

**Ahmad Alnasser**

***The Role of ER Stress in Regulation of Glioblastoma cancer stem cells***

Research Director: Dr. Christian Badr

Endoplasmic Reticulum (ER) Stress is a state of the cell where homeostasis is disrupted, and often manifests itself through protein misfolding and accumulation of misfolded proteins in the cell. In a state of ER stress, the cell undergoes what is known as the unfolded protein response (UPR), which allows cells to survive and promotes metabolism via kinases such as PERK and eIF2 $\alpha$ , implicated in Glioblastoma (GBM). This thesis investigates the role of ER stress in the activation of the PERK-eIF2 $\alpha$ -ATF4 signaling pathway, and its effects on tumor growth and glioma stem cell self-renewal. In characterizing this pathway, there is hope of finding GBM therapeutics that would target tumorigenic stem cells and prevent them from metabolizing lipids during ER stress, leading to apoptosis. We cultured GBM cells and targeted different proteins within the signaling pathways and amplified the samples across different primer targets in Quantitative RT-PCR. Through viral transmission of tumor cells into a mouse model, and subsequent treatment with signaling inhibitors and Temozolomide (TMZ), we found that tumor growth in mice decreased due to lack of fatty acid metabolism. Future studies are needed in order to establish a compact functional relationship through which fatty acid metabolism is inhibited, and this could be in the form of experiments seeking to understand the role of Gliomal stem-cells in atypical environments.

**Bella Beckett**

***Molecular Mechanisms Mediating the Effect of Fever on Social Behavior in Mice***

Research Director: Dr. Catherine Dulac

When a pathogen invades the body, an animal's immune system launches a series of brain-mediated responses including fever. Fever is the body's primary defense against an infection, and is highly conserved across species. Adjustments in social behavior constitute another adaptive symptom of infectious disease. While it is generally thought that sick animals display decreased social interactions, preliminary data from the Dulac lab found that sick mice display long durations of close proximity with other sick mice but not with healthy mice, indicating that social behavior during sickness may be dependent on the body's internal state and external social context. Additionally, a population of hypothalamic oxytocin-expressing neurons were found to be active during fever and displayed strong colocalization with the EP4 receptor. Oxytocin plays a major role in coordinating social behavior, and the EP4 receptor binds E-type prostaglandins, which mediate fever. Based on these observations, we proposed a mechanism by which the EP4 receptor on oxytocin-expressing neurons, and subsequent oxytocin signaling, regulate circuit elements responsible for social behaviors. To determine the role of EP4, oxytocin-expressing neurons, and oxytocin signaling in modulating social behavior during sickness, we performed behavioral assays and quantified the duration of specific social behaviors in various experimental conditions. We subsequently performed in situ hybridization to determine the class of oxytocin neurons involved in sickness behavior. Our results showed that EP4 and oxytocin signaling from magnocellular neurons are important for promoting huddling behavior between sick mice. Ultimately, this study identifies a potential molecular mechanism mediating the specific effects of fever on social behavior in mice.

**Kaelyn Brown**

***Investigating the Role of Smoking Cue Reactivity in General Attention Processing***

Research Director: Dr. Amy Janes

**Objective:** There are currently no mainstream treatments that prevent smoking relapse for all nicotine dependent individuals. Previous studies indicate that nicotine dependent individuals who display higher reactivity to smoking-related stimuli are more likely to relapse during a cessation attempt. The current study aimed to elucidate whether nicotine dependent individuals who demonstrate increased smoking cue reactivity—as evaluated by an emotional Stroop task—also experience more general disruptions in attention processing—assessed by the Multi-Source Interference Task (MSIT).

**Methods:** Seventeen nicotine dependent participants underwent functional magnetic resonance imaging (fMRI) as they completed the MSIT. Following scanning, participants completed a computerized emotional Stroop task, which tested for attentional biases towards smoking-related words—a behavioral measure of smoking cue reactivity. Both behavioral and functional data was collected. Group-level analysis investigated brain reactivity during the MSIT and explored whether smoking cue reactivity and smoking severity impacted functional brain activation during the task.

**Results:** A whole brain contrast revealed that participants experienced increased subgenual Anterior Cingulate Cortex (sgACC) activation during the MSIT control vs. interference contrast. A follow-up analysis showed that this activation pattern was driven by greater sgACC suppression during the interference vs. control trials. Individuals that demonstrated increased reactivity to smoking-related cues during the Stroop did not exhibit significant behavioral differences nor significant differences in functional brain activation during the MSIT. While there was a weak association between increased smoking severity and poorer smoking Stroop performance, there was no relationship between smoking severity and the MSIT.

**Conclusions:** This data does not support the hypothesis that smoking-related interference and more general disruptions in cognitive interference are related. Smoking severity was related to smoking-related behavioral interference, but not MSIT performance, suggesting a meaningful relationship between smoking behavior and smoking cue processing instead of interference processing more generally. Inhibition of the sgACC during MSIT interference vs. control trials, has not been consistently observed in studies with non-smoking individuals, suggesting that nicotine dependent individuals may use an alternative neuronal strategy during cognitive interference.

**Ahab Chopra**

***A Methodology for the Selection and Production of Antigen-Specific, Dual-Fluorescent, Nanobodies to Label Distinct Neuronal Cell Types***

Research Director: Dr. Catherine Dulac

Joint Concentration with Chemistry

Parenting and infanticide are two highly conserved, infant-driven behaviors exhibited by adult mice. While specific populations of neurons responsible for parental care and infant-directed aggression have been identified in the hypothalamus of both males and females, relatively little is known about the cell biology and synaptic connectivity of these genetically defined cell types. By combining the resolution of electron microscopy with the specificity of immunofluorescence, we can reveal the ultrastructure of these behaviorally associated neurons. This approach relies on nanobodies, which are approximately one-tenth the size of traditional antibodies, to penetrate non-permeabilized hypothalamic sections and achieve uniform immunolabeling while preserving tissue structure. Utilizing biochemical approaches to select antigen-specific nanobodies, we developed a methodology to produce dual-fluorescent nanobodies in order to simultaneously label a number of distinct cell populations. Our findings suggest that this tool can be applied to uncovering the connectivity in circuits underlying complex behaviors including parenting and infanticide with nanometer resolution.

**Ashley Cooper**

***Racism's Health Harm on Black Youth Mental Health: From (Neuro)Scientific Orthodoxy to Neuroscience as a Vessel of Visibility***

Research Director: Dr. Marisa Silveri

Joint Concentration with Anthropology

Early Life Stress has been epidemiologically linked as one of the largest risk factors for developing adolescent depression, catalyzing a disruption of neural pathways necessary for proper cognitive function. This research seeks to expand the lexicon of Early Life Stress to incorporate Early Life Stress related to Perceived Racial Discrimination as a category of both neurodevelopmental and anthropological interest. We aim to examine the impact of early life perceived racial discrimination on a mental health outcome in Black youth. We examined relationships between perceived discrimination and mental health outcomes via expected resting state fMRI (rsfMRI) outcomes.

Methods: Statistical analysis of pre-processed, longitudinal Resting State fMRI (rs-fMRI) acquired data utilizing the ABCD Study Data (1.0, 2.0.1, 3.0 Release) using McLean computing server. Seed-based correlational analysis of the Default Mode Network via the medial prefrontal cortex as the a priori Region of Interest (ROI)/seed region. We hypothesized that Black youth in the ABCD study will experience greater levels of perceived discrimination as compared to their white counterparts. We additionally hypothesized that there would be significant associations between early perceived racial discrimination and negative mental health outcomes in Black youth. We finally hypothesize that children exposed to early perceived racial discrimination would have lower overall activity of the Default Mode Network (as indicative of depression). Anthropologically, I investigate the lack of neuroscientific literature on racism and its neurodevelopmental consequences for Black Youth. Ultimately, the research will allow for us to draw characterizations concerning how exposure to Early Life Stress Perceived Racial Discrimination may affect the neurodevelopment outcomes of Black children.

**Mohamed El-Abtah**

***Predictive Value of Myo-inositol Measured by Magnetic Resonance Spectroscopic Imaging during Anti-angiogenic Treatment in Recurrent Glioblastoma***

Research Director: Dr. Eva Ratai

Recurrent glioblastoma (rGBM) patients are often treated with anti-angiogenic agents such as bevacizumab (BEV). Despite therapeutic promise, conventional MR methods fail to determine which patients do not benefit from this treatment. The purpose of this study was to use magnetic resonance spectroscopic imaging (MRSI) to investigate new biomarkers to predict response to BEV treatment. We evaluated spectroscopic data of myo-inositol (ml), a glial marker and osmoregulator within the brain, normalized to contralateral creatine (ml/c-Cr) in the tumor of 21 rGBM patients prior to BEV treatment (baseline), as well as 1 day, 4 weeks, and 8 weeks after treatment. Lower ml/c-Cr in the tumor prior to and during BEV treatment predicts poor survivorship. ROC analyses for ml/c-Cr within the tumor yielded an AUC of 0.75 at baseline, 0.87 at 1 day, and 1 at 8 weeks. A similar result was observed in contralateral normal appearing tissue, with shorter-term survivors having lower levels of ml/Cr. This was predictive of survivorship at baseline with an AUC of 0.72, 0.83 at 1 day, 0.69 at 4 weeks, and 0.80 at 8 weeks. Lower levels of ml/c-Cr within intratumoral and contralateral volumes were predictive of poor survivorship and anti-angiogenic treatment failure as early as before BEV treatment. Adapting MRSI alongside conventional MR imaging modalities can convey critical information regarding tumor microenvironment to help better manage rGBM patients.

**Emmanuel Garrison-Hooks**

***Mouse Foraging Behavior in a Dynamic Virtual Environment***

Research Director: Dr. Nao Uchida

As animals navigate through their environments, they must determine when abandoning a cluster of resources to search for another is better than remaining. Charnov's Marginal Value Theorem offers a way to characterize animal foraging behavior, predicting that animals should leave a depleted 'patch' of resources as soon as the expected value of remaining on that given patch is exceeded by the average expected reward value of the environment. Using a virtual reality patch-foraging paradigm, wherein mice are head-fixed as they run on a 1-D track, we assessed how mice behavior is affected by different patch values by randomly varying size and frequency of rewards across patches. During the task, the mice are presented with visual cues that signal that a patch is available. If they stop, water rewards are delivered probabilistically, with that probability monotonically decreasing over time to mimic the depletion of resources that is typical of natural environments as the mouse forages. Furthermore, we were interested in whether the mice could adapt their behavior based on net value of the environment by varying whether the mice could either receive only Small and Medium rewards or Medium and Large rewards across trial blocks. We found that the mice behavior was modulated by the quality of their environment, with longer patch residency times on higher-value patches in the high-value environment than in the low-value environment. Ultimately, we found cases where the mice remained on Medium value patches longer in the high-value environment but left sooner in the low-value environment.

**Jonathan Garzon**

***Utilizing a novel naturalistic paradigm to systematically assess social need in WT and ASD mice***

Research Director: Dr. Catherine Dulac

Social need motivates animals to seek social interactions and maintain social bonds. By contrast, social isolation induces a negative emotional state (loneliness) that enhances the drive for social interactions, leading in turn to an observable rebound in social investigation. Social need is disrupted in autism spectrum disorders (ASD), and children with ASD display impaired orientation to social stimuli and reduced response to social reward. Therefore, a better understanding of neural mechanisms underlying social need should provide significant insights into the basic mechanisms underlying ASD pathology and suggest new avenues for treatment. By using a novel naturalistic behavioral paradigm, I systematically measured the frequencies and durations of bouts of various social interactions in two wild-type (WT) mouse strains FVB/NJ and C57BL/6J, and two autism spectrum disorder (ASD) model mice *Shank3b*<sup>-/-</sup> and *CNTNAP2*<sup>-/-</sup> following a short period of social isolation. Both WT strains exhibit significant social rebound after isolation when compared to their baselines. Specifically, FVB/NJ mice showed stronger social rebound than C57BL/6J mice. Using the elevated plus maze and open field tests, I found no difference in stress levels between isolated and socially housed WT mice, which indicates that social rebound is not a result of isolation stress. In comparison to the WT mice in the same strain background (C57BL/6J), ASD model mice showed abnormal social behaviors during social reunion: *CNTNAP2* mutants showed little rebound while *Shank3b* mutants showed hyperactivity in specific modules of social behaviors. To further reveal the behavioral details in ASD mice, I have trained a deep-learning network via DeepLabCut and have analyzed the body pose features in two interacting mice across video frames. Overall, my study uncovered unique social behavior patterns in both WT and ASD model mice following social isolation. This study provides a fruitful behavior reservoir for future mechanistic studies of the nature and function of neuronal circuits associated with basic social drive.

**Lina Ghosh**

***Investigating the Role of Klf9 in the Division Pattern and Differentiation of Neural Stem Cells in the Adult Hippocampus***

Research Director: Dr. Amar Sahay

Adult hippocampal neurogenesis is maintained by the limited activation and proliferation of neural stem cells. Upon activation, radial-glia like neural stem cells (RGLs) symmetrically divide into more RGLs or asymmetrically differentiate into astrocytes or neural progenitors. A balance between quiescence and activation as well as the two modes of RGL division is crucial for maintaining hippocampal homeostasis, maturation, and response to pathogenesis in adulthood. Kruppel-like factor 9 (Klf9) is a transcription factor hypothesized to play a critical role in maintaining RGL quiescence and determining cell fate. This thesis investigates the potential regulatory mechanisms of Klf9 on RGL division and differentiation by characterizing adult-born hippocampal cell populations in Klf9<sup>f/f</sup> versus Klf9<sup>+/+</sup> mice. Population analysis in Gli1-CreERT2 and Ascl1-CreERT2 mice revealed significantly higher proportions of RGLs in postnatal and young adult Klf9<sup>f/f</sup> mice after 1-4 weeks of lineage tracing. Therefore, Klf9 may be important for maintaining RGL quiescence and preventing symmetric expansion at these time points. Genetic profiling of young adult Klf9<sup>f/f</sup> mice confirms the upregulation of genes associated with stem cell activation and expansion as well as downregulation of genes associated with stem cell quiescence. Interestingly, population analysis of mature adult mice failed to show differences between Klf9<sup>f/f</sup> and Klf9<sup>+/+</sup> mice, suggesting that the regulatory role of Klf9 in adult neurogenesis may diminish in the aging niche. Further investigation of Klf9 expression as well as clonal analysis and 2-photon imaging is needed to confirm the role of Klf9 in maintaining postnatal and adult RGL homeostasis.

**Kristen Gilyard**

***The Implicit Learning Processes in Young Adults during Artificial Grammar Learning Tasks***

Research Director: Dr. Yael Arbel

Joint Concentration with Mathematics

This thesis explores the neurological processing of grammatical violations at the electrophysiological level in an Artificial Grammar Learning task (AGL) using a novel approach of time-locking the EEG to the visual fixation on a grammatical violation using eye-tracking data.

This thesis delves into the learning outcomes of healthy young adults ages 22-35 years old who performed an Artificial Grammar Learning task which is typically a good indicator for implicit learning. Following the known Knowlton AGL task, individuals participated in a training phase and a testing phase. During the training phase, individuals passively viewed exemplar stimuli; during the testing phase individuals subsequently decided whether the stimuli were grammatical. The study used eye-tracking data that were collected during the AGL task to evaluate processing at the electrophysiological level of violations in the AGL sequence. Although some patterns have emerged in the EEG data of differences between the processing of grammatical and non-grammatical sequences, these apparent differences did not reach statistical significance. Additionally, sequences were given a score based on grammaticality and similarity to the training stimuli (chunk strength). Finally, this thesis uses a SIRS model to better understand the costs and benefits of learning with implicit learning strategies. Overall, implicit learning strategies are useful to create a learning environment. However, the exact processes that individuals employ to learn when viewing the violating letter within a non-grammatical sequence remain yet to be discovered.

**Josh Glauser**

***Neural Measures of Social Attention as an Indicator of Communication and Social Development in Infants at-risk for Autism Spectrum Disorder***

Research Director: Dr. Chuck Nelson

Identifying neural markers of autism spectrum disorder (ASD) before they clinically emerge can improve outcomes through early treatment. This study aimed to characterize the neural correlates of face recognition in 12-months-old infants at familial risk of developing ASD. The study's objectives were (1) to compare face-sensitive event-related potentials (ERP) (Nc, N290, P400) between high-familial-risk infants who develop ASD (HR-ASD), high-familial-risk infants without ASD (HR-NoASD), and low-familial-risk controls (LRC), and (2) to determine how face-sensitive ERP components correlate with the core ASD clinical symptoms of communication and social development. 12-month old infants participated in the mother/stranger paradigm (Nc n = 102, N290/P400 n = 64), with EEG data collected as infants observed pictures of their mother and a similarly-looking stranger. Parent-reported and laboratory-observed communication measures were recorded at 12 months, and laboratory-observed social measures were conducted at 18 months. Multiple linear regressions were conducted with maternal education and outcome groups as covariates. For each of the Nc, N290, and P400 analyses, the amplitude difference between mother and stranger (Mother-Stranger) trials was not statistically different between the three outcome groups (Nc p = 0.72, N290 p = 0.88, P400 p = 0.91). Controlling for maternal education and outcome group, a significant association was observed between expressive communication measures and the Nc Mother-Stranger ( $R^2 = 0.11$ ,  $p = 0.002$ ) and between receptive communication measures and the P400 Mother-Stranger ( $R^2 = 0.35$ ,  $p = 0.005$ ); Larger P400 Mother-Stranger differences were also associated with higher social development scores ( $R^2 = 0.17$ ,  $p = 0.04$ ).

**Dani Gomez-Ochoa**

***The Effect of parental monitoring on epigenetic age and CRP levels among young adults in the ALSPAC cohort***

Research Director: Dr. Erin Dunn

Parental monitoring may be a protective factor against depression, potentially becoming biologically embedded through epigenetic marks and inflammatory factors such as C-reactive protein (CRP). However, it remains unknown whether epigenetic age and CRP influence the relationship between parental support and depressive symptoms. This study aimed to determine the extent to which epigenetic age and CRP levels in peripheral blood during adolescence can moderate the impact of parental monitoring on adult depressive symptoms. The analyzed data came from a subset of the ALSPAC cohort, a longitudinal study that has collected multiple variables of parental monitoring, depressive symptoms, and epigenetic data across development. To capture parental monitoring, I created a cumulative parental monitoring score that included five parental monitoring qualities measured at age 12.5 years. Furthermore, epigenetic age was measured from peripheral blood DNA methylation at ages 15-17 years using the Horvath and Hannum epigenetic clocks (n=966). CRP was measured from blood at age 15.5 years (n=720). Depressive symptoms were measured using the Short Mood and Feelings Questionnaire (SMFQ) at age 21 (n=455). This project tested three hypotheses. First, I assessed the effects of the cumulative parental monitoring score on epigenetic age, CRP concentration, and depressive symptoms. Second, I evaluated the biological influences on depressive symptoms. Finally, I gauged the moderation of the effects of the parental monitoring score on SMFQ by molecular outcomes. Overall, this research suggests that neither epigenetic age nor CRP concentration levels moderate the effects of parental monitoring on depressive symptoms as measured by SMFQ score. Considering the limitations of sample size in genomics research, future studies should consider performing imputation on missing variables to prevent a loss in power.

**Catherine Ho**

***Aging, Episodic Retrieval, and Metacognition during Everyday Problem Solving***

Research Director: Dr. Daniel Schacter

When faced with a difficult problem, people often rely on past experiences. Memory impairments, whether due to aging or hippocampal lesions, impair problem-solving abilities. On the other hand, brief training in recollecting the details of a recent event helps people to solve social means-end and personally worrisome problems. While episodic retrieval clearly benefits performance, feelings of ease during recall may also leave people feeling more prepared for problems than they really are. My thesis tests whether this illusion occurs in young and older adults, since aging increases the effort associated with retrieval and may mitigate overconfidence. Young and older participants learned tips for "worst case scenarios" (e.g., shark attack). Later, they listed steps to solve these problems (retrieval), as well as new ones (generation), and indicated how prepared they felt for each scenario. With a retrieval focus, young adults not only provided higher-quality solutions, but also felt more prepared for serious problems. Better performance in the retrieval condition did not fully explain young adults' increased preparedness ratings. Older adults, on the other hand, performed similarly in both conditions and felt equally prepared when remembering old solutions and generating their own. These results suggest that remembering only misleads us to overestimate our abilities during problem solving when retrieval feels easy, or fluent.

**Claire Hotchkin**

***Exercise, Anxiety, and Heart Rate Variability: An Ecological Study Using Wearable Technology***

Research Director: Dr. Richard McNally

Heart rate variability (HRV), controlled by the autonomic nervous system, is a neurophysiological indicator of stress. HRV holds much potential as a biomarker in the field of psychiatry; individuals with depression and anxiety have lower levels of HRV. Notably, HRV increases in response to regular exercise, and exercise is also associated with improved emotional well-being. HRV therefore offers a mechanistic link to help explain the psychological benefits of exercise. The present study explored the relationship between HRV, anxiety, and exercise. Specifically, the temporal dynamics of daily emotions were investigated using an ecological momentary assessment design. Ninety-three participants each received 105 question prompts over the course of 21 days. Additionally, HRV was tracked throughout this period using WHOOP, a wearable heart rate monitor. Average exercise duration was negatively correlated with the emotional variability of anxiety. The construction of multilevel models also revealed that as exercise intensity and HRV increased, the persistence of anxiety decreased. This suggests that daily HRV levels are a useful indicator of anxiety and points to clinical applications for the treatment of anxiety.

**Ray Jiang**

***Electron Microscopy Analysis of Novel Merged Cells***

Research Director: Dr. Jeff Lichtman

Human brain development is a keystone question in modern neuroscience. Difficulty in accessing human brain features for research, especially for topics as dynamic as brain development, has been a roadblock for much of the history of neuroscience research. However, a newly developed large-scale human cortical dataset created through serial electron microscopy (EM) methods provides unprecedented access to neurological structures and motifs at nanometer resolution. In this paper, I will present the first studied instance of merged cell types in the neocortex, coined “Host/Guest Pairs.” Using series EM images and 3-D digitally saturated reconstructions from this dataset, I was able to manually identify and categorize 531 host/guest pairs. My analysis of these cell pairs revealed supporting evidence for existing theories of neuronal and glia migration pathways during cortical development, including the radial unit theory and the tangential migration theory of interneurons.

**Emily Johns**

***Analysis of the Neural Correlates of Psychosis: From Antiquity to Modern Research***

Research Director: Dr. Martha Shenton

Joint Concentration with Classics

Understanding the relationship between neural aberration and severity of hallucinations and delusions using modern neuroimaging techniques, as well as analysis of ancient medical documents is an important area of study. In this study, we aimed to characterize variation in cortical thickness of language processing brain regions as a function of patient status to determine if hallucinations and delusions have a central neural basis. We also aimed to analyze the medical text, *On The Differentiae of Symptoms*, written by Galen (129-216 CE) to understand how hallucinations and delusions were understood in antiquity. From a close textual analysis, we observed that hallucinations and delusions were characterized by Galen as distinct presentations connected by a central region of mental (brain) malfunction. Investigating this premise in a modern neuroscientific context, we examined subjects who participated in the Human Connectome Project for Early Psychosis, which included 157 individuals suffering from psychosis and 72 comparable healthy individuals. Structural differences in cortical thickness in three brain regions of interest (ROI), the left frontal, dorsal, and temporal gyri, were evaluated using analysis of covariances and post-hoc Tukey's contrasts. We also observed a significant difference in cortical thickness in all ROI when comparing controls, symptomatic patients (i.e., hallucinations and/or delusions present), and asymptomatic patients (i.e., no hallucinations or delusions present). Of note, cortical thickness was reduced in symptomatic patients compared to controls, with asymptomatic patients intermediate in all ROI. These findings suggest that these language regions play an important role in patients suffering from hallucinations and/or delusions.

**Dim Karev**

***Context-Robust Object Recognition via Object Manipulations in a Synthetic 3D Environment***

Research Director: Dr. Gabriel Kreiman

Joint Concentration with Computer Science

The remote control is a small object that does not fly in the air and is generally found on a table, not in the sink. Such contextual regularities are ingrained in our perception of the world and previous research suggests that they can even influence human and computational models object recognition ability. However, the exact effects of contextual information on object recognition are still unknown for both humans and machine learning models. Here, we introduce a novel way of studying the effects of different contextual cues in a qualitative and systematic way. We present a diverse synthetic dataset created via a 3D simulation engine that allows for complex object modifications. Our dataset consists of more than 15000 images across 36 object categories and it is designed specifically for studying the effects of gravity, object co-occurrence statistics, and relative size regularities. We conduct a series of psychophysics experiments to assess human performance and establish a benchmark for computational models on the dataset. Additionally, we test state-of-the-art deep learning models on the same dataset and study how contextual information influences their object recognition accuracy. Finally, we propose a context-aware recognition transformer network that integrates contextual and object information via multi-head attention mechanism. Our model captures useful contextual information that allows it to achieve human-level performance and significantly better robustness in out-of-context conditions compared to baseline models across our dataset and another existing out-of-context natural image dataset. Moreover, our model performs in a way that is consistent with human object recognition and shows similar recognition artefacts.

**Brigid Kennedy**

***The Impact of Distraction on the Effortful Control of Preschool-Age Children with Autism Spectrum Disorder***

Research Director: Dr. Susan Faja

The presence of distraction can influence effortful control, the ability to control behavior to achieve objectives, in typically developing (TD) children. This study aimed to determine whether significant differences exist in the effortful control and neural correlates of error-monitoring in preschool-age children with autism spectrum disorder (ASD) as compared to TD controls. Thirty-four preschoolers ranging from four to six years old with and without ASD participated in this study. The Delay of Gratification and Rabbit/Turtle tasks were used to evaluate effortful control and were compared to adapted conditions with additional toys for distraction. EEG was recorded during the Attention Network Test for 26 of the above participants and analyzed to determine whether the error related negativity (ERN) waveform—a neural measure of effortful control—differed between diagnostic groups. ASD and TD groups did not differ on Delay of Gratification completion or attentions measures but differed in their ability to slow for Rabbit versus Turtle ( $F(1, 23) = 5.422, p = .029$ ). There were no significant correlations between Delay of Gratification and Rabbit/Turtle, indicating that the tasks targeted different components of effortful control. The ERN Fz cluster peak amplitude correlated with Mullen nonverbal development quotient ( $r(18) = -.480, p = .044$ ) and Rabbit/Turtle without distraction reaction time difference score ( $r(18) = -.617, p = .014$ ). The ERN mean theta power only correlated with age ( $r(18) = .508, p = .031$ ). These findings indicate that greater negativity of the ERN is correlated with increased cognitive ability and effortful control.

**Angela Kim**

***Combined Neurophysiological and Behavioral Assessment of Prolonged Recovery from Neuromuscular Blockade in Human Infants***

Research Director: Dr. Charles Berde

Infants in critical care units are frequently administered neuromuscular blocking agents (NMBAs) to aid postoperative recovery or mechanical ventilation. NMBAs provide reversible muscle paralysis by preventing electrical transmission at the neuromuscular junction. However, only subjective observational methods exist to monitor these drugs in infants. This thesis investigated a novel method to assess neuromuscular blockade in infants, specifically how it changes as patients recover from the drug. We tested whether electromyography (EMG) analysis could be used to monitor recovery of muscle activity. The ulnar nerve of the wrist was electrically stimulated to evoke muscle twitch (Train-of-Four), and twitch decay was measured using surface EMG and thumb accelerometry. Infants (37-57 weeks gestational age) receiving the drugs vecuronium and rocuronium were studied in the Neonatal Intensive Care Unit at Boston Children's Hospital. Electrical stimulation (5-60 mA) was applied to the ulnar nerve; accelerometry measured thumb adduction; and EMG recorded muscle activity. After EMG signals were preprocessed, stimulation events were marked and area under the curve (AUC) was calculated to quantify muscle activity. Our outcome measures were twitch decay for thumb adduction and EMG AUC. First, we observed that EMG AUC values increase with stimulus intensity. However, the difference in evoked response AUC between paralyzed and recovering infants was not significant ( $z=1.56$ ,  $p=0.059$ ). In conclusion, further study is required to determine the sensitivity of EMG to changing depth of neuromuscular blockade. Quantitative EMG analysis has the potential to create age-appropriate methods for NMBA monitoring.

**Katelyn Li**

***Charting the Cerebral Stars: A Comprehensive Molecular Profile of Astrocytes Across Species and Brain Regions***

Research Director: Dr. Guoping Feng

Astrocytes have recently emerged as central contributors to nervous system function. Constituting the most abundant class of glial cells, they have been found to take on a wide array of roles, from metabolic support to modulation of neurotransmission. Though recent studies have opened up new insights into astrocyte heterogeneity at the molecular level, these findings largely remain confined to murine models. Given the accumulating evidence for the expansion of astrocytic complexity over the course of evolution, a more nuanced understanding of cross-species differences in astrocyte transcriptomic architecture will be crucial for study of human cognition and disorder. This thesis presents the first large-scale analysis of astrocyte snRNAseq data from the common marmoset (*Callithrix jacchus*), a prominent NHP model for neuroscience research. It provides a detailed comparison of astrocyte transcriptomic patterns in eight brain regions of the marmoset and across three species (mouse, marmoset, and human), which altogether span over 90 million years of evolutionary divergence. We identified a total of 12 astrocyte subtypes in the marmoset brain, each marked by a distinct molecular fingerprint and regional distribution. While several of these marmoset astrocyte subtypes showed broad similarities in gene expression profile with previously characterized mouse subtypes, we found substantial evidence of evolutionary innovation. In particular, through matched integrative comparison, we proposed both the emergence of novel marmoset-specific and human-specific subtypes, as well as evolutionary shifts within conserved subtypes. Ultimately, this study supplies a foundational atlas of astrocyte transcriptomic diversity, spearheading future examination into astrocyte involvement in the CNS.

**Matthew Mardo**

***NF- $\kappa$ B as a Potential Pathway of Environmental Toxicants in the Development of Parkinson's Disease***

Research Director: Dr. Lee Rubin

Parkinson's disease (PD) is the second-most common neurodegenerative disorder with a prevalence of 2-3% for individuals at least 65 years of age, second only to Alzheimer's disease. PD is pathologically characterized by  $\alpha$ -synuclein protein aggregates and the progressive loss of dopaminergic (DA) neurons in the substantia nigra and striatum. Previously performed drug screens in the Rubin lab have shown that several compounds leading to high levels of DA neuronal death in vitro also target NF- $\kappa$ B, a protein complex notably involved in the regulation of genes for anti-apoptosis and neuroinflammation. Using DA neurons derived from PD-patient induced pluripotent stem cells (iPSCs), we aimed to elucidate the potential role of NF- $\kappa$ B through treatment with compounds known to inhibit or activate this family of transcription factors. Following compound treatment of DA neurons, live image analysis and immunocytochemistry techniques were used to quantify the effects of NF- $\kappa$ B pathway perturbation on DA neuron survival and downstream signaling events, respectively. Our results suggest that high levels of NF- $\kappa$ B inhibition are associated with increased DA neuron death and provide evidence for the involvement of canonical NF- $\kappa$ B pathway signaling in DA neuron survival. Additionally, decreases in survival corresponded to lower levels of p65 subunit phosphorylation, a key event for NF- $\kappa$ B translocation into the nucleus. Thus, we establish a potential role for NF- $\kappa$ B using a stem cell model for DA neurons with implications on the molecular pathways through which environmental toxicants and other exogenous agents may increase the risk associated with developing PD.

**Claire Millett**

***Calcium Signaling in Schizophrenia: Exploring the Role of CACNA1C in Human Synaptogenesis with High-Throughput Imaging***

Research Director: Dr. Kevin Eggan

Schizophrenia is a crippling neuropsychiatric disorder whose cause—which is in large part genetic—has remained elusive for centuries. However, recent studies suggest alterations in neuronal connectivity, potentially caused by decreased numbers of synapses, could underlie key schizophrenic symptoms. CACNA1C, a gene which encodes for a subunit of a calcium channel found on neurons, is both commonly mutated in patients with schizophrenia and is responsible for regulating a variety of processes important in synaptic growth. Although CACNA1C is widely recognized to be an important locus for schizophrenia research, there are currently few studies of CACNA1C which utilize human neurons to study how this gene impacts synapses. Therefore, this research creates a new methodology for analyzing the development of iPSC-derived human neurons. This method combines immunohistochemistry with machine learning to produce accurate and objective measures of neuronal development and synaptogenesis. After editing neural progenitor cells in the CACNA1C gene using lentiviral CRISPR constructs, this new technique was used to determine the effect of CACNA1C mutations on human neuronal growth. We found that mutations in CACNA1C cause highly significant reductions in synaptic density (numbers of synapses per unit area) of cortical neurons. This not only further defines the role of CACNA1C in schizophrenia, but also supports the idea that severe alterations in synaptic connectivity could be the cause of schizophrenia.

**Jess Moore**

***Reading Minds: A Neurocognitive Perspective on How Reading Evokes Emotion***

Research Director: Dr. Joanna Christodoulou

Joint Concentration with English

Literature not only has the capacity to relay information about emotive states to readers, but also the ability to elicit emotional responses from those readers. In doing so, it may be the case that literature makes use of the arousal and valence emotion networks in the brain. In order to show that these affective regions of interest make connections with reading centers in the brain, and that the strength of these connections varies in individual readers, this thesis analyzes functional fMRI data captured in both typical and struggling readers. Preliminary findings have shown significant functional connectivity from the amygdala to reading centers like Broca's area. Strength of these connections has also been shown to correlate with participants' reading-specific anxiety levels, showing not only that emotive and reading-centric centers in the brain can work in tandem with one another, but also that the strength of those connections is correlated with reading-specific affective responses in readers. Based on this evidence, I surmise that neurocognitively, readers are capable of processing both the literal meaning of a text and the emotional meaning of it in an interactive way. In doing so, they must first decode the meaning of the text itself, then ascribe an emotional value to that meaning that, in turn, influences their process of deducing meaning from the rest of the work. I argue that as a result of this process, diction in literature can benefit from a neurocognitive analysis in order to understand how authors optimize the valence and arousal levels of their texts for their desired emotion responses from readers. This argument is developed through a proof-of-concept neurocognitive literary analysis of recorded single word edits in drafts of the poems "Dulce et Decorum Est" and "Anthem for Doomed Youth" by Wilfred Owen. This work not only shows that emotion and reading are intricately linked in the brain, but also that authors make use of this biological mechanism, whether knowingly or unknowingly, in the crafting of their works.

**Kevin Ogonuwe**

***The Marginalized Mind in Constant Crisis: Racism-Related Adversity Alters Neurobehavioral Response to Threat and Portends Risk of Internalizing Psychopathology***

Research Director: Dr. Kate McLaughlin

Racism is a pervasive aspect of our society that actively harms people of color in a number of complex and diffuse ways. From a biopsychosocial perspective, chronic racism-related stress has been found to contribute to the development of negative physical and mental health outcomes in people of color, though the underlying mechanisms are not clearly understood. To that end, a nascent body of research has sought to ascertain how exposure to discrimination impacts children of color. Within this thesis, we sought to extend the literature in our consideration of exposure to racial discrimination as a form of early-life adversity. The objective of the present work was to investigate whether discrimination resulted in neurobehavioral threat responses that mediated associations between discrimination and psychopathology in children of color. In this sense, we aimed to characterize a neuropsychological process whereby racism-related adversity has developmental consequences that may contribute to the cumulative wear-and-tear effects of racism-related stress. We examined this neuropsychological model using behavioral and neurobiological measures drawn from two complementary datasets: one of which consisted of a sample of 158 youth aged 8 – 17, while the other was a nationally representative sample of 4,738 youth aged 10 – 13 from the Adolescent Brain Cognitive Development study. We confirmed that exposure to discrimination was associated with increased psychopathology severity. We also observed that reduced neural threat responses in the dorsal anterior cingulate cortex (dACC) and anterior insula were associated with increased depression severity. Moreover, we found that reduced neural threat response in the right dACC mediated depressive severity in non-White youth. These preliminary findings validate the neuropsychological implications of racism-related stress during child development, supporting the need for further research within this domain.

**Chris Okine**

***The Role of Prediction Errors in the Positive Memory Deficit in Depression***

Research Director: Dr. Dan Dillon

Major Depressive Disorder (MDD) is associated with an atypical memory bias. Compared to healthy adults, depressed adults typically display intact or enhanced memory for negative material, but impaired memory for positive material. Although this positive memory deficit is poorly understood, dopaminergic Positive Prediction Errors (PPEs) may be involved as they are associated with positive memory formation. Depression is linked to dopaminergic abnormalities that may result in blunted PPEs, possibly impairing hippocampal-based memory processes, such as recollection. To test this hypothesis, this study investigated the effects of PPEs on memory accuracy and confidence in 49 adults with elevated depressive symptoms and 46 healthy controls. Participants completed an oddball task where positive, negative, and neutral images were rarely presented and expected to elicit PEs with a sign dependent on image valence (e.g., positive image = positive PE). Twenty-four hours later, participants completed a recognition memory test. Relative to controls, depressed adults showed lower hit rates only for old positive images. There were no group differences in accuracy for old neutral or negative images, for accuracy in response to new images, or for confidence. ROC curves confirmed poor memory for old positive images in the depressed group but did not reveal a group difference in recollection. Investigating decision-making processes at retrieval through computational modeling revealed slower evidence accumulation exclusively for old positive images in depressed adults. Our results suggest that this positive memory deficit in depressed adults reflects blunted PPEs, although electroencephalography (EEG) data are needed to corroborate this account.

**Olivia Okoli**

***Neuronal Control of Sexually Dimorphic Behaviors: Investigation of the effects of Neuromodulation in the Ventral Premammillary Nucleus of the Hypothalamus***

Research Director: Dr. Catherine Dulac

Sexual dimorphisms in social behaviors are typically observed in socially naive animals, suggesting that genetically pre-programmed neural circuitry and physiological regulators modulate these behaviors. Certain sensory cues and sex hormones are known to be essential to the development of neural circuitry that governs sex-specific behaviors. This study was conducted to elucidate how the brain processes sensory signals and integrates them with hormonal signals in order to modulate dimorphic behavior. The Dulac lab has genetically identified Tachykinin-1 (Tac1) expressing neurons within the hypothalamic ventral premammillary nucleus (PMV) as a specific hypothalamic node gating sexually dimorphic behaviors that acts downstream of the sensory vomeronasal organ VNO. We used single molecule fluorescence in situ hybridization (smFISH) gene expression profiling to characterize the dimorphic expression of oxytocin receptors (Oxtr) in the PMV neurons and found more Oxtr+ cells in males than females. We next sought to identify the role of Oxtr in the function of PMV neurons in males. Viral mediated deletion of Oxtr from the PMV of adult male mice revealed a modulatory role for Oxtr in controlling inter-male aggression. Overall, this study sheds light on the neural circuits that underlie sex-specific behaviors, and their modulation by hypothalamic neuropeptides. Our data support the hypothesis that sex differences in social behavior can arise from the sensory and hormonal modulation of architecturally similar, but molecularly different, neural circuits.

**Ifedayo Omotunde**

***The Effect of SRGAP2 Knockout on the Temporal Properties of Critical Periods in Visual, Auditory, and Anterior Cingulate Cortices***

Research Director: Dr. Takao Hensch

Human brain development lasts relatively longer than other animals. However, the mechanisms governing the trajectory of brain development in humans remain unknown. An intriguing candidate is SRGAP2, a gene uniquely duplicated in humans implicated in regulating the maturation of excitatory/inhibitory balance. Deletion of SRGAP2, or overexpression of the human-specific SRGAP2C which inhibits SRGAP2, delays E/I maturation. Evidence indicates that E/I balance is linked to critical period timing suggesting that SRGAP2 may regulate critical period plasticity and circuit maturation timing. We can use animal deletion of SRGAP2 to model SRGAP2C's inhibition. We predicted that SRGAP2 knockout animals would display characteristics of delayed critical periods. We performed immunohistochemistry tests on the visual, auditory, and anterior cingulate cortices to get a broad view of SRGAP2's role in circuit maturation throughout the brain and across different critical period trajectories. We used immunohistology to study parvalbumin and perineuronal net expression in Het knockouts of SRGAP2. Our immunohistology found mice with a heterozygous knockout of SRGAP2 broadly displayed lower PV intensity and PV/WFA colocalization (representing perineuronal net formation), pointing to effective delay of critical periods. We then performed an optomotor task to test the visual behavioral response to SRGAP2 knockout. The optomotor task confirmed delayed visual development in Het mice. We concluded that SRGAP2 knockouts displayed delayed critical periods and had more juvenile visual behavior. These results help us answer essential questions about human evolution and development, and open avenues to new therapies such as life-long learning, treatments for neurodevelopmental disorders, and rescue of lost sensations.

**Oliver Piltch**

***Changes to Human Sleep in Long-Duration Spaceflight***

Research Director: Dr. Bob Stickgold

Previous projects showed that astronauts sleep significantly worse in mission than on Earth. However, it is unclear how sleep architecture is influenced by microgravity. Such information could inform our understanding of the adaptive mechanisms NREM and REM sleep on Earth. We investigated how sleep was affected during spaceflight relative to on Earth. Sleep was recorded using the Nightcap before (pre-flight, n=112 nights), during (in-flight, n=83 night), and after (post-flight, n=61 nights) missions aboard the Mir space station for four cosmonauts and one astronaut. We compared hand-scored REM, NREM, and wake during spaceflight to sleep on Earth, both preflight and postflight, using mixed-effects regression to account for subject variability. A variety of metrics demonstrate worse sleep in space. Participants averaged an hour less sleep in space ( $5.7 \pm 0.62$ ) compared to preflight ( $6.7 \pm 0.66$ ;  $p < .001$ ) and spent significantly more time awake in bed, leading to a 17.7% reduction in sleep efficiency. Sleep architecture was also affected by spaceflight: percentages of time in bed for NREM and REM decreased significantly by 14.1% and 25.8% respectively. REM latency also increased by nearly 50% during spaceflight. We also used mixed-effects modeling to assess if trends evolved over the course of the mission. Sleep latency increased significantly from start to finish ( $\beta: 0.40$ ;  $p < 0.001$ ), and the percent of sleep spent in REM also recovered with time in space ( $\beta: 0.04$ ;  $p \leq 0.01$ ). These longitudinal data add value to our nebulous understanding of how sleep functions in and adapts to microgravity.

**Paulina Piwowarczyk**

***Predictability and detectability affect processing of syntactic category violations:  
An EEG study***

Research Director: Dr. Jesse Snedeker

Joint Concentration with Linguistics

In language comprehension, listeners can use information to make predictions about the words and sentence structures that they are about to hear. This thesis asks specifically what happens when predictions about sentence structure are violated (e.g. “It takes two the tango”). We used electroencephalography (EEG) to record participants’ neural responses to structural errors (specifically syntactic category violations) that were spliced into a recording of a children’s story. We reasoned that if listeners had stronger expectations about upcoming words, there would be faster and/or more robust neural responses to the errors. Thus, we manipulated the predictability of the environment in which the violations occurred (high or low). We also investigated how detectable our violation manipulations were. Given the prior literature, we expected to find an Early Left Anterior Negativity (ELAN) in highly predictable environments, reflecting a rapid error response and increased processing difficulties associated with the errors. We also predicted a late positive-going response (P600) regardless of predictability, reflecting the slower process of reanalyzing the violations. However, we did not find either response; we instead found a sustained negativity, which has been argued to reflect difficulties in integrating information during comprehension. Moreover, this sustained negativity only appeared when the errors were highly noticeable and occurred in place of highly predictable words. Taken together, these findings suggest that, in naturalistic contexts, only errors that are detectable and that violate strong expectations lead to increased comprehension difficulties; all other errors may be disregarded or simply not recognized when listening to an engaging story.

**Kathleen Ran**

***Identifying novel AD-risk genes implicated in microglia engulfment function using iPSC-derived iMGLs***

Research Director: Dr. Beth Stevens

Recent genetic studies, including GWAS meta-analyses, heavily implicate the innate immune system in Alzheimer's disease (AD) and have generated intense interest in the role of microglia, the resident macrophages of the central nervous system. Well-known AD risk genes, including APOE and TREM2, have been found to modulate microglial phagocytic activity, further supporting its functional significance to AD pathogenesis. Few studies have directly investigated the correlation between changes in gene expression at the transcriptional level and changes in phagocytic activity at the functional level. This study sought to identify novel genetic regulators of phagocytosis in microglia using a genotype-to-function approach in iMGLs, human microglia-like cells differentiated from iPSCs. In part one, bioinformatic analysis of single cell RNA sequencing (scRNA-seq) data was conducted to survey the gene expression profiles of iMGLs challenged with different substrates. In part two, CRISPR-Cas9 knockout of known AD risk genes in iMGLs followed by flow cytometry measurement of synaptosome engulfment was performed to determine the functional effect on phagocytosis. This study's transcriptome analysis identified shared upregulation of genes associated with disease-relevant microglia states as well as genes significant within the lysosome pathway in substrate-challenged iMGLs. Furthermore, results from the CRISPR-Cas9 screen demonstrate that knockout of many newly identified AD risk genes directly impacts microglia phagocytic activity. Overall, our findings support a central role for microglia phagocytosis in AD pathogenesis and indicate that impacting microglia phagocytic function is a key mechanism by which genes confer AD risk.

**Nivi Ravi**

***The Modern Infant Listening Subject: Examining White Matter Organization, Music Environment, and Listening in Early Childhood***

Research Director: Dr. Nadine Gaab

Joint Concentration with Music

Longitudinal studies offer evidence for musical training-induced white matter plasticity in school-age children. The literature also suggests that putative neural predispositions may engender neural substrates for musical perception prior to formal musical training. The present research is three-fold: Study I examines relationships between music exposure and white matter organization in infancy, Study II explores impacts of the COVID-19 pandemic on childhood interactions with music, and the interdisciplinary final chapter imparts a humanistic approach to characterize the modern infant listening subject. Study I used diffusion tensor imaging and Automated Fiber Quantification to estimate fractional anisotropy of key white matter tracts in 22 infants (ages 2-13 months). The amount of music exposure was quantified using a parental questionnaire assessing infants' music environment. Controlling for age and socioeconomic status, findings suggest that relationships between white matter and music exposure are evident within the first year of life. In Study II, the COVID-HELP questionnaire was developed and administered to analyze the impact of the pandemic on music exposure and engagement in 1568 children (ages 0-11 years). During the pandemic, children are exposed to a richer home music environment but engage with fewer musical learning experiences when compared to pre-pandemic conditions. Findings carry implications for the hypothesis that neural predispositions for musical training are established prior to training onset and emphasize the importance of future research that considers the impact of dynamic home environments during times of crisis. Ultimately, the present research advocates for the integration of scientific and humanistic approaches to interdisciplinary inquiry.

**Vanessa Roser**

***Towards a Neural Mechanism of Associative Learning: Phasic Dopamine Activity Shifts from Rewards to Cues During Conditioning***

Research Director: Dr. Nao Uchida

After decades of investigation, the neural mechanisms behind associative learning still remain a fundamental research question in neuroscience. One of the most prominent theories regarding associative learning is the temporal difference model, which proposes that learning is driven by reward prediction errors that are thought to be encoded by midbrain dopamine neurons. When a reward is repeatedly paired with a preceding cue, the temporal difference model predicts that the burst of dopamine activity initially evoked by unexpected rewards will gradually shift earlier in time as the agent learns, eventually coinciding with the presentation of the cue. This central prediction that dopamine activity temporally shifts from reward to cue has not yet been observed in behaving animals, however, raising uncertainty about the mechanism behind associative learning. To address this unresolved question, we have recorded dopamine activity in the ventral striatum in mice using fiber fluorometry during the initial learning phases of a Pavlovian conditioning task. We also completed a reversal learning task and serial cue task to determine if previously trained animals will adopt different learning strategies in response to changes in task structure. Across all paradigms, we have been able to observe a gradual shift of the dopamine transient during learning, supporting the predictions of the temporal difference model. Confirming that this shift of dopamine occurs in the brain has the potential to bridge areas of ambiguity between computational theory and biological accounts of midbrain circuits, providing a clearer understanding of neural learning mechanisms.

**Aba Sam**

***The Fever Effect: Behavioral Changes Induced by Fever in Autistic Mouse Model CNTNAP2-/-***

Research Director: Dr. Catherine Dulac

Autism is a disorder characterized by deficits in social communication, restricted repetitive patterns of behavior, and language impairment; its etiology remains largely unknown. The fever effect is a phenomenon in which subsets of children with autism experience temporary abatement of aberrant behaviors while febrile. Patients improve in cognition, communication, repetitive behaviors and social interactions during fever. The fever effect offers an opportunity to investigate the neural circuits implicated in autism, provided that one can identify model organisms that exhibit analogous changes in behavior while febrile. In order to explore potential model mice, my project has attempted to characterize changes in behavior caused by fever in Contactin Associated Protein-like 2 knockout autism model mice (CNTNAP2-/-). Previous investigation from the Dulac lab found that CNTNAP2-/- mice showed a significant increase in time spent in close proximity with other mice during fever. However, a precise characterization of the observed behavior was not performed. Thus, we sought to identify the specific changes in social behavior during febrile episodes. Specifically, we examined sniffing, allogrooming, fighting and huddling behavior and hypothesized that fever would cause an increase in sniffing and huddling behavior. To test this, we analyzed behavioral changes in CNTNAP2-/- mice during social interactions with either sick or healthy conspecific mice. Our results indicate that fever causes an increase in huddling behavior in CNTNAP2-/- mice, specifically when interacting with other febrile mice. This thesis identifies the differences in behavior caused by fever in autism model mice, which may help better understand how fever may affect the behavior of children with autism spectrum disorder.

**Jake Schwencke**

***Movies & Memory: How Film Editing Can Impact Episodic Memory Formation***

Research Director: Dr. Gabriel Kreiman

Joint Concentration with AVFS

While we experience life as a continuous stream of input, memories are organized as discrete events. Event Segmentation Theory states that cognitive boundaries segment and structure memory, but the underlying mechanism for this process remains unclear. We hypothesize shifts in neural response within the medial temporal lobe reflect event segmentation and influence subsequent memory retrieval. To test this, we recorded activity from single neurons in patients with drug-resistant epilepsy during the viewing of movie clips. Patients were tasked with recalling the clips and order of events within them. We used “cuts” as visual cues for event segmentation and evaluated how the manipulation of cut locations can influence the temporal structure of episodic memory. Behaviorally, subjects tended to have improved memories of the temporal order of events from clips where cuts coincided with event boundaries. Neurally, we found single-units that responded significantly to abstract cognitive boundaries between events. Some of these neurons responded to a specific boundary in the clip, presumably maintaining temporal structure of events. This increased neuronal firing in the encoding associated with cuts that coincide with event boundaries may be a neural explanation for the improved temporal discrimination accuracy as well as an indication of encoding for temporal structure. Overall, these results reveal neural signatures associated with event segmentation as well as the impact an editor can have on an audience’s memory in the making of a film.

**Izzy Shaw**

***Hippocampal Correlations: A Fine-Scale, Trial-Specific Investigation of the Subcortical Brain and Distributed Cortical Networks Within Individuals***

Research Director: Dr. Randy Buckner

In the human brain, the hippocampus is a crucial subcortical structure known to be involved in memory and learning. By using a dense sampling approach to functional magnetic resonance imaging (fMRI) scanning of individual participants while they completed a series of memory and processing tasks, the full brain volume was able to be imaged and processed preserving high resolution. This presented an opportunity to consider the hippocampus in the context of distributed cortical networks. Using the specific functional connectivity of each individual, I first identified the portion of the hippocampus included within a hypothesized memory network (default network A, DN-A). I then correlated, using a trial-specific approach, the activity within this hippocampal region with activity in the cortical portions of DN-A, default network B (DN-B) and the Parietal Memory Network (PMN). I also correlated activity in the hippocampus with memory task conditions and semantic task behavioral strategies. I found that activity in the hippocampus was positively correlated with activity in DN-A, reinforcing the connection between the network and memory processes. Activity in the hippocampus was less correlated with activity in DN-B, further showing the distinction between the two networks. Surprisingly, activity in the hippocampus also did not correlate with activity in the PMN. Most importantly, I found that the hippocampus activated in response to semantic task conditions, supporting the role of the hippocampus in semantic memory processes. My findings confirm known relationships and more deeply explore the hippocampal role in memory, learning, and semantics.

**Taylor Shirliff-Hinds**

***Troublesome Teenagers: Developing an Experimental Paradigm to Quantify Socially Mediated Alcohol Consumption in Juvenile *Mus musculus****

Research Director: Dr. Catherine Dulac

The common laboratory mouse, *Mus musculus*, exhibits a myriad of social behaviors that provide unique insight into the complexities of the mammalian social brain. Interestingly, juvenile mice display increased alcohol consumption when interacting with peers, similar to what has been observed in human adolescents. However, the neural circuitry underlying the socially mediated increase in juvenile mice alcohol consumption has not yet been established. Based on previous studies on reward circuitry in the mouse brain, we hypothesize that interactions between the prefrontal cortex, which regulates impulsivity; the ventral tegmental area, which encodes reward prediction error and social reward; and the nucleus accumbens, which encodes alcohol and social rewards, modulate this risk-taking behavior. Probing this pathway first requires establishing an experimental paradigm to quantify alcohol consumption in juvenile and adult mice in the presence or absence of peers. As such, we tested a custom-built drinking setup where mice are presented with four bottles of liquid fitted with an electronic lick detector. We developed a data analysis pipeline to accurately characterize drinking behavior for individual mice and report behavioral trends over a continuously monitored period. To corroborate the lick sensor data, we set up a video camera illuminated by infrared light to manually count licks at night as a positive control. In sum, this thesis introduces a novel drinking setup and data analysis pipeline to measure mouse liquid consumption over multiple days, thus establishing a protocol for future experiments to examine social risk-taking in juvenile mice.

**Raymond So**

***Breath Metabolomics: Identifying Exhaled Biomarkers Associated with Acute Sleep Deficiency***

Research Director: Dr. Charles Czeisler

Joint Concentration with Chemistry

Sleep deficiency and sleep disorders have emerged as some of the most widespread individual and public health risks associated with adverse metabolic, cardiovascular, immune, and mental health changes. Likewise, disruption of circadian rhythms, which are self-sustaining, near-24-hour biological cycles, is understood to promote detrimental effects on cell, tissue, and whole-organism function. Despite such clinical implications, current gold-standard protocols to diagnose sleep states and circadian phase remain prohibitively difficult, time-consuming, and expensive. In this study, we laid groundwork establishing human breath as a potential alternative diagnostic tool for chronobiological applications. A novel Selected-Ion Flow-Tube Mass Spectrometry (SIFT-MS) was optimized and leveraged for a clinical study assessing changes in human breath profile of sleep-deprived night shift-workers before and after a sleep event. Our results show, for the first time, that successful deployment of SIFT-MS in clinical settings may be achieved, and that concentrations of 75 candidate biomarkers of acute sleep deficiency change as a result of dissipation of homeostatic sleep drive. Compounds emerging as significant from this study will be assessed further in future, more rigorous clinical studies tracking breath analyte concentrations hourly under controlled sleep deprivation conditions. This study contributes a novel methodology to conduct chronobiological diagnoses and adds insight to the rapidly-developing field of clinical breath metabolomics.

**Zoi Urban**

***Mapping the Emotional Mind: Investigating the Fornix Using Diffusion MRI-Based Tractography Techniques***

Research Director: Dr. Chiara Maffei

The fornix is the major white matter projection of the hippocampus and it may play an important role in the neuropathology of mental illness. Yet despite its establishment as a prominent limbic white matter pathway, very few neuroimaging studies using high quality data and large sample sizes have sought to understand how the fornix is implicated in depression and anxiety disorders, due to its unique curvature, small size, and location. Diffusion magnetic resonance imaging (dMRI) tractography allows for the 3D in vivo mapping of white matter pathways in the human brain, and can be used to quantify tissue properties in much greater detail than what is possible with other neuroimaging approaches. The contribution of this work is twofold: i) we provide accurate, manual tractography dissections of the fornix on high-quality dMRI data, that we used as a training dataset for an automated probabilistic tractography algorithm; ii) we use this algorithm to automatically reconstruct the fornix in a cohort of 206 adolescents (ages 14-17 years) on a spectrum of mental health and we quantified fornix-specific microstructural differences compared to 68 healthy adolescent controls. The manual dissection protocol presented here will be available for use by other studies, and the automated reconstruction of the fornix will be available to the community in the public software program, FreeSurfer. Our results i) show we could reconstruct the fornix manually in 16 subjects with high-anatomical accuracy, ii) indicate that the fornix microstructure, proxied by along-tract fornix-specific diffusion-derived measures, is significantly different in adolescents with anxiety, compared to healthy controls. Our findings suggest that the microstructure along the fornix may be used as a biomarker of anxiety disorders, as we observed a lateral disruption in fornix integrity in correlation with disordered mental health.

**Evelyn Wong**

***Towards a Technology for Single-Molecule Protein Sequencing: Engineering Binders for the Detection of N-terminal Amino Acids***

Research Director: Dr. Edward Boyden

Quantitative information regarding protein localization, such as subcellular coordinates of key neuropeptides, is crucial to understanding biological phenomena, allowing researchers to form hypotheses about their role in various pathological states and normal functions. The ability to gather such information constitutes a significant barrier to revealing principles that underlie physiological functions and informational processing within the brain. Current methods for proteomic analysis face the dilemma of gathering spatial information while maintaining scalability to the entire proteome and connectome. Here, we work toward the creation of a new technology that provides single-molecule resolution for identifying and localizing peptides and is scalable to proteins in all biological systems. Recently, we engineered “clickable” phenyl isothiocyanate, a chemically modified Edman’s reagent that conjugates and cleaves terminal amino acids for effective identification. In this project, we aim to develop, validate, and optimize N-terminal amino acid binders (NAABs) that differentiate between 20 proteinogenic amino acids. Polyclonal antibodies targeting ClickP-Lysine, ClickP-Glutamate, and a mixture of ClickP-amino acids were assayed for specificity and binding intensity toward their intended targets. ELISA tests indicated that candidate binders for ClickP-Lys and ClickP-Glu were highly discriminatory for their targets ( $P < 0.01$ ), and mixed candidate binders displayed positive binding intensity toward 18 amino acids ( $P < 0.05$ ). Antibody RNA sequences were transferred into yeast display vectors for directed evolution of binders with enhanced specificity and affinity. Applying this technology to model cellular dynamics during informational processing and disease will provide us with one of the tools needed to uncover potential biomarkers and develop therapeutic strategies.

**Melissa Yamada**

***Dissociation of Speed and Reward Maximization in Motor Skill Learning***

Research Director: Dr. Nao Uchida

Learning how to perform a set series of actions is a critical component of animal motor behavior, as these individual action sequences serve as the basis for more complex motor skills that are necessary for daily life. Furthermore, action sequence learning is impaired in neurodegenerative disorders such as Parkinson's and Huntington's disease. Therefore, studying this behavior may provide valuable insight into the pathophysiology of such movement disorders. In this study we sought to examine the behavioral patterns that emerge during action sequence learning in order to elucidate the factors and motivations underlying this process. We trained a cohort of mice (n=9) to perform an odor-cue-directed hierarchical action sequence task in which the animals had to complete two successive turns in opposite directions based on different odor cues to receive a reward. To assess motor behavior, we measured parameters such as reaction and movement time and trained a deep neural network using the software DeepLabCut to analyze video footage from training sessions. We determined that despite being given the same amount of time to respond to both odor cues in a sequence, the mice began to react more quickly to the second odor cue in a sequence than the first, indicating an increase in task automaticity. We also observed that the animals exhibited a continual decrease in sequence performance time throughout learning to the point of sacrificing accuracy for speed, suggesting that factors other than maximizing reward and reinforcement learning may play a role in driving sequential action learning.