Research Program Summary Cory Inman, Ph.D.

Emotion and memory for the important moments of life serve as the foundation for our sense of self in the moment and through time. People are stripped of their identity when control of these abilities is lost due to neural disease. To fully understand and control the neural systems underlying emotion and memory we must study these behaviors in humans. However, traditional methods of studying the human brain, like functional MRI and EEG, are limited in their ability to assess and manipulate the precise temporal and spatial patterns of neural activity in deep brain structures, like the amygdala and hippocampus, which mediate these fundamentally human behaviors. A more holistic approach to the study of emotion and memory in humans is needed. My laboratory aims to dissect the emotion and memory functions of the human brain with three complementary lines of research aimed at: 1) *understanding* the dynamic organization of neural circuits from single neurons to whole brain networks during emotion and memory processes using human intracranial electrophysiology and functional neuroimaging, 2) *modulating* the activity and organization of these networks to gain control of emotional experience or enhance memory using direct brain stimulation in humans, and 3) *translating* these laboratory-based discoveries to neuromodulation therapies that can restore functional behavior in real-world settings to help those suffering with neural disorders. My research draws upon theoretical perspectives and experimental techniques from multiple fields, including network neuroscience, cognitive science, neuroengineering, human neurophysiology, computer science, and neuromodulation. My research program is constructed upon studies using behavioral, neuroimaging, and neuromodulation approaches to study how the brain operates in traditional laboratory experiments with the explicit objective to gradually work toward neuroscience studies of real-world cognitive behaviors that extend from laboratory-based discoveries. With the promise shown by my neuromodulation studies aimed at understanding and treating a variety of memory and mood disorders (e.g. Inman, Manns, et al., 2018, *PNAS*; Riva-Posse, Inman et al., 2019, *Brain Stimulation;* Stangl, Topalovic, Inman et al., 2021*, Nature*), working towards neuroscientific studies of real-world cognition is the key translational step needed to push our neuroscientific insights from the laboratory to restoring real-life cognitive function in those suffering from devastating disorders of emotion and memory.

In the sections below, I describe my past and current contributions to the field and look ahead to specific studies my laboratory will perform to accomplish my goals to *understand* neural networks underlying emotion and memory functions, *modulate* these networks, and *translate* our discoveries to explore and treat real-world cognitive disorders. This work will ask fundamental questions such as: How do we study the neural formation of episodic memories in rich, complex real-world settings? How does the human brain prioritize specific experiences for long-term memory storage? What is the role of the human amygdala and emotion in this process? How do we modulate these systems with direct brain stimulation to treat debilitating disorders? Can we enhance memory for real-world experiences through direct stimulation of the human brain?

Past, Current, and Future Research

Modulating emotion and memory networks with DBS. My work in DBS for depression (Riva-Posse, Inman, et al., 2019, *Brain Stimulation*) led to pursuing an opportunity to perform large-scale electrophysiology and DBS studies in patients with drug-resistant epilepsy undergoing intracranial monitoring to identify brain regions that caused their seizures. For my primary postdoctoral project, I developed a series of experiments examining the cognitive, emotional, and physiological effects of direct brain stimulation to the human amygdala. In our first studies, we examined the effects on changes in measures of autonomic reactivity (e.g. skin conductance and heart rate) and safety of human amygdala stimulation. This work demonstrated that amygdala stimulation in humans was safe and effective for modulating autonomic reactivity in a dose-dependent manner (Inman et al., 2018b, *Neuropsychologia)*. Pairing these insights with the known functions of the amygdala in enhancing memory for emotional experiences, I developed a study with Dr. Joseph Manns to test whether direct amygdala stimulation could enhance declarative memory for neutral stimuli without inducing any changes in emotion physiology or experience. In this study, we found that brief electrical stimulation to the human amygdala reliably improved long-term recognition memory for images of neutral objects without eliciting an emotional response and that this memory enhancement was accompanied by neuronal oscillations during retrieval that reflected increased interactions between the amygdala, hippocampus, and perirhinal cortex (Inman, Manns, et al., 2018, *PNAS*). This finding demonstrates that the human amygdala plays a *causal* role in the prioritization of specific declarative memories for long-term consolidation. With further tuning, this study also suggests that amygdala-mediated memory enhancement (AMME) is a unique neuromodulation technique to enhance declarative memory, unlocking new approaches to dissecting the human emotion and memory system. These results addressed fundamental questions about the causal role the amygdala plays in emotional memory and opens a path to future experiments and therapies.

After the success of our amygdala stimulation studies, I lead the writing and construction of a NIHM R01 grant application to further examine the “Mechanisms of amygdala-mediated memory enhancement in humans” that was funded late last year (R01 MH120194-01A1; $750,347 at Utah). Over the first year, this project was necessarily stalled due to COVID-19 and the lead PIs move from Emory University to Washington University in St. Louis. As part of this move the lead PI asked me to become a Co-I/Site PI and to help transfer the grant. Since receiving this grant, we have collected amygdala stimulation data on over 20 intracranial EEG recording patients across both the Utah and Washington University sites. Throughout the 2 completed years of this grant I have led all project meetings and research efforts. My postdoctoral fellow is directly responsible for the day-to-day operation of this project and my graduate students have directly contributed to building experiments in service of the aims of this grant. In this grant, we will leverage amygdala stimulation to interrogate

connections to regions of the MTL network to manipulate neural network activity and enhance memory using intracranial electrodes in awake neurosurgery patients to isolate the contribution of the human amygdala to neural dynamics of memory. I and my lab will lead the research efforts both at Utah and across all 3 study sites. This includes the mentorship of a postdoctoral fellow and 3 graduate students. In analyses of our first executed specific aim, we've found that direct stimulation to the human amygdala preferentially enhances memory for images of objects versus scenes. This finding is in line with our hypothesis that the connectivity of the amygdala to object recognition-related brain areas like the anterior hippocampus and perirhinal cortex biases the amygdala's influence on memory for objects relative to scenes encoded via the posterior hippocampus and parahippocampal cortices (Aim 2). We are completing analyses on this initial finding and aim to submit this work for publication within the next year. Martina Hollearn has contributed to this project by designing two experiments relevant to her overall interests to investigate the influence of amygdala stimulation on memory over long delays (1 week; Aim 1) and the precision of patients' recognition memory after amygdala stimulation. Justin Campbell has generated an approach to perform closed-loop, theta phase-aligned amygdala stimulation in service of Aim 3 of the grant. Finally, Carson Miller, an undergraduate RA and UROP trainee, has completed a thorough analysis of free recall data from our prior amygdala stimulation datasets under my and my postdoc's mentorship, culminating in a recent presentation at the Utah Conference for Undergraduate Research.

Translating laboratory discoveries to understand and treat real-world cognitive disorders. In a second postdoctoral fellowship, I developed a neural recording and stimulation platform to perform real-world navigation and memory experiments using a suite of wearable and wireless 1st person experience sensors and augmented reality (AR; i.e., technology that superimposes immersive, 3D imagery onto a user's view of the real-world). The overall goal of this work is to establish techniques for *translating* DBS-based memory enhancement approaches to real-world environments and experiences. My lab's current research project based on these developments uses mobile recording of deep brain activity to examine how the brain parses our continuous, large-scale, real-world experiences into memorable episodes and will demonstrate a brand-new method for investigating the neuronal mechanisms underlying real-world human cognition and behavior (i.e., navigating a ¾ mile route around a college campus). The advantage of a wireless chronic implant in humans is that freely moving behaviors can be explored unlike in traditional neuroimaging and neuromodulation methods.

My lab was awarded an NSF Foundations grant from the Integrative Strategies for Understanding Neural and Cognitive Systems program to continue making this vision a reality in 2021 (NSF 2124252; $1,000,000 between Utah and USC). The goal of this project is to build and evaluate a system for exploring how the human brain processes information about the real-world environments we navigate every day. To accomplish this goal, we have directly recorded from the brain while participants navigate the real world while synchronously recording information about the participant's first-person experience from a set of sensors that capture different human senses, including cameras, microphones, eye-tracking, and physiological recordings. Neurosurgical participants with epilepsy who have an implanted neural recording and stimulation system used to control their seizures mentioned earlier have volunteered for our experiments and provided rare direct recordings from the human brain while they navigate a complex, real-world environment. We are analyzing the rich sensor data captured from the participant's first-person experience using interpretable deep learning in relation to the neural data to infer how changes in neural oscillations relate to changes in one's experience. Despite only receiving the NSF grant at the end of August 2021, we have already completed aim 1 of this project throughout the pandemic by synchronizing the human experience relative to neuronal events by developing a robust, portable framework to record and synchronize both the neuronal activity along with data from wearable sensors that represent a broad subset of human sensory channels. Working towards aim 2 over this past year, we have collected hippocampal oscillatory data with 5 participants as they navigate the real world with our collaborators at UCLA (over 28 miles of real-world hippocampal navigation data). My lab has started to analyze this incredibly rich and valuable dataset from a variety of angles, and we are preparing to start collecting data at Utah (Aim 2 and 3). As part of aim 2, primarily undergraduate RAs in my lab have collected over 300 participants' worth of behavioral event segmentation data on the first-person videos generated from this study using the psychology participant pool. Aim 3 consists of testing whether we can enhance episodic memories of real-world experiences. We are designing this novel augmented reality experiment now in collaboration with colleagues throughout the CNS program. The platform developed and proven as part of this NSF grant that allows for neural recording, direct brain stimulation, and synchronization with external, wearable devices will open an entirely new area of research at the intersection of computer science, neuroengineering, cognition, and clinical neuroscience. These studies will launch and accelerate an emerging and pivotal area of research that will provide therapeutic interventions, *proven in the real world*, for participants afflicted with debilitating cognitive disorders. In service of this goal, I have recently submitted a large, multisite (4 sites) BRAIN initiative grant to continue this work and create a novel, lightweight system for recording a person's first-person experiences in truly real-world settings (museums, gardens, hikes, etc.) in sync with direct brain recordings. We are collaborating with several pioneers in the cognitive neuroscience field at UCLA, USC, and UCSD in this grant that, if awarded, would total nearly $6,000,000 in total funding over the next 5 years. We received an Impact Score of 28 on this grant in June and are awaiting the final funding decision this Fall. Overall, we are well on our way toward realizing the lab's research program. These initial grants are encouraging endorsements of the potential of our lab's research program. My students and trainees have made key contributions to these research aims and have developed their own research projects for their Master's thesis and dissertation out of this experience. I'm excited to continue working with my lab and collaborators to answer cognition and neuroscience questions that have never been possible to explore.