Title: Memory, epilepsy and brain stimulation: Oscillatory patterns during real-world navigation and free recall in chronically implanted humans

Project summary:

There is a fundamental gap in treating and understanding cognitive dysfunction in epileptic disorders. Brain stimulation therapy, already established to reduce seizures, has potential to close the gap. Rational stimulation therapy requires a thorough understanding of the underlying neurophysiological temporal dynamics of memory and translation of animal work to humans. The long-term goal is to develop treatments that not only address seizures but also memory dysfunction in epilepsy. This project will study the underlying temporal dynamics of memory processing during real world-spatial navigation and free recall in patients with temporal lobe epilepsy and a chronically, implanted electrocorticographic recording device (RNS®, Neuropace Inc.). The central hypothesis is that brain stimulation targeted at epileptiform activity improves memory function by restoring healthy oscillations. Guided by preliminary data above hypothesis will be tested with the four following specific aims: 1. Determine oscillatory markers of real world spatial navigation and memory as compared to virtual navigation. 2. Determine the oscillatory markers of short and long term free recall including the oscillations of especially disabling long-term accelerated forgetting. 3. Determine the influence of abnormal interictal epileptiform discharges on spatial memory and free recall. 4. Study whether scheduled hippocampal stimulation or responsive stimulation has an effect on memory acutely and long term. Within the first aim oscillations will be recorded during real world spatial memory tasks while the subject is walking. Within aim 2 accelerated forgetting, a common complaint of epileptic patients, will be investigated via a stimulus-rich, real world movie, modeling a free recall task and a well validated free word recall task. Oscillatory activity and performance will be recorded at four different time points over at time period of 30 days and oscillations for good long-term memory identified. Epileptiform discharges and their disturbance on memory and spectral content during memory processing will be investigated using previously developed automated detection algorithms. The influence of epileptic discharges during above mentioned memory tasks will be measured. Stimulation, similar to stimulation for seizures, will be delivered either triggered by epileptiform activity or in a scheduled manner during encoding or recall. The effect of both paradigms for improving memory and temporal dynamics will be compared. The approach is innovative, because it enables the study of intracranial oscillations in the real world and allows monitoring of chronic oscillatory activity long-term. In addition, it provides a clinically feasible brain stimulation paradigm for memory enhancement. The proposed research is significant because the results will inform the future design of brain stimulation devices in epilepsy and possibly for other disease states. Determining electrographic markers for memory encoding and recall in “freely ranging humans” provides unprecedented real-world, longitudinal evidence to facilitate further study of human memory.

Project narrative:

The proposed research is relevant to public health and NIH mission, because understanding the effects of brain stimulation in epilepsy on memory function, can ameliorate some of the devastating cognitive consequences of epilepsy, which is frequently more debilitating than seizures themselves. Understanding memory function and brain oscillations and brain stimulation in an ambulatory real life human setting will contribute to fundamental knowledge about brain activity than promotes good memory encoding in epileptic humans and will inform further design of “electrotherapeutics” to not only address seizure but also cognitive impairment.