**Project Summary**

One in 26 people in the United States will develop epilepsy at some point in their lifetime, and nearly 1/3 of these continue to live with uncontrollable seizures because no available treatments work for them. In addition to seizures, many epileptic individuals suffer from impaired cognitive function such as memory loss. These memory impairments are often *even more debilitating for the patients than the seizures themselves*. Impairment of long-term autobiographical memory is especially disabling, because our autobiographical memories are how we define our sense of *who we are*. Nevertheless, current clinical approaches to treating epilepsy have focused almost exclusively on reducing the frequency and severity of seizures rather than on addressing cognitive impairments, including memory loss. **Our proposed project will provide the first insights into potential treatments for the debilitating cognitive impairments associated with drug-resistant epilepsy.**

Recently developed implantable brain stimulation devices appear to hold particular promise for drug-resistant epilepsy. The *responsive neurostimulator* device (RNS; Neuropace Inc.) records electrocorticography continuously from chronically implanted electrodes in the patient’s brain. The RNS device is fully battery powered, allowing the patients to go about their normal routines (rather than being required to stay in the hospital or operating room for electrocorticography). When the RNS device’s onboard computer determines that a seizure is imminent, the device automatically stimulates the epileptic tissue the electrodes are recording from according to a pre-specified stimulation protocol. The stimulator’s pulse sequences are calibrated to block seizure activity from spreading. Over the past five years, our ongoing work suggests that these RNS devices can significantly reduce seizure activity in patients where epilepsy surgery is not an option.

Because the RNS device records continuously from implanted electrodes as the patients go about their normal routines at home, we believe this affords us an unprecedented opportunity. Specifically, we will be able to gain insights into the neural mechanisms underlying seizure formation and memory impairments associated with epilepsy, and develop brain stimulation-based treatments that seek **not only to reduce seizures but also to begin to restore healthy memory function**. Further, because the RNS devices record even while the patients are outside of the hospital (unlike other methods for recording from implanted electrodes in humans), it means that we will be able to study cognitive function as the patients behave in the real world (rather than being confined to a hospital bed).

Our central hypothesis is that the memory impairments associated with epilepsy arise due to impaired hippocampal function. This hypothesis has gained widespread support over the last half century, drawing on findings in patients with hippocampal lesions as well as a large number of neuroimaging studies. We will use the RNS device to study the dynamics of hippocampal activity during memory formation and retrieval (both in and out of the lab), and to understand how hippocampal function is disrupted by seizures. Informed by our findings, we will also seek to develop hippocampal stimulation protocols that seek to restore memory function (in addition to reducing seizure frequency and severity) in patients’ everyday lives.

Critically, **this project represents a substantial interdisciplinary effort** that spans Dartmouth researchers in **Psychological and Brain Sciences** (Assistant Professor Jeremy Manning, an expert in autobiographical memory and building computational models of neurophysiological processes) and **Neurology** (Barbara Jobst, Director of the Dartmouth-Hitchcock Epilepsy Center). 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, and for helping to develop the novel brain stimulation protocols. Both PIs will collaboratively present the data at scientific meetings, publish the research findings, and will apply for an NIH R01 grant (or similar) to complement and follow up on the proposed research.

Our proposed research project is ambitious: the RNS device has never been used in cognitive experiments, and the real-world memory phenomena we are interested in studying have never been explored in ambulatory participants. Nevertheless, understanding the neural mechanisms underlying memory formation and retrieval in the real world (and how they are affected by seizures) will require studying these processes in the real world, using devices like the RNS. We expect that our findings will be hugely informative to the memory and epilepsy research communities. Further, the RNS device’s ability to directly stimulate key memory systems adds another exciting dimension to our proposed work that has the potential to directly impact patients’ lives.

**Goals and Outcomes**

Our overarching goal is to identify the neurophysiological mechanisms underlying successful memory formation and to understand how these mechanisms are disrupted during seizures. We also seek to identify how brain stimulation may be used to affect these processes. We will study two groups of people: epilepsy patients implanted with RNS devices and healthy “controls” recruited from the Upper Valley community.

**Specific aim 1: what are the hippocampal correlates of lab-controlled memory formation, retrieval, and forgetting at varying timescales?** In a *free recall* memory task, we will ask participants to study lists of words and verbally recall them in any order after a brief delay. We will study the neural correlates of successful memory formation and retrieval using recordings from the RNS device (epilepsy patients) or using functional neuroimaging (healthy controls). We will also ask the participants to come back to the lab after 1 hour, as well as after 1, 7, and 30 days following the initial experimental testing session. We will use a recognition memory test to evaluate participants’ memories for the studied words in these followup sessions. We will ask how forgetting over time is affected by seizures (both neurally and behaviorally), using the healthy controls as a baseline. *We will test the hypothesis that seizures impair memory function by disrupting the ongoing maintenance and reconsolidation of lab-controlled memories.*

**Specific aim 2: what are the neural correlates of real-world memory formation, retrieval, and forgetting?** The RNS device affords an unprecedented opportunity to record from implanted electrodes in patients as they go about their daily lives. We will ask the patients to wear an iPod-like device (hung from a neck strap) configured to automatically take a picture and record its GPS coordinates once every hour while the patient is awake. (The patients will be able to disable this functionality or remove the devices for privacy whenever they want.) We will also timestamp the recordings from the implanted RNS devices to align the neural recordings with the snapshot times. After 7-day *memory collection interval* of wearing the device, we will bring the patients back into the lab and use the recorded images to probe their memories over the preceding week (e.g. we will ask the patients to imagine what was going on when the images were taken and to rate the quality of their recollections). We will also repeat this study in healthy controls (control participants will not contribute brain data during the 7-day memory collection interval, but will be scanned using fMRI as they recall the past week’s events). By comparing epileptics to healthy controls, we will study the effects of seizures on autobiographical memory. *We will test the hypothesis that seizures impair memory function by disrupting the ongoing maintenance and reconsolidation of real-world (autobiographical) memories.*

**Specific aim 3: how do therapeutic stimulation protocols affect memory formation?** We will repeat the free recall experiment from Aim 1 (only in epilepsy patients) with one modification. Specifically, during some of the word presentations, we will “manually” trigger a stimulation event in the RNS device. The stimulation protocols we use will be identical to the existing stimulation protocols used to disrupt seizures in the same patients. (In other words, each patient currently receives a stimulation pattern individually calibrated to treat their seizures, and we will trigger the same stimulation pattern during some of the word presentations.) *We will test the hypothesis that therapeutic stimulation protocols targeting the hippocampus disrupt memory function by shutting down hippocampal encoding machinery.*

**Specific aim 4: how can therapeutic stimulation protocols be adapted to improve memory function?** Calibrating the RNS device to minimize seizure activity is an iterative process that requires repeated office visits. During each visit, careful adjustments are made to the device’s stimulation protocol and seizure detection algorithm; afterwards we interrogate the device’s onboard memory to determine the number of seizures the patient experienced under the new protocol. Here we propose modifying this calibration procedure to optimize memory function in addition to continuing to minimize seizures. Rather than solely detecting seizures that are about to occur, we will use insights gained from Aims 1 and 2 to also detect “missed” memory encoding events. In other words, we will calibrate the device to detect times when the patients’ neural patterns are similar to those recorded during word presentations (Aim 1) or events (Aim 2) that were subsequently forgotten. These events will serve as an additional trigger for a second stimulation protocol intended to improve memory. (The seizure-related detection and stimulation will remain unchanged.) Over the course of several office visits, we will perform a systematic search of the stimulation protocol parameters (analogous to when we attempt to minimize seizures) to attempt to minimize the numbers of these missed memory encoding events. *Specifically, we will test the hypothesis that brain stimulation can reduce the number of failed encoding events, thereby improving patients’ memories.*

**Project Plan**

We expect that this research project will take approximately 3 years. The first two years will be primarily centered around Aims 1 – 3. Specifically, we will be studying the neural correlates of memory formation, retrieval, and forgetting (Aims 1 and 2) and asking how stimulation affects these processes (Aim 3). The experimental data collected during this initial period will also serve as support for our planned R01 application. The third year will be primarily centered around Aim 4, where we calibrate our stimulation protocols to enhance memory performance (in part using the insights gained from Aims 1 – 3). Below we have outlined our proposed research plan.

**Patient recruitment and participation**

All epilepsy patients with implanted RNS devices at Dartmouth-Hitchcock Medical Center will be given the opportunity to volunteer for our study. We will ask the patients to make a commitment to participate for the duration of the study, but will make it clear that they may terminate their involvement at any time. We expect approximately 5 patients per year will participate in the study.

**Control participant recruitment and participation**

We will recruit members of the Dartmouth, DHMC, and broader Upper Valley communities to participate in our study by posting flyers around town and online. All control participants will be compensated for their involvement in the study, and we will make it clear that they may terminate their involvement at any time. We will attempt to recruit approximately 30 control participants over the course of the first two years of our project.

**Recording and stimulating from the implanted RNS device**

The RNS is an FDA-approved implantable device for treating partial seizures. In its typical configuration, the device continuously records from 4 bipolar channels (each attached to a hippocampal electrode). When a seizure pattern is detected (signaling that a seizure is imminent) the device can deliver a pre-programmed stimulation pattern that is calibrated to disrupt the seizure. Although the device contains limited onboard memory (enough to store approximately 6 minutes of data), the data may be downloaded at any time using a wireless “want” and a programming device. For FDA regulatory reasons we will be unable to modify the device itself, so for our ambulatory studies (Aims 2 and 4), our experimental protocol asks the patients to download the device buffer periodically throughout each day. We will design the protocol to minimize the burden on the patients and to accommodate “missed” events (when the patient forgets to download their device’s memory).

After downloading and collating the recorded data, we will preprocess the recordings to focus in on electrophysiological oscillations (e.g. 3-8 Hz “theta” oscillations, which have been found to appear during memory encoding and retrieval). We will also carry out unsupervised “exploratory” analyses to identify previously undiscovered memory-related brain patterns.

**Functional Magnetic Resonance Imaging (fMRI)**

We will measure hippocampal activity in our control participants using fMRI with the Department of Psychological and Brain Sciences’s MRI machine (Moore Hall). We will design our imaging protocol to specifically target the bilateral hippocampi so that we can (grossly) compare the measured brain patterns in the control participants to the electrophysiological RNS recordings from the patients.

After collecting the imaging data, we will use standard image processing algorithms to align the shapes of different people’s hippocampi. This will enable us to compare the data from different patients and control participants during memory encoding and retrieval.

**Within-group and across-group analyses**

To statistically evaluate the hypotheses outlined in Aims 1 – 4, we will carry out both within-group and across-group analyses (where each participant will be categorized into either the “patient” group or the “control” group). We will use within-group analyses to identify brain patterns that are reliably similar across individuals within a group. In other words, this will help us to identify which brain patterns are idiosyncratic to a particular person, and which are likely to be generally representative of the broader population (of epilepsy patients or controls). We will use across-group analyses to identify key differences *between* the epileptic and control participants. These will provide important insights into the neurophysiological underpinnings of the memory impairments associated with epilepsy.

**Aim 1: free recall memory experiment with followup recognition memory tests**

Participants will be exposed to 20 lists of 15 pseudo-randomly chosen words. (The words will be selected from a carefully curated word pool that has been used in our prior memory studies.) We will present the words one at a time on a computer screen, with a brief pause between each word presentation. After the last word on a list is shown, the participant will (verbally) freely recall the words they just studied (i.e. the recalls may be any order participants wish to make them). We will use the RNS recording wand (patients) or fMRI (controls) to record ongoing hippocampal activity as the participants study and recall the words. Data from this initial testing session will be used to identify, compare, and contrast the neural correlates of encoding and retrieval in patients and controls.

In brief followup testing sessions (1 hour, 1 day, and 7 days after the end of the initial testing session), we will invite the participants back to the laboratory. In these followup testing sessions we will present participants with 600 words (including the 300 words from the initial experiment and an additional 300 words chosen uniquely for each followup session). During each word presentation the participant will rate their memory of the word on a sliding scale: 1 (certain it appeared in the original testing session); 2 (more certain than not it appeared in the original testing session); 3 (more certain than not the word is novel); or 4 (certain the word is novel). We will use data from these followup *recognition memory* sessions to study the neural correlates of retrieval, and also to gain insights into the neural correlates of forgetting. Further, because participants will have slept in the intervening interval between the initial testing session and the 1 and 7 day followup sessions (but not for the 1 hour followup), we will be able to study potential effects of sleep (reconsolidation) on memory. We will also study how seizures affect memory performance.

**Aim 2: memory for real-world events**

In this experiment, participants will wear an iPod-like device around their necks for 7 days as they go about their daily lives. The device will take a photograph and record its GPS coordinates every hour (unless the device is turned off by the participant). Shortly before taking a photograph, the device will sound a brief warning alarm chirp. In addition to warning the patient that a photograph is about to be taken, the chirp will remind the patient to use the RNS magnet. This prompts the RNS device to store a short electrocorticographic trace that will be downloaded when the patient next has access to the downloading computer.

After 7 days of photographs are collected, participants will perform a cued recall memory task back in the lab. Specifically, the participants will be shown each image in turn (in a random order) and will be asked to imagine, as vividly as possible, what they were doing around the time the photograph was taken. They will rate the subjective quality of their reconstructions (1 = vivid memory of the event; 4 = no memory of the event). We will record ongoing hippocampal activity from the RNS (patients) or using fMRI (controls) during the cued recall task. We will ask how brain patterns reflect the similarities and differences between events, how brain patterns differ between well-remembered and (subjectively) forgotten events, and how these patterns differ across the patients and control participants.

**Aim 3: free recall memory task with seizure-related therapeutic stimulation**

In this experiment we will ask the patients to participate in another free recall task (as during the first session of the experimental protocol for Aim 1). During some of the word presentations, we will cause the RNS device to implement its seizure treatment stimulation protocol. We will compare the patients’ abilities to recall stimulated vs. unstimulated words, as well as surrounding words on the lists.

**Aim 4: memory-improving stimulation protocol**

Existing RNS stimulation adjustment protocols are designed to minimize the number of seizures patients experience. After implanting the RNS device and programming it with a default stimulation protocol, the patients undergo an adjustment period whereby the stimulation parameters must be iteratively recalibrated over a period of dozens of hospital visits. The effects of these adjustments, in terms of the number of seizures the patient experiences under the new protocol, inform future adjustments. The device is normally set to detect and treat electrocorticographic patterns that represent seizure onset patterns. When seizures are eliminated (or reach what is felt to be a minimum occurrence rate), the adjustment period ends.

We are proposing an adjustment to this procedure, whereby two types of events are measured: seizures and “missed” memory encoding events (i.e. times when the patient’s ongoing hippocampal patterns are sufficiently similar to patterns measured in Aims 1 and 2 during failed encoding). While leaving the seizure-related stimulation protocol intact, we will iteratively adjust a second stimulation protocol (triggered on the neural signature of failed encoding) in an attempt to minimize the number of failed encoding events.

**Concluding remarks**

The memory impairments associated with epilepsy are debilitating for patients, as well as for their friends and families. Our proposed research leverages the unique opportunity to use an already-implanted device to attempt to vastly improve patients’ lives by improving their memory performance. In addition to helping patients, friends, and family, the insights gained from this study will also provide invaluable insights into how memory works in healthy individuals, and how memory can be affected by seizures.