Boston Area
Neuroscience Group
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Boston Area Neuroscience Group Fall Symposium 2018

Thursday, October 25th, 2018
Tufts University
School of Dental Medicine
1 Kneeland Street, Boston

PROGRAM FOR THE MEETING

Start Time	Location	Event
3:00 PM	Merritt Auditorium Floor 7, Room 700	*Doors Open - Onsite Registration* Refreshments Served
3:30 PM	Merritt Auditorium Floor 7, Room 700	*Keynote Speaker* Dr. Sandeep Robert Datta
4:15 PM	Board Room Floor 15, Room 1533	*Poster Session* Dinner and Drinks Available
6:15 PM	Rachel's Amphitheater Floor 14, Room 1414	*Career Panel* Dr. Elizabeth Bless, Dr. Zoë Hughes, Emily Martersteck
7:00PM	Rachel's Amphitheater Floor 14, Room 1414	*Poster Awards Presented*

All events take place at Tufts University School of Dental Medicine, 1 Kneeland Street.
Time has been allotted for transition between events.

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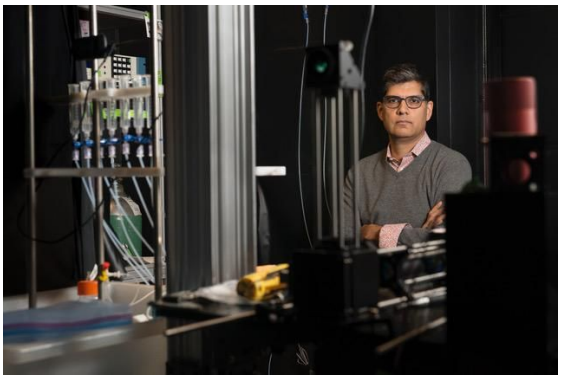
MEET OUR INVITED SPEAKER AND PANELISTS



Dr. Sandeep Robert Datta obtained a Bachelor of Science degree in Molecular Biochemistry and Biophysics from Yale University in 1993, and obtained an M.D./Ph.D degree from Harvard University in 2004. After working as a postdoctoral fellow at Columbia University with Nobel laureate Richard Axel, he joined the Harvard Medical School Department of Neurobiology in 2009. His lab focuses on understanding how sensory cues — particularly odors — are detected by the nervous system, and how the brain uses information about the presence of salient sensory cues to compose complex patterns of motivated action on a moment-to-moment basis. This work involves studying genes involved in detecting odors, revealing the patterns of neural activity deep in the brain that encode sensory maps of the outside world, exploring motor circuits that transform sensory codes into action, and probing the fundamental statistical structure of behavior itself. Dr. Datta has published numerous articles on his research in journals including Cell, Science and Nature, is a reviewer and an editor at multiple scientific journals, is an Associate Member of the Broad Institute, and is a Principal Investigator in the Italian Institute of Technology/Harvard Medical School joint program in the neurosciences. Dr. Datta has received the NIH New Innovator Award, the Burroughs Welcome Career Award in the Medical Sciences, the Alfred P. Sloan Research Fellowship, the Searle Scholars Award, the Vallee Young Investigator Award, the McKnight Endowment Fund Scholar Award and has been named a fellow of the National Academy of Science/Kavli Scholars program. In addition, Dr. Datta is a cofounder of Optogenix (which manufactures biocompatible optical fibers for recording/manipulation of the brain), Syllable Life Sciences (which has developed an advanced behavioral phenotyping platform for drug development) and Abelian Therapeutics (which is developing novel treatments for neurodegenerative disorders).

Dr. Elizabeth Bless earned her Master's degree from Northeastern University and her Ph.D. in neuroscience from Boston College. Dr. Bless' research has ranged from the interplay between hormones and drug addiction to neurogenesis and the gut microbiome. In addition to academia, Dr. Bless spent five years in biotechnology working toward the development of a treatment for stroke. Most recently, Dr. Bless started a nonprofit consulting firm with the mission of helping elementary school teachers adjust to the new MA state science standards.

Dr. Zoë Hughes got her Bachelor's degree in Pharmacology from University of Bristol, UK, followed by her PhD in Pharmacology from University College London. After completing a post-doc at Oxford University, Zoë left academia to join the Neuroscience Research Unit at SmithKlineBeecham and subsequently the Psychiatry Centre of Excellence at GlaxoSmithKline. In 2004 Zoë moved to the USA to continue her career in Neuroscience drug discovery at Wyeth Research where she took on increasing leadership roles for preclinical drug discovery projects in the depression and anxiety field. After moving to Pfizer in 2010 she developed preclinical and translational approaches to address common domains of function affected in psychiatric and neurodegenerative disease. Zoë has held leadership roles on a number of projects which delivered candidates for clinical development; she also built a Translational Pharmacology lab focused on generating preclinical data to inform the design of early clinical studies across CNS disorders. Zoë's research interests span psychiatry and neurodegeneration and has recently focused on the role of neuroinflammation in CNS disorders. She has actively contributed to a number of multi-national translational research consortia involving leading academic and industry groups and published her work in over 50 peer reviewed articles. While at Pfizer, Zoë led the FAAH inhibitor program where she gained support to re-position the molecule for PTSD. She was instrumental in this molecule being successfully out-licensed to SpringWorks Therapeutics, a small development company conceived by Pfizer. After getting a taste of the 'start-up world', in June 2018 Zoë joined Praxis Precision Medicines, a small biotech inspired by breakthroughs in the genetics of epilepsy and overlapping biology with broader neuropsychiatric disorders.

A Colorado native, **Emily Martersteck** studied Molecular, Cellular, and Developmental Biology at CU Boulder. Having moved to Boston, she worked as a Research Assistant/Lab Manager at the Sanes Lab at Harvard University. Recently, she joined Advanced Cell Diagnostics as a Field Application Scientist and helps to train researchers who use RNAscope and BaseScope. Her free time is usually spent rock climbing, running or indulging in chocolate chip cookie dough ice cream.

POSTERS BY PRESENTING AUTHOR

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During the poster session, be sure to visit information tables hosted by the following organizations:

GWISE - Graduate Women in Science and Engineering
SPINES - Scientists Promoting Inclusive Excellence at Sackler
MASS AWIS - Massachusetts chapter of the Association for Women in Science
BPDA - Boston Postdoctoral Association

On behalf of the Boston Area Neuroscience Group we thank all these organizations working to support scientists in the Boston area.

To learn about future BANG events go to NeuroBoston.org or follow us on Twitter @NeuroBoston

POSTER ABSTRACTS BY STAND NUMBER

STAND 1
TITLE: Developing a Model of Sex Difference in Post-Stroke Depression
Authors: Delaney Teceno, BA, Trevor Patton, BS, Fair Vassoler, PhD, Elizabeth Byrnes, PhD
Affiliation: Cummings School of Veterinary Medicine at Tufts
Abstract: In the United States, over 600,000 people suffer from a stroke each year, with roughly 87% of those strokes being ischemic. While the prevalence of stroke is higher among men, women experience poorer outcomes, specifically related to post-stroke depression. Despite stroke being the leading cause of serious long-term disability in the U.S., preclinical models of post-stroke depression are sparse, specifically those including females. The purpose of the current study is to examine levels of depressive-like behaviors in male and female Sprague Dawley rats using well-validated measures of anhedonia following an ischemic stroke. We predicted that post-stroke depression-like behaviors would be more severe in young males as compared to young females. Animals were trained to self-administer sucrose pellets in standard operant chambers for several weeks prior to stroke. Progressive ratio results following training were used as an indication of baseline motivation levels. In addition to sucrose self-administration, sensorimotor analysis (sunflower seed test), anxiety levels (elevated plus maze), and home cage activity were measured one week prior to stroke and one week post-stroke. Stereotaxic surgery was used to replicate a cortical ischemic insult by infusing endothelin-1, a vasoconstrictor, in line with either the left or right middle cerebral artery of experimental animals. Control animals participated in an identical surgical procedure excluding the vasoconstrictor and instead received an infusion of artificial cerebral fluid. Preliminary results indicate no significant difference in overall home cage activity or anxiety measures as a function of sex, time, or treatment. Furthermore, there was no difference in progressive ratio related to treatment or time. However, following either stroke or sham surgery, females worked significantly harder for sucrose compared to males. Lastly, there was no difference in sensorimotor deficits between sexes, but stroke animals had significantly more sensorimotor deficits than sham animals 1-week following the stroke. This data indicates that our ET-1 model of ischemic stroke does not impact activity, anxiety, or anhedonia at early time points. However, there were significant sensorimotor deficits observed in animals that experienced a stroke. Additionally, both groups of females demonstrated increased motivation for sucrose reward, regardless of the presence of a stroke. The current study is ongoing and will continue to collect data from 5, 9, and 13 weeks post-stroke. We hypothesize that post-stroke depression-like behaviors may become more apparent at later time points. Additionally, future studies will include infarct volume and the effect of neuropeptides in post-stroke recovery.
Keywords: stroke, anhedonia, ischemic, sex differences

STAND 2
TITLE: Histone Deacetylase 3 as a Novel Therapeutic Target for Ischemic Stroke
Authors: Rudy Matheson, BS; Kohei Chida, MD; Amjad Shehadah, MD
Affiliation: Beth Israel Deaconess Medical Center
Abstract: Histone deacetylase 3 (HDAC3) has been implicated as neurotoxic in several neurodegenerative conditions. However, the role of HDAC3 in ischemic stroke has not been thoroughly explored. We tested the hypothesis that selective inhibition of HDAC3 after stroke affords neuroprotection. **Methods:** To investigate the effects of ischemia on HDAC3 expression, adult male Wistar rats (n=6/group) were subjected to middle cerebral artery occlusion (MCAO) and sacrificed 24 h later. Double immunohistochemistry was performed with antibodies against HDAC3 and NeuN (a neuronal marker). To investigate whether selective HDAC3 inhibition affords neuroprotection after stroke, another set of rats (n=7/group) was subjected to 2-h MCAO, and randomly selected animals were treated with either vehicle (1% Tween 80) or a selective HDAC3 inhibitor (RGFP966, 10 mg/kg) at 2 and 24 h after MCAO. Behavioral tests were performed at 3 h, 1 d, and 3 d after MCAO. Rats were sacrificed 3 d after MCAO. Infarct volumes were measured with H&E. Immunostaining for Akt, TNF-alpha, toll-like receptor 4 (TLR4), cleaved poly (ADP-ribose) polymerase (PARP), and TUNEL assays were performed by blinded investigators. **Results:** The numbers of HDAC3+ cells and HDAC3+/NeuN+ neurons were

increased in the peri-infarct cortex compared to the contralateral cortex ($p<0.05$). Total and neuronal HDAC3 expressions were positively and significantly correlated with infarct volumes ($r=0.8$, $p<0.001$; $r=0.6$, $p=0.03$; respectively). Selective HDAC3 inhibition improved functional outcome ($p=0.01$) and reduced infarct volume ($p<0.001$). RGFP966 treatment reduced apoptosis—as measured by the numbers of TUNEL+ and cleaved PARP+ cells—in the ischemic brain ($p<0.05$). Selective HDAC3 inhibition reduced total and neuronal TNF-alpha and TLR4 in the ischemic border compared to vehicle control ($p<0.05$). RGFP966 treatment also increased Akt expression in the ipsilateral cortex ($p=0.007$).
Conclusions: HDAC3 is upregulated after stroke and correlates with infarct volumes. Selective HDAC3 inhibition after stroke improves functional outcome and decreases infarct volume. The neuroprotective effects of HDAC3 inhibition are associated with a reduction in apoptosis and attenuation of inflammation.
Keywords: Epigenetics; Histone Deacetylase; Ischemic stroke

STAND 3
TITLE: Generation of Gap Models to Assess Impact of Age/Pathology on Neocortical Operations
Authors: Yasmine Hashemi, BS; Donald M. O'Malley, PhD
Affiliation: Northeastern University
Abstract: It is a challenge to understand or model the impacts of age and pathology on cognitive operations: Alzheimer's disease is especially problematic given its complexity and prevalence. While brain-region level (fMRI) modeling efforts have revealed deficits in functional connectivity, and highlighted compromised brain regions and operations, details of neuronal- circuit level damage are absent. There is thus a huge gap between local-circuit models simulating a few dozen nerve cells vs. fMRI maps that encompass millions of neurons: new approaches are needed. We introduce Gap Models comprised of specialized neocortical modules that implement computations deemed necessary for simulating cognitive functions that are often damaged by age (such as word retrieval and working memory). Building upon recent computational results, using e.g. integrate and fire neurons to represent large populations, and spiking-neuron models for finer-grained cellular details, it is possible to emulate network disconnection syndromes, or the degradation of neuromodulation and ion channels, at the cellular level. This allows e.g. the competing etiologies of Alzheimer's disease to be simulated: tau protein dysfunction, amyloid- beta toxicity, inflammation, vascular and white-matter damage and cortical atrophy. By (speculatively) projecting specific damage into the gap models, this framework can quantify potential cellular and network level impacts of defined pathologies. Cortical thinning, for example, is associated with impaired cognition and tau-pathology (Xia et al., 2015; Thaker et al., 2017) and must involve some loss of tissue, such as glial/neuronal loss or shrinkage, demyelination, or loss of spines, dendrites and/or axonal branches. Such pathological changes are imported into Gap Models to assess their impact on network operations: the ensuing network/cognitive failures can then be compared with actual patient deficits. Mechanistically, this framework is an extension/conjunction of recent computational studies ranging from spiking models (Fiebig and Lansner, 2017), synapse loss/dysfunction (Yadav et al., 2012; Schmid et al., 2016), changes in temporal binding and Hebbian STP (Kastellakis, 2017) and mean-field models (Pereira and Brunel, 2018). The Pulvermuller-Garagnani (2014) approach explicitly tests overall neocortical performance based upon specialized sensory/association area modules. Our poster extends this by incorporating auto-associative nets into neocortical gap models enabling them to utilize stored brain experiences (Rolls and Deco, 2014; Chaudhuri and Fiete, 2016): such experiences are essential for healthy cognitive activity.
keywords: Alzheimer, cognition, computational, autoassociative

STAND 4
TITLE: Like-on-Like Templating: In Vivo and In Vitro Models for Pathological Tau Spread
Authors: Benjamin Sanders, Undergraduate; Aaron Wolman, MS/BS; Chris Ware, BS; Jianhua Huang, Michelle Potter, PhD; and Matthew Kennedy, PhD.
Affiliation: Northeastern University
Abstract: Tau protein aggregation, along with extracellular accumulation of amyloid plaques resulting in neuronal death, is a pathological hallmark of Alzheimer's Disease (AD). Tau, a microtubule-associated

protein, is essential for the assembly and stabilization of microtubules. In AD and other tau pathologies, tau becomes hyper-phosphorylated (phospho-tau) and misfolded resulting in the formation of insoluble filamentous deposits. The mechanisms by which tau forms aggregates and propagates are not well understood, but are thought to occur through a prion-like mechanism by which normal endogenous tau is corrupted to form neurofibrillary tangles (NFTs) and is propagated transcellularly via synaptic connections. Phospho-tau pathology spreads throughout the brain in a stereotypical spatial pattern following distinct neural pathways from the CA1 region of the hippocampus and spreading to synaptically connected regions in the entorhinal cortex and CA2/3. Tau transgenic mice (Tg4510) that express the human tau (h-tau) P301L mutation can be used as accelerated and robust models for tau pathology spread.The P301L mutation, which is indicative of frontotemporal dementia, heightens phosphorylation of tau and formation of insoluble fibrillar aggregates. Previously, mutant tau homogenates were infused into Tg4510 mice that carried some expression of P301L h-tau which was available for the homogenate to template on. Here, we determined the role of like-on-like templating in both *in vivo* and *in vitro* models. We described *in vivo* phospho-tau pathology spread in wild-type mice (W:W), with no P301L expression, receiving 24-week old Tg4510 homogenate infusions. We generated an *in vitro* model for P301L-mutant tau expression in neuroblastoma cell lines and induced aggregation of tau through seeding with the Tg4510 homogenates. The role of tau spread in the progression of AD highlight abnormal tau as a possible therapeutic target, and Merck continues to evaluate immunotherapies as a method to counteract tau spread.
Keywords: Tau, Alzheimer's, Model development

STAND 5
TITLE: A Novel Paradigm Reveals Marking Behavior in the Absence of Social Experience
Authors: Lauren Miner; Minsuk Hyun, BS; Bernardo Sabatini, MD/PhD
Affiliation: Harvard Medical School
Abstract: When housed in groups, mice establish social hierarchies that reduce conflict and determine the distribution of resources. These social dominance hierarchies have been used to study the relationship between rank and health, the effects of social stress, learning, and memory. However, the neuronal mechanisms underlying this behavior are still unclear. To identify the changes that occur in the mammalian brain after a social position is established, it would be useful to understand the innate state that precedes these changes. Here, we present a novel paradigm for social isolation which we use to elucidate this default mode. We use the territorial marking assay to demonstrate that mice socially isolated at weaning respond to conspecific urine cues in a manner similar to their dominant, socially experience cohorts. These results suggest subordinate behavior is a learned response to social conflict and validate the social isolation paradigm for future use in behavioral studies.
Keywords: Social Behavior, Dominance, Social Isolation

STAND 6
TITLE: Insular cortex projections to nucleus accumbens mediate social affective behavior in rat
Authors: Morgan M. Rogers-Carter MA; , Anthony Djerdjaj, BS; Katherine B. Gribbons, BS; and John P. Christianson, PhD
Affiliation: Boston College
Abstract: Social animals detect the affect of others to organize appropriate social behaviors. Age-specific responses to social affect are evident when an adult male rat is presented with a pair of unfamiliar male conspecifics, one of which is stressed via 2 footshocks and the other naïve to treatment. Test rats prefer to interact with a stressed juvenile (PN30) conspecific, but will avoid a stressed adult (PN50) conspecific. This pattern depends upon the insular cortex (IC) which is anatomically connected to the nucleus accumbens core (NAc). Prior network analysis of fos immunoreactivity indicated greater involvement for the NAc during social interactions with stressed juvenile conspecifics. Here, bilateral pharmacological inhibition of the NAc (tetrodotoxin 1μM; 0.5ul/side) abolished the preference for stressed juvenile conspecifics, but not naive adults. To explore if NAc projecting IC neurons contribute to social exploration we chemogenetically activated IC terminals in the NAc. After insular transduction of

AAV5-hSyn-hM3Dq-mCherry, bilateral microinjection of clozapine-N-oxide (1μM; 0.5ul/side) to the NAc increased social exploration with juvenile, but not adult conspecifics. Ongoing analysis using functional retrograde tracing and chemogenetic inhibition will establish the necessity of this pathway to social approach. The current findings suggest that behavioral responses to stressed juveniles involve the NAc and activation of NAc-projecting IC neurons is sufficient to elicit prosocial behaviors.
Keywords: insula, nucleus accumbens, DREADDs, social

STAND 7
TITLE: Genetic and neural mechanisms of infant vocalization in wild mice
Authors: Nicholas Jourjine, PhD; Hopi Hoekstra, PhD
Affiliation: Harvard University
Abstract: Vocalization is an essential mode of social communication in diverse vertebrate species. While learning is required for a subset of these vocalizations, many are innate and heritable, arguing that they have a genetic basis. Among innate vertebrate vocalizations, few are as essential as the cries of infants. These cries play a key role in eliciting parental care in mammals as diverse as humans and rodents, and are frequently altered in neurocognitive disorders such as autism. While studies in traditional genetic models of vertebrate behavior (e.g., *Mus musculus*) have identified a small number of genes influencing infant cries, these genes fail to explain much of the heritable variation in this behavior. Thus, additional genes contributing to infant vocalization likely remain to be identified. One approach to identify these genes, and understand neural mechanisms by which they shape behavior, is to perform genetic mapping in wild-derived populations, that, unlike many inbred laboratory stains, still harbor behaviorally relevant genetic variation.

Here, we present evidence that this approach is feasible in a behaviorally diverse, yet experimentally accessible, model of rodent behavior: the deer mice (genus *Peromyscus*). *Peromyscus* mice are among the most abundant mammals in North America, where they have diversified to occupy nearly every available ecological niche and have evolved a range of social systems. Unlike other experimental rodent models, the natural history of *Peromyscus* has been documented extensively, and many species are inter-fertile, making it possible to link genetic variation to adaptive behavior in natural settings. Moreover, many tools to study *Peromyscus* in the laboratory have recently been developed, including sequenced genomes for two inter-fertile species, molecular tools for forward genetic mapping, and viruses for tracing and manipulating neural circuits.

We have recorded isolation induced vocalizations from seven day old pups belonging to eight *Peromyscus* taxa sampled from across North America. These taxa differ in social system, parental care behaviors, and natural habitat. They also emit vocalizations with reproducible spectral and temporal features, and these features differ between species. We propose to document these features in two inter-fertile species across development, identify the features that are most relevant for parental approach behavior, and use unbiased forward genetic mapping to discover their genetic basis. This work will address how genetic variation acts through nervous systems to produce evolved behavioral differences.
Keywords: genetics, vocalization, *Peromyscus,* behavior

STAND 8
TITLE: Roles of the Rac1 GEF Farp1 in mammalian synapse and dendrite development
Authors: Andrew Coleman; Li Li, PhD; Jeff Cottrell, PhD; Atsushi Kumanogoh, PhD; Thomas Biederer, PhD
Affiliation: Tufts University
Abstract: Regulators of the actin cytoskeleton are critical for the structural and functional maturation of neurons and synapses, allowing for proper development of neuronal connectivity and cognitive function. The formation and plasticity of dendritic spines are regulated by select small G proteins, including the Rho GTPase Rac1, and proteins involved in dendritic spine development have been genetically linked to neurodevelopmental disorders including intellectual disability and autism. We have previously characterized the roles of the Rac1 activator Farp1 (FERM RhoGEF and pleckstrin domain-containing protein 1) in synapse and dendrite development in dissociated hippocampal neurons, where it acts

downstream of the trans-synaptic adhesion molecule SynCAM 1 and the Semaphorin/Plexin signaling pathway. To elucidate the in vivo roles of Farp1 in neuronal differentiation, we have generated Farp1 conditional knockout (cKO) mice. Glutamatergic neurons from juvenile Farp1 cKO mice exhibit altered dendrite structure, including reduced dendritic spine density and dendrite complexity in CA1 pyramidal neurons. These effects can be relevant for neurodevelopmental disorders, as we have found that an autism-linked variant of Farp1 exhibits strongly reduced expression. Moreover, Farp1 may have dynamic roles in synaptic remodeling and plasticity. We hypothesize this based on an unbiased phosphoproteomic analysis of changes after either BDNF stimulation or LTP induction, which identified a phosphorylation site in Farp1 that is transiently modified upon induction of these plasticity paradigrms. We are testing Farp1 as a candidate novel player in synaptic plasticity and whether the activity-dependent phosphorylation site in Farp1 contributes to the development of synapses. Using neurons from conditional KO mice, we have determined that the acute deletion of Farp1 from cortical neurons results in increased basal surface expression of glutamate receptor subunits, motivating us to test whether the dynamic range of synaptic plasticity is impaired in Farp1 deficient neurons. Finally, we are characterizing the role of Farp1 in hippocampal-dependent learning and memory in juvenile and adult cKO mice. The results highlight the role of the Rac1 GEF Farp1 in dendrite and synapse development as well as its impact of synaptic plasticity and memory processes.
Keywords: Synapse, Dendrite, Plasticity, Rac1

STAND 9
TITLE: Synapse-specific control of circuit maturation and plasticity by SynCAM 1
Authors: Adema Ribic[1], Michael C. Crair[2], Thomas Biederer[1]
Affiliation: Tufts University
Abstract: Experience-dependent plasticity of brain circuits tapers off as the brain matures. Maturation of cortical inhibition, as well as a steady increase in the expression of axonal growth inhibitors, is thought to direct circuit maturation and restrict cortical plasticity. However, cell-autonomous synaptic factors that control these processes remain unknown. We here demonstrate that visual activity selectively regulates Synaptic Cell Adhesion Molecule 1 (SynCAM 1/Cadm1) expression during the cortical critical period. Mice deficient in SynCAM 1-mediated synaptic adhesion show increased plasticity at all ages after monocular deprivation, indicating that synaptic adhesion restricts cortical plasticity. SynCAM 1 selectively controls thalamocortical inputs onto Parvalbumin (PV^+) interneurons in the visual cortex and loss of SynCAM 1 in PV+ interneurons retards the maturation of cortical inhibition and upregulates plasticity in the adult brain. Our work identifies a synaptic locus of critical period closure and the synaptic factors that restrict adult plasticity. These findings further underscore the emerging role of trans-synaptic interactions in the wiring and remodeling of functional circuits.

STAND 10
TITLE: Neurosteroids modulate β3-containing GABAAR trafficking via activation of mPRs
Authors: Catherine Choi, Manasa L. Parakala, Jennifer Yoo, Paul A. Davies, & Stephen J. Moss
Affiliation: Tufts University
Abstract: Background Neurosteroids (NASs) are endogenous steroids synthesized in the brain and positive allosteric modulators of γ-aminobutyric acid type A receptors (GABAARs). We have recently shown that NASs modulate GABAAR α4 subunit phosphorylation, surface expression, and activity through PKC/PKA signaling pathways and that this modulation is independent of allosteric modulation (Abramian et al., 2014). However, it is unclear whether the metabotropic modulation is specific to α4. Also, the molecular mechanism and the significance of this modulation remain unknown. We hypothesized that a) NASs metabotropically modulate β3 subunit, b) NASs activate membrane progesterone receptors (mPRs), G- protein coupled receptors that regulate PKC signaling, and c) metabotropic modulation mediates seizure behaviors in mice. **Methods** Acute hippocampal slices from 8-12 week old male C57BL/6J mice were treated with vehicle or NASs for 20 minutes and lysates were subjected to SDS/PAGE for immunoblotting with antibodies against phospho-S408/9, β3, and actin. For

surface expression, slices were treated with vehicle or NASs for 20 minutes and biotinylated. After incubation with NeutrAvidin beads, bound material was subjected to SDS/PAGE for immunoblotting against β3 and actin. To evaluate activity, whole-cell currents were recorded from dentate gyrus granular cells in slices from 3-5 week old male mice. Slices were incubated with vehicle or NASs for 15 minutes and with ACSF before recordings began. **Results** 100 nM of allopregnanolone (ALLO) and SGE-516 (synthetic analogue of ALLO) enhanced the phosphorylation of the residue S408/9 in β3 subunit, the surface expression of β3, and tonic currents. Pre--treatment with 10 uM GFX (PKC inhibitor) and 1 uM KT5720 (PKA inhibitor) abolished these effects. 300 nM of ORG-OD-20 (ORG; a non-specific mPR agonist) showed enhanced phosphorylation of S408/9, β3 surface expression, and tonic currents. These effects were absent after pre-treatment with GFX and KT5720. **Conclusion** These results show that NAS modulation of GABAAR subunits is not specific to α4. ALLO and SGE- 516 activate PKC/PKA signaling pathways to enhance the phosphorylation of S408/9, which then increases surface expression of β3 and tonic currents. ORG modulates β3 the same way, suggesting that NASs bind mPRs for metabotropic modulation. To better understand the mechanism, NAS effects on GABAARs will be studied in S408/9A and mPR KO mice. To evaluate the significance of the modulation, WT and S408/9A mice will be injected with NASs and subjected to anxiety and seizure-related behavioral assays. Results from these studies will provide insight into the physiological role of NASs and the potential for NASs to be a treatment option for epilepsy.
Keywords: GABAAR trafficking, mPR

STAND 11

TITLE: Exploring the role of delta GABAa receptors in the anxiolytic and anxiogenic effects of alcohol
Authors: Alyssa DiLeo, BA; Laverne Melón, PhD; Samantha Howard, BA; Jamie Maguire, PhD
Affiliation: Tufts University
Abstract: According to the CDC, about 6% of the US adult population is diagnosed with an alcohol use disorder (AUD), characterized by compulsive alcohol use with disregard for negative consequences and negative emotional states during withdrawal. Despite the societal and economic impact AUD has on our communities, the underlying neuronal mechanisms contributing to alcohol abuse are not well understood. Inhibitory GABAergic neurons have been implicated in both mediating and regulating effects of alcohol consumption and withdrawal. Specifically, the fast responding $GABA_A$ receptor ($GABA_AR$) is directly modulated by ethanol. The $GABA_AR$ can be composed of five different subunits, α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, θ, π, ρ_{1-3} (Barnard et al., 1998) combining to produce unique developmental, pharmacological, and electrophysiological properties (Miner and Sigel, 2004). Generally, $GABA_ARs$ containing α, β, and γ subunits located synaptically mediate phasic inhibition, while receptors containing α, β, and δ subunits located extrasynaptically mediate tonic inhibition (Thomas et al., 2005; Farrant and Nusser, 2005). Low concentrations of ethanol, relevant to levels experienced with social drinking, have been shown to potentiate δ containing extrasynaptic receptors (Hanchar et al., 2006).
We hypothesized that anxiolytic and anxiogenic effects of alcohol are mediated through δ-$GABA_A$ receptors and therefore these effects will be absent in mice lacking the δ subunit. Using an established binge drinking paradigm (Melón et al., 2013) which modulates δ expression and δ-mediated tonic inhibition, particularly in PV+ interneurons in the basolateral amygdala (Melón et al., 2018), we measured anxiety-like behavior during ethanol withdrawal. Globally deleting PV:δ-$GABA_A$ receptors further increased drinking in males and blocked the emergence of anxiety-like behavior in withdrawal. However, selectively deleting δ-$GABA_A$ receptors in the BLA reduced drinking while still blocking the emergence of anxiety-like behavior in withdrawal. Selectively knocking down δ-$GABA_A$ receptors in PV interneurons in the BLA blocked anxiolytic effects of low dose ethanol, further implicating these receptors in mediating ethanol induced anxiety behavior. Further studies will investigate if neurosteroids are helping ethanol mediate anxiety-like behavior through δ-$GABA_A$ receptors in the BLA.
Keywords: GABAaR, alcohol, anxiety

STAND 12
TITLE: Sex differences in the effects of acute fluoxetine in a fear discrimination paradigm
Authors: Emily E Zona, Allison R Foilb, MA, Julia Bals, BS, John P Christianson, PhD
Affiliation: Boston College: Morrissey College of Arts and Sciences
Abstract: Human survival depends on appropriate differentiation of safety from danger, whether discerning poison from nourishment or an incoming bomb from fireworks. Individuals with post-traumatic stress disorder (PTSD) are unable to inhibit fear even in the presence of safety signals. To mitigate the symptoms of PTSD by increasing the amount of serotonin in the brain, clinicians have prescribed selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (Prozac). Fluoxetine (FLX) has demonstrated contradictory anxiogenic effects during the acute phase of treatment. Here, we sought to study whether the acute anxiogenic effect of FLX worsened female and male discrimination when administered before conditioning in a CS+/CS- fear discrimination paradigm. This study has clinical relevance given that more females are diagnosed with PTSD than males and previous studies in rodent models have shown that female rats exhibit enhanced discrimination of fear and safety cues compared to male rats. FLX was administered before acquisition and recall testing was performed 24 hours and 7 days later. While no main effects were observed during acquisition or 24-hour recall testing, males displayed significantly more freezing (behavioral measure used for fear) than females during recall testing 7 days after conditioning and FLX treatment. The results may indicate that serotonin plays a greater role in fear discrimination in males than in females.
Keywords: sex differences, fluoxetine, fear discrimination

STAND 13
TITLE: Sex-specific effects of endocannabinoid action on cued fear conditioning and extinction
Authors: M. MEJDELL; A. LI; J. LAPETINA-COLOM; B. BROWN; I. SHURNAYTE; A. WINTER; S. BEGLEY; J. ABETTAN; R. SHANSKY, PhD
Affiliation: Northeastern University
Abstract: Experiencing a traumatic event is twice as likely to cause post-traumatic stress disorder in women as it is in men. Despite this imbalance, most of what we know about the neural mechanisms that underlie PTSD comes from research in male animals. One especially under-studied area is the endocannabinoid (eCB) system, whose role in modulating the stress response is just beginning to be uncovered. A better understanding of sex differences in these processes is critical to progress in developing more personalized therapies for PTSD patients of both sexes. To explore the influence of eCB signaling on aversive learning and memory processes, we tested male and female rats in a standard cued fear conditioning and extinction paradigm after systemic administration of FAAH inhibitor URB597, CB1 receptor antagonist AM251, MAGL inhibitor MJN110, or vehicle. We measured both cue-elicited freezing and darting in all animals, finding that as we have previously reported, females were more likely than males to engage in darting behavior. In addition, AM251 elicited enhanced context generalization and impaired extinction in females, but not males. These results demonstrate sex differences in the mechanisms related to associative learning and memory processes, and point to a specific role for the endocannabinoid system.
Keywords: endocannabinoid; sex-differences; AM251

STAND 14
TITLE: Effects of stressor timing on adult threat estimation and alcohol use initiation for males and females
Authors: Taylor Perison, Rebecca Suthard, Kevin Enabulele, Rachel Walker, MA, and Michael McDannald, PhD
Affiliation: Boston College
Abstract: Previous studies have shown that early adolescent adversity (EAA) inflates threat estimation in female rats compared to males and promotes alcohol use initiation in both sexes. Threat estimation may be disrupted in males due to EAA if these experiences occur earlier in life, but rigorous comparisons of

EAA effects on males and females have yet to be conducted at various time points. In the present study, we exposed male and female Long-Evans rats to EAA on P22 – P31, beginning earlier than previous experiments. Stressors included forced cold water swim, tail pinch, restraint stress, cat hair exposure, and rotation stress. During adulthood, all rats underwent a fear discrimination procedure in which three cues were associated with unique probabilities of foot shock: danger (p=1.00), uncertainty (p=0.25), and safety (p=0.00). After 16 fear discrimination sessions, the uncertainty cue was selectively extinguished over 8 sessions. Rats were then given voluntary intermittent access to 20% ethanol over 8 separate 24-hour drinking sessions post-extinction. Results indicated that EAA was effectively stressful; EAA rats had significantly lower body weights on P27-P36 compared to controls. There were no significant differences in adult fear discrimination or extinction due to EAA. During voluntary alcohol drinking, females consumed more alcohol during initial sessions compared to males, and a trend toward significance for a session x group x sex interaction indicated that EAA exposed females drank more during initial sessions compared to control females. Together these results indicate that earlier exposure to EAA stunts physical development, increases alcohol use initiation for females but not males, and does not impact fear discrimination.
Keywords: fear, alcohol, adolescence, stress

STAND 15
TITLE: A8 dopamine depletion promotes matching behavior in Pavlovian fear discrimination
Authors: Kristina M. Wright, BS; Euna Lee; Michael A. McDannald, PhD
Affiliation: Boston College
Abstract: Whereas exaggerated fear is maladaptive and has clinical implications in anxiety disorders, accurate appraisal of and response to threat is adaptive. Matching behavior, commonly examined in reward learning, refers to the ability to match reinforcement and response frequencies. Disruptions to brain regions underlying matching behavior may contribute to maladaptive fear. Here, we reveal matching behavior in Pavlovian fear discrimination and propose a role for retrorubral field (RRF) A8 dopamine in its modulation. Male, Long Evans rats were given bilateral neurotoxic A8 RRF lesions, dopamine depletions or sham procedures. Following recovery, rats received fear discrimination in which three auditory cues predicted unique foot shock probabilities. After discrimination was achieved, sham rats demonstrated matching behavior at cue onset; however, mismatching behavior dominated during the remainder of cue presentation. In contrast, A8-lesioned and A8 DA-depleted rats demonstrated matching behavior throughout cue presentation. These results reveal a role for A8 RRF dopamine in modulating matching behavior in aversive learning.
Keywords: Retrorubral Field, Dopamine, Fear

STAND 16
TITLE: The Effects of Novelty on Food Consumption in Male and Female Rats
Authors: Eliza M Greiner, BS; Gorica D Petrovich, PhD
Affiliation: Boston College
Abstract: Novel foods and novel environments impact consumption, but research into how the two interact, and whether there are sex differences, is lacking. Here, we sought to determine if exposure to a novel context enhances food neophobia—defined as a lower intake of a novel food compared to familiar—and whether the effect is sex dependent. We also wanted to establish whether the effects of novelty on food consumption in either sex were mediated by anxiety and thus could be attenuated by administration of sub-anesthetic doses of ketamine. Male and female Long Evans rats were tested for consumption in either their home cage or in a novel context (n=8 per group) and were given two foods, one familiar (rat chow) and one novel (Test Diet pellets; TD). They received 8 testing sessions on separate days and were acutely deprived of food for 20 hours prior to each. During Test 1 and 2, males and females tested at home had a significant preference for the familiar (rat chow) over novel (TD) food (p=0.001, both), while rats tested in a novel context ate similar, small amounts of each food. Total consumption was lower in the novel context groups compared to home cage tested groups for both sexes (p=0.002) but females tested in the novel context ate the least. In Test 3, male and female rats tested at

home consumed equal amounts of the two foods and by Test 8 were showing a significant preference for TD (males, p=0.03; females, p=0.016). Males tested in the novel context showed higher consumption of TD by Test 4 (p=0.014) whereas females showed equal consumption of both foods during all tests. Further analysis of total consumption in Test 6, 7, and 8 showed that males tested in a novel context ate significantly more than females (T6, p=0.009; T7, p=0.008; T8, p=0.003). These results indicate that rats in a familiar context, regardless of sex, and males in a novel context habituate to novelty faster than females in a novel context. On-going experiments are examining if the sustained, suppressed consumption that females tested in the novel context show throughout testing is mediated by heightened anxiety and could be alleviated by anxiolytic ketamine.
Keywords: Novelty, Feeding, Sex Differences

STAND 17
TITLE: ER Stress Induced by Tunicamycin can induce locomotor dysfunction: new Parkinson Disease's model
Authors: Clarissa F Cavarsan Muller, PhD; Flavia Gulak, BA; Katharina A Quinlan, PhD; Silvio Marques Zanata, PhD
Affiliations: University of Rhode Island
Abstract: Parkinson's disease (PD) is a neurodegenerative disorder characterized by progressive death of dopaminergic neurons of the substantia nigra pars compacta (SNpc), leading to the major clinical abnormalities that characterize this disease. Although PD's etiology is unknown, α-synuclein aggregation plays a pivotal role in PD pathogenesis, which could be associated to some pathological processes such as oxidative stress, endoplasmic reticulum (ER) stress, impaired protein degradation, and mitochondrial dysfunction. Increasing experimental evidence indicates that ER stress is involved in PD, however most of the described results employed cultured cell lines, and genetically modified animal models; models of study without the whole physiological dysfunction complexity. In this study, we analyzed a new rat model of ER stress employing the well-known ER stressor tunicamycin (Tm). The classical 6-OHDA neurotoxin model was used as an established positive control for PD. PD features were induced with an intranigral injection of Tm and motor dysfunction was analyzed 30 and 60 days post injection. We showed that Tm injection induced locomotor impairment, mainly in the swing phase of walking, similar to the results found with 6-OHDA injection. In summary, ER stressor Tm recapitulates some of the phenotypic characteristics observed in rodent models of PD, reinforcing the concept that ER stress could be an important contributor to the pathophysiology of PD. Therefore, we propose the intranigral Tm injection as a new ER stress-based model for the study of PD in vivo.
Keywords: Parkinson's Disease; motor dysfunction; endoplasmic reticulum stress; tunicamicin

STAND 18
TITLE: The Role of the Endocannabinoid System in Sexually Divergent Responses to Inescapable Stress
Authors: Tatiana C. Pelegrina, Jose Colom-Lapetina, B.S., M Fanikos, and RM Shansky, Ph.D
Affiliation: Shansky Lab of Neuroanatomy and Behavior- Northeastern University
Abstracts: Women suffer from trauma and stress-related illnesses such as PTSD in a disproportionate manner. As a result, it is imperative to understand the underlying neurobiological sex differences in order to develop more effective treatments for such diseases. The endocannabinoid system is a promising pharmacological target, given that it plays an important role in the activation and regulation of the stress response. Here, we use a classic Forced Swim Test (FST) paradigm as a model for acute, inescapable stress in order to investigate the effects of potentiating or inhibiting endocannabinoid signaling in the prefrontal cortex (PFC) on behavior in males and females. Administering localized infusions of URB597, a FAAH inhibitor, and AM251, a CB1 receptor antagonist, our results thus far suggest that there is no significant difference in behavior upon manipulations of endocannabinoid signaling. We observed stable time differences on immobility in both sexes, across all experimental groups. Together, our preliminary data points towards a trend between CB1 receptor inhibition in the PFC and reduced immobility, which will be further corroborated with additional experiments.
Keywords: Endocannabinoid System, Sex Differences, Forced Swim Test

STAND 19
TITLE: Early life stress leads to sex-specific alterations in the formation of perineuronal nets around parvalbumin-expressing interneurons in the developing rat prefrontal cortex
Authors: Kelsea Gildawie, MS; Jennifer Honeycutt, PhD; Heather Brenhouse, PhD
Affiliation: Northeastern University
Abstract: Early life exposure to a low security setting, characterized by a scarcity of resources and limited food access, increases the risk for psychiatric illness and metabolic dysfunction. We utilized a translational rat model to mimic a low security environment and determined how this manipulation affected offspring behavior, metabolism, and puberty. Because food insecurity in humans is associated with reduced access to healthy food options the “low security” rat manipulation combined a Western diet with exposure to a limited bedding and nesting manipulation (WD-LB). In this setting, dams were provided with limited nesting materials during the pups’ early life (P2-P10). This manipulation was contrasted with standard rodent caging (SD) and environmental enrichment (EE), to model “medium security” and “high security” environments, respectively. To determine if transitioning from a low to high security environment improved outcomes, some juvenile WD-LB offspring were exposed to EE. Maternal care was impacted by these environments such that EE dams engaged in high quality care when on the nest, but spent less time on the nest than SD dams. Although WD-LB dams excessively chased their tails, they were very attentive to their pups, perhaps to compensate for limited resources. Offspring exposed to WD-LB only displayed subtle changes in behavior. However, WD-LB exposure resulted in significant metabolic dysfunction characterized by increased body weight, precoscious puberty and alterations in the hypothalamic kisspeptin system. These negative effects of WD-LB on puberty and weight regulation were mitigated by EE exposure. Collectively, these studies suggest that both compensatory maternal care and juvenile enrichment can reduce the impact of a low security environment. Moreover, they highlight how utilizing diverse models of resource (in)stability can reveal mechanisms that confer vulnerability and resilience to early life stress.
Keywords: early life stress, sex differences, perineuronal nets

STAND 20
TITLE: Altered corticolimbic connectivity in a rat model of early adversity: Evidence from fMRI and neuroanatomical tracing suggests sex-dependent effects of early experiences
Authors: Jennifer A. Honeycutt, PhD; Camila Demaestri, BS; Xuezhu Cai; Rahul Mehta; Praveen Kulkarni, PhD; Craig F. Ferris, PhD; Heather C. Brenhouse, PhD
Affiliation: Northeastern University
Abstract: Adverse early life experiences significantly alter behavioral and neural trajectories, and such disruptions during early developmental periods likely set the course for aberrant brain maturation. Indeed, children with a history of early life stress (ELS) often exhibit deleterious effects, manifesting as maladaptive behaviors, cognitive impairment, and/or increased risk of mental illness later in life. Evidence in ELS human populations points to a role of atypical corticolimbic circuit development leading to changes in connectivity between limbic (i.e. amygdala, hippocampus) and the prefrontal cortex (PFC). Importantly, children with a history of ELS show patterns of precocially mature corticolimbic functional connectivity (FC) which is comparable to adolescent patterns. While these findings indicate compelling influences of early adversity on neural circuit maturation, the underlying neurobiological substrates remain poorly understood. Recent work from our group utilizing a rat model of ELS via maternal separation reveal sex- and age-dependent effects on amygdala-derived axonal innervation of the PFC. Specifically, we have reported that juvenile ELS females show patterns of axonal innervation comparable to adolescent and adult controls, with ELS-dependent changes in males not appearing until later in development. To explore whether these neuroanatomical changes confer alterations in corticolimbic connectivity, we utilized resting state FC and anisotropy assessments to directly compare ELS and control males and females from juvenility to adolescence. Here, we present data delineating sex- and age-dependent effects of resting FC which suggest thatmay help explain how females with a history of adversity may be more vulnerable to later psychiatric illness resulting from alterations in FC driven by precocial maturation of amygdala-derived PFC innervation. Furthermore, we present behavioral data suggesting that these

neural alterations may also be predictive of anxiety-like behaviors mediated by corticolimbic circuitry. Taken together, this data provides evidence for a critical role of early experience, and provides putative preliminary mechanistic insight into the underlying etiology of adversity-induced vulnerability.
Keywords: early life stress, fMRI, corticolimbic development, PFC

STAND 21
TITLE: Immediate and long-term effects of early life stress of H3K9me3 in the hippocampus in Long-Evans rats
Authors: Hannah E. Lapp BS, Madhu Badri, Ashley Doucet, Marrissa Pinto, Madeline Clark, Andrew A. Bartlett, BS, & Richard G. Hunter, PhD
Affiliation: University of Massachusetts Boston
Abstract: The hippocampus is particularly sensitive to the effects of elevated glucocorticoids following stress. Histone 3 lysine 9 trimethylation (H3K9me3; a histone modification associated with transcriptional silencing) has been previously shown to increase following acute restraint stress in the hippocampus of adult male rats. However, it remains unknown whether stress experienced during early postnatal life affects H3K9me3 in the developing hippocampus and whether adults with a history of early life stress that are subsequently exposed to an acute stressor in adulthood display the same increase in H3K9me3 as non-early life stressed animals. In this pilot study, we used the low nesting/bedding material paradigm as a chronic early life stressor and examined hippocampal H3K9me3 levels in male and female Long-Evans rats immediately following early life stress (postnatal day 15), at baseline in adulthood, and following novel environment stress in adulthood. H3K9me3 levels were measured using immunocytochemistry and optical density levels were determined for CA1, CA3, and dentate gyrus regions of the hippocampus. This pilot study will inform future research on how the epigenetic landscape changes in response to stress throughout the lifespan in both sexes and build on research demonstrating the immediate and enduring effects of early life adversity on the hippocampus.
Keywords: Epigenetics, glucocorticoids, development

STAND 22
TITLE: Closed nest pre-weaning environment improves the development of physical characteristics and buffers hippocampal injury in neonatal hypoxic ischemic injury
Authors: L.G. Rollins, PhD; Briana Marie Mason, B.S.; S.T. Donaldson, PhD
Affiliation: University of Massachusetts Boston
Abstract: Term neonates with hypoxic-ischemic (HI) injury are at risk for devastating neurological sequelae. Maternal care taking behavior has been found to alter the trajectory of normal brain development and may also impact neurodevelopment with exposure to HI injury. Maternal care-taking behavior can be highly influenced by environmental stress and may, therefore, mediate the effects of such stressors on injury and repair for these neurologically high-risk neonates. In the present study, we investigated whether altering early environment for maternal care-taking impacts neurodevelopment and neuroprotection in HI rat offspring. The Rice-Vannucci model was used to induce HI in 26 postnatal day (PND) 7 Long-Evans pups. Dams and litters were randomized to a closed nest (CN) or normal standard housing (SH) condition. Performance on a neurodevelopmental battery and characteristics of physical development were assessed daily from PND8-PND21 to quantify effects of the CN condition on HI injury. Brains were harvested at PND 60 and analyzed for morphological differences. Results indicate that HI injured animals reared in the CN condition showed significantly earlier development of physical characteristics, exhibiting ear unfolding an average of 2.23 days earlier ($p < 0.001$), eye opening 1.85 (L) and 1.07 (R) days earlier ($p < 0.05$) and audible startle response 1.46 days earlier ($p < 0.05$), indicating potential neuroprotection for vulnerable white matter areas. These findings indicate that, in comparison to SH housing, CN housing during the pre-weaning period promotes maternal care-taking behavior to increase weight gain, improves the development of reflexes, physical characteristics, and supports neuroprotection in pups exposed to neonatal HI.
Keywords: HYPOXIA ; ENVIRONMENTAL ENRICHMENT ; HIPPOCAMPUS

STAND 23
TITLE: Access to a high resource environment protects against accelerated maturation following early life stress: A translational animal model of high, medium and low security settings
Authors: Arielle R. Strzelewicz; Alejandro N. Rondón-Ortiz; Anthony R. Raneri; Amanda Speno; Amanda C. Kentner, PhD
Affiliation: Massachusetts College of Pharmacy and Health Sciences
Abstract: Early life exposure to a low security setting, characterized by a scarcity of resources and limited food access, increases the risk for psychiatric illness and metabolic dysfunction. We utilized a translational rat model to mimic a low security environment and determined how this manipulation affected offspring behavior, metabolism, and puberty. Because food insecurity in humans is associated with reduced access to healthy food options the “low security” rat manipulation combined a Western diet with exposure to a limited bedding and nesting manipulation (WD-LB). In this setting, dams were provided with limited nesting materials during the pups’ early life (P2-P10). This manipulation was contrasted with standard rodent caging (SD) and environmental enrichment (EE), to model “medium security” and “high security” environments, respectively. To determine if transitioning from a low to high security environment improved outcomes, some juvenile WD-LB offspring were exposed to EE. Maternal care was impacted by these environments such that EE dams engaged in high quality care when on the nest, but spent less time on the nest than SD dams. Although WD-LB dams excessively chased their tails, they were very attentive to their pups, perhaps to compensate for limited resources. Offspring exposed to WD-LB only displayed subtle changes in behavior. However, WD-LB exposure resulted in significant metabolic dysfunction characterized by increased body weight, precoscious puberty and alterations in the hypothalamic kisspeptin system. These negative effects of WD-LB on puberty and weight regulation were mitigated by EE exposure. Collectively, these studies suggest that both compensatory maternal care and juvenile enrichment can reduce the impact of a low security environment. Moreover, they highlight how utilizing diverse models of resource (in)stability can reveal mechanisms that confer vulnerability and resilience to early life stress.
Keywords: early life stress; limited bedding; western diet; environmental enrichment

STAND 24
TITLE: Effects of early life stress on AMPA receptor composition and cocaine conditioned place preference are sex-specific and driven by TNF
Authors: Prabarna Ganguly, MA; Jennifer Honeycutt, PhD, June Rowe, BS, Lilly Ryll, Camila Demaestri, BS, Heather Brenhouse, PhD
Affiliation: Northeastern University
Abstract: Exposure to early life adversity can predispose adolescents to the formation of substance abuse disorders. In rodents, early stressors such as repeated maternal separation (MS) impact AMPAR activity in the prefrontal cortex (PFC) and nucleus accumbens (NAc), regions involved in drug-cue association after cocaine-induced conditioned place preference (CPP). Notably, previous reports suggest that the pro-inflammatory cytokine tumor necrosis factor (TNF) regulates AMPAR subunit composition; increased TNF levels are reported to reduce GluA2-positive AMPARs. Since MS can elevate adolescent TNF levels, the stressor may therefore alter AMPAR subunit composition via neuroimmune signaling, thereby affecting cocaine-induced CPP. We tested the specific role of soluble TNF in MS-induced GluA2 loss and cocaine-induced CPP with biologic disruption of TNF signaling. TNF gene and protein expression were elevated in both PFC and NAc of MS males, but not females. GluA2 expression was reduced in both regions in only male MS rats, and systemic treatment with either ibudilast - a phosphodiesterase inhibitor, or XPro1595 - a blood-brain barrier-permeable blocker of soluble TNF - reversed such loss. MS males also formed greater preference for a cocaine-paired environment, the expression of which returned to control levels after XPro1595 administration. These data suggest a sex-specific mechanistic link between TNF signaling and changes in GluA2 expression and drug-cue conditioning, thereby providing further evidence for a role of MS and neuro-immune activity in cortical and striatal AMPAR changes. Moreover, manipulation of the TNF signaling pathway represents a novel approach for influencing response to rewarding effects of drug use.

Keywords: AMPA receptor, stress, neuroinflammation, TNF

STAND 25

TITLE: Mapping the Proteome of the Synaptic Cleft Through Proximity Labeling Reveals New Cleft Proteins

Authors: Tony Cijsouw, Ph.D.
Affiliation: Tufts University School of Medicine, Neuroscience Department

Abstract: Synapses are specialized neuronal cell-cell contacts that underlie network communication in the mammalian brain. Across neuronal populations and circuits, a diverse set of synapses is utilized, and they differ in their molecular composition to enable heterogenous connectivity patterns and functions. In addition to pre- and post-synaptic specializations, the synaptic cleft is now understood to be an integral compartment of synapses that contributes to their structural and functional organization. Aiming to map the cleft proteome, this study applied a peroxidase-mediated proximity labeling approach and used the excitatory synaptic cell adhesion protein SynCAM 1 fused to horseradish peroxidase (HRP) as a reporter in cultured cortical neurons. This reporter marked excitatory synapses as measured by confocal microcopy and was targeted to the edge zone of the synaptic cleft as determined using 3D dSTORM superresolution imaging. Proximity labeling with a membrane-impermeant biotin-phenol compound restricted labeling to the cell surface, and Label-Free Quantitation (LFQ) mass spectrometry combined with ratiometric tagging of membrane vs synaptic surface proteins was used to identify the proteomic content of excitatory clefts. Novel cleft candidates were identified, and Receptor-type tyrosine-protein phosphatase zeta was selected and successfully validated. This study supports the robust applicability of peroxidase-mediated proximity labeling for synaptic cleft proteomics and its potential for understanding synapse heterogeneity in health and changes in diseases such as psychiatric disorders and addiction.

Keywords: Synaptic Cleft, SynCAM, Peroxidase Mediated Proximity Labeling, Synapse

STAND 26

TITLE: From Anaesthetics to Zebrafish: Developing a Dose-Response Assay for Propofol with Larval Zebrafish

Authors: Jamie Chan, BA; Leah M. Corson, BA; Juliet W. Cheng, BA; Delna K. Kapadia, BA; Adam C. Hall, PhD and Narendra H. Pathak, PhD
Affiliation: Smith College

Abstract: GABA-A receptors (GABAAR) are important target sites for modulation by general anesthetics with extrasynaptic GABAAR being particularly sensitive to many anesthetic agents. Our current research focuses on the delta (δ) subunit of GABAAR since inclusion of this subunit in the pentamer results in localization of the receptors to extrasynaptic sites and may be responsible for the exquisite anesthetic sensitivity of these receptors. Using the CRISPR/cas9 system, we have generated a zebrafish line with KO mutations on the δ subunit of GABAAR. We chose two regions to target the CRISPR guide RNA: gabrd-i-crispr (located in exon 4) and gabrd-ii-crispr (located on exon 6). The potential differences in anesthetic sensitivity between δ subunit mutant zebrafish and wildtype zebrafish will be compared using a dose response assay currently under development. We are standardizing an assay using zebrafish larvae to obtain a concentration-anesthesia response for propofol, a commonly used intravenous anesthetic. Video monitoring is used to capture both larval locomotion and startle reflexes at various propofol concentrations (0.5-5M) in a 48-well plate format. Ultimately, this assay will help determine whether the δ subunit confers a level of anesthetic sensitivity in order to gain insight into specific anesthetic targets. The assay will also be used to assess the potency of some novel anesthetics with the aim of designing agents with improved therapeutic indices.

Keywords: Anaesthetics, Zebrafish, Delta Subunit, Assay

STAND 27
TITLE: Transparent microelectrode arrays for simultaneous high-density electrophysiology, electrical stimulation and two-photon imaging.
Authors: Pietro Artoni, PhD.*; Yi Qiang, MS; Kyung Jin Seo, MS; Stanislav Culaclii, MS; Victoria Hogan, BA; Wentai Liu, PhD; Hui Fang, PhD; Michela Fagiolini, PhD
Affiliation: Boston Children's Hospital - Harvard Medical School
Abstract: Electrophysiology and Calcium (Ca++) imaging are two complementary physiology techniques heavily adopted in vivo to study brain activity. While the first has great temporal precision, the latter has excellent spatial and cellular resolution. Significant attention has been given to the study of LFP/EEG oscillations in the time domain as different frequency bands of the LFP/EEG reflect the interaction between different neuronal populations. Two-photon imaging, on the other hand, allows the study of Ca++ transients of large networks with cell resolution capabilities. Combining these two powerful techniques would represent a significant advance in our ability to dissect how network activity is generated and propagates across brain region in health and disorders. To achieve such goal transparent microelectrodes arrays (transparent MEAs) would be ideal. However, scaling down the size of the electrodes in a microelectrode array to allow dense spatial recordings is very challenging when the electrodes and the interconnections have also to be transparent for imaging. Here we developed a nanomesh composite structure with bilayers of Au/PEDOT:PSS to allow high transparency for imaging while with low impedance for high-performance LFP/single-unit recordings, by leveraging the existing from multi-decade-long development and in vivo application of commercial MEAs. We were able to generate microelectrodes with 130 kΩ at 1 kHz for 20-μm-diameter microelectrodes, which are comparable to the performance of microelectrodes in non-transparent, Michigan- style arrays. This approach also allowed high transparency of the film and high conductance on the wiring itself between each electrode and the recording system. The electrodes were tested for stimulation and for online artifacts rejection, together with a state-of-the-art wireless recording. The newly generated transparent MEA were implanted in adult mice and LFP, multi- unit, and single-unit recordings were acquired simultaneously with epifluorescence or 2-photon imaging in the awake animals. We measured visual evoked responses using a 32-channel flexible and transparent device, along with the concurrent 2-photon imaging of single neurons in the layer 2-3 in the mouse visual cortex. We then evaluated the biocompatibility of the MEAs by ex vivo staining of both the implanted and control cortex for the marker for microglia activation IBA. We did not detect any significant inflammation up to 3 weeks after the surgery. Together our results indicate that these electrodes are scalable to high density, are reliable and can be coupled with the Ca++ imaging across different neuronal populations.
Keywords: Electrophysiology, imaging, network

STAND 28
TITLE: Evaluating commercially-available antibodies for RIC3
Authors: Zhiyuan. WANG, BS; Sneha SUKUMARAN, BS; Jaya. Prakash THUMMAPUDI, BS; Ralph LORING, PhD
Affiliation: Northeastern University
Abstract: α7 nicotinic acetylcholine receptors (nAChRs) depend on chaperone proteins that allow folding, assembly and transport to the cell surface membrane. Resistance to Inhibitors of Cholinesterase 3 (RIC3) is one known chaperone for α7 nAChRs. Antibodies validated to cross-react with human, mouse and rat RIC3 would be very useful, but currently, only antibodies raised against human RIC3 epitopes are commercially available. Also, RIC3 has alternate splice variants, including an alternate extra serine (S+) or not (S-) encoded at the boundary between exons 4 and 5. Mutations due to single nucleotide polymorphisms (SNPs) are also common. We tested existing antibodies that might cross-react between species and whether SNPs and splice variants make any difference. DNA encoding either human or S+mouse RIC3 (S+mRIC3 from Genescript) was linked to a Flag (DDK) epitope to allow detection by anti-DDK antibodies. Human RIC3 (S-hRIC3-YN) purchased from Origene had SNPs C130Y and D352N present in one version without the serine but with a DDK tag, while S-hRIC3-HF, also from Origene, had SNPs P57H and I165F and a DDK tag. Western Blotting detected anti-hRIC3 or anti-DDK antibodies that

bound to protein from hRIC3 or mRIC3 constructs transiently expressed in human embryonic kidney (HEK) cells and blotted onto nitrocellulose following electrophoresis. Rat RIC3 (S-rRIC3) expressed without an extra serine or a DDK tag was also tested as an antigen. Four rabbit anti-human RIC3 antibodies (two antibodies from ThermoFisher Scientific and one each from Abcam and Santa Cruz Biotechnology) were tested. Three of these antibodies recognized only hRIC3-YN and hRIC3-HF, while one antibody strongly reacted with S+mRIC3 at a dilution of 1:5000 and showed weak reactions with both S-hRIC3 isoforms and with S-rRIC3. An antibody that recognizes mouse or rat RIC3 will allow us to evaluate whether RIC3 protein is expressed in animal tissues that expresses surface α7 nAChRs in the presence or absence of other known α7 nAChR chaperones. Further experiments are planned to evaluate the effects of the serine splice variants in cross-reactions between species, and whether this antibody also detects Xenopus RIC3.
Keywords: Antibody validation, splice variants, single nucleotide polymorphism, α7 nicotinic receptor

STAND 29
TITLE: Brain vigilance state modulates sensory evoked potential responses in rodents
Authors: Shushi Kabu, Daniel J. Graziano, Marlyn Torres and Michelle M. Sidor
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Abstract: Various neuropsychiatric conditions are associated with impairments in basic sensory processing that can be detected at the cortical level using electroencephalography (EEG) recordings. Furthermore, these deficits can be modeled in rodents and are widely considered a robust translatable biomarker between humans and rodents in EEG-based studies. Paradigms frequently used to evaluate cortical sensory processing include auditory mismatch negativity (MMN) that produces an EEG evoked potential in response to deviation (oddball: pitch or duration) from an established pattern of stimulation (standard). In this study, we sought to establish and validate a rat model of MMN to study the underlying neurophysiology of deviance detection. EEG recordings were performed in awake-behaving male Sprague-Dawley rats using the Data Sciences International wireless telemetry system with skull screws implanted over the frontal cortex for signal and cerebellum for reference. Auditory stimuli were delivered at 6kHz and 8kHz frequencies in a flip-flop sequence. Average evoked responses to the same pitch standard and deviant stimuli were compared quantitatively to calculate mismatch responses. Rats displayed a similar neuro-oscillatory signature to human MMN – deviant tones resulted in a higher amplitude N1 (30-50ms) and P2 (80-150ms) response compared with standard tones. This effect, however, was found to be highly variable over time. To investigate the source of this variability, EEG traces were manually inspected to identify vigilance states and power spectral analyses conducted on epochs defined as being NREM, REM and wakefulness (active and passive). There was a distinct spectral fingerprint associated with each vigilance state: slow-wave activity (spectral power < 4Hz) was highest during NREM sleep whereas wakefulness was associated with large high frequency activity (>30Hz). Evoked responses were then averaged within distinct vigilance states using these spectrally-defined parameters. The magnitude of the deviant evoked response (both N1 and P2) was found to be largest during NREM sleep and lowest during active awake periods, resulting in an overall larger MMN response during NREM compared to wakefulness. This differential response across sleep-wake states may explain the high variability reported in rodent MMN studies and suggests that vigilance state be controlled for, particularly in studies where vigilance state is expected to be impacted. Current work is aimed at using deep learning strategies to better define and detect vigilance states based solely on spectral content.
Keywords: Mismatch negativity, EEG, animal models, sensory evoked potentials

STAND 30

TITLE: A high-throughput platform for neurophysiological and behavioral monitoring combined with optogenetic capabilities in awake-behaving rodents

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Abstract: There is a growing need for a consolidated high-throughput system to study specific neural circuit perturbations, while simultaneously recording the electrophysiological and behavioral response to these inputs in awake-behaving rodents. There are multiple ways to modulate circuit activity, either endogenously through optogenetic-based technologies and/or exogenously through sensory evoked potentials. Current available tools to accomplish this, however, are relatively low-throughput in design. Furthermore, the tethered nature of electrophysiological setups makes integrating this technology with tethered optogenetic-based circuit modulation difficult for awake-behaving studies. Here we describe an innovative system using a wireless radiofrequency telemetry device for EEG recordings (Data Sciences International) combined with both optogenetic and auditory sensory stimulation that permits real-time simultaneous modulation of neural activity and EEG recordings in awake-behaving rodents. The telemetry device also collects continuous 24 hour activity data which was validated using video tracking software to be an accurate surrogate measure of ambulatory activity. Various TTL triggered optogenetic laser/LED set-ups can be integrated with the EEG recording system via the included BNC inputs. The proposed enclosed-laser/LED system is comprised of separate but simultaneously controlled lasers, that have the ability to individually modulate light intensity output at each fiber end. Pulse trains are recorded by a TTL signal input integrated into the recording hardware that can reliably track pulse trains up to 200Hz in order to time-lock light delivery with EEG activity. The flexibility of the system also enables direct input of delivered exongenous sensory stimuli, in addition to or in combination with optogenetic stimulation, and recording of the EEG sensory evoked response. This offers a unique system by which to interrogate the specific cortical circuitry involved in sensory evoked responses which are perturbed across multiple neuropsychiatric diseases and which are readily modeled in rodents. In addition to its high-throughput advantage, the wireless nature of the EEG system is compatible with long-term, chronic monitoring of brain activity and behavior in awake-behaving mice following either acute or chronic neural circuit modulation.

Keywords: Optogenetics, EEG, sensory evoked potentials, psychiatry, mouse models

Stand 31

TITLE: What is Pulse Width Modulation?

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Abstract: Music, speech, echo-location, sonar, dancing, poetry, telegraphy, and early Fax telegraphics are all based upon Pulse Width Modulation (PWM). These human activities store and transmit information that is encoded as time extents (durations called pulse widths) within periodic (repeating) periods. The brain must be able to decode these durations, and encode new actions and messages based upon PWM to participate in these activities. Clocks and timers are designed to move at a constant rate. So duration can be expressed by a movement extent (displacement) of a device that moves at a constant velocity. The movement of muscles can be based upon time also if individual muscle cells contract and extend at a constant rate, which is possible because of their small mass. An antagonistic (symmetrical) arrangement of two or more positive moving (+1) and negative moving (-1) muscle cells can produce rotation movements at a constant angular velocity when they are connected with ligaments to a rotary joint and arm (limb). Adding more cells in series increases the velocity of the limb, and adding more cells in parallel increases the torque on the limb. A pulse generator can be used to move both muscles at the same rate. Separate positive and negative moving muscles can be connected to a single joint, forming a differential muscle wherein the output of the joint is equal to the sum of the motions of each muscle, allowing them to compute complex motions using the three (ternary) values (+1, -1, and 0). Multiple differential muscles can be combined so as to sense and avoid objects in the path of its output arm using PWM. The neural

circuits need to produce these muscle movements can be used without the muscle cells to form memory registers that can send and receive messages, and produce complex logic computations and thought within the brain, without movement, using PWM. A muscle circuit can be employed that returns the limb to a zero (0) position after every excursion. This produces a symmetrical, zero-sum PWM format that provides order (certainty) in a system like the brain that contains a lot of information (uncertainty). The repetition of the basic, symmetrical, two-cell positive and negative muscle circuit forms the nested fractal PWM configuration that provides a comprehensive plan for the organization of the brain.
Keywords: Pulse width modulation, ternary computation, shift register, fractal organization