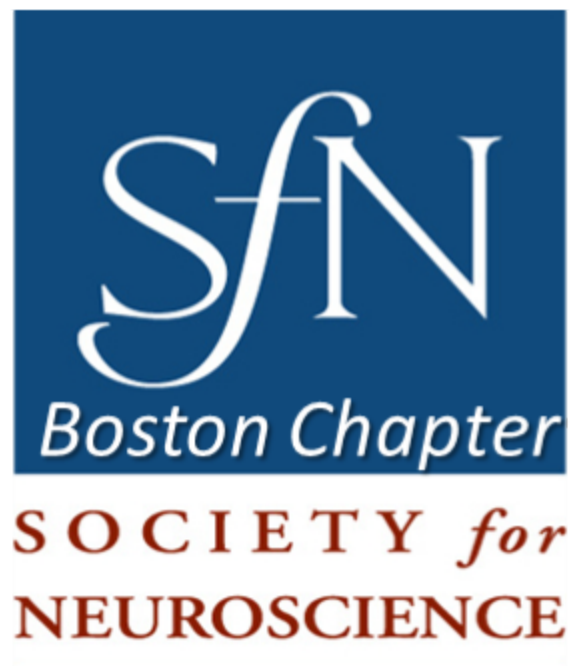


The Boston Area Neuroscience Group (BANG)
proudly presents:

The Summer 2017
Boston Area Neuroscience Group
Symposium and Reactivation Meeting



Thursday, June 1st 2017
MCPHS University
White Hall

PROGRAM FOR THE MEETING

- 12:30 pm **Poster set-up**
- 1:00 pm **Welcome and opening remarks**
- 1:15 pm **Dr. Stacie Bilbo**, Massachusetts General Hospital for Children
- 1:40 pm **Dr. Elizabeth Byrnes**, Tufts University Cummings School of Veterinary Medicine
- 2:05 pm **Dr. Steve Ramirez**, Harvard University
- 2:30 pm **Business Meeting for Chapter Reactivation**
- 4:00 pm **Poster Session** *with coffee and refreshments*
- 5:15 pm **Closing Comments**

To all poster presenters: please arrive at 12:30pm to hang up
your poster before the talks begin

**A reminder that all visitors to MCPHS University will need to
supply their event ticket and a photo ID to security at White
Hall upon entry**

MEET OUR INVITED SPEAKERS

Dr. Staci Bilbo is an Associate Professor of Pediatrics and Neuroscience at Harvard Medical School and the Director of Research for the Lurie Center for Autism at Massachusetts General Hospital for Children. Her research is broadly focused on the mechanisms by which the immune and endocrine systems interact with the brain to impact health and behavior. Current research in her laboratory focuses on understanding the consequences of early life events, including infection, stress, environmental toxins, and maternal obesity on neural and immune system development, with a particular emphasis on autism spectrum disorder.

Dr. Elizabeth Byrnes is an Associate Professor of Biomedical Sciences at Tufts University, with a primary appointment at the Cummings School of Veterinary Medicine and a secondary appointment at the Sackler School of Graduate Biomedical Sciences. Currently the Head of the Section of Neuroscience and Reproductive Biology, she has an active, NIH funded research laboratory examining a number of topics. Current areas of research include transgenerational epigenetic effects of opioid exposure, sex differences in animal models of psychiatric disease and age-related modifications in neural systems that regulate anxiety and depression. Both privately and federally funded, she publishes regularly in peer-reviewed journals and frequently serves on NIH study sections. She has also served on a number of external review and advisory committees, including substance use guideline development for the World Health Organization. She received her PhD in Neuroscience from The Ohio State University and received additional postdoctoral training as a NIH fellow in Neuroimmunology (OSU) and Neuroendocrinology (Tufts University). Her current teaching commitments include lecturing in both Veterinary Physiology and Neurobiology. She also serves as Course Director for Problem Based Learning and is actively involved in the Laboratory Animal Masters program at the Cummings School. Additionally, her interests include both education and community outreach. In that capacity, she has a long-standing interest in substance abuse prevention and currently serves as Chair of the Decisions at Every Turn Coalition, a community-based youth substance abuse prevention coalition funded by a Federal Drug Free Communities grant.

Dr. Steve Ramirez is a Junior Fellow and Principal Investigator at Harvard University, and an assistant professor at Boston University. He received his B.A. in neuroscience from Boston University where he began researching learning and memory. He went on to receive his Ph.D. in neuroscience at MIT, where his work focused on artificially modulating memories in the rodent brain, and his current work focuses on leveraging these manipulations to alleviate symptoms associated with psychiatric diseases. Steve has also received the Smithsonian's American Ingenuity award, National Geographic's Breakthrough Explorer prize, Forbes and Technology Review's Top 35 Innovators Under 35 award, and has given a TED talk.

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POSTER ABSTRACTS BY STAND NUMBER

STAND 1

Title: Reactivating hippocampus-mediated positive memories to lastingly disrupt the reconsolidation of fear.

Authors: Stephanie L. Grella, Yosif Zaki, Nathen J. Murawski, Emily Doucette, Emily Merfeld, Monika Shpokayte & Steve Ramirez

Affiliation: Centre for Brain Science, Harvard University. Cambridge, MA

Abstract: Background: Fear conditioning has been used to model memory and stress-related behaviors in rodents. While fear is often adaptive, dysregulation of fear circuits can lead to maladaptive states comprising mood and anxiety disorders. A promising prospect of attenuating the strength of fear memories is through the disruption of reconsolidation - a process by which activated memories are susceptible to modification, thus allowing for subsequent manipulation (e.g. enhancement / disruption). In previous studies, interventions such as protein synthesis inhibitors and beta-blockers have been used to target and disrupt conditioned fear during the reconsolidation process. Here, we propose a novel intervention based on the hypothesis that optogenetic reactivation of a reward-related memory during reconsolidation will alter and disrupt the original fear memory, thereby reducing the behavioral expression of fear. Method: We used the activity-dependent inducible cFos-tTA system for neuronal tagging in c57BL/6 mice to tag dentate gyrus (DG) cells active during positive or neutral memory formation. Mice were then fear-conditioned and given a 20-min test for fear memory recall the following day. During the last 10 min of the session, when the reconsolidation window is thought to be open - we optogenetically reactivated the DG-mediated positive or neutral memories. Results: We found that artificial reactivation of a positive memory during reconsolidation of a fear memory resulted in 1) decreased freezing during reactivation 2) faster rates of extinction learning and 3) attenuation of stress-induced reinstatement. Significance: This work highlights the therapeutic value of memory modulation as a viable treatment for lastingly suppressing fear responses, implicating DG engram cells as specific nodes of intervention.

Keywords: Engram, Memory, Hippocampus, Optogenetics, Reconsolidation, Contextual Fear Conditioning

STAND 2

Title: Artificially enhancing or suppressing hippocampus-mediated fear memories

Authors: Nathen J. Murawski, Stephanie L. Grella, Monika Shpokayte, Emily Merfeld, Yosif Zaki, Emily Doucette, and Steve Ramirez.

Affiliation: Center for Brain Science, Harvard University. Cambridge MA.

Abstract: Cognitive and emotional disruptions underlie many stress disorders and are also known to affect hippocampus function. The dorsal hippocampus is thought to process spatial, temporal, and contextual information whereas the ventral hippocampus is thought to mediate stress and emotional aspects of learning and memory. Here, we asked if artificial activation of positive or negative memories in the dorsal or ventral hippocampus could promote appetitive or aversive-related behaviors. We also examined if chronic activation of a fear memory is sufficient to mimic extinction-like reductions in fear responses. We first infused an activity-dependent AAV-TRE-ChR2 into the dorsal or ventral dentate gyrus (DG), which allowed for optical control over DG neurons expressing the immediate-early gene c-Fos in a doxycycline (Dox)-dependent manner. Mice received a positive, negative, or neutral experience while off Dox to tag cells processing a discrete memory. Next, mice underwent a battery of behaviors to measure

appetitive and aversive responses during light-on and light-off epochs. Our conclusions are threefold: 1) activation of dorsal and ventral hippocampus cells were sufficient to drive freezing, avoidance, and preference; 2) the ventral, but not dorsal, hippocampus is sufficient to modulate anxiety-like states; 3) and finally, chronic activation of the dorsal hippocampus cells produces extinction-like reductions in fear responses, whereas ventral hippocampus stimulation induces a context-specific enhancement of a fear memory. Together, we demonstrate the functionally overlapping and segregated roles of the dorsal and ventral hippocampus and that artificially activating positive and negative memories are sufficient to mitigate or mimic stress-related behavioral states.

Keywords: Memory; Hippocampus; Emotion; Cognition; Extinction

STAND 3

Title: Artificially Modulating Negative Memories to Prevent the Reinstatement of Fear in a Model of PTSD

Authors: Yosif Zaki; Emily Doucette, BS; Stephanie L. Grella, MS; Emily Merfeld, BA; Nathen J. Murawski, PhD; Monika Shpokayte, BA; & Steve Ramirez, PhD

Affiliation: Center for Brain Science, Harvard University. Cambridge, MA

Abstract: Post-traumatic stress disorder (PTSD) is a condition that precipitates from a highly aversive experience and is manifested by overgeneralized fear in innocuous situations. Interestingly, a striking proportion of patients who undergo exposure therapy, which can lead to the suppression, or "extinction," of the original fear memory, are highly vulnerable to relapse, especially when the conditioned stimulus is delivered outside a clinical context. Here, we seek to delineate the neural substrates supporting the acquisition of fear as well as the subsequent extinction of fear to gain a causal understanding of its underlying neural components. We used a combination of activity-dependent labeling of memories, or "engrams," in multiple brain regions associated with PTSD and further manipulated these engrams to probe the changes that a fear memory undergoes during extinction and during fear reinstatement.

Keywords: Learning, Memory, Amygdala, Hippocampus, Fear Learning, Fear Extinction, Fear Reinstatement

STAND 4

Title: Central gray neurons rapidly signal threat probability

Authors: Kristina M. Wright and M.A. McDannald

Affiliation: Boston College

Abstract: The ability to discriminate between a range of safe and dangerous stimuli is vital. Further, the rapidity and accuracy of fear responses informed by this discrimination are imperative. Fear conditioning procedures, combined with single unit recording, allow for investigation of neural activity relevant to appropriate discrimination across a range of threatening stimuli. Using a fear conditioning procedure, we examined the relationship between neural activity in the central gray, an area highly relevant to fear-output, and discrimination of threat. Adult, male, Long Evans rats were implanted with drivable, microelectrode bundles aimed at the central gray. Following recovery, rats were presented with three auditory cues, each associated with a different probability of foot shock: safety, $p = 0.00$; uncertainty, $p = 0.38$; and danger, $p = 1.00$. All rats demonstrated excellent fear discrimination: achieving high fear to the danger cue, little or no fear to the safety cue, and intermediate fear to the uncertainty cue. Our analysis of central gray activity *during* discrimination revealed a large population of neurons demonstrating both rapid and phasic increases in firing at the onset of one or all three cues.

Interestingly, the magnitude of increased firing at cue onset was best explained by the probability with which the corresponding cue predicted foot shock. This neural representation of precise fear discrimination, preceding a behavioral response, may play a critical role in the rapid and accurate organization of an appropriate fear response.

Keywords: Central Gray, Rapid Fear, Accurate Fear, Threat Prediction

STAND 5

Title: The role of posterior insular cortex in recall of remote fear memory

Authors: Allison R. Foilb, Mary C. Sarlitto, John P. Christianson

Affiliation: Boston College

Abstract: Memories of dangerous experiences endure over time. Unfortunately, the persistence of fear memories in individuals with PTSD can interfere with behavior. While the circuitry underlying fear learning is well known the mechanisms by which these memories are able to last a lifetime still need to be uncovered. We hypothesized a role of posterior insular cortex (pIC) in remote fear memory based on the bidirectional connectivity between pIC and the basolateral amygdala. In addition, insula is known to be hyperactive in individuals with PTSD. Here, as hypothesized, we show that inhibition of pIC before recall testing results in a significant decrease in fear 7 days after fear conditioning. Ongoing studies further investigate the timeline of the role of the pIC in remote fear memory, including in the initial acquisition.

Keywords: insula, fear, amygdala, PTSD

STAND 6

Title: A causal role for the ventrolateral periaqueductal grey in aversive prediction error signaling

Authors: Rachel A. Zacharias & Michael A. McDannald

Affiliation: Boston College

Abstract: Prediction error signaling is a crucial mechanism for proper fear regulation, especially in situations of uncertainty. Positive aversive prediction errors are generated when a received outcome is worse than expected, and they function to increase fear upon future encounters. Evidence suggests the ventrolateral periaqueductal grey (vLPAG) may be the source of these prediction errors. However, no studies have used temporally precise inhibition of vLPAG activity at the time of prediction error. This would provide strong, causal evidence that this prediction error originates in the vLPAG. In this study we trained male and female Long-Evans rats in a fear discrimination paradigm in which three cues were associated with three different probabilities of foot shock: safety $p=0.00$, uncertainty $p=0.38$, and danger $p=1.00$. Of most interest was the uncertainty cue, for which positive prediction error signaling is necessary to demonstrate appropriate fear. In order to causally link vLPAG activity to aversive positive prediction error signaling, we transfected the vLPAG with halorhodopsin under control of the human synapsin promoter or with control YFP only virus. An optical ferrule was implanted over the vLPAG, and 532 nm light was delivered precisely during the time of shock receipt on reinforced uncertainty trials, exactly when positive prediction errors would be generated. Light was also delivered during the shock on danger trials as a control. Results showed that optogenetic inhibition of the vLPAG at the time of positive prediction error decreases fear to the uncertain cue over trials. Importantly, inhibition on danger cue trials did not change fear to the danger cue, indicating this effect is specific to prediction errors. This study implicates the vLPAG as the site of aversive positive prediction error signaling and provides a neural locus of possible disruption in disorders, such as PTSD, that are characterized by excessive positive prediction error signaling.

Keywords: PAG, positive prediction error, optogenetics

STAND 7

Title: Complementary learning systems within the hippocampus: A neural network modeling approach to reconciling episodic memory with statistical learning

Authors: Anna C. Schapiro, PhD; Nicholas B. Turk-Browne, PhD; Matthew M. Botvinick, PhD; Kenneth A. Norman, PHD

Affiliation: BIDMC/Harvard Medical School

Abstract: A growing literature suggests that the hippocampus is critical for the rapid extraction of regularities from the environment. Although this fits with the known role of the hippocampus in rapid learning, it seems at odds with the idea that the hippocampus specializes in memorizing individual episodes. In particular, the Complementary Learning Systems theory argues that there is a computational trade-off between learning the specifics of individual experiences and regularities that hold across those experiences. We asked whether it is possible for the hippocampus to handle both statistical learning and memorization of individual episodes. We exposed a neural network model that instantiates known properties of hippocampal projections and subfields to sequences of items with temporal regularities. We found that the monosynaptic pathway—the pathway connecting entorhinal cortex directly to region CA1—was able to support statistical learning, while the trisynaptic pathway—connecting entorhinal cortex to CA1 through dentate gyrus and CA3—learned individual episodes, with apparent representations of regularities resulting from associative reactivation through recurrence. Thus, in paradigms involving rapid learning, the computational trade-off between learning episodes and regularities may be handled by separate anatomical pathways within the hippocampus itself.

Keywords: neural network modeling, hippocampus, memory, statistical learning

STAND 8

Title: Lateral orbitofrontal cortex regulation of Aversive Prediction Errors

Authors: Madelyn H. Ray, Emma Hanlon, & Michael McDannald

Affiliation: Boston College

Abstract: The capacity to correctly discriminate cues signaling danger and safety is crucial especially in situations of uncertainty, and dysfunction of this capacity is a hallmark of anxiety disorders, including PTSD. We tested whether the lateral orbitofrontal cortex (LOFC) is necessary for employing aversive prediction errors related to changes in uncertainty. Rats received either bilateral neurotoxic LOFC lesions or no infusion (Sham). Rats then received fear discrimination in which three cues were associated with different probabilities of foot shock. The safety cue never predicted foot shock ($p=0.00$), the danger cue always predicted foot shock ($p=1.00$), and the uncertainty cue predicted shock on 25% of trials ($p=0.25$). Rats were then subjected to shifts in the probability of the uncertainty cue. We found that when inducing a large positive prediction error the Sham rats increase in fear was confined to the uncertainty cue whereas in LOFC rats the increase generalized to the danger and safety. When inducing a large negative prediction error, Sham rats decrease in fear was generalized to the danger and safety cues, whereas in the LOFC-lesioned rats no generalization was apparent. These results suggest that the lateral orbitofrontal cortex is involved in regulating the generalization of positive and negative aversive prediction errors.

Keywords: prefrontal cortex, prediction errors, fear conditioning, associative learning

STAND 9

Title: Behavioral flexibility during Pavlovian appetitive reversal learning is regulated by the basolateral amygdala-medial prefrontal cortex pathway

Authors: Sara E. Keefer, MA, & Gorica D. Petrovich, PhD

Affiliation: Boston College

Abstract: Appetite is not only regulated by internal homeostatic mechanisms, but can be controlled by learned environmental cues for food. Through Pavlovian appetitive conditioning, animals and humans can learn that initially neutral environmental cues (e.g. tone) can predict food. Two brain regions involved in this learning are the basolateral amygdala (BLA) and medial prefrontal cortex (mPFC). Each region and the BLA-mPFC pathway are activated when a single cue reliably signals food. These results suggest the BLA may update the mPFC about the value of the learned cue. The current study further explored this hypothesis using two cue discriminative conditioning and reversal of that learning. Male rats received contralateral, ipsilateral, or sham excitotoxic lesions of the BLA-mPFC. After recovery, rats underwent ten sessions of discriminative conditioning. These sessions included two distinct 10s auditory stimuli (tone and white noise); each were presented six times within a session. One stimulus was co-terminated with the delivery of two palatable food pellets (CS+), and the other stimulus was unrewarded (CS-; counterbalanced) throughout discriminative conditioning. Learning was measured through assessment of conditioned responding: the percentage of time rats spent at the food cup during the presentation of the CSs. All groups successfully discriminated between the two stimuli by the last session, suggesting the BLA-mPFC pathway is not necessary for this learning. Then, the stimulus outcomes were reversed: the CS+ was now unrewarded (reversal CS-; rCS-), and the CS- was now rewarded (reversal CS+; rCS+). Rats underwent 15 sessions of reversal learning. Rats that received contralateral disconnection of the BLA-mPFC showed faster increased responding to the rCS+ compared to the other groups, suggest less inhibition to the previous CS- based on previously learned information. Current results show the BLA-mPFC connection is necessary for appropriate responding during periods of behavioral flexibility, specifically during reversal learning when the outcomes of cues are altered.

Keywords: Associative learning, behavioral flexibility, basolateral amygdala, medial prefrontal cortex

STAND 10

Title: DREADD manipulations of ventromedial prefrontal cortex neurons during renewal of Pavlovian conditioned responding to food cues in male and female rats

Authors: Lauren C. Anderson, MA; Gorica D. Petrovich, PhD

Affiliation: Boston College

Abstract: Cues associated with food can stimulate appetite and food consumption independently of hunger. Renewal, or reinstatement, of responding to food cues after extinction may explain the inability to resist palatable foods and change maladaptive eating habits. Recently, we found sex differences in context-dependent renewal of responding to extinguished Pavlovian food cues and differential recruitment within the ventromedial prefrontal cortex (vmPFC). Male rats exhibited renewal of responding and had higher Fos induction within the vmPFC compared to a control group, while females failed to show renewal of responding and had lower Fos induction within the vmPFC compared to a control group. Here, we used DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) to silence vmPFC neurons in males (Experiment 1) and to stimulate the vmPFC in females (Experiment 2) during renewal. In Experiment 1, male, Long-Evans rats received bilateral injections into the vmPFC of a viral vector containing the gene for a synthetic inhibitory G-protein-coupled receptor (AAV5-hSyn-HA-hM4D-IRES-mCitrine) or a control viral vector (AAV5-hSyn-EGFP). After recovery rats

were trained in a within-subjects Pavlovian context-dependent renewal protocol. Rats were trained to associate a tone (conditioned stimulus, CS) with food (unconditioned stimulus) in acquisition sessions in Context A. Acquisition was followed by extinction sessions with CS-only presentations in Context B. Rats were tested for renewal of responding with CS-only presentations in Context A and Context B, counterbalanced for order, on separate days. 30 minutes prior to each test, rats were injected with clozapine N-oxide (CNO, biologically inert, DREADD-selective ligand; 3mg/kg, i.p.) or vehicle. Rats either received CNO on both days or vehicle on both days. The resulting groups were: DREADD+CNO, DREADD+Vehicle, and Control Virus+CNO. The measure of learning was an increase in the expression of food cup behavior (conditioned response, CR) during CSs. Renewal of responding was determined by significantly higher CRs in the acquisition context (Context A) compared to the extinction context (Context B). On tests, the DREADD+CNO group failed to show renewal responding with similar low responding to CS in both contexts, while DREADD+Vehicle and Control+CNO groups showed renewal responding with higher induction of CR to the CS in the acquisition context. In Experiment 2, female rats received a viral vector containing the gene for a synthetic stimulatory G-protein-coupled receptor (AAV5-hSyn-HA-hM3D-IRES-mCitrine) and were trained in the same behavioral procedure as males. At test, the DREADD+CNO group had higher induction of CR to the CS in the acquisition context, while control groups had similar responding to the CS in both contexts. Therefore, silencing vmPFC neurons in males disrupted renewal of food cup responding while exciting vmPFC neurons in females induced renewal of food cup responding. These results demonstrate the vmPFC activation is critical during renewal of responding to food cues and a site of sex differences.

Keywords: Renewal, medial prefrontal cortex, Pavlovian

STAND 11

Title:Female adolescent opioid exposure confers vulnerability to metabolic dyshomeostasis in F1 offspring in a diet-specific context.

Authors: Anika Toorie, PhD; Fair Vassoler, PhD; Annie Kuberek, BS; Cristina Wyse, BS; Christopher Schonoff, PhD; Elizabeth Byrnes, PhD

Affiliation: Tufts University-CSVM

Abstract: In the US, opioid abuse is a current major public health issue. Opioid misuse/abuse amongst adolescents has increased significantly; yet, the long-term consequences of this experience has yet to be realized. Data from animal models, however, reveal that adolescently opioid-exposed females transmit to F1 offspring transgenerational neurobehavioral and endocrine changes at both baseline and in the context of various stimuli. For example, the offspring of females that were exposed to morphine during adolescence (Mor-F1) display significant differences in hypothalamus-pituitary-adrenal axis function, and increased ARC POMC gene expression in a sex-specific manner. In the brain, POMC is the precursor to several neuropeptides involved in homeostatic and adaptive processes. Two bioactive derivatives of POMC, β -EP and α -MSH, are central regulators of energy homeostasis and metabolism. In the present study, Mor-F1 and Sal-F1 (maternal history of adolescent saline exposure; control) animals were maintained under different dietary conditions (control, high fat diet, or high sucrose diet) to assess neuroendocrine and metabolic changes. Specifically, we tested the hypothesis that Mor-F1 offspring are vulnerable to the development of metabolic dyshomeostasis when challenged with excessive fat or sugar. In the current study, Mor-F1 offspring displayed increased POMC levels and alterations in β -EP and α -MSH levels in a diet-specific manner. F1 animals also displayed differences in fasting glucose levels, alongside changes in the glucoregulatory hormones, insulin and corticosterone. In addition, Mor-F1 animals sex-specifically displayed changes in sexual maturity. Collectively, results demonstrate sex-dependent alterations to neuroendocrine systems that facilitate development and metabolism as a

function of maternal opioid use during adolescence. Moreover, results suggest that female adolescent opioid exposure increases the risk of diet-induced metabolic derangement in F1 progeny.

Keywords: opioid, proopiomelanocortin, glucose, F1

STAND 12

Title: Transgenerational Heterotypic Transmission of Enhanced Cocaine Reward

Authors: Fair M. Vassoler, Anika Toorie, and Elizabeth M. Byrnes

Affiliation: Department of Biomedical Sciences, Cummings School of Veterinary Medicine at Tufts University

Abstract: The United States is in the midst of an opiate epidemic, with abuse of prescription and illegal opioids increasing steadily over the past decade. While it is clear that there is a genetic component to opioid addiction, there is a significant portion of heritability that cannot be explained by genetics alone. The current study was designed to test the hypothesis that maternal exposure to opioids prior to pregnancy alters abuse liability in subsequent generations. Female adolescent rats were administered morphine at increasing doses (5-25 mg/kg, s.c.) or saline for 10 days (P30-39). Animals then remained drug free for at least 3 weeks. During adulthood (P70-P90), animals were bred with drug-naïve colony males. Male and female adult offspring (F1 animals) were tested for either morphine or cocaine self-administration acquisition, progressive ratio, extinction, and reinstatement (0.75-morphine and 0.5-cocaine mg/kg/infusion). In addition, mu-opioid receptor expression levels as well as β -endorphin peptide levels were measured in the nucleus accumbens and ventral tegmental area. There were both drug- and sex- dependent effects on all phases of the self-administration paradigm that indicate decreased morphine reward and attenuated relapse-like behavior and yet increased cocaine reward and enhanced relapse-like behavior in Mor-F1 animals compared with Sal-F1 animals. Additionally, both receptor and cognate peptide levels were altered in Mor-F1 animals. The results demonstrate that even limited opioid exposure during adolescence can have lasting effects across multiple generations, which has implications for mechanisms of the transmission of drug abuse liability in humans.

STAND 13

Title: Generation of a microglial developmental index in mice and in humans reveals a sex difference in maturation and immune reactivity.

Authors: Richa M. Hanamsagar¹, Mark D. Alter², Carina S. Block³, Haley Sullivan³, Jessica L. Bolton³, and Staci D. Bilbo^{1,3}

Affiliation: ¹Department of Pediatrics, Massachusetts General Hospital for Children, Harvard Medical School, Boston, MA 02129; ²Department of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104; ³Department of Psychology and Neuroscience, Duke University, Durham, NC 27708.

Abstract: **Purpose:** Increasing evidence suggests that many neurological disorders emerge because of a disrupted neuronal developmental trajectory. Considering the critical role of microglia, the immune cells of the brain, in integration of neurons into brain proper circuitry and synaptic pruning, there is a pressing need to understand 1) mechanisms underlying normal and abnormal microglia development, 2) their interactions with specific neuronal subsets, and 3) the utility of microglial analyses in preclinical models for human tissue. Moreover, as there are pronounced sex differences in the presentation of many neurological disorders, it is critical to understand these mechanisms in both males and females. Thus, the goal of this study was four-fold: (i) to analyze microglial development over time in purified mouse tissue using a data simplification strategy, (ii) to assess potential sex differences in the microglial development, (iii) to assess sex differences in the microglial response to immune challenge, and (iv) to

adopt and validate via multiple measures the same data simplification strategy for analyzing heterogeneous human brain tissue. **Materials & Methods:** We isolated microglia from male and female mice hippocampi from different developmental ages ranging from embryonic day 18 (E18) to postnatal day 60 (P60). Following whole transcriptome analysis in purified mouse microglia, we developed a microglia-specific developmental index (MDI) based on global gene expression patterns. Specifically, genes were divided into groups based on whether they were significantly up- or down-regulated during development and gene expression was scaled to equally weigh all genes. An index for a sample was calculated by taking the ratio of the average of the scaled expression of all up-regulated genes and that of all the down-regulated genes. In order to generate an index to measure microglial development in human brain tissue samples, genes common between purified microglial transcriptome and the human brain transcriptome datasets were identified. A sub-index was created from the common genes by identifying the genes that were developmentally regulated in purified microglial transcriptome. By averaging measurements from thousands of different genes, information about microglia development was enriched to provide an estimate of the developmental maturity of microglia in a given tissue sample. **Results:** MDI tracked with chronological age as expected; and as microglia developed, the expression of immune-related molecules increased. Next, we found that female microglia are more developed than male microglia, and male microglia are more immune reactive than female microglia. We show using multiple validation tests, that MDI derived from mice can be applied to human brain transcriptome datasets, and can accurately track microglial development in these samples. Upon applying this index to human transcriptome datasets of Alzheimer's disease and autism, we found that in the diseased brain, microglial development is significantly accelerated compared to controls. **Conclusion:** . In conclusion, we show that microglial development is closely related to immune activity and can be used to determine the immunoreactive state in healthy and diseased human brain.

Keywords: Microglia, development, sex differences

STAND 14

Title: Feminization of the sexually dimorphic nucleus of the preoptic area requires serotonin, but not dopamine D1 and D2 receptor activation.

Authors: Amanda M.K. Madden, Kellianne D. Alexander, and Susan L. Zup

Affiliation: Psychology Department, University of Massachusetts Boston, Boston, MA, 02125

Abstract: The sexually dimorphic nucleus of the preoptic area (SDN) is a canonical sexually dimorphic brain area, and a model for sexual differentiation of the brain. Indeed, the SDN is a now-classic example of hormone-mediated brain development, where gonadal testosterone and its metabolites masculinize (i.e., increase) the volume and cell number of the SDN, likely through anti-apoptotic mechanisms. In the absence of these hormones, the female SDN undergoes dramatic apoptosis and is comparatively smaller. Interestingly, serotonin also acts on SDN development, since both administration of a general serotonin agonist given across perinatal development, or a 5HT_{2A/2C}-specific agonist (-DOI) given during the second week of life, can feminize the SDN in males. Yet this effect of serotonin may *itself* be mediated by dopamine: concomitant administration of a dopamine antagonist (haloperidol) during the same timeframe blocked the feminizing effects of DOI in male rats. If dopamine is necessary for feminization of the SDN, then blocking dopamine should masculinize the SDN. Thus, we administered specific dopamine D1 and D2 antagonists (eticlopride 0.3mg/kg, SCH39166 0.03mg/kg) to both male and female rats from postnatal day (PND) 8 to PND16, then examined SDN volume on PND18. Surprisingly, the antagonists had no effect on the SDN of either sex, whether visualized with thionin or calbindin-immunoreactivity. These results challenge the notion that the effects of serotonin are simply the result of interference with the dopamine system. Instead, the effects of haloperidol may be explained

by that drug's affinity for some serotonin receptors, or dopamine receptors other than D1/D2.

Keywords: serotonin, dopamine, developmental, sexual differentiation

STAND 15

Title: A sex difference in oxytocin-expressing cells and serotonin receptors in the paraventricular nucleus after developmental serotonin exposure

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Abstract: The developmental hyperserotonemia (DHS) model of Autism Spectrum Disorder (ASD) utilizes perinatal administration of serotonin agonist 5-methoxytryptamine (5-MT) to mimic the elevated blood serotonin levels observed in many ASD individuals. DHS produces behavioral and brain morphological changes relevant to ASD, such as dysregulation of oxytocin- a hormone implicated in the regulation of social behavior. Serotonin can influence oxytocin release via its receptors 5-HT_{1A} and 5-HT_{2A}, which co-localize in OXT+ cells in the paraventricular nucleus (PVN) of the hypothalamus. Thus, DHS may induce abnormal social behavior by decreasing the number of OXT+ cells and/or the likelihood of OXT+ cells to release oxytocin into circulation via alteration of serotonin receptors. Interestingly, there are pronounced sex differences in both developmental serotonin regulation and ASD diagnosis. Despite this, most DHS studies are only performed in males. Here, we report sex differences in the number of OXT+ cells as well as their innervation by 5HT_{1A} and 5HT_{2A} receptors in the PVN of adult DHS rats. In agreement with previous findings, adult DHS males had fewer OXT+ cells than controls. Adult DHS females, however, had the same amount of OXT+ cells as controls. Both DHS males and females had a lower percentage of OXT+ cells expressing 5HT_{2A} receptors than controls, but only DHS females had a higher percentage of OXT+ cells expressing 5HT_{1A} receptors. This expression pattern suggests that females, but not males, can regulate serotonin receptors after DHS in a manner that promotes OXT+ survival and functional efficiency.

Keywords: Serotonin, Oxytocin, Sex difference, Autism, Hypothalamus

STAND 16

Title: DREADD-Induced Silencing of the Medial Amygdala Reduces the Preference for Male Pheromones and the Expression of Lordosis in Estrous Female Mice

Authors: Elizabeth A. McCarthy¹, Matthew Bass¹, Arman Maqsdudlu¹, Sofia Georghiou¹, James A. Cherry² and Michael J. Baum¹

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Abstract: The medial amygdala (MeA) integrates socially relevant chemosensory cues that control courtship in female mice. Electrolytic lesions of the MeA permanently disrupt sexually naïve estrous females' preference for male pheromones and the expression of lordosis, but it is unknown if the role of the MeA changes with sexual experience. We used a reversible chemogenetic technique (Designer Receptors Exclusively Activated by Designer Drugs; DREADDs) to reassess the role of the MeA in regulating pheromone preference and mating behavior, first in sexually naïve and then in experienced females. After bilateral MeA injection with an inhibitory DREADD, sexually naïve females were tested for urinary odor preference after receiving intraperitoneal injections of clozapine-N-oxide (CNO) or saline. CNO hyperpolarizes DREADD-infected neurons. After CNO injections, females lost their preference for male vs female urinary odors when nasal contact was allowed but not when access was restricted to volatiles only. Five consecutive mating tests were then given, with sub-groups of females

treated with saline or with CNO. Treatments were then reversed during two additional tests. Females initially treated with CNO during Tests 1-5 showed decreased receptivity (lordosis) compared to the saline treated group, but no difference was observed when treatments were switched. Additional sub-groups of estrous females without MeA DREADD-infections showed no difference in olfactory preference or receptivity in the presence or absence of CNO. Our results confirm the importance of MeA function in pheromone preference and in the progressive increase in lordotic responsiveness normally observed in estrous female mice with repeated testing with a stud male. (Supported by NIH grant DC 008962)

Keywords: Olfaction, DREADD

STAND 17

Title: BACE1 axonal trafficking: A new role for the clathrin adaptor GGA3.

Authors: Selene Lomoio, PhD, Rachel Willen BS, Giuseppina Tesco, MD PhD

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Abstract: Recent studies demonstrated that endogenous BACE1 localizes within normal presynaptic terminals and accumulates within endosomes in dystrophic neurites surrounding A β plaques in AD brains and APP transgenic mice suggesting that extracellular A β deposits cause impairment in retrograde axonal transport. We have previously shown that depletion of the clathrin adaptor GGA3 results in BACE1 stabilization by impairing its sorting to lysosomes, where is normally degraded. We also reported that GGA3 levels are decreased and inversely correlated with BACE1 in AD brains. The identification of GGA3-mediated BACE1 axonal transport machinery would be extremely important to determine the extent to which GGA3-mediated regulation of BACE1 may represent a potential treatment for AD. Our new data demonstrated that genetic deletion of GGA3 results in BACE1 accumulation in axons in hippocampal neurons both *in vitro* and *in vivo*. Using live cell imaging experiments we have found that BACE1 axonal trafficking is disrupted in GGA3 null neurons. Rescue experiments clearly showed that GGA3 reintroduction is alone sufficient to drive the polarized distribution and axonal trafficking of BACE1 back to the wild type condition. Finally we found that BACE1 localization in late endosomes/lysosomes is decreased in GGA3 null neurons. These data indicate that GGA3 plays a pivotal role in BACE1 polarity and axonal trafficking most likely by regulating its trafficking to lysosomes. Therefore, the depletion of GGA3 observed in AD brains is a leading candidate mechanism underlying BACE1 accumulation in dystrophic axons observed in AD.

Keywords: Alzheimer's Disease, Clathrin Adaptor Protein GGA3, BACE1 Trafficking, Hippocampal Primary Cultures, Microfluidics Chamber, Axonal Trafficking, Axonal Pathology

STAND 18

Title: Treating Epilepsy by Molecular Manipulation of Inhibitory Synapse Formation

Authors: Daniel Acker, Irene Wong, Suzanne Paradis

Affiliation: Brandeis University

Abstract: Reduced inhibition in the nervous system is an underlying cause of epilepsy, a disease characterized by runaway excitation in the brain. Sixty five million people suffer from epilepsy, and 1/3 of patients do not respond to the available treatments. Further, all currently available anti-epilepsy drugs (AEDs) only treat the symptoms of epilepsy (i.e. seizure) without addressing the underlying cause of the seizures: impaired inhibition. Our laboratory discovered a previously unknown role for the protein Semaphorin4D (Sema4D) as a positive regulator of inhibitory synapse development. Using an *in vitro*

model of epileptiform activity, we demonstrated that 2 hours of Sema4D treatment rapidly and dramatically reduces the hyperexcitability of this tissue. Recently, we found that Sema4D treatment promotes inhibitory synapse development *in vivo* as well as *in vitro*. Further, we found that 3 hours of Sema4D treatment ameliorates seizure severity in three *in vivo* mouse models of epilepsy: pharmacological activation of kainate glutamate receptor by kainate, GABA_AR antagonism by pentylenetetrazol, and kindling by low-frequency electrical stimulation of the hippocampus. Taken together, our data suggest that Sema4D treatment protects against seizures by inducing the formation of new inhibitory synapses in the hippocampus, shifting the excitatory/inhibitory balance in favor of inhibition. Our work indicates that a novel therapeutic approach to treat seizures could be to harness the synaptogenic potential of signaling pathways that enhance inhibition in neural circuits by increasing GABAergic synapse number.

Keywords: Epilepsy, Translational, Synaptogenesis, Semaphorin

STAND 19

Title: The microtubule plus-end-tracking protein TACC3 promotes persistent axon outgrowth and mediates responses to axon guidance signals during development.

Authors: Burcu Erdogan, Garrett Cammarata, Eric Lee, Ben Pratt, Erin Rutherford, Laura Anne Lowery

Affiliation: Boston College

Abstract: Precise neuronal connection requires proper axon guidance. Microtubules (MTs) of the growth cone are the driving force to navigate the growing ends of axons. Pioneering microtubules and their plus-end resident proteins, +TIPs, play integrative roles during this navigation. Recently, we introduced the protein TACC3 as a member of the +TIP family regulating microtubule dynamics in *Xenopus laevis* growth cones and showed manipulation of TACC3 levels affects axon outgrowth by regulating axon outgrowth velocity and the frequency of axon retraction. Here, we examine the impact of the highly conserved domains of TACC3 on MT dynamics regulation and axon outgrowth. We find that deletion of the TACC domain, the domain that ensures plus-end localization, significantly reduces both MT and axon growth length. Additionally, we show that over expressing TACC3 mitigates Nocodazole-induced reduction in MT dynamics parameters, such as MT growth speed, length and lifetime. While this mitigation could result from increased MT stability, immunocytochemical analysis of growth cones for stable (de-tyrosinated tubulin) and dynamic (tyrosinated tubulin) MTs demonstrates that neither TACC3 knockdown nor its overexpression have impact on the levels of dynamic versus stable MTs, suggesting TACC3 antagonizes Nocodazole-induced reduced MT dynamics by a different mechanism. We had previously shown that TACC3 co-localizes with its well-known partner XMAP215 at the extreme plus-ends of MTs in a co-dependent manner (Nwagbara et al 2014). Our epistasis analysis demonstrates that TACC3 and XMAP215 cooperate to promote axon outgrowth and rescue axon growth defects. Moreover, we demonstrate that manipulation of TACC3 levels interferes with the growth cone response to the axon guidance cue Slit2 *ex vivo*. We also show that ablation of TACC3 causes pathfinding defects in axons of developing spinal cord motor neurons and retinal ganglion cells in *Xenopus laevis* *in vivo*. Together, our results suggest that by regulating MT behavior, the +TIP TACC3 is involved in axon outgrowth and pathfinding decisions of neurons during embryonic development.

Keywords: microtubule, +TIPs, TACC3, XMAP215, *Xenopus laevis*, neuronal development, growth cone, axon guidance

STAND 20

Title: Investigating the protective role of environmental enrichment against inflammatory-induced disturbances in placental programming

Authors: Jenny Nguyen, Karen Nunez, MScs & Amanda C. Kentner, PhD

Affiliation: MCPHS University

Abstract: Background: Prenatal infection is associated with an elevated risk for neurodevelopmental disorders in human offspring and the appearance of related neurophysiological and behavioral symptoms in laboratory animals such as rats and mice. In our previous work [Connors et al. (2014). *Brain, Behavior, and Immunity*, 42:178-90], we demonstrated that life-long rearing in environmental enrichment (EE) prevented disruptions in adolescent social behavior and associated reductions in central glucocorticoid receptors (GR) following prenatal inflammation in rats. However, it is unknown if the EE rearing during gestation attenuated the maternal inflammatory response at the time of prenatal infection, or if the offspring instead benefited from EE during the postnatal period. Methods: Female Sprague-Dawley rats were reared and bred in either EE or standard laboratory conditions (SC). On gestational day 15, animals received either 100 µg/kg of the inflammatory endotoxin lipopolysaccharide (LPS; i.p.) or pyrogen-free saline. At 3 and 24-hours post injection, maternal plasma, placenta, and fetal brain were collected and levels of maternal plasma corticosterone was evaluated by a commercially available ELISA. Placental interleukin (IL)-1 β , 11-beta hydroxysteroid dehydrogenase (HSD11b)₁ and HSD11b₂, and fetal GR gene expression were determined in male and female offspring using real-time polymerase chain reaction (qPCR). Results: Prenatal LPS significantly elevated maternal corticosterone, placental IL-1 β , and fetal GR while downregulating HSD11b₂ gene 3 hrs after challenge in both EE and SC animals. Interestingly, EE male and female placentas had higher HSD11b₂ and lower HSD11b₁ compared to SC animals, but no differences in fetal GR were observed as a function of housing. Conclusions: EE housing did not attenuate the prenatal inflammatory response. This suggests that the benefits of EE following prenatal LPS are likely acquired by the offspring postnatally.

Keywords: maternal immune activation; environmental enrichment; placenta

STAND 21

Title: Nesting Environment Impacts Hypoxic-Ischemic Injury in Rodents

Authors: Briana Mason, B.S.; Laura-Grace Rollins, M.S.; Vanessa Romero, B.S.; Paola-Londono-Gamez, B.S.; Evans Asumadu, B.S.; S. Tiffany Donaldson, Ph.D.*

Affiliation: University of Massachusetts Boston

Abstract: Hypoxic-ischemic encephalopathy (HIE) is a brain injury that follows difficult perinatal birth conditions and can lead to substantial white matter damage, neuron loss in motor and cognitive brain areas, motor impairment and cognitive decline. Adverse environments such as poverty and stress may worsen these consequences. In rodent models, a strong link has been established between levels of maternal care-taking behavior (mCTB) and neurogenesis in neonatal pups, where high mCTB may decrease stress and promote neuroprotection. Therefore, we hypothesized that cage modification with a closed nestbox (CN) during pre-weaning would promote mCTB and pup weight gain, and in turn, protect against neuronal loss in HI injured postnatal day (PND) 7 Long Evans rats. Utilizing a cohort of both male and female pups ($N = 42 - 51$) under three conditions (control, sham, hypoxic-ischemic/HI injury) reared in CN or standard facility (SF), we recorded offspring weight and development through PND 60, tested anxiety-like behavior (elevated plus maze/EPM), and spatial learning (Morris Water Maze/MWM). Our findings show that CN rearing significantly increased weight gain for males [$F(13, 520) = 4.818, p < 0.001$] and shifted the appearance of neurological characteristics (i.e., earlier eye opening, ear unfolding, and day of incisor eruption) for HI pups reared in the CN condition. In addition, CN

housing decreased anxiety-like behavior on the EPM by increasing the number of open-arm entries [$F(1,49)=4.191, p < 0.05$] and diminished mean latency to find the invisible platform in MWM trials for females and CN-reared HI pups. Finally, preliminary evidence from morphometry analysis shows that CN rearing altered HI injury infarct size and lead to greater retention of ipsilateral and contralateral hippocampus and cortex for both male and female pups. These results support our hypothesis that the CN environment would facilitate neurological development following HI, and highlight the importance of environment in mediating lifetime outcome following an early-life brain injury.

Keywords: nesting environment, rodents, maternal care, hypoxia-ischemia

STAND 22

Title: Early life stress leads to sex-specific precocial corticolimbic circuit maturation

Authors: Jennifer A. Honeycutt, PhD, Camila Demaestri, BS, Shayna Peterzell, Heather C. Brenhouse, PhD

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Abstract: Early life experiences significantly shape the behavioral and neural trajectory of an organism across development. Therefore, disruptions during early developmental periods likely set the course for aberrant brain maturation. Indeed, children who have experienced early adversity often exhibit deleterious effects that manifest as maladaptive behaviors, cognitive impairment, and/or increased susceptibility to mental illness. Increasing evidence in humans with a history of adversity points to a role of atypical corticolimbic circuit development, leading to changes in functional connectivity between the basolateral amygdala (BLA) and prefrontal cortex (PFC). In rodent models of early adversity via maternal separation (MS) during the postnatal period, comparable neural and behavioral phenotypes are observed, including loss of PFC inhibitory tone and increased anxiety-like behaviors. The neural mechanisms underlying these findings following MS remain unknown, though it is likely that dysfunction is in part driven by precocial BLA innervation of the PFC. To determine the impact of sex and MS on this circuitry, targeted anterograde tracer microinjections into the BLA were performed at key developmental milestones spanning juvenility and adulthood. Labeled axonal fibers from BLA-PFC projecting neurons were quantified within the PFC. We present novel data indicating that MS drives increased BLA innervation of the PFC in a sex- and age-dependent manner, such that juvenile MS female innervation patterns resemble that of their adult control counterparts. This suggests a critical role for early experiences on corticolimbic development and provides putative mechanistic insight into the underlying etiology of adversity-induced vulnerability and resilience.

Keywords: prefrontal cortex, amygdala, early life stress, maternal separation, anxiety

STAND 23

Title: Anxiety-like responses in rats presented with playback of 22 kHz ultrasonic vocalizations

Authors: Camila Demaestri, BS, Jennifer A. Honeycutt, PhD, Heather C. Brenhouse, PhD

Affiliation: Developmental Neuropsychobiology Laboratory, Northeastern University

Abstract: The basolateral amygdala (BLA) plays a role in processing emotions, such as fear and anxiety-like states. When humans are presented with a fearful face during functional magnetic resonance imaging (fMRI), corticolimbic circuitry associated with anxiety can be functionally studied. Previous work supports the use of the fearful face task to investigate aberrant circuitry in populations who have experienced early adversity. Children with a history of adversity show functional connectivity comparable to adolescents/young adults, indicating premature activation of anxiety-related circuitry. Limitations in human studies make it difficult to systematically manipulate neuronal and

environmental variables to understand the etiology of this precocial connectivity. We seek to model this phenomenon in rodents by implementing novel methodology to investigate the changes underlying aberrant connectivity patterns. We aim to study this using an ethologically relevant analogue of the fearful-face task via the presentation of pre-recorded fear-induced ultrasonic vocalizations (USV; 22 kHz) during awake fMRI scanning to determine the degree of anxiolytic response on task-based BLA-PFC connectivity. The present study provides critical proof-of-concept preliminary data characterizing anxiety-like responses in rats presented with the fear-induced USVs. Rats exposed to 22 kHz USVs show: 1) anxiety-like behaviors during playback; 2) increased heart rate variability; and 3) increased neural activation of the BLA compared to rats exposed to a synthetic tone control stimulus in the 22 kHz range. These results provide groundwork for developing a novel way of studying anxiety circuitry following early stress and aids in improving our understanding of anxiety-related dysfunction and psychiatric illnesses such as anxiety and schizophrenia.

Keywords: ultrasonic vocalizations, anxiety, heart rate variability, amygdala

STAND 24

Title: Early life stress alters microglia activation in juvenile rats and confers sensitization in microglia to LPS induced immune activation

Authors: Kelsea R. Gildawie, BS; Shelby A. Goff, BS; June R. Rowe-Hill, BS; Prabarna Ganguly, MA; Vanessa Thompson, BA; Heather C. Brenhouse, PhD

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Abstract: Overwhelming evidence suggests that adversity during early life markedly increases vulnerability to a myriad of neuropsychiatric disorders including depression, anxiety, and schizophrenia. Importantly, stress during this time may negatively impact overall neural development via neuroimmune signaling, particularly within the prefrontal cortex (PFC). While the etiological mechanisms are not fully understood, resident microglia are thought to be a common source of increased neuroimmune activity through production of inflammatory molecules (e.g. cytokines, chemokines) in response to disruption in homeostasis. Microglia are capable of provoking long-term changes in brain structure and function. Importantly, they have the ability to become chronically sensitized, or 'primed,' to over-activation following insult, amplifying systemic inflammation. Early life stress via maternal separation (MS) is thought to alter microglial reactivity to subsequent immune activation across development. In order to better understand the impact of MS on microglial priming in the developing immune system, rat pups were separated from their dams for 4 hours per day from P2-20. In order to stress immune reactivity following MS, rats were exposed to the endotoxin lipopolysaccharide (LPS) at distinct developmental time points (P9, P20, or P40), and the concentrations of ramified and amoeboid PFC microglia were quantified to gain insight to activity states. Additionally, in order to assess the level of release of pro-inflammatory cytokines, quantitative RT-PCR was conducted on isolated microglia, allowing for the analysis of transcripts encoding only microglia-associated molecules. Our findings will provide compelling evidence for a role of early life adversity in altering microglia function in later life.

Keywords: microglia, prefrontal cortex, early life stress, development

STAND 25

Title: Sex-specific effects on TNF- α derived changes in GluA2-containing AMPARs after early life stress

Authors: Prabarna Ganguly M.A.¹, Jennifer A. Honeycutt¹ Ph.D.¹, June H. Rowe-Hill¹, Camila Demaestri¹, Heather C. Brenhouse Ph.D.¹

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Abstract: Maternal separation (MS) during the early postnatal period alters neural development, especially within the prefrontal cortex (PFC). α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) are glutamate-gated ion channels crucial for proper PFC neuronal communication. Previous reports suggest that neuro-immune signaling molecules, such as the pro-inflammatory cytokine TNF- α , regulate AMPAR subunit composition. Increased TNF- α levels have been shown to reduce GluA2-positive AMPARs, which are associated with increased excitotoxicity. Since MS induces neuro-immune changes, it is likely that these alterations impact AMPAR subunit composition. Here, we examined the contribution of MS to selective loss of GluA2 subunit in the PFC of male and female rats. We evaluated whether MS alone, or in concert with a later immune challenge of lipopolysaccharide (LPS), increased TNF- α expression. Finally, we investigated whether administration of ibudilast, a phosphodiesterase inhibitor that suppresses TNF- α production, prevents these changes. We report that MS leads to increased adolescent PFC TNF- α expression, only in males. A history of MS also appeared to sensitize PFC TNF- α production in response to LPS. MS alone decreased GluA2 protein, but not mRNA, in males but not females. LPS, conversely, affects both mRNA and protein expression in both males and females. We show evidence that increased TNF- α , as well as decreased GluA2 levels, can be partly mitigated by treatment with ibudilast. This suggests that decrease in GluA2 subunits are mediated by neuro-immune activity through increased TNF- α , particularly in males. However, we see a different pattern in females, suggesting a sex-specific timeline of vulnerability. Taken together, this work is the first to mechanistically link TNF- α levels to changes in GluA2 expression, thereby providing further evidence for a role of MS and neuro-immune activity changes in PFC AMPARs. This study was funded by the National Institute for Mental Health (R01MH107556-01) and awarded to H.C. Brenhouse.

Keywords: early life stress, sex differences, neuro-immune; AMPAR, GluA2, TNF- α

STAND 26

Title: Neuroelectronic device based on open-ended nanocoaxial arrays

Authors: Jeffrey R. Naughton, MS; Juan M. Varela, PhD; John P. Christianson, PhD; Thomas C. Chiles, PhD; Michael J. Burns, PhD; Michael J. Naughton, PhD;

Affiliation: Boston College

Abstract: We report on the development of a nanocoax-based neuroelectronic array. A nanocoax consists of concentric conductor core, a dielectric annulus and an outer conductor shield. Computer simulations with this architecture indicate that a nanocoax array can pixelate local field potentials (LFPs) at a spatial pitch far smaller than bare wire sensors of equal size. Moreover, the shielded nature of the nanocoax provides improved signal-to-noise ratio at any pitch. We have developed fabrication techniques in which nanocoax arrays, consisting of individual coaxes as small as 300 nm diameter, can be deployed as multielectrode arrays for neural LFP recordings. First, we made extracellular LFP recordings from leech *Hirudo medicinalis* ganglion sacs. Biphasic waveforms with amplitude and duration akin to published leech action potentials were evident. Next, we cultured HEK293-Channelrhodopsin2 cells (HEK-ChR2) on 5 \times 6 arrays of 2 μ m coaxes. Brief application of blue light (0 to 30 mW/mm²) evoked negative LFPs with a linear optical dose-response relationship. Importantly, optically-evoked LFPs were only observed on nanocoax sensors found to be in direct

contact with HEK-ChR2 as determined after recording with fluorescent microscopy. In addition, we have characterized the optical throughput of such coaxial arrays, and find strong near-field transmission, favorable for multiplexed optogenetic interrogation of proximate neurons. These results encourage future development of nanocoax electrode arrays for optogenetic neural recordings with high spatial and electronic resolution.

Keywords: multielectrode array, optrode, extracellular recording. Optogenetics

STAND 27

Title: Rhythmic motor patterns are robust to changes in pH

Authors: Jessica Haley and Eve Marder

Affiliation: Brandeis University

Abstract: Most neural circuits found in marine animal species must maintain function despite significant environmental changes such as temperature, dissolved oxygen concentration, and pH fluctuations in sea water. Here, we examine the effects of acute pH changes on two rhythmic motor patterns generated by the stomatogastric and cardiac ganglia of the crab, *Cancer borealis*. The pH of the haemolymph of *C. borealis* is around 7.9 while that of seawater ranges from 7.5 to 8.4 and averages 8.1. This is a 25 percent increase in acidity compared to 200 years ago, a result of ocean acidification. In this experiment, we recorded the pyloric and cardiac rhythms while varying the pH of the bath from 5.9 to 11.0. These experiments reveal animal-to-animal variability in the sensitivity of both the cardiac and stomatogastric ganglia to acute changes in pH with preparations “crashing” at varying pH values. Despite this variability, these neural circuits are extremely robust in response to external perturbations, even in extreme conditions, as preparations exhibit a normal rhythm over a 1000-fold change in proton concentration. Moreover, there appear to be fundamental differences in the pH-sensitivity of these two central pattern generating circuits that exist within the same animal with the cardiac ganglia displaying more sensitivity to basic conditions (pH > 9.5) and the stomatogastric ganglia exhibiting greater sensitivity to acidic conditions (pH < 6.5). Research supported by the National Institute of Health grant NS097343.

Keywords: crustacean, pH, stomatogastric