Title: Inactivation of the hippocampus by electrical stimulation to preview post resection verbal recognition memory deficits

Verbal memory impairment is a frequent complication of hippocampal resection for the treatment of mesial temporal lobe epilepsy (MTLE), yet few clinical tools are available to preview these potential memory deficits at the same level of precision as the surgical techniques used for resection or lesioning. The Wada test, developed when temporal lobectomy was the primary surgical treatment for MTLE, has been used for decades to guide surgical decisions by anesthetizing the anterior 2/3 of each hemisphere to lateralize language or memory function. However, modern surgical techniques such as open selective amygdalohippocampectomy (AH) and laser interstitial thermal therapy (LITT) enable precise, selective lesions while minimizing damage to surrounding tissue. The precision of these surgical techniques underscores a critical need for a corresponding proxy memory assessment paradigm to accurately predict the functional consequences of hippocampal tissue resection. Clinically useful tests should inactivate the approximate spatial volume of the resection target to mimic memory effects caused by surgical resection.

Electrical stimulation (ES) has been a standard of care in functional mapping to localize speech, motor, and sensory functions in the cerebral cortex of MTLE patients. However, ES has not been used clinically to evaluate memory function in the hippocampus. We propose using ES through stereoelectroencephalography (SEEG) depth electrodes, placed in the hippocampus for clinical seizure monitoring, to generate temporary memory deficits at the spatial scale of intended surgical resection that approximate the real-world post-surgical verbal memory difficulties patients often experience. ES of the hippocampus has been shown to affect memory in both animal and human studies, but there has been limited study on how to apply ES to the hippocampus for surgical decisions. Because the Wada test remains the clinical standard and a necessary reference point for our findings, we will employ the same verbal recognition memory measures examined by the Wada test. Our proposal explores **where** to stimulate in the hippocampus (head/body/both), **when** to stimulate during memory testing (encoding/consolidation/recall), and **how** to stimulate (low/high frequency). The outcomes of these experiments will elucidate the clinical utility of ES as a more precise and accurate tool to preview the effects of hippocampal lesioning on verbal recognition memory. Since the hippocampus is susceptible to ES-induced seizures, the applied electric stimulation must be minimized; thus, temporal and spatial precision is a critical component to developing clinical tools utilizing SEEG. All stimulation will be conducted below afterdischarge thresholds under careful clinical monitoring due to the risk of triggering seizure activity.

Aim 1: Identify hippocampal locations to stimulate to disrupt verbal recognition memory function.
The involvement of the hippocampus in memory function is undisputed, but where to stimulate within the hippocampus to disrupt this function is less clear. Logically, broader hippocampal disruption should result in greater memory impairment compared to more selective stimulation of the hippocampal head or body alone. However, this comparison has not been empirically tested in awake patients undergoing memory testing. Our first aim will examine the effects of stimulating SEEG contacts located in the hippocampal head vs. hippocampal body vs. both structures simultaneously on memory function. Our goal is to establish *where* SEEG contacts should be placed and stimulated in the hippocampus to generate maximal memory impairment.

Aim 2: Identify task epoch to stimulate the hippocampus to disrupt verbal recognition memory function.
Impaired recall memory performance is often confounded by poor initial encoding of the to-be-remembered material/information, and the hippocampus' role in each memory subprocess (encoding/consolidation/recall) varies. Thus, it is not known which of these epochs should be disrupted via ES of the hippocampus to mimic the real-world experience of patients who undergo surgical resection. Specific Aim 2 will determine *when* to deactivate the hippocampus during memory testing to impair overall memory performance.

Aim 3: Identify electrical stimulation frequency to disrupt verbal recognition memory function.
The hippocampus has variable, frequency-dependent responses to ES that can either enhance or disrupt memory performance. Mapping by epileptologists during SEEG typically occurs at 50 Hz; however, whether 50 Hz is the ideal ES frequency to reliably impair memory performance is unclear. As such, our third aim is to determine frequencies of ES that best impede memory function. We will utilize a broad but safe radius between XX Hz and XXX Hz to identify the stimulation frequency range that consistently impairs memory performance.

This proposal, a new research direction, will examine how to translate ES of the hippocampus, which has long been used for research, into a clinically viable tool to inactivate the hippocampus in order to preview verbal recognition memory deficits resulting from resection of the hippocampus in the treatment of MTLE.