganglia that is instrumental for forebrain function, various forms of learning, and sensorimotor performance. In the dorsal striatum, medium spiny neurons (MSNs) are the predominant and primary output neurons. As such, MSNs are fundamental components of the circuits which underlie striatal-mediated behaviors. Importantly, MSNs express membrane-associated estrogen receptors and demonstrate estrogen sensitivity. However, the effects of cyclical hormone changes across the estrous cycle on the basic electrophysiological properties of MSNs have not been investigated. Here, I test the hypothesis that dorsal striatal MSN intrinsic excitability is a dynamic property that is modulated in adult females across the estrous cycle via the associated changes in steroid sex hormone levels. I performed whole-cell patch clamp recordings on male, diestrus female, proestrus female, and estrus female MSNs in acute brain slices obtained from adult rat dorsal striatum. Assessment and analysis of the electrophysiological properties is ongoing, with a particular emphasis on intrinsic excitability and miniature excitatory synaptic currents (mEPSC). Preliminary results indicate that the properties that govern cellular excitability differ over the course of the estrous cycle for female MSNs. Additional analysis is needed to further inform these results. Overall, given the estrous-dependent sex differences in the normal and pathological behavioral output of circuits involving the dorsal striatum, understanding the nature of neuroendocrine modulation of MSN function is an important research goal.

SESSION 2; ABSTRACT NO. 20

Real-Time Striatal Measurements of Oxidative Stress and Dopamine in the Dyskinetic Rat During Chronic L-DOPA Treatment for Parkinson's Disease

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Parkinson's disease (PD) is a neurodegenerative disease characterized by the slow degeneration of dopaminergic neurons found in a region of the midbrain called the substantia nigra. Dopamine (DA) plays a key role in regulating motor function. Thus, the destruction of these neurons and the consequential decrease in DA concentrations in the striatum leads to the deterioration of motor control. The drug

Levodopa has been used to treat PD by helping to increase the concentration of DA in the brain. This drug has been proven to alleviate the motor symptoms of PD; however, after a short period of time, dyskinetic symptoms can develop. Treatment with Citalopram, a serotonin reuptake inhibitor, before administration of Levodopa has proven to attenuate the dyskinesia side-effects. Furthermore, it is thought that oxidative stress is a principal contributor to the destruction of dopaminergic neurons, and possibly to the development of dyskinesias, in PD and its treatment. To date, oxidative stress has been difficult to measure due to the high reactivity of oxygen radicals; however, hydrogen peroxide can serve as an indicator of the presence of oxidative stress. This experiment uses fast-scan cyclic voltammetry coupled with carbon-fiber microelectrodes to simultaneously monitor real-time fluctuations of DA and hydrogen peroxide in the dorsal striatum. These neurochemical dynamics can be time-locked to dyskinetic episodes. Striatal tissue imaging with infrared-matrix assisted laser desorption electrospray ionization (IR-MALDESI) coupled to Q-Exactive Plus was used to validate DA tissue content in non-lesioned controls vs the PD modeled rats. Overall, these studies will aid in our understanding of how oxidative stress modulates nigrostriatal DA signaling, as well as the behavioral consequences of this interaction. The results will inform improved therapeutic strategies for the treatment of PD.

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Notes


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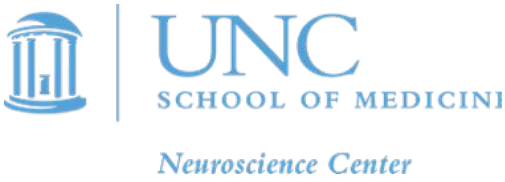
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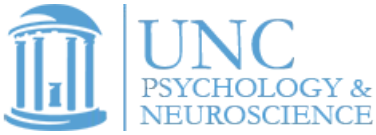
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