Cindy Chau

Long-term Glial Response To 56Fe Radiation In APP/PS1 Transgenic Mice, the.

Research Director: Dr. Cindy Lemere

We seek to determine cognitive impairment, CNS changes, and risks for Alzheimer's disease following exposure to 56Fe irradiation (IRR) in preparation for future interplanetary missions to deep space. Previously, we demonstrated that a single dose 56Fe IRR (1000 MeVlu; 10 CGy or 50 CGy) in young adult mice increased susceptibility to cognitive decline and enhanced Alzheimer's Disease (AD) amyloid-β (Aβ) pathogenesis in male, but not female, APP/PS10E9 transgenic (Tg) mice 8 months later. Female Tg mice were resistant to long-term 56Fe IRR effects in neurobehavioral measurements in addition to changes in insoluble Aβ levels and plaque load, despite having greater overall Aβ plaque burden than male Tg mice. Thus, we undertook a follow-up study to further elucidate the sex- and dose-specific effects of 56Fe IRR on plaque-specific glial pathologies in order to understand whether glia mediate Aβ plaque clearance in irradiated Tg mice. We used immunofluorescence (IF) staining and confocal microscopy in addition to 3,3 diaminobenzidine (DAB) staining to quantify morphological changes and co-localization between glia and Aβ plaques. We found that female Tg mice had more plaque-associated gliosis (IF) than male Tg mice (4 plaques per mouse). After increasing analysis to 30-40 plaques per mouse (DAβ), we also found modest radiation-specific effects in female, but not male Tg mice. We conclude that while 56Fe IRR may increase overall gliosis in both female and male APP/PS1 mice, there may be sex specific and radiation-specific effects in the recruitment of microglia and macrophages to Aβ plaques.

Sarah Chun

Frontal gamma activity is associated with language ability in 18-month-olds with high familial risk for autism.

Research Director: Dr. Chuck Nelson

The goal of this research was to investigate whether induced gamma power during a passive language-based task is associated with language ability in 18-month-olds at high familial risk for autism. This study analyzed 18-month EEG data and language measures collected as part of the longitudinal Infant Sibling Project, comparing infants by their risk level for ASD development. Infants with a sibling with ASD were assigned to high-risk group (HRA) and those without siblings or first degree relatives with ASD were assigned to low-risk group (LRC). Language abilities were measured using the Mullen Scales of Early Learning (MSEL). Two types of auditory stimuli were presented while EEG was continuously recorded; words were identified as either "familiar" or "unfamiliar" based on typical language development standards of MacArthur-Bates Communicative Development Inventories (MBCDI). Linear regression models were used to examine group differences in the relationship between language-induced frontal gamma power and receptive language ability. A negative relationship between language-induced low gamma power (40-45Hz) in response to familiar words was observed in the HRA+ group ($p=0.053$). In addition, the relationship between gamma and language in HRA+ group was significantly different from HRA- group ($p=0.014$) and marginally different from LRC group ($p=0.078$) in response to familiar stimulus. No significant relationship was shown in any groups between the gamma response to unfamiliar words and language ability. This study demonstrates early differences in brain-language associations between high-risk 18-months-olds with and without ASD. Future directions can include investigation of the longitudinal trajectory of language-induced EEG power.

Mark Czeisler

Characterizing the Morphology of Suprachiasmatic Nucleus Neuronal Interactions: Exploring Ultrastructural Features that May Subserve Circadian Synchronization in Mammals.

Research Director: Dr. Jeff Lichtman

Circadian rhythms are near-24-hour oscillations of daily cycles including those of rest and activity, feeding and metabolism, and hormone production. Mammalian circadian rhythms are coordinated by a hypothalamic pacemaker called the suprachiasmatic nucleus (SCN). The SCN receives light-dark signals via axonal innervation by intrinsically photosensitive retinal ganglion cells (iPRGCs). Dense SCN connectivity contributes to the generation of a coherent wave-like output rhythm propagated from the SCN to other brain areas and the body. Understanding the neuroanatomical foundations of intercellular coupling could help to elucidate communicative mechanisms of the SCN. In this study, I used serial electron microscopical techniques to generate a 2.97x10^6-um3 super-high-resolution image volume of 180(um)x330(um)-50(nm) sections of SCN and optic chiasm tissue. I traced a cluster of SCN neurons, plus axonal and dendritic processes extending from each neuron, to create a digitized wiring diagram. The wiring diagram reveals structures providing potential mechanisms for photic entrainment and intercellular communication. SCN neurons projected into the optic chiasm, where they displayed significant synaptic connectivity. Moreover, myelinated axons contacting SCN neurons could originate from ipRGCs. SCN neurons displayed extensive somato-somatic contact, providing a potential opportunity for ephaptic coupling via ion exchange between closely apposed cells, which could have a strong influence on synchronization and enable the observed wave-like patterns driven en mass. Several neurons also projected toward to outer shell of the SCN. Helping to elucidate structural features of SCN connectivity that may lead to an improved understanding of photic entrainment and circadian synchronization, which will better inform sleep and circadian physiology.

Shenyece Ferguson

Exploration of the Effects of Attention on Neural Processing of Visual Information, an.

Research Director: Dr. George Alvarez

Attention is a major cognitive feature that constantly works to identify salient information. The principal objective of this experiment was to determine whether the way attention was allocated has an effect on the processing of visual information. The main hypothesis states that during bilateral attention, in which there are objects in both halves of the visual field, each brain hemisphere processes information from the contralateral visual field, but during unilateral attention, in which there are objects only in one half of the visual field, both hemispheres are involved in processing the information in that visual field. Functional MRI was used to gain information about changing patterns of neural activity, specifically in the intraparietal sulcus, while participants completed a multiple object tracking task that involved both bilateral and unilateral attention. A machine learning classifier was used to analyze the dissimilarities in activity during the two attentional conditions and to determine if there were considerable differences between the patterns of activity in each condition. The classifier was responsible for extracting patterns of neural activity from a subset of the data and applying that information to predict which condition corresponded to which pattern of brain activity in a different subset of data. The results of the classifier did not show a significant difference between the classifier's accuracy during unilateral and bilateral attention in either hemisphere, however through the use of brain preference maps and a cross decoder, there is evidence that visual processing does change depending on the way attention is allocated.

Heather Forbes

Oxytocin and the Induction of Labor in Determining Early Neurodevelopment in Prairie Vole Models.

Research Director: Dr. Marcy Kingsbury

My thesis examines how the administration of synthetic oxytocin (sOT) at birth affects the development of brain circuitry in offspring. We know that OT signaling at birth is neuroprotective in that it 1) mediates the GABA excitatory/inhibitory switch and establishes normal patterns of neural synchrony, and 2) serves as a buffer against oxidative stress by reducing the metabolic demand of neurons. Previous studies have demonstrated that brain perineuronal nets (PNNs) which surround parvalbumin-expressing interneurons (PVIs) are sensitive to early hypoxic-like conditions and that their malformation may contribute to the dysregulation of GABA interneurons and aberrant neural activity. It is not currently known if different concentrations of OT impact neural circuitry development. Pregnant prairie voles received a low, medium or high dose of sOT prior to labor. At postnatal day 20, we examined the brains of offspring born to sOT-injected moms and compared them to the brains of offspring born via an untreated vaginal birth. Specifically, we examined PVIs, PNNs and microglia, immune cells that respond to inflammatory events. By tracking the density of these cells within the anterior cingulate cortex, we examined the relationship between oxytocin administration and the development of PVIs, PNNs and microglia. We found that the low and high dose of sOT administration gives rise to the development of normal PVI/PNN brain circuitry while the medium dose does not. We have examined only male offspring so it will be important to investigate if there are sex differences in neural circuitry following the administration of sOT at birth.

Polly Gabrieli

Neuronal and Genetic Correlates of Prosocial Behavior in Mice.

Research Director: Dr. Ziv Williams

Prosocial behavior – volunteering to help others – plays a central role in human society. Understanding the pathways that drive prosocial behavior is a key question in modern psychology. Better models of this behavior may also provide insights into the pathology of social disorders in humans. However, no assays have been developed to assess prosocial behavior in mice, a key model animal. In this study, we developed a novel behavioral assay in which mice could save a conspecific from the aversive experience of shock by moving between zones. Our results demonstrate that these mice avoid the shock-inducing zone only for cagemates but not unfamiliar animals, indicating prosocial behavior towards familiar conspecifics. We also recorded from the anterior cingulate cortex (ACC) in the medial prefrontal cortex during the assay. Using these recordings, we identified a subset of neurons in this region that predict the decision to move out of the shock-inducing zone, as well as neurons that selectively respond to a cagemate being shocked. Finally, we studied the behavior of mice from two models of altered social cognition, including the Shank3+/fx model of autism and Gtf2i-2+/- model of Williams Syndrome. Our preliminary results indicate that these mice behave differently in the prosocial assay. Ultimately, studying the differences between the behavior of wild-type and socially disordered mice may provide shed light information on understanding the root causes of these disorders. Moreover, examining helping behavior in mice may be a step forwards towards unlocking the complex neural mechanisms behind human prosocial behavior.

Emma He

Development of 5-HT3AR-Expressing Interneurons in Auditory Cortex, the.

Research Director: Dr. Anne Takesian

During early life, the brain experiences critical periods of heightened plasticity to represent the external world. Our lab has identified a class of inhibitory interneurons in the primary auditory cortex (A1) that gate critical period plasticity. These cells reside in cortical layer 1 (L1) and express ionotropic serotonergic receptors (5-HT3AR). The mechanisms by which 5-HT3AR cells integrate neuromodulatory and thalamic input to control critical period timing remain unclear. Here, we characterize how the activation of 5-HT3AR cells changes within and outside of the critical period. First, we performed immunocytochemistry on Brainbow-expressing 5-HT3AR interneurons to reveal distinct morphological changes across development. Next, we characterized neuromodulatory and thalamic inputs on specific subtypes of 5-HT3AR cells. We used vesicular glutamate transporter 2 (vGluT2), a marker of thalamocortical boutons, to reveal a preferential thalamic innervation of 5-HT3AR cells that did not express vasoactive intestinal peptide (non-VIP). We then used in situ hybridization to find that these non-VIP cells also preferentially expressed nicotinic acetylcholine receptors (nAChRs) containing the α4 subunit. Finally, since past studies have shown that prenatal exposure to serotonin reuptake inhibitors (SRIs) affects critical period timing in humans, we examined whether 5-HT3AR cells may be implicated. We performed functional studies using voltage-sensitive dye imaging (VSDI) to reveal a heightened sensitivity to SRIs in A1 during the auditory critical period. Taken together, our preliminary data suggest that neuromodulatory and thalamic inputs strongly activate 5-HT3AR cells during the critical period, and that this activation changes across development.

Chris Hinojosa

Optimizing In-Vitro Motor Neuron Differentiation from Pluripotent Stem Cells via Epigenetic Alteration.

Research Director: Dr. Kevin Eggan

Pluripotent stem cells differentiate into motor neurons according to highly specific epigenetic regulation of DNA. However, this process occurs slowly, diminishing the feasit motor neuron regeneration and limiting the rate of research on neurodegenerative disease in vitro. We aimed to address these issues in accordance with previous research-by inhibiting the activities of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) in differentiating cells, with the intent of elucidating the effects of these particular epigenetic alterations on the rate of motor neuron differentiation. Specifically, we treated multiple lines of differentiating embryonic stem cells with 5-azacytidine, valproic acid, and vitamin C, each of which modify the activities of particular epigenetic mechanisms. 5-azacytidine and vitamin C reduce DNA methylation levels via inhibiting DNMT activity and inducing demethylation, respectively, whereas valproic acid functions as an HDAC inhibitor. After 7 and 14 days, we used immunofluorescence staining to quantify the presence of known differentiation markers in treated and control cell lines, allowing us to determine the extent of motor neuron differentiation within each line. Quantification analysis is still being performed, though we expect to observe that DNMT-inhibited cells experienced slowed differentiation, whereas HDAC-inhibited cells experienced accelerated differentiation, relative to that undergone in control cell lines by the end of the experiment. These results would provide greater insight into the role of epigenetic mechanisms in motor neuron differentiation, in addition to how such mechanisms may be modified to optimize the rate of differentiation for research and/or therapeutic purposes.

Isabelle Iversen

Fetal Alcohol Spectrum Disorder: Alcohol's effect on the brain and the risk for chronic adult diseases.

Research Director: Dr. Wolfram Goessling

Fetal alcohol spectrum disorder (FASD) is the leading preventable cause of mental retardation in America and is estimated to affect 2 – 5% of the United States population, including 200,000 new cases each year. The disorder occurs when the developing fetus is exposed to alcohol through maternal drinking habits. Alcohol and its primary metabolite acetaldehyde are toxic and can impair fetal development. We aimed to describe the pathogenesis of FASD in zebrafish and identify novel biochemical targets for drug treatment. FASD was induced in zebrafish by exposing fertilized embryos to ethanol at varying concentration and duration. Developmental damage was assessed by measuring the size of various tissues with Image J, and statistical analysis was performed with Prism. We found that greater ethanol exposure was associated with severe edema, facial abnormalities, shorter length, organ damage (including the liver, pancreas, and the brain), and mortality. We also found that FASD fish had significantly more fat accumulation when given a high fat diet. Thirdly we found a significant rescue effect of FASD characteristics using Vitamin C, an antioxidant, and N-Acetyl Cysteine, a supplement form of cysteine. Finally, we found that prenatal alcohol exposure causes anxious behavior which can be rescued by current anti-anxiety medications. These results suggest that prenatal alcohol exposure greatly effects the development of the fish, FASD is a risk factor for diet induced obesity, and some developmental and behavioral effects of FASD may be prevented.

Anahita Iyer

Identifying Phospholipid Pathway Proteins as Modifiers of α-Synuclein Phenotypes in Cellular Models of Parkinson's Disease.

Research Director: Dr. Dennis Selkoe

Parkinson's disease (PD) is a neurodegenerative disorder that causes severe motor dysfunction, While current therapies treat symptoms, they do not slow or reverse disease progression. PD is characterized by the presence of Lewy bodies, abnormal cytoplasmic inclusions composed of insoluble aggregates of the protein alpha-synuclein (as), within neurons in the brain. These vesicle-rich inclusions are believed to result from the binding of as to membranes, contributing to progressive neuronal degeneration. Understanding as-membrane interactions that contribute to as toxicity may lead to the identification of new targets for PD treatment. Membrane properties such as saturation, fluidity, charge, and curvature have been found to mediate the lipid binding ability of as. Because the major membrane phospholipid types have different structures that influence such membrane properties, we investigated whether altering membrane phospholipid composition affects as inclusion formation. We strategically increased or decreased the production of these different phospholipids according to known lipid pathways using both a genetic and biochemical approach. We overexpressed candidate genes involved in these lipid pathways and tested pathway activators or inhibitors in inducible human neuroblastoma cell lines expressing a toxic form of aS prone to aggregation, and observed the effects on inclusion formation. From these screens, we identified candidates likely to rescue inclusion formation for further analysis, including lipid profiling and additional parameters of toxicity. We performed inclusion assays with the most promising lipid-modifying overexpression targets in rat cortical neurons to better model disease. This work contributes to a mechanistic understanding of how as-membrane interactions may participate in PD.

Alec Jones

Exploring the Glymphatic System: A Foray into the Function of Paravascular Spaces.

Research Director: Dr. Charles Czeisler

Background: While sleep is necessary for proper cognitive function, the physiological need for sleep is still uncertain. Recently, it was discovered that the cerebral glymphatic system, which is a network of perivascular spaces containing cerebrospinal fluid (CSF), may be meaningfully affected by sleep-wake states. Importantly, research suggests that CSF flow rates are significantly higher during the sleep state, enabling more efficient clearance of small-molecule waste products like amyloid-beta from the brain. Although these findings have been shown in animal models, there is not yet direct evidence that the glymphatic system works the same way in the human brain. | ¶ | Methods: We studied healthy adults between the ages of 18-25 using magnetic resonance imaging (MRI) and electroencephalogram technology throughout a four-day sleep study. Individuals underwent a 36-hour constant routine protocol during which they participated in neurobehavioral tests including the psychomotor vigilance test, Karolinska sleepiness scale, addition-calculation task, and visual analogue scale. Following this, anatomical changes in participants' brains were monitored in the MRI while they slept and later analyzed using biostatistical analyses. | ¶ | Results: Statistically-significant numerical differences in perivascular spaces between sleep and wake states were found in the midbrain, but not in the centrum semiovale, basal ganglia, or hippocampus regions of the brain. | ¶ | Conclusions: Participants with numerical increases in perivascular spaces that trended towards statistical significance performed better than those individuals without visible differences. Further experiments involving higher resolution MRI scanners, larger sample sizes, and longer duration rapid eye movement sleep data might show significant differences in more regions of the brain.

EJ Kim

Electrodermal Reactivity and Distress Tolerance in Adults with a History of Non-suicidal Self-Injury (NSSI).

Research Director: Dr. Matthew Nock

Greater emotional reactivity and lowered distress tolerance have been suggested as explanatory factors in the development and maintenance of non-suicidal self-injury (NSSI). This thesis investigated whether heightened level of arousal is correlated with NSSI. Adults with a history of NSSI and healthy controls performed a distressing card task, and electrodermal activity (EDA) levels were measured at baseline and during the task. Physiological arousal was calculated using tonic skin conductance level (SCL) and non-specific skin conductance responses (NS-SCRs). Individuals with recent, but not lifetime history of NSSI, showed larger SCL increase and higher frequency of NS-SCRs during the distress task compared to controls. These findings suggest that greater emotional reactivity contributes more to the development and maintenance of NSSI behavior. The neurobiological implications of the EDA findings are further explored given that EDA activation is directly downstream of the autonomic nervous system arousal.

Deepika Kurup

Investigation of Endosomal and Lysosomal Biology in Alzheimer's Disease Using Patient-Derived Induced Pluripotent Stem Cells.

Research Director: Dr. Tracy Young-Pearse

Alzheimer's disease (AD) is the leading cause of dementia, which affects 40 million people worldwide. In this study, induced pluripotent stem cells (iPSCs) coupled with comprehensive clinical studies are used to model the spectrum of pathological and clinical phenotypes seen in AD, and to investigate the role of endosomal and lysosomal biology in contributing to these phenotypes. It was hypothesized that in vitro phenotypes from iPSC lines could be used to understand the molecular basis of the heterogeneous pathological and clinical phenotypes of AD. iPSC-derived neuronal lines were generated from subjects in the Religious Order Study (ROS) and Memory Aging Project (MAP), two studies for which pre- and post-mortem information has been collected. Immunostaining was used to identify AD-, endosomal- and lysosomal-relevant markers. These results were qualitatively analyzed using confocal microscopy and quantitatively evaluated using an InCell Analyzer combined with optimized CellProfiler image-processing modules. AD-relevant proteins synthesized and secreted by the cultured neurons were quantified through ELISA. Significant differences in the number of lysosomes and endosomes per cell and ratios of Aβ42 to Aβ40 among the lines studied show heterogeneity in the aging population. These results indicate that patient-derived iPSC lines from the ROS/MAP cohorts serve as a valuable tool for probing the heterogeneity of AD and investigating how differences in endosomal and lysosomal biology may contribute to pathology and cognitive decline. Ultimately, this study seeks to provide further insight into the mechanisms of AD progression and may facilitate the discovery of novel pathways involved in AD-related cognitive decline.

Tyler LeComer

Prefrontal Cortex Responses in Infancy Predict Anxious Behaviors in Early Childhood.

Research Director: Dr. Chuck Nelson

Anxiety is the most prevalent mental disorder in the world, affecting one-third of the population. Despite this prevalence, little is known about the neural correlates underlying its onset. It is generally believed that the onset of anxiety in children results from a combination of individual-specific and environmental factors, but the respective impact of either group is not well defined. Past studies have revealed a correlation between anxiety and metabolic activity in the prefrontal cortex in adult humans, suggesting that individual brain activity may play a role in producing anxiety. This, however, does not provide insight to the disorder' s onset. This research sets out to better characterize the role of brain metabolic activity in the onset of anxious behaviors throughout early childhood by investigating the behavior of individual toddlers, as reported on the Infant-Toddler Social and Emotional Assessment (ITSEA), and their respective brain activity during infancy, as measured using near-infrared spectroscopy. While the results do not indicate a statistically significant relationship between the Internalizing' score of the ITSEA at three years old and the magnitude of the hemodynamic effect in the prefrontal cortex during infancy, there is a slight trend toward a negative correlation. The results additionally suggest a significant positive correlation between the 'Fear' score of the Infant Behavior Questionnaire and the Internalizing' score of the ITSEA. Overall, the results suggest the complexity of the relationship between individual brain activity and anxious behaviors. Anxious behavior at three years old cannot be fully explained with only infant brain metabolic activity.

Melissa Li

Effect of age on the pattern of blood-brain barrier disruption, matrix metalloproteinase-9 upregulation, and damage in a large animal model of severe traumatic brain injury with unilateral hemispheric hypodensity, the.

Research Director: Dr. Beth Costine-Bartell

Hemispheric hypodensity (HH) is an injury pattern associated with severe abusive head trauma (AHT) in children. Unilateral HH, under a unilateral subdural hematoma, results in destruction of the ipsilateral cortex with relative sparing of the contralateral hemisphere. It is common in toddlers but not infants, and its pathophysiology remains poorly understood. We hypothesized that blood-brain barrier (BBB) disruption regulated by matrix metalloproteinase-9 (MMP-9) results in unilateral HH in piglets developmentally similar to human toddlers (1 month old) but not in piglets developmentally similar to human infants (1 week old). | ¶ | In our model of HH, piglets aged 1 week (“infant”) or 1 month (“toddler”) received unilateral focal injuries and global insults (N = 19) or sham surgery (N = 7). Damage, MMP-9 expression, and BBB disruption patterns were determined in coronal sections encompassing each hemisphere. | ¶ | Albumin extravasation, indicating BBB disruption, and MMP-9 expression paralleled the damage pattern and was greater in the ipsilateral vs. contralateral hemisphere in “toddlers” but not “infants”. The parallel patterns of albumin extravasation, MMP-9 upregulation, and damage along with significant sparing of the contralateral hemisphere in ”toddlers” indicates BBB disruption is key in the pathophysiology of HH. “Toddlers” may have greater spreading of damage in one hemisphere due to a greater increase of MMP-9 and BBB disruption, while “infants” have a blunted increase in MMP-9 and less BBB disruption and damage. Further clarifying these age-related pathophysiological differences may result in improved therapies for AHT.

Karen Malacon

Effects of prenatal exposure to air pollution and maternal stress on social behavior and underlying neuro-immune mediators.

Research Director: Dr. Staci Bilbo

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by impaired social interaction and communication, engagement in repetitive behaviors, and a sex bias in prevalence (higher in males). Several epidemiological studies have linked prenatal air pollution exposure, as well as maternal stress during pregnancy, with an increased risk of ASD. Our lab has developed a prenatal exposure paradigm in mice which combines diesel exhaust particles (DEP) with a maternal stressor (resource deprivation; MS) during pregnancy. Using this model, we found that DEP/MS exposure decreases sociability and social novelty preference in male offspring only. Microglia, the resident immune cells of the brain, are key regulators of the neural response to immune activation and appear to be chronically activated in a subset of patients with ASD, making them good candidates for translating such environmental exposures into neural outcomes. Therefore, we assessed microglial cell number/density, as well as social- and microglial-related gene expression patterns in the nucleus accumbens (NAc) and basolateral amygdala (BLA), regions important for social behavior and implicated in ASD. We found that although DEP/MS exposure had no effect on microglial cell number in the NAc, we did observe sex-specific effects in social- and microglial-related genes in the NAc, including dopamine receptor mRNA. These effects appeared to be brain region specific as we did not observe gene expression changes in the BLA. Together, these results advance our knowledge of the neuro-immune mechanisms by which prenatal immune activation might lead to ASD-relevant changes in social behavior.

Theodora Mautz

Anatomical Folding Predicts the Locations of Face-Selective Domains in Macaque Inferotemporal Cortex.

Research Director: Dr. Marge Livingstone

Gyrification in the developing brain leads to a drastic increase in the topological features of the cortex. Previous research has demonstrated a structure-function relationship between cortical topology and brain function in the primate primary visual cortex. The present study expands this line of research to the organization of the higher-order visual cortex. Macaque brains have focal regions within the superior temporal sulcus (STS) of the inferotemporal cortex that are selectively active when viewing images of faces as compared to other types of images. Using functional and structural data from twelve macaques, we investigated the relationship between anatomical topology in the STS and the location of the middle lateral (ML) face patch. Within the STS, we identified three focal bumps (convex curvatures) that were in consistent locations along the anterior-posterior axis across individuals. We found that the ML face patch was localized to the middle of these bumps in all individuals, demonstrating that focal anatomical features of the STS can serve as landmarks for the localization of function. In addition to normally-reared monkeys, this cortical feature also existed in two groups of macaques raised under conditions that prevented the functional development of face-selective regions. This suggests that the structure-function relationship is not necessarily causal, but could instead come about from early organizing principles, such as low-level tuning and retinotopy, that correlate with the localization of face-selective domains. An improved understanding of the nature of this relationship holds interesting implications for brain development and the pressures that shape gyrification.

Orgilmaa Munkhbaatar

Mother's Pain, a: The Effects of Postpartum Depression and Childhood Maltreatment on Maternal Neurobiology.

Research Director: Dr. Marty Teicher

Extensive research has identified the enduring effects of childhood maltreatment on brain structure and function and has implicated these changes with psychopathology development. However, the relationship and associated neural correlates of early adversity and postpartum depression remain poorly understood. To address this, the present study aims to assess the influence of childhood maltreatment, quantified by the Maltreatment and Abuse Chronology of Exposure scale, in contributing to postpartum depression, measured by the Edinburgh Postnatal Depression Scale. We hypothesized childhood maltreatment is associated with aberrant resting- state functional connectivity and cortical changes that may mediate the development of depression. Functional activity in 13 regions of interest compelling in mothering, postpartum depression, and childhood maltreatment was analyzed using the Brain Connectivity Toolbox and cortical area, volume, and thickness analyses were conducted with FreeSurfer software for 65 mothers. We identified childhood sexual abuse as the most important predictor of postpartum depression with a 14.4-fold increased risk with exposure. Assessment of maternal neural differences showed increased connectivity between the left amygdala and left cerebellum mediates 14.5% of the relationship between exposure to childhood sexual abuse and postpartum depression. Given the role of the amygdala in threat detection and the cerebellum in emotion processing, the observed altered connectivity between these regions may contribute to the development of symptoms as early experiences may sensitize vulnerability to depression. These findings may contribute to understanding the predictive neurobiology of postpartum depression and highlights the importance of childhood sexual abuse as a potential risk factor.

Chinaza Ochi

Investigating Visual Evoked Potentials as a Possible Biomarker for Autism Spectrum Disorder in Tuberous Sclerosis Complex.

Research Director: Dr. Chuck Nelson

Children with Tuberous Sclerosis Complex (TSC), a rare genetic disorder, are at an elevated risk for developing autism spectrum disorder (ASD), a developmental disorder that leads to impairment in social interaction and communication skills. Research suggests that early interventions for ASD may be most effective in remediating these impairments, but it is difficult to predict which infants will go on to develop ASD. TSC can be diagnosed in utero and may provide unique insight into the neural mechanisms that give rise to ASD later in development. In this study, we will use visual evoked potentials (VEPs) to evaluate the mechanisms underlying elevated risk for ASD in infants with TSC. VEPs are event-related electrical potentials induced by a visual stimulus that can be measured with electroencephalography (EEG). This neural marker reflects basic cortical processing and is not dependent on language, motor coordination, or auditory abilities making it a useful measure to utilize for infants. Our hypothesis is that children that later develop ASD will have a characteristic difference in their VEP trajectories. If our hypothesis is supported, we expect to find a potential marker of risk for developing ASD. This information, in combination with other measures, could be used to help predict which kids will go on to develop ASD, thereby allowing for early identification of kids who would benefit most greatly from intervention services.

Edwin Owolo

Investigating the role of the PAG in processing pup vocalizations in mice.

Research Director: Dr. Catherine Dulac

The maternal response to an infant's cries is an adaptively advantageous behavior that is highly conserved among mammals. In my undergraduate thesis I aimed to identify cells in the periaqueductal gray (PAG) that are involved in processing pup vocalizations. The PAG receives synaptic input from areas of the "emotional brain" including the cortex, amygdala, and hypothalamus and is involved in functions such as pain, analgesia, fear, anxiety, and autonomic regulation. My investigation began with mapping the PAG's auditory processing network. Retro adeno-associated virus (AAV) was injected into the rostral, medial, and caudal PAG in order to visualize known auditory centers where the PAG receives projections from. Imaging of these injections revealed the connectivity the PAG shares with the auditory cortex as well as the inferior colliculi. Projection sites were confirmed to be specific to the PAG by injecting a virus that labels cell bodies and their synapses from auditory cortex to the PAG. After mapping the PAG's auditory processing network, cells that were activated by pup vocalizations in adult virgin females, males, and mothers were identified and quantified, using the immediate early gene c-fos as a marker of recent neural activity. The results of my thesis help to elucidate the role of the PAG in the processing of pup vocalizations

Leslie Ramos

Role of RUNX1 in the Progression of Epithelial to Mesenchymal Transition in Proliferative Vitreoretinopathy, the.

Research Director: Dr. Leo Kim

Proliferative Vitreous Retinopathy (PVR), most commonly occurring after eye trauma, is one of the most common causes of surgical failure for retinal detachment surgery. PVR is characterized by the formation of scar tissue, and pathological membranes overlying and underneath the retina, and is the most common cause of recurrent retinal detachments. The formation of this scar tissue is widely believed to be caused by epithelial to mesenchymal transition (EMT), which affects the retinal pigmented epithelial cells in the eye and turns them fibrotic. In this thesis, we explored the role that transcription factor RUNX1 plays in the progression of EMT, and thus formation of the retinal PVR scar. We were able to collect PVR retina samples from real patients, as well as culture PVR cells from these scar tissues, creating the most accurate in-vitro disease model for PVR. There is a number of papers linking RUNX1 to EMT, however, this is the first time that RUNX1 has been shown to play a role in the the progression of PVR. This novel interplay between RUNX1 and EMT in the retina can help decipher the therapeutic future of PVR. Furthermore, we will explore the importance of researching EMT and potential therapeutics promises of RUNX1 in treating numerous devastating fibrotic and cancerous diseases.

Pablo Reimers

Stochastic Individuality in Drosophila melanogaster: An Investigation of the Neural Generation of Idiosyncratic Behavior.

Research Director: Dr. Ben de Bivort

Determining what makes us “us” is at the heart of individuality research. Though investigations into this field have often looked through the lens of genetic or environmental factors, an underappreciated branch of individuality research is the effect of randomness. Here, we study the effect that neural morphological differences, which could occur stochastically, have on behavioral bias in the fruit fly Drosophila melanogaster. Using high throughput technologies to track flies as they walk freely in a three-armed chamber, individual identities were maintained as behavior was recorded for each animal over the course of many hours. With the help of established genetic drivers which can silence a specific group of neurons, a screen was conducted to identify key neurons involved in establishing a fly’s individual bias. Using immunohistochemistry and confocal imaging, pre-synaptic volume of these target neurons was quantified, and left-right asymmetry was correlated to the individual’s behavioral bias. The final experiment in this project aimed to test the sufficiency of the identified target neurons in creating a bias for the fly, by using heat shock-FLP recombination to stochastically induce functional left-right asymmetries in physiological properties of the target neurons and tracking the effect on behavioral bias. In the first experiment, a group of neurons with post-synapses in the Protocerebral Bridge (PB) and Fan-shaped Body (FB) and pre-synapses in the Lateral Accessory Lobe (LAL) were identified as highly involved in establishing a bias in turning behavior. With further analysis, asymmetry at the basal-most tip of these PF-LAL neurons between the left and right side was significantly predictive of a fly’s bias. Analysis of sufficiency for these neurons is still being conducted. Here, we have successfully identified a key morphological feature, a few cubic microns in volume, whose asymmetries have magnified effects visible in the behavior of an organism. This feature is explanatory of the idiosyncrasies which exist between genetically identical animals raised in the same environment, whose stochastic asymmetries suggest a root of randomness in individuality.

Emma Stone

Consequences of early sight deprivation in macaques and the role of motion following sight restoration.

Research Director: Dr. Marge Livingstone

As humans, we rely on vision more than any other sense. We understand and navigate our world by seeing it, which makes normal visual development and function crucial. When individuals are deprived of visual information at an early age, they suffer from severe limitations in visual ability and perception due to missed critical periods. However, studies show that both normal and vision deprived individuals can process visual input most effectively when it contains motion. The present study aims to explore how motion modulates and reshapes form recognition in both the visually normal and deprived brain. Physiology from a visually normal macaque was examined to understand how motion modulates object recognition in inferotemporal cortex. Motivated by the finding that motion is essential for processing shape information after normal visual development, a motion-based training task was used to introduce visually deprived macaques to novel shapes. Monkeys under investigation experienced bilateral visual form deprivation, meaning they only had access to diffused light until full sight was restored after 1 year. We tested whether monkeys would recognize forms more effectively when it was learned in motion. One of two monkeys learned the complex visual task over 20 days, but still had deficits compared to a visually normal monkey. Findings showed that learning a form in motion is not conducive for promoting recognition outside the task. Thus, the presented motion-based training paradigm does not appear to strengthen circuitry for diminished visual function in the sight deprived brain. Evidence suggesting that the one vision deprived monkey could still learn important motion information and often sought moving stimuli over static equivalents confirms that motion is an essential cue for perception, particularly when recovering from form deprivation. This study helps to inform and advance alternative training regimes that may reduce barriers for attaining full visual function during sight deprivation recovery.

Eily Sullivan

Statistical learning and language outcomes of 5-year-old urban Bangladeshi children: An fNIRS investigation.

Research Director: Dr. Chuck Nelson

When a child grows up in poverty, they are more likely to experience various forms of adversity that can negatively impact their brain development. Language is one domain that is particularly vulnerable to adversity. Cognitive stimulation, or the level of environmental enrichment, has been linked to better language outcomes in children. In this study, we investigated whether cognitive stimulation is related to language outcomes of 81 five-year-old children from low-income backgrounds living in Dhaka, Bangladesh. Results reveal that cognitive stimulation was significantly related to verbal intelligence quotient (IQ) scores ($p<0.01$), over and above the influence of socioeconomic status (SES) and nutritional status. Next, we investigated whether statistical learning, or the extraction of patterns from the speech train, could underlie this association. Each participant's brain was imaged using functional near- infrared spectroscopy (fNIRS), which uses light to measure hemodynamic responses in the brain, while listening to an auditory statistical learning paradigm containing a series of tone patterns with varying transition probabilities (TPs) between tones. We hypothesized that statistical learning responses in the inferior frontal gyrus (IFG) and superior temporal gyrus (STG) would mediate the association between cognitive stimulation and verbal IQ. Preliminary analyses reveal that both the STG and IFG are sensitive to differences in statistical structure of tone patterns. Participants' statistical learning responses in these brain regions were somewhat distinct based on cognitive stimulation level and verbal IQ. Future analyses are needed to investigate whether statistical learning responses mediate the association between cognitive stimulation and language outcomes.

Joanna Tao

Toward Understanding the Role of Physical Activity and Functional Connectivity in Health and Pathology Using Machine Learning.

Research Director: Dr. Justin Baker

Psychotic disorders, are both economically and personally costly. Diagnoses of psychotic disorders are subjective, and do not account for underlying mechanisms that produce symptoms. Identification of individualized biomarkers in factors like behavior and functional connectivity that can predict and track symptom levels could make it much easier to diagnose and treat patients. The present study used machine learning to develop methods for identifying biomarkers in behavior and functional connectivity and collected a longitudinal data set to which these methods could be applied. Actigraphy data collected with actigraphy monitors were first analyzed in lab to verify that different types of movements could be identified and categorized using machine learning. Then, an iterative approach was used to produce individualized maps of functional connectivity networks in 131 patients with psychotic disorders, then used to predict each individual's symptom levels. Concurrently, data were collected at high frequency on eleven participants with psychotic disorders over more than two years. Participants completed daily surveys while objective measures were collected using actigraphy devices, a custom smartphone application, and fMRI. Though still incomplete, the study has been able to collect large amounts of data and capture changes in the participants' illnesses. The methods from the first two analyses could thus be applied to the third study. Results from the first two parts suggest that biomarkers can be identified from the data in the third part, and that the data can be clustered using various machine learning techniques to predict the course of each individual's illness during the study.

Ellie Underwood

Behavioral Test of Depth Perception: Measuring Binocular Vision in Mice.

Research Director: Dr. Takao Hensch

Plasticity in the visual cortex of the mouse brain has been shown to rise and fall in successive cri tical periods over the course of development. One such critical period involves the binocular ma tching of orientation preference of neurons receiving inputs from both eyes, allowing for integr ation of this input necessary for depth perception. The principal objective of this thesis is to est ablish a behavioral test to assess the functional effect of binocular matching on depth perceptio n. The visual cliff test was used in this study to assess binocular vision over development, with n o significant differences found in performance between juvenile (ages P21 and P30) or adult mi ce (over P60). Adult mice with specific mutations in molecular factors of interest including NR2A , Icam5, CDKL5, and GAD65 were also tested with no significant differences observed. If there ar e functional differences between these mouse lines, the visual cliff test as currently implemente d is unable to detect these differences. Future studies may look at mice at a younger age before other aspects of visual processing have fully developed, as well as mutant mice predicted to ha ve more severe phenotypes.

Melonie Vaughn

Fever Effect, the: Investigating Behavioral Changes Observed During Febrile Periods in Autistic Mouse Models.

Research Director: Dr. Catherine Dulac

Past observational studies have demonstrated that children with Autism Spectrum Disorder (ASD) exhibit decreases in behavioral deficits while febrile. However, the mechanism(s) behind this fever effect and the extent to which the effect can be replicated in other ASD models remains unknown. In an effort to further our understanding of this phenomenon, we have conducted several behavioral assays which quantified changes in multiple ASD model mouse lines after the induction of fever. Our findings suggest CNTNAP2 -- and Shank3B -/- lines may exhibit improvements in social behvavior and social-induced vocalization while febrile, respectively. These results allow for further investigation using ASD mouse lines to understand the circuitry responsible for these changes.

Sonia Wang

How Microglia Affect Adult Neurogenesis and Learning in the Olfactory Bulb.

Research Director: Dr. Venki Murthy

Plasticity in the adult mammalian brain plays a critical role in learning and memory. This phenomenon has been linked to adult neurogenesis, or the process of generating new neurons that integrate into existing brain circuitry throughout adulthood, in the olfactory bulb and the dentate gyrus. By studying these adult-born neurons and their regulators, it is possible to better understand how these cells contribute to plasticity. Possible regulators of these adult-born cells include microglia which are typically associated with immune functions, including initiating inflammatory responses and phagocytosis of dying cells involved in disease. However, more recent work has linked microglia function to adult-born neuron regulation in the healthy adult brain. By incorporating methodologies that ablate microglia, which decreases their effects on adult-born neurons regulation of adult neurogenesis, we investigated performance on odor discrimination tasks that require adult neurogenesis. Focusing on the olfactory bulb in mouse models, we hypothesized that microglia ablated mice would perform similarly to control, non-ablated mice on easier olfaction tasks, but would exhibit significantly decreased performance on more difficult fine discrimination tasks because of a decrease in adult neurogenesis regulation and integration of the adult-born cells into existing brain circuitry. Our results, however, demonstrated similar performance on easier trials and more difficult trials between ablated and control groups in both head-fixed and free-roaming experimental setups signifying that microglia ablation may not significantly impair performance on olfactory discrimination tasks as previously believed.

Grace Xiao

Interictal Spike Characteristics and Seizure Risk in BECTS Epilepsy.

Research Director: Dr. Catherine Chu

Even though epilepsy is a common neurological disorder affecting more than 2 million people in the U.S. (AES), it is frequently treated according to probabilistic data instead of a clear understanding of disease progression and seizure risk. Current clinical treatment of epilepsy requires trial-and-fail method for anti-epileptic medication since there are currently no indicators available to predict ongoing seizure risk. Thus, there is need for a biomarker to develop objective measures of disease progress to avoid the adverse effects of over or under-medication on cognitive, psychosocial, and behavioral function. Interictal EEG epileptiform discharges (IEDs) are a well-recognized hallmark of epilepsy, defined as a brief (<250 ms) electrical discharge that creates a sudden peak on a EEG recording (Staley and Dudek, 2006). Since benign epilepsy with centrotemporal spikes (BECIS) has a transient period of epilepsy and unique pattern of EEG spikes, we identified it as a natural model to develop objective measures to evaluate seizure risk and predict the onset of remission. We investigated whether epileptiform spike characteristics like frequency, amplitude, sharpness and width evolve over the course of BECTS disease progression. We found that spike rate decreases as time since last seizure increases, suggesting that there may be a relationship between spike rate and disease stage. We found that spike morphology like amplitude, duration and frequency do not change significantly as BECTS epilepsy progresses. These results suggested that only spike rate and not spike morphology matters for predicting seizure risk, but further research is needed.

Megan Yerton

Pharmacological Disruption of Prepulse Inhibition of Acoustic Startle in Intervendor Sprague Dawley Rats.

Research Director: Dr. Barak Caine

Prepulse inhibition (PPI) refers to the neurologically-based process of sensorimotor gating where a weak stimuli (prepulse) precedes a stronger stimuli (pulse) and inhibits the reaction to the pulse. Deficits in sensorimotor gating as measured by PPI are seen in humans with schizophrenia and other disorders. Drugs that act on neurotransmitters involved in the sensorimotor gating pathway can be used to induce PPI disruption in animal models such as rats. Apomorphine (a dopamine agonist), scopolamine (a muscarinic antagonist), dizocilpine (a NMDA antagonist), and DOI (a serotonergic agonist) have all been shown to disrupt PPI. Though research has shown that there are differences in PPI disruption among different strains of rats, none have studied differences between different vendors supplying the same strains. This study used the pharmaceutical interventions listed above to measure potential differences in disruption of PPI in Sprague Dawley rats from either Charles River (n = 7 male; n = 8 female) or Envigo (n = 7 male; n = 7 female) vendors. PPI was measured using startle response following the subcutaneous injection of vehicle, apomorphine (0.5 mg/kg, 1.5 mg/kg, and 3.0 mg/kg), scopolamine (0.1 mg/kg, 0.5 mg/kg, and 1.0 mg/kg), dizocilpine (0.5 mg/kg and 1.5 mg/kg), and DOI (0.25 mg/kg, 0.5 mg/kg, and 1.0 mg/kg). Results showed that percent PPI disruption was related to vendor in all cases except vehicle and DOI, suggesting that vendor choice is a significant factor in studies involving selective disruption of PPI via apomorphine, scopolamine, and dizocilpine.

Sofia Zoullas

Brain activity as a mediator of institutional rearing on social communication in adolescence.

Research Director: Dr. Chuck Nelson

Institutional rearing has been demonstrated to have detrimental effects on several developmental domains. Notably, the severe psychosocial deprivation experienced by children in institutions significantly affects their cognitive and socioemotional capabilities. The current study examined the relation between brain activity and social communication among children raised in institutions by drawing from a prospective longitudinal study. Specifically, the Bucharest Early Intervention Project (BEIP), a randomized control of foster care as an alternative to institutional care. Children living in institutions around Bucharest, Romania were randomized into a foster care group or remained in the institutions compared with a never-institutionalized control group. Brain electrical activity was acquired at age 12 using resting electroencephalogram (EEG) data. Social communication skills were assessed at age 16 using the Social Communication Questionnaire (SCQ). We tested a longitudinal mediation model with resting EEG alpha power at age 12 as a mediator between institutionalization and SCQ scores at age 16. Path analysis was used to test the proposed mediation model. EEG alpha power at age 12 did not significantly mediate the relationship between institutionalization and SCQ scores at 16. However, institutionalization was predictive of SCQ at age 16. Furthermore, EEG at age 12 is predictive of certain SCQ subscores at age 16. These findings elucidate a longitudinal relation between brain development and subsequent social ability.