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 complimentary 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 towards 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. Simultaneous to my dissertation work, I learned to use deep brain stimulation (DBS) to study the *modulatory* influence direct electrical stimulation can have on the human brain and body. These studies showed that DBS to the subcallosal cingulate, the leading target for treatment of TRD, produced reliable changes in autonomic arousal. These findings provided a potential objective biomarker of effective stimulation target and depression network engagement (Riva-Posse, Inman, et al., 2019, *Brain Stimulation*).

My work in DBS for depression 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 past 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. We received the new transfer NOA from NIMH on July 30th and are restructuring the timeline of this project with our Program Officer. I also independently coordinated and completed IRB approval at all 3 study sites, with single IRB reliance on the Washington University IRB. Due to administrative issues related to COVID-19, these tasks were enormous professional efforts on my part, but now that we have the award and approval, we will be able to start this project in earnest. We will start collecting data on this project as soon as November but have been actively building the experiments for each aim while data collection stalled. 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 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 mentorship of a postdoctoral fellow that will lead day-to-day project operations and 3 graduate students.

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. Our ability to understand and treat debilitating neurological disorders, like Alzheimer's disease, will depend on our knowledge of the neural mechanisms involved in memory loss, not only in controlled laboratory experiments, but also in neuroscience experiments that capture the complexity, scale, and functional characteristics of memories made in the real-world. 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). There are currently over 2,000 potential research participants who have sensing and stimulation devices chronically implanted within a variety of brain regions for the treatment of epileptic seizures and other neural disorders. The University of Utah epilepsy neurosurgery program is a leader in this approach with over 45 patients with these devices in their care. The advantage of a wireless chronic implant in humans is that freely moving behaviors can be explored unlike in traditional neuroimaging and neuromodulation methods, which require participants to be immobile.

My lab was recently awarded an NSF Foundations grant from the Integrative Strategies for Understanding Neural and Cognitive Systems program to continue making this vision a reality (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 will directly record 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 that have an implanted neural recording and stimulation system used to control their seizures mentioned earlier volunteer for our experiments providing rare direct recordings from the human brain while they navigate a complex, real-world environment. We will analyze 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. In addition, we will apply targeted and safe brain stimulation to determine whether we can enhance memory for specific real-world events presented in augmented reality.

Despite only receiving the NSF grant at the end of August, we have already completed aim 1 of this project throughout the pandemic by synchronizing the human experience relative to neuronal events through developing a robust, portable framework to record and synchronize both the neuronal activity along with IoT data from wearable sensors that represent a broad subset of human sensory channels. Working towards aim 2 over this past summer, we have collected hippocampal oscillatory data with 3 participants as they navigate the real-world with our collaborators at UCLA (over 15 miles of real-world hippocampal navigation data). My lab is starting to analyze this incredibly rich and valuable dataset from a variety of angles as we prepare to start collecting data at Utah. Crucially, we have recently received IRB approval to start performing all aspect of these studies at Utah. This IRB approval is a ***significant*** step towards completing this project given the major hurdles to performing intracranial recordings and stimulation as epilepsy patients navigate the real-world. We will begin aim 3 of this project next year. Aim 3 consists of testing whether we can enhance episodic memories of real-world experiences with direct brain stimulation. Under medical supervision, we will stimulate the human amygdala at and between event boundaries in subjects with implanted stimulation devices as they encounter novel, 3D augmented reality objects while navigating a large-scale, real-world environment. Memory will be subsequently tested in laboratory and real-worlds settings. 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. Overall, we are well on our way, in less than a year, towards making the research program I described in my job application a reality. These initial grants are encouraging endorsements in the potential of our lab's research program. I'm excited to work with my lab and Utah collaborators to study questions that have never been possible to explore about the human brain.