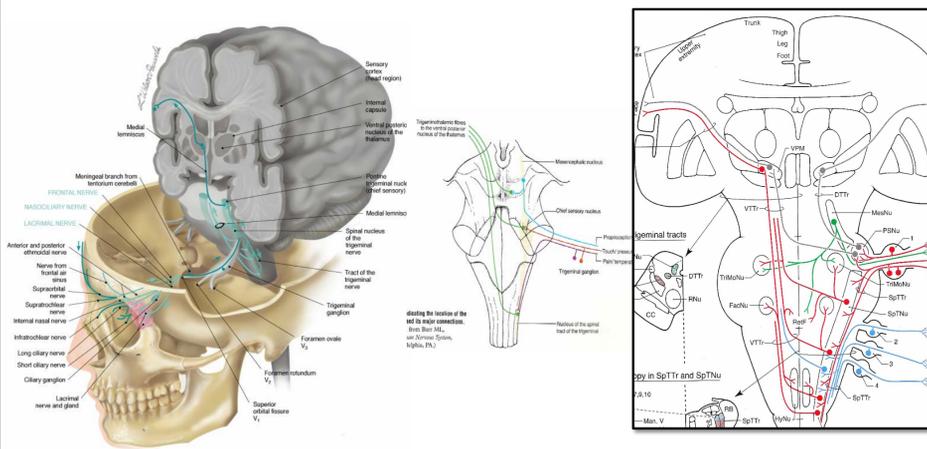


# An Overview of Trigeminal Nerve Stimulation: Basic Science, Clinical Results and Future Directions

## Background

- Trigeminal Nerve Stimulation (TNS) is a promising neuromodulation technique that uses gentle electrical impulses to stimulate the trigeminal nerve.
- The Trigeminal nerve (CN V) is the largest cranial nerve, supplying sensation to the face and motor to the muscles of mastication and the palate.
- The Trigeminal nucleus is located in the brainstem with connecting fibers to the thalamus and cortex; providing a high-bandwidth pathway to structures throughout the brain.
- TNS has several advantages over other neuromodulation techniques, including:
  - Stimulation can be delivered via external or subcutaneous systems
  - Stimulation can be delivered bilaterally and at a wide range of frequencies
  - Low-risk therapy that is well-tolerated by patients
  - Possibility to screen for responders with a non-invasive external system prior to implantation of subcutaneous system
  - Cost-effective, patient-directed treatment
- Functional neuroimaging studies have demonstrated significant metabolic alterations in brain regions associated with seizures and mood in subjects receiving eTNS™.
- Phase I and II clinical trials of external TNS (eTNS™) for the treatment of drug resistant epilepsy (DRE) and major depressive disorder (MDD) have been completed with favorable results.
  - A Phase II double-blind randomized control trial of eTNS™ for the treatment of drug resistant epilepsy demonstrated that 40.5% of patients in the treatment group had a  $\geq 50\%$  reduction in seizure frequency after 18 weeks.
  - A Phase I open-label pilot study of eTNS™ for MDD demonstrated a mean reduction in depression severity of 51.5% after 8 weeks. Results of a Phase II double-blind RCT are expected in Q1 2012.
- Phase I studies of eTNS™ for ADHD and PTSD are ongoing with results expected in early 2012.

## The Trigeminal Nerve – USB Port to the Brain™



The Trigeminal Nerve (CN V) is the largest cranial nerve, supplying sensation to the face

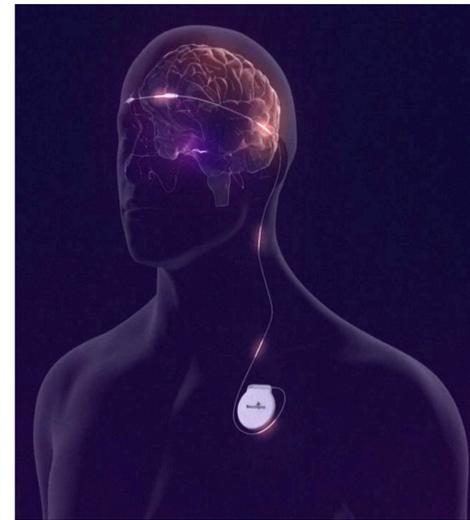
The Trigeminal Nucleus in the brainstem has direct projections to the ventral posterior nucleus of the thalamus and the cortex.

## Embodiments

Trigeminal Nerve Stimulation can be delivered via two different embodiments



External Trigeminal Nerve Stimulation eTNS™

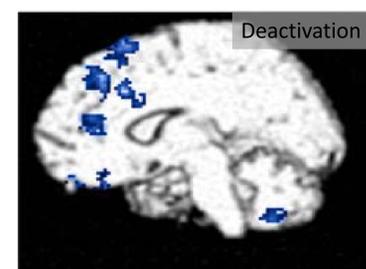
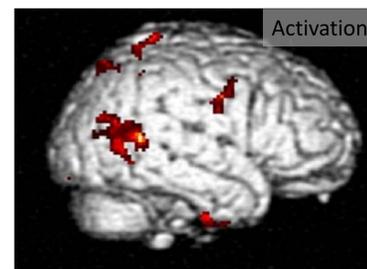


Subcutaneous Trigeminal Nerve Stimulation sTNS™

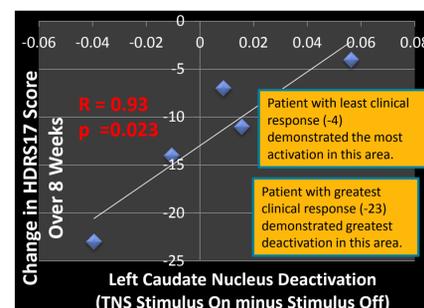
## Basic Science

Functional Neuroimaging –  $O^{15}$  PET Data

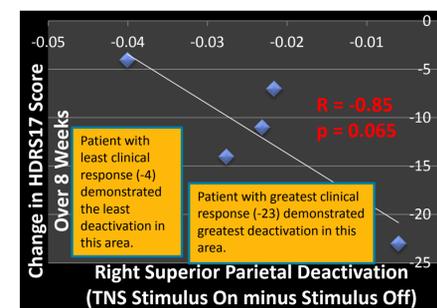
- Five subjects with major depressive disorder (MDD) were enrolled to receive 8 weeks of eTNS™ as adjunctive therapy and underwent  $O^{15}$  PET scanning during first use of eTNS™
- Significant metabolic changes were found in brain structures associated with seizures, mood, and attention.
- Stronger caudate nucleus activation was associated with improved clinical response. Stronger superior parietal deactivation was associated with less clinical response.



$O^{15}$  PET scanning of subjects receiving eTNS™ for the first time revealed significant metabolic changes in cortical structures associated with seizures, mood, and attention.



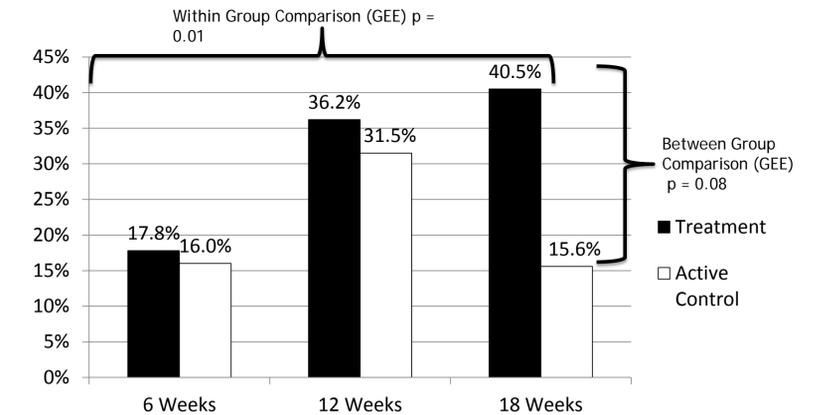
Stronger caudate nucleus activation was associated with improved clinical response



Stronger superior parietal deactivation was associated with less clinical response

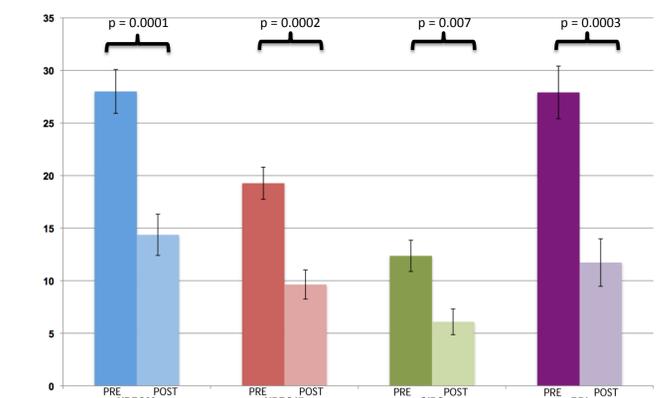
## Clinical Results

Phase II Randomized Control Trial of eTNS™ for Drug Resistant Epilepsy



Responders were defined as subjects having a  $\geq 50\%$  decrease in seizure frequency. At the end of 18 weeks 40.5% of subjects in the treatment group responded versus only 15.6% of subjects in the active control ( $p = 0.08$ ).

Phase I Trial of eTNS™ for Major Depressive Disorder



A Phase I study of eTNS™ for depression enrolled 11 subjects for an 8 week period. At the end of 8 weeks there were significant improvements in depression scores as measured by HDRS-28, HDRS-17, QIDS, and BDI.

## Future Directions

- Trigeminal Nerve Stimulation is a novel neuromodulation treatment modality for epilepsy and other neuropsychiatric disorders.
- Functional neuroimaging of subjects receiving eTNS™ shows significant changes in cerebral metabolism that correlate with clinical response.
- Phase I and II studies of eTNS™ for MDD and DRE are encouraging, and show dramatic reductions in seizure frequency and severity of depression. These results warrant confirmation in larger clinical trials with more patients.
- A Phase II RCT of eTNS™ for depression is ongoing, with results expected in early 2012.
- Results of Phase I clinical trials of eTNS™ for PTSD and ADHD are expected in 2012.

