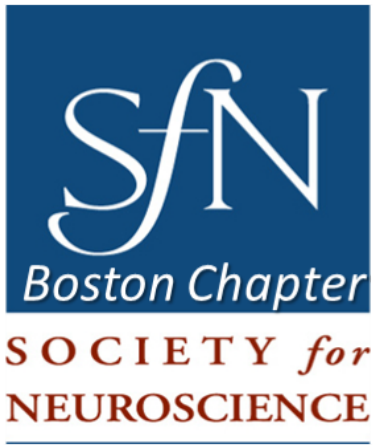

Boston Area
Neuroscience Group
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Boston Area Neuroscience Group Fall Symposium 2021

Tuesday, November 9th, 2021
Virtual Format

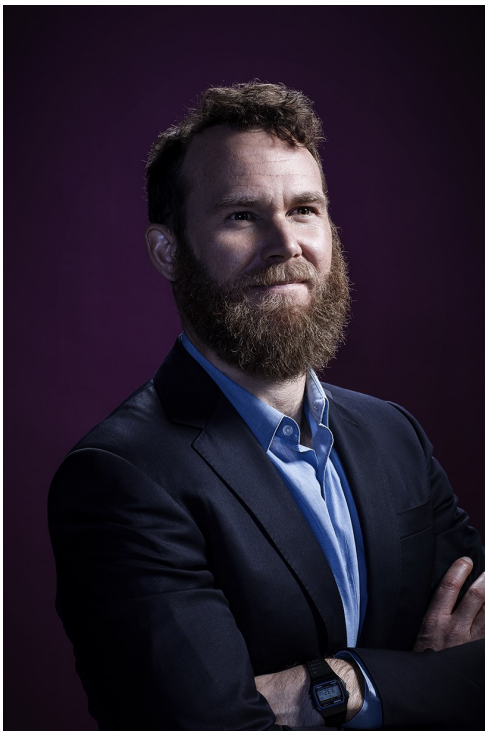
PROGRAM FOR THE MEETING

Start Time	Event
12:55 PM	*Opening Comments*
1:00 PM	*Keynote Speaker* Dr. Benjamin Scott
1:30 PM	*Trainee Talks* Dr. Jasmin Strickland Dr. Mikaela Laine Hamilton White Will Lynch
2:30 PM	*Coffee Break & Poster Session*
4:45 PM	*Keynote Speaker* Dr. Nikolaos Daskalakis
5:15 PM	*Closing Comments* Poster Awards & Notice of Available Positions

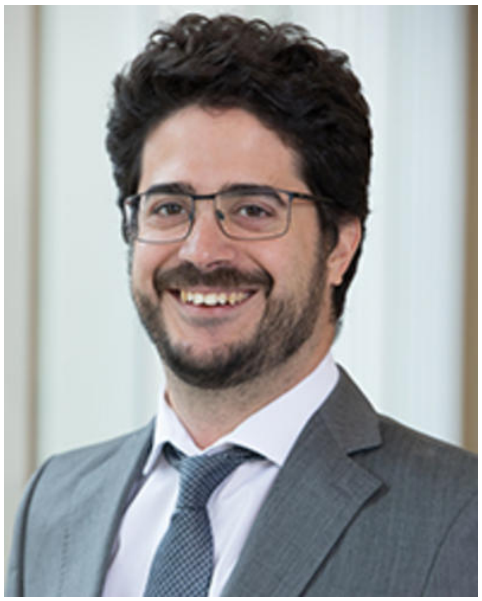
All events take place on Zoom.

Time has been allotted for transition between events.

MEET OUR INVITED SPEAKERS



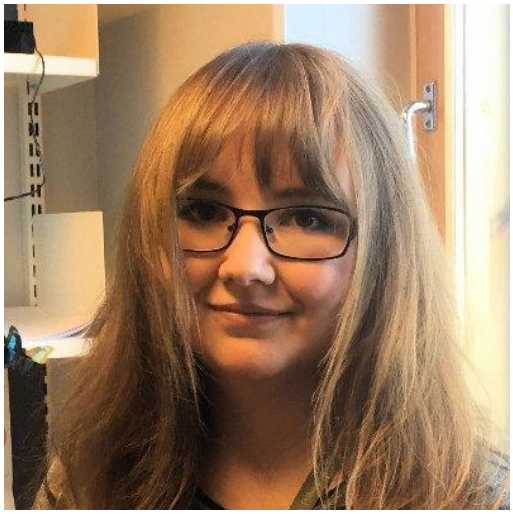
Dr. Benjamin Scott is an Assistant Professor in the Department of Psychological and Brain Sciences at Boston University where he is the DIrector of the Laboratory of Comparative Cognition. Dr. Scott's research interest is to develop and apply new technologies to study the neural basis of cognition and complex learned behavior. His approach involves a combination of two fields. The first is biomedical engineering, particularly the development of novel optical imaging and genetic methods to observe and perturb the activity of neurons in their native habitat – the intact brains of living organisms. The second is neuroethology, the study of brain circuits that underlie natural behaviors in order to elucidate basic principles of brain function. His current work brings together high-throughput behavioral training with advanced techniques for imaging brain activity in order to identify and characterize the neural circuits involved in evidence-based decision making.



Nikolaos P. Daskalakis, MD, Ph.D., is the director of the Neurogenomics and Translational Bioinformatics Laboratory, part of the Advanced Bioinformatics and Computational Discovery Hub, at McLean Hospital and an assistant professor of psychiatry at Harvard Medical School. He is also an affiliate member of the Broad Institute, MIT Computer Science and Artificial Intelligence Laboratory, and the National Center for PTSD. Dr. Daskalakis received his MD from the University of Athens, his PhD in neuropsychopharmacology from Leiden University, and completed post-doctoral research fellowships in clinical neuroendocrinology at Leiden University and in systems biology at the Icahn School of Medicine. Dr. Daskalakis focuses on the interaction between stress and the brain, conducting translational studies and following an integrative systems biology approach. His lab uses transcriptomic and epigenomic profiling of brain and blood samples to identify gene networks associated with vulnerability and resilience to PTSD. Dr. Daskalakis leads the Systems Biology working group of the Psychiatric Genomics Consortium for PTSD. He is an editor for Brain

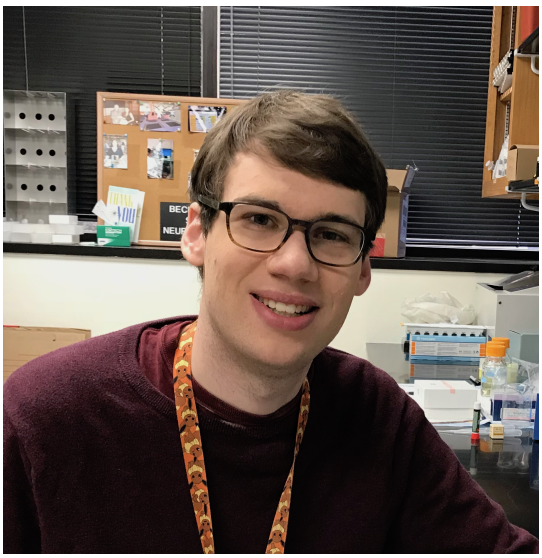
Sciences and Frontiers (in Behavioral Neuroscience, Endocrinology, Neuroscience, and Psychiatry).

Dr. Jasmin Strickland is a postdoctoral research fellow at Boston college in the McDannald lab. She received her bachelors, masters, and PhD in Psychology at Durham University (UK). Her doctoral work looked at the role of glutamate in associative learning. Their current research is using high channel ephys in rats (Neuropixels probes) to investigate threat computation networks across brainstem regions. Follow me on Twitter @JasStrickland18.



Dr. Mikaela Laine completed her PhD in Neuroscience at the University of Helsinki (PI: Prof Iiris Hovatta, Neurogenomics lab), and joined the Shansky Lab at Northeastern University in February 2021 as a post-doctoral research associate. Her research interests encompass a broad range of brain plasticity mechanisms and their role in stress-related psychiatric disorders, and how individual differences may determine the outcomes of stressful exposures. Her current work additionally emphasizes sex as a biological variable, investigating how the aforementioned mechanisms do or do not differ between individuals of different sexes.

Hamilton White joined the Worcester Polytechnic Institute – University of Massachusetts Medical School Joint Ph.D. program in 2018, studying Biomedical Engineering with a concentration in Neurobiology. Previously, Hamilton was a student at the University of Rochester studying Biomedical Engineering with a focus in Biomechanics, and research/technical training in Optical Engineering. His current work uses the nematode C. elegans to examine the subtle structural, neurofunctional, and behavioral responses occurring after chemosensory and optogenetic stimulation. Tools built during his time in the Joint Program include microfluidic geometries enabling simultaneous 3D neural imaging, chemosensory and optogenetic stimulation along with methods for initiating traumatic brain injury and studying short/long-term neural effects. Outside of his primary work, Hamilton is passionate about value creation, and has helped several new Ph.D. students and young faculty learn about sensory adaptation, microfluidic methods and pipelines for repeatable, reproducible experimentation using MATLAB as a computational base.



Will Lynch received his B.A. from Oberlin College, with a Major in Neuroscience and a Minor in Chemistry. He previously conducted research with Dr. Michael Beckstead at the Oklahoma Medical Research Foundation, analyzing morphological decline in single dopamine cells across age in a mouse model of Parkinson's disease while also investigating how neuromodulators of the dopaminergic system influence addiction-related behaviors. Now a graduate student at Boston University, Will works in the Laboratory of Addiction Genetics with Dr. Camron Bryant. Part of his research assesses the mechanistic actions by which the RNA-binding protein gene *Hnrnph1* regulates methamphetamine behavioral and neurochemical effects. Additionally, he is investigating how the transcriptional repressor gene *Zhx2* influences oxycodone addiction-related behaviors through manipulating brain and hepatic drug metabolism.

POSTERS IN ORDER OF PRESENTING AUTHOR

THEME 1: ADDICTION		
Presenter	**Affiliation**	**Poster Title**
1_Jacob Beierle	Boston University School of Medicine	A reduced complexity cross between BALB/c substrains identifies Zhx2 as a candidate gene underlying oxycodone metabolite brain concentration and state-dependent learning of opioid reward
2_Kristyn Borrelli	Boston University School of Medicine	Perinatal morphine induces behavioral indices of opioid withdrawal and affects myelin-related gene expression in the nucleus accumbens
3_Sebastian Magnotti	The University of Rhode Island	Prescription stimulant misuse among nursing students: A systematic review of the literature
THEME 2: NEUROVASCULAR, DEMENTIA, NEURODEGENERATION		
Presenter	**Affiliation**	**Poster Title**
4_Rachel McLaughlin	Brown University	Capillary-like network disruption after oxygen-glucose deprivation in a 3D cortical spheroid model
5_Songlin Xie	Boston University	Anti-inflammatory drugs – A treatment for vascular dementia?
6_Ian Mahar	Boston University	Clinicopathologic correlates of psychiatric symptoms in chronic traumatic encephalopathy across brain regions
THEME 3: IMMUNE RESPONSES, MICROGLIA, AND BRAIN FUNCTION		

Presenter	Affiliation	Poster Title
7_Daniela Delphus	Massachusetts General Hospital/Harvard Medical School	Screening for COVID-19: A self-administered, at-home smell test
8_Hieu Tran	Massachusetts College of Pharmacy and Health Sciences	Poly (I:C)-induced maternal immune activation affects mouse visual discrimination performance and reversal learning in a sex-dependent manner
9_Holly DeRosa	Massachusetts College of Pharmacy and Health Sciences	The effects of environmental enrichment on lactation quality and offspring social behavior.
10_Holly DeRosa	Massachusetts College of Pharmacy and Health Sciences	Got Milk? Maternal immune activation affects nutritional milk quality and offspring sensory processing in male and female rats
11_Hannah Bues	Massachusetts General Hospital/Harvard Medical School	Similar patterns of increased microglial activation in the dorsal anterior cingulate cortex observed in both long-term chronic fatigue syndrome and recent onset 'Long-COVID'
12_Kelsea Gildawie	Northeastern University	Differential impacts of neonatal microglia depletion on social and working memory in males and females following early life adversity
THEME 4: NEGATIVE EMOTIONAL VALENCE, LEARNING AND MEMORY, AND HORMONES		
Presenter	**Affiliation**	**Poster Title**

13_Julia Mitchell	Northeastern University	Neural modulators of conditioned fear responses in male and female rats
14_Lauren Granata	Northeastern University	The role of early life adversity and pubertal timing in the development of the acoustic startle response in rats
15_Daria Kotov	University of Massachusetts, Boston	Exploring correlation between post-partum depression and the 5-HTTLPR gene
16_Karen Kandalaft	University of Massachusetts, Boston	Serotonin receptor gene and maternal postpartum depression in humans
17_Rylei Donovan	University of Massachusetts, Boston	Investigating the relationship of testosterone levels between fathers and infants

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THEME 1: ADDICTION

1. A reduced complexity cross between BALB/c substrains identifies Zhx2 as a candidate gene underlying oxycodone metabolite brain concentration and state-dependent learning of opioid reward

Authors: Jacob A. Beierle, Emily J. Yao, Stan I. Goldstein, Julia L. Scotellaro, Katherine D. Sena, Olga Averin, David E. Moody, Christopher A. Reilly, Andrew Emili, Gary Peltz, Martin T. Ferris, Camron D. Bryant

Affiliation: Boston University School of Medicine

Understanding the pharmacokinetic profile of an opioid drug is vital to therapeutic success, and mutations in human PK genes can drastically alter therapeutic efficacy of opioids. We observed that 30 min post-oxycodone administration (1.25 mg/kg, i.p.) BALB/cJ mice showed a higher whole brain concentration of oxycodone, and female specific increase in noroxycodone, and oxymorphone compared to BALB/cByJ that likely accounts for the sex-specific increase in

oxycodone state-dependent conditioned place preference in BALB/cJ female mice. To potentially link behavioral differences with PK differences, we conducted quantitative trait locus (QTL) mapping of whole brain oxycodone and metabolite concentrations in a reduced complexity cross (RCC). Because BALB/cJ and BALB/cByJ substrains differ by ~8,500 SNPs/indels, large genetic loci identified in an F2 cross are offset by dramatic reduction in potentially causal variants. QTL mapping in 133 BALB/cJ x BALB/cByJ F2 mice (68F, 65M) revealed a single QTL on chromosome 15 associated with brain oxymorphone concentration that explained 29% of the phenotypic variance in females. Oxymorphone is bioactive at the mu opioid receptor, with 8x the potency of oxycodone, and likely contributes to its addictive properties. Hippocampal and striatal cis-eQTL analysis revealed genetically regulated expression of Zhx2, a transcriptional inhibitor known to harbor a private BALB/cJ retroviral insertion that dramatically reduces protein expression and leads to sex specific dysregulation of CYP450 genes within the liver. Whole brain mass spectroscopy proteomics in parental strain mice corroborated these eQTL findings. We hypothesize that decreased Zhx2 expression leads to increased CYP450 expression, increased brain oxymorphone, and increased oxycodone-induced behaviors. Interestingly, human GWAS of nicotine consumption identified a nominal association (10^-7) with ZHX2, indicating that this transcriptional repressor could influence metabolism of multiple drugs of abuse.

2. Perinatal morphine induces behavioral indices of opioid withdrawal and affects myelin-related gene expression in the nucleus accumbens

Authors: Kristyn N. Borrelli, Emily J. Yao, Catalina Zamorano, Michelle Roos, Katherine N. Sena, Jacob A. Beierle, and Camron D. Bryant

Affiliation: Boston University School of Medicine

Prenatal exposure to opioids is a growing concern in the United States, and the number of neonates exhibiting signs of opioid withdrawal has increased rapidly over the last 20 years. Neonatal opioid withdrawal syndrome (NOWS) is diagnosed based on a set of symptoms that result from the disruption of both the sympathetic and parasympathetic nervous systems. Following cessation of *in utero* opioid exposure, NOWS-affected infants commonly display increased irritability, disrupted sleep patterns, high-pitched crying, and erratic feeding behavior. A common treatment approach for NOWS focuses on the alleviation of withdrawal symptoms through opioid maintenance therapy with an opioid agonist such as methadone or buprenorphine. The effects of opioid exposure on neurodevelopment and long-term effects on behavior and overall health are poorly understood. Mouse models of perinatal opioid exposure can expedite discovery of molecular mechanisms driving withdrawal phenotypes and detection of detrimental effects on neurodevelopment and behavior. In this study, we utilize 3rd-trimester-equivalent exposure to morphine (15 mg/kg, s.c.) once daily from postnatal day (P) 1-14 in outbred Swiss Webster Cartworth Farms White (CFW) mice to study model withdrawal phenotypes and transcriptional adaptations within the nucleus accumbens during the third trimester-equivalent period. We additionally performed behavioral assays in adulthood to gauge

differences in a spectrum of behavioral tasks probing cognition, reward sensitivity, and cue-associated fear conditioning. We observed significant weight deficits, indications of hyperalgesia, and altered ultrasonic vocalization (USV) profiles during the neonatal period. Transcriptome-wide analysis of gene expression also revealed downregulation of myelin-related genes within the nucleus accumbens (NAc), a brain region critical for reward processing and learning. Adult behavioral assays revealed no significant long-term effects of perinatal morphine exposure on spatial memory function (Barnes Maze), reward-potentiation following exposure to methamphetamine (MA) (intracranial self-stimulation), or cue-associated fear conditioning. Our findings suggest robust behavioral and transcriptional effects of perinatal morphine during the pre-weaning period, but do not indicate long-term effects on spatial memory, MA-facilitated reward sensitivity, or fear conditioning.

3. Prescription stimulant misuse among nursing students: A systematic review of the literature

Authors: Magnotti, S., Beatty, A., Bickford, E., Channell, I., & Weyandt, L*

Affiliation: The University of Rhode Island

Prescription stimulants including methylphenidate (e.g., Ritalin), amphetamine compounds (e.g., dextroamphetamine; Adderall), and lisdexamfetamine dimesylate (Vyvanse) are commonly used in the treatment of attention deficit hyperactivity disorder (ADHD). Decades of research support that stimulants are widely regarded as safe and effective at reducing neurocognitive symptoms of ADHD including inattention, impulsivity, and hyperactivity in children, adolescents, and adults, however, serious side effects can occur when stimulant medications are misused. Despite the potential health and judicial consequences, misuse of prescription stimulants has become a serious public health problem in the general population, particularly among college students. Studies exploring the motivations for prescription stimulant misuse among college students suggest that neurocognitive and academic enhancement are often the primary reasons that college students misuse prescription stimulants. Nursing students may be at particular risk for misusing prescription stimulants due to the academic requirements of these programs and high stress levels and grade strain reported by nursing students (Norman & Ford, 2018). Furthermore, research supports that a substantial percentage of RNs with substance use disorder report using prescription stimulants for the first time in college. Given the substantial number of studies published during the past two decades concerning prescription stimulant misuse among the general population of college students, the present study sought to systematically review and summarize the literature within the past decade with respect to prescription stimulant misuse specifically among nursing students. The purposes of the present systematic review was to explore the a) percentage of prescription stimulant misuse studies that have included information regarding nursing students, b) the prevalence of prescription stimulant misuse among nursing students c) motivations for prescription stimulant misuse among nursing students, and d) demographic factors such as age, sex, gender, and ethnicity that may be associated with increased risk of misuse among nursing students. Results

unexpectedly revealed that only 1% of studies that investigated prescription stimulant misuse among college students during the past decade included nursing students. Findings also indicated that neurocognitive enhancement was the primary motivation for prescription stimulant misuse among nursing studies sampled. Future studies are sorely needed to further explore the nature of prescription stimulant misuse among nursing students.

THEME 2: NEUROVASCULAR, NEURODEGENERATION, DEMENTIA

4. Capillary-like network disruption after oxygen-glucose deprivation in a 3D cortical spheroid model

Authors: Rachel McLaughlin, MA; Dowlette-Mary Alam El Din, BS; Amanda Laguna, BS; Ilayda Top, BS, Diane Hoffman-Kim, PhD

Affiliation: Brown University

Neurovascular dysfunction is linked to many pathologies, such as stroke and traumatic brain injury. Our three-dimensional self-assembled spheroids composed of primary postnatal rat cortical cells have the cellular composition, tissue stiffness, and cell density similar to the *in vivo* brain. At about 2 to 6 days *in vitro* (DIV2-6), our model contains spontaneously formed capillary-like networks formed from endothelial cells with lumens. These structures are associated with high concentrations of laminin. We exposed these spheroids to glucose deprivation, oxygen deprivation, or oxygen-glucose deprivation for 24 hours to model the different components of ischemic injury, and stained for laminin. We analyzed the changes in capillary-like network morphology using two different analysis methods, naïve participant analysis and image quantification. Both of these analysis methods showed that oxygen deprivation and oxygen-glucose deprivation significantly alter capillary-like network morphology.

5. Anti-inflammatory drugs – A treatment for vascular dementia?

Authors: Songlin Xie, BA; Yandan Wang, MS; Kathleen G. Morgan, PhD

Affiliation: Boston University

The aim of this study is to investigate causal relationships between neuroinflammation, microbleeds, and vascular dementia in an aging mouse model. Microbleeds have been found to be worse in aged mice comparing to young adult mice by applying Prussian Blue histology. Immunofluorescence assay on microglia was used to assess inflammation status of mice. The Novel Object Recognition (NOR) test and the locomotor activity test were used to assess animal behavior and cognition ability change. Histology data and immunofluorescence data indicate that as mice age, microbleeds and inflammation both get worse. The behavioral test also suggest that mice have cognition decline with aging. Here, the current study aims at a possible treatment for cognition decline and vasculature damage by targeting neuroinflammation. This

study will also determine a timeline of the occurrence of different age-associated damages in mouse brain.

6. Clinicopathologic correlates of psychiatric symptoms in chronic traumatic encephalopathy across brain regions

Ian Mahar, PhD, Sarah E. Chancellor, PhD, Bertrand R. Huber, MD, PhD, Thor D. Stein, MD, PhD, Victor E. Alvarez, MD, Rebecca Mathias, MSc, Jonathan Cherry, PhD, Ann C. McKee, MD

Boston University

BACKGROUND

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease with cognitive, behavioral, and psychiatric symptoms, with depression and suicidality present in a large proportion of CTE cases. Pathologically CTE is defined by a distinctive accumulation of hyperphosphorylated tau (pTau) predominately involving the frontal and temporal cortices, medial temporal lobe, and brainstem. However, the association between pathology in particular brain regions and psychiatric CTE symptoms is unknown.

METHODS AND RESULTS

Human postmortem brains from CTE cases and controls were obtained from the VA-BU-CLF Brain Bank. Trained neuropathologists examined each brain for gross and microscopic pathology, and provided semi-quantitative assessments. Regions of interest (including frontal, temporal, limbic, and brainstem structures) were sectioned and stained for pathological markers of interest (e.g. pTau, β-amyloid, α-synuclein, pTDP43, etc). Stained slides were scanned and traced digitally, with staining quantified using a Leica Aperio system. Preliminary analyses suggest alterations in specific cortical, limbic, midbrain, and white matter structures may associate with depressive and suicidal features in CTE. In particular, cortical white matter loss as well as hippocampal and midbrain pathology were associated with psychiatric features. We have also found myelination and inflammation-associated changes in the anterior cingulate cortex of depressed CTE cases. Cytotoxic t-cells may be involved in depressed mood and disease progression in CTE.

CONCLUSIONS

This investigation is the first to explore associations between neuropathology in particular brain regions and psychiatric features in CTE. Preliminary results suggest increased neurodegenerative pathology, loss of white matter, neuroinflammation, and gliosis could underlie psychiatric phenotypes in CTE.

THEME 3: IMMUNE RESPONSES, MICROGLIA, AND BRAIN FUNCTION

7. Screening for COVID-19: A self-administered, at-home smell test

Authors: Daniela Delphus, BS; Colin Magdamo, BS; Alefiya Albers, PhD; Liliana Ramirez Gomez, MD; Joseph Locascio, PhD; Edward W. Boyer, MD PhD; Ross Zafonte, DO; and Mark W. Albers, MD PhD.

Affiliation: Massachusetts General Hospital

Most patients with COVID-19 infection report severe smell and taste loss. However, self-reports of anosmia or hyposmia are not sufficient indicators of the risk of COVID-19 infection as surveys of self-reported smell function are routinely unreliable. Since smell loss is validated as a sign of COVID-19 in asymptomatic individuals, a validated objective smell test could be used as a screening tool to provide results and an interpretation immediately related to potential risk of COVID-19 infection. This smell test could serve as a screening tool for healthy asymptomatic people, such as health care workers. Combining objective smell function with COVID-19 test results may lead to an improved algorithm to provide pre-test probability of COVID-19 infection, may improve pooling procedures for the RT-PCR tests, may improve sensitivity of COVID-19 testing, and provide guidance for self-quarantine at home with instantaneous return of results. To determine whether smell function/symptoms is associated with COVID-19 status, we created a web-based application paired with a smell card, to collect symptoms and to administer olfactory tests to quantify smell function in subjects with documented COVID-19 status (+ or -) as determined by nasopharyngeal RT-PCR testing. We found that COVID positive patients performed significantly worse on odor intensity ratings ($p < 0.0017$), odor percept identification ($p < 0.0025$), and odor discrimination ($p < 0.0007$) compared to COVID negative individuals. Incorrect responses on the objective smell test together with asking the subject about their impression of smell loss survived backwards elimination and increased the odds ratio of having COVID-19 5-7-fold. We used a multivariable logistic regression model to predict overall Covid-19 status defined by PCR with a final model convergence of $p < 0.0001$. These results demonstrate a **robust** association of olfactory dysfunction with infection by Covid-19, based on the results of the subjective symptom survey and the objective olfactory tests.

8. Poly (I:C)-induced maternal immune activation affects mouse visual discrimination performance and reversal learning in a sex-dependent manner

Authors: Hieu Tran; Xin ZHao, PhD; Holly DeRosa, BS; Ryland C. Roderick BS; Amanda C. Kentner, PhD

Affiliation: Massachusetts College of Pharmacy and Health Sciences

Maternal immune activation (MIA) has been shown to be associated with deficits in offspring in terms of social behavior and brain development. However, little attention is directed towards the potential advantages of early life challenges. In this study, we used a polyinosine-polycytidylic

acid (poly(I:C)) MIA model to test visual pairwise discrimination (PD) and reversal learning (RL) in mice using touchscreen technology. There were significant sex differences where MIA reduced latency for males to make a correct choice in the PD task, while females reached criterion sooner, made fewer errors, and utilized fewer correction trials in RL compared to saline controls. These improvements were accompanied by sex-specific upregulation of genes critical to cognitive functioning, which is indicative of compensatory plasticity in response to MIA. Moreover, MIA mice with induced loss of the social component of environmental enrichment (EE) in the 'two-hit' stress model did not display anhedonia but required an increased number of PD and RL correction trials. These animals also had significant reductions of CamK2a mRNA in the prefrontal cortex. The regular functioning of this protein kinase and other mediators of synaptic plasticity, are crucial for behavioral flexibility. Though EE has been implicated in rescuing symptoms associated with brain disorders in offspring, our findings show that EE also makes individuals more vulnerable to its loss. Ultimately, with the right 'dose', early life stress can result in some functional advantages, which are lost when the magnitude of these exposures become too great.

9. The effects of environmental enrichment on lactation quality and offspring social behavior.

Authors: Holly DeRosa, MA, Hieu Tran, Amanda C. Kentner, PhD.

Affiliation: Massachusetts College of Pharmacy and Health Sciences

Breastfeeding confers both short- and long-term benefits on offspring development, including those related to growth, immunity, and even brain physiology. While alterations in the neonatal environment can have dramatic effects on offspring outcomes, the mechanisms that drive this phenomenon remains unclear. Improving environmental complexity (i.e., environmental enrichment; EE) has been shown to contribute to robust differences in offspring development in both humans and animal models. Using Sprague-Dawley rats, we explored the effects of EE on maternal milk quality, maternal behavior, and offspring development. Maternal milk samples were collected from EE and standard-housed (SD) dams on postnatal 10 and quality was assessed with several assays. Although EE dams spent less time nursing, postnatal enrichment was associated with greater offspring bodyweight. In support of these findings, milk from EE dams contained greater triglyceride levels compared to SD dams. Milk from EE dams also contained greater microbiome diversity, and a significantly higher abundance of bacterial families related to bodyweight and energy metabolism, including *Erysipelotrichaceae, Christensenellaceae,* and *Lachnospiraceae.* In addition to changes in lactational quality, we also observed sex- and time-dependent effects of EE on offspring social behavior which was revealed by cross fostering. Specifically, postnatal EE was associated with greater sociability in males, while prenatal EE was associated with greater sociability in females. Together, these results underscore the multidimensional impact of the combined neonatal and maternal environments on offspring development and behavior.

10. Got Milk? Maternal immune activation affects nutritional milk quality and offspring sensory processing in male and female rats.

Authors: Holly DeRosa, MA, Hieu Tran, Amanda C. Kentner, PhD

Affiliation: Massachusetts College of Pharmacy and Health Sciences

Exposure to maternal immune activation (MIA) during gestation is a major risk factor for developing psychiatric disorders such as autism and schizophrenia, but the effects of MIA after parturition need further elucidation. The neonatal environment requires a high level of maternal demand; previous studies have underscored the importance of breastfeeding and maternal care on offspring development and behavior. In the present study, we investigated how MIA exposure during postnatal day 10 (P10) of the lactational period affects milk quality, maternal care, and subsequent offspring outcomes in Sprague-Dawley rats. *Lipopolysaccharide* (LPS)-induced MIA was associated with decreased maternal licking and grooming 3-hours post-challenge, which was followed by a compensatory rebound of maternal care on P11. This paralleled milk corticosterone, which was increased in LPS dams on P10 but recovered by P11. Milk percent crematocrit values were decreased both 3- and 24-hours post-injection compared to vehicle controls. Milk triglyceride levels were also decreased at P11. Treatment with LPS contributed to sustained changes in milk microbial communities, where milk from LPS dams contained a greater abundance of the bacterial families *Pseudomonadaceae* and *Xanthomonadaceae* on P10 and P11. We also found MIA-associated changes in neonatal huddling and sex-specific effects on adolescent sensorimotor gating, and tactile processing as revealed by the von Frey test. These results suggest that MIA exposure during mid-lactation confers multifaceted and compounding effects on both maternal and neonatal physiology and behavior.

11. Similar patterns of increased microglial activation in the dorsal anterior cingulate cortex observed in both long-term chronic fatigue syndrome and recent onset 'Long-COVID'

Authors: Hannah Bues BA, Minhae Kim BA, Ludovica Brusaferri PhD, Zeynab Alshelh PhD, Donna Felsenstein MD, Darin Dougherty MD, Marco Loggia PhD, Michael VanElzakker PhD

Affiliation: Massachusetts General Hospital/Harvard Medical School

Objective:
The COVID-19 pandemic has caused an epidemic of "Long-COVID" or PASC (post-acute sequelae of COVID-19). People who fail to fully recover from acute COVID-19 report symptoms of fatigue, cognitive problems, light and noise sensitivities, and difficulty recovering from exertion. These symptoms strongly overlap with the existing symptom-based diagnostic label of chronic fatigue syndrome or myalgic encephalomyelitis (ME/CFS). While preliminary evidence suggests that ME/CFS symptoms may be driven by inflammatory processes in the central

nervous system, little is known about the mechanisms of Long-COVID. Thus, the goal of the current study is to use positron emission tomography (PET) to study neuroinflammation in ME/CFS and Long-COVID patients.

Methods:

In this ongoing study, neuroinflammation is quantified with the PET radioligand [11C]PBR28 which binds to a microglial activation-associated protein called TSPO. After injection with [11C]PBR28, participants' brains are scanned by a dual PET-MR (magnetic resonance) scanner. The current pilot data show PET scans from one 29-year-old male with recent-onset 'Long-COVID' and one 66-year-old female with ME/CFS for 18 years. Healthy control scans are age, sex, and genotype matched. In this analysis, the occipital lobe was used as a reference region.

Results:

In this preliminary analysis, the Long-COVID and the ME/CFS cases show similar patterns of increased PBR28 uptake in the dorsal anterior cingulate cortex (dACC), relative to control scans.

Conclusion:

The dACC is a key structure in the maintenance of cognitive control, and is also known to be particularly sensitive to neuroinflammation. Thus, increased uptake in the dACC may explain the subjective "brain fog" symptoms that these patients experience. We hypothesize that analyses following further recruitment will show increased [11C]PBR28 uptake in the dACC, caudate nucleus, insular cortex, and dorsal brainstem. Future analyses will include fMRI of a dACC-activating task and MRS (magnetic resonance spectroscopy).

12. Differential impacts of neonatal microglia depletion on social and working memory in males and females following early life adversity

Authors: Kelsea Gildawie, PhD, Michaela Fanikos, BS, Lakshanyaa Thamarai Kannan, Alissa Valentine, MS, Abigail Parakoyi, BA, Heather Brenhouse, PhD

Affiliation: Northeastern University

Early life is rife with sensitive periods during which aberrant experiences can have lasting effects on cognitive development. Importantly, adversity-induced consequences often vary between males and females; however, the mechanism driving this sex difference is not fully understood. Microglia are the main immune cells in the brain that have been implicated in regulating sex-dependent neural and cognitive maturation. To determine whether microglial presence in the neonatal brain mediates the sex-dependent behavioral consequences of early life adversity, Sprague Dawley rat pups underwent bilateral intracerebroventricular infusions of liposomal clodronate (LC) or vehicle (Veh) liposomes at postnatal day (P)2 to transiently deplete microglia. Pups were then exposed to maternal separation (MS) 4h per day from P2-20 (or control rearing), followed by juvenile social isolation (SI) from P21-35 (or standard pair-housing). In adulthood (P70-71), working memory (spontaneous alternation in the Y-maze) and social

recognition was assessed. We found varying effects of early life adversity in males and females on social and working memory following MS that was mediated by the presence of neonatal microglia. Specifically, neonatal MS impaired working memory in females – but not males – which was prevented by LC treatment, suggesting that microglia depletion may protect against aberrant maternal caregiving. In contrast, social memory was not impacted by adversity in Veh-treated animals; however, following LC injection, males – but not females – exposed to juvenile social isolation demonstrated impaired social recognition. This may suggest that typical microglial development is essential for cognitive maturation in males. These findings reveal a critical role for microglia in the sex-dependent, long-term cognitive response to adversity early in life, which has important implications for potential interventions for children who have experienced childhood maltreatment.

THEME 4 NEGATIVE EMOTIONAL VALENCE, LEARNING AND MEMORY, AND HORMONES

13. Neural modulators of conditioned fear responses in male and female rats

Authors: Mitchell, J.R., Potgieter, L., Shansky, R.M.

Affiliation: Northeastern University

Darting is a sex-dependent conditioned fear response characterized by a quick movement across a fear conditioning chamber in response to a conditioned stimulus (CS). Forty percent of females dart while only ten percent of males do. The underlying circuitry involved in darting is unknown. The dorsal periaqueductal gray (dPAG), known to control active threat responses, receives inputs from the caudal portion of the infralimbic cortex (cIL). If the cIL regulates threat responses in the dPAG, activation of this circuit could increase an animal's likelihood to engage in active threat responses such as darting. In this study we used intersectional, excitatory DREADDs to activate the cIL-dPAG pathway, hypothesizing that excitation of this pathway would increase the number of darters across the sexes. We injected a cre-dependent, excitatory Gq virus into the cIL, and a retrograde-cre virus into the dPAG. After 6 weeks the animals received an injection of clozapine-n-oxide (CNO), to activate the cIL-dPAG circuit, before undergoing classic Pavlovian Fear Conditioning. Using ScaredyRat, a custom Python tool designed in our lab to analyze raw Ethovision Data files, we were able to quantity the number of darters, as well as the animals' response (in cm/s) to the shock and their post-shock maximum velocities reached. Although we did not see an increase in darters, we observed a significant decrease in freezing for females with an excited cIL-dPAG circuit compared to controls. There was no difference between males with the excited circuit and their control group, and no difference in shock and post-shock response between groups in either females or males. These data indicate that excitation of the cIL-dPAG circuit, although not apparently involved in darting, might influence an animals' propensity to freeze in response to a CS in a sex-dependent

manner. Future studies will investigate the IL-PAG circuit involved in freezing as well as the organization of the projections from the IL to the dorsal and ventral PAG.

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14. The role of early life adversity and pubertal timing in the development of the acoustic startle response in rats

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Early life adversity significantly increases the risk of developing anxiety disorders later in life, particularly during and following adolescence. Hormonal changes during puberty affect the development of neural circuits subserving cognitive and affective regulation, creating a window of vulnerability. Anxiety-related psychopathologies in humans are often characterized by increased sensitivity to potential threats, which can be modeled in rodents via the acoustic startle response, a reflex modulated by neural systems associated with anxiety disorders. Implementing the acoustic startle test in rodent models enables scrutinization of the relationship between early adverse experiences, pubertal development, and threat responsivity over the lifespan. The current study investigated the development of the startle response across the pubertal transition (postnatal days 25, 35, and 55) and assessed the impact of maternal separation (MS) on startle progression in males and females. Furthermore, we assessed the startle response after presentation of a social threat: a pre-recorded conspecific's ultrasonic vocalization alarm call. Similar to the potentiating effects on anxiety when humans are presented with a fearful face, the alarm call is a species-specific signal of potential danger in the environment that may differentially modulate the acoustic startle response. With evidence that MS-exposed females experience accelerated pubertal development and the notion that pubertal timing can impact mental health outcomes, we also investigated whether the timing of puberty was associated with startle amplitude. Understanding how the startle response develops across puberty will contribute to our understanding of anxiety-related disorders to identify opportunities for intervention during critical transitional windows.

15. Exploring correlation between post-partum depression and the 5-HTTLPR gene

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Post-partum depression (PPD) is a mood disorder that can be detrimental to mothers. There are underlying biological risk factors for PPD. The serotonin transporter gene promoter (5-HTTLPR; responsible for uptake of serotonin from the synapse into the pre-synaptic cell) has been shown to be related to depression vulnerability in females. Allelic variation in 5-HTTLPR

(short/long) has been implicated in this relationship with mixed results. Much less is known about allelic variation's relationship with paternal postpartum depression. In a subset of a U.S. sample of first-time parents and (n=48 dyads), we collected saliva using oral swabs. Briefly, participants were asked to place a swab underneath one's tongue for 3 minutes; swabs were retrieved and frozen (-50°C). DNA was extracted from saliva. Genotyping was conducted according to manufacturer standards (Salimetrics, LLC; full protocol available upon request). To measure depression, participants were asked to fill out the Beck Depression Inventory. Data were analyzed using a series of independent sample t-tests. Our results suggest that there is no relationship between postpartum depression and allelic variants L_A/L_A and L_A/L_G of the 5-HTTLPR region. This was the case for mothers and fathers. These results correspond to mixed results in the current literature. In this preliminary study using only a subset of a larger sample, we may have failed to detect differences due to an inadequate sample size (i.e., low power). It is also possible that the use of a rudimentary t-test occludes effects that may be detectable given more precise statistical modeling in the future. For example, there has been mixed evidence of increased risk vulnerability for homozygous short (S/S) allelic variants based on exposure to early stressors. As a future direction, the inclusion of a measure of early life stress may reveal novel effects or replicate important extant relationships.

16. Serotonin receptor gene and maternal postpartum depression in humans

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According to extant work, the psychological and physiological toll of PPD affects infants through a number of pathways. One common candidate for maternal effects is the infant hypothalamic pituitary adrenal (HPA) axis—a system that produces the "stress hormone' cortisol. There is some evidence of a relationship between PPD vulnerability and a polymorphism (5-HTTLPR) within the promoter of the serotonin transporter gene. While findings on the allelic variation in 5-HTTLPR (short/long) and PPD are mixed, very little is known about whether infant cortisol modulates in response to behaviors common of PPD (decreased investment). We predict that allelic variants of 5-HTTLPR (L_A/L_A and L_A/L_G) will influence the infant HPA axis as measured by cortisol. In this study, mother participants (n=48) filled out the Beck Depression Inventory. Mothers were also asked to place a swab underneath their tongue for 3 minutes. For infant cortisol, a trained research assistant placed a child safe swab underneath the infants' tongue for 3 minutes. We retrieved all swabs, and they were frozen (-50*) locally. DNA was extracted from saliva. Genotyping was conducted according to manufacturer standards (Salimetrics, LLC; full protocol available upon request). Using a series of t-tests., we did not find a difference between a given allele in HTTLPR (L_A/L_A and L_A/L_G) and self-reported depression. We speculate that the absence of an effect may be due to a small sample size or a homogenous sample lacking diversity.

17. Investigating the relationship of testosterone levels between fathers and infants

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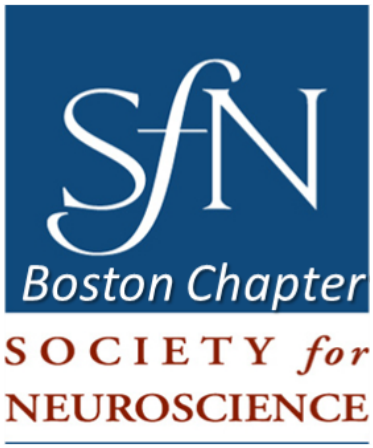
Testosterone (T) declines in human fathers shortly after the birth of offspring and “rebounds” through the first year of an infants’ life. Concurrently, human infant T fluctuation occurs during a period in development known as “mini puberty”—a surge in T that influences growth. It is not clear whether the relationship (if any) between the timing of T modulation in infants and their fathers exists. In this exploratory U.S. sample (n=225 families) of first-time fathers and infants, we measured salivary T in infants (2-3 months old) and male T (slope from 3 to 10 months postnatal). Briefly, fathers were asked to place a swab underneath their tongue for 3 minutes; swabs were retrieved and frozen (-50*). A trained research assistant collected saliva from infants by holding an infant-safe swab underneath the Infant’s tongue for 3 minutes. We used a difference score to calculate change in T (log) infant T (log). A Pearson correlation revealed no relationship between these two variables. The endocrine system in parents and infants is complex and multi-dimensional. We speculate that we did not find our proposed relationship due to the sample characteristics (homogenous) and the use of a simplified correlational model with potential covariates absent. Future follow-up on this exploratory study should include more sophisticated statistical modeling and a larger, more diverse sample of fathers.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