Hippocampal Response to Ultra Low-Frequency Electrical Stimulation is Both Stimulation Parameter- and Brain State-Dependent: Lessons from Sensing-Enabled Neurostimulation in Idiopathic Nonhuman Primate Epilepsy

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Introduction

The use of implantable neurostimulators to deliver high-frequency electrical stimulation (>100Hz) has garnered considerable interest for the treatment of intractable epilepsy, with two separate devices showing modest efficacy in clinical trials [1,2]. In contrast, low-frequency stimulation (LFS, <10Hz) remains relatively under-explored despite offering the advantage of considerably lower current requirements and extended battery life. In this study, we explored the effects of LFS on hippocampal local field potentials (LFP) in a non-human primate (NHP) with idiopathic epilpesy.

Methods

Simultaneos with continuous video monitoring, a sensing-enabled neurostimulator (Activa RC+S; Medtronic) was used to record LFP activity while LFS was delivered in an awake, freely behaving rhesus macaque implanted with bilateral hippocampal DBS leads. 2Hz stimulation frequency was used for all experiments as it was the lowest frequency the neurostimulator could deliver and was efficacious in previous studies [3]. Stimulation trains of variable duration were delivered in a trial-wise fashion while pulse width and current amplitude were varied (**Fig. 1**). The energy of neural responses were quantified using line-length and employed in parameter selection for chronic testing. Chronic testing consisted of 12 days of continuous LFS during which seizure rates were monitored and scheduled LFP recordings collected for later modeling with multiple linear regression.

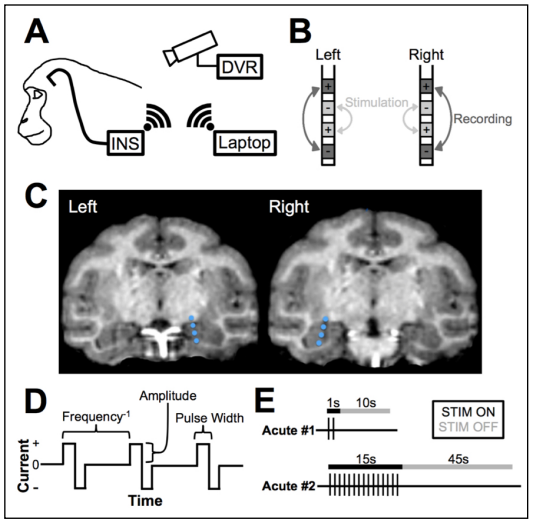

Figure 1: Experimental Design Intracranial electrodes interface with an implanted neurostimulator (INS) which wirelessly communicates with a laptop using distance telemetry while digital video is recorded (DVR; **A**). An bipolar recording-stimulating montage was used for both DBS electrodes (**B**) implanted in bilateral hippocampi (**C**). Stimulation parameters of frequency, amplitude, and pulse width are represented (**D**) as well as trial-wise stimulation testing paradigm for acute experiments (**E**).

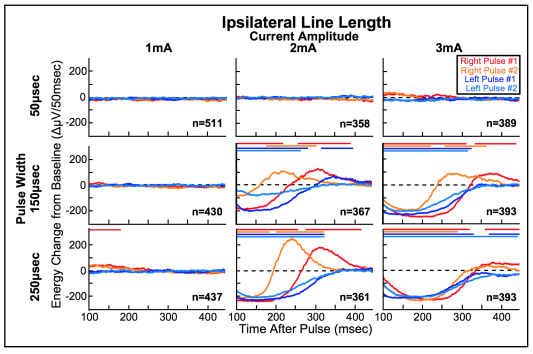

Figure 2: Acute Experiment #1 The interacting effects of pulse width and current amplitude for short trains (1sec; 2 pulses) of unilateral right and left LFS on ipsilateral hippocampal LFP energy are shown. Black dashed line (zero) denotes pre-stimulation baseline energy levels with statistically significant modulation of energy shown by color -coded bars.

Results

LFS at current amplitudes >1mA simultaneous with pulse widths >50usec induced a transient suppression in LFP energy after each stimulation pulse (**Fig. 2**). Stimulation on the right was pursued in further testing since previous work demonstrated it as the seizure onset side [4]. LFS became more suppressive as the duration of the pulse train increased (up to 15sec) and was most effective at 4mA and 150usec (**Fig. 3**). As evidenced by regression modeling of chronic stimulation, efficacy diminished as pulse trains became very long (>1hr) and varied with circadian rhythms (**Fig. 4**). No reduction in seizures was observed.

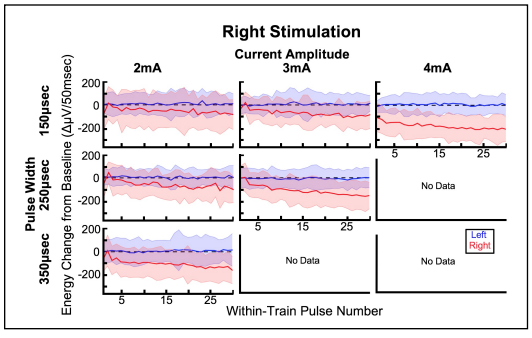

Figure 3: Acute Experiment #2 Net effects of right sided LFS for 15sec (30 pulse) stimulation trains is summarized. Median +/- interquartile range is shown with colored lines and shaded regions, respectively.

Conclusions

LFS of the hippocampus shows a promising ability to suppress LFP energy for short pulse trains, but this efficacy is lost for very long pulse trains. This finding suggests that cycling LFS between the on and off state may be effective at suppressing hippocampal excitability while avoiding the observed attenuation in stimulation-induced neural response.

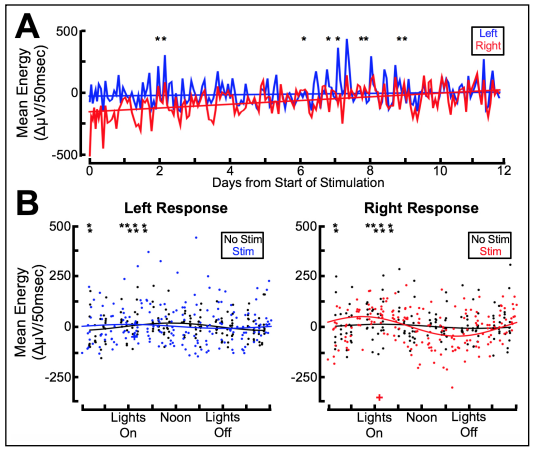

Figure 4: Chronic Experiment Right sided suppressive effects of LFS significantly diminished over time (**A**) and were modulated by circadian rhythms as evidenced by regression modeling. Seizures are denoted by black asterisks.

References

[1] Fisher, Robert, et al. "Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy." Epilepsia 51.5 (2010): 899-908.
[2] Heck, Christianne N., et al. "Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: Final results of the RNS System Pivotal trial." Epilepsia55.3 (2014): 432-441.
[3] Toprani, Sheela, and Dominique M. Durand. "Fiber tract stimulation can reduce epileptiform activity in an in-vitro bilateral hippocampal slice preparation." Experimental neurology 240 (2013): 28-43.
[4] Lipski, Witold J., et al. "Sensing-enabled hippocampal deep brain stimulation in idiopathic nonhuman primate epilepsy." Journal of neurophysiology 113.4 (2015): 1051-1062.

Learning Objectives

1) Describe the current state of implantable neurostimulators for intractable epilepsy, 2) Describe the range of clinically relevant electrical stimulation parameter settings and their differential effects on neural activity, 3) Discuss the utility of sensing-enabled implantable neurostimulators in optimizing stimulation therapy for epilepsy.