Approximately 1 out of every 26 people in the United States will develop epilepsy sometime in their life. Memory impairments associated with epilepsy can be more debilitating than the seizures themselves. Accelerated forgetting – the impairment of long-term autobiographical memory – is especially disabling because our autobiographical memories define our sense of “who we are.” Our proposed research is aimed at (a) providing insights into the underlying causes of memory impairments in epileptics, and (b) exploring a potential treatment regime using intracranial brain stimulation.

Our research program is centered around a chronic ambulatory human electrocorticographic recording and stimulation device (RNS®, Neuropace Inc., Mountainview CA) that has been FDA-approved for treating partial seizures. Critically, this self-powered and fully enclosed device allows one to both record ongoing ECoG activity and to stimulate implanted electrodes. In addition to continuing to use this device to effectively treat seizures by reducing interactal epileptiform discharges (IEDs), as in our previous and ongoing work, here we are specifically interested in elucidating the electrophysiological underpinnings of memory formation and retrieval, understanding how memory function is disrupted by IEDs, and treating the associated epilepsy-induced memory impairments using electricial stimulation supported by the Neuropace device. Our central hypothesis is that brain stimulation that reduces abnormal epileptiform activity will improve memory function by restoring healthy neural patterns. The results of this study will inform future stimulation paradigms for cognitive function, including the design of future brain stimulation devices for epilepsy that will simultaneously reduce seizure frequency and restore cognitive function.

*Specific Aim 1: Determine hippocampal oscillatory markers of short and long-term free recall, including the oscillatory signature of accelerated forgetting over a time period of 30 days.*

*Hypothesis: Items recalled short and long-term have a distinct oscillatory signature during encoding as compared to items not recalled.*

We will use a two free recall tasks two assess the neural correlates of accelerated forgetting associated with temporal lobe epilepsy. The first task will be a well-studied list learning paradigm that will enable us to study the “pure” neural signatures of memory encoding and recall of tightly controlled (but psychologically impoverished) word stimuli. The second task will entail watching and recalling scenes from a movie. This second task will enable us to study encoding and recall in a cognitively richer (but less tightly controlled) stimulus set. In both experiments, we will measure the dynamics and memory behavior immediately, after 1 hour, and after intervals of 1, 7 and 30 days. We will compare (within and across subjects) the spectral patterns recorded during the successful vs. unsuccessful encoding of items and scenes recalled (at the various intervals). This will enable us to study within- and across-group differences of patients who do (or do not) exhibit accelerated forgetting.

*Specific Aim 2: Determine hippocampal oscillatory markers of memory processing during physical, real world spatial navigation as compared to virtual navigation in humans.*

*Hypothesis: There are reliable, predictable intra-hippocampal markers of memory encoding during real world spatial navigation that differ from virtual navigation.*

The neurophysiological temporal dynamics of spatial memory have been extensively studied during spatial navigation in animals, suggesting a central role of theta oscillations. Analogous studies in human neurosurgical patients (using virtual navigation paradigms) have been confounded by numerous factors of the acute, perioperative setting, and are less consistent regarding oscillatory power. We will compare and contrast the neural correlates of virtual and real-world navigation. (The self-contained nature of the Neuropace devices provide a unique opportunity to record ECoG signals during real-world navigation.) We will also compare the neural patterns observed during virtual and real-world spatial encoding and retrieval to the neural patterns recorded during the list learning and movie-based free-recall tasks employed in Aim 1. As in Aim 1, we plan to test spatial memory at a variety of intervals.

*Specific Aim 3: Determine the effect of abnormal interictal epileptiform discharges (IEDs) on spatial, short- and long-term memory and on oscillatory activity.*

*Hypothesis: Hippocampal IEDs inhibit spatial memory, short term memory and promotes accelerated forgetting*.

In our previous work, we used a recognition working memory task to show that hippocampal IEDs interfere with memory retrieval but not encoding. Here we intend to study the effect of IEDs during spatial navigation and free recall. We will take advantage of the intrinsic, chronic recording capabilities of the Neuropace device to study the memory consequences of IEDs observed during the memory experiments, during the intervals between memory tests, and during the memory tests themselves (at various intervals, as in Aims 1 and 2).

*Specific Aim 4: Determine the effect of brain stimulation on memory function and oscillatory activity during scheduled stimulation of encoding and recall and responsive brain stimulation triggered by abnormal epileptiform activity during memory processing.*

*Hypothesis: Brain stimulation tailored to influence epileptiform activity improves memory function.*

Our previous work has shown that brain stimulation using the Neuropace device can substantially reduce IEDs. Here, we will study the effect of brain stimulation specifically tailored to improve memory performance (e.g. timed to specific task-relevant events), as compared with brain stimulation protocols triggered in response to predicted future epileptiform activity. Understanding the temporal dynamics of memory encoding and retrieval, and the interaction between brain stimulation, epileptic process and oscillatory activity in real-life settings will advance “electrotherapeutics” for the treatment of cognitive impairment in epilepsy.