Diamond Endowment Project

Interdisciplinary Neuroscience Grant Competitive Letter of Intent

Key/Contact Principle Investigator (PI):

Manning, Jeremy, R	Assistant Professor	Ph.D.
Name (Last, first, middle initial)	Title/Position	Degree(s)
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Institution/Department	Phone number	Email address

Title of Proposed Project:

Restoring memory dysfunction in drug-resistant epilepsy using implanted brain stimulators

Key Personnel:

Project Role:

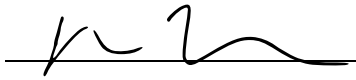
- PD/PI: Program Director/Principal Investigator. Those who share the authority and responsibility for leading and directing the project.
- Co-I: Co-Investigator. Supports the PD/PI with the scientific development or execution of the project.
- Other: Please explain.

Role	Full Name	Institution/Department
PI	Jeremy R Manning	Psychological and Brain Sciences
PI	Barbara Jobst	Neurology

Previous Submission History:

Has this project been submitted to any other funding mechanism within the past 2 years?

◯Yes ◉No. If yes, note specific mechanism(s):



November 10, 2015

Contact PI Signature Date

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.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Manning, Jeremy R.

eRA COMMONS USER NAME (agency login): MANNINGJ

POSITION TITLE: Assistant Professor of Psychology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Brandeis University, Waltham, MA	BS	05/2006	Neuroscience, Computer Science
University of Pennsylvania, Philadelphia, PA	PHD	05/2011	Neuroscience
Princeton University, Princeton, NJ	Postdoctoral Fellow	07/2015	Neuroscience, Computer Science

A. Personal Statement

I am broadly interested in how the ways our brains acquire, process, store, and retrieve information are affected by the current context or situation. My primary research program is centered on how we encode and retrieve episodic (autobiographical) memories. For example, I ask questions like “how do our past experiences affect how we perceive what is happening now,” “how does what is happening now affect how we remember this moment later,” or “how does what is happening now affect what memories spontaneously come to mind?” I use computational models, behavioral experiments, and neuroimaging techniques (fMRI, EEG, ECoG) to gain insights into these questions and processes. In addition to elucidating the neural mechanisms underlying memory and context and developing formal theories of memory, my work has direct implications for treating memory disorders (e.g. Alzheimer’s, PTSD) and for developing training programs that leverage real-time neurofeedback to help (healthy and impaired) individuals to learn as quickly and efficiently as possible. To this end, the current application supports my research program by furthering our understanding of memory dysfunction in epilepsy patients, and how healthy memory function might be restored in these individuals.

Four most relevant publications:

1. Manning J, Polyn S, Baltuch G, Litt B, Kahana M. Oscillatory patterns in temporal lobe reveal context reinstatement during memory search. Proceedings of the National Academy of Sciences. 2011; 108(31):12893-12897.

2. Manning J, Sperling M, Sharan A, Rosenberg E, Kahana M. Spontaneously Reactivated Patterns in Frontal and Temporal Lobe Predict Semantic Clustering during Memory Search. Journal of Neuroscience. 2012; 32(26):8871-8878.
3. Manning J, Lew T, Li N, Sekuler R, Kahana M. MAGELLAN: A cognitive map–based model of human wayfinding. Journal of Experimental Psychology: General. 2014; 143(3):1314-1330.
4. Manning J, Ranganath R, Norman K, Blei D. Topographic Factor Analysis: A Bayesian Model for Inferring Brain Networks from Neural Data. PLoS ONE. 2014; 9(5):e94914.

B. Positions and Honors

Positions and Employment

2011 - 2015	Postdoctoral Research Associate, Princeton University, Princeton Neuroscience Institute and Department of Computer Science, Princeton, NJ
2015 -	Assistant Professor of Psychology, Dartmouth College, Hanover, NH

Honors

2006	Systems and Integrative Biology Training Grant, NIH
2008	Computational Neuroscience Training Grant, NIH
2010	Ruth L. Kirshstein National Research Service Award for an Individual Predoctoral Fellowship, NIMH

C. Contribution to Science

1. One major scientific contribution of my work has been to further our understanding of the relation between single-neuron action potentials and population (local field) activity in humans. The dominant view in the human electrocorticography literature has been that single-neuron action potentials are best characterized by high frequency (gamma band) spectral changes in the local field potential. I undertook a systematic study of rare simultaneous single-neuron and population recordings taken from human neurosurgical patients. I found that, somewhat surprisingly, broadband (non-oscillatory) changes in the local field potential were a much stronger correlate of single-neuron firing than were oscillatory changes (including in the gamma band). My Journal of Neuroscience paper reporting these results has since been cited over 200 times in the 5 years since its publication, and many of these citations are from papers that have carried out direct follow-up studies of this work.

    a. Manning J, Jacobs J, Fried I, Kahana M. Broadband Shifts in Local Field Potential Power Spectra Are Correlated with Single-Neuron Spiking in Humans. Journal of Neuroscience. 2009 October 28; 29(43):13613-13620.

2. Another major contribution of my work has been to expand our understanding of how episodic (autobiographical) memories are encoded and retrieved by our brain's memory systems. A fundamental historical intuition held by philosophers and psychologists such as Aristotle, Hume, James, and others has been that our experiences are "tagged" using the ever-changing stream of contextual cues that defines our subjective experience. For example, hearing a particular song on your way to work might remind you of

another time you heard the same song years ago, which might in turn dredge up other related information (where you were, who you were with, etc.). Despite an extensive behavioral and computational literature hypothesizing a central role for contextual information in how we encode and retrieve autobiographical memories, prior to my work there had been no direct neural evidence for such representations. I carried out a series of studies using data from human neurosurgical patients who volunteered to study and recall lists of randomly chosen words. I used computational models to isolate neural patterns that behaved like contextual representations, and studied these representations as the patients encoded and retrieved memories. This framework allowed me to directly observe the neural basis of these contextual representations, and the role they play in memory encoding and retrieval.

a. Manning J, Polyn S, Baltuch G, Litt B, Kahana M. Oscillatory patterns in temporal lobe reveal context reinstatement during memory search. Proceedings of the National Academy of Sciences. 2011; 108(31):12893-12897.
b. Manning J, Sperling M, Sharan A, Rosenberg E, Kahana M. Spontaneously Reactivated Patterns in Frontal and Temporal Lobe Predict Semantic Clustering during Memory Search. Journal of Neuroscience. 2012; 32(26):8871-8878.
c. Manning J, Kahana M. Interpreting semantic clustering effects in free recall. Memory. 2012; 20(5):511-517.

3. A third contribution of my work relates to how patterns of interactions (connectivity) across brain regions reflects ongoing cognitive processes. Standard approaches to examining how patterns of brain connectivity reflect cognition entail computing functional connections between every pair of observed measurements. For example, standard functional connectivity approaches to fMRI data entail computing the correlation between every pair of voxel time series. The number of computations required to relate these full brain functional connectivity patterns to cognitive states can become prohibitive. Further, computing full brain voxel-by-voxel connectivity matrices effectively treats each voxel as independent, even though it is well known that brain data exhibit strong spatial correlations. I have developed a probabilistic modeling approach for looking at brain connectivity patterns in a much more mathematically compact way. The general approach involves re-representing patterns of brain activity using a relatively small number of network "hubs" distributed throughout the brain. This turns connectivity analysis into an optimization problem: given a brain dataset, we must compute the most probable number of network hubs, where the hubs go in the brain, how big the hubs are, and how the hubs are connected to each other at each moment in time during an experiment. Because most neuroimaging datasets may be adequately described by on the order of a few hundred network hubs, this reduces the computational complexity of analyses of connectivity patterns by several orders of magnitude.

   a. Manning JR, Ranganath R, Norman KA, Blei DM. Topographic factor analysis: a Bayesian model for inferring brain networks from neural data. PLoS One. 2014;9(5):e94914.
   b. Manning J, Ranganath R, Keung W, Turk-Browne N, Cohen J, Norman K, Blei D. Hierarchical topographic factor analysis. 2014 International Workshop on Pattern Recognition in Neuroimaging. 2014 International Workshop on Pattern Recognition in Neuroimaging (PRNI); IEEE; c2014.

4. A fourth contribution of my work relates to our understanding of how our memory systems encode, organize, and retrieve spatial information. For example, how do we build up useful representations of novel environments? Or how do we use our existing knowledge to explore efficiently? Electrophysiological studies in animals and humans over the past half-century have led to the discovery of networks of navigationally relevant neuronal populations, such as place cells and grid cells (which respond

preferentially when an animal is located in a particular place), head direction cells (which respond preferentially when an animal is headed in a particular direction), and others. These findings have inspired a number of low-level biologically detailed models of how the known neural machinery might support higher level cognitive representations. However, these low-level models are not intended to explain high-level navigation behaviors such as exploration strategies. Meanwhile, an extensive behavioral literature on navigating humans and non-human animals has inspired high-level descriptive models based on egocentric and allocentric spatial encoding strategies. These high-level models attempt to explain complex behaviors like exploration strategies, but do not attempt to connect these strategies to the underlying neural machinery. I undertook a major modeling effort to bridge these two spatial modeling literatures. The result was the MAGELLAN model of spatial navigation, which operates at the same high level as strategy-based models, but makes quantitative predictions about the way in which people build up mental representations of unfamiliar environments and use those representations to navigate efficiently.

   a. Manning J, Lew T, Li N, Sekuler R, Kahana M. MAGELLAN: A cognitive map–based model of human wayfinding. Journal of Experimental Psychology: General. 2014; 143(3):1314-1330.

5. A fifth contribution of my work is in the domain of color vision. I have developed a Bayesian framework for exploring how our visual systems form predictions about the visual world from observed photoreceptor responses. For example, at each location on our retinas, we may have a single rod or cone photoreceptor. Each photoreceptor class is maximally sensitive to a particular wavelength of light. (This is similar to the notion that a digital camera may have at most a single red, green, or blue sensor at each location on its sensory array.) Nonetheless, our subjective experience is that each point in space has an identifiable color that matches the objects in the environment rather than the placements of receptors on our retinas. This means that our visual systems must fill in the missing information. To explore the deeper theoretical properties of these processes, I build models of the visual world, retinal responses, and inference algorithms for reasoning and making predictions about the world given receptor responses. I then ask questions like: given some statistical facts about the visual world, how should we arrange our receptors to achieve the best expected prediction accuracies? Or, if we knew nothing about the statistical properties of natural images, or the identities (i.e., peak wavelength sensitivities) of the receptors on our retinae, under what physical conditions could our visual systems learn to see in color? In other words, how much knowledge must be "pre-programmed" into our visual systems, and how much can be learned through experience? This works applies the same sorts of contextual effects that dominate how we organize our memories to the much lower-level domain of color vision.

   a. Manning JR, Brainard DH. Optimal design of photoreceptor mosaics: why we do not see color at night. Vis Neurosci. 2009 Jan-Feb;26(1):5-19.
   b. Benson NC, Manning JR, Brainard DH. Unsupervised learning of cone spectral classes from natural images. PLoS Comput Biol. 2014 Jun;10(6):e1003652.

D. Research Support

Completed Research Support

2010/02/01-2011/05/31

5F31MH088118-02, National Institute of Mental Health

Jeremy Manning (PI)

The neural representation of context and its role in free recall

Role: PI

BIOGRAPHICAL SKETCH

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NAME: Jobst, Barbara C

eRA COMMONS USER NAME (credential, e.g., agency login): BJOBST

POSITION TITLE: Professor of Neurology, Director Dartmouth-Hitchcock Epilepsy Center, Section Chief Department of Neurology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Friedrich-Alexander University, Erlangen, Germany	MD	07/1993	Medicine
Friedrich- Alexander University, Erlangen, Germany	Dr. med	06/1995	PhD equivalent- Clinical Neurosciences
Krankenhaus der Barmherzigen Brüder, Regensburg, Germany	Resident	06/1996	Neurology
Dartmouth Medical School, Hanover, NH	Resident	06/1999	Neurology
Dartmouth Medical School, Hanover, NH	Postdoctoral	07/2001	Epilepsy

A. Personal Statement

I am a physician-scientist and currently directing the Dartmouth-Hitchcock Epilepsy Center, a well-recognized center for epilepsy surgery and for work on cognition and epilepsy. I have the leadership skills, specific knowledge and necessary experience to conduct the proposed research. We have protocols in place to study intracranial electrophysiology during cognitive tasks during neurosurgical admissions for epilepsy surgery. Two of the proposed cognitive tasks proposed are already implemented in this setting. I direct the Epilepsy and Cognition Lab at Dartmouth which studies neural patterns of cognitive impairment in epilepsy with extramural funding. It is my long term goal to improve devastating cognitive impairment in epilepsy, a frequent complaint of my patients in clinic. I am a board certified electroencephalographer and have extensive experience with ECoG. Our lab has developed an automated detection algorithm for interictal epileptiform activity and advanced signal processing methods.

I have served as principle investigator (PI) in multiple clinical trials and have experience in multidisciplinary, translational research. Innovative brain stimulation for epilepsy has been my focus for several years. I was the site-PI for the pivotal and long-term trial of responsive brain stimulation in epilepsy at Dartmouth that helped with the approval of the device. I have published extensively in the field of electrical stimulation for epilepsy. This trial was industry sponsored and the device was approved by the FDA in 2013. Through those studies I have been integrally involved with the technical details of the device. My experience with intraoperative monitoring has helped to gain insight into the engineering part of intracranial devices and ECoG recording. Dartmouth- Hitchcock Epilepsy Center is part of the Department of Defense Restoring Active Memory (RAM) project. The project is aimed to study brain stimulation to improve memory function in acute, neurosurgical patients and some of the work performed in this project, led to the insight that memory function may be more reliably studied in chronically implanted patients as compared to patients in the acute, neurosurgical setting with many confounding factors and that epileptiform activity may play a critical role.

1. Jobst BC, Cascino GD (2015). Resective epilepsy surgery for drug-resistant focal epilepsy: a review. JAMA Jan 20;313(3):285-293. http://www.ncbi.nlm.nih.gov/pubmed/25602999
2. Heck CN, King-Stephens D, Massey AD, Nair DR, Jobst BC, Barkley GL, Salanova V, Cole AJ, Smith MC, Gwinn RP, Skidmore C, Van Ness PC, Bergey GK, Park YD, Miller I, Geller E, Rutecki PA, Zimmerman R, Spencer DC, Goldman A, Edwards JC, Leiphart JW, Wharen RE, Fessler J, Fountain NB, Worrell GA, Gross RE, Eisenschenk S, Duckrow RB, Hirsch LJ, Bazil C, O'Donovan CA, Sun FT, Courtney TA, Seale CG, Morrell MJ (2014). Two year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: Final results of the RNS system Pivotal Trial. Epilepsia Mar;55(3):432-441. PMCID: PMC4233950.
3. Bergey GK, Morrell MJ, Mizrahi EM, Goldman A, King-Stephens D, Nair D, Srinivasan, S, Jobst B, Gross RE, Shields DC, Barkley G, Salanova V, Olejniczak P, Cole A, Cash SS, Noe K, Wharen R, Worrell G, Murro AM, Edwards J, Duchowny M, Spencer D, Smith M, Geller E, Gwinn R, Skidmore C, Eisenschenk S, Berg M, Heck C, Van Ness P, Fountain N, Rutecki P, Massey A, O'Donovan C, Labar D, Duckrow RB, Hirsch, LJ, Courtney T, Sun FT, Seale CG (2015). Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. Neurology Feb 24; 84(8):810-817. PMCID: PMC4339127.
4. Van Straten AF, Jobst BC (2014). Future of epilepsy treatment: integration of devices. *Future Neurol.* 9(6), 587–599. http://www.futuremedicine.com/doi/pdf/10.2217/fnl.14.54

B. Positions and Honors

Positions and Employment

1999-2001	Postdoctoral Research Fellow, Dartmouth Hitchcock Medical Center, Lebanon, NH
1998-2001	Instructor in Medicine (Neurology), Dartmouth Medical School
2001-	Attending Physician, Dartmouth-Hitchcock Medical Center, Lebanon, NH
2001-2004	Consulting Neurologist, Littleton Regional Hospital, Littleton, NH
2001-2004	Consulting Neurologist, Cottage Hospital, Woodville, NH
2001-2007	Assistant Professor of Medicine (Neurology)
2001-2010	Director, Intraoperative Monitoring Program, Dartmouth-Hitchcock Medical Center
2005-2008	Director, Women's Epilepsy Clinic, Dartmouth-Hitchcock Medical Center
2006-2008	Director, Neurophysiology and EEG, Dartmouth-Hitchcock Medical Center, NH
2007-2013	Associate Professor of Neurology
2009-	Director, Dartmouth-Hitchcock Epilepsy Center (NAEC level 4)
2013-	Professor of Neurology
2013-	Section Chief Adult Neurology, Department of Neurology

Other Experience and Professional Memberships

1996-	Member, American Academy of Neurology
1999-	Member, American Epilepsy Society
2002-	Diplomat of the American Board of Psychiatry and Neurology
2002-2003	Member, Scientific Committee, American Epilepsy Society
2006-	Fellow, American Clinical Neurophysiology Society Fellow
2004-2008	Member, Annual Course Committee, American Epilepsy Society
2004-2006	Member, Scientific Committee, American Epilepsy Society
2005	Member, Education Subcommittee Epilepsy, American Academy of Neurology
2005	Diplomat of the American Board of Clinical Neurophysiology with special certification in epilepsy monitoring
2006-	Member, Steering Committee Pivotal multicenter trial of responsive neurostimulation (RNS™)
2008-2011	Member, CME Committee, American Epilepsy Society
2010-	Fellow, American Academy of Neurology
2011-	Editor Epilepsy Currents
2012-	Editor Epilepsia
2013-	Scientific Chair Epilepsy American Academy for Neurology

Honors and Awards

1999	Clinical Research Gowers Fellowship awarded by the Epilepsy Foundation of America
1999	Tiffany Blake Fellowship Award (Hitchcock Foundation)
2001	Fellowship Award American Clinical Neurophysiology Society.

2002 Fellowship Award for the International School of Epilepsy, San Servolo, Italy, sponsored by the International League of Epilepsy and NATO.
2013- Elected physician member Board of Governors and Board of Trustees, Dartmouth-Hitchcock Medical Center
2015- Executive Leadership in Academic Medicine Fellowship (ELAM)

C. Contribution to Science

1. My early scientific career was focused on the clinical description of epilepsy syndromes and the outcomes of epilepsy surgery. We established fundamental clinical manifestations of frontal lobe epilepsy, occipital lobe epilepsy and tonic-clonic seizures, based on meticulous videoEEG analysis. Our group also reported good clinical outcomes in difficult to diagnose epilepsy syndromes such as frontal lobe epilepsy.

    a. Jobst BC, Siegel AM, Thadani VM, Roberts DW, Rhodes HC, Williamson PD (2000). Intractable seizures of frontal lobe origin: Clinical characteristics, localizing signs and results of surgery. *Epilepsia* 41:1139-1152. http://www.ncbi.nlm.nih.gov/pubmed/10999553
    b. Jobst BC, Williamson PD, Thadani VM, Gilbert KL, Holmes GL, Morse RP, Darcey TM, Duhaime AC, Bujarski KA, Roberts DW (2010). Intractable Occipital Lobe Epilepsy: Clinical Characteristics and Surgical Treatment. *Epilepsia* 51 (11): 2334-2337. http://www.ncbi.nlm.nih.gov/pubmed/20662891
    c. Jobst BC, Williamson PD, Neuschwander TB, Darcey TM, Thadani VM, Robert DW (2001). Secondarily generalized seizures in mesial temporal lobe epilepsy: clinical characteristics, lateralizing signs and association with sleep-wake cycle. *Epilepsi*a 42: 1279-1287. http://www.ncbi.nlm.nih.gov/pubmed/11737163
    d. Kriegel M, Roberts DW, Jobst BC (2012). Orbitofrontal and Insular Epilepsy. *Journal of Neurophysiology* 29 (5): 385-91. http://www.ncbi.nlm.nih.gov/pubmed/23027095

2. As epilepsy surgery can have devasting psychiatric and cognitive consequences, my interest in epilepsy surgery shifted to explore other venues to treat drug-resistant epilepsy, which made brain stimulation as a possible treatment quite attractive. For this reason, I initiated study of novel stimulation devices at our center, such as the Responsive Neurostimulator System RNS®, Neuropace Inc. I participated in the pivotal and long-term trial for efficacy, and I am currently the PI on the post-approval study. As the device has unprecented opportunities to study ambulatory intracranial electrophysiology, together with other centers we validated the use of the device for ECoG recordings.

    a. King-Stephens D, Massey AD, Heck CN, Nair DR, Barkley GL, Cole AJ, Gwinn RP, Jobst BC, Salanova V, Skidmore CT, Smith MC, Van Ness PC, Bergey GK, Duchowny M, Geller EB, Park YD, Rutecki PA, Spencer DC, Zimmerman R, Edwards JC, Mizrahi E, Berg MJ, James Fessler III A, Fountain NB, Leiphart JW, Wharen RE, Hirsch LJ, Richard Marsh W, Gross RE, Duckrow RB, Eisenschenk S, O'Donovan CA, Bloch DA, Crabtree T, Loring D, Plenys Loftman A, Sun FT, Morrell MJ (2011). Responsive cortical stimulation for the treatment of medical intractable partial epilepsy. *Neurology* 77(13):1295-1304. http://www.ncbi.nlm.nih.gov/pubmed/21917777
    b. Quigg M, Sun F, Fountain NB, Jobst BC, Wong VS, Mirro E, Brown S, Spencer DC (2015). Interrater reliability in interpretation of electrocorticographic seizure detections of the responsive neurostimulator. *Epilepsia* Apr 20. http://www.ncbi.nlm.nih.gov/pubmed/25895054

3. With continued clinical practice, it became apparent that the cognitive consequences of epilepsy can be more debilitating than the seizures themselves. Therefore we at Dartmouth developed HOBSCOTCH (Home-Based Selfmanagement and Cognitive Training CHanges lives), a cognitive intervention based on behavioral problem-solving therapy for memory problems in epilepsy. We conducted a randomized controlled trial that proved efficacy on quality of life and objective memory measures. Within this work I am also the PI of the Managing Epilepsy Well Network, a thematic research network of the Center for Disease Control, focused on the self-management strategies in epilepsy.

    a. Caller TA, Secore K, Ferguson RJ, Roth RM, Alexandre FP, Harrington JJ, Henegan PL, Jobst BC (2015). Design and Feasibility of a Memory Intervention with Focus on Self-Management for

Cognitive Impairment in Epilepsy. *Epilepsy Behav* Mar; 44:192-194. http://www.ncbi.nlm.nih.gov/pubmed/25731132

b. Chen JJ, Caller TA, Mecchella JN, Tahkur DS, Homa K, Finn CT, Kobylarz EJ, Bujarski KA, Thadani VM, Jobst BC (2014). Reducing Severity of Comorbid Psychiatric Symptoms in an Epilepsy Clinic using Co-location Model: Results of a Pilot Intervention. *Epilepsy Behav.* 39:92-96. http://www.ncbi.nlm.nih.gov/pubmed/25238553

c. Kobau R, Cui W, Kadima N, Zack MM, Satatovic M, Kaiboriboon K, Jobst B (2014). Tracking psychosocial health in adults with epilepsy- Estimates from the 2010 National Health Interview Survey. *Epilepsy Behav* 41:66-73. http://www.ncbi.nlm.nih.gov/pubmed/25305435

4. Another approach to alleviate cognitive problems in epilepsy is to understand the underlying pathophysiology and invent interventions that correct the underlying problem. With this goal in mind, we started to investigate the underlying oscillations related to memory impairment in epilepsy. We showed that interictal spikes interfere with good memory performance if they occur contralateral to the seizure onset zone or bilaterally during memory retrieval, a direct translation of animal work that was performed at Dartmouth by Dr. Gregory Holmes. To further translate animal research, we established single neuron recordings in humans to identify place cells in humans and to study single neuron activity in relation to field potentials. Within this work we validated and tested several cognitive tasks, where some of them focused on spatial navigation. We found that place cell recordings in humans are difficult, due to the paucity of cells recorded, and that virtual spatial navigation does not as consistently show theta activity during navigation as observed in animals. To study the influence of brain stimulation on memory, especially in a less problematic population than the perioperative one, is the next logical step in finding a treatment for cognitive impairment in epilepsy. It is part of my personal challenge to determine whether memory problems are easier treated with brain stimulation versus a cognitive behavioral intervention.

   a. Kleen JK, Scott RC, Holmes GL, Roberts DW, Rundle MM, Testorf M, Lenck-Santini PP, Jobst BC (2013). Hippocampal interictal epileptiform activity disrupts cognition in humans. Neurology 81(1):18-24. PMCID: PMC3770206.

   b. Kleen JK[1], Testorf ME[2], Robbins AA[2], Roberts DA[2], Scott RC[3,4], Holmes GL[3], Jobst BJ[2], Lenck-Santini PP[3] Reset of human hippocampal oscillations during a working memory task: relevance to performance (submitted to Neuroimage).

   c. Liu JV, Kobylarz EJ, Darcey TM, Lu Z, Wu YC, Meng M, Jobst BC (2014). Improved mapping of interictal epileptiform discharges with EEG-fMRI and voxel-wise functional connectivity analysis. *Epilepsia*. 55(9):1380-1388. http://www.ncbi.nlm.nih.gov/pubmed/25060924

   d. Robbins A, Titiz A, Scott R, Holmes G, Lenck-Santini P, Jobst BC (2013). Single unit recordings during virtual navigation tasks in patients with temporal lobe epilepsy. Abstract No. 3.054, American Epilepsy Society Annual Meeting, www.aesnet.org

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1052Uc3dLP4kZ/bibliography/48022980/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

U48DP005018 Jobst (PI) 09/29/2014 – 09/28/2019
CDC
Title: *Home based self-management and cognitive training changes lives (HOBSCOTCH)*
Goal: The goal of this program is to reduce disparities in health for vulnerable populations in NH and VT by studying a cognitive behavioral intervention for memory impairment in epilepsy with a pragmatic trial to distribute HOBSCOTCH to four states, develop a purely virtual intervention system, and study cost effectiveness. The project also involves being the PI of the Managing Epilepsy Well Network, a thematic research network of the CDC focused on self management and providing research leadership to seven other universities.
Role: PI

DN 1009075 Jobst (PI) 05/20/2008 – present
Neuropace Inc.
Title: *Responsive Neurostimulator (RNS) System Long-term Treatment Clinical Investigation*
Goal: The goal of this project is to assess ongoing safety and evaluate the long-term efficacy of the RNS System as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than two epileptogenic foci, that are refractory to two or more antiepileptic medications, and currently have frequent or disabling seizures.
Role: PI

N66001-14-2-4-31 Jobst (PI) 07/16/2014 – 07/15/2018
DARPA
Title: *Memory Enhancement with Modeling, Electrophysiology, and Stimulation*
Goal: It is the goal of this project to identify a stimulation paradigm that enhances memory independent of the epileptic process. The project involves seven centers that perform memory experiments in the perioperative setting. PI of the project is Michael Kahana from the University of Pennsylvania.
Role: Site PI

5R01NS074450-02 Jobst (Co-PI) 08/01/2011 – 04/30/2016
NIH
Title: *Mechanisms of cognitive impairment in temporal lobe epilepsy*
Goal: The goal of this project is to study single unit activity in human during memory processing and to explore the relationship of interictal epileptiform discharges in the acute perioperative epilepsy surgery setting.
Role: Co-PI

Jobst (PI) 12/12/2013 – present
American Epilepsy Society
Title: Imaging neuroinflammation with Ferumoxytol-MRI
Goal: The project is an innovative project to image inflammatory changes associated with seizures with MRI after ferumoxytol, a marker for microglial activation, is injected IV after a seizure. This is followed by an MRI scan 72 hours later to search for iron deposition in the brain.
Role: PI

COMPLETED
DN 1008934 Jobst (PI) 12/12/2005 – 11/30/2012
NeuroPace, Inc.
Title: *Responsive Neurostimulator (RNS) System Pivotal Clinical Investigation*
Goal: To assess the safety and to demonstrate that the Responsive Neurostimulator (RNS) system is effective as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures that are refractory to two or more antiepileptic medications. The project lead to the indication of the device to treat seizures.
Role: Site-PI

3U48DP001935-04S3 Jobst (PI) 09/30/2012 – 09/29/2014
CDC
Title: *Home-based self-management and cognitive training changes lives for patients with epilepsy*
Goal: We developed a home based cognitive intervention for memory training and performed a randomized controlled trial in 66 patients. We could demonstrate improvement in quality of life and objective memory measures.
Role: PI