The hippocampus is of central importance to the brain’s memory systems and is also frequently the site of seizure generation.) We will record from the implanted RNS devices to gain insights into the neurophysiological underpinnings of the memory impairments associated with epilepsy. We will also

In addition to

A “rising star” in

The first step to developing epilepsy treatments that restore cognitive function is to understand how and why the cognitive impairments arise in epileptic brains from a neurophysiological perspective. The second step will be to develop targeted treatments that ta

Recently,

There is a critical need to identify treatments such as brain stimulation and understand the underlying **electrophysiological temporal dynamics** **of memory** processing. The research is aimed at (a) providing insights into the underlying neural dynamics of memory impairments in epileptic subjects and (b) exploring potential treatment regimens using **hippocampal brain stimulation**. Our central hypothesis is that hippocampal brain stimulation in temporal lobe epilepsy improves memory by **restoring healthy neural patterns** and **reducing epileptiform activity.** The results of this study will inform future stimulation paradigms for cognitive function including the design of future devices for epilepsy that will simultaneously reduce seizure frequency and restore cognitive function.

The research is based on performing cognitive and memory experiments in patients who have a responsive neurostimulator (RNS, Neuropace Inc.) implanted. The device is capable of chronically recording electrocorticography and therefore is unique to study long term memory over weeks. In rodents memory is frequently study using spatial navigation but it is difficult to replicate those experiments in humans as patient are usually spacially constraints either in the MRI scanner (for functional MRI) or by the EEG equipment. Virtual reality that often is utilized in those experiments may not exactly mirror real navigation. The RNS provides the unique opportunity to record electrocorticography while the patient is mobile and has the potential to confirm findings in rodents in humans. The group of one of the PI has studied the influence on epileptiform activity on memory and shown that epileptic spikes impair memory. Brain stimulation could reduce epileptiform activity and therefore improve memory processing or stimulation by itself may improve memory. It is our plan to study the interaction between epileptiform activity and brain stimulation in well validated but realistic memory paradigms. The project is a collaboration between Psychology and Brain Sciences at Dartmouth College (Jeremy Manning, PhD, Assistant Professor) and Barbara Jobst (Director, Dartmouth-Hitchcock Epilepsy Center) at the Department of Neurology. Jeremy Manning will provide the necessary expertise in cognitive neuroscience and memory models for experimental design, data analysis and interpretation. Barbara Jobst will be responsible for data collection and patient recruitment.

It is our goal to study long-term memory and spatial navigation. Our experimental design consists of performing four memory tasks. One is a well studied and validated free recall task of word lists, a newly designed task of recalling objects, animals and scenes of a real life movie, a virtual spatial navigation task and a real work spatial navigation task similar to the virtual task. Patients will be tested four times over the course of one month to assess for long term memory and accelerated forgetting. Epileptiform activity will be recorded during the task and half of the experiments will be performed with stimulation. Stimulation will be delivered if epileptiform activity occurs.

It is our goal to identify the patterns intracranial oscillatory (dynamic ) patterns of good memory, encoding and retrieval. Our analysis will include advanced signal processing methods such as examining spectral power, phase-amplitude couples, phase relationships and coherence between channels. Multivariate pattern analysis will be utilized to determine patterns of good encoding and recall versus bad encoding and recall. We will quantify the effects of epileptiform activity on the memory behavior and oscillation and the effects of therapeutic brain stimulation.

Our overall hypothesis is that there are particular cortical signatures of good and bad memory encoding and brain stimulation is effective in improving memory and the oscillatory patterns by eliminating epileptiform actvitiy.

Specific Aims:

The overall goal of this research is to identify biomarkers of good memory encoding and examine the interaction with epileptiform activity regarding memory and the effects of brain stimulation.

*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.*

A well validated simple free recall task and a cognitively richer recall task, using a real world movie, will be presented to subjects with temporal lobe epilepsy and hippocampal recordings. We will measure dynamics and memory behavior immediately, and after intervals of 1, 7 and 30 days. We will compare within and across subjects the spectral patterns during successful vs unsuccessful encoding of items and scenes. This will enable us to study neural patterns of long-term learning and recall, including the identification of the neural signature of 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 intrahippocampal markers of memory encoding during real world spatial navigation which differ from virtual navigation.*

The neurophysiological temporal dynamics of memory are extensively studied during spatial navigation in animals suggesting a central role of theta oscillations. Human studies in neurosurgical patients utilizing virtual navigation have been confounded by numerous factors of the acute, perioperative setting and are less consistent regarding oscillatory power. We will compare neural patterns during real-world with virtual navigation, which allows us to compare naturalistic stimuli to more impoverished stimuli analogous to aim 1.

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

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

In our previous work, we used a recognition memory task to show that hippocampal IED interfere with memory retrieval but not encoding. We intend to study the effect of IEDs during spatial navigation and free recall and determine the effect on performance and oscillatory patterns.

*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: High frequency brain stimulation improves memory function and reduces epileptiform activity.*

Hippocampal responsive brain stimulation reduces seizure frequency. We will study the effect of responsive (triggered by IED) and scheduled high frequency stimulation during above memory tasks and compare to no stimulation. We will determine the relationship between epileptiform activity and memory performance during both stimulation paradigms. We postulate that by reducing abnormal epileptic oscillations, memory function is improved and allows for the occurrence of healthier oscillatory patterns associated with good memory.

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.

Project Plan: