

Sope Adeleye

Probing Dysregulation of Early Endosomes and Lysosomes in Late Onset Alzheimer's Disease Using Induced Pluripotent Stem Cells

Director: Dr. Tracy Young-Pearse

There were two principle objectives for this thesis. The first was to develop a more precise method to characterize early endosomes and lysosomes in neurons derived from induced pluripotent stem cells (iPSCs). The second was to examine endosomal and lysosomal characteristics in late onset Alzheimer's disease (AD) compared to healthy controls using an iPSC derived neuron model. We produced neurons derived from human iPSCs and used immunostaining to mark characteristics of endosomes and lysosomes. Then, we improved an analyzing pipeline developed by two former lab members by comparing the outputs of the original pipeline to a new pipeline that more accurately identified nuclei and endosomal and lysosomal puncta. Through our early endosomal characterization, we found that early endosomal area per early endosome was similar between the control and AD groups, but the total number of early endosomes per cell was greater in the AD group. Through our lysosomal characterization, we were unable to determine whether the AD group had a significant increase in the average lysosome area per lysosome compared to healthy controls. However, we did demonstrate that the AD group had a lower lysosomes per cell count compared to the healthy control group. Because of these findings, further research should be conducted to see if higher early endosome count per cell and lower lysosome count per cell in AD groups compared to controls are consistently present in other AD model systems so that we can deepen the understanding of how early endosomal and lysosomal dysregulation relates to AD pathology.

Ellie Bernstein

Blood-Brain Barrier Permeability in a Mouse Model of Repetitive Mild Traumatic Brain Injury

Director: Dr. Mike Whalen

Mild traumatic brain injury (mTBI), or concussion, occurs when brain function is altered due to the transmission of biomechanically-induced forces to the head. Concussion can lead to serious cognitive, emotional and behavioral impairments in both the short and long-term, but at this time the molecular mechanisms underlying these deficits are not well understood. Break-down of the blood-brain barrier (BBB) is known to lead to neurodegeneration and cognitive deficits, and may represent one potential mechanistic link between mTBI and cognitive impairments post-injury. The aim of this study was to determine whether repetitive mTBI (rmTBI) leads to persistent BBB leakage. A validated 10 hit daily adult mouse model was used to mimic rmTBI. Six to ten months after injury, injured and sham mice were injected with biotin which was allowed to circulate through the brain. The injured and sham mice were sacrificed and brains were sectioned and imaged using fluorescence microscopy. Biotin extravasation was assessed using ImageJ software and was used as a proxy for BBB permeability. Results showed no increase in extravasated biotin in the cortex hippocampus or striatum of 10 hit daily mice compared to sham. BBB permeability was not a feature of our repetitive mild TBI model. Future studies should examine different injury severities, later time points, and genetic or environmental factors that might predispose to BBB breakdown to better understand its relevance to human concussion.

Camiren Carter

Exploration of Trichromatic Plasticity in Juvenile Macaques

Director: Dr. Marge Livingstone

The objective of this thesis is to explore the degree of plasticity that exists within the primate visual system with regard to trichromatic vision. A juvenile male macaque was reared for 9 months with rose lenses placed in front of his eyes that filter out shorter wavelengths of light. Another juvenile male reared under normal conditions serves as the control for this experiment. Both subjects were trained to complete a match to sample task in which the subject was required to display an ability to distinguish between colors of similar or random RGB composition. Thus far, a test pairing adjacent colors on a 26-membered color wheel, similar to the trichromatic test used by ophthalmologists to detect color blindness in human patients, has proven to be the most successful method of evaluating subject ability. Using this test, we have been able to confirm the effectiveness of the lenses to alter visual perception as the subject fitted with these lenses displays a significantly impaired ability to distinguish between colors of similar hue composition compared to the subject granted an uninhibited visual spectrum. Less successful methods of analysis that show potential with refinement are mapping task success rate as a function of individual hue (red, green, or blue) difference or as a function of distance between displayed colors in 3-dimensional RGB space. Analysis of the experimental subject's performance following exposure to a full visual spectrum revealed a dramatically impaired ability to differentiate between colors similar in RGB composition when compared to the control. This impairment improved slightly over time, but remained below control performance after three weeks of normal spectral exposure, suggesting the possibility of a sensitive period for trichromatic vision during development.

Channing Cimarusti

Does predictable prosodic timing facilitate spoken language processing in people with aphasia?

Director: Dr. Lauren Zipse

Aphasia is a language impairment caused by brain damage, commonly characterized by difficulty producing speech. Many effective aphasia therapies involve unison speech with a clinician, particularly with rhythmic speech patterns. The mechanisms by which such therapies provide benefit is unknown, but may involve predictive entrainment and attentional processes. In this study, we aim to determine whether metrical speech leads to increased accuracy and speech entrainment between people with aphasia and a model speaker, and to discover whether metrical speech increases attention paid to speech. The behavioral experiments involved presenting sentences of either metrical or conversational speech rhythm to people with aphasia and controls. Participants were recorded repeating the sentences alone and in unison with the recording, and their speech production was scored for accuracy and alignment to the original recording. The EEG experiment involved presenting healthy participants with metrical and conversational sentences, some with phonemic errors inserted. We recorded EEG from participants and analyzed the signal for ERP components associated with error detection, using this as a proxy for attention. In the behavioral experiments, we found evidence that both accuracy and entrainment are improved in metrical speech conditions for both controls and PWA, with no significant difference in benefit between the two cohorts. We did not find significant results in the EEG experiments. This study supports the conceptualization of metrical speech as a critical factor in the efficacy of speech therapy for PWA, and further experimentation is needed to determine whether PWA are affected by metrical speech differently than controls.

Cydnee Colpaert

Characterizing Neural Noise using the Vestibulo-Ocular Reflex

Director: Dr. Faisal Karmali

Neural noise, the intrinsic random fluctuation of signals, in the Vestibulo-Ocular Reflex (VOR) can have detrimental effects in motion perception and navigation. The VOR pathway has three main components: the peripheral sensory apparatus, a central processing mechanism, and the motor output. Throughout the VOR pathway, noise will and can accumulate leading to imprecision in target fixation, defined as VOR variability. The source of this noise can be sensory, mainly stemming from the peripheral sensory apparatus, or motor, such as in the eye movement itself. This thesis aims to characterize neural noise in the VOR by differentiating between the amount of VOR Variability between multiple motions that require varying levels of motor output to stay fixated on a target. The sources of neural noise were characterized in multiple subjects. Six subjects were fixed unto a moving chair with eye velocity tracking goggles. The subjects are asked to fixate on a red LED light which is then turned off as they are moved randomly in one of six different motions. The experimental design relies on the fact that horizontal eye movements are a summation of those elicited by Interaural (IA) Translation and Yaw Rotation of the head. Specifically, two of the motions consisting of Yaw Rotation and IA Translation had the same speed but different directions. The two motions were crafted so that only one motion necessitated significant eye movement, effectively singling out motor noise and allowing differentiation between sensory and motor noise. Neural noise was characterized by percent of neural noise that could be attributed to motor noise. Subjects had a wide range of percent motor noise: 25%, 102%, 74%, 87%, 10%, and 34%. This study presents promising preliminary data that suggests 1) the sources of neural noise can be characterized, and 2) that neural noise predominance is subjective.

Christina Cruz

Serine Racemase Expression During Post-Natal Development and Involvement of SR-Expressing Neurons in Fear Extinction Learning

Director: Dr. Darrick Balu

Schizophrenia is a leading cause of disability worldwide, affecting ~1% of the population. Much evidence has demonstrated that hypofunction of the N-methyl-D-aspartate receptor (NMDAR) contributes to the pathophysiology of schizophrenia. In addition to its ligand glutamate, the NMDAR requires a co-agonist, D-serine, which is converted from L-serine, by the neuronal enzyme serine racemase (SR). The Balu laboratory and others have studied the role of SR and D-serine in regulating NMDAR function in adult mice. However, there is a gap of knowledge regarding SR expression in the developing postnatal brain. Therefore, we systematically examined SR expression during postnatal development. We perfused mice at several postnatal timepoints and performed dual-antigen immunofluorescence to quantify the number of SR-positive neurons in limbic brain regions involved in schizophrenia (medial prefrontal cortex [mPFC], amygdala, hippocampus, and striatum). We found that SR expression was low at early postnatal timepoints (P8) and peaked by P16 or P28, with ~50% of neurons being SR+. Interestingly, the pattern and onset of SR expression varied between and within brain regions. In another project, we investigated the involvement of SR-expressing neurons that are activated during fear learning and extinction. D-serine enhances acquisition and maintenance of fear extinction, while extinction increases SR protein levels in the mPFC, amygdala and hippocampus. Using a dual transgenic mouse line combined with immunofluorescence, we found that the acquisition and extinction of fear memories activated neural ensembles containing SR-expressing neurons, suggesting that D-serine mediated NMDAR activation plays an important role in circuits activated during learning.

Ashish Dahal

Evidence for Conserved Interactions between Fat3 and LAR Family Proteins in Amacrine Cell Development

Director: Dr. Lisa Goodrich

The Inner Plexiform Layer (IPL) of the retina contains synapses between bipolar, ganglion, and amacrine cells that organize the receptive fields involved in visual processing. Amacrine cells contribute to the IPL by extending their processes into the region and forming inhibitory synapses with bipolar and ganglion cells. Proper formation of the IPL requires the atypical cadherin Fat3, which controls amacrine cell migration and neurite retraction in the mouse retina. The molecular mechanism through which Fat3 affects amacrine cell morphogenesis is not known.

Clues from the *Drosophila* egg chamber system suggested that Fat3 works alongside the LAR family of Receptor-type Protein Tyrosine Phosphatases (LAR-RPTPs). Using RT-PCR and RNAscope in-situ hybridization, we demonstrated that the LAR-RPTP family member *ptprf* (*Lar*), *ptprs* (*Ptpσ*), and *ptprd* (*Ptp!*) are all expressed in amacrine cells throughout development and in the mature retina. Immunohistochemistry on WT retina revealed that both Fat3 and *Ptpσ* localize to processes in the IPL. In *fat3* mutant retinas, *Ptpσ* stayed enriched in the IPL layer but is also distributed to ectopic amacrine cell synapses. In *ptprs* mutant mice, Fat3 distribution did not change. Furthermore, levels of the inhibitory synaptic protein *Vgat* were significantly reduced in the IPL of *ptprs* mutant retinas. In summary, we identified that loss of Fat3 impacts *Ptpσ* distribution in amacrine cells, while loss of *Ptpσ* does not affect Fat3 localization. The decrease in *Vgat* suggests that *Ptpσ* could regulate inhibitory synapse formation in the IPL. Overall, Fat3 may work through *Ptpσ* to determine where amacrine cells form synapses.

Cameron Decker

Investigating the Relationship Between Behavioral Inhibition and Responses to Emotional Stimuli in Infancy: an ERP Study

Director: Dr. Chuck Nelson

Anxiety is the most prevalent mental illness in the US. As such, it is crucial that early signs of anxiety be recognized so that interventions can be made as quickly as possible. This thesis, conducted within the Emotion Project at the Labs of Cognitive Neuroscience, investigated whether neural responses to emotional faces captured in infancy could predict typically developing children's predisposition to anxiety, which was calculated when the children were 3 years old (n=51). Event-related potentials were recorded as 5- and 12-month-old infants were presented with pictures of angry, happy, and fearful faces of varying intensities. At age 3 years, the same children were scored on behavioral inhibition to novelty, which involved them participating in unfamiliar play scenarios. Using the behavioral inhibition results as a measure of anxiety predisposition, this study examined the differences in the N290, P400, and Nc ERP components between children who were later categorized as behaviorally inhibited vs. not. Greater N290 amplitudes to fearful face conditions in the right occipital region in infancy correlated with reduced behavioral inhibition scores. There did not appear to be a statistically significant correlation between behavioral inhibition and ERP response across all groups for the P400 and Nc components. Based on these findings, it is possible that facial emotion processing in infancy could be a useful tool in the early detection of anxiety, though the relationship between the two measures may require further study.

Hart Fogel

Examining the Role of Parts in Object Recognition for Artificial Neural Networks

Director: Dr. George Alvarez

The histories of neuroscience and machine learning are inextricably intertwined, and these fields of study continue to inform each other. One ongoing area of inquiry within the realm of machine learning research is the extent to which biological brains and artificial neural networks use analogous methods to process visual information and recognize objects. Specifically, the question of whether artificial neural networks rely on an object's constituent parts to classify it in a manner akin to the geon-mediated recognition-by-components model in humans remains largely unexamined. This thesis represents a first foray into this subject. Using animation software, I generated 50 simple four-geon objects and rendered hundreds of thousands of images of them from many perspectives. Then, I prepared seven artificial neural networks to recognize these stimuli and tested each algorithm on its ability to identify the objects as their individual parts were progressively removed. All of the networks aside from the SE-ResNet-50 fixed feature extractor pretrained on a facial recognition dataset were relatively successful, suffering gradual accuracy loss in accordance with geon removal rather than immediately failing as one might expect an overfit network neglecting components to do. Participants in a human study with a subset of the objects displayed a distinct but similar pattern of performance. While far from conclusive, these results gesture toward artificial neural networks being capable of humanlike component-based object recognition and with improvement perhaps someday matching human accuracy on the geon deletion task. The experimental paradigm established here helps pave the way for significant further exploration.

Oliver George

The Associations of socioeconomic status and autism spectrum disorder with EEG power in 12-month-old infants

Director: Dr. Chuck Nelson

Both socioeconomic status (SES) and autism spectrum disorder (ASD) influence many aspects of cognitive and neural development. However, it is currently unknown whether SES moderates the neural patterns associated with ASD in children. The present study analyzed resting baseline electroencephalography (EEG) in 12-month-old infants to gain insight into the underlying cognitive processes impacted by ASD and SES. Participants from the Infant Study Projects at Boston Children's Hospital were grouped using a two-by-two design: lower and higher SES, as determined by maternal education, and low risk of autism (who did not later develop autism) and high risk of autism (who did later develop autism), based on the diagnosis of an older sibling. EEG resting baseline activity was decomposed into six main frequency bands across four scalp regions of interest (frontal, posterior, left temporal, and right temporal). Two-way ANOVAs revealed a main effect of SES across the frontal region in every frequency band, as well as some bands in the posterior region, such that higher SES associated with lower EEG power. Limited effects of ASD were found in the lower frequency bands in frontal and posterior regions, with the diagnosis of ASD associated with higher EEG power. There were no significant interaction effects between SES and ASD, and multiple regressions revealed a generally stronger effect of SES on EEG signals than ASD risk/status. Results suggest that SES is a highly significant predictor of neurophysiology in infants at high and low risk for ASD, which has important clinical implications for early brain development.

Rachael Han

Novel Reflexive Gap Junctions in Cortical Inhibitory Neurons: Functional Implications of Neuronal Self-Recognition

Director: Dr. Jeff Lichtman

Newly developed large volume serial electron microscopy methods provide unprecedented access to the structural details of the nervous system. In this work, I present the first observations on a novel inhibitory neuron junction between sister dendritic processes of the same cortical interneuron, a “reflexive” junction. Using serial section electron microscopy images and computer-assisted reconstructions from the human temporal lobe, I found 920 reflexive gap junctions among 400 inhibitory neurons (from the total 833 inhibitory neurons). High resolution imaging showed that the ultrastructural features of these junctions exhibited a high degree of similitude to previously described dendro-dendritic gap junctions between branches of different inhibitory neurons. My analysis of the spatial distribution and morphological features of the interneurons harboring these junctions indicated that there were multiple subtypes of junctions and that several different classes of inhibitory neurons possessed reflexive junctions. I also found that reflexive junctions were not restricted to human temporal lobe cortex, as serial electron microscopy data from rat primary visual cortex demonstrated an inhibitory neuron with the same kind of junction. Together, these findings challenge the concept of self-avoidance between sister neurites of the same cell in the inhibitory network and motivate consideration of the possible advantages of self-recognition in the micro-circuitry of inhibitory neurons.

Terzah Hill

Stress-dependent Olfactory Modulation of Larval Zebrafish

Director: Dr. Florian Engert

Experiencing the world around us requires a multitude of sensory processes that help us to acquire, process, and integrate sensory information, such as the sound of siren or the smell of a rose. Animals can adapt to changing environments, especially while under stress, by modulating their sensitivity to these sensory cues, creating a dynamic range of novel stimuli. One such important sense is olfaction, which has been shown to display increased sensitivity under stress in humans. It remains unclear how this sensory modality is modulated at the neuronal level during stress. We demonstrate that the larval zebrafish is an excellent model organism to study the effects of stress on olfaction. Inducing stress with confirmation from cortisol quantifications, a significant increase in avoidance to an aversive odor was observed in freely swimming larval zebrafish, consistent with findings in humans. To eventually image this novel behavior at the neuronal level, we constructed a head fixed behavioral assay to uncover the active neural signatures in real time. We commenced utilizing and classifying tail flick behavior under stress, while controlling odor presentation at the olfactory epithelium. Through p-ERK immunostaining and confocal imaging, we did not identify a significant increase in the activation of the olfactory bulb and dorsal raphe, regions thought to modulate olfactory behavior. Stress can be beneficial, but prolonged stress can be harmful and lead to a multitude of disorders. Therefore, understanding the underlying neural circuitry of stress and its effects on behavior and sensory modulation is an important field of research.

Dong Hur

Ethometer: Mapping animal behavior using unsupervised machine learning

Director: Dr. Venki Murthy

Internal and external stimuli initiate neurobiological activities that orchestrate behaviors. Therefore, quantifying behavior is crucial for understanding the nervous system in animals. While past studies have used human observation to quantify behavior manually, this may lead to a biased and inconsistent classification of behaviors. This paper proposes a computational solution to quantify and classify both previously explored as well as new behaviors using computer vision and unsupervised machine learning algorithms. The two animal models used in this experiment are the carpenter ants *Camponotus pennsylvanicus* and C57BL/6 mice. Through this unsupervised pipeline, we quantified 22 types of head movements from the mice and 18 types of antennae movements from the ants. Furthermore, ants of different castes in specific environmental conditions appear to have different predisposed set of antennal movements, illustrating how behavioral quantification and classification via this unsupervised pipeline can help answer biologically relevant questions about the heterogeneity of behaviors. The quantified and classified clusters of behavioral movements found via “Ethometer” can then be used to form ethograms and other higher-level behaviors in the future. Using the ant and the mice as a proof of concept, we demonstrate that Ethometer offers a computational pipeline to efficiently quantify and classify low-level behavior for any model organism with minimal human bias.

Kelsey Ichikawa

The Reward of Others' Pain: The Morality of Schadenfreude and Neural Correlates of Latent Preferences for Out-Group Harm

Director: Dr. Mina Cikara

Divisions between social groups often produce conflict and harm. In addition to sociological and institutional structures, individual psychology and emotions like schadenfreude—pleasure in another's misfortune—facilitate and attenuate such harmful actions. However, we still know relatively little about the neural mechanisms underlying decisions that cause intergroup harm, and moreover, how evidence about those neural mechanisms should impact our moral evaluation of an emotion like schadenfreude.

I investigated the neural basis of behaviorally revealed, latent preferences (as opposed to explicitly stated preferences) for out-group harm. We examined the different brain regions involved in processing two kinds of rewards: a spiteful one that harms an opposing political party (in addition to benefitting one's own political party), and a benign one that only benefits the participant's own political party. We used functional magnetic resonance imaging (fMRI) to assess neural activity while participants made a series of choices in a reinforcement learning task. Using computational models of behavior and mass univariate analysis, we identified significant activity in the ventral striatum that tracked reward prediction error. Our analyses did not identify any regions that significantly differentiated between the two kinds of reward.

I also synthesize psychological and philosophical investigations of schadenfreude to establish the variety of situational features that modulate schadenfreude. I argue that evidence from neuroscience can help establish a key bad-making feature of the emotion: schadenfreude potentially involves a positive reward signal that disposes a person to aggress against those whose misfortune she enjoyed. When it inculcates a motivational vector to harmful actions or omissions, pleasure in another's pain brings about morally bad consequences. In addition, I discuss other aspects of schadenfreude that may make it ill-fitted for a situation. Justice-based arguments for schadenfreude are inadequate moral defenses.

Allison Kao

Single-Cell Atlas of the Peromyscus Retina: Evolution at the Cell-Type Level, a

Director: Dr. Josh Sanes

While evolution has historically been studied through the micro- and macro- lenses of DNA and anatomical structure, advances in RNA sequencing technology provide the opportunity to bridge these two levels of comparative analysis at a resolution not previously possible. In particular, single-cell RNA sequencing (scRNA-seq), looking at gene expression at a single-cell resolution, provides a nuanced approach to directly map molecular to functional differences. As the first mammalian CNS tissue for which a complete cellular atlas exists, the retina is an ideal playground to study cell-type evolution. First, the major cell classes of the retina are conserved among nearly all vertebrates. Second, types within classes demonstrate a characteristic correspondence between transcriptomic profile, morphology, and spatial arrangement. This study presents the first single-cell retinal atlas of the prairie deer mouse (genus *Peromyscus*) and a valuable point of comparison to the retina of the well-understood lab mouse (genus *Mus*). Both are in the rodent order, but twenty-five million years diverged. Using scRNA-seq and immunohistochemistry, we proposed a total of 100 retinal cell types. We established similarities and differences at the cell type level between *Peromyscus* and *Mus*. Particularly, we noted several transcription factors that are similarly highly expressed in shared sets of cell types. Across cell classes, we also observed that retinal ganglion cells exhibited the least cell-type conservation. Ultimately, this study contributes a foundational biological resource for the *Peromyscus*, a unique model organism for probing questions of vision and evolution, and identifies novel retinal cell-type differences between the two murine animals, *Mus* and *Peromyscus*.

Spencer Kim

The Role of the Ventral Striatum in Olfactory Learning and the Exceptional Ability of Olfactory Associations to Evoke Emotional Memories

Director: Dr. Venki Murthy

The exceptional ability of olfactory associations to cue emotional memories has been repeatedly described in both scientific and popular literature. However, the neurobiological mechanisms responsible for these strong odor associations are not well understood. Given its position at the intersection of the olfactory and reward systems, we hypothesized that the ventral striatum, specifically the olfactory tubercle (OT) and nucleus accumbens (NA), may play a role in olfactory association learning and these exceptionally powerful odor associations. We designed a behavioral paradigm to study the formation of olfactory associations and the relative strength of odor and sound preferences in mice and identified the effects of OT and NA ibotenic acid lesions on behavioral task performance. Control mice exhibited similar asymptotic association task performance for olfactory and auditory stimuli but demonstrated a greater preference for previously rewarded olfactory stimuli compared to auditory stimuli. Partial OT and NA lesions did not significantly reduce the ability of the experimental group to ultimately form olfactory associations, but partial OT lesions decreased olfactory association learning rate. Mice with partial OT and NA lesions did not demonstrate an observable preference for previously rewarded olfactory stimuli compared to auditory stimuli. Our novel behavioral paradigm effectively formed olfactory associations while also revealing a greater preference for previously rewarded odors compared to sounds. The effects of partial OT and NA lesions suggest that these regions may not be necessary for the formation of odor associations but may impact the learning rate of olfactory associations and the strength of odor preferences.

Taimur Kouser

Connectomics: An Analysis of Human Cortical Layer 1 & Implications for Theory of Mind and Personal Identity

Director: Dr. Jeff Lichtman

Cortical lamination is a fundamental feature of mammalian brains. In humans, the cortex has traditionally been divided into six layers based on the locations of distinct cell types. However, despite our ability to distinguish layers from each other, little is currently known about their functions. Particularly, cortical layer 1 has been poorly studied because of its low cellular density. Therefore, this study aimed to explore the structural basis of human cortical layer 1. Connectomics provides a powerful method for investigating structural questions in unprecedented detail. Electron microscopy images and three-dimensional reconstructions were used to investigate cell types and their morphological characteristics, as well as the synaptic input patterns onto two cortical layer 1 neurons. This study found that cortical layer 1 contains distinct interneuron sub-types with different patterns of synaptic inputs. Moreover, the study found specific “target regions” of en passant and terminal synapse formation. These findings are crucial to understand how synapse formation on distinct dendritic sites influences neuronal activity at the circuit level. Furthermore, this study showcased the type of information we will gain by mapping the entire human connectome. Although some claims about the connectome’s implications are limited to science, one claim argues that our entire human essence lies in the connectome (i.e. we are our connectomes). This study further explored what would need to be true about the nature of the connectome, the mind, and personal identity in order for that claim to be true as well. Ultimately, I concluded that we cannot be our connectomes.

Chloe LI

Examining links between music, emotion, and reading: An investigation of structural brain differences in school-aged children with and without musical training and dyslexia

Director: Dr. Nadine Gaab

Developmental dyslexia, characterized by deficits in phonological processing, has established behavioral manifestations and neural underpinnings. The term “dyslexia effect” refers to characteristic alterations in brain structure and function associated with dyslexia. Longitudinal studies regarding children with dyslexia typically reflect neuroplasticity in predominantly auditory and motor regions. In addition, these regions have indicated functional brain differences between musically trained children with dyslexia and musically untrained children. The use of musical training as a tool of intervention for speech and reading is not yet established as a formal approach, but the current research investigating the overlapping nature between music and speech highlights the potential effect of dedicated training, such as musical training, in brain regions associated with dyslexia. Furthermore, a growing body of literature has explored music-evoked emotions and how brain regions associated with emotion could be involved as the link between music and speech - as both music and speech draw upon emotion processing and recognition. Therefore, we sought to examine the neural basis of emotion as a key factor bridging music training with enhanced speech and reading skills. Structural neuroimaging analysis was conducted with a retrospective sample of children ages 8 to 13 years old. Using SPM12 through MATLAB, we ran whole-brain voxel-based morphometry and subsequent region-of-interest ANCOVA analyses to examine differences between three groups: musically trained children (n = 16), musically untrained children (n = 20), and children with dyslexia (n = 13). We hypothesized that key brain regions associated with emotion processing would indicate group differences in gray matter indices. Our results reveal a bilateral putamen and cerebellar effect in whole brain and region of interest ANCOVA analyses. Pairwise comparisons show differences between typical readers and those with dyslexia, for no significant differences were reflected between children with musical training versus without. Therefore, no “musician effect” was found in the present data. Rather, these findings highlight the strong implications of the “dyslexia effect” in these brain regions and suggest the presence of key structural brain differences in children with developmental dyslexia.

Olivia McGinnis

Physical Knowledge Emerges from the Visually Modulated Escape Behavior of Larval Zebrafish

Director: Dr. Florian Engert

Navigational strategies are crucial to life in a three-dimensional world. Escape behaviors are one example of a complex navigational program influenced by cognitive capacities and are exhibited by organisms across the animal kingdom. Indeed, successful evasion of threats determines survival for many animals, particularly prey like the larval zebrafish. Zebrafish engage in highly stereotyped, adaptive escape responses exquisitely tuned to features of the physical universe that are generated by a well-studied escape circuit called the brainstem escape network (BEN). We posited that avoidance of collision with obstacles upon escape should be a primary goal of zebrafish's escape strategy, and intriguingly that this strategy appears to require elements of physical knowledge – namely, a representation of object solidity. In order to test this hypothesis, we designed an escape arena outfitted with barriers to carefully describe how obstacles modulate zebrafish's escape response. We showed that by encoding three-dimensional forms, color and luminance cues, and distances, zebrafish robustly bias their escapes away from visually-perceived solid, three-dimensional shapes. Zebrafish build behavioral rules around each of these three features that when employed simultaneously, encode the principle of object solidity in their physical knowledge of the environment. Through laser-ablation of cells central to the BEN, we presented evidence for a novel inhibitory motif that neurally implements the escape bias we observed.

Jacob McLennan

Role of Serotonin in Auditory Perceptual Learning

Director: Dr. Anne Takesian

Neuroplasticity, the ability of neurons to alter their connections with one another, is thought to be a biological mechanism underlying learning. Work from our laboratory and others suggests that activation of a group of superficial cortical interneurons, vasoactive intestinal peptide (VIP) cells, promotes plasticity in cortical regions, including primary auditory cortex (A1). VIP interneurons integrate neuromodulatory and sensory information, suggesting that these cells signal relevant sensory stimuli. Specifically, these interneurons are characterized by expression of an ionotropic serotonin receptor, proposing that serotonin could play a key function in coordinating neuroplasticity and learning. However, the role of serotonin in auditory learning and the origin of serotonergic inputs to A1 is unknown. To understand the role of serotonin in auditory learning, we established a perceptual learning task in which mice gradually improve their ability to discriminate sound frequencies over weeks of training. Our ongoing studies are testing for a potential novel role of VIP interneurons in learning and whether enhancing serotonin signaling, via chronic administration of a selective serotonin reuptake inhibitor (fluoxetine), will improve performance in this learning paradigm. To characterize brain regions where serotonergic projections to A1 arise, we used immunocytochemistry and a retrograde tracer to reveal cells in serotonergic regions that project to superficial A1. Future studies will explore how manipulations of these serotonergic projections to A1 will affect perceptual learning. This study could provide insight into how VIP interneurons and serotonergic projections might be candidate sites for therapies to treat children and adults with learning deficiencies and disorders.

Katherine Miclau

Selective Activation, Collective Suppression: Provisional Evidence for Broad Modulation of Large-Scale Networks from Within-Individual Analysis of the Default Network

Director: Dr. Randy Buckner

The primate association cortex is organized into multiple large-scale distributed networks. Two of these cortical networks, the Default and Dorsal Attention Networks, have been linked to competitive modes of processing for internally constructed and externally oriented stimuli, respectively. In humans, this antagonistic relationship has been studied using both electrophysiology and neuroimaging techniques. Recent within-individual analyses revealed that the Default Network comprises two fully distinct, parallel networks (termed DNA and DNB), which can be differentially recruited for tasks across different domains. Whether both networks exhibit collective suppression during externally oriented tasks is unknown. Using functional magnetic resonance imaging (fMRI) and repeated scanning of individuals, DNA and DNB activation patterns were characterized during two external attention tasks (working memory and visuomotor). Time series and mean task activity were analyzed across the full networks and within five cortical regions, and were subsequently compared to those within the Dorsal Attention Network (dATN). Within- individual (n=10) and group-wise time series show patterns of joint suppression of DNA and DNB during tasks demanding external attention, both at the network level and across specific network regions. The dATN shows the opposite pattern. In conjunction with findings that DNA and DNB can be selectively recruited by domain-specific tasks, we provide evidence that DNA and DNB exhibit collective task-related suppression for externally oriented tasks, as well as functional anti-correlations with the dATN. These findings further inform debates regarding competitive relationships for processing resources between large-scale networks.

Miranda Mize

Neural Correlates of Over-Sensitivity to Negative Valence Expressions in Three-Year-Old Children

Director: Dr. Chuck Nelson

The ability to discern emotion from facial expressions is a necessary component of social interaction. Deficits in this ability, such as individuals who are highly sensitive in response to negative expressions, have been suggested to indicate deficits in socio-emotional functioning and regulation of emotion. This longitudinal study investigated the typical developmental trajectory of facial emotion perception in children at three years of age and five years of age. It also examined individual differences in sensitivity to negative expressions, testing facial perception accuracy through a behavioral emotion sorting task, and using functional near-infrared spectroscopy to measure neural activity in the prefrontal cortex in response to faces of positive and negative valence. In studying developmental trajectories of accuracy, we found that children sorted negative valence emotions — fear and anger — with greater accuracy at five-years-old compared to three-years-old, but did not show this improvement in accuracy with age for happy faces. In studying sensitivity to negative faces, we found a linear relationship between the demonstrated sensitivity to negative valence expressions in the behavioral task and the deoxygenated hemoglobin response in the ventromedial prefrontal cortex, such that greater sensitivity to negative faces in the behavioral task was correlated with a greater condition difference in deoxygenated hemoglobin response. Our research suggests that the medial prefrontal cortex responds differentially to the valence of facial emotion and may play a role in accurately perceiving facial emotion during development.

Ali Nasser

Effects of Early Life Stress on the Myelination of Parvalbumin Interneurons in the Prefrontal Cortex of Mice

Director: Dr. Takao Hensch

Chronic early life stress (ELS) leads to various changes in brain function and development. Studies have shown that children that have suffered from early adverse experiences, such as neglect and abuse, have increased difficulty in learning as well as a higher risk for depression and disease/disorders later in life. ELS has also been associated with impairment of cognitive flexibility in mice. Dysfunction of Parvalbumin interneurons in the mPFC have been demonstrated to contribute to cognitive impairment observed in ELS mice. This thesis investigates the effects of ELS on the myelination in the PFC, as well as the myelination of parvalbumin interneurons in the ACC, in the hopes of understanding the mechanism of dysfunction in these cells that leads to impairment of cognitive flexibility. We modeled chronic ELS using the limited bedding and nesting material paradigm. Through immunohistochemical staining of myelin basic protein (MBP), an important component and marker of myelin, we found that the mPFC has decreased myelin intensity in P40 ELS mice. We also virally labeled parvalbumin interneurons in the anterior cingulate cortex of parvalbumin-cre mice and discovered a significant decrease in both the number of PV axon myelin segments and the percent of myelin segments sheathing PV axons in ELS mice compared to control. Future studies are needed to establish a mechanism through which this may occur, and this could be in the form of experiments seeking to understand the changes oligodendrocytes may be undergoing in ELS mice.

Nadeen Odeh

Comparing patterns of cortical thickness between developmental prosopagnosics and typically-developed controls: A case where deficient face recognition performance is associated with thicker cortex

Director: Dr. Joe DeGutis

Neuroimaging studies have typically associated increased cortical thickness (CT) with superior cognitive performance. Here, we demonstrate a case where deficient face recognition performance is correlated with greater CT. Some studies have examined the relationship between facial recognition and CT of the fusiform face area (FFA), and found a negative correlation, however, none have examined this relationship in a prosopagnosic population. In this study, we investigated patterns of CT between developmental prosopagnosics and typically-developed controls. We focused our analyses on anatomically-defined regions and mapwise-difference regions between groups. We also conducted several tests to assess facial recognition ability and severity of prosopagnosia, with the goal of further understanding how structural abnormalities relate to behavioral deficits. In our analysis of anatomically-defined regions of interest, we reported four regions (LH lingual gyrus, RH cuneus cortex, RH lateral occipital cortex, and the RH lingual gyrus) where prosopagnosics had significantly greater CT than controls, and no regions where the opposite was the case. Our results point to a consistent pattern of increased CT in prosopagnosics, compared to controls—an effect that survives even when controlling for age-related CT thinning. In our mapwise analysis, we found a region in the RH fusiform gyrus that had significantly greater CT in prosopagnosics than controls. However, this region was slightly medial to the middle fusiform sulcus, and did not correspond to the FFA. These results indicate a consistent pattern of CT being negatively associated with performance within prosopagnosic subjects and contributes to growing body of research on how structural MRI can inform behavior deficits in human populations.

Emil_Radyt_

Reading the Mind: Semantic Representations of Self and Others in the Theory of Mind Network

Director: Dr. Jason Mitchell

Humans navigate social environments daily: understanding the minds and thoughts of others, known as mentalizing, is crucial to performing this activity. Recent work in social cognitive neuroscience has suggested that the brain may have a cognitive architecture to process complex information. In this thesis, I study whether a specific architecture that is used to process information about other people's thoughts can be found, and if that architecture remains stable when "mentalizing" about oneself. In order to conceptualize this system of explicit neural representations of cognitive processes, we used a linguistic metaphor of "semantic" relations between "agent" (the person having the thought) and the "patient" (the target of the thought). Our experiments used functional magnetic resonance imaging (fMRI), where participants are prompted to engage with the thoughts of other personally familiar people over a series of adapted scenarios that either include themselves (self-others task) or do not include themselves (other people task). We interpreted collected neuroimaging data using representational similarity analysis (RSA). Preliminary results do not support the semantic metaphor of "agent" and "patient" for neural representations. However, while distinct role-based categories are unlikely, there may be emergent representations in the bound relation between role and thought, suggesting directions for further research. I use the empirical findings of linguistic anthropology to highlight and explain the more, and less, promising parts of the cognitive theories and linguistic metaphors at the core of this research and reflect on the methodology through an interdisciplinary lens that could lead to future improvements in research design.

Danny Ragheb

How Our Brains Vote: Neurobiological Differences Moderate the Impact of Sleep on Voter-Related Behavior

Director: Dr. Josh Buckholtz

Although there have been a multitude of studies interrogating the predictors of voter turnout, the majority of them focus on political factors such as affiliation, income, and race. However, no previous literature has considered the impact that neuroanatomical structures have on voter behavior. In fact, there has been no previous interrogation of political science questions using volumes of neuroanatomical structures. This thesis thus interrogates how brain volume interacts with sleep quality to predict patience, and subsequently, how patience predicts voter turnout. I hypothesize that decreased sleep quality reduces patience. Additionally, I predict that this effect is more severe among individuals with smaller brain structures. Patience and validated voter turnout are provided by the Cooperative Congressional Election Study. Sleep quality, patience and brain volume are provided by the Human Connectome Project. Results confirm my hypothesis and show the following: (1) increased patience predicts increased voter turnout and (2) reduced sleep quality reduces patience, and this relationship is exaggerated in individuals with lower brain volumes. The implications of this research range from public policy suggestions focusing on neuroanatomical health to ethical questions considering that neuroanatomical qualities can reliably and individually be targeted to produce political behavior.

Alex Ren

Modeling NaV1.7 Channelopathies Using Genetically-Engineered Human iPSC-Derived Sensory Neurons

Director: Dr. Clifford Woolf

Chronic pain represents an immense medical burden in the United States. Developing novel analgesics that lack the adverse effects of opioids will require the identification of more clinically-relevant models for painful conditions. Human induced pluripotent stem cells (hiPSCs) and genome engineering technologies offer promising strategies for creating these preclinical models. In this project, we engineered hiPSCs to express a sodium channel mutation relating to one of two extreme pain disorders—inherited erythromelalgia (IEM) or paroxysmal extreme pain disorder (PEPD)—and sought to characterize the electrophysiological properties of differentiated sensory neurons. Using CRISPR-Cas9, we knocked-in a single point gain-of-function mutation into the SCN9A gene of normal patient-derived iPSCs. Immunocytochemistry and calcium imaging results indicate that we successfully generated functional hiPSC-derived nociceptors using an established combined small-molecule and growth factor differentiation protocol. Multi-electrode array (MEA) recordings of neuronal populations showed that our heterozygous mutant (Het) lines exhibited greater spontaneous excitability compared to their respective wild-type (WT) lines. Interestingly, in some cases, this difference in excitability became more pronounced at higher temperatures. Moreover, current-clamp recording revealed greater evoked repetitive firing among Het lines, with lowered thresholds for action potential firing. Our results illustrate the utility of an engineered- hiPSC platform, and further demonstrates our ability to model painful channelopathies in a dish. Such a model would prove immensely useful for analgesic drug discovery efforts.

Maggie Reynolds

EEG Theta/Beta Ratios as an Index of how Early Institutionalization Impacts Externalizing Problems and Callous-Unemotional Traits in Early Adolescence

Director: Dr. Chuck Nelson

It is well established that early life adversity can dramatically alter developmental trajectories. A particularly egregious form of adversity is severe psychosocial deprivation, common among institutionalized children. The Bucharest Early Intervention Project (BEIP) is a longitudinal randomized controlled trial in which institutionalized children were placed into foster care as a form of environmental enrichment. Following a baseline assessment conducted in infancy, institutionalized infants were randomly assigned to a high-quality foster care intervention or continued institutional care. Age-matched community children (i.e., who had never been in an institution) served as a comparison sample. The present study examines the effects of institutionalization on early adolescent resting brain activity, callous-unemotional (CU) traits, and externalizing problems (EXT), including Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD). Electroencephalography (EEG) was used to collect resting state brain activity at age 12. The Health and Behavior Questionnaire (HBQ) and the Inventory of Callous-Unemotional Traits (ICU) were administered to measure EXT and CU traits, respectively. A modest relation between the ratio of whole-brain theta and beta power (TBR) and CD was observed, although this effect was lost after controlling for ADHD, treatment arm (foster care vs. institutionalized care), and sex. No relations between TBR and ODD or CU traits were observed. Because of the controversy surrounding TBR and ADHD, their relationship was also examined in this sample. No significant relations between TBR and ADHD were maintained after controlling for institutionalization history. These findings do not support the use of TBR to identify ADHD and other EXT problems. A post-hoc analysis was conducted to examine the role of theta and beta power individually. Increased theta power but no change in beta power were associated with ODD and CD, but not with CU traits. Although these results support the strong linkage between psychosocial deprivation and the development of EXT and CU traits, this relationship cannot be explained solely by deviations in resting state TBR.

Aleeza Shakeel

The Role of the Hippocampus in Dopamine Ramping During Spatial Navigation

Director: Dr. Nao Uchida

The neurotransmitter dopamine facilitates learning, motivation, and decision making. To prevent and treat disorders that result from abnormalities in dopamine we must understand how it functions normally. Prior research shows that dopaminergic neurons respond with a short burst of activation when one receives reward. Recent studies show that dopamine gradually ramps up as the animal approaches a reward location. My research aims at understanding the mechanism behind dopamine ramping. Since dopamine ramping occurs when the animal moves in space to obtain reward, I hypothesize that the hippocampus, the region responsible for spatial memory, is involved in dopamine ramping during spatial navigation. To see if there is a causal relationship between the hippocampus and the dopamine ramping, I quantitatively examined behavioral and neural parameters, including licking rate, running speed, dopamine response, and magnitude of dopamine ramping, when the hippocampus was inactivated. I measured these parameters while the mice approached a reward in a virtual reality maze in normal trials and inactivation trials. I measured dopamine activity in the ventral striatum by implanting a thin fiber where neurons express transduced proteins that change fluorescence with dopamine activity (fiber fluorometry). I also inhibited neuronal activity in hippocampus by transducing light-sensitive chloride pumps and delivering laser in randomly interleaved trials (optogenetic manipulation). After training the mice and measuring dopamine ramping, I found no significant differences for the control mice but did find significant decreases for the experimental mice in the magnitude of dopamine ramping and running speed between the normal and inactivation trials. This suggests that there could be a causal relationship between the hippocampus and dopamine ramping.

Samantha Shao

Role of Caspase-3 in Visual Plasticity

Director: Dr. Takao Hensch

Synaptic plasticity is the ability of synapses, which are specialized junctions between neurons, to weaken or strengthen in response to changes in neuronal activity. Its dysfunction is associated with neurodevelopmental disorders, such as autism and schizophrenia. Our lab focuses on the development of the mouse visual cortex, a brain region characterized by strong experience-dependent plasticity. Previous research from our lab has found that active caspase-3 (aCasp3), known executor of apoptosis, is expressed at cortical synapses in the primary visual cortex in the absence of cell death, suggesting a possible involvement in activity-dependent synaptic refinement. The goal of this thesis is to deepen our understanding of the role of aCasp3 in visual cortical development at the anatomical and functional level. To this aim, we have determined both layer-specific and synapse-specific expression of aCasp3 in postnatal day 32-44 mice, and investigated whether prolonged sensory manipulations, such as 1-week and 2-weeks dark exposure, alter its basal expression. We used immunohistochemistry (IHC) assays, confocal microscopy, and super-resolution microscopy to visualize synapses and aCasp3 localization. Applying a machine-based learning approach we then identified synapses and quantified the expression of aCasp-3 at the synaptic level in response to sensory manipulations. Altogether our results show that aCasp-3 is expressed at excitatory, but not inhibitory, cortical synapses and is sensitive to changes in neuronal activity, suggesting a central role in cortical visual functioning. aCasp-3 may function as a mediator of synaptic scaling, a mechanism of homeostatic plasticity.

Hayat Sherif

The Neurobiological effects of Ketamine on Anxiety Circuitry in Patients with Fear of Harm Phenotype of Bipolar Disorder

Director: Dr. Marty Teicher

Thermoregulatory Fear of Harm disorder was initially identified by Dr. Paplos and colleagues. This disorder is a phenotype of Bipolar disorder that is characterized by elevated levels of anxiety. Common characteristics of the presence of the FOH phenotype of bipolar disorder in youths are early age of onset, severe mood swings, treatment resistance, separation anxiety, fearful-aggressive obsessions, parasomnias, and thermal dysregulation. Key distinguishing features of the FOH phenotype of bipolar disorder that are helpful in distinguishing these youth from other youth with bipolar disorder are the presence of thermal dysregulation and fear sensitization. In this study, we obtained results that indicate that ketamine reduces hyperactivation of the amygdala in response to fearful and threatening stimuli. Furthermore, we observed different activation patterns for subliminal and supraliminal threatening stimuli, indicating the processing of these stimuli through distinct anxiety circuitries.

Becky Soilson

Disruption of Amyloid- β Aggregates Using Targeted Magnetic Nanotherapy in a 3D Human Neural Cell Culture Model of Alzheimer's Disease

Director: Dr. Rudolph Tanzi

Although the underlying pathogenesis of Alzheimer's disease (AD) is not fully understood, research shows that AD is largely driven by the extracellular accumulation of amyloid- β (A β), specifically the pathogenic isoform A β 42. After observing successes in the biotechnology sector utilizing nanotechnology to safely modify targeted proteins, specifically in a liminal study showing in vitro modulation of synthetic A β protein, this thesis sought to demonstrate the potential for an AD nanotherapy. Using a novel three-dimensional (3D) human neural progenitor cell culture model that recapitulates the key mediators of AD pathogenesis, this thesis explored and determined the effects on A β aggregation after the 3D cell cultures were incubated with superparamagnetic iron oxide nanoparticles (SPIONs) that were conjugated with anti-A β antibodies to specifically target the A β protein and that were subsequently exposed to various alternating magnetic fields (AMFs). This thesis explored a frequency range between 10-1000 Hz, finding a notable therapeutic effect when the anti-A β -conjugated SPIONs are exposed to 30 Hz of AMF for one hour in the 3D cell culture model of AD. Further, this study found evidence that this therapy may be a viable option for AD treatment as cell viability after treatment remained high and cytokine activation remained constant throughout the tested frequency range. These results demonstrate the potential for this nanotechnology to help AD researchers better understand how to modulate a key pathological hallmark of the disease and to inform further research into the parameters necessary to optimize AMF nanotherapy for the preventative intervention and treatment of AD.

Matt Spence

The Neural Basis of the Effect of Future Simulation on False Episodic Memory

Director: Dr. Dan Schacter

People often use their episodic memories—memories of specific past experiences—to imagine, simulate, and plan for upcoming future events. Previous research has shown that future thinking is tightly linked to the neural circuits for episodic memory, and that it can aid in the creation of memory distortions. This analysis was aimed at identifying the neural networks responsible for the influence of future simulation on subsequent episodic memory retrieval. After imagining everyday events going either well or poorly in the future and reading neutral stories about hypothetical outcomes in each scenario, participants were tested on their memory of valenced (positive and negative) details in the stories. We scanned participants' brains using functional magnetic resonance imaging (fMRI) during imagination and recognition sessions. We attempted to: 1) uncover the effect of subjective ratings of imagined events on subsequent false alarms, 2) discover brain regions in the imagination phase whose activation predict false alarms in the recognition phase using multivoxel pattern analysis (MVPA), 3) train a classifier program to distinguish between false alarms and hits in the recognition phase, focusing on regions involved in memory monitoring. While the first two analyses yielded null results, the third analysis identified the left anterior cingulate cortex, left inferior frontal gyrus, left inferior parietal lobe, and bilateral precuneus as providing adequate information to distinguish false alarms from hits. This provides a novel insight into which regions of the brain code for objectively true information at the time of episodic memory retrieval.

Tori Tong

The Evolution of Defensive Behavior Against Visual Threat in Deer Mice

Director: Dr. Hopi Hoekstra

Despite a growing understanding of the neural circuits that underlie behavior, little is known about the neural basis of behavioral evolution. Defensive behavior is a good model to study behavioral evolution because it is often robust, important for species survival, and under strong selection pressure. Recent studies show that *Mus musculus* exhibit various defensive responses to a laterally moving ('sweeping') or rapidly expanding ('looming') visual stimulus. I investigated these behaviors in wild-derived colonies of ecologically distinct *Peromyscus* mice. First, I conducted a comparative experiment to quantify the defensive response of seven *Peromyscus* strains to a compound sweep-looming stimulus. I found that *Peromyscus* exhibited a similar defensive behavioral repertoire to *Mus*, but that the frequency of behaviors differed significantly between strains. This behavioral variation partially correlates with the environment in which these strains occur, suggesting that habitat structure may affect the evolution of defensive behavior. Second, I selected two closely related yet behaviorally divergent strains to investigate how position, orientation, and speed affected the choice of defensive response. Though many variables appear to be weakly correlated with response choice, species identity was the only variable that exhibited a strong correlation. Third, I assessed if the two species show differences in anxiety as measured by the elevated plus maze. My results suggest that they differ in anxiety in a direction consistent with their looming response differences, and that vision is important for expressing these anxiety differences. Together, my work provides a foundation for future research that can investigate the neural and genetic mechanisms of defensive behavior evolution in *Peromyscus* mice.

Ariel Vilidnitsky

Investigating the CIC Protein's Role in Neurodevelopment Using Patient-Derived iPSC Models

Director: Dr. Steve Haggarty

The transcription factor Capicúa (CIC) regulates cell proliferation and migration in various mammalian tissues. Recent research suggests that mutations in the CIC gene may contribute to neurodevelopmental disorders, such as Autism Spectrum Disorder (ASD), though the mechanisms by which such mutations lead to disease are not well understood. We sought to investigate CIC's role in typical neurodevelopment and disease by generating an induced pluripotent stem cell (iPSC) model from the skin biopsy of a young, female subject with ASD. The subject carries a de novo heterozygous truncating point mutation in CIC, which we hypothesize is responsible, at least in part, for certain clinical symptoms. We characterized CIC expression in cells derived from the subject and found that CIC mRNA levels were 50% lower than in healthy control cells from the subject's mother, thereby confirming the predicted functional consequence of the mutation. We next attempted to use CRISPR genome editing to create an otherwise isogenic, mutation-corrected cell line that would serve as a precise control. Though work to produce this line remains ongoing, we successfully generated several cell lines with homozygous disrupted CIC sequences due to unintended mutations, which are predicted to either produce truncated CIC proteins or elicit mRNA quality control mechanisms that prevent protein production. Finally, we tested protocols for differentiation of the iPSCs into neural progenitor cells (NPCs) and neurons. Overall, our research is an important first step toward understanding the neurodevelopmental consequences of CIC mutations, with applications to precision medicine and the treatment of rare genetic conditions.

Diana Wang

Potential of Receptive Music Intervention on Mild Cognitive Impairment: A Resting-State fMRI Study

Director: Dr. Maiya Geddes

Music-based interventions have become increasingly widely adopted for dementia and related disorders. Previous research shows that music engages reward-related regions through functional connectivity with the auditory system. Here I characterize intrinsic connectivity of the auditory and reward systems in healthy aging, mild cognitive impairment (MCI) – a prodementia phase of cognitive dysfunction – and Alzheimer’s disease (AD) individuals. Using resting-state functional Magnetic Resonance Imaging (rsfMRI) data from the Alzheimer’s Database Neuroimaging Initiative, I tested functional connectivity within and between auditory and reward systems in older adults with MCI, AD, and age-matched healthy controls (N=105). Seed-based correlations were assessed from regions of interest (ROIs) in the auditory network, i.e. anterior superior temporal gyrus (aSTG), posterior superior temporal gyrus (pSTG), Heschl’s Gyrus, and the reward network, i.e. nucleus accumbens, caudate, putamen, and frontal orbital cortex. AD individuals were lower in both within-network and between-network functional connectivity in the auditory network and reward networks compared to MCI and controls. Furthermore, graph theory analyses showed that MCI individuals had higher degrees and strengths than both AD and control individuals and was indistinguishable to controls in betweenness centrality. Together, the auditory and reward systems show preserved within- and between-network connectivity in MCI relative to AD. These results suggest that music-based interventions have the potential to make an early difference in individuals with MCI due to the preservation of functional connectivity in reward-related regions and between auditory and reward networks at that initial stage of neurodegeneration.

Samantha White

An Examination of How Anxiety Sensitivity Relates to PTSD Symptoms and Resting-State Functional Connectivity in a Trauma-Exposed Sample

Director: Dr. Isabelle Rosso

The goal of this study was to explore the relationship between anxiety sensitivity (AS) and PTSD, focusing on symptom severity and resting-state functional connectivity. AS levels tend to be higher in those with PTSD compared to other trauma-exposed healthy control (TEHC) groups. Therefore, we predicted that people with PTSD would score higher on the anxiety sensitivity index (ASI) compared to TEHC. Also, we hypothesized that AS would be positively correlated with PTSD symptom severity, specifically hyperarousal and avoidance. In resting-state fMRI studies (rsfMRI), the salience network (SN) has been shown to have hyperconnectivity in PTSD and consists of brain regions that mediate AS, such as the anterior insula (AI). Also, the mid and posterior insula are involved in interoception and anxiety. I hypothesized that rsfMRI connectivity of the SN and insula subregions would be related to ASI scores. This study consisted of 59 participants who completed rsfMRI, the Clinician Administered PTSD Scale (CAPS), ASI, and other measures. To examine group differences on ASI, I ran t-tests and ANCOVAs. To test the relationship between AS and PTSD symptom severity, I ran multiple regressions with CAPS and ASI, controlling for confounding factors. The rsfMRI data was analyzed with CONN using the bilateral AI as seeds for a whole-brain analysis. AS was significantly higher in the PTSD group compared to TEHC, and was associated with total and avoidance PTSD symptoms. AS was not significantly associated with functional connectivity. This study provides evidence that AS has an important relationship with PTSD.

Josie Wolf

Investigating Neuronal Circuit Processing of Sensory Cues During Parenting Behavior

Director: Dr. Catherine Dulac

Specific cell types in the medial pre-optic area (MPOA) are essential for the control of parenting in males and females. However, the neural mechanisms and pathways that integrate and carry sensory information to the MPOA are not yet characterized. This study aimed to identify the brain regions that encode and process the sensory information essential to evoke stereotyped motor actions during parenting behavior. We presented an adult parenting female mouse with a combination of pup cues (chemosensory, auditory and somatosensory) to measure precisely the activation in sensory regions involved in the parenting circuit during parenting behavior. We find that exposure to chemosensory stimuli in the form of pup urine in combination with a silicone blob (partial shape of pup body) resulted in parental behavior in all cases, with increased latency compared to the exposure to pup. 50% of dams subjected to the auditory stimulus (pup calls) retrieved the blob to the nest, and none of the dams fully retrieved the blob with no additional stimulus to the nest. Increased activation in the olfactory bulb (OB), accessory olfactory bulb (AOB), and the MPOA was observed in the pup group compared to the other three stimulus groups. Next, using machine-learning based tools (DeepLabCut) and unsupervised clustering methods we identified postures associated with stereotypical parenting behavior in these different sensory contexts to allow detailed quantification of parenting behavior. In sum, our results suggest that the presentation of pup-related chemosensory stimuli elicited similar activation and motor actions to the presentation of a live pup.

Thomas Xin

Impact of Chronic Sleep Restriction on Sleep Continuity and Sleep Structure

Director: Dr. Charles Czeisler

Chronic sleep restriction has become a prevalent condition that has been associated with adverse effects on cognitive impairment and increased risks of diabetes and cardiovascular diseases. On the other hand, sleep restriction is used therapeutically in the treatment of insomnia, as a central component of Cognitive Behavioral Therapy for Insomnia (CBT-I) because of reported benefits on sleep continuity and structure in that patient population. However, little is known about the impact of chronic sleep restriction on sleep continuity and structure in healthy people without sleep complaints. Therefore, we investigated the impact of chronic sleep restriction on sleep continuity and structure in a group of 9 healthy participants. They had a 4-night Laboratory Sleep Extension condition, 2-night Baseline Sleep condition, 21-night Chronic Sleep Restriction condition (5/5.6-hour time in bed) and a 9-night Recovery Sleep condition. During Chronic Sleep Restriction, average sleep duration was reduced by 88.63 ± 26.60 minutes per night compared to Baseline Sleep. Slow-Wave Activity was significantly increased, and sleep was more consolidated as compared to Baseline Sleep. During Recovery Sleep, the sleep duration was increased by 106.72 ± 33.49 minutes compared to Chronic Sleep Restriction, and the Chronic -Sleep-Restriction-induced increase in Slow-Wave Activity persisted, particularly after the 5-hour Chronic Sleep Restriction. Our results suggest that chronic sleep restriction improves traditional metrics of sleep quality and may have a persistent impact on sleep depth, perhaps accounting for the post-treatment efficacy of CBT-I. However, further research is required to evaluate the potential tradeoff between sleep duration and sleep quality on health, safety, and performance.