Memory impairment in epilepsy can be more debilitating than the seizures themselves. Accelerated forgetting – the impairment of long-term autobiographical memory – is especially disabling. There is a critical need to identify treatments and understand the underlying electrophysiological dynamics of memory processing in epilepsy. Intracranial brain stimulation addresses both.

With the long term goal not to only treat seizures but also associated memory problems, we will study study the temporal dynamics of real-world spatial memory and long term free recall in subjects with a FDA approved, chronic ambulatory, human electrocorticographic recording device (RNS®, Neuropace Inc., Mountainview CA), approved for the treatment of partial seizures. We will determine the effect of interictal epileptiform discharges (IED) and stimulation on memory. Our central hypothesis is that brain stimulation targeted at abnormal epileptiform activity improves memory by restoring healthy oscillations. 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 be targeted not only at improving seizure frequency but also cognition.

*Specific Aim 1: 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 utilize virtual navigation after implantation of intracranial electrodes for epilepsy surgery. Studies are confounded by numerous factors of the acute, perioperative setting and are less consistent regarding oscillatory power. We will assess oscillations during real-world navigation as compared to virtual navigation and expect to find robust oscillatory patterns during navigation that are correlated to correct memory encoding.

*Specific Aim 2: Determine hippocampal oscillatory markers of short and long-term memory 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 realistic real world free recall task utilizing a stimulus rich movie and a well validated free recall task will be used to assess accelerated forgetting in temporal lobe epilepsy. We will measure dynamics and memory behavior immediately, after 1 hour, 1, 7 and 30 days. Oscillatory power during encoding of items recalled long-term will be compared to items not recalled within subjects. Group differences of patients with and without accelerated forgetting will be measured.

*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 IED inhibit spatial memory, short term memory and promotes accelerated forgetting*.

We have previously shown that epileptiform activity in the hippocampus interferes with recall but not encoding in a working memory task in humans. 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 RNS-device to determine the number of IEDs in between memory experiments at 1,7 and 30 days to measure the influence of IEDs on accelerated forgetting.

*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.*

Neuromodulation by brain stimulation can be achieved by scheduled stimulation as applied in therapeutic deep brain stimulation therapy or responsively to oscillatory activity such as IED. We will study the effect of scheduled brain stimulation on memory in comparison to responsive brain stimulation targeting 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.