

I.A. Cook*^{1,2}, A.F. Leuchter¹, F.A. Jain¹, M.M. Caudill¹, M. Abrams¹, C.M. DeGiorgio^{1,2}
¹University of California, Los Angeles, USA ²NeuroSigma, Inc., USA *icook@ucla.edu

SUMMARY:

Modulation of brain activity via external Trigeminal Nerve Stimulation (eTNS) is an emerging therapy for epilepsy and neuropsychiatric disorders, with an excellent safety profile and significant improvements in seizures, mood, and anxiety in preliminary studies of treatment-refractory subjects. Prior open proof-of-concept studies in MDD found significant within-subject improvements in symptom severity. In this dose ranging project, eTNS was examined under double-blind conditions in MDD as an adjunct to pharmacotherapy. Here we present the first findings of the initial dose six-week phase of the 12-week cross-over protocol, and contrast active stimulation with the control sham condition. Active eTNS stimulation was associated with a significantly greater symptom reduction than sham, and similar benefits arose across a wide range of stimulation frequencies.

BACKGROUND:

• Neuromodulation via Cranial Nerve Pathways:

- Vagus Nerve Stimulation (VNS) initially demonstrated the potential for clinical neuromodulation of key CNS structures via stimulation of cranial nerves.
- Cranial nerve stimulation may alter the activity of deeper structures via pathways that traverse multiple synapses.
- Fibers of the *trigeminal* nerve (Fig 1) innervate the face and project to the nucleus tractus solitarius (NTS), locus coeruleus, reticular formation, raphe nuclei, and thalamic structures, and from there to sensory, limbic, and other cortical and subcortical structures [1,2].

- **Neuroimaging MOA Data** (Fig 2) from ¹⁵O PET imaging indicated rapid and robust acute increases in rCBF from stimulation in anterior cingulate (BA 24, 32), inferior frontal gyrus (BA 44,6,22), and medial and middle frontal gyri incl DLPFC (BA 6,8,45,46) [2].

- **Trigeminal Nerve Stimulation in Epilepsy:** In Phase I and Phase II trials in drug-resistant epilepsy (DRE), significant reduction in seizure frequency was shown without serious adverse events [cf 1,3], using at-home neuromodulation with external Trigeminal Nerve Stimulation (eTNS), primarily while asleep.

- **TNS in Major Depressive Disorder:** Subjects in the epilepsy trials reported significant improvement in mood symptoms [3], independent of seizure improvement, prompting an open adjunctive trial in unipolar MDD.

- In an 8-week open trial in a treatment-resistant sample (average ATHF 5.2), significant improvements in mood were detected, with 55% achieving response and 36% achieving remission at the end of the 8-week trial [4].
- Independent open replication confirmed the observation of therapeutic benefit of eTNS in MDD [5].

OBJECTIVE: The present trial studied the effects of adjunctive eTNS in MDD under double-blind conditions across multiple stimulation frequencies, to inform future trial design.

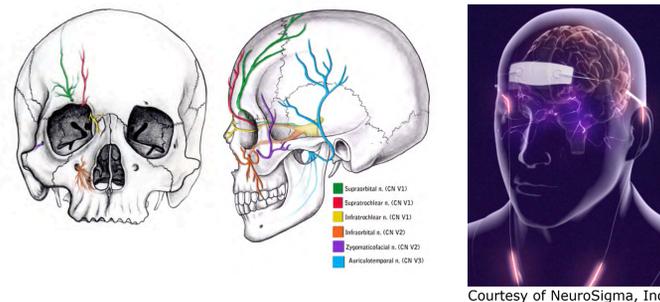


Fig 1. Neuroanatomy of the Trigeminal Nerve and Placement of Stimulating Electric Patch

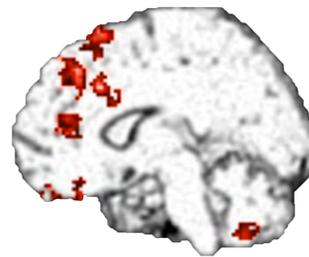


Fig 2. ¹⁵O PET showed acute increases in rCBF from TNS [2]



Fig 3. Electric Patch over V1 connects to pulse generator

METHODS:

- **Subjects:** 43 adults (age 23-65, avg 43.0 (11.5 sd)) with evaluable data were enrolled with: nonpsychotic unipolar MDD; current MDD episode >4 months; non-response with >6 week use of at least one antidepressant in current episode (ATHF 1-10); ongoing treatment with at least one antidepressant medication, with dose held constant during trial participation.
- **Trial Design:** Under double-blind conditions, the dose ranging period lasted 6 weeks to the primary endpoint, with randomized assignment to an active stimulation regimen (2Hz N=9; 20Hz N=12; 120Hz N=14) vs a sham regimen (0Hz N=8); subjects were then crossed over to active stimulation (120Hz) for an additional 6 weeks.
- **Assessments** made every 2 weeks included the Beck Depression Inventory (BDI), Inventory of Depressive Symptomatology (IDS-SR) and Hamilton Depression Rating Scale (HDRS17).
- **TNS Intervention:** Subjects placed stimulating electrodes over supraorbital branches of the trigeminal nerve nightly for ~8 hr, primarily while asleep (Figs 1 & 3). All subjects continued on their medications without change in dose during the trial.
- **Statistical Analyses:** performed with SPSS using t-test, ANOVA, chi square

RESULTS:

Using ANOVA, active stimulation groups did not differ on outcomes, and so were combined for subsequent analyses. *F* ranged 0.15 to 1.10, all *p* n.s.

Subjects receiving active stimulation had significantly greater symptom improvement than subjects randomized to the control condition on BDI (Fig 4) and approached significance on IDS-SR

- BDI -41.7% vs -10.9% 2-tail *p*=0.013
- IDS-SR -30.3% vs -2.5% 2 tail *p*=0.060
- HDRS17 -36.8% vs -30.5% 2 tail *p* n.s.

Symptom severity improved significantly for subjects receiving active stimulation (2-tail t-test)

- BDI 24.6 (8.5 sd) fell to 14.2 (7.3), *p*<0.00001
- IDS-SR 38.3 (10.2) fell to 26.1 (10.5), *p*<0.00001
- HDRS17 19.4 (4.5) fell to 12.1 (6.4), *p*<0.00001

A blinding assessment questionnaire surveyed subjects' beliefs that they were receiving effective (active) treatment and confirmed that active and sham subjects did not differ on their responses (*p* n.s.). Staff were not assessed for their beliefs.

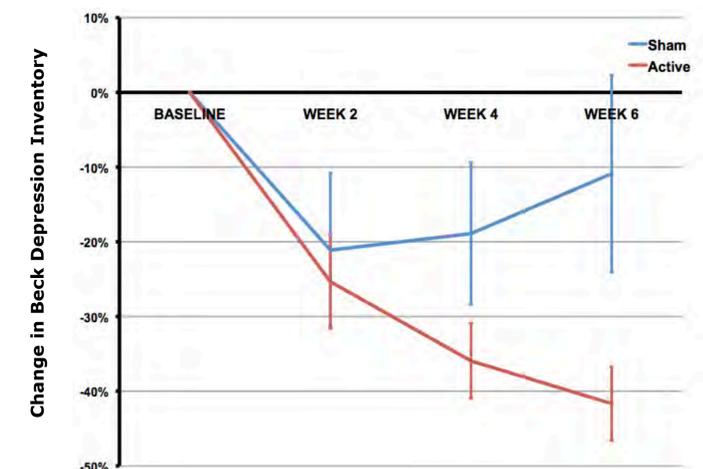


Fig 4. Change in Symptom Severity over Time

CONCLUSIONS:

- Significantly greater reductions in depression severity were achieved in the 6 weeks of acute eTNS treatment than in our sham control condition; blinding assessment supports integrity of the blind.
- These findings replicate open trial results, extend them under double-blind controlled conditions, and justify further development of this intervention.
- Symptom improvement did not differ across the three active stimulation frequencies ('doses'), suggesting that low doses of stimulation may lead to meaningful symptom improvement in MDD and that the cumulative integration of stimulation events may be an important determinant of clinical effects.
- This novel approach to brain stimulation may have use as an adjunct to pharmacotherapy, once efficacy and tolerability are confirmed with additional studies.

REFERENCES:

- [1] DeGiorgio CM, Fanselow EE, Schrader LM, Cook IA. "Trigeminal Nerve Stimulation: Seminal Animal and Human Studies for Epilepsy and Depression." *Neurosurgical Clin N Amer.* 22:449-56. 2011
- [2] Cook IA, Espinoza R, Leuchter AF. Neuromodulation for depression: invasive and noninvasive (deep brain stimulation, transcranial magnetic stimulation, trigeminal nerve stimulation). *Neurosurg Clin N Am.* 25:103-16. 2014.
- [3] DeGiorgio CM, Cook IA, Soss J, Markovic D, Gornbein J, Murray D, Oviedo S, Corral-Leyva G, Kealey C, Heck C. "Randomized Double Blind Controlled Trial of Trigeminal Nerve Stimulation (eTNS) in 50 subjects with Drug Resistant Epilepsy." *Neurology.* 80:786-91. 2013
- [4] Cook IA, Schrader LM, DeGiorgio CM, Miller PR, Maremont ER, Leuchter AF. "Trigeminal Nerve Stimulation in Major Depressive Disorder: Acute Outcomes in an Open Pilot Study." *Epilepsy Behav* 28:221-6. 2013.
- [5] Shiozawa P, Duailibi MS, da Silva ME, Cordeiro Q. Trigeminal nerve stimulation (TNS) protocol for treating major depression: an open-label proof-of-concept trial. *Epilepsy Behav.* 39:6-9. 2014.

Disclosures: Dr. Cook reports relationships Allergan (consultant), Aspect Medical Systems/Covidien (consultant, grant), Cyberonics (grant), Eli Lilly and Company (grant), NIH (grant, service on ITVA review group), NeoSync (grant), Neuronetics (consultant), NeuroSigma (management, stock options), U.S. Departments of Defense and of Justice (consultant), U.S. Veterans Administration (Data Safety Committee). Dr. DeGiorgio reports relationships with NIH (grant) and NeuroSigma (management, stock options). Dr. Leuchter reports relationships with Aspect Medical Systems/Covidien (consultant), Brain Biomarker Analytics LLC (management, equity), Brain Cells, Inc. (consultant), Eli Lilly and Company (grant, consultant), Genentech (grant), NeoSync (consultant, stock options), Neuronetics (grant), NeuroSigma (grant), NIH (grant), Novartis Pharmaceuticals (grant), Seaside Therapeutics (grant), Shire (grant), Taisho Pharmaceuticals (consultant), Wyeth Pharmaceuticals (grant).

Licensing: An exclusive, worldwide license for IP related to trigeminal nerve stimulation has been issued by UCLA to NeuroSigma, Inc., who have CE Mark and Health Canada approval for use in depression.