Analyzing the behavior and neuronal circuits associated with the learning and memory related to aggression in Drosophila melanogaster

Research Director: Dr. Edward A. Kravitz

Aggression is widely observed across the animal kingdom and is influenced by a broad range of genetic and environmental factors. Individuals use aggression to acquire resources like food, territory, and mates, or to establish a social hierarchy. However, aggressive behavior, especially when in excess, can be indicative of brain or hormonal abnormalities in the organism. Past studies in the lab have clearly demonstrated that Drosophila melanogaster exhibit aggressive behavior, and that the aggressive behavior can be reliably and clearly measured. In Drosophila, flies that have lost a fight modulate their fighting strategies in subsequent fights in a way that results in an increased probability of losing agonistic encounters, highlighting a loser effect. Current research in the lab also points to a winner effect. I set out to further investigate the question of recognition between experienced individuals, the recognition that I hypothesized contributed to those loser and winner effects; I asked: how will two previous winners or two previous losers, if paired together, behave in the second fight? I used the paradigm developed in the lab that matches two similarly aged and size-matched flies that have been isolated since emerging from the pupal case for two encounters of 20 minutes with a rest interval of 10 or 60 minutes, where the 2nd encounter is with a previous loser or winner. I observed two results. First, the latency to lunge, the delay between the flies’ first encounter and first aggressive encounter (the lunge) is shorter after a 60-min interval of rest than after a 10-min period of rest for the loser-loser experiment. Second, the latency to lunge is longer after a 60-min interval of rest than after a 10-min period of rest for the winner-winner experiment. I hypothesize that these differences in the latency to lunge provide further evidence for, first, the modulation of a fly’s behavior after fighting, and, second, for a fly’s ability to recognize that modulation in an opponent fly.
**Characterization of a Novel Family of Odorant Receptors Associated with Innate Behavior**

Research Director: Dr. Sandeep Robert Datta

The Datta laboratory has identified a family of candidate receptor proteins that appear to drive specific innate behaviors using a novel neural circuit for olfaction. This project elucidated the functions and properties of these uncharacterized candidate receptor proteins, which will be referred to as Atypical Nasal Detectors (ANDs).

This AND family could serve as putative chemoreceptors for several reasons. These proteins have been identified in a unique neural cell type that defines a distinctive olfactory signal transduction pathway, which do not involve canonical GPCR olfactory receptors. The AND family seems to be expressed in an anatomically distinct subpopulation of sensory neurons. Possible odorants that these receptors detect have also been identified. The ligand binding to AND proteins results in a large influx of calcium into the cell that is dependent on external but not internal calcium stores. Behavioral experiments have shown that mice display avoidance behaviors towards ligands identified for this AND family. While evidence suggests that AND proteins may be calcium channels, they could just be helper proteins of a larger calcium mobilization complex.

To further characterize the nature of the AND family, the surface expression of these mutants using confocal microscopy and immunohistochemical staining was demonstrated. Conserved amino acids of interest were identified that could serve as a putative pore selectivity filter and constructed expression vectors of ANDs containing mutations in these conserved amino acids of interest. There is evidence suggesting that ANDs are ligand-induced calcium channels using functional calcium imaging assays.
Characterization of the Activity of Glutamatergic Neurons in the Pedunculopontine Tegmentum During Decision-Making

Research Director: Dr. Naoshige Uchida

Many studies have indicated that midbrain dopamine neurons encode “reward prediction error” (RPE) signals, signifying the difference between expected reward and actual reward. However, the mechanism underlying this process is still unknown. One important monosynaptic input to dopamine neurons is the pedunculopontine tegmentum (PPTg). Activation of PPTg increases burst firings in midbrain dopamine neurons, which resembles the activity of these neurons during positive RPE, in which actual reward is greater than expected reward. In addition, PPTg neurons have been found to respond to sensory cues. Thus, it is hypothesized that the PPTg may regulate conditioned responses in dopamine neurons. To test this hypothesis, we used a classical conditioning paradigm to train mice to associate odor cues with different probabilities of reward, simultaneously recording electrophysiological data from neurons in PPTg. Of the two main cell types in PPTg, glutamatergic and cholinergic neurons, the former seem to be the main inputs to dopamine neurons. We tagged glutamatergic neurons with Channelrhodopsin2 and identified them based on their response to optical stimulation. We found that glutamatergic neurons in PPTg encoded sensory information in a value-dependent manner; units responding to a cue that predicted a greater probability of reward had a significantly higher firing rate relative to the firing rate of units responding to a cue that predicted a smaller probability of reward. These results suggest that responses to cues are value-dependent in the PPTg and may be conveyed to dopamine neurons through glutamatergic inputs.
Comparison of the nest-building behavior of Peromyscus polionotus and Peromyscus maniculatus as a mechanism of thermoregulation

Research Director: Dr. Hopi Hoekstra

Previously conducted experiments indicate a species difference in the latency to nest of Peromyscus maniculatus and Peromyscus polionotus. In the following experiments, I address whether both species are equally able to construct and maintain nests, and whether our holistic nest scoring scale is functionally relevant. Because our nest scoring scheme addresses only the structure of the nest, I developed a functional measure of the nests’ insulation. Analysis of this data is ongoing, but results are expected to confirm a correlation between high structural nest score and high insulation. In order to determine whether animals fatigue during repeated behavioral experimentation, I ran the standard nesting protocol twice on 22 Peromyscus maniculatus animals and 29 Peromyscus polionotus animals, with differing amounts of time elapsing between the two trials. The results of this experiment reveal that animals of both species scored approximately 0.4 lower on the nesting score (of 4) during the second round of experiments (p=0.00), but this effect still paled in comparison to the difference due solely to the species, which accounted for a difference of approximately 1.4 at the 1 hour time point (p=0.00). In order to determine whether the two species are equally able to construct and maintain complex nests, I left 29 animals undisturbed with nesting material for 7 days. The results indicate that there was no significant difference (p=0.57) between the species’ resulting nests, suggesting that observed differences in nesting behavior between these species is a difference in the latency to nest rather than a difference in ability.
Development and neural bases of happy and angry facial processing in infants: A study in NIRS and eye tracking

Research Director: Dr. Charles A. Nelson

The ability to detect and classify faces is critical to navigating one's social environment. Facial features encode individual identity, while facial expressions present an individual's emotional response in an interaction. In the absence of the ability to communicate verbally, it is particularly important for infants to distinguish emotions from facial expressions. Recent work using behavioral and brain-based measures has specifically explored the development of this capability in infants, displaying a clear shift in the recognition of fearful faces at seven months of age. At this point in the first year of life, infants are able to distinguish fearful faces from other emotional expressions. The development of the capability to perceive angry and happy faces, emotional conditions with which the infants are more familiar, has remained understudied. In an attempt to explore the development of this ability, I employed functional Near-Infrared Spectroscopy (fNIRS) to examine the hemodynamic response to happy and angry faces in the temporal cortex of typically developing five-month-old (n=30) and seven-month-old infants (n=32). Time course data suggests that the processing patterns of these emotional categories at five-months-old were distinct from those at seven-months-old. At five-months-old, the change in concentration of total-hemoglobin in response to happy faces in the right temporal cortex was significantly different from the change seen in response to the same emotional condition in the left temporal cortex (p=.007). In addition, using eye tracking, we explored if infants attend to a particular region of the face when viewing a specific emotional category. (Analysis still under review)
Differential Susceptibility to Early Adverse Experiences: The Effects of Oxytocin Receptor Gene Variations and Institutional Rearing on Emotional Processing

Research Director: Dr. Charles A. Nelson

Children exposed to the adverse early experience of institutional rearing exhibit impairments in various domains of development, including social and emotional development. The biological mechanism behind the observed social and emotional behavioral deficits may be influenced by neural circuitry modulated by oxytocin as previous research suggests that oxytocin gene variants predict prosocial behavioral outcomes. This analysis investigated how individual variations in oxytocin receptor gene (r53576 OXTR SNP) predict atypical neural activity in response to emotion stimuli and deficits in emotion processing, which may be associated with poor prosocial peer behavior. Furthermore, this project examined how early rearing conditions may interact with the genetic variant in predicting social development outcomes. The current study tested the ability of three groups of eight-to ten-year-old Romanian children—children randomly assigned to remain in institutional care, children randomly removed from institutional care and placed in foster care, and community children in their biological homes—to discriminate emotional stimuli and process emotional information in making social decisions. The study measured the brain electrophysiology measurement of event related potentials (ERPs) in an emotion discrimination task and the behavioral measurements of the direct observation of children, teacher reports of peer social behavior and emotion processing behavioral task. Results revealed no significant association between 1) the OXTR variant allele and 2) the OXTR variant and the rearing environment with the electrophysiology variable, emotion discrimination task, social behavior observation or the teacher report of social skills. The OXTR variant and the interaction between the genetic variant and the environment were predictive of the individual’s social judgment. This finding further supports the role of oxytocin and the caregiver environment in determining peer social functioning.
Evaluating the effects of candidate proteins on APP cleavage and Alzheimer’s disease phenotypes in human iPSC derived neurons

Research Director: Dr. Dennis Selkoe

The Amyloid Precursor Protein (APP) is initially processed by α- or β- secretase to generate APPsα or APPsβ. Further cleavage by γ-secretase results in Aβ, which has been implicated in Alzheimer’s Disease. To study the normal function and processing of APP, we have investigated the effect of candidate ligands on APP cleavage in numerous cell lines and found Reelin, Lingo-1, and Pancortin have the most robust effects. However, their role in human neurons, as well as their underlying molecular mechanisms, remains unclear. Here we have used neuronal precursor cells (NPC) and neurons derived from human induced pluripotent stem cells (hiPSC) and overexpressed or knocked down proteins of interest to observe the effects on APP processing. Furthermore, we also used neurons derived from familial Alzheimer’s Patients to study the potential role of these proteins in Alzheimer’s Disease. Using AMAXA nucleofection, I was able to overexpress Pancortin, Reelin, and Lingo-1 in NPCs. For Pancortin, we found an isoform specific reduction on APP processing, as we did in other cell lines. Lingo-1 overexpression lowered APPsβ levels as expected from results in other cell lines, but unexpectedly produced no changes in APPsα. We have also developed a protocol to knockdown specific gene targets using lentiviral transduction. We obtained almost complete knockdown of target proteins in NPCs and 50% knockdown in neurons. Furthermore, we have identified an interaction between Pancortin and Lingo-1. Finally, we have tested the effect of these proteins on cellular phenotypes associated with AD - Tau level, Tau phosphorylation, and astrocyte activation.
**Evidence for Synchronous Theta and Gamma Oscillations during Ketamine-induced General Anesthesia**

Research Director: Dr. Emery Brown

Like all other general anesthetics, alfentanil has the ability to cause unconsciousness. However, this drug has also been shown to produce seizures in patients with epilepsy, a trait which is considered to be paradoxical in comparison to alfentanil’s general anesthetic effects, and which is also shared by only a few other anesthetics. Though induced seizure activity has also been observed while using the anesthetic methohexital, this drug binds to GABA receptors, whereas alfentanil mainly acts on opioid receptors, and so the two likely use different mechanisms to generate the similar effect. While previous studies have proposed possible mechanisms that underlie the paradoxical excitation that occurs under the influences of the anesthetic propofol, such methods have not yet been to potentially explain paradoxical seizure activity in drugs such as methohexital and alfentanil. Understanding the underlying mechanisms that govern the effects of these drugs on epileptic patients would not only provide a better understanding of how the drug causes seizures, but would also allow for a better understanding of seizures in general. Unfortunately, current knowledge about the production of seizure activity in epileptic patients while under alfentanil is limited. The current study uses data analysis techniques to evaluate the consistency, reliability, and potency of the observed effect of alfentanil on patients with epilepsy.
Examining Differences in the Default Mode Network between Individuals at Clinical High Risk for Psychosis and Healthy Controls in China

Research Director: Dr. Larry Seidman

Objective: The default mode network (DMN) is a neural network that represents a fundamental characteristic of human experience, free and voluntary thought. It is typically shown to be abnormal in individuals with schizophrenia (SZ), exhibiting hyperactivity and hyperconnectivity. In this study, we hypothesize that the default mode network of clinical-high risk individuals for SZ would show abnormal connectivity compared to healthy controls. Clinical high-risk individuals are those in the prodromal state for SZ, characterized by a decline in functioning and the appearance of or worsening of mild psychotic-like symptoms before the full onset of illness. Method: Clinical-high risk individuals (N=20) and healthy controls (N=22) group matched for age and sex remained at rest with eyes open during functional magnetic resonance imaging (fMRI). Seed-to-voxel analysis was used to identify the default mode network. Differences in connectivity were identified between healthy controls and CHR. We examined across group and across sex differences. Results: Healthy controls had significantly more anticorrelations between the MPFC and DLPFC than the CHR. Results on across sex differences to be included after analysis is complete. Conclusions: Clinical-high risk individuals for SZ show greater anticorrelation between the MPFC and DLPFC, an area known to be important for working memory task performance. Patients with SZ also exhibit this pattern. These findings suggest that the normal ability to switch between the DMN and task-positive network (TPN) in healthy individuals is reduced in both patients with schizophrenia and CHR. This inability to switch attention from internal to external may explain some of the cognitive deficits that are commonly seen in patients with SZ.
“Spatial Regulation of Chr15qD3 Imprinted Genes in the Brain” had a two-fold aim: the first aim was to address the issue of whether the parentally biased expression of genes in the chr15qD3 imprinted cluster was spatially regulated across brain and body tissues, while the second aim was to investigate whether the methylation status of differentially methylated regions (DMRs) within the cluster correlated to the potential spatial regulation in the parental biases of each gene. To fulfill the first aim, I relied on Pyrosequencing, a PCR-based sequence by synthesis technology that permits allele-specific quantitation, to measure the contribution of each parental allele to the expression of each gene in the cluster across 16 brain regions and seven body tissue regions. The Pyrosequencing data revealed that all genes in the cluster exhibited a parent-specific expression bias that was restricted to the brain, and that all but one gene, Peg13, had a maternal bias. Moreover, the Pyrosequencing data highlighted varying degrees of the maternal bias across different brain and body tissues in one gene of special interest in the cluster – Argonaute 2 (Ago2). For example, Ago2 had high maternal bias in the Cortex, intermediate bias in the Cerebellum, and virtually biallelic expression in the Liver. This key piece of data enabled us to then answer our second aim, by using bisulfite sequencing techniques to quantify whether the levels of DNA methylation correlated to the observed spatial regulation of the parental bias. The second aim is about 30% complete as of now.
Inducible chronic overexpression of transcription factor Krüppel-like factor 9 (Klf-9) as a model for neurodegeneration

Research Director: Dr. Amar Sahay

The functioning of the hippocampus is compromised in several age-related neurodegenerative diseases. The preservation of cognitive function during aging is largely dependent on the integrity of the entorhinal cortex projections onto the dentate gyrus and CA1 sub regions of the hippocampus. Alterations to the hippocampal circuit such as oxidative stress, neurogenesis, DNA damage, and changes in excitability also accompany neurodegeneration, but the progression of these events remains unknown. To begin to address this question, our lab has developed a murine genetic system in which induced overexpression of the transcription factor Kruppel-like factor 9 (Klf-9) leads to the loss of spines of mature neurons in the dentate gyrus. By overexpressing Klf-9 for four and eight weeks, I used this model as a tool to map the sequelae of neurodegenerative events following synaptic loss. Overexpressing Klf-9 for four and eight weeks increased levels of neurogenesis and reactive astrocytes, consistent with established models of Alzheimer’s disease. There was a transient decrease in spine density in CA1, but a more prolonged reduction in dendritic spine density in the outer molecular layer of the dentate gyrus. Examination of levels of calcium-binding protein Calbindin, revealed a persistent reduction as seen in the mouse and human dentate gyrus associated with Alzheimer’s disease. In contrast, levels of inhibitory neurotransmitter Neuropeptide Y, did not differ between groups. These results suggest that our genetic model recapitulates some, but not all the characteristics of neurodegeneration. Specifically, the loss of synaptic inputs to the dentate gyrus may be implicated in changes in reactive neurogenesis and gliosis, loss of calbindin immunoreactivity, reduced dendritic spine density and altered mossy fiber connectivity, but may not be directly contribute to aberrant inhibitory circuit activity. Thus, preserving synaptic input to the hippocampus could potentially offset some of the detrimental effects of neurodegeneration seen in Alzheimer’s disease.
**Investigating Differences in Neural Activity of Young Children with and without Attention Deficit/Hyperactivity Disorder**

Research Director: Dr. Margaret Sheridan

Affecting approximately 5% of school-age children worldwide, Attention Deficit/Hyperactive Disorder (ADHD) is a neurodevelopmental disorder characterized as impulsivity, hyperactivity, and inattentiveness to a degree that is disrupting across settings. Despite the high prevalence and the detrimental outcomes associated with ADHD, there remains a lack of a clear pathophysiological profile and neurodevelopmental underpinnings of ADHD. Consequently, ADHD diagnosis remains reliant on behavioral assessments. While these methods provide a relatively stable diagnosis for children over the age of 7, ADHD diagnoses for children between the ages of 3-7 fail to achieve above a fifty-percent accuracy rate (Willcutt & Carlson, 2005). Addressing this issue, the first objective of this thesis aims to describe the potential differences in neural activity between ADHD and control children of 3-7 years of age using electroencephalogram (EEG). Interested in the association of adverse environmental factors and ADHD, the second part of this thesis will compare the EEG of high-risk ADHD participants to the EEG of low-risk ADHD participants. In the final portion of this thesis, we will test if EEG measures, the presence of risk factors, or a combination of both can predict which ADHD participants will continue to meet diagnosis after the age of 7. Using a linear regression, we found no significant differences in the EEG data of young children with and without ADHD. We also did not find any significant differences between the EEG of ADHD children exposed to known ADHD risk factors compared to ADHD children not exposed risk factors. As EEG of older ADHD children have been shown to have significant differences, we propose that perhaps the children were too young to demonstrate significant differences in their neural activity.
Investigating Intrinsic Brain Networks in Adult and Pediatric Patients with Complex Regional Pain Syndrome
Research Director: Dr. David Borsook

Chronic pain is a significant national public health burden. About one-third of United States adults has chronic pain. Complex regional pain syndrome (CRPS) is a type of chronic pain that often affects the limbs and can be precipitated by injuries, such as fractures, sprains, and surgery, which may cause damage to the peripheral nervous system. This project uses functional magnetic resonance imaging to investigate the intrinsic brain network activity of adult and pediatric patients with CRPS compared to the healthy population through whole brain connectivity analysis. This study is the first to examine resting state networks (RSNs) of adult CRPS patients through whole brain connectivity analysis. It extends previous work comparing RSNs of pediatric CRPS patients with healthy controls. This study found that for the adult CRPS patients, all the RSNs displayed both increased and decreased connectivity in CRPS patients compared to controls. The cerebellum, sensorimotor, visual lateral, and central executive networks had the most significant increase in connectivity in patients compared to controls. The left frontoparietal network had the least increase in connectivity for patients versus controls out of all the networks. For decreased connectivity in CRPS adults compared to healthy adults, the left frontoparietal network, right frontoparietal network, auditory, and sensorimotor network had the most drastic decreases in connectivity. The default mode network and visual medial network had the smallest amounts of decreased connectivity for patients versus controls among all the networks. There were relatively fewer differences in RSNs for CRPS children compared to healthy children subjects.
Localizing subtypes of impulsivity to subregions of the striatum
Research Director: Dr. Joshua Buckholtz

It is known that impulsivity is not a unitary construct, yet little attention has been paid to the neural substrate of its subtypes. Substantial research has linked heightened impulsivity to impaired dopamine (DA) function in the striatum. More specifically, low striatal D2/D3-autoreceptor availability was found to predict increased impulsivity. This paper aims to map the common distinction of impulsivity into choice impulsivity vs. motor impulsivity onto subregions of the striatum. Combining Magnetic Resonance Imaging (MRI) with Positron Emission Tomography (PET), the D2R-availability in the ventral and dorsal striatum is measured in healthy volunteers. It is hypothesized that D2R availability in the dorsal striatum will correlate more with motor impulsivity while D2R availability in the ventral striatum will correlate more with choice impulsivity. Action-cancellation performance in the Stop-Signal Reaction task is used to measure motor impulsivity. Intertemporal choice as measured by the Delayed Discounting task is used to assess choice impulsivity.
Objective: Cocaine abuse and depression are frequent comorbidities in HIV infection that have been associated with worse treatment outcomes and impaired neurocognition. However, the effect of cocaine use on longitudinal trajectories of neurocognitive function and depressive symptoms in HIV-infected cocaine users remains unknown, particularly in subjects from the post-HAART era.

Methods: Neurocognitive test and depression data from 341 HIV- and HIV+ men enrolled in the Multicenter AIDS Cohort Study (MACS) from 1996 to 2009 were analyzed at baseline and over time. Through a nested case-controlled design, groups with and without heavy cocaine use were matched for HIV, HCV, education level, age, and race. A latent class mixed model approach was used to empirically identify group trajectories of neurocognitive function and depressive symptoms over time. Subsequent multivariate logistic regression models were used to determine the odds of group membership by demographic and clinical risk factors, including heavy cocaine use.

Results: At baseline, crack cocaine use was associated with impairment in global cognition among HIV subjects. However, self-reported depressive symptoms predicted impairment in global cognition among HIV- and HIV+ subjects, learning and memory in HIV+ subjects, executive function in HIV- subjects, and the Stroop Test Interference Trial Errors in HIV- subjects. However, analysis of group trajectories suggested a potential longitudinal interaction between HIV infection and cocaine use. Among HIV+ subjects, crack cocaine use predicted worsening performance on the Rey-Auditory Verbal Learning Test (RAVLT) Interference Trial 6. Cocaine and crack cocaine use also predicted persistently high levels of depressive symptoms in HIV+ subjects. Heavy smoking, but not cocaine use, predicted decreased functioning in learning and memory for HIV+ subjects.

Conclusions: Among HIV+ subjects, crack cocaine use is associated with longitudinal neurocognitive decline in RAVLT Interference Trial 6, which suggests an additive effect on attention and outcome monitoring. Cocaine and crack cocaine use predict persistently high levels of depressive symptoms in HIV+ subjects, and depressive symptoms are associated with baseline neurocognitive impairment in HIV- and HIV+ men. Therefore, depression and drug use are important factors to consider in the treatment and care of HIV+ men in the post-HAART era.
Maternal care or neuronal despair? Impact of fragmented maternal care and the BDNF Val66Met polymorphism on the prefrontal cortex in mice

Research Director: Dr. Takao Hensch

Maternal care plays a critical role in the neurobiological and behavioral development of infants. Disruptions of maternal care during infancy is a form of early life stress that can have profound consequences, with response to stressors mediated by genetic factors. One such factor, the brain-derived neurotrophic factor (BDNF) neurotrophin, has an essential role in brain functions and neuroprotection; a common single nucleotide polymorphism in this gene, substituting a methionine for a valine at position 66 (Val66Met), can alter the processing, trafficking, and amount of BDNF. We examined the effect of this polymorphism in adult mice on their response to fragmented maternal care during PND 2-9, using a reduced nesting material paradigm to disrupt mother-infant interactions. We used the elevated plus maze and open field test to measure anxiety, and the acoustic preference paradigm to assess the critical period of the medial prefrontal cortex. This was followed by RT-PCR of the frontal part of the brain to test for markers of plasticity.

Results indicate a significant effect of genotype, sex, and early life care on anxiety. Anxiolytic effects of music were limited to control care males and males with a heterozygous BDNF Val66Met polymorphism. Mice who experienced fragmented maternal care showed no acoustic preference shifts, while mice under control care demonstrated increased preference for music, indicating a shift in mPFC plasticity. The gene by environment interaction of the Val66Met polymorphism and fragmented maternal care, modulated by gender, resulted in decreased mPFC plasticity and differences in anxiety levels later in life.
Microglia Mediate Synapse Loss in Early Stage Alzheimer’s Disease Via the Classical Complement Cascade

Research Director: Dr. Beth Stevens

In brains of Alzheimer’s Disease (AD) patients, microglia, the resident macrophages of the brain, are often seen surrounding plaques, which are mostly composed of aggregated Aβ. Another hallmark of AD is early, region-specific synapse loss. Synapse loss highly correlates with memory loss and is an early event in AD pathology. It is thought that the oligomeric form of Aβ is the key species, rather than Aβ plaques, that induces synapse loss in the AD brain. Whereas much of the research on microglia has focused on its potential interaction with Aβ plaques, the role of microglia in early, pre-plaque AD brains, in particular its role in mediating synapse loss, is unknown. Previous studies have highlighted microglia as key cellular mediators of synapse loss in the developing brain via the classical complement cascade. Therefore, I hypothesized that microglia are activated early in pre-plaque AD brains to mediate synapse loss and that this involves the complement cascade. To address this, I used in vivo microglia activation and engulfment assays, synapse quantification, immunohistochemistry and confocal imaging in transgenic (J20 and APP/PS1) and acute mouse models of AD. Microglia in the hippocampus of pre-plaque (1 and 3 month) J20 hAPP mice had increased lysosomal activity (as measured by CD68 staining) compared to wild type controls. I also observed significant upregulation of CD68 in wildtype mice that received Aβ oligomers compared to monomers. To understand if the increased lysosomal activity indicates increased synaptic engulfment by microglia, we performed acute intracerebroventricular injections of soluble Aβ oligomers or monomers in mice whose post-synaptic marker, Homer, is tagged with a green-fluorescent transgene. We observed a greater engulfment of Homer by microglia in the hippocampus of mice challenged with Aβ oligomers versus Aβ monomers. Further, there was no significant difference in microglial lysosomal activity when mice deficient in the complement molecule C1q were treated with Aβ oligomers, suggesting that C1q is necessary for this process. I also saw C3, the downstream component of C1q, decorate more synapses in the hippocampus of J20 and APPPS1 mice versus wildtype controls. CR3, the high affinity receptor for C3, was also upregulated in J20 mice. Taken together, my findings suggest that microglia, via a complement dependent mechanism, aberrantly prune synapses in pre-plaque AD-like brains.
Microglia-Specific Contribution to Rett Syndrome Behavioral Phenotypes
Research Director: Dr. Beth Stevens

Rett Syndrome is an X-linked neurodevelopmental disorder that affects 1 in 10000 females. It is characterized by the appearance of Autism Spectrum Disorder (ASD)-like symptoms along with visual, motor, and breathing abnormalities after two years of normal postnatal development. In 1999, the MECP2 gene, which encodes for the methyl-CpG-binding protein 2 (MECP2), was implicated in the disorder. Although the gene has been found, the mechanisms behind the disease progression are still unknown. A recent study has suggested that microglia play a role in the pathology of Rett Syndrome. To test this hypothesis, we developed a strain of mice that had a wild type MECP2 background with a MECP2-knockout present only in microglia. We conducted a variety of behavioral tests using these mice and compared them to their wild type littermates. The tests included a rotarod performance test, a pre-pulse inhibition test, a plethysmography test, an open field test, a visual acuity test and a neurological assessment to observe mobility, gait, tremors, hind limb clamping, and general condition. We found that the mice without a functional MECP2 expressed in microglia have decreased sensory reactivity to auditory stimulation, have a shorter latency to fall on a rotarod performance test, have more mobility and gait abnormalities, and have smaller velocities in the open field test. These results suggest that microglia do play a role in the development of hallmark symptoms of Rett Syndrome.
Microglial Responses to Environmental Enrichment in Alzheimer’s Disease Models
Research Director: Dr. Dennis Selkoe

Alzheimer’s disease, marked by the progressive cerebral accumulation of amyloid-β protein as amyloid plaques, is the most prevalent form of neurodegenerative disorder in the United States and other developed countries with similarly high life expectancies. There is some evidence suggesting that exposure to environmental novelty protects the brain against the effects of amyloid-β accumulation. Here, we aimed to determine the bioactivity of soluble amyloid-β oligomers on microglia from wild-type mice with and without environmental enrichment training. Using confocal microscopy, we studied the morphology of microglia and quantified functional markers thereof, looking for morphological changes or microglial-specific protein changes induced by amyloid-β oligomers. We found that microglia in the hippocampus of environmentally enriched mice displayed a more ramified morphology compared to standard housing mice, while hippocampal injection of amyloid-β in standard housing mice resulted in the retraction of microglial branching, typical of activated microglial morphology. These results suggest that environmental enrichment attenuates the microglial activation observed following the injection of amyloid-β oligomers. Thus, the opposing effects of environmental enrichment and amyloid-β oligomers on hippocampal microglia may contribute to the apparent neuroprotective role of environmental enrichment in Alzheimer’s disease progression.
Mindfulness meditation as a potential intervention to improve future self-continuity
Research Director: Dr. Sara Lazar

Mindfulness meditation is an increasingly popular therapeutic training that has been shown to have numerous positive effects on quality of life and wellbeing. Mindfulness meditation has been shown to lead to increases in cortical thickness in areas in the default mode network, which is associated with decreased mind wandering and improved self-awareness. Researchers in decision making have also found evident that this network could be associated with perceptions and feelings of similarity and connectedness to one’s future self. This study aims to link the two areas of research by exploring the hypothesis that a 4-week Mindfulness-Based Stress Reduction (MBSR) intervention can increase mindfulness, future self-continuity and cortical thickness in the default mode network when compared with an active control. Surprisingly, the data showed no significant difference in the mindfulness measure between the two groups, and showed increase in future self-continuity in the active control condition when compared to the MBSR condition. The data collected through fMRI showed another unexpected finding that cortical thickness of brain structures in the default mode network increased in the active controls, which has been typically seen only in MBSR conditions. Both results show changes in the active control that were expected from in the MBSR condition, and lead to many new questions on necessary time for MBSR as well as the potential for this active control to become a novel therapeutic intervention.
Neural Correlates of Imitation in Children with ASD
Research Director: Dr. Charles A. Nelson

Autism spectrum disorder (ASD) is characterized by deficits in social communication. Previous neuroimaging work has revealed that during social processing tasks, unaffected siblings (UnS) of children with ASD have regions of shared dysfunction with the ASD children, in addition to regions of unique activity. This project builds upon these findings by comparing brain activation patterns between ASD, UnS, and typically developing (TD) children in the context of imitation, a behavior important for social learning and understanding. In our study, TD, ASD, and UnS children (ages 3.5 -- 6.5) engaged in an imitation task where they first observed a video demonstration of an actress activating a toy's outcome, and then played with the toy themselves. Functional Near-Infrared Spectroscopy (fNIRS) was used to measure changes in oxy- and deoxyhemoglobin in the bilateral frontal and temporal cortical regions during these activities. They were eyetracked during video observation, and their behaviors during free play were manually coded. The data streams from ASD, UnS, and TD children will be compared to determine differences in behavior, visual attention, and neural processing. We hope to use this data to explain discrepancies in imitation between the groups. By analyzing the brain activity unique to UnS, we may better understand the mechanisms that allow UnS to compensate for ASD risk and avoid fully manifesting the signs of ASD. These mechanisms may provide useful targets for ASD interventions, which capitalize upon the unique ways that those at risk for ASD learn.
Optogenetic manipulation of hippocampal place cells causes impairment of stereotyped tracking behavior
Research Director: Dr. Venkatesh N. Murthy

The hippocampus’ role in spatial navigation relies on distinct firing patterns of place cell ensembles; however, its role during tracking of natural sensory stimuli remains unclear. The work in this thesis uses optogenetic techniques to investigate the role of hippocampal place cells in olfactory-driven spatial navigation. Mice, when trained on an odor-tracking paradigm for several weeks, changed their searching strategy from an adaptable, odor-tracking pattern to a more stereotyped approach that relied on past encounters with reward locations. To manipulate CA1 cells during this tracking pattern, I forced hippocampal CA1 place cells to produce a light-sensitive protein (channelrhodopsin 2), allowing those cells to be overexcited by blue light. I engineered a circuit that would both deliver light to these deeper brain regions and be controlled wirelessly by infrared light. High frequency (20 Hz) pulses of light during searching behavior resulted in an “unlearning” of the past search strategy as stereotyped behavior weakened. Following initial light stimulation, mice were unable to navigate to rewards as effectively. Following several half hour sessions of stimulation across multiple days, tracking patterns resembled those from the first days of training, indicating an extinction of reward location memories. Interestingly, these results were frequency dependent: during slower, 2 Hz stimulation, mice did not change their foraging strategy or lose memory of reward locations. These results suggest that above a certain frequency threshold, overexcitation of CA1 pyramidal cells impairs proper hippocampal functioning, which can lead to drastic adaptations in searching strategies.
Optogenetic stimulation of auditory corticofugal projections modulates activity in the auditory midbrain

Research Director: Dr. Daniel Polley

Sensory signals are known to be processed in increasingly complex ways as they move from the peripheral nervous system into the central nervous system and “ascend” toward the cortex on corticopetal pathways. Corticofugal pathways, which travel away from the cortex, have the potential to modify these signals by feeding back on subcortical processing. Prior studies of the effects of corticofugal pathways in the auditory system have yielded mixed conclusions with respect to the modulatory characteristics of these pathways. As these results were obtained through methods that affect the entirety of auditory cortex, the finding that corticofugal pathways originating from different layers of this area have different properties and targets may explain this variation. We used an optogenetic approach to specifically activate layer 6 corticothalamic neurons and examine the characteristics of corticofugal signals that modulate the firing rate of the medial geniculate body (MGB). We then used optogenetics to similarly examine the effects of layer 5 pyramidal cells on the inferior colliculus (IC), an auditory midbrain nucleus. We did not find any optogenetic parameters whose variation consistently modified the firing rate of the MGB, but we found that modulation of laser power and onset timing relative to the presentation of sound modified the firing rate of the IC. This suggests that the firing rate of pertinent corticofugally-projecting cells and the timing of this firing relative to the receipt of an ascending auditory signal are two key features that may modify the strength of the ascending signal, at least in the IC.
Plasticity of dopaminergic neural circuits in the mouse olfactory bulb

Research Director: Dr. Venkatesh N. Murthy

Dopaminergic (DA) neurons populate the outer layer (glomerular layer) of the olfactory bulb in mammals. Unlike most periglomerular cells, DA neurons form connections to more than one glomerulus and are therefore believed to be involved in odor processing across multiple channels. In this project, I studied how DA neuron response patterns to odors are changed by previous exposure and ability to identify the odors. Mice from the DAT-GCaMP3 strain were trained to identify odors through a two odor forced choice discrimination task. After training, strength and scope of dopaminergic neuron responses to odor stimulation was determined using two photon and wide field imaging of the olfactory bulb in the anesthetized, head-fixed mice. Mice demonstrated the capability to discriminate between odors at a near-perfect accuracy following two weeks of training. Two photon imaging results showed a spatial clustering of dopaminergic neurons exhibiting significant responses to specific odors. Imaging data comparing DA neuron odor responses in trained versus untrained mice suggests that trained mice had a smaller proportion of neurons responding to the odors used for training. However, the relative magnitude of responses in responding neurons to the training odors was stronger in the trained mice than the untrained mice. These results shed light on how DA neural circuits change in response to demand in order to facilitate odor recognition.
Human consciousness cyclically alternates between wakefulness and sleep. On one hand, sleep has been implicated in a variety of cognitive processes, such as memory consolidation after learning. Interestingly, sleep-dependent offline memory reactivation in the absence of external stimuli has been shown to contribute to memory formation as well. On the other hand, the role of wakefulness in this complex process is not well understood.

Electroencephalographic recordings have provided a means to characterize neural activity during wakefulness as within either alpha (8-12 Hz) or beta (16-25 Hz) frequency bands. In particular, alpha wave activity during wakefulness helps shape cognition in a top-down manner by determining the levels of engagement or disengagement, respectively, of certain brain regions. Functional connectivity studies on resting state activity have shown that alpha wave fluctuations correlate with a decrease in blood oxygen level-dependent connectivity between the visual cortex, the prefrontal cortex, and the thalamus. In turn, this suggests that alpha wave activity plays a role in functional inhibition of these networks, perhaps during memory replay.

The current EEG study aims to investigate if relative alpha power during quiet rest preceding and/or following a validated learning-dependent maze task would predict retest performance. The hypothesis posits that more relative alpha wave activity would serve as a measure of increased attentional capacity for processing internal, rather than external, information, and as such predict more subsequent improvement. The expected (currently pending) results are that alpha power will be a reliable predictor of improved retest performance. A potential conclusion for these findings would be that alpha waves are more prevalent during quiet rest with eyes closed because they are involved in filtering out irrelevant information.
Adrenoleukodystrophy (ALD) is a devastating X-linked disorder caused by mutations in the ABCD1 gene. Blood brain barrier (BBB) disruption with migration of leukocytes to the brain, as indicated by a rim of contrast enhancement on MRI, has for long time been implicated as responsible for the most devastating inflammatory demyelination seen in the disorder. Moreover, recent ex-vivo histopathology indicates dysfunction of brain endothelium at the leading edge of the lesion. In this thesis, I used a human brain microvascular endothelial cell (HBMEC) model of the BBB to quantify the impact of ABCD1 upon gene and protein expression of molecules involved in 1) leukocyte-endothelial cell interactions (adhesion assay) and 2) permeability (transmigration assay). I discovered that ABCD1 is highly expressed in brain but not in other endothelium and that its deficiency causes upregulation of adhesion molecules and decreased tight junction protein expression. This resulted in an increase in adhesion and permeability of monocytes. These changes were exclusive to HBMEC and not other endothelial cells. Together this data demonstrated that the absence of ABCD1 in brain endothelium causes increased permeability to monocytes and may be critical to the pathophysiology of inflammatory demyelination in ALD. This thesis identified potential novel therapeutic targets and provides a functional in-vitro assays that will allow high-throughput screening of various compounds in their ability to restore BBB function in ALD.
Role of Kif21a in peripheral spinal motor and sensory neuron development
Research Director: Dr. Elizabeth Engle

The human disorder congenital fibrosis of the extraocular muscles type 1 (CFEOM1) is characterized by restricted eye motility, strabismus, and ptosis. It is believed to be caused by dysinnervation of the extraocular muscles by the oculomotor nerve. Previous studies in the Engle lab established that CFEOM1 is the result of recurrent and sometimes de novo heterozygous missense mutations in KIF21A, which encodes for KIF21A, a member of the kinesin motor protein superfamily, and that CFEOM1-related amino acid substitutions result in attenuation of the protein’s autoinhibition and increased microtubule binding by mutant KIF21A without affecting the motor’s velocity or run length. Ultimately, the mutant KIF21A causes stalling of the developing oculomotor axon and dysinnervation of the extraocular muscles.

Although the gain-of-function mechanism of mutant KIF21A in the etiology of CFEOM1 has been determined, the physiological role of wild type KIF21A during development has not been elucidated. In order to study this question, the Engle lab generated a mouse model in which Kif21a had been truncated (Kif21aKOMT/KOMT). The heterozygous Kif21a+/KOMT mice are indistinguishable from wild-type, while Kif21aKOMT/KOMT mice die shortly after birth and harbor very low levels of motor-truncated Kif21a during development. Thus, Kif21aKOMT/KOMT mice provide a model to study the roles of Kif21a in neural development. The Kif21aKOMT/KOMT mice do not exhibit the CFEOM-related phenotypes at early developmental stages, which had been reported in CFEOM1 mutant mice by the Engle lab. However, we have found developmental defects including shorter length and less branching of spinal axons, followed by axon degeneration, in Kif21aKOMT/KOMT mice in vivo. Our in vitro spinal motor neuron and DRG neuronal culture data are consistent with these developmental defects. Using DRG explant cultures and live cell imaging, we found that there was an increase in retracted growth cones and that growth cones underwent more wandering trajectories for Kif21aKOMT/KOMT DRG cultures compared to wild-type. These observed defects of Kif21aKOMT/KOMT axon growth demonstrate that Kif21a is critical for normal spinal peripheral axon development.

Furthermore, because Kif21aKOMT/KOMT mice die at birth we used conditional Kif21aKOMT/KOMT mice with Cdx2-Cre, which knocks out Kif21a only in the caudal region of the developing embryo, in order to observe the functional consequence of development loss-of Kif21a function in the caudal half of adult mice. These mice show severe locomotor behavior defects, supporting a role for Kif21a in the spinal nerve development. Altogether, our findings support a critical role of Kif21a in spinal peripheral axon development.
Role of Ror in retinal development and Age-related Macular Degeneration pathophysiology
Research Director: Dr. Neena Haider

Age-related macular degeneration (AMD) is a progressive medical condition that causes vision loss in the center of the visual field. The wet form of advanced AMD results from abnormal blood vessel growth and blood/protein leakage underneath the macula. Microarray expression data, linkage data, and clinic based cross-sectional studies have revealed the influence of the retinoic acid receptor (RAR)-related orphan receptor α (Rorα) on neovascular AMD. Rorα is found in both the ganglion cell layer and the inner nuclear layer (layers which are reduced by nearly 50% in the eyes of wet AMD patients) and has demonstrated roles in regulating the development of cone photoreceptors.

Methods: The following study uses Rorα knock out models to investigate the role of this receptor in retinal development. Two mouse lines, one where Rorα is not expressed in M-opsin and S-opsin cones and another where Rorα is knocked out from retinal progenitors, are used to examine the roles of Rorα in the development of these various cell types at different embryologic time points.

Results: Immunohistochemistry revealed that deletion of Rora in Cone yields reduced expression of M and S opsins in the adult mouse while deletion of this receptor in Chx10 yields reduced expression of S opsins alone.

Conclusion: This led to the conclusion that Rora is more directly implicated in the development of cone cells sensitive to short wavelengths than their middle wavelength counterparts. Another nuclear receptor or perhaps another gene that regulates Rora plays a role in the final development of M-opsin cones.
Role of Vomeronasal Receptors Vmn2r65 and Vmn2r88 in Pheromone Detection
Research Director: Dr. Catherine Dulac

Communication and the exchange of information play a crucial role in the lives of numerous living organisms. Communication can come in several different forms and serve various purposes. Among this rich diversity of communication, one type of communication that is still not very well understood is chemical signaling via pheromones. Pheromones are odorless chemicals secreted by an individual that can influence the behavior and development of another individual. An olfactory organ known as the vomeronasal organ (VNO) detects pheromones and triggers genetically preprogrammed sets of behaviors in various vertebrate species. Among vertebrates, the house mouse (Mus musculus) makes extensive use of pheromone signaling to communicate with conspecifics. Two particular VNO transmembrane receptors known as Vmn2r65 and Vmn2r88 were found to detect pheromonal cues from both mouse pups and adult mice. To gain more insight into the neural basis of pheromone detection and the behavioral specificity of VNO receptors, behavior assays were performed to characterize the behavior of Vmn2r65 and Vmn2r88 wild type (WT), heterozygous (Het), and knockout mutant (KO) strains of male mice. Three different types of behavior were assessed: (1) Parental, (2) Mating, and (3) Aggression. Video recordings of each behavior assay were taken by using an overhead camera. These video recordings were subsequently scored for specific behavior parameters by using a computer software program called Observer (Noldus). Preliminary results suggested that the deletion of Vmn2r65 and Vmn2r88 receptors specifically affected behavior directed toward mouse pups, but not adult mice.
Selectively Altering Intertemporal Decision-Making Using Transcranial Direct Current Stimulation
Research Director: Dr. Joshua Buckholtz

Decision-making is a multifaceted phenomenon studied in a variety of disciplines ranging from economics to psychology, where researchers have a growing interest in the field due to the correlations between psychopathologies and poor decision-making. Two types of decision-making, intertemporal (impulsive) and probabilistic (risky), have been found to utilize distinct neural circuits, with intertemporal decision-making localized in the dorsolateral prefrontal cortex and probabilistic decision-making localized in the superior parietal cortex and middle occipital gyrus. Participants received either active (30 minutes) or sham (30 seconds) anodal stimulation applied to the dorsolateral prefrontal cortex through transcranial direct current stimulation (tDCS). During and following the stimulation, decision-making tasks measuring delay and probability discounting were administered as measures of intertemporal and probabilistic decision-making, respectively. The participants who underwent active stimulation selected a significantly lower amount of the impulsive choice (a smaller, immediate reward) compared to participants who underwent sham stimulation. On the other hand, there was no significant difference between the sham and active participants when comparing the proportions of selecting the risky choice (a larger, riskier reward). These results suggest that intertemporal decision-making can be selectively altered through the use of tDCS without altering probabilistic decision-making, indicating that tDCS could potentially be used as a treatment to assist people with deficits in intertemporal decision-making.
Small molecule that binds Max, inhibits Myc activity and reduces the viability of human cancer cell lines
Research Director: Dr. Angela Koehler

Dysregulation of the transcription factor Myc has been observed in a wide range of human cancers, including glioblastoma multiforme and neuroblastoma. Transgenic experiments that inappropriately express Myc in model organisms reveal a host of cellular consequences including uncontrolled cell proliferation and growth, while Myc knockdown reduces proliferation and increases apoptosis in cancer cell lines and mouse models. Pharmacologic inhibition of Myc would be appealing for many cancers; however, oncogenic transcription factors are often deemed "undruggable" by conventional methods. Here we used a small-molecule microarray screen to identify MS2, a compound that binds Myc associated protein X (Max). In follow up reporter assays MS2 was a potent inhibitor of Myc mediated transcription. MS2 also lowered Myc and Max protein levels in a dose dependent fashion in 293T cells, and reduced the viability of a panel of Myc dependent cancer cell lines. MS2 did not disrupt Myc-Max heterodimer formation, mandating future mechanism of action experiments. Lastly, RNA sequencing in the mouse embryonic stem cells was performed to assess MS2’s effects on gene expression, and 19 MS2 analogs were synthesized to generate preliminary structure activity relationship data.
**Social Isolation Stress in Male and Female Rats: Role of Kappa Opioid Receptors**

Research Director: Dr. Elena Chartoff

Dynorphin, an endogenous ligand at the kappa opioid receptor (KOR) is necessary for anxious and depressed mood states in male rats. The aim of our current study was to assess the role of KORs in the ability of a stressor, social isolation (SI), to produce negative affective states in male and female Sprague-Dawley rats. If the KOR system is necessary for the onset of these states, then SI stress should increase endogenous dynorphin tone and blunt the depressive-like effects of the selective KOR agonist U50,488. To test the effects of SI stress on KOR-induced depressive-like states, we used the place conditioning paradigm. To test the effects of SI stress on anxiety, we used the elevated plus maze (EPM). We found that a low dose of U50 (1.25 mg/kg) produced a trend towards conditioned place aversions in group-housed rats of both sexes, but SI stress resulted in potentiation of U50-induced place aversion in males and a blockade of aversion in females. In the EPM, isolated male and female rats spent a smaller percentage of time in the open arms compared to group-housed rats. Additionally, JDTic, a KOR antagonist, increased open arm time in both male and female rats. These results indicate that SI stress produces negative affective states that involve activation of the KOR system. They also raise the possibility that SI stress produces higher endogenous KOR tone in females that occludes effects of exogenous KOR activation.
Sound Asleep: Auditory Reactivation of Emotional Memory Consolidation During Sleep
Research Director: Dr. Robert Stickgold

How does our brain determine which memories are retained and which are forgotten? Previous studies have shown that covertly reactivating memories during sleep may influence the retention of stored memories. Ken Paller’s study in 2013 tested the effect of targeted memory reactivation of object-location associations during sleep and wakefulness. Results showed that reactivating memories rescued memories that otherwise would have been forgotten. In the present study, we use Paller’s learning task to test the effect of covert reactivation of emotional memories during different stages of sleep.

Through a computerized learning task, participants memorized the locations of 50 emotional images located at random locations on the computer screen, each of which was paired with a corresponding sound. Half of the 50 corresponding sounds were then used as auditory cues to reactivate memories of the images’ locations during sleep. These sounds were presented during either slow-wave sleep (SWS) or during rapid eye movement sleep (REM). Control participants in the wake group received no nap opportunity. We expect those who received auditory cues to show improved memory of the objects’ locations at retest. Because REM sleep is strongly associated with emotions, we hope that reactivating emotional memories during REM would be more effective. To test the role of auditory reactivation on long-term memories, participants return for another re-test one week after their first visit. If memories selectively reactivated during the nap show improvement during immediate and delayed re-test, these results could clarify the potential role of sleep-dependent memory reactivation on learning and memory consolidation.
Use Of Stem Cells Loaded With Hyaluronidase-Expressing Oncolytic Viruses To Treat Malignant Brain Tumors

Research Director: Dr. Khalid Shah

Oncolytic viruses provide a safe treatment alternative for glioblastoma multiforme (GBM) as they are capable of selectively targeting tumor cells while circumventing any unfavorable side effects; however, certain delivery obstacles prevent adequate distribution of the viruses at the tumor site and thus hinder their antitumor efficacy. In this study, hyaluronic acid (HA) is shown to be an important component of the tumor extracellular matrix (ECM) that not only hinders viral spreading within the tumor mass but is also expressed in elevated amounts in both established and patient-derived GBM lines. As such, intratumoral injection of a conditionally replicating adenovirus expressing soluble hyaluronidase (ICOVIR17) into nodular GBM resulted in degradation of the HA, enhanced viral spread, and a greater antitumor effect that allowed for a significant increase in mouse survival. Furthermore, in order to improve transportation of ICOVIR17 from the administration site to the tumor, human adipose-derived mesenchymal stem cells (MSC) were used as delivery vehicles. This provided an additional increase in antitumor efficacy by ensuring targeted migration to the GBM cells and a greater distribution of viruses around the tumor site. Nevertheless, a means of translating this strategy to suit more clinically relevant settings was necessary. By applying a biodegradable synthetic extracellular matrix (sECM) to encapsulate the ICOVIR17 loaded MSCs within the resection cavity, a significantly decrease in tumor regrowth was achieved in post-resection mouse models. Finally, since viral replication reduces the effectiveness of vector-mediated oncolytic therapy, the antitumor potential of inducible, replication-defective proAdenovirus-GFP-Fluc and proAdenovirus-TRAIL was explored.
Using Functional Connectivity to Understand Memory System
Communication During Off-line Learning
Research Director: Dr. Edwin Robertson

As humans learn different facts and skills each day, the ability to retain this new information is essential and often reliant on different types of memory systems, particularly procedural and declarative systems. Traditionally thought to be influenced separately, behavioral studies have found that declarative memories are capable of interfering with procedural memory consolidation, suggesting communication between the two. To investigate the underlying biological mechanisms of this interference, functional connectivity MRI (fcMRI) was used to measure changes in participant resting state functional connectivity after learning a procedural task immediately followed by an interfering declarative or control task. A behavioral effect was induced; subjects who received the declarative task showed procedural interference during retesting. Control subjects showed no significant difference between procedural tests. fcMRI data showed that changes in somato-motor network after learning could predict off-line procedural consolidation. Control subjects showed an increase in somato-motor connectivity post-task, while interference subjects showed a decrease. There was a positive correlation between somato-motor network connectivity change and procedural learning scores. These results demonstrate that off-line consolidation is measurable at rest following learning. Network functional connectivity serves as a useful indicator of biological mechanisms that create memory enhancement across memory systems.
Winner Effect in Female Dendrobates tinctorius Dominance Contests

Research Director: Dr. Lauren O'Connell

The majority of current research on the development of a social hierarchy due to dominance contests between conspecifics has focused exclusively on male-male challenges and entirely excluded amphibians. This experiment sought to understand the hormonal and neural responses following such encounters between a set of residential Dendrobates Tinctorius and conspecific intruders. Single-fight trials were employed, in which the subjects were filmed interacting for 30 minutes. Of the 17 residential females, roughly half participated in physical actions around a dominance contests (i.e. lunging towards the intruder or wrestling), and won these encounters. Behavior was scored to analyze latency to stalking behavior and its duration, number of attacks, and the duration of each attack and successful mount. This behavior was regressed with resident subject terminal blood samples, which were assayed for testosterone, progesterone, estradiol, and cortisol. Immunohistochemistry was used to analyze AVT and TH expression and colocalization with pS6 in each resident’s brain across 12 regions associated with aggression and motivation. Results have not been analyzed though behavior has been scored and blood assayed. IHC has been used as described, and images will be taken of these regions (findings subsequently quantified) over the next several weeks.