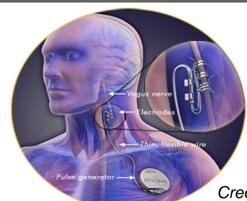


Background

MicroTransponder has developed a VNS-based rehabilitation therapy for tinnitus and stroke. Our recent animal research has shown that VNS can reverse maladaptive plasticity and improve behavioral outcomes when given during tone presentation (for tinnitus) or movement (for motor rehabilitation after stroke). VNS may exert these effects on neuroplasticity via activation of nucleus basalis and locus ceruleus neurons, which release acetylcholine and norepinephrine onto the cortex. Our hypothesis is that short bursts of VNS paired with sensory or motor events will drive targeted plasticity and improve tinnitus or facilitate motor recovery after stroke, respectively.

Methods

Tinnitus: Our therapy pairs VNS with randomly interleaved pure tones excluding frequencies in the region believed to be responsible for the tinnitus. In a feasibility and safety study involving 10 tinnitus patients, patients heard tones paired with brief electrical stimulation of the vagus nerve for 2 ½ hours each day for 20 days. **Stroke:** In our pre-clinical studies VNS was paired with two different types of motor training in a rat Endothelin-1 model of ischemic stroke (n=15). All studies included an intensive therapy control arm (n=17). A twenty patient randomized, controlled clinical trial with blinded endpoint assessment is underway in the UK (10 VNS device plus rehabilitation and 10 rehabilitation only). The primary endpoint is safety and feasibility and secondary endpoints include measures of upper limb function (ARAT score, Fugl Meyer score, etc).



Credit: Cyberonics

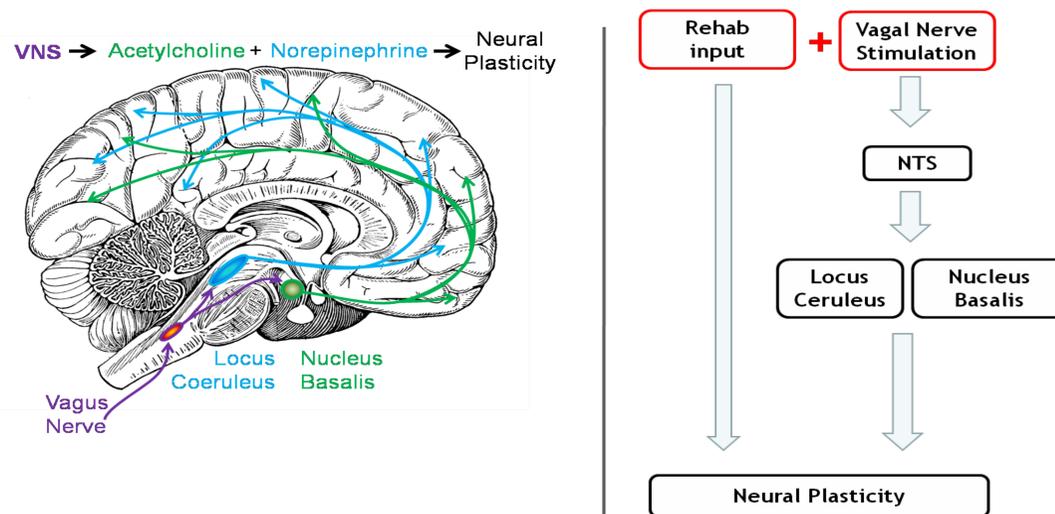
- Well understood by FDA and clinicians. Good safety profile

- The Cyberonics device has been implanted into 90,000 patients since 1997 (epilepsy)

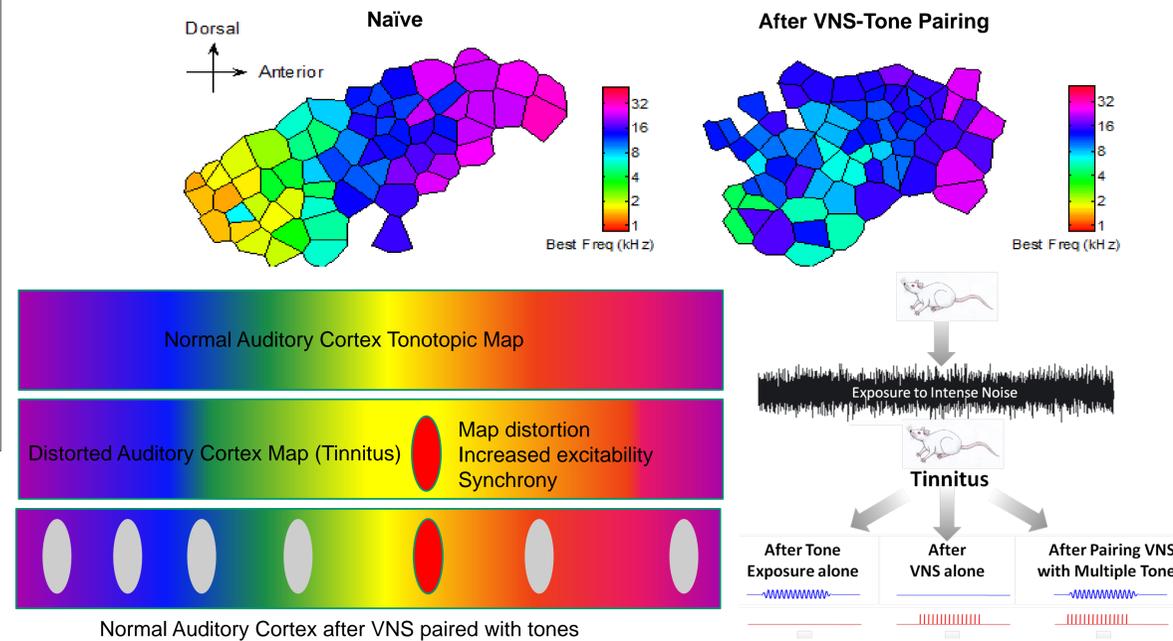
- Most common adverse event is a hoarse voice during stimulation

- Typical stimulation paradigm for epilepsy is unpaired stimulation (typically 30 seconds ON/5 min OFF)

MECHANISM OF ACTION



TINNITUS PRECLINICAL STUDIES



SUMMARY:

A tone was paired with Vagus Nerve Stimulation 300 times per day for 20 days in naïve rats

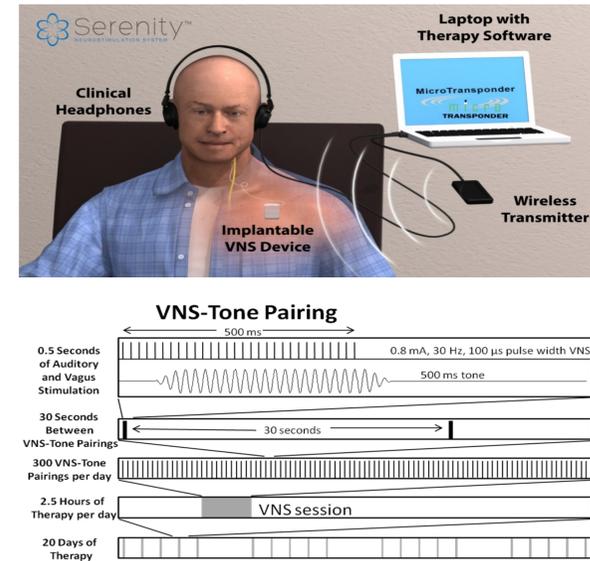
After 20 days, expansion of the auditory cortex map specific to the paired tone

Paired stimulation of another cranial nerve – trigeminal nerve did not induce auditory cortex plasticity

Repeatedly pairing tones with brief pulses of VNS reversed the physiological and behavioral correlates of tinnitus in noise exposed rats.

Targeted neural plasticity can provide the specificity required to restore normal neural activity in dysfunctional neural circuits that are assumed to underlie many forms of tinnitus

TINNITUS CLINICAL STUDIES



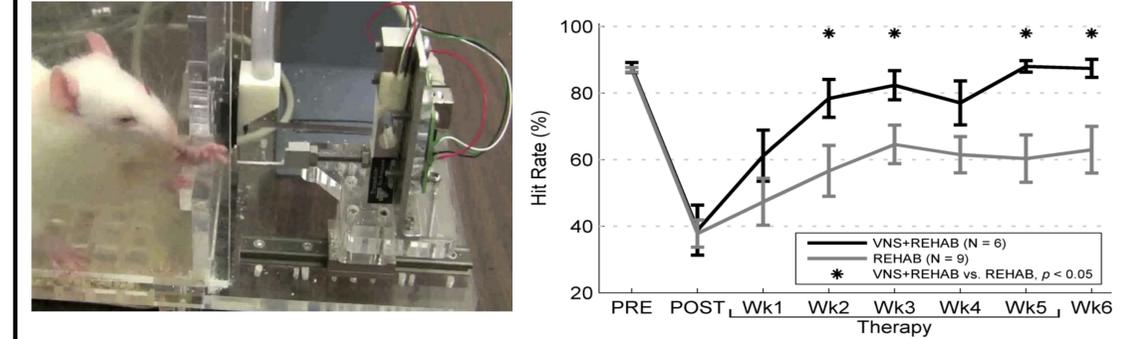
RESULTS FROM BELGIUM STUDY

- Ten patients with severe chronic tinnitus were implanted with electrodes on their left vagus nerve.
- Patients heard tones, two and a half hours each day for 20 days, excluding the tinnitus-matched frequency, paired with brief electrical stimulation of the vagus nerve
- The therapy was well tolerated, and no patient withdrew from the study due to complications or side-effects
- Four of the ten patients exhibited clinically meaningful improvements in their tinnitus, both for the affective component, as quantified by the Tinnitus Handicap Inventory, and for the sound percept, as quantified by the minimum masking level (MML).
- Improvements were stable for more than two months after the end of therapy.
- Of the ten patients, five were on medications that included muscarinic antagonists, norepinephrine agonists, and γ -amino butyric acid agonists, thereby possibly interfering with acetylcholine and norepinephrine release and blocking the effects of VNS. These patients had no improvement in contrast to medication-free patients. 60 & 80% of patients in the no-drug group had a clinically meaningful decrease in THI (44.3% decrease) and MML (26.7 dB decrease), respectively.

TINNITUS US CLINICAL TRIAL (NIH)

- Blinded Randomized Pilot Study: VNS Paired with Tones vs. VNS with Unpaired Tones
- 4-site, 30 patient study; All implanted, ½ randomized to VNS+tones therapy, ½ randomized to sham VNS+tones
- After implant, 6-weeks of daily at home therapy
- Long-term all patients receive paired VNS treatment
- IDE approval received September 25, 2013
- Enrollment projected for winter 2013 with a 12-month enrollment period expected
- Visit tinnitustrial.com for more information. Sites:
 - University of Buffalo Christina Stocking, AuD
 - Wayne State University Anthony Cacace, PhD
 - University of Iowa Rich Tyler, PhD
 - University of Texas at Dallas Sven Vanneste, PhD

STROKE PRECLINICAL STUDIES



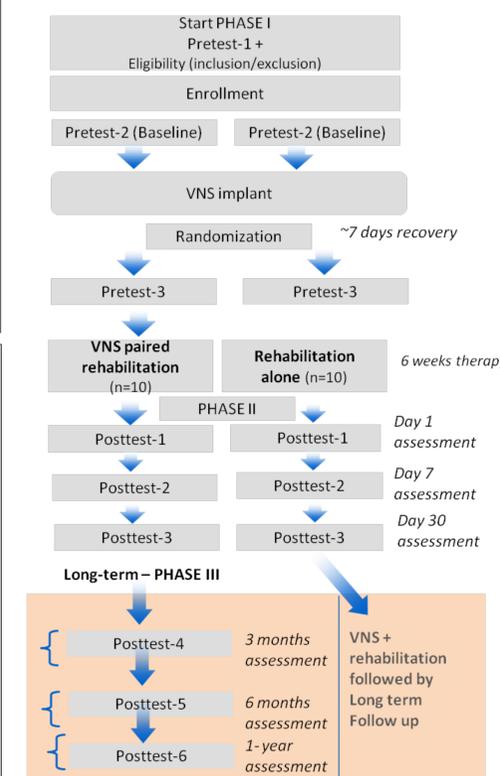
STROKE CLINICAL STUDIES



Glasgow Stroke Trial - Human Feasibility Stroke Study

- A 20 subject (10 implant, 10 non-implant control) randomised, controlled clinical trial with blinded endpoint assessment
- Ischemic stroke patients; ARAT score of 15 to 50 (inclusive)
- To date 11 subjects are enrolled and eight subjects have completed the acute study (5 have been implanted).
- All five subjects tolerated surgery well; no significant adverse effects have been reported.
- Patients randomised to intensive physical therapy vs. intensive physical therapy with paired VNS
- 3 sessions a week (~ 2 hrs each session) for 6 weeks
- Subjects perform ~300-400 movements per 90 minute session across 8-10 different tasks
- In VNS+rehab patients, therapist delivers VNS (1/2 second pulse) during each movement trial
- Clinical benefits are as yet unproven since we have data from only 40% of patients

US Stroke Trial



- De Ridder D, Vanneste S, Engineer ND, Kilgard MP. Safety and Efficacy of Vagus Nerve Stimulation Paired With Tones for the Treatment of Tinnitus: A Case Series. *Neuromodulation*. 2013 Nov 2
- Engineer N, Riley J, Seale J, Vrana W, Shetake J, Sudanagunta S, Borland M, and Kilgard M, "Reversing pathological neural activity using targeted plasticity", *Nature*, vol. 470, pp. 101-104, January 2011
- Khodaparast N, Hays SA, Sloan AM, Hulsez DR, Ruiz A, Pantoja M, Rennaker RL, Kilgard MP, Vagus Nerve Stimulation During Rehabilitative Training Improves Forelimb Strength Following Ischemic Stroke. *Neurobiology of Disease*, 2013 Aug
- Porter BA, Khodaparast N, Fayyaz T, Cheung RJ, Ahmed SS, Vrana WA, Rennaker RL 2nd, Kilgard MP, "Repeatedly Pairing Vagus Nerve Stimulation with a Movement Reorganizes Primary Motor Cortex.", *Cerebral Cortex*, November 10, 2011

