Mohammed Abuelem

Role of Juvenile Shank3 Re-Expression on Autistic-like Cognitive Flexibility Deficits in Male Mice

Hoopes Prize Winner

Research Director: **Dr. Takao Hensch**

Rigid and repetitive thinking patterns (i.e., cognitive flexibility deficits) are hallmark symptoms of autism spectrum disorder (ASD). The early developmental onset of ASD symptoms points to a critical period with heightened neural plasticity that can be targeted to rescue autistic- like deficits. This thesis investigates the role of the prominent autism candidate gene Shank3 (which encodes a postsynaptic density scaffold protein) in cognitive flexibility by examining rule-reversal learning in a tamoxifen-induced CreER-mediated Shank3 conditional knock-in mouse model that activates Shank3 re-expression during the postnatal day P21-P25 juvenile critical period. Then, four-choice odor discrimination and reversal foraging tasks examined rule-reversal learning behavior, Western blot analysis of synaptosome fractions from the anterior cingulate cortex (ACC) and dorsal striatum measured synaptic Homer1b/c and CDKL5 protein levels in relation to Shank3 expression, and functional ultrasound imaging recorded resting-state neural network activity patterns. We show that Shank3 deficient male mice display a rule- reversal learning impairment that can be rescued by Shank3 re-expression during the P21-P25 juvenile critical period. We further provide evidence that Shank3 haploinsufficiency retains normal synaptic Homer1b/c protein levels while Shank3 re-expression restores cortico-striatal synaptic CDKL5 protein levels. Finally, we report a decrease in indirect neural network energy state transitions among Shank3 deficient mice that can be restored by juvenile Shank3 re- expression. Together, these results present a novel role for juvenile Shank3 expression in rule- reversal learning, highlight a synaptic SHANK3-CDKL5 relationship, and elucidate intrinsic neural activity patterns reflecting juvenile Shank3 expression that may explain autistic-like cognitive flexibility deficits.

Athena Capo-Battaglia

Characterization of Sex Differences in the Neural Control of Social Homeostasis

Research Director: **Dr. Catherine Dulac**

Social interactions are critical to our lives, and there are serious health consequences of prolonged isolation in humans and animals alike. Social seeking behavior increases soon after the onset of isolation, suggesting an internal motivation to interact with others. Presumably this is controlled by internal states similar to homeostatic drives, which would serve to balance the level of social satiety. So far, the specific neural mechanisms underlying internal social drive remain unclear. Recent work from our lab has uncovered two novel neuronal populations in the medial preoptic nucleus of hypothalamus that regulate either social drive during social isolation or social satiety during social reunion in female mouse interactions. However, the involvement of these neurons in males has yet to be tested.

In this project, juvenile male mice were observed during post-isolation reunion and compared to female mice. We found that females initiated social behaviors and vocalized with a higher frequency than males throughout days of isolation despite similar distribution patterns. Activity mapping and cell type analysis in the medial preoptic nucleus of hypothalamus after isolation revealed less activity in the neuronal cluster thought to drive social isolation in male mice even though no difference was noted in the size of the region as measured by genetic markers. Preliminary data in resting behavior suggests that sleep is mostly consistent throughout 3 days of isolation; however, males on average slept for shorter periods of time. Together, this work will help us to better understand sex differences in neural circuits controlling social homeostasis.

Evan Casalino

Determining the Effects of Substrate Stiffness on Neuronal Morphology and Metabolism in Rat Cerebral Cortex

Research Director: **Dr. Kit Parker**

Despite the fact that the brain itself does not have its own somatosensory modalities, its cells are indeed sensitive to mechanical perturbations. The native microenvironment of the brain is extremely soft, with a Young's modulus similar to yogurt. Changes in environmental mechanical cues, such as stiffness, can induce changes in neuronal cell biology. Understanding the ways in which stiffness might affect neuronal function is important for understanding the pathology of diseases such as cancer and Alzheimer's—which can alter the stiffness properties of the brain. It is also relevant to the emerging field of neuronal tissue engineering, in which researchers designing organoids, organs-on-chips, etc. must consider the mechanical environment of their model systems in order to ensure biomimetic functionality. Because stiffer growth substrates are more dissimilar to the native environment of the brain, we expected that they would lead to maladaptive changes such as decreased dendritic growth and lower metabolic activity. To investigate this, we grew neurons from neonatal rat cerebral cortex in a monolayer on both a stiff and soft version of a silicone elastomer. We then imaged these cells and conducted a metabolic stress test to quantify stiffness-dependent changes in neuronal morphology and mitochondrial respiration. Indeed, we find that a relatively stiffer growth substrate results in deformed nuclei, less dendritic extension, and lower mitochondrial respiration. These effects suggest that stiffness should be considered as an important environmental component for experimental design, neuropathology, and drug development.

Selim Chalyshkan

Investigating the temporal relationship between striatal activity and learned motor behaviors in rats

Research Director: **Dr. Bence Ölveczky**

From tying your shoelaces to performing dance choreography, the range and complexity of movements we can learn is incredible. How does our brain acquire and drive these learned motor behaviors? Prior work has shown that the sensorimotor input region of the basal ganglia, termed dorsolateral striatum (DLS) in rodents, is required for the acquisition and execution of learned movements. Specifically, it is hypothesized that DLS stores, and ultimately controls, learned movements (Dhawale & Wolff et al., 2021). Under this hypothesis, DLS activity should predict the animal's upcoming movements after learning. Here, we test this idea by examining DLS activity, including the activity of its main cell types – spiny neuronal projections (SPNs) and fast-spiking interneurons (FSIs) – in rats after they have learned to execute a specific movement for reward. To determine whether DLS activity predicts the kinematics of upcoming movements, we first track the animal's 3D pose over time using machine vision and subsequently employ a statistical modeling framework that relates neural activity to past, current, or future movements (poses). Across 6 sessions and 243 neurons, we observe that most cells are fit by the model, with SPNs being more kinematically tuned than FSIs. We also found that most DLS neurons predict future movements, consistent with the hypothesis that DLS controls learned movements. Intriguingly, however, a subset of cells also reflected past movements, suggesting DLS may also represent movements that just occurred. This suggests a potential mechanism by which the outcome of a behavior (e.g. reward) becomes linked to that behavior.

Allison Chang

Age-Specific Functions of Microglial C1q in Neuronal Translational Regulation and Synaptic Plasticity

Research Director: **Dr. Beth Stevens**

Within the nervous system, interactions with various elements of the immune system contribute to a wide range of essential brain functions. C1q, an innate immune complement component produced and secreted by microglia in the brain, represents one of these key immune factors, with the protein having been previously implicated in critical processes such as synaptic refinement. Notably, a significant age-mediated aspect has been observed to exist regarding changes in C1q expression, with important consequences for function and behavior in the adult brain that are still not fully understood. This thesis aimed to investigate the functional consequences of age-dependent, microglial-derived C1q in translational regulation and plasticity. After confirming the co-localization of C1q and a subset of ribosomal and RNA-binding proteins at neuronal synapses in the aging brain via proteomic analysis and Proximity Ligation Assay, we identified changes in translational regulation resulting from the age-dependent modulation of C1q expression via the development of a puromycin non-canonical amino acid incorporation assay for the in vivo surveillance of active translation in the brain. Lastly, we observed behavioral changes in relation to age-dependent C1q interactions with RNA and RNA-binding proteins via the use of a fear extinction model. Overall, our work contributed to describing a novel property of the microglial-derived complement protein, C1q, in integrating into neuronal ribonucleoprotein structures and mediating age-specific intraneuronal interactions with translation-implicated RNA- binding proteins. These results support future inquiry into the role of C1q in plasticity, aging, and disease, and continue to motivate the exploration of highly diverse downstream impacts resulting from neuroimmune and glial interactions.

Rachel Chau

Investigating Long Non-Coding RNAs as Novel Therapeutic Targets in Alzheimer's Disease

Research Director: **Dr. Anna Krichevsky**

Despite the prevalence and burden of Alzheimer's disease (AD), there is a lack of effective treatments for this neurodegenerative disease. Drug development historically focuses on disease-associated proteins, but RNAs have shown great promise as new therapeutic targets. About 70% of the human genome encodes for non-coding RNAs (ncRNAs) that are not translated into proteins. ncRNAs play critical roles in modulating gene and protein expression at the epigenetic, transcriptional, and post-transcriptional levels, and ncRNA dysregulation has been associated with neurological disorders. Long ncRNAs (lncRNAs) comprise the largest and most diverse class of ncRNAs. However, their physiological functions in the healthy brain and dysfunctions in AD remain unclear. Utilizing publicly available datasets from the Religious Orders Study, the Memory and Aging Project, and the AD Knowledge Portal, we identified candidate lncRNAs differentially expressed between healthy and AD brains and validated their aberrant levels in stressed human cell lines and additional human AD samples with RT-qPCR. We found that a novel transcript, lnc-HPCA-1:1, was significantly upregulated in stressed human cell lines and AD samples. We further determined that lnc-HPCA-1:1 was transcriptionally upregulated in stress conditions. Future experiments include examining the function of lnc-HPCA-1:1 in AD through knockdown and overexpression and potential role as a miR- 501 and let-7a sponge. This research will inform further investigations of lncRNA dysregulation in neurological disease and expand the pool of biomarkers and therapeutic targets in AD, paving the way for new ncRNA technologies to treat neurological disorders.

Drew Cheng

Functional Investigation of Somatic Variants in Pediatric Epilepsy with Single-Cell DNA/RNA Assays from Patient-Derived Lymphocytes

Research Director: **Dr. Chris Walsh**

Genetic diagnosis for epilepsy and other neurological disorders are not optimized to detect somatic mutations, representing a significant unsolved challenge in clinical neurology. The Walsh laboratory has identified candidate somatic variants from the Epi4K consortium, a large cohort of epilepsy trio exomes, using MosaicHunter, a sensitive framework to identify candidate somatic variants. Once somatic variants have been identified and characterized in-silico, their functional and biological consequences must be experimentally validated. Here, we analyze a specific loss-of-function somatic single nucleotide variant (sSNV) in ARHGAP31 to determine its functional effect as a potential novel epilepsy gene. To determine the effect of the variant on ARHGAP31 gene expression, concurrent genotyping and RNA expression analysis of individual patient-derived lymphoblasts were performed using a single-cell workflow with primers for Sanger sequencing and probes for digital droplet PCR (ddPCR). Additionally, we re-analyzed Epi25K, a cohort of exome sequencing data from epilepsy cases and controls, to determine whether ARHGAP31 somatic variants are preferentially present in epilepsy cohorts. We hypothesized that wild-type cells express ARHGAP31 at a higher level than cells carrying the sSNV and report that in a population of 13 patient single-cells expressing ARHGAP31 at the highest level, 100% (13/13) were wild-type genotype (p-value = 0.00005). Additionally, we report several loss-of-function somatic variants in ARHGAP31 in large cohort analysis from Epi25K. Based upon single-cell gene expression data and large epilepsy cohort data, we present evidence for ARHGAP31 as a new epilepsy candidate gene. Clinically, this work is foundational to future efforts to determine additional somatic mutations which may contribute to idiopathic cases of pediatric epilepsy.

Karen Cortina

The Corticospinal Tract and the Evolution of Fine-Motor Skills in Forest and Prairie Deer Mice

Research Director: **Dr. Hopi Hoekstra**

Animals are known to develop habitat-specific adaptations and can do so in a relatively short period of time. One such example is the improved climbing behavior of forest deer mice. However, little is known about the neurological basis that contributes to the morphological differences one can observe. To explore the neural circuitry involved in complex motor behavior, this thesis compares the fine motor skills between two coastal forest-prairie deer mice pairs (American East Coast and West Coast). I began experimentation by developing a restriction method that could effectively train deer mice to participate in behavioral experiments. I found that an individualized food-based restriction using high-calorie pellets was an effective method. I then quantified the dexterity of the mice pairs through a pellet reaching task and found that, although the East Coast forest deer mice are more dexterous than the East Coast prairie mice, the West Coast prairie mice were not more successful than their forest counterparts. Lastly, I compared the CST size of the East Coast mice and found that forest mice had larger CSTs than prairie mice. My results suggest that there is a positive correlation between CST size and the dexterity of deer mice, but that the mice likely did not evolve the arboreal adaptations in parallel. This thesis thus adds to our understanding of the evolution of neural networks involved in complex motor behavior. It also provides a methodological foundation for future behavioral experiments in deer mice.

Evie Coxon

Examining Frontolimbic Connectivity and Childhood Trauma as Predictors of Non-Suicidal Self Injury in a High-Risk Cohort of Children

Research Director: **Dr. Lois Choi-Kain**

Background: Non-Suicidal Self Injury (NSSI) constitutes a significant global health concern. Childhood trauma has been identified as a risk factor for NSSI and associated with reduced patterns of frontolimbic connectivity. This study examines whether alterations to frontolimbic resting-state functional connectivity (rs-FC) are associated with the development of NSSI in a high-risk cohort. Secondly, it investigates whether childhood trauma has any discernible effects on frontolimbic connectivity in individuals with NSSI.

Methods: N = 100 scans were analyzed from a sample of high-risk children in Brazil. The CONN toolbox was used to analyze rs-FC. The Deliberate Self-Harm Inventory (DSHI) and Childhood Maltreatment Assessment were used to measure NSSI and trauma. Between group ROI-to-ROI analysis was performed to characterize patterns of frontolimbic rs-FC. A multivariate F test was conducted to examine effects of childhood trauma and dimensional self-harm (DSHI total score) on brain connectivity.

Results: Findings indicated reduced functional connectivity between left and right orbitofrontal cortices in self-harming individuals, compared to healthy controls. Age, site, and gender had no effect on frontolimbic connectivity in self-harm and control groups. Additionally, there were no significant effects of childhood trauma or dimensional self-harm on frontolimbic connectivity in the self-harm group.

Conclusions: Findings suggest that reduced connectivity within the orbitofrontal cortex may be associated with the development of NSSI in children at high risk for psychopathology. Low endorsement of childhood trauma and a small sample size may account for a lack of further significant findings in this study.

Odessa Deng

Breaking into Song: Neural Activation and Functional Connectivity of Music with and without Vocals

Research Director: **Dr. Psyche Loui**

Pleasurable music listening experiences involve the interaction between auditory and reward systems. Interestingly, humans respond differentially to vocal cues, and recent neuroimaging work has shown selective activation in the superior temporal gyrus for vocal music compared to instrumental music. Less is known about functional connectivity patterns of auditory and reward networks during vocal music listening. In the present study, we compared neural activation and functional connectivity in response to vocal and nonvocal music (i.e. music with and without the human voice). We analyzed a music listening task dataset containing fMRI data from younger adults (N = 33; ages 18-25) and older adults (N = 21; ages 56-89) as they listened to self-selected and researcher-selected music. Whole-brain univariate analyses revealed greater activation in bilateral auditory regions (Heschl's gyrus, superior temporal gyrus, middle temporal gyrus) in response to vocal music compared to nonvocal music. Seed-based and ROI-to-ROI analyses additionally revealed greater within-network functional connectivity of the auditory system during vocal music listening, and greater out-of-network functional connectivity between the reward and auditory systems during nonvocal music listening. These results remained consistent across age and sex. Brain regions that preferentially responded to vocal music did not show sensitivity to emotional valence of lyrics, and remained sensitive to vocal music in English and in other languages as well. Altogether, these results highlight the privileged role of vocal music in the brain, particularly within auditory system activation and within-network functional connectivity patterns.

Udochi Emeghara

Examining the Moderating Impact of Positive Parenting on the Association between Early Life Adversity and Neurodevelopment

Research Director: **Dr. Kate McLaughlin**

A majority of children and adolescents report experiencing early life adversity. Early life adversity or ELA is defined as the occurrence of one or more experiences of threat and/or deprivation during childhood or adolescence. Research highlights the negative impact of ELA on well-being and neurodevelopment- specifically hippocampal volume, amygdala volume, and amygdala function. Yet, there may be protective factors that could facilitate a more normative neurodevelopmental trajectory. This paper explored how one of those factors, positive parenting during childhood, which was categorized by levels of responsiveness, scaffolding, and warmth, could moderate the association of adversity with brain structure and function in adolescence. I hypothesized that higher levels of positive parenting would reduce the associations of ELA, specifically threat, with neurodevelopment. Results for the relationship between adversity and brain measures departed from hypotheses and previous literature for threat but was consistent for deprivation. Similarly, the relationship between adversity and parenting was also insignificant. For the moderator analysis, scaffolding has a moderating effect on the link between threat and amygdala reactivity and a marginal moderating impact on threat and amygdala volume. This is one of the first studies to shed light on how positive parenting inputs can impact the neural pathways of development and how they influence the relationship between ELA and brain metrics. Through this work, more interventions centered on parenting can be created to reduce the effects of ELA.

Eloise Freitag

Exploring the Neurobiological Association between Temperament and Polygenic Risk for Psychopathology

Research Director: **Dr. Chuck Nelson**

Evidence suggests that certain temperament characteristics, such as low effortful control and high negative affectivity, confer risk for later psychopathology. Although genetic risk has been linked to a number of psychiatric conditions, little work has examined the genetic overlap between early temperamental profiles and later mental health outcomes or the variety of neurobiological mechanisms that mediate this relationship. The present study examined associations between polygenic risk scores for anxiety (PRS-Anxiety) and ADHD (PRS-ADHD), frontal asymmetry (FA), and temperament characteristics in a longitudinal sample of children assessed from infancy through age 7 years. Analyses were conducted on two subsamples, a discovery sample (N = 484) and a test sample (N = 122). An age by polygenic risk score interaction effect on negative affectivity and effortful control was observed, such that as children aged, there were stronger positive associations between PRS-Anxiety and negative affectivity and stronger negative associations between PRS-ADHD and effortful control. Results also showed a significant association between FA and temperament such that greater relative left FA was associated with increased effortful control in infancy, and greater relative right FA was associated with increased surgency in infancy and five years old. Overall, the findings suggest shared genetic underpinnings for childhood temperament characteristics and psychopathology.

Catherine Gallori

Two major brainstem outputs for interoception

Hoopes Prize Winner

Research Director: **Dr. Steve Liberles**

Internal sensation allows organisms to monitor the status of internal organs to properly adjust bodily homeostasis. Interoceptive information from many organs is relayed through the vagus nerve to the nucleus of the solitary tract (NTS), which distributes information to a variety of regions brain-wide, generating perceptions of internal space and regulating behavioral and physiological responses. However, the specific logic by which the NTS organizes interoceptive information to regulate functions remains poorly understood. We used a viral-genetic tracing strategy to examine the output logic of the NTS, and identified two major NTS output streams with complementary projection patterns. One stream conveys information primarily to forebrain regions including the paraventricular hypothalamus (NTSàPVH), while the other projects to brainstem nuclei including the ventrolateral medulla (NTSàVLM). Optogenetic activation of NTSàPVH neurons significantly reduced food intake, without significant impacts on motivational valence or broader autonomic physiology. By contrast, optogenetic stimulation of NTSàVLM neurons dramatically reduced food intake, produced strong negative valence, and broadly impacted autonomic physiology, including body temperature, gastric pressure, gastrointestinal motility, and respiration. Our results suggest that NTSàPVH and NTSàVLM populations execute different functions. Further investigation into the specific interoceptive information processed and relayed by these two populations will provide more insight into the precise roles of these different pathways, helping us gain a deeper understanding of the role of the NTS in interoception.

Katie Gao

Reward Network Connectivity Distinguishes Antidepressant Mechanisms of Action in ECT and TMS: A Resting-State fMRI Study

Research Director: **Dr. Joan Campodron**

Electroconvulsive Therapy (ECT) and Transcranial Magnetic Stimulation (TMS) are neuromodulation interventions used to treat major depressive disorder (MDD). Anhedonia is a core diagnostic symptom of MDD, described as the inability to experience pleasure. Previous research shows that ECT and TMS are comparably effective in alleviating depressive symptoms, with some differences in remission and tolerance. However, there is little consensus on ECT and TMS' mechanisms of action, particularly in the domains of anhedonia and reward processing. In this study, we investigated how ECT and TMS influenced anhedonia and reward processing in MDD patients (N=40). Patients with MDD completed pre- and post-treatment assessments, including functional magnetic resonance imaging (fMRI) and clinical measures. Following treatment, ECT and TMS cohorts reported significantly decreased depressive symptoms, reductions in anhedonia, and increased ability to experience reward. Functional connectivity within and between reward, dorsal attention, and ventral attention networks did not change significantly before and after treatment for ECT and TMS cohorts. For the ECT cohort alone, however, linear regression analysis demonstrated significant correlations between baseline functional connectivity and symptoms of anhedonia. Finally, graph theory analyses showed that only ECT modulated connectomics measures of clustering coefficient, eigenvector centrality, and page rank centrality in reward-related regions of interest (ROIs). Altogether, these results preliminarily indicate that ECT and TMS may operate through different mechanisms of action, which warrants future between-group analysis. These findings help to elucidate clinical and mechanistic differences between ECT and TMS that can inform clinical decision-making in MDD treatment.

Ilai Gavish

Less Than Reckless: Assessing the Role of Consciousness in the Moral Appraisal of Risky Action

Research Director: **Dr. Gabriel Kreiman**

The law typically defines criminal recklessness as having conscious awareness of an unjustifiable risk of harm and choosing to act despite this risk. This thesis investigates the validity of this requirement of conscious awareness using the methods of both neuroscience and philosophy. First, I conducted an electroencephalography (EEG) experiment in which subjects were presented with a binary choice wherein one of the options was sometimes preceded by a stimulus signaling risk of harm to a future participant. This risk-stimulus was presented either consciously or subliminally using a metacontrast masking paradigm. In some analyses, electrical activity at the midline central (Cz) electrode showed a significantly greater post-choice P300 amplitude for risky trials than for trials without a signal of risk, and there was significant interaction with the conscious/unconscious presentation of the stimulus as well as with the strategy employed by the participant. These preliminary results suggest that there is a detectable difference in neural activity between conscious versus unconscious processing of risk. This neuroscientific experiment is supplemented by a broader philosophical discussion of the relationship between consciousness and moral responsibility. I argue that volitionalism, which requires conscious awareness for blameworthiness, prevails over consciousness-optional views on theoretical grounds, and I rebut a set of anti-volitionalist moral intuitions by introducing a distinction between the concepts of responsibility and ownership. In combination, the neuroscience and philosophy research helps to validate both that there is a distinction between conscious and unconscious representation of risk and that this difference is morally meaningful.

Ream Gebrekidan

Validation of OCT for the Imaging of Infant Brainstems: A Step in the Study of SIDS

Research Director: **Dr. Lilla Zollei**

Sudden infant death syndrome (SIDS) remains a leading cause of neonatal infant death in the US (Ely and Driscoll, 2022). However, very little is known about the underlying physiological risk factors that can hinder autonomic responses and lead to SIDS. It has been theorized that disruptions in brainstem structures such as in the ascending arousal network can prevent proper autonomic responses and increase the risk of SIDS, however, this theory is yet to be confirmed. This is in large part due to the difficulty of studying infant brainstems. To better investigate infant brainstems, we have utilized optical coherence tomography (OCT). OCT has the potential to take high-resolution images prior to the slicing of brain tissue, allowing for the preservation of 3-dimensional structure while imaging. However, it has not been tested and validated in infant/unmyelinated tissue. In this project, we have investigated the validity of OCT as an imaging technique for infant brainstem tissue in comparison to histology, the current gold standard. Through a comparison of manually segmented images of both OCT and histology data, we demonstrate the potential of OCT as an imaging technique that reliably provides the contrast needed to segment infant brainstem regions. Thus, through the use of OCT, we have the potential to investigate differences in brainstem anatomy that can increase the risk of SIDS, getting one step closer to understanding and finding ways to prevent this tragic syndrome.

Rahul Guda

Genomic Characterization of Genetically Engineered Mouse Model Derived BALB/c Cell Lines for Glioblastoma, Implications for Efficacy of Oncolytic Virus Immunotherapies

Research Director: **Dr. Antonio Chiocca**

Glioblastoma (GBM) presents as the most aggressive form of primary brain tumors. Oncolytic viruses (OVs) represent an emerging class of GBM immunotherapies. Presently however, there remains significant gaps in our understanding of OVs, including their efficacy for viral infection and viral replication in GBM cells. Moreover, the best model for mimicking GBM conditions observed in clinical trials is unclear. Genetically Engineered Mouse Model (GEMM) derived BALB/c cell lines are currently being explored as one such viable model. Hence, this thesis aimed to (1) characterize the BALB/c cell lines 1620 and 1694 through Whole Exome Sequencing and confocal microscopy (2) elucidate potential mechanisms of action of OVs via genomic pathway analysis and variant mapping, and (3) evaluate their permissiveness to viral infection and replication of OVs using GFP labeling and flow cytometry. Whole Exome Sequencing revealed a greater degree of genomic instability in 1694 than in 1620. Confocal microscopy showed that both cell lines express Nestin, the promoter utilized by the OV rQNestin34.5v1 to initiate viral transcription. GFP expression in BALB/c cells increased as OV treatment concentration increased and was overall greater in 1694 than in 1620. These results were validated by flow cytometry, as 1620 showed an infection rate of approximately 30%, while 1694 showed an infection rate of approximately 80% at the same concentration (MOI .25). Together, these results support the feasibility of OVs as a GBM immunotherapy, alongside the viability of BALB/c cell lines as accurate models for GBM as it presents itself in patients.

Cade Herrera

Eternal Sunshine of the Spotless Mind: A Longitudinal fMRI Study on the Efficacy Of Mindfulness Training to Offset Age-Related Cognitive Decline

Research Director: **Dr. Sara Lazar**

A healthy memory is essential for maintaining one's wellbeing. Memory impacts all aspects of day-to-day life, from the execution of essential daily tasks to the formation and maintenance of social relationships. Given the national increased life expectancy, identifying interventions to slow down or reverse cognitive decline has become of great interest in research and a priority in public health. Mindfulness meditation practice may be an alternative method for promoting cognitive function and slowing the normal age-related decline of neural structure and function. This thesis assesses the effects of mindfulness meditation using a longitudinal study design with an active control. To test this, we administered a validated memory task while conducting an fMRI brain scan, then searched for behavioral group-by-time interactions in memory scores, as well as differences in activation and connectivity in and between regions of interest. To our knowledge, this is the first study to include a 12-month functional imaging follow-up study on the benefits of mindfulness meditation in aging populations. The meditation group showed increased memory scores after one year. Further, this thesis shows mindfulness-mediated increases in hippocampal activation and key nodes of the default mode network. The connectivity analysis showed increases between the hippocampus and the default mode network connectivity, interhemispheric hippocampal connectivity, and a prominent increase in a minor memory network in the meditation group. This thesis provides sufficient novel evidence that long-term mindfulness meditation provides cognitive benefits and contributes to the maintenance of episodic memory in advanced age.

Shifa Hossain

Investigating the Dynamics of Cell Death and Cell Proliferation in Dorsal Root Ganglia of Axolotls during Peripheral Nerve Regeneration

Research Director: **Dr. Jessica Whited**

Peripheral nerve injuries (PNI) arise from various trauma accidents, such as sports, motor vehicle accidents, gunshot wounds, and even during birth. Unlike other specialized organ systems, the peripheral nervous system has some regenerative capacity in humans. However, it is limited depending on factors such as age, degree of PNI, and location of the injury. To explore the repair of PNI, we utilized axolotls, highly regenerative salamanders, as a complement to the regeneration of PNI in mammalian studies. Given its ability to completely regenerate its limb and attain functional recovery, we hypothesized that axolotls have an enhanced nerve repair mechanism compared to mammals. To investigate peripheral nerve regeneration, we specifically targeted the brachial plexus nerves, which innervate the forelimbs and provide sensory and motor function. Transection of the brachial plexus leads to a loss of function. Here, we hypothesize that cell death pathways are active and even support nerve regeneration through their dynamic relation with cell proliferation. To characterize peripheral nerve regeneration, we applied single and repeated transections at the brachial plexus nerves and collected the dorsal root ganglia (DRG) across time points throughout nerve regeneration. Then, we explored our hypothesis by applying immunohistochemistry stains to mark cells undergoing apoptosis and to tag cells undergoing proliferation. Next, these DRG samples were quantified and analyzed, where we observed a significant upregulation in proliferation, but cell death was nonsignificant across all timepoints. This concluded that during peripheral nerve regeneration, DRGs undergo apoptosis but not at significant rates as proliferation.

Miyu Imai

Individuality in Phototactic Preference in Tethered Adult Drosophila melanogaster

Research Director: **Dr. Ben de Bivort**

Individuals, even when inbred and raised in similar environments, have variable behaviors. However, the mechanistic underpinnings of individuality remain poorly understood. Drosophila melanogaster is a useful model system for studying individuality, as flies have short lifespans and thus can be raised very quickly, and they are small/easy to handle, allowing us to collect behaviors for many individuals. Genetically similar flies raised in the same environments display individual variability in behaviors such as turn bias, temperature difference, olfaction, and other behaviors. This thesis set out to identify signals of individuality in tethered flies walking on a ball, which is a paradigm that is especially useful for the simultaneous measurement of circuit activity and walking behavior. I built a fly-on-a-ball setup that yields robust walking behavior and includes a visual assay that I use to analyze choices flies make when faced with boundaries between lights on and lights off. My experiments showed that individual flies display variable behavioral preferences in response to light stimuli and that the extent of variation exceeds that of blind control flies that do not perceive differences between lights on and off. I calculated several different light preference metrics and found significant signs of individuality by comparing these scores. Establishing individuality in this tethered setting will aid future investigations that measure calcium activity with behaviors simultaneously.

Autumn Johnson
Touch as a Key Regulator of Social Need
Hoopes Prize Winner
Research Director: **Dr. Catherine Dulac**

Social interaction is essential to the well-being and survival of both humans and animals. Lack of social activity during periods of isolation effectively enhances the motivational drive for social interactions as revealed by an observable rebound in social contacts once animals are reunited after isolation. This raises the question of how do animals know they are “together” or “alone”? Until now, the sensory contribution to the emergence and fulfilment of social drive has been unclear. Our preliminary data showed that isolated mice with access to visual, auditory, pheromonal, and olfactory cues from other cage mates can still develop a significant social rebound after isolation, suggesting that a different sensory modality such as touch may play a role in informing animals of social encounters and in turn in modulating social drive.

In this study, we measured touch seeking behaviors in mice and found that social isolation increases gentle touch seeking following social isolation. Moreover, genetic ablation of touch sensory neurons leads to attenuated social response to isolation, and acute pharmacological inhibition of touch sensation slows down social satiation during reunion. Finally, providing comforting touch during isolation reduces subsequent social rebound. Together these results support that animal-animal somatosensory contact is a critical regulator of internal social drive. Perhaps the importance of touch in social interaction explains why no Zoom call can measure up to the embrace of a loved one.

Maria Kaltchenko

Maternal Exogenous Oxytocin Administration and the Enduring Effects of Birth Manipulations on the Fetal Brain

Research Director: **Dr. Marcy Kingsbury**

The hormone oxytocin (OT), a pleiotropic mammalian neuropeptide that coordinates various aspects of social behavior and reproduction, facilitates the delivery process by stimulating uterine contractions, and it is widely administered in hospitals to induce or augment labor. OT is generally thought of as a neuroprotective hormone, particularly during stressors such as the major physiological stress of birth. Previous research has found that perinatal stressors may contribute to aberrant behaviors such as those observed in autism spectrum disorder (ASD). While endogenous OT is protective for the fetal brain, the long-term effects of maternal exogenous OT administration at birth on offspring are poorly understood. Here, we model induction of labor with high-dose OT to investigate the effects of maternal OT administration on the prairie vole brain at adolescence, conducting behavioral assays at postnatal days 24-28 and analyzing brain oxidative stress levels via an aconitase assay at postnatal day 29. We find that female offspring exhibit lower levels of oxidative stress at every maternal treatment level as compared to their male counterparts. In females alone, maternal administration of OT reduces oxidative stress levels as compared to the no treatment control, establishing a sexually dimorphic difference in the neuroprotective effects of exogenous OT administration. Behavioral data reveal that the saline injection acts as a stressor and not as a benign control in males with resulting behavioral deficits, which high OT treatment rescues. Increased aggression against an unrelated pup in high-OT females in the alloparental care assay supports the social salience hypothesis of OT.

Christine Lee

Systemic Inequity and Structural Integrity: A Neuroimaging Investigation of Socioeconomic Status and Brain Development in Adolescents

Research Director: **Dr. Anastasia Yendiki**

The Adolescent Brain Cognitive Development (ABCD) Study is the largest longitudinal study of early adolescent brain development in the United States. The ABCD dataset tracks trajectories of neuroanatomical change throughout adolescence in nearly 12,000 adolescent subjects across the country, collecting data on both the biological and behavioral development of the subjects into adulthood. This work utilizes the latest qualitative and quantitative ABCD data to examine influences of critical socioeconomic status (SES) factors on adolescent brain development as measured by diffusion tensor imaging data. SES characterizes the combined sociological and economic measures of an individual's social position and access to resources, including metrics such as combined family income and area deprivation indices. Symmetrized percent changes in diffusion imaging metrics of fractional anisotropy (FA) and mean diffusivity (MD) over a two-year period are used to characterize the relationship between white matter maturation and socioeconomic indicators. Statistical analyses of these associations are performed with a general linear model (GLM) framework over a Linux-based brain imaging software. Significant differences in rate of change of FA and MD among children from varying socioeconomic resource deprivation areas and varying combined family incomes emerge across the corpus callosum, left inferior fronto-occipital fasciculus, right and left uncinate, right and left fornix, and the right and left superior longitudinal fasciculi. These findings will open further avenues for policy-related research to promote economic resource equity and accessibility to adolescents on a systemic level.

Nadine Lee

Modeling Temporal Lobe Epilepsy through Prime Editing of RAS-MAPK Variants

Research Director: **Dr. Chris Walsh**

Temporal lobe epilepsy (TLE) is one of the most common types of epilepsy and is frequently resistant to treatments, leaving many patients with little choice except to undergo surgery. The RAS-MAPK pathway has been reported to be dysregulated in cancer, and it is closely connected to the misregulation of protein expression at synapses in epilepsy. Prior work from Dr. Khoshkhoo and Walsh identified pathogenic somatic variants in the hippocampus surgically resected from patients with drug-resistant TLE, all of which were predicted to activate RAS-MAPK signaling. Notably, many of these somatic variants were in the PTPN11 gene, but the molecular mechanisms of how variants in this gene give rise to epilepsy remain unresolved. To explore PTPN11 variants and their effects within TLE, we attempted to first create a model of PTPN11 mosaicism with admixed mutant and wild type cells through prime-editing (PE). For this thesis, two variants were specifically chosen due to their recurrence in TLE, p.G503R and p.N308D. Given the constraints of the specific genomic loci, 4 guides were each designed for p.N308D and p.G503R. These guides were cloned into the PE constructs available from Anzalone et al. and then tested in the HEK 293T cell line. Amplicon sequencing performed on the DNA derived from edited cells, did not identify the desired edits, suggesting likely guide failure which can be common in PE experiments due to the high precision of the technique. The methodological framework developed as part of this thesis, however, will be implemented in future rounds of experimentation until the desired outcome is achieved.

Rick Lee

Identifying long noncoding RNAs as regulators of genes associated with autism spectrum disorder

Research Director: **Dr. Chris Walsh**

Autism spectrum disorder (ASD) is a heritable neurodevelopmental disorder affecting approximately 1 in 54 children in the United States. While many studies have identified variants in protein-coding genes that are associated with ASD, noncoding genes have not been studied to the same extent. This paucity of research applies to long noncoding RNAs (lncRNAs), which are noncoding transcripts that are longer than 200 nucleotides, despite evidence of their relevance to neurodevelopment. Thus, we conducted an array of knockdown experiments to identify lncRNAs that may regulate ASD-associated genes. We first prioritized 20 lncRNA candidates based on evidence of their differential expression in ASD brains and the function of their nearby ASD- associated protein-coding genes, because lncRNAs have often been found to regulate closely neighboring genes. Subsequently, we knocked down our 20 pairs of lncRNA candidates and their nearby ASD-associated genes using the CRISPR-Cas13d system in human induced pluripotent stem cell (hiPSC)-derived neural progenitor cells. We then performed bulk RNA sequencing and differentially expressed gene analysis. Finally, we performed a proliferation assay to understand their functional significance. 3 of 6 lncRNAs whose knockdown efficiencies were greater than 50% led to decreased expression of their neighboring ASD-associated genes. Moreover, 9 of 11 lncRNAs whose knockdown efficiencies were greater than 20% led to significant enrichment for differentially expressed ASD-associated genes. Functionally, KMT2E-AS1 and ASH1L-AS1 knockdowns significantly decreased proliferation and led to enrichment for differentially expressed genes associated with mitosis. This project establishes an effective analytic framework to study lncRNAs and offers foundational knowledge about promising lncRNAs that may contribute to ASD.

Soo Lee

Investigating the Relation Between Infant Functional Connectivity and Child Internalizing Behavior

Research Director: **Dr. Chuck Nelson**

Specific functional brain networks have been associated with distinct domains of psychopathology, including depression and anxiety. However, little is known about the developmental origins of these brain-behavior associations. Furthermore, maternal depression has been associated with child psychopathology, but how infant functional connectivity may moderate or mediate this relation has not been studied. The current study examined the link between functional connectivity in infants and 5-year emotional and behavioral outcomes (N = 91; M [age] = 8.62 months). Specifically, we measured resting-state functional connectivity in three major functional networks – homologous-interhemispheric connections, frontoparietal network, and default mode network – using functional Near Infrared Spectroscopy. Our results show that functional connectivity in the networks can be detected from as early as infancy. Furthermore, homologous-interhemispheric connections were positively associated with later 5- year internalizing symptoms (B = 6.75, SE = 2.93, p = .023). The default mode network was also associated with stress (B = 0.91, SE = 0.47, p = .05), a subscale of internalizing symptoms, but the frontoparietal network did not exhibit significant associations. Contrary to my hypotheses, infant functional connectivity did not moderate or mediate the relation between maternal depression in infancy and 5-year internalizing symptoms. These findings further our understanding of the development of functional brain networks and help identify potential risk markers for internalizing problems, which may inform early intervention efforts.

Shaked Leibovitz

Overcoming Fear-Neuroadaptive Changes Following Mindfulness Training Enhance Fear Extinction Learning

Research Director: **Dr. Sara Lazar**

The ability to extinguish a maladaptive conditioned fear response is crucial for healthy emotional processing and resiliency to aversive experiences. Therefore, enhancing fear extinction learning has immense potential emotional and health benefits. Mindfulness training enhances both fear conditioning and recall of extinguished fear; however, its effects on fear extinction learning are unknown. Here we investigated mindfulness training's capacity to enhance brain mechanisms associated with fear-extinction learning. We investigated blood- oxygenation-level-dependent (BOLD) activations in response to a previously learned fear-inducing cue during an extinction paradigm, before and after an 8-week mindfulness-based stress reduction program (MBSR, n=42) or exercise-based stress management education program (SME, n=27). The MBSR group was uniquely associated with neuroadaptive changes, including enhanced activation of salience network nodes, and increased hippocampal engagement which was correlated with increased gray matter volume of the presubiculum. In addition, we investigated dynamic functional connectivity changes in the hippocampus and amygdala during stages of extinction learning, which facilitate the rapid response necessary to adapt to changes in threat signals. In the MBSR group, the amygdala increased functional connectivity with the somatosensory cortex during early extinction, implying increased interoceptive attention; and the hippocampus increased functional connectivity with the precuneus during late extinction, supporting reconsolidation and strengthening of the extinction memory during learning. Our results suggest that mindfulness training increases attention to anticipatory aversive stimuli and enhances reappraisal of the extinction memory which can support the development of resiliency to aversive experiences and potentially improve mental health and well-being.

Vivian Li

Evidence for a Reduced Neural Capacity in Children with Attention Deficit Hyperactivity Disorder

Research Director: **Dr. Anne Arnett**

Electroencephalography (EEG) studies have consistently reported reductions in P3a and P3b amplitudes in children with attention deficit hyperactivity disorder (ADHD) compared to typically-developing (TD) children. The present thesis examined whether these reduced amplitudes could be explained by two competing hypotheses: a decreased neural capacity versus an inefficient allocation of neural resources. The primary objectives were to (1) identify differences in P3a and P3b amplitudes between groups across task difficulty and stimulus relevance, and (2) determine which hypothesis better explains these amplitude reductions. 7-11 year-old children diagnosed with ADHD (n = 78) and TD children (n = 28) completed EEG recordings for an easy and hard task. Linear mixed effects models were conducted with a random intercept, and age, sex, and IQ as covariates. Significant differences in novel P3a and both novel and target P3b amplitudes were found between groups across task difficulty. Regarding the second objective, novel P3a and target P3b amplitudes for TD children did not significantly differ between tasks. However, both novel P3a and target P3b amplitudes for children with ADHD significantly decreased during the hard task. This present work found evidence supporting the reduced capacity hypothesis. Compared to the TD group, when task difficulty increased, the ADHD group did not appear to have extra neural capacity to give to either the task-irrelevant novel nor the task-relevant target stimuli. Ultimately, additional research is necessary to understand the etiology of reduced P3 amplitudes in children with ADHD and progress towards the utilization of ERP biomarkers to supplement ADHD diagnoses.

Sophia Liang

Trying Times: Assessing the Psychiatric Impact of the COVID-19 Pandemic in Recent Trauma Survivors

Research Director: **Dr. Nathaniel Harnett**

Recent studies demonstrate that the COVID-19 pandemic contributed to an increase in symptoms of psychiatric illness worldwide. Pandemic stressors may pose a greater risk to individuals with recent exposure to a traumatic event, as well as women and ethnoracially minoritized individuals. However, the full mental health impact of the pandemic is not yet fully understood. Using data collected from the national Advancing Understanding of RecOvery afteR traumA (AURORA) study, we investigated the pandemic's effects on symptoms of PTSD, depression, and anxiety, as well as the reward-related brain circuitry, among recent trauma survivors. We examined how individual risk factors, gender, and ethnoracial status moderate outcomes in the one year post-trauma. Mixed-measures ANOVAs showed no significant difference between pre- and peri-pandemic participants' symptoms of PTSD, depression, or anxiety. Although women experienced greater symptoms than men, and symptoms significantly differed between certain ethnoracial groups, these trends were not dependent on the pandemic. Voxel-wise analyses of fMRI data did not meet the cluster-forming threshold. Uncorrected results indicated the peri-pandemic cohort exhibited decreased reward reactivity in the dorsomedial prefrontal cortex. Independent of the pandemic, women exhibited greater reward reactivity compared to men, and Hispanic and non-Hispanic Other participants exhibited greater reward reactivity compared to white participants in certain brain regions. We concluded that participants' mental health may have been slightly impacted by the pandemic overall, but there is considerable heterogeneity across individuals with different backgrounds and experiences. Greater attention toward individualized risk factors is needed to better direct mental health resources to those most impacted.

Nathaniel Liberman

Feature-Conditional Probing of Human Neural Data and Artificial Natural Language Models

Research Director: **Dr. Josh Greene**

Natural language comprehension is a relatively easy task for humans, yet the mechanisms by which we process language are not well understood. A common theory is that neural processing of language involves creating representations of semantic and syntactic components of language–words and their grammatical relations – and composing them into phrase meanings. In this study, we examined the neural processing of parts of speech–an important linguistic feature–with a machine learner used for natural language processing (NLP) serving as our model of the brain. We found the representational subspace of the machine learning model that maximally separated part-of-speech (POS) classes by using rank-reduced linear discriminant analysis (LDA). We then fit a linear regression from the dimensionally reduced word embeddings of the model onto the neural response to the same words in the same context recorded using stereo-electroencephalography (sEEG) and calculated correlations as a measure of similarity between model and brain representations. We found that these correlations were lower than those reported for machine learner word embeddings that were not similarly reduced, but significant correlations could still be found within the neural language network. Our results support the conclusion that higher-level semantic or word identity information is represented similarly in the brain and NLP models, whereas syntactic features are not. However, more research will be needed to rule out other explanations of the data, and this study offers future directions of inquiry with a novel, task-conditional approach to comparing neural and artificial language processing.

Mariam Markabani

Development of the Brain-Heart Sensory Feedback: The emergence of cardiac encoding neurons in larval zebrafish vagal sensory ganglia

Research Director: **Dr. Florian Engert**

Interoception is a fundamental concept in neuroscience that aims to disclose how the brain senses changes in the body's internal state. The vagal sensory ganglion plays a significant role in interoception by serving as a potential mediator between the brain and the heart - the only two electrical organs in the human body. Given that the zebrafish heart is an effective model for studying human cardiovascular function, we created different transgenic lines (VGLUT(2a)- GAL4 x UAS-GCAMP6s, HuC-H2B-GCAMP7, Phox2b-GFP) that allow us to locate vagal sensory neurons in intact, living zebrafish models in vivo. By introducing different stimuli that stimulate spontaneous activity in transgenic larval zebrafish, we identify, classify, and quantify the number of neurons that encode for cardiac activity using a laser-scanning confocal microscope. Fluorescent transgenic zebrafish were also used to assess the anatomical development of the vagal sensory ganglia, which revealed the onset of the heart (sensory) innervation at 7 dpf. Although the primary function of the vagal sensory ganglia is responsible for relaying sensory information to the brain on the internal states of visceral organs like the heart, we found that this superganglion complex is comprised of vast neuronal subtypes, which include 1) HR-tracking neurons, 2) Delayed HR-tracking, and 4) Anti-correlated HR-tracking neurons.

Rio McLellan

Targeting Proteostasis Machinery in the Brain Vasculature to Treat Neurodegenerative Disease

Hoopes Prize & Dowling Award Winner

Research Director: **Dr. Lee Rubin**

Aging is the largest risk factor for late onset neurodegenerative diseases. Using experimental models of heterochronic parabiosis, the surgical joining of young and old mice, seminal studies from our lab demonstrated it is possible to reverse some negative effects of brain aging. To gain insight into the aging reversal process, our lab profiled transcriptional changes occurring throughout the mouse brain during aging and parabiosis. Among the many aging- affected processes, protein homeostasis (proteostasis) was among the most notable. We identified several heat shock proteins (HSPs) which were elevated with age and reduced via parabiosis in brain endothelial cells (BECs) of the blood-brain-barrier. Given chaperone expression generally declines with aging, we were curious as to why these select chaperones exhibited robust upregulation in these critical barrier cells. To investigate this, we overexpressed the most differentially expressed HSP (Hspa1a) in young mouse primary BECs to levels comparable in aged mouse BECs finding that Hspa1a upregulation significantly enriched several functional pathways related to protein degradation. We hypothesized that aged BECs upregulate HSPs as a protective mechanism to limit aging-associated protein aggregate formation. To test this hypothesis, we differentiated human induced pluripotent stem cells genetically engineered to contain a pathogenic Alzheimer's disease mutation into BEC-like cells and utilized lentiviral constructs to globally inhibit or activate the heat shock response via an engineered HSF1 moiety, the master transcription factor regulating downstream HSP expression. As hypothesized, downregulation of HSF1 increased protein aggregates and decreased cellular viability rendering HSPs in the vasculature as potential therapeutic targets for neurodegeneration.

David Melville

Exploring the Presence and Function of C1q within Neurons Across Aging

Research Director: **Dr. Beth Stevens**

The complement system is a large family of proteins traditionally known for conducting signaling cascades that elicit various immune responses upon activation. Several complement components, including C1q and C3, have been shown to play functional roles in critical nervous system processes such as tagging synapses for microglial-mediated pruning. Past work has largely described the extracellular activity of complement molecules in the nervous system. In this study, we show there to be significant levels of C1q within neurons that are detectable through immunohistochemistry. In addition to identifying C1q's presence, we demonstrate that this novel C1q signal is derived from microglia using cell specific C1q deletion. Furthermore, we demonstrate the intensity of C1q's intracellular signal to be dependent on both postnatal age and tissue pretreatment with RNase. Following the characterization of this novel signal, we explore potential functional roles of internalized C1q by investigating its unique biochemical traits. From these experiments, we confirmed the ability of C1q to undergo liquid-liquid phase separation (LLPS) in the presence of total brain RNA using a live-imaging assay. We also established these condensates to have a striking sensitivity to RNase. Beyond this assay, we demonstrate C1q to associate with polysomes isolated from brain tissue, suggesting potential functional roles of C1q with RNA and its associated translational machinery within neurons.

Keilina Monteiro do Canto

Studying the Relationship Between Neuropeptides Regulating Stress and Anxiety Circuitry in the Bed Nucleus of the Stria Terminalis: An Investigation Through the Pathology of Post-Traumatic Stress Disorder

Research Director: **Dr. Sabina Berretta**

Post-traumatic stress disorder (PTSD) is a severe anxiety disorder affecting approximately 10% of persons exposed to traumatic events. Altered responses to threat and stimuli associated with the initial traumatic event can lead to re-experiencing traumatic emotions. Growing evidence indicates that neural circuitry processing fear responses and stress is dysregulated, with expression and functions of several neuro-modulatory peptides having been found to be altered. Among these, the pituitary adenylate cyclase-activating polypeptide (PACAP) plays a key role in plasticity, stress response, and anxiety, and PACAP signaling is thought to regulate neurons expressing corticotropin-releasing hormone (CRH), which plays a fundamental role in coordination of peripheral and central responses to stress. Little is known on the cell-level expression signaling pathways of these proteins, specifically within the bed nucleus of the stria terminalis (BNST) in PTSD. Various neuroimaging studies have shown an increased level of BNST activation in healthy human brains as a result of stressful stimuli, illustrating the importance of the BNST in the consolidation of fear memories. We investigated the relationship between PACAP and CRH pathways using RNAScope, an in-situ hybridization technique that uses probes specific to these proteins. We hypothesized that our data would indicate altered PACAP and CRH positive pathways in the BNST in postmortem brain samples in individuals with PTSD as opposed to healthy human controls. Studying these changes may help us in furthering our understanding of PTSD and psychiatric anxiety disorders.

Siofra Murdoch

Toward Therapeutic Control of Circadian Rhythms: Optimisation of Pharmaceutical Administration Models for Circadian Entrainment via Nonlinear Model Predictive Control

Research Director: **Dr. Frank Doyle**

The ability to shift circadian phase in vivo has the potential to offer substantial health benefits, and constructing an appropriate model — from therapeutic administration to phase response—will enable this possibility. The blood-brain barrier (BBB), however, prevents the absorption of essentially all large and many small molecules, posing a challenge to neurological pharmaceutical development. Motivated by the presence of the circadian molecule KL001, which is capable of causing phase shifts in a circadian oscillator, this work explores the effect of two passive and three active transport mechanisms on the dynamics of circadian phase. Specifically, this thesis investigates the effect of melatonin, which passively diffuses across the BBB, triiodothyronine (T3), amine, and neutral amino acid carrier mediated transport (CMT), and polymeric nanoparticle adsorptive transcytosis administration mechanics. The pharmacokinetic/pharmacodynamic (PK/PD) modeling approach has been considered to describe the physiological dynamic behavior in response to such delivery mechanisms and provides an accurate estimate of the cerebrospinal fluid (CSF) concentration curves. The introduction of the PK/PD models achieves a physiologically accurate prediction of the phase response curve of the circadian oscillator and informs a constrained, infinitesimal parametric phase response curve (ipPRC)-defined, nonlinear model predictive controller (MPC) to compute appropriate dosing for clock re-entrainment. The phase-resetting capacity of these models is investigated through the real-world scenario of jet lag.

Sam Murdock

Theories of Theory of Mind: Investigating the Dimensions and Supportive Neural Architecture of the "Mentalizing Module"

Research Director: **Dr. Randy Buckner**

Many psychologists and neuroscientists have looked for empirical evidence to illuminate the “structure” that underlies cognition, while many philosophers of mind and computer scientists have approached the question using formal logic and theoretical models. In this thesis, methods from all these disciplines were synthesized to provide a comprehensive analysis of a candidate mental module: that which supports cognition for theory of mind. Using data from two tasks that involve cognizing about others’ mental states – the False Belief task and the Other Pain task – we conducted two experiments to investigate the behavioral dimensions and neural correlates of theory-of-mind-related cognition. In experiment one, we examined the domain of the theory of mind tasks with trial-level data from behavioral participants who identified cognitive strategies used during task performance. In experiment two, these strategies were correlated with trial-level functional magnetic resonance imaging (fMRI) data from different participants completing the same theory of mind tasks. This revealed that strategies related to Social Inference and Mind Attribution were most strongly and selectively predictive of activity in Default Network B (DN-B), a network in the association cortex that has been previously associated with theory of mind tasks. Further examination also revealed that some strategies were highly related to task condition and exhibited modified relationships with networks when conditions were analyzed separately. This investigation provides strong evidence for high domain-specificity in DN-B recruitment that is linked to task context, indicating that the network may support a functional module selectively involved in cognition of others’ mental states.

Ezechukwu Nduka

Posttranslational Modifications of α-Tubulin in Axons of Dorsal Root Ganglion Neurons

Research Director: **Dr. Roz Segal**

Dorsal root ganglion (DRG) cells are sensory neurons that are integral in the body's reception of pain. These cells are unique because of their pseudo-unipolar morphology where a short axon stem protrudes from the cell body and is then divided into two distinct axons. The peripheral axon (PA) extends towards the skin and forms multiple branches to innervate it. The central axon (CA) extends towards the spinal cord and forms synapses on secondary neurons in the dorsal horn of the spinal cord. These axons require microtubule-based transport where kinesin motors serve to transport materials along microtubules towards the distal end of axons and dynein motors serve to transport materials back to the soma. Tubulin, the protein that forms microtubules, goes through several different posttranslational modifications (PTMs) that determine the properties of microtubules in a "tubulin code". For example, acetylation of tubulin is associated with the stabilization of microtubules and microtubule polarity, while other tubulin PTMs, such as polyglutamylation, have been shown to affect the binding of microtubule-associated proteins. We hypothesize the anterograde transport of kinesin motors preferentially travel to the peripheral axon versus the central axon at the point of bifurcation in the DRG axon stem based on different levels of tubulin PTMs, specifically tubulin acetylation, polyglutamylation, and tyrosination, between the two axons. We also hypothesize that mutations in the forward and reverse enzymes that catalyze tubulin PTMs negatively impact axon-specific sorting and nociception. To accomplish this, we performed immunohistochemistry on tissue slices of mouse DRG neurons to stain for all three PTMs along with β3-tubulin, which is a β-tubulin isotype that is almost solely expressed in neuronal microtubules. We also stained these tissues for Nav1.8, which we used as a marker for nociceptors since it is a voltage-gated sodium channel that is expressed in sensory neurons.

Jennifer Near

Associations Between Caregiver Depression, Caregiver-Child Play Interactions, and Early Childhood Social Information Processing: An fNIRS Investigation

Research Director: **Dr. Chuck Nelson**

Caregivers experiencing symptoms of depression – and similar expressions of emotional distress or low mood – exhibit significantly higher levels of disengaged and negative parenting behaviors than non-depressed caregivers. Quality of caregiving, along with the caregiver-child relationship, all influence a child's brain and behavioral development; however, many of the underlying mechanisms of how this neurobiological embedding takes place remain elusive. The current study aims to explore the mechanisms determining deficits in the neural underpinnings of children's social information processing due to compromised caregiver-child relationships. In this study, we used functional near-infrared spectroscopy (fNIRS) to assess neural responses to social and nonsocial stimuli in 2-year-old Bangladeshi children. Additionally, free-play sessions involving the caregiver and child were observed and coded for factors such as caregiver sensitivity, intrusiveness, and detachment. We evaluated the associations among the neural correlates of social information processing over the inferior frontal to posterior temporal cortices, caregiver-child interactions, and markers of caregiver depression assessed using the Childhood Psychosocial Adversity Scale (CPAS) via a proposed mediation model. Consistent with previous work, social discrimination to visual and auditory stimuli was observed over the inferior frontal and posterior temporal cortices. While no mediation was observed, findings suggest that further research centered on elucidating the relationships between caregiver depression and childhood socio-cognitive development in LMICs is warranted, in order to begin developing targeted interventions that mitigate the risks of childhood exposure to caregiver depression.

Iqra Noor

Many Facets of Language Impairment: Exploring Learning Abilities in Individuals with Aphasia

Research Director: **Dr. Sofia Vallila-Rohter**

Aim: To better characterize learning in aphasia, the current study explores observational implicit learning ability in individuals with aphasia by examining how it is reflected in one's behavioral responses and neural connectivity of networks associated with learning. Method: 15 individuals with aphasia completed several cognitive-linguistic assessments which determined the type and severity of aphasia. Observational (implicit) learning was evaluated using the Serial Response Time (SRT), with eye-tracking programming and Artificial Grammar Learning (AGL) tasks. Reaction times (RTs) and implicit rule learning were examined and compared to classify each participant as having impaired implicit learning ability or not. Three participants also underwent a magnetic resonance imaging (MRI) scan, and resting state functional MRI (rs-fMRI) data was collected to examine the neural connectivity of networks associated with implicit learning for each subject and the potential relationship between connectivity and learning ability and, as a consequence, on their response to different aphasia treatments. Results: this study showed differences in learning profiles across people with aphasia, which was not completely attributed to the structural brain damage and was further examined through resting-state functional connectivity data which revealed variability among participants in their functional architecture of the selected regions and networks.

Abby Obeng-Marnu

Investigating the Effects of Sex and Bedding and Nesting Conditions on Communicative and Social Behaviors in Mouse Models of Autism Spectrum Disorder

Research Director: **Dr. Evan Bordt**

Autism Spectrum Disorder (ASD) is a collection of complex neurodevelopmental disorders characterized by alterations in social interactions, communication, and repetitive behaviors. ASD is heavily sex-biased, with ~4 males being diagnosed with ASD to every female. Although the etiology of ASD is not yet fully understood, studies have linked early-life stressors and the dysregulation of microglia, the primary innate immune cells of the brain, to ASD. To mimic resource deprivation stress, our lab used a limited bedding and nesting (LBN) paradigm in which dams do not have enough bedding and nesting material to facilitate a comfortable living environment, leading to fragmented maternal care. We found that early-life resource deprivation decreased pup weight and worsened motor coordination only in female offspring. To assess the impact of this early-life stressor on offspring communication, we studied the emission of ultrasonic vocalizations (USVs) using a pup separation-induced paradigm. Interestingly, LBN decreased the average duration of pup USVs. LBN also decreased sociability in offspring, an alteration that was prevented by ablating microglial proinflammatory signaling through toll-like receptor 4 (TLR4), suggesting that microglial immune signaling was responsible for the behavioral alterations observed in LBN offspring. Finally, proteomic analyses demonstrated that LBN altered the expression of more proteins in the brains of female offspring than in their male counterparts. Importantly, these altered proteins were related to microglial innate immune signaling, further implicating microglia in LBN behavioral alterations. Together, these results advance our knowledge of the various sex-specific factors that lead to ASD-relevant changes in the behavior of mice.

Ije Okereke

Examining the Impact of Early Life Stress on Social Behaviors in Translational Mouse Models

Research Director: **Dr. Catherine Dulac**

Early postnatal life is a period of high plasticity, where the brain undergoes dramatic changes that prime the organism for future stages of life. Much research has been dedicated to early postnatal life (i.e., infancy through adolescence) and the impacts that environmental inputs can have on later behavior. Early life stress (ELS) is one such environmental input that has been connected to long-term negative consequences such as memory deficits and social impairment. Currently, ELS research relies on observational studies in human populations and translational studies using model animals. Translational studies in mice have demonstrated that animals can experience resilience or vulnerability later in life as a response to different early life stressors. However, this research has predominantly relied on methods of inducing stress that require high levels of researcher interference. Additionally, the assays used to measure the impacts of ELS in these studies are limited in their ethological applications, particularly regarding the impact on social behaviors, which are an important translational outcome.

This research seeks to investigate the impacts of ELS on complex social behaviors in mice, such as mating, parenting, and aggression that have previously been absent from ELS studies. Here I use the Limited Bedding and Nesting (LBN) paradigm, an ELS model which minimizes experimenter interference. Using more ethologically valid paradigms and assays can provide a more comprehensive understanding of the impacts of ELS on behavior. Eventually, this may be used as a foundation for later studies on the molecular impacts of ELS and translational applications for humans.

Anna Peters

Diffusion-weighted imaging biomarkers predict survival for recurrent glioblastoma patients undergoing anti-angiogenic treatment

Research Director: **Dr. Eva Ratai**

Patients with recurrent glioblastoma (rGBM) experience a median survival time of 6-9 months. Most patients are treated with anti-angiogenic agents, such as bevacizumab. Various imaging modalities are utilized to provide biomarkers to predict survival, evaluate treatment response, or manage treatment to increase survivorship. Diffusion-weighted imaging reports the apparent diffusion coefficient (ADC), which provides insight into tumor cellularity. Previous studies found that the mean value of the lower Gaussian distribution (ADCL) of the ADC histogram can predict survival of rGBM patients prior to starting anti-angiogenic treatment. However, ADCL is tedious to extract and often lacks two distinct peaks in the ADC histogram, which may confound what ADCL represents biologically. This thesis investigated simpler and more straightforward DWI-derived biomarkers that predict survival for rGBM patients undergoing anti-angiogenic treatment. We acquired prospective longitudinal data incorporating structural MRI and DWI before (BL), 4 (4W), 8 (8W), and 16 (16W) weeks after starting anti-angiogenic treatment. After image analysis, the following parameters were generated for each patient: ADCL and the mean ADC of the lowest 2.5% (ADCL2.5%), 5% (ADCL5%), and 10% (ADCL10%). Univariate linear fit modeling revealed significant positive correlations between ADCL2.5% and survivorship at BL ($p=0.011$) and 4W ($p=0.048$) and ROC analysis demonstrated that ADCL2.5% effectively predicts survival at BL (AUC=0.726, 95% CI= 0.59, 0.86) and 16W (AUC=0.7, 95% CI=0.509, 0.891). Our results suggest that ADCL2.5% is an equal and potentially more valuable predictor of 9 months overall survival at 9 months for rGBM patients before initiation of anti-angiogenic treatment.

Cole Petersen

Investigating the Protective Role of FBXO17 in the Integrated Stress Response of Glioblastoma Stem Cells

Research Director: **Dr. Christian Badr**

Glioblastoma Multiforme is the most common and deadly malignant tumor of the central nervous system, marked by invasiveness, self-renewal, and proliferation. It is resistant to surgical resection and chemotherapy with a median survival time of 12-14 months. A subpopulation o Glioblastoma Stem Cells (GSCs) play a significant role in both the tumorigenic traits and treatment resistance seen in Glioblastoma largely through their capacity to reduce and mitigate stress. Through bioinformatics, we identified the poorly characterized F-box protein FBXO17 as a target that is significantly upregulated in Glioblastoma and whose potential as an agent of stress resistance is promising but unexplored (p=0.0011**). Through cell viability and immunoprecipitation, we determined that FBXO17 protects against activation of the Integrated Stress Response (ISR) in GSCs through Protein Phosphatase 2A (PP2A) dependent mechanisms. Using short-hairpin RNA knockdowns and HA-tagged overexpression plasmids, we altered FBXO17 expression in several GSC lines and treated with ISR activators. Using Western Blot and RT-qPCR, we found that FBXO17 expression alters the progression of the Integrated Stress response, protecting against otherwise pro-apoptotic CHOP effects. Further, we characterized Insulin growth factor-2 binding protein 3 (IGF2BP3) - which is only notably highly expressed in Glioblastoma and other Cancer Stem Cells - as a translational regulator of FBXO17 and show that FBXO17 can transcriptionally regulate IGF2BP3. We propose a mechanism by which IGF2BP3 could be a specific, novel therapeutic target in Glioblastoma that sensitizes GSCs to treatment and other exogenous stressors via its interaction with FBXO17.

Selorm Quarshie

Pupillometry signatures of neural activity and serotonin release within the auditory cortex of behaving mice

Research Director: **Dr. Anne Takesian**

The auditory cortex receives bottom-up sensory inputs and top-down neuromodulatory inputs that convey information about behavioral states, such as arousal, attention, and reward acquisition. Therefore, the auditory cortex is uniquely positioned to integrate sensory and behavioral signals. Indeed, behavioral states have been shown to modulate the activity of auditory cortical neurons as well as performance in behavioral auditory tasks. However, the mechanisms by which these states modulate auditory behavioral performance are not yet fully understood. To answer these questions, optical fibers were implanted into the primary auditory cortex (A1) of adult mice. Mice were head-fixed in an operant chamber, where two cohorts of mice were trained on two distinct auditory behavioral tasks, one assessing perceptual discrimination and the other associative learning. We performed in-vivo fiber photometry imaging of bulk fluorescence activity, measuring changes in the fluorescent signals from either a calcium indicator (GCaMP6s) to measure neuronal activity or a serotonin (5-HT) sensor (GRAB-5HT) to measure serotonin release. This was done while simultaneously recording pupil size and whisker motion data as measures of animal behavioral state using infrared video. We observed that behavioral states correlate with activity within A1 and reflect performance during auditory discrimination tasks. We found that performance was best at arousal states when pupil size was neutral or slightly constricted. Furthermore, pupil size correlated closely with excitatory pyramidal neuron activity within A1. Auditory associative learning was associated with an increase in 5-HT release in A1, and ongoing work is determining how this 5-HT release correlates with arousal, as measured using pupillometry. Understanding how behavioral states and neuromodulation affect A1 will further elucidate the mechanisms underlying auditory perception and behavioral performance.

Charles Reilly

Effects of Gap Junction-Blocking Drugs on the Survival and Behavior of Larval Zebrafish Implanted with Glioblastoma

Research Director: **Dr. Florian Engert**

Glioblastoma (GBM) is the most common malignant brain tumor in adults comprising almost half of malignant CNS tumors, and is accompanied by a grim 6.8% 5-year survival rate. GBM have neuron-glioma interactions which are augmented via gap junctional connections. These connections also confer chemotherapeutic resistance to the tumor, and as such, are a prime target for drug intervention. Studying GBM is difficult due to its location within the brain and its high mortality rate, so preclinical models of larval zebrafish have been developed. Larval zebrafish are favorable over in vitro studies of glioblastoma because larval zebrafish transplanted with GBM from a human tissue culture go on to develop disease that is characteristic of glioblastoma in humans, eventually succumbing to the tumor and dying. The effects, particularly behavioral effects, of gap junction blocking drugs have not been extensively studied in larval zebrafish. Using high-speed cameras to capture swimming activity, we have determined the behavioral and development effects of gap junction blocking drugs on healthy fish. We used flow cytometry to determine the apoptotic effects of gap junction blocking drugs in vitro. We began to characterize the effects of various gap junction blocking drugs on the survival and behavior of larval zebrafish with GBM, and we have begun developing a framework for the future study of drug discovery in larval zebrafish with GBM.

Katie Rotenberg

Bayesian Localization of the Seizure Onset Zone A Theoretical Framework for Surgical Decision Making

Research Director: **Dr. Joe Madsen**

This thesis seeks to apply a theory of Bayesian Search to the clinical decision-making task of seizure onset zone (SOZ) localization in surgical candidate patients with medically refractory epilepsy, creating several standardized tools to aid in the localization process. First, the thesis divides patients undergoing invasive monitoring via stereotactic electroencephalogram (sEEG) into three broad categories of principle questions that may be answered with further data. This category system was then tested for reliability by a physician showing a useful method of sorting surgical candidates. Next, the probability of neuroanatomical regions being in the SOZ was visualized using a Gaussian Process model trained on digitized, physician labeled MRIs, showing the change in the suspected SOZ target before and after learning further information from sEEG. This method was used to closely analyze 5 patients and yielded useful metrics of confidence in SOZ localization. Finally, the coordinates of implanted sEEG electrodes were analyzed to show that sampling from regions closer to a 50% probability of being in the SOZ had the greatest shift in probability, and therefore the greatest gain in information. However, in a preliminary analysis far fewer sEEG electrodes are implanted in the potentially high-yield areas. This thesis provided useful tools and metrics to help the surgical planning of epilepsy resection by applying a Bayesian theory to the problem.

Daniyal Sachee

Epilepsy Prediction in Patients with Succinic Semialdehyde Dehydrogenase Deficiency

Research Director: **Dr. Alexander Rotenberg**

Succinic Semialdehyde Dehydrogenase Deficiency (SSADHD) is a rare disorder with a prevalence of 1 in ~460,000 worldwide. It causes the inhibition of the γ-aminobutyric acid (GABA) degradation pathway, leading to overuse and downregulation of postsynaptic GABAA/B-receptor expression. The severity of symptoms varies from patient to patient, with epilepsy being one of the most severe. Epilepsy occurs in ~50% of patients, the reason for which is unknown, and generally appears in childhood rather than infancy warranting the value of being able to predict it. The goal of this study was to develop predictive mechanisms to determine the likelihood of future SSADHD patients developing epilepsy. To achieve this, a cohort of 20 SSADHD patients currently undergoing treatment at Boston Children's Hospital was used to create logistic regression, gradient boosting, and random forest models. Each patient's age, intelligence quotient (IQ), and sex were included, as well as metrics derived from transcranial magnetic stimulation (TMS), including resting motor threshold, cortical silent period, and long-interval intracortical inhibition, which are measures of cortical activity. Due to low SSADHD prevalence and limited sample size, Synthetic Minority Oversampling Technique was used to increase the size of the data set and improve the accuracy of each model. The predictive models had varying accuracies, and receiver operator characteristic curves were used to determine the optimal classification threshold for maximum sensitivity and specificity. All models indicated that age, IQ, and TMS-derived metrics were useful predictors of epilepsy, IQ being the strongest predictor, while sex had no predictive power. These findings suggest an association between the chosen variables and epilepsy in patients with SSADHD, enabling earlier epilepsy treatment for those at high risk of epilepsy. The models also have the potential to stratify inclusion criteria for new anti-epilepsy drug clinical trials for SSADHD patients.

Lev Sandler

Interplay of α-Synuclein and Mitochondrial Bioenergetics in Parkinson's Disease

Hoopes Prize Winner

Research Director: **Dr. Vamsi Mootha**

Accumulation of α-synuclein is a key pathological marker of both familial and sporadic Parkinson's Disease, yet its mechanism and role in Parkinson's Disease remains relatively unknown. One key pathological target of α-synuclein is the mitochondrion. While decades of Parkinson's Disease research have implicated the mitochondria and mitochondrial dysfunction as critical features of the disease, the exact mechanism of α-synuclein's mitochondrial toxicity has yet to be established. Questions remain as to where the protein directly interacts with the mitochondria, what effects this interaction might yield, and whether these effects drive disease pathology. To assess this protein-organelle interaction, we used bioenergetic measurements to investigate isolated liver mitochondria, isolated brain mitochondria, and murine primary cortical neurons. We show that treating isolated brain and liver mitochondria with α-synuclein increased reactive oxygen species (ROS) production through reverse electron transport (RET). In murine primary cortical neurons, but not immortalized cancer cell lines, treatment with α-synuclein caused a disruption to the electron transport chain (ETC), as evidenced by measurements of mitochondrial membrane potential and oxygen consumption. Strikingly co-incubation with metformin alleviated the observed membrane potential defects. These findings suggest that α- synuclein interferes with core ETC components – creating imbalances in ROS homeostasis, impairing membrane potential maintenance, and reducing respiratory capacity. These disruptions to mitochondrial and cellular homeostasis may be one of the underlying drivers of Parkinson's Disease pathology.

Deepak Singh

Synaptic Failure is a Flat Minima Optimizer

Research Director: **Dr. Gabriel Kreiman**

Synaptic failure is a well-known phenomenon in which weaker synapses fail more frequently. Whether this has any purpose is still unknown. In this work, we modify Dropout to implement synaptic failure in artificial neural networks, through a novel activation function we call NormOut. NormOut sets a neuron's probability of successfully firing equal to the ratio p of its activation to the maximum activation in some set of neurons. We propose variants inspired by lateral inhibition and firing thresholds and show that they have hugely different effects on activation dynamics. We find that NormOut improves the performance of a baseline VGG-16 on CIFAR-10, with one variant even outperforming Dropout in achieving both better test accuracy and a significantly flatter minimum. In addition to the effect on overfitting, we explore NormOut's impact on adversarial robustness against a suite of white and black-box attacks. Intriguingly, we find that some variants of NormOut produce extreme gradient masking without obfuscation. Rather than masking through flattening, we find that these variants actually induc high curvature in the loss landscape, suggesting an as yet unknown form of gradient masking. Overall, we show that simply modelling synaptic failure in two layers has a significant impact on the topology of the loss landscape, with the best implementations of synaptic failure optimizing strongly for flat minima. We claim this as evidence that synaptic failure is a feature, and not a bug, of the brain.

Isabella Trasolini

Regulation of CPN circuit development by Bcl11a through control of mitochondrial function

Research Director: **Dr. Jeff Macklis**

Callosal projection neuron (CPN) circuitry connects the hemispheres through the corpus callosum and is central to higher-order cognition. The autism spectrum disorder risk gene and transcription factor Bcl11a/Ctip1 regulates CPN subtype differentiation and area acquisition in the cortex. Bcl11a deletion alters the composition of transcripts within CPN growth cones (GCs), suggesting that Bcl11a regulates CPN circuit development by controlling how GCs respond to cues in their environment. Here, we conduct literature research to identify mitochondrial genes as candidates to explain the regulation of CPN circuitry by Bcl11a. Bcl11a deletion alters the abundance of many mitochondrial gene transcripts in the soma and GC. As the primary energy providers of the neuron, mitochondria play an important role in axon growth and GC motility. Quantitative analysis of CPN mitochondria indicates no difference in the number of mitochondria per neuron in wild type and Bcl11a null mice, hinting that Bcl11a could regulate the development of CPN circuitry by altering mitochondrial function. Lars2 and Coq8a, nuclear- encoded mitochondrial genes under the transcriptional control of Bcl11a, are identified as candidates for a knock-down study based on their crucial roles in mitochondrial function. We find that Coq8a knockdown slightly alters deep layer CPN circuitry, suggesting that Bcl11a potentially regulates CPN circuit development through altering Coq8a levels. This thesis investigates one example of how Bcl11a could regulate CPN circuit formation, expanding knowledge of the relationship between Bcl11a, mitochondrial genes, and CPN circuit development.

Elizabeth Wang

Relationships between Irritability and Ventromedial Prefrontal Cortex, Nucleus Accumbens, and Basolateral Amygdala Structural Volumes and Structural Connectivity in Post-Traumatic Stress Disorder

Research Director: **Dr. Elizabeth Olson**

Irritability is a clinically significant feature of post-traumatic stress disorder (PTSD). Current research suggests that brain regions that contribute to irritability may overlap with regions implicated in PTSD. Areas of particular interest because of their role in irritability and PTSD include the ventromedial prefrontal cortex (vmPFC), basolateral amygdala (BLA), and nucleus accumbens (NAcc), as well as the accumbofrontal tract, a white matter tract joining the NAcc and vmPFC. Although these structures have been separately shown to be involved in PTSD and irritability, their role in posttraumatic irritability has not been identified. Thus, this study aimed to 1) analyze the relationship between vmPFC, BLA, and NAcc structural volumes and irritability in PTSD and 2) reconstruct the accumbofrontal tract to assess its relationship with irritability in PTSD. Participants completed a questionnaire assessing irritability (the Irritability Questionnaire: IRQ) and underwent magnetic resonance imaging to obtain whole-brain anatomical and diffusion-weighted images. We did not find a significant difference in NAcc and vmPFC structural volumes between the PTSD or healthy control groups, and volumes did not correlate with irritability scores in either group. In the left BLA, we found a significant positive correlation between structural volume and irritability scores within the PTSD group ($F(3, 38) = 7.82$, $p = 0.006$) and across all participants ($F(3, 63) = 8.84$, $p = 0.017$). Finally, we were able to successfully reconstruct the accumbofrontal tract in our participant sample, but accumbofrontal tract FA values were not statistically different between the PTSD or healthy control groups and did not correlate with irritability scores in either group. These results differ in part from prior findings regarding the structural neural correlates of irritability and PTSD, highlighting variability in how these phenomena present in the brain. Further studies are needed to better understand the neural circuitry underlying irritability in PTSD.

Julia Welsh

Brain Reactivity to Personalized Alcohol Cues is Related to Severity of Alcohol Use Disorder But Not Subjective Craving in Treatment-Seeking Adults

Research Director: **Dr. Scott Lukas**

Objective: Individuals with alcohol use disorder (AUD) experience difficulty controlling cravings, especially in the presence of alcohol cues (e.g., sight of beer, smell of alcohol). Prior research indicates that when viewing general alcohol cues, individuals with AUD show increased activity in regions of the salience network (SN) and default mode network (DMN). However, it is unclear whether brain reactivity to personally relevant alcohol cues (i.e., of preferred alcohol type) shows similar activation patterns and whether brain activation is linked to clinically relevant individual differences, including cue-induced craving, AUD severity, and motivation to change drinking behaviors.

Methods: Fifty-one treatment-seeking adults completed a cue- reactivity task during functional magnetic resonance imaging (fMRI) before starting AUD treatment. Brain activity was compared for images of preferred alcohol (drink of choice, DOC) versus neutral images in regions of interest (ROIs) in the DMN and SN. Exploratory whole-brain analyses were also conducted.

Results: Participants reported significantly increased alcohol craving following the cue-reactivity task versus before the task. Neuroimaging analyses revealed no significant differences between neural activation in the DMN or SN ROIs to DOC versus neutral images. Similarly, exploratory whole-brain analyses did not differ in brain activity to DOC versus neutral images. AUD severity was negatively correlated with right insula reactivity to DOC compared to neutral images.

Conclusions: These findings suggest that the salience of personally-relevant alcohol cues may be less pronounced in treatment-seeking individuals with more problematic alcohol use. Future work will explore whether cue-induced craving or brain reactivity to alcohol cues predicts treatment response.

Justin Wong

Hypersensitivity: The Impact of Altered Sensory Circuits on Cortical Development and the Implications for Autism Spectrum Disorder

Hoopes Prize Winner

Research Director: **Dr. Lauren Orefice**

Autism spectrum disorder (ASD) is a highly prevalent class of neurodevelopmental disorder that has been characterized by cognitive deficits in social communication and interaction, as well as restricted repetitions in behavior. However, a growing body of research has pointed to the sensory origins and manifestations of ASD symptoms. Sensory input from peripheral somatosensory neurons drives circuit formation in developing brains, and recent studies have suggested that aberrant sensory input due to peripheral somatosensory dysfunction can disrupt cortical interneuron development. This may culminate in ASD behavioral phenotypes through cortical excitatory/inhibitory balance disruptions. Understanding the role of sensory input in brain development can help elucidate the etiology of sensory over-reactivity and other behavioral symptoms in ASD. However, the mechanisms through which altered peripheral sensory neuron function leads to changes in brain development and ASD-related behaviors are unknown. In this thesis, using a mouse line with a conditional deletion of Gabrb3, an ASD-related gene, in peripheral sensory neurons, we hypothesized that aberrant sensory input disrupts the postnatal development of inhibitory interneurons and inhibitory synapses and leads to an altered pattern of neuronal activation. We first investigated whether alterations in peripheral somatosensory neurons impact the development of inhibitory interneuron subtypes expressing calbindin (CB) and parvalbumin (PV) in the S1trunk region. We also began to elucidate if mutations in peripheral somatosensory neurons will lead to a change in the development of S1trunk cortical inhibitory synapses. Finally, we assessed if a loss of Gabrb3 results in changes to S1trunk neuronal activation, measured by cFos expression, in adult mice after tactile stimulation. Although the experiments do not have sufficient statistical power for conclusive results, we observed a decrease in PV- expressing inhibitory interneurons in layer 4 at P14, an increased GAD67 expression in layer 6 and possibly a decreased expression in layer 1 at P28. Our result might also suggest an increased cFos expression in layer 6 after stimulation. Future studies can further illuminate the role of sensory input in shaping brain development and ASD etiology.

Outside of neuroscience, popular portrayals of ASD have increasingly focused on its sensory and peripheral dimensions, in a turn away from prevailing cognitive theories. Cognitive theories, such as the theory of mind theory and simulation theory, explain the social difficulties experienced by autistic people through cognitive deficits. However, due to its focus on cognitive deficits, these theories neglect the social abilities of autistic people as well as their difficulties in sensorimotor processing. Instead, by viewing social interactions as a shared activity driven by sensorimotor coordination, alternative theories can better describe autism through a framework of different but not deficient. Finally, when considering treatments of autism and the neurodiversity movement, I argue that instead of approaching disputes as an ethical dilemma about the use of science, we should question the notion of science as neutral grounds for knowledge. This framing of the dispute can allow us to appreciate the normative claims that are embedded in science and envision a version of science that embraces diversity and lived experiences.