

Interim Progress Report

This investigation will answer the following question: is it possible for the parameters for transcutaneous trigeminal nerve stimulation as used by NeuroSigma to elicit an action potential in the infraorbital branch of the trigeminal nerve? Eliciting an action potential in the trigeminal nerve will serve as a proxy for locus coeruleus stimulation, which has an anticonvulsant effect on epileptic seizures.¹

The Monarch external Trigeminal Nerve Stimulation (eTNS) device has claimed to provide an effective and safe alternative to drug-resistant epilepsy. Vagal nerve stimulation (VNS) has been potential alternative therapy for anti-epileptic drugs (AEDs) and involves both the locus coeruleus (LC) and the solitary nucleus (NTS) which both have projections to the trigeminal nucleus.² Thus, given that antiepileptic effects of TNS have been demonstrated in a rodent model³ and in preliminary clinical trials, transcutaneous stimulation of the trigeminal nerve provides a non-invasive and reversible method for electrical stimulation for drug-resistant epilepsy. eTNS can be applied unilaterally or bilaterally to either the infraorbital and supraorbital tracts of the trigeminal nerve potentially allowing for customized and more effective stimulation.^{4 5}

Commented [WG1]: Good progress on background information, but lack of progress on model.

7.5/10

Commented [WG2]: Outstanding. Very clear hypothesis and rationale.

Commented [WG3]: Does not make sense?

Commented [WG4]: Data to support this?

¹ Weiss, Gerald K. 1990. "Anticonvulsant Effects of Locus Coeruleus Stimulation: Mediation by Ascending Noradrenergic Projections." *Experimental Neurology* 108 (2): 136–40.

² Handforth A, et al. Vagus nerve stimulation therapy for partial onset seizures. A randomized active-control study. *Neurology* 1998;51:48–55.

³ Fanselow, E. E., Reid, A. P., & Nicolelis, M. A. (2000). Reduction of pentylenetetrazole-induced seizure activity in awake rats by seizure-triggered trigeminal nerve stimulation. *The Journal of Neuroscience*, 20(21), 8160–8168.

⁴ DeGiorgio, C. M., Murray, D., Markovic, D., & Whitehurst, T. (2009). Trigeminal nerve stimulation for epilepsy: long-term feasibility and efficacy. *Neurology*, 72(10), 936–938.

⁵ DeGiorgio, C. M., et al. (2006). Pilot Study of Trigeminal Nerve Stimulation (TNS) for Epilepsy: A Proof-of-Concept Trial. *Epilepsia*, 47(7), 1213–1215.

In clinical and feasibility trials, transcutaneous TNS was powered by a battery-powered neurostimulator at 120 Hz for 20-30 seconds on and 20-30 seconds off. An asymmetrical biphasic square wave pulse between 0 to 100 mAs was delivered across 1.25-inch disposable, adhesive electrodes. The positive electrode was positioned above the infraorbital foramen and the negative electrode ½ to 1 inch posteriorly, above the nasal-labial fold.⁶ TNS in the rat model has indicated that seizure reduction is associated with increasing current levels likely due to increased fiber activation in the infraorbital branch of the trigeminal nerve.⁷ Clinical stimulation of < 8 mA (device settings of 0 or 1) has reported no sensation while stimulation at 8-25 mA (device settings of 2 to 4) has been reported as comfortable without any associations with muscle contractions. Higher current stimulation amplitudes could potentially result in twitching of the eye or mild sensations in the mouth or teeth. There were no changes in blood pressure or cardiac rhythm from EKG and continuous Holter monitoring. The pilot study reported a reduction in seizures at six months in two patients of 39% and 76%, respectively.⁸ The pilot feasibility study reported an average reduction of 43.7% in seizure frequency at last treatment visit (at either 3 or 6 months) across seven patients.⁹

A computational model was designed to model the function of this device and judge its efficacy. The model is visualized in the block diagram shown in Figure 1.

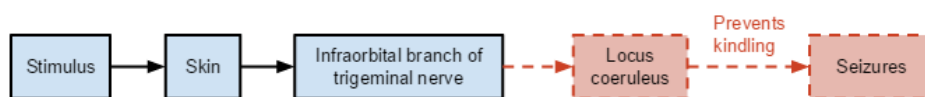


Figure 1. Red figures indicate important downstream assumptions and proxies in the model. Blue figures indicate actual modeled components. Arrows denote the flow of stimulation.

⁶ DeGiorgio (2006).

⁷ DeGiorgio, C. M., Fanselow, E. E., Schrader, L. M., & Cook, I. A. (2011). Trigeminal nerve stimulation: seminal animal and human studies for epilepsy and depression. *Neurosurgery clinics of North America*, 22(4), 449–456.

⁸ DeGiorgio, C. M., Shewmon, D. A., & Whitehurst, T. (2003). Trigeminal nerve stimulation for epilepsy. *Neurology*, 61(3), 421–422.

⁹ DeGiorgio (2006).

Commented [WG5]: Blinded? Controlled? PLacebo? Adverse events?

The model concerns the stimulus electrode-skin interface and the transmission of the stimulus through the skin to the trigeminal nerve. It will be assumed that an action potential, once induced in the infraorbital branch of the trigeminal nerve, will be conducted to the terminus of the trigeminal nerve in the brain stem, stimulating the locus coeruleus to produce an antikingling effect on epileptic seizures.¹⁰ In essence, if stimulation of the locus coeruleus is possible by means of the trigeminal nerve, then it will be assumed that epileptic activity will be inhibited.¹¹ The physical properties and geometry of the trigeminal nerve and the locus ceruleus are incredibly complex, and so such simplifying assumptions must be made.

However, the maximum strength of the stimulation applied by the device is limited by the patient's pain tolerance. As mentioned earlier, stimulation above 25 mA was perceived as uncomfortable, so that will remain an upper limit for stimulation in this model.¹² The efficacy of the device can be refuted if no action potential can be generated at this stimulus intensity: stimulation above this threshold will be uncomfortable for the patient, and it is unlikely that a patient would continue use of the device if it is exceedingly uncomfortable to use.

The next part of the model involves the propagation of the stimulus through the skin to the infraorbital branch of the trigeminal nerve. The impedance of the skin will be calculated using average skin thickness (for cheek epidermis and dermis, $1141.1 \pm 292.3 \mu\text{m}$), conductance values (assuming a lumped skin conductivity of 11 S/m at 64 MHz stimulation) and the formula

$Z_{\text{skin}} = \frac{d}{\sigma A}$ for the impedance of the skin in ohms.^{13 14} This allows realistic

Commented [WG6]: There is no propagation in this problem; the conductor can be treated as a pure resistance (quasi-static assumption)

Commented [WG7]: Not relevant to frequency content in neural stimulation pulses

Commented [WG8]: Your formula does not yield the correct units and is not a reasonable representation. Think about a conducting half space model.

¹⁰ Weiss (1990).

¹¹ Ibid.

¹² DeGiorgio (2003).

¹³ Lee, Y, and K Hwang. 2002. "Skin Thickness of Korean Adults." Surgical and Radiologic Anatomy : SRA 24 (3-4): 183–89.

calculation of the amount of stimulus travelling through the skin to the **nerve**. The distinguishing feature of this device is its transcutaneous method of stimulation, as opposed to direct stimulation of nerves from an implant, and this is a major focus of quantitative evaluation to ensure it behaves as expected.

Commented [WG9]: Need to calculate voltages outside the nerve

The final part of the model will include application of the scaled stimulus to a simulated nerve bundle. This will be accomplished with simple NEURON modeling of a bundle of C-fibers to represent the infraorbital branch of the trigeminal nerve. Based on published values of C-fiber diameters, the model will determine if the stimulus produces an action potential: if it does, then it is assumed that the device is feasible.¹⁵ **C-fibers** are chosen to model the infraorbital branch of the trigeminal nerve because these are both types of sensory fibers in the somatosensory system with similar diameters and properties.¹⁶

Commented [WG10]: What is model of c-fibers?

Commented [WG11]: Lack of progress on implementation and simulation of model is a significant concern.

In summary, the quantitative model of this device will test whether the device settings cited by NeuroSigma are below the pain threshold of 25 mA and can elicit action potentials in the trigeminal nerve from stimulation of the infraorbital branch of the trigeminal nerve. Elicited action potentials will be a proxy for locus coeruleus stimulation, which has been found to have an anticonvulsant effect on epileptic seizures.¹⁷

Regarding the financial health and feasibility of this company and device, NeuroSigma remains a promising firm. Most recently, as of October 21, 2014, NeuroSigma has been issued a Notice of Allowance for a U.S. Patent Application for commercialization of the non-invasive Monarch eTNS system. NeuroSigma has an exclusive license with UCLA and the Regents of the

¹⁴ Sunaga, T., Ikehira, H., Furukawa, S., Shinkai, H., Kobayashi, H., Matsumoto, Y., Yoshitome, E., et al. (2002). Measurement of the electrical properties of human skin and the variation among subjects with certain skin conditions. *Physics in medicine and biology*, 47(1), N11.

¹⁵ Collins, WF, FE Nulsen, and CT Randt. 1960. "Relation of Peripheral Nerve Fiber Size and Sensation in Man." *Archives of Neurology* 3 (4): 381–85.

¹⁶ Ibid.

¹⁷ Weiss (1990).

University of California for this patent application.¹⁸ NeuroSigma had planned to schedule a \$50MM IPO on the NASDAQ under the symbol NSIG on October 9, 2014, but was postponed, citing poor market conditions.¹⁹ NeuroSigma is currently seeking FDA approval for the Monarch eTNS, which is currently limited to investigational use, and faces competition from Cyberonics (FDA approved VNS therapy for epilepsy) and NeuroPace (closed-loop Responsive Neurostimulation System).^{20 21}

¹⁸ "NeuroSigma Receives Notice of Allowance of U.S. Patent Application." *Subcutaneous Trigeminal Nerve Stimulation (sTNS) for the Treatment of Neuropsychiatric Disorders*. PR Newswire, 21 Oct. 2014. Web. 06 Nov. 2014.

¹⁹ Renaissance Capital. "NeuroSigma Postpones \$50 Million IPO." NASDAQ, 9 Oct. 2014. Web. 06 Nov. 2014.

²⁰ IPO Desktop. "IPO Preview: NeuroSigma." Seeking Alpha, 8 Oct. 2014. Web. 6 Nov. 2014.

²¹ Baruchin, Aliyah. "Implantable Devices Could Detect and Halt Epileptic Seizures." *Scientific American Global* RSS, 3 July 2012. Web. 06 Nov. 2014.

References

- Baruchin, Aliyah. "Implantable Devices Could Detect and Halt Epileptic Seizures." Scientific American Global RSS, 3 July 2012. Web. 06 Nov. 2014. <<http://www.scientificamerican.com/article/implant-epilepsy-seizure/>>.
- Collins, WF, FE Nulsen, and CT Randt. 1960. "Relation of Peripheral Nerve Fiber Size and Sensation in Man." Archives of Neurology 3 (4): 381–85. <http://archneur.ama-assn.org/cgi/content/summary/3/4/381>.
- DeGiorgio, C. M., Shewmon, D. A., & Whitehurst, T. (2003). Trigeminal nerve stimulation for epilepsy. *Neurology*, 61(3), 421–422. doi:10.1212/01.WNL.0000073982.42650.57
- DeGiorgio, C. M., Shewmon, A., Murray, D., & Whitehurst, T. (2006). Pilot Study of Trigeminal Nerve Stimulation (TNS) for Epilepsy: A Proof-of-Concept Trial. *Epilepsia*, 47(7), 1213–1215. doi:10.1111/j.1528-1167.2006.00594.x
- DeGiorgio, C. M., Murray, D., Markovic, D., & Whitehurst, T. (2009). "Trigeminal nerve stimulation for epilepsy: long-term feasibility and efficacy." *Neurology*, 72(10), 936–938. doi:10.1212/01.wnl.0000344181.97126.b4
- DeGiorgio, C. M., Fanselow, E. E., Schrader, L. M., & Cook, I. A. (2011). Trigeminal nerve stimulation: seminal animal and human studies for epilepsy and depression. *Neurosurgery clinics of North America*, 22(4), 449–456. doi:10.1016/j.nec.2011.07.001
- Fanselow, E. E., Reid, A. P., & Nicoletis, M. A. (2000). "Reduction of pentylenetetrazole-induced seizure activity in awake rats by seizure-triggered trigeminal nerve stimulation." *The Journal of Neuroscience*, 20(21), 8160–8168.
- Handforth A, DeGiorgio CM, Schachter SC, et al. "Vagus nerve stimulation therapy for partial onset seizures. A randomized active-control study." *Neurology* 1998;51:48–55.
- IPO Desktop. "IPO Preview: NeuroSigma." Seeking Alpha, 8 Oct. 2014. Web. 6 Nov. 2014. <<http://seekingalpha.com/article/2549555-ipo-preview-neurosigma>>.
- Lee, Y, and K Hwang. 2002. "Skin Thickness of Korean Adults." *Surgical and Radiologic Anatomy* : SRA 24 (3-4): 183–89. doi:10.1007/s00276-002-0034-5.
- "NeuroSigma Receives Notice of Allowance of U.S. Patent Application." *Subcutaneous Trigeminal Nerve Stimulation (sTNS) for the Treatment of Neuropsychiatric Disorders*. PR Newswire, 21 Oct. 2014. Web. 06 Nov. 2014. <<http://www.prnewswire.com/news-releases/neurosigma-receives-notice-of-allowance-of-us-patent-application-530573626.html>>.
- Renaissance Capital. "NeuroSigma Postpones \$50 Million IPO." NASDAQ, 9 Oct. 2014. Web. 06 Nov. 2014. <<http://www.nasdaq.com/article/neurosigma-postpones-50-million-ipo-cm400043>>.

Sunaga, T., Ikehira, H., Furukawa, S., Shinkai, H., Kobayashi, H., Matsumoto, Y., Yoshitome, E., et al. (2002). Measurement of the electrical properties of human skin and the variation among subjects with certain skin conditions. *Physics in medicine and biology*, 47(1), N11.

Weiss, Gerald K., Johnnie 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.