Brian Huynh, Jessie Wilson
BME 515
09 OCT 2014

Written Proposal for Course Project

We will evaluate NeuroSigma's Monarch eTNS (External Trigeminal Nerve Stimulation) system, which is intended to treat epilepsy. Trigeminal nerve stimulation (TNS) was applied using a Food and Drug Administration (FDA) approved device. In the proof of concept trial by DeGiorgio and colleagues in 2006, stimulation was set at 120 Hz with a pulse width of 250 us and delivered as an asymmetric biphasic rectangular wave pulse between 0 to 100 mAs through replaceable 1.25-inch self-adhesive electrodes with power supplied via a 9-volt lithium battery. Infraorbital stimulation was used unilaterally, alternating between right-sided and left-sided stimulation every other day. Supraorbital stimulation allowed for bilateral stimulation with only two electrodes. Similar stimulation parameters were set for later trials by DeGiorgio in 2009 and 2013.

A physiological basis for trigeminal nerve stimulation can be found in existing peer-reviewed literature. In 2000, Faneselow et al. found that TNS significantly reduced pentylenetetrazol-induced seizures in rats by means of cortical and thalamic desynchronization. Unilateral TNS reduced electrographic seizure activity by up to 78% while bilateral TNS was even more effective. In 2012, Fanselow et al. further determined projections of the trigeminal nuclei to the locus coeruleus (LC) and nucleus of the solitary tract (NTS). It has been hypothesized that the locus coeruleus is an integral component in the mechanism of TNS. This has been substantiated by Krahl et al. who demonstrated that lesioning of the LC attenuates anticonvulsant effects of VNS since VNS increases the firing and bursting rates of LC neurons.

Accordingly, to judge the efficacy of this device on the treatment of epilepsy, the firing rate of the LC will be used as a proxy for reduction in epilepsy, as LC stimulation correlates with an "anti-kindling effect" and less frequent seizures, as discussed in a study conducted by Weiss et al. We will stimulate the trigeminal nerve and model upstream projections to the LC. If stimulation originating in the trigeminal nerve can match the parameters for LC stimulation cited by Weiss et al.

Commented [WG1]: Too much background. Describe your project, hypothesis or question, and approach,

Commented [WG2]: The structure / what you will be modeling is not clear. This should be as simple as possible to address your hypothesis.

(ie, “20- to 30-min trains of 0.2-ms pulses at 100 Hz, applied for l-s periods alternating with 1-s nonstimulation periods” with intensity such that LC stimulation “elicited jaw and facial movements... indicative of the spread of current to the motor nucleus of the trigeminal nerve”), we will assume that TNS is effective. However, if those parameters cannot be obtained through TNS, we will judge the device to be ineffective.

Commented [WG3]: Not clear how you would assess these side effects w/o developing a very complex model.

Commented [WG4]: Since you are doing this in a model, you can achieve any parameters that you desire.

Commented [WG5]: Proposal is too general and lacks a clear hypothesis or question. I like the idea of looking at the response in the LC, but this will require some appropraite model of TN inputs and the appropriate synapses. You need to refine your question and then determine an approach to the model.

7.5 /10

References

DeGiorgio, Christopher M, Erika E Fanselow, Lara M Schrader, and Ian a Cook. 2011. “Trigeminal Nerve Stimulation: Seminal Animal and Human Studies for Epilepsy and Depression.” Neurosurgery Clinics of North America 22 (4): 449–56, v.

DeGiorgio, Christopher M, Diana Murray, Daniela Markovic, and Todd Whitehurst. 2009. “Trigeminal Nerve Stimulation for Epilepsy: Long-Term Feasibility and Efficacy.” Neurology 72 (10): 936–38.

DeGiorgio, Christopher M, Alan Shewmon, Diane Murray, and Todd Whitehurst. 2006. “Pilot Study of Trigeminal Nerve Stimulation (TNS) for Epilepsy: A Proof-of-Concept Trial.” Epilepsia 47 (7): 1213–15.

Fanselow EE, Reid AP, Nicolelis MA. “Reduction of pentylenetetrazol-induced seizure activity in awake rats by seizure-triggered trigeminal nerve stimulation.” *J Neuroscience* 2000;20:8160–8.

Krahl SE, Clark KB, Smith DC, Browning RA. 1998. “Locus Coeruleus Lesions Suppress the Seizure-Attenuating Effects of Vagal Nerve Stimulation.” Epilepsia 39 (7): 709-714.

Pop, Juliana, Diana Murray, Daniela Markovic, and Christopher M DeGiorgio. 2011. “Acute and Long-Term Safety of External Trigeminal Nerve Stimulation for Drug-Resistant Epilepsy.” Epilepsy & Behavior : E&B 22 (3). Elsevier Inc. 574–76.

Weiss, Gerald K., Johnnye Lewis, Carlos Jimenez-Rivera, Anthony Vigil, and Michael E. Corcoran. 1990. “Antikindling Effects of Locus Coeruleus Stimulation: Mediation by Ascending Noradrenergic Projections.” Experimental Neurology 108 (2): 136–40.