Neuromodulation Therapies for Tinnitus

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Neuromodulation:

"The alteration of neural activity through targeted delivery of a stimulus, such as electrical stimulation, light, or chemical agents, to specific neurological sites in the body"

International Neuromodulation Society

San Francisco

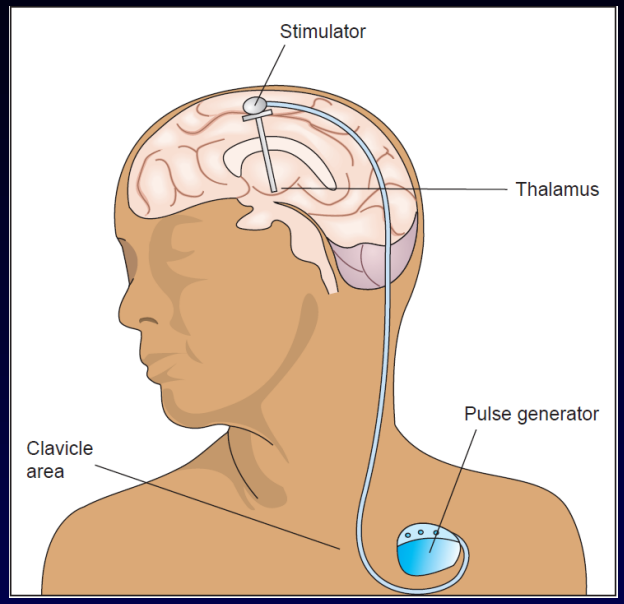
"Neuromodulation devices are the fastest growing segment of the medical device industry"

Anyone who has never made a mistake
has never tried anything new.

Albert Einstein (1879–1955)

Neuromodulation for Tinnitus

- Deep Brain Stimulation (DBS)
- Brain Surface Stimulation
- Vagus Nerve Stimulation
- Transcranial Magnetic Stimulation (TMS)
- Transcranial Direct Current Stimulation (tDCS)
- Electroconvulsive Therapy (ECT)



Electroconvulsive Therapy (ECT)

- Patient is anesthetized and given a muscle relaxant
- Unilateral or bilateral electrodes deliver brief-pulse current to the patient's head
- Effective for approx. 50% of patients with major depression who did not respond to other therapies

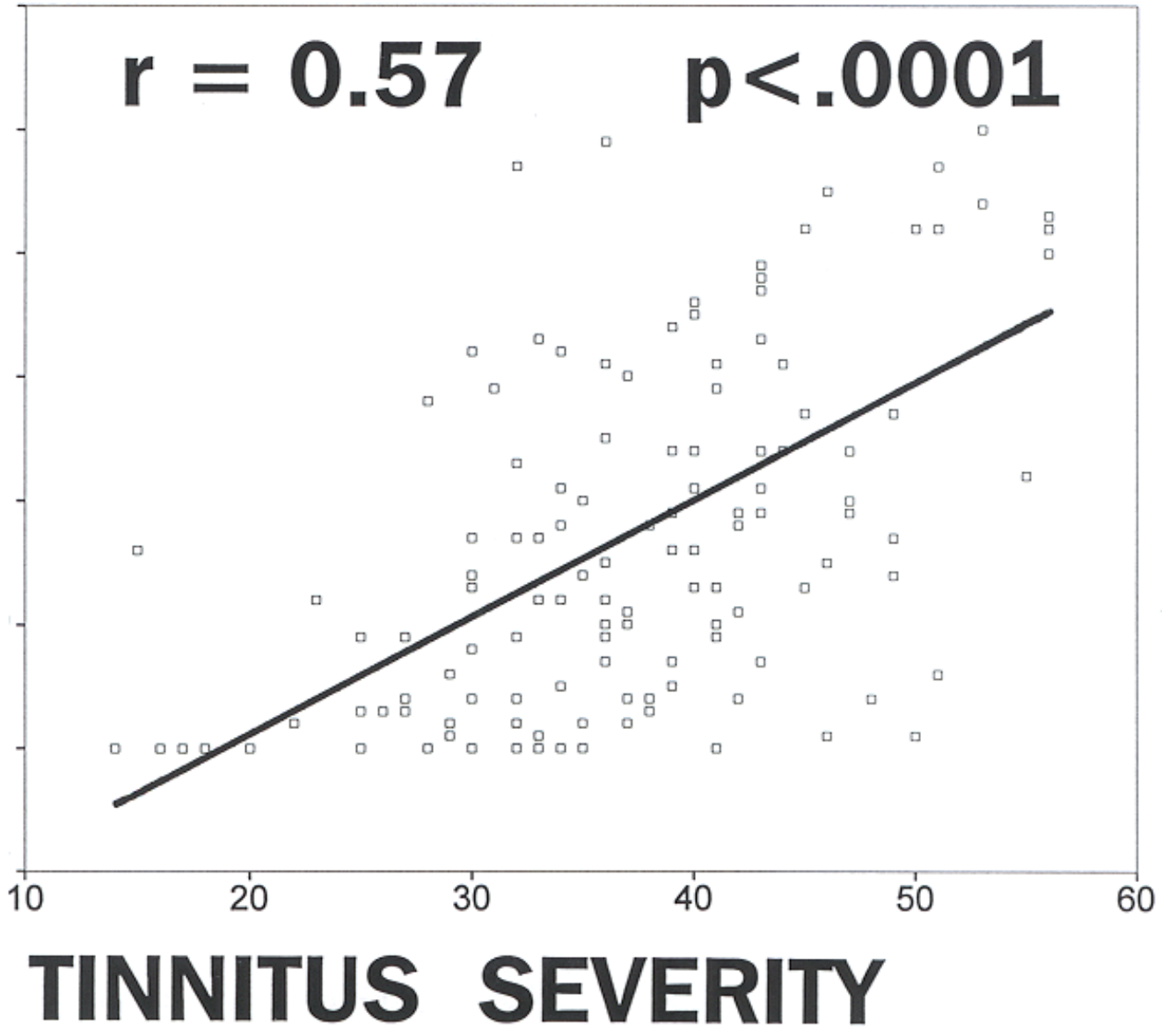
Adverse effects: confusion, memory loss, muscle soreness

ECT for Tinnitus

- Salah et al., *Convulsive Therapy*, 1995
  69-year-old male with major depression + tinnitus
  Received ECT 4 times and "responded well" each time

- Popeo et al., *Journal of ECT*, 2011
  51-year-old female with major depression + tinnitus
  - Tinnitus "resolved" with successful treatment of her depressive episode with ECT

BECK DEPRESSION INVENTORY SCORE



ECT Causing Tinnitus?

Case Reports in Psychiatry
Volume 2011, Article ID 607061, 3 pages
doi:10.1155/2011/607061

Case Report

Chronic Tinnitus following Electroconvulsive Therapy

Robert L. Folmer,[1,2] Yongbing Shi,[2] and Sarah Theodoroff[1]

[1] *National Center for Rehabilitative Auditory Research, Portland VA Medical Center, Portland, OR 97239, USA*
[2] *Department of Otolaryngology, Oregon Health & Science University, Portland, OR 97239, USA*

43-year-old female with major depression + obsessive-compulsive disorder underwent a series of 4 ECT sessions. After the 4th treatment, she experienced tinnitus in her right ear

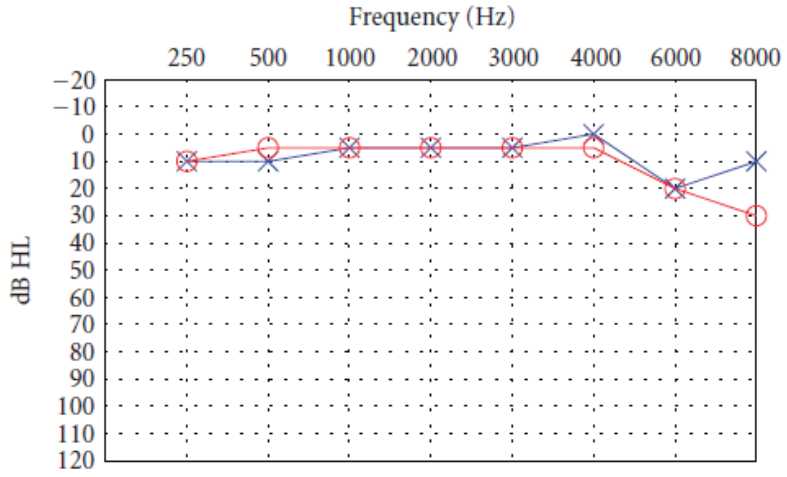


FIGURE 1: Pure-tone air conduction thresholds one day after ECT.
◯: right ear thresholds; ×: left ear thresholds.

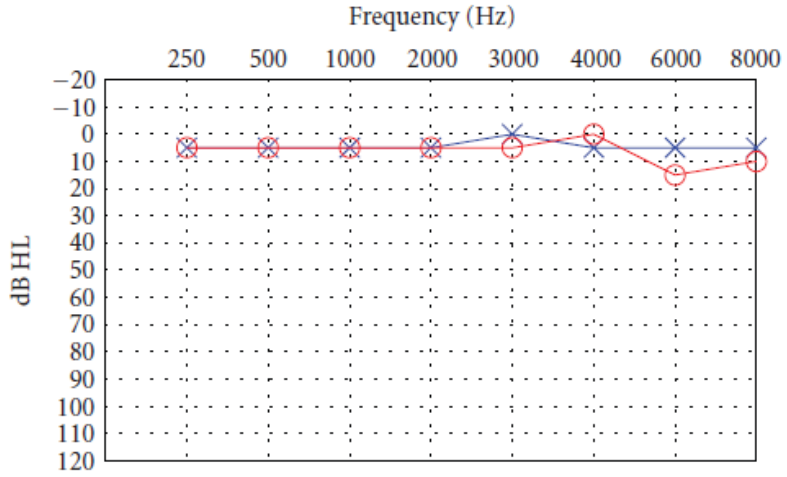


FIGURE 2: Pure-tone air conduction thresholds six weeks after ECT.
◯: right ear thresholds; ×: left ear thresholds.

One day after the last ECT treatment, she heard high-pitched tinnitus in the right ear

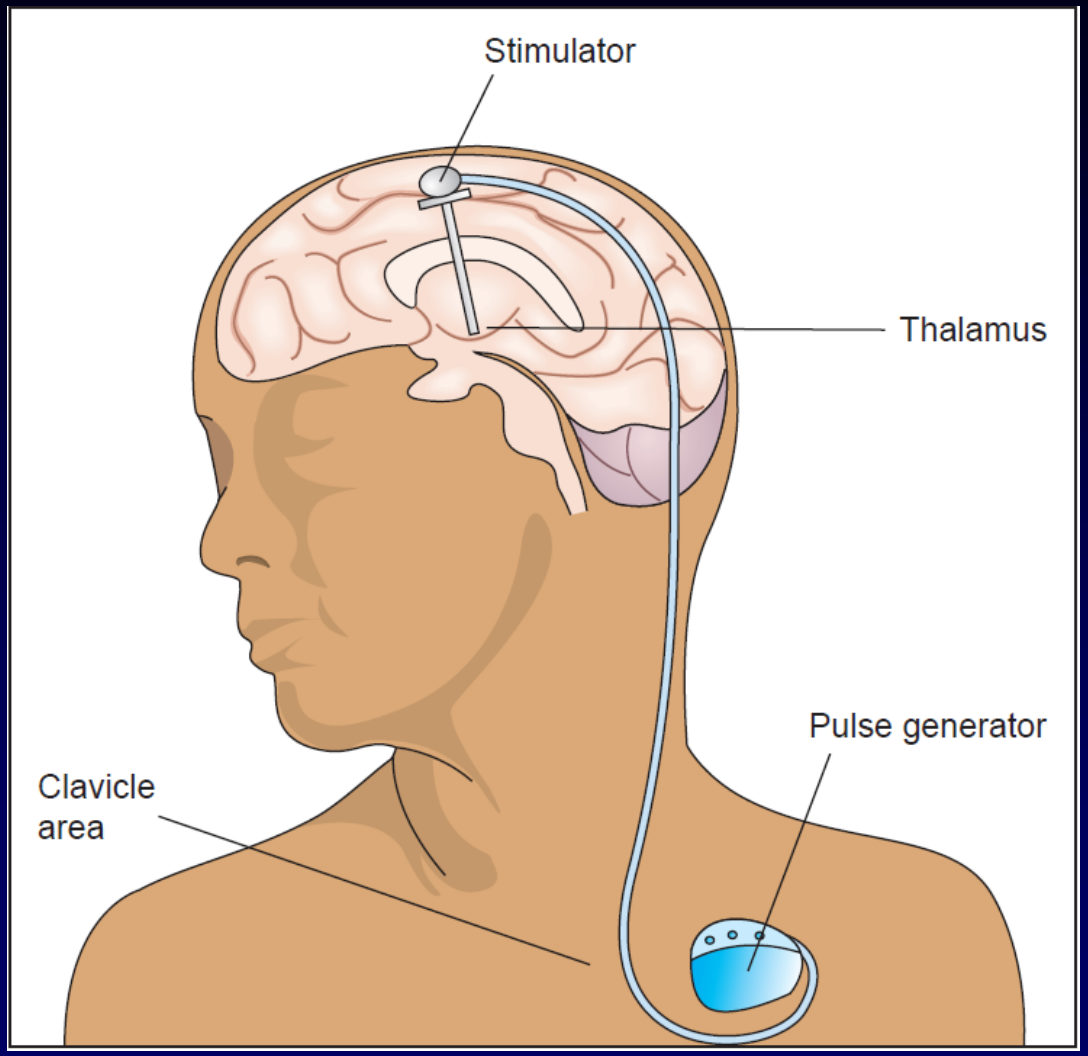
6 weeks after the last ECT treatment, 4000 Hz tinnitus continued but was reduced in intensity

What caused the tinnitus & changes in pure tone thresholds?

Was it ECT, medications, or a combo of these?

Fortunately, the tinnitus continued to decrease in loudness and went away after 2 years

Deep Brain Stimulation (DBS)



Treatment Option for

- Parkinson Disease
- Chronic Pain
- Essential Tremor
- Dystonia
- Severe Depression

DBS for Tinnitus

Shi et al. *Otolaryngol Head Neck Surg*, 2009

- interviewed 7 patients with tinnitus who were implanted with DBS electrodes in the ventral intermediate nucleus of the thalamus for movement disorders

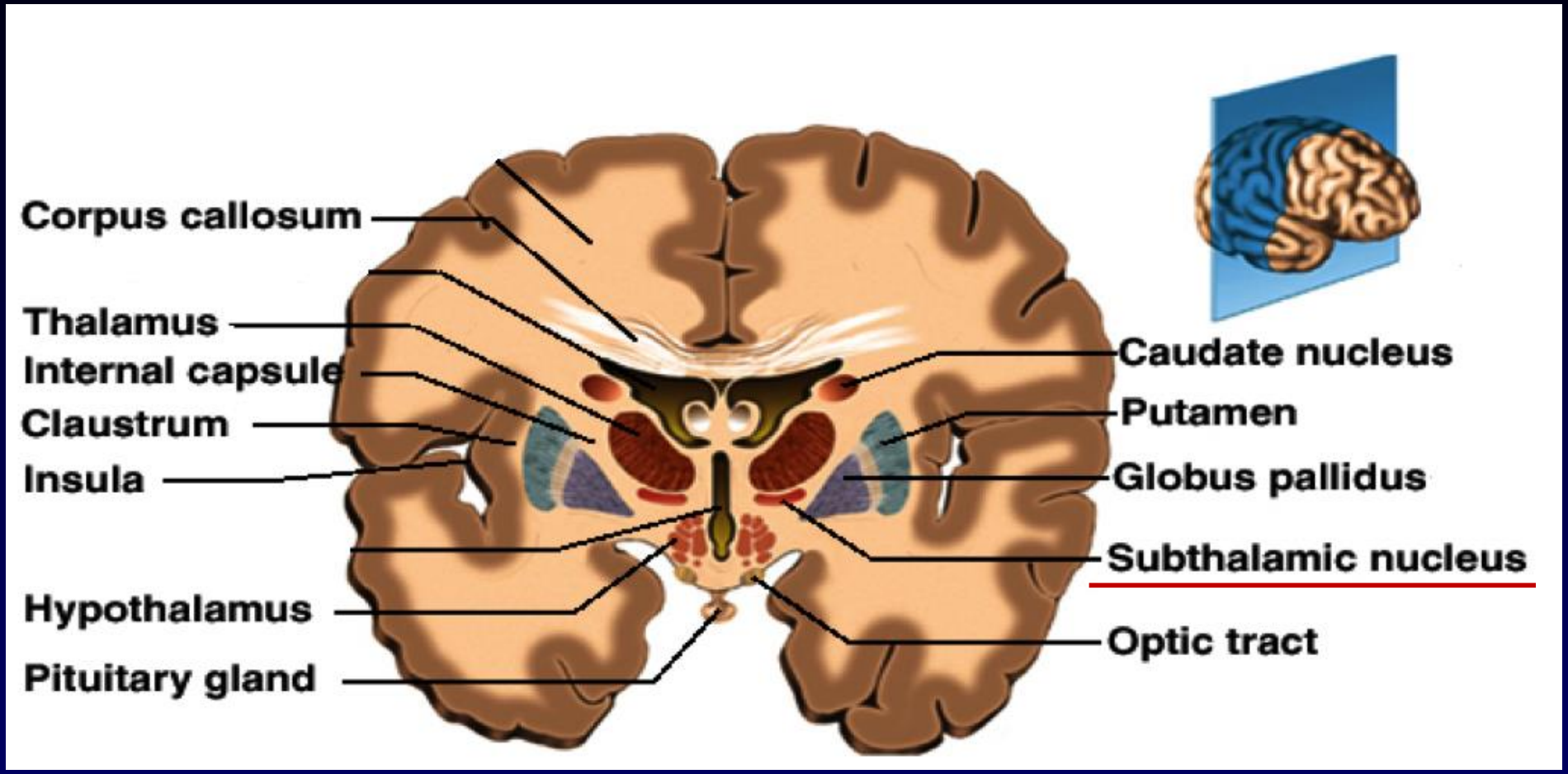
- Three of the patients reported reduced loudness of tinnitus when the DBS electrode was activated (compared to “OFF”)

DBS for Tinnitus

Cheung & Larson *Neuroscience*, 2010
Recruited 6 patients with tinnitus who were scheduled for DBS surgery for Parkinson's or Essential Tremor

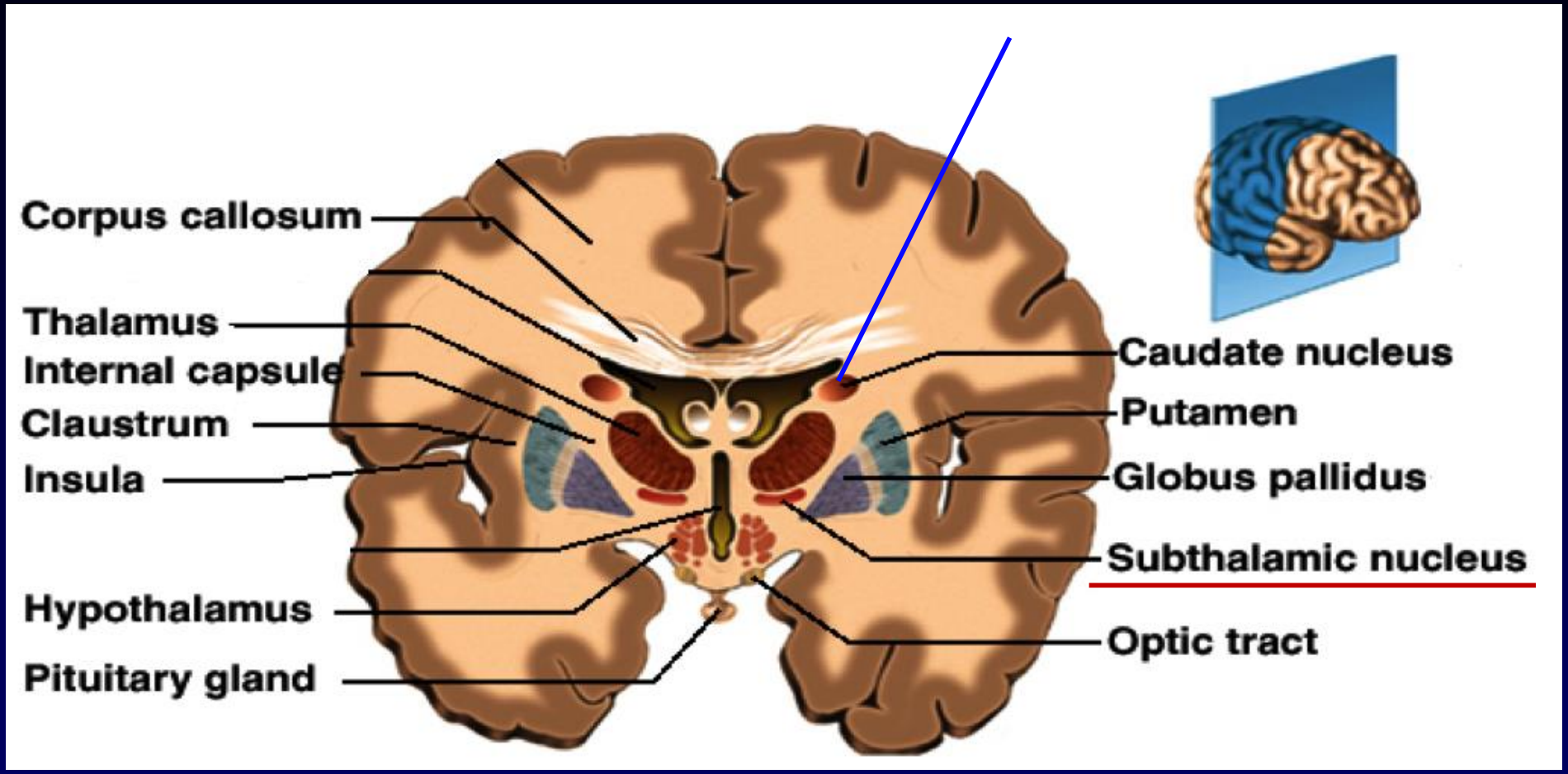
DBS targets: subthalamic nucleus or
ventral intermediate nucleus of thalamus

DBS for Tinnitus



in 5 patients, the electrode was paused within the caudate nucleus to deliver electrical stimulation

DBS for Tinnitus



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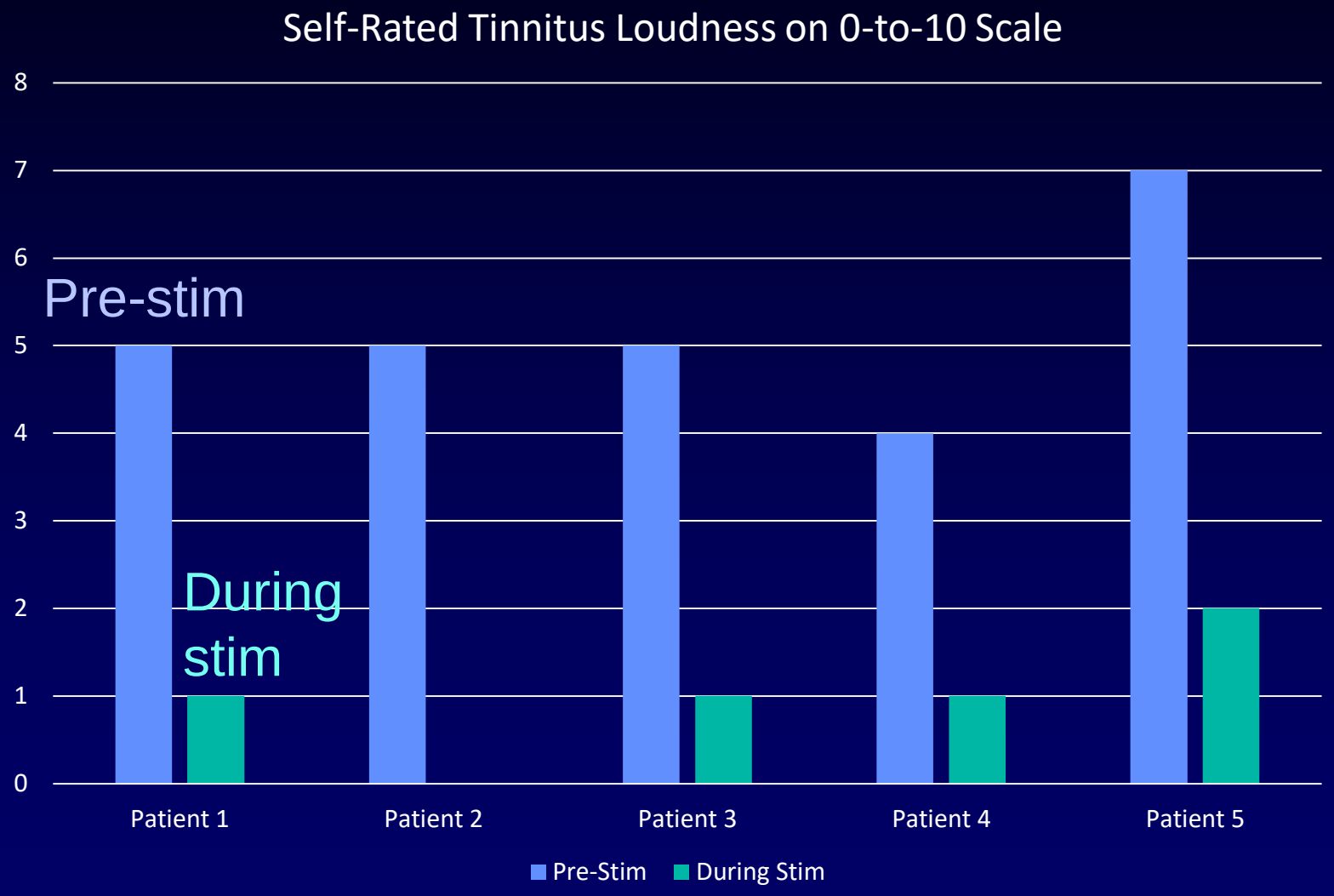
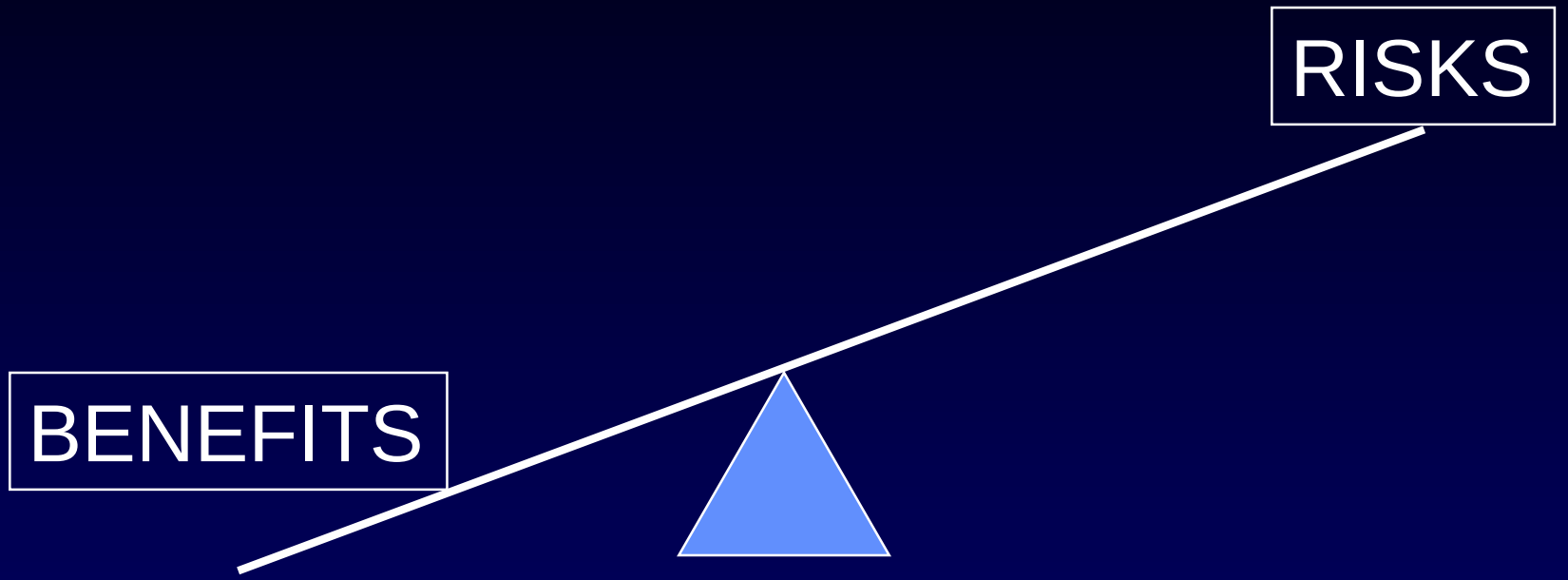
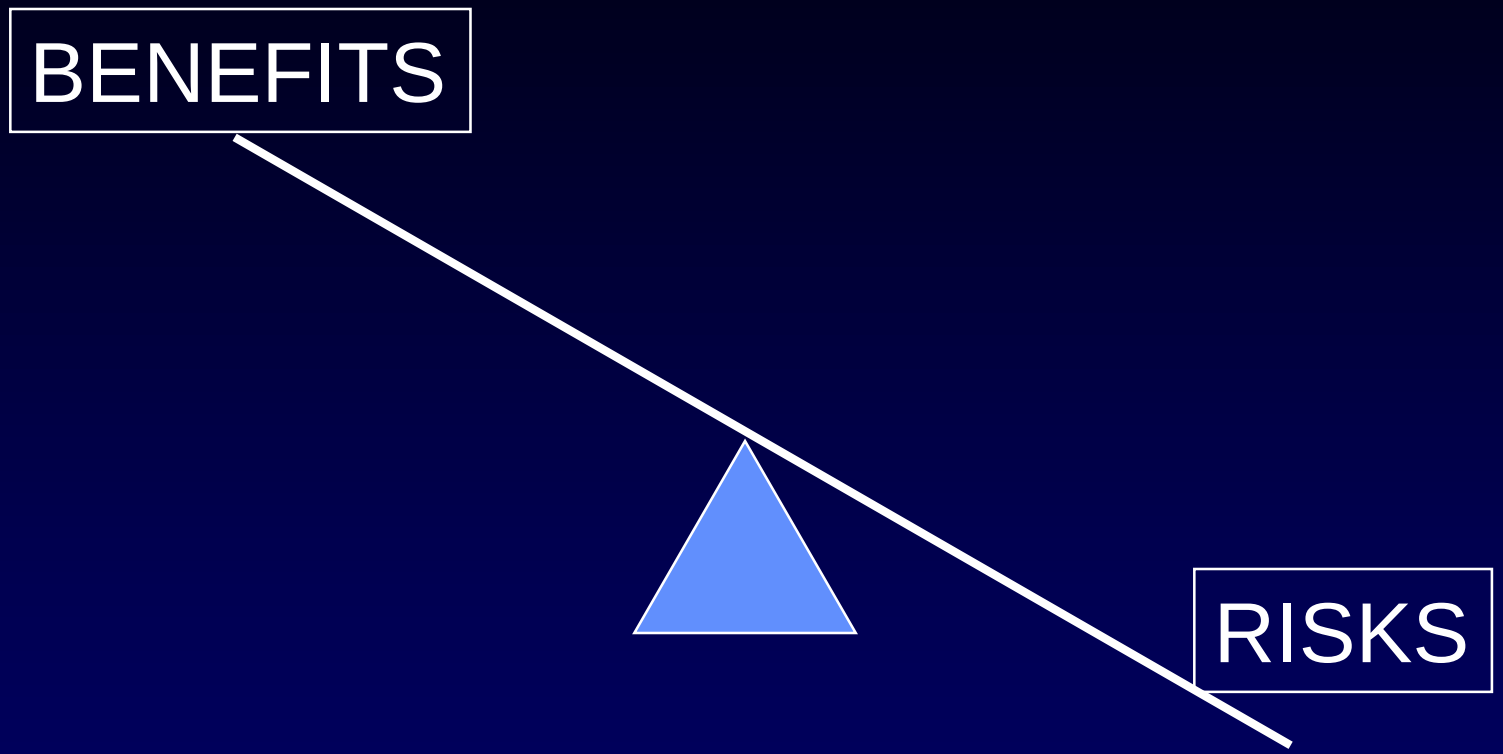
DBS for Tinnitus - Results





Safety Requirement for Tinnitus Treatments



Brain Surgery for Tinnitus

Brain Surface Electrodes for Tinnitus

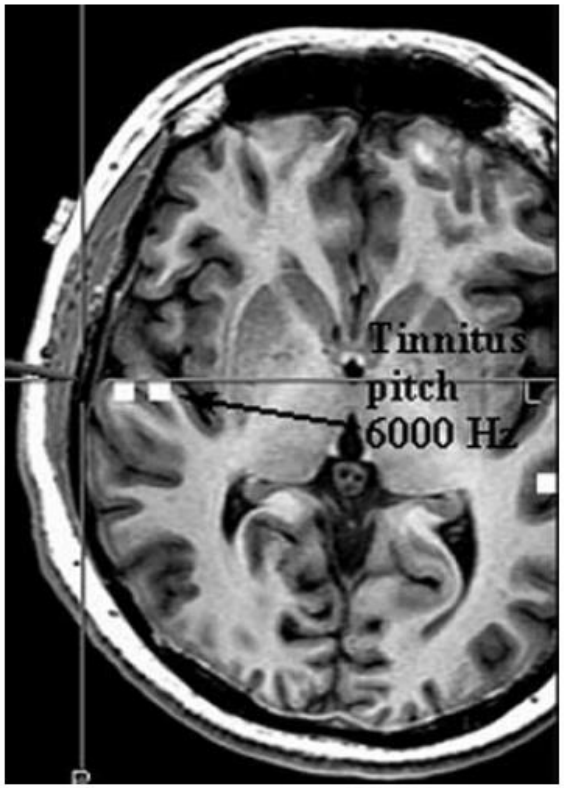


Fig. 7. *Left*: Magnetic source image showing the location of the structure that is presumed to generate the patient's tinnitus, centered at 6000 Hz. *Right*: Intraoperative pictures of electrode insertion. Images courtesy of Dr. Seidman

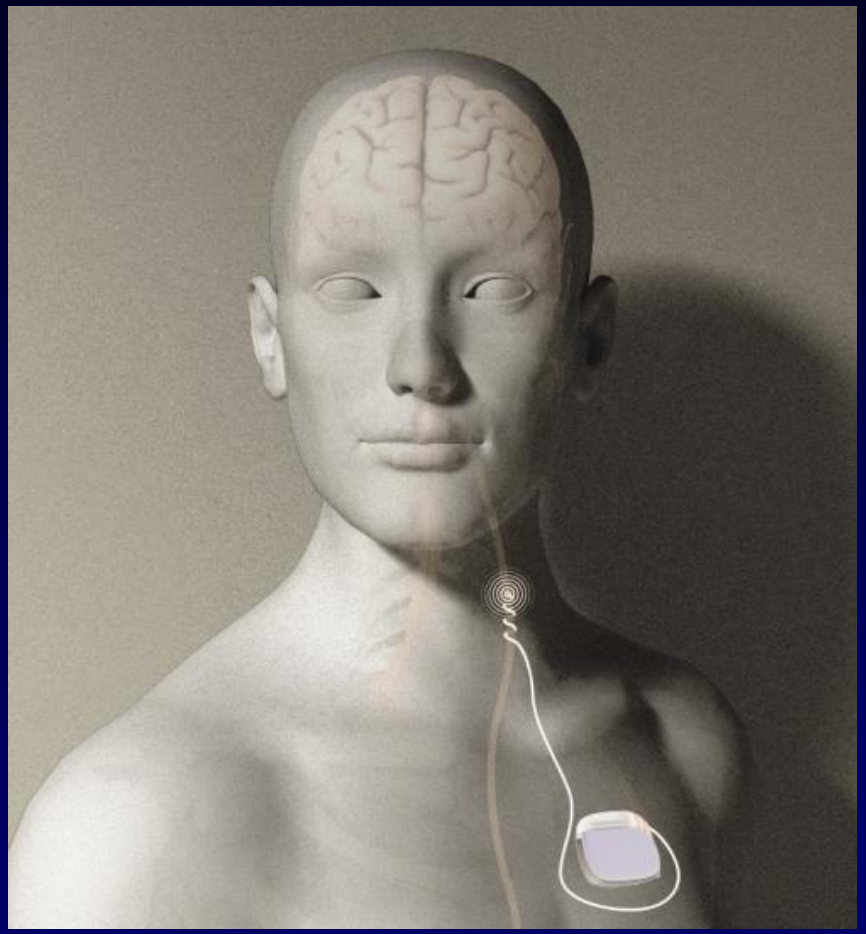
De Ridder et al., *Acta Neurochir* Supplement, 2007

Brain Surface Electrodes for Tinnitus Results

De Ridder et al., *Acta Neurochir* Supplement, 2007
n=5 patients
3 patients experienced suppression of tinnitus;
2 patients did not have suppression of tinnitus

Friedland et al., *Otology & Neurotology*, 2007
n=8 patients
2 patients had long-term suppression of tinnitus;
6 patients had shorter-term suppression of tinnitus

Vagus Nerve Stimulation



FDA-approved to treat
Depression
and Epilepsy

Research ongoing for many other applications, including tinnitus

Vagus Nerve Stimulation for Tinnitus

Surgical Method

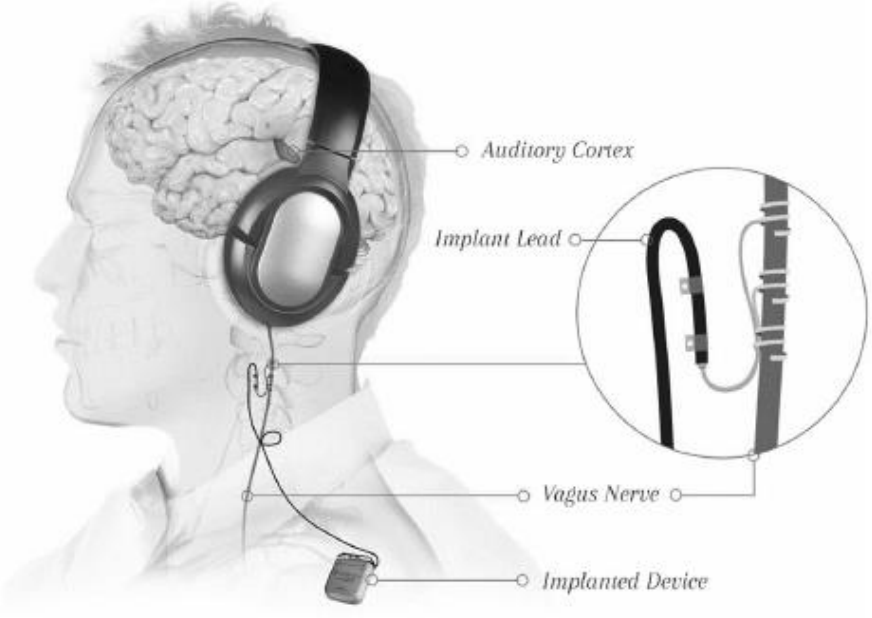


Figure 4. Setup using the Serenity® System that pairs Vagus Nerve Stimulation (VNS) with tones. The inset shows the electrode lead wrapped around the cervical vagus nerve. The device is the pulse generator that is implanted under the chest wall. The implant lead connects to the pulse generator. Image courtesy of *MicroTransponder, Inc.*

Tyler et al.,
Scientific Reports, 2017

Used the "Serenity System" that "pairs" VNS with tones

30 patients implanted

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16 received VNS ***"paired"*** with tones

14 received ***"unpaired"*** VNS + tones (Control Group)

for 6 weeks

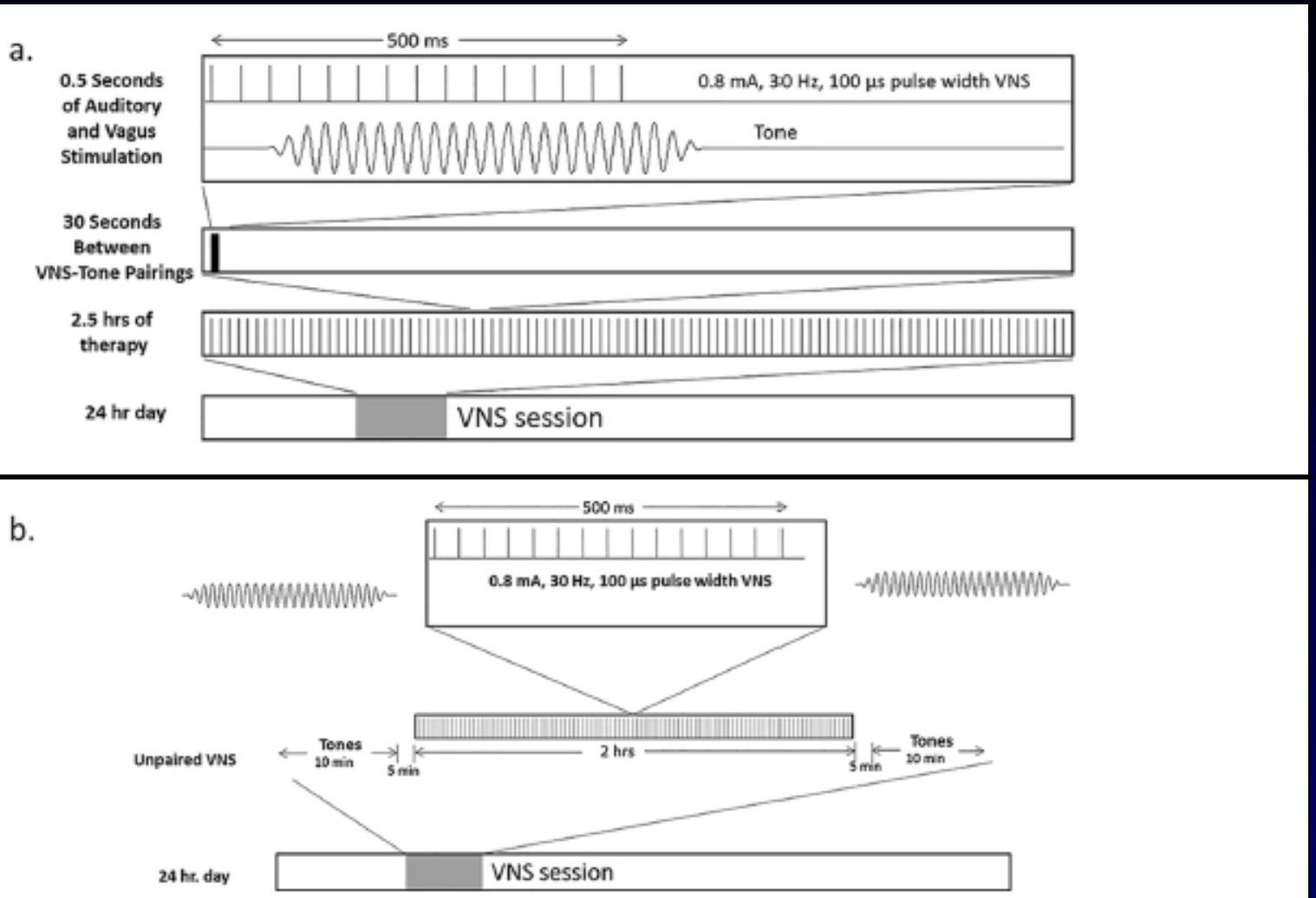

Figure 5. (a) Stimulation settings for paired VNS therapy. The lower panel shows the stimulation settings (0.8 mA, 30 Hz), which overlaps with the tone. Each VNS tone pairing was presented every 30 seconds, for approximately 2.5 hrs per session over a period of 24 hrs. (b) Stimulation settings for the Unpaired (Control) group. During each session, participants received 10 minutes of tones only, 5 minutes of silence and no VNS; 2 hours of VNS only; 5 minutes of silence and no VNS, and 10 minutes of tones only.

"Paired" VNS Therapy

"Unpaired" VNS Therapy (Control Group)

Vagus Nerve Stimulation for Tinnitus

Surgical Method – Results (change from baseline)

Outcome Measure	Paired VNS	Control Group
THI (%)	-17.7%	-7.3%
THQ	-2.5	-7.5
TFI	-2.0	-7.5
Self-rated Tinnitus Loudness (0-to-100 scale)	-6.7	-8.5
Matched Loudness	+1.1	+0.4
Minimum Masking Level (MML)	+3.5	-3.8

Vagus Nerve Stimulation for Tinnitus

Surgical Method – Results (change from baseline)

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THI (%) ←	-17.7% ←	-7.3% ←
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Vagus Nerve Stimulation for Tinnitus

Surgical Method – Results (change from baseline)

Outcome Measure	Paired VNS	Control Group
THI	-9.3	-3.9
THQ	-2.5	-7.5
TFI	-2.0	-7.5
Self-rated Tinnitus Loudness (0-to-100 scale)	-6.7	-8.5
Matched Loudness	+1.1	+0.4
Minimum Masking Level (MML)	+3.5	-3.8

Vagus Nerve Stimulation for Tinnitus

Surgical Method – Results (change from baseline)

Outcome Measure	Paired VNS	Control Group
THI	-9.3	-3.9
THQ	-2.5	-7.5
TFI	-2.0	-7.5
Self-rated Tinnitus Loudness (0-to-100 scale)	-6.7	-8.5
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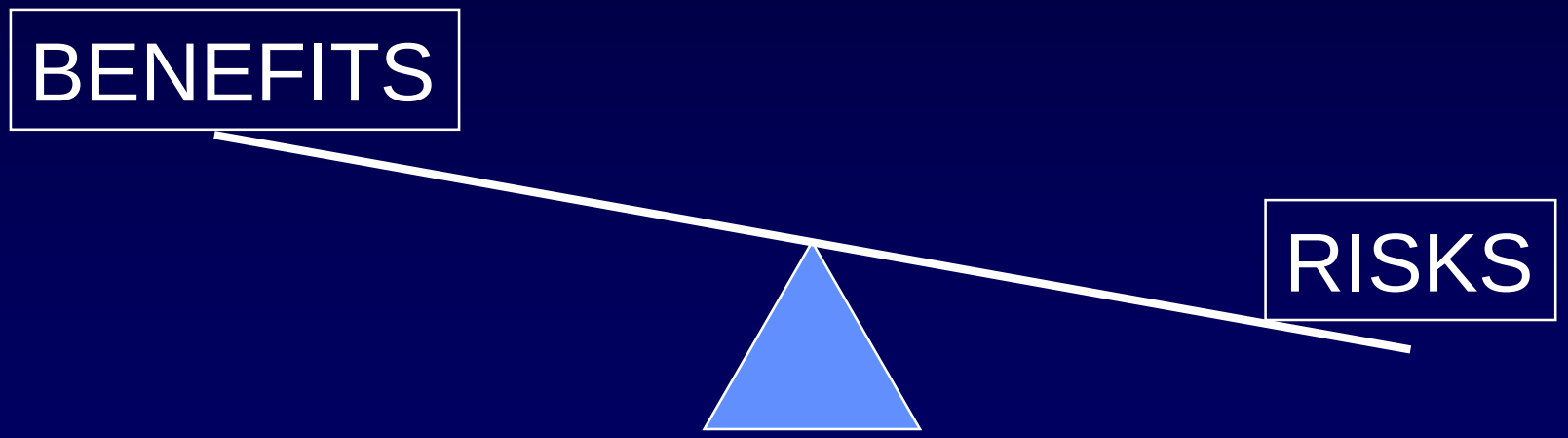
Vagus Nerve Stimulation for Tinnitus

Surgical Method



Vagus Nerve Stimulation for Tinnitus
Non-Surgical Methods

Feasibility Publications:

Kreuzer et al., *Brain Stim*, 2014

Shim et al., *J Audiol Otol*, 2015

Ylikoski et al., *Acta Otolaryngol*, 2017

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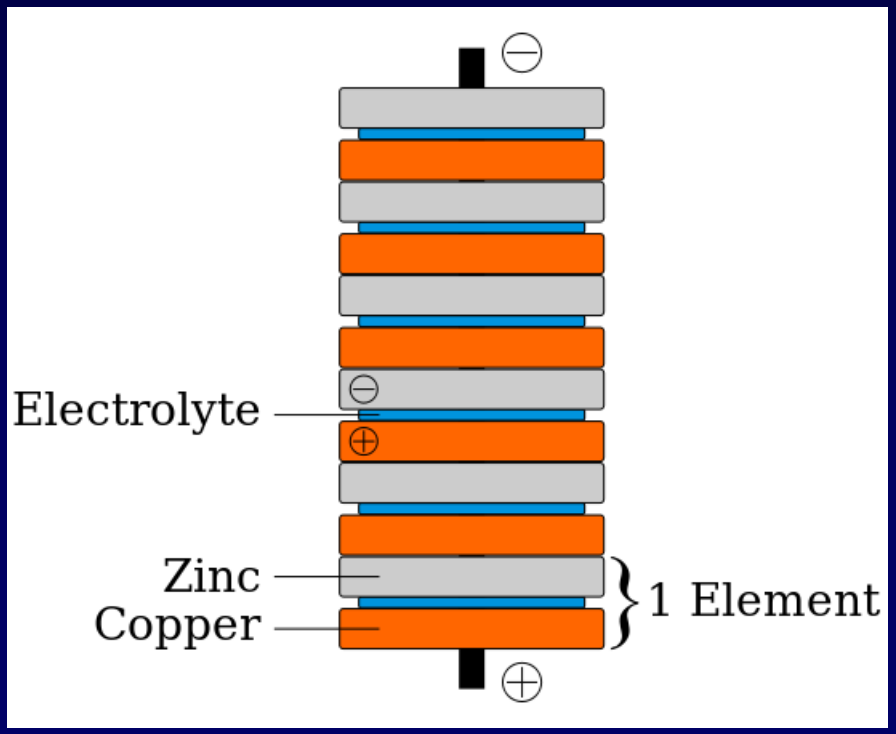
“uses bi-modal neuromodulation via simultaneous auditory stimulation in the ear and sensory stimulation on the tongue to promote positive changes in neuroplasticity in parts of the brain implicated in tinnitus”

Transcranial Direct Current Stimulation (tDCS)

1800 - Alessandro Volta developed the first battery



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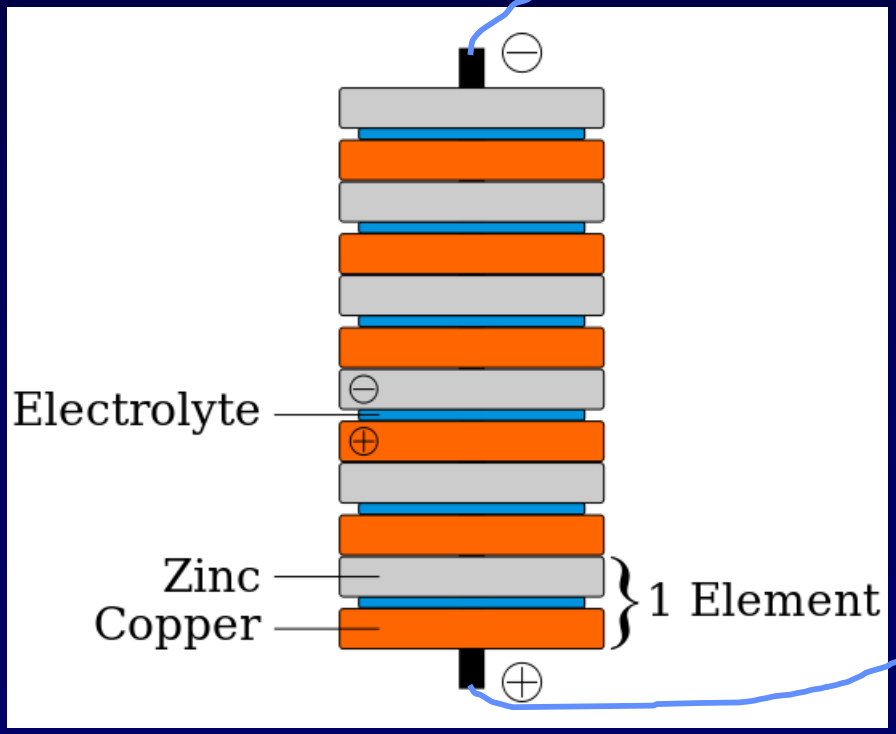
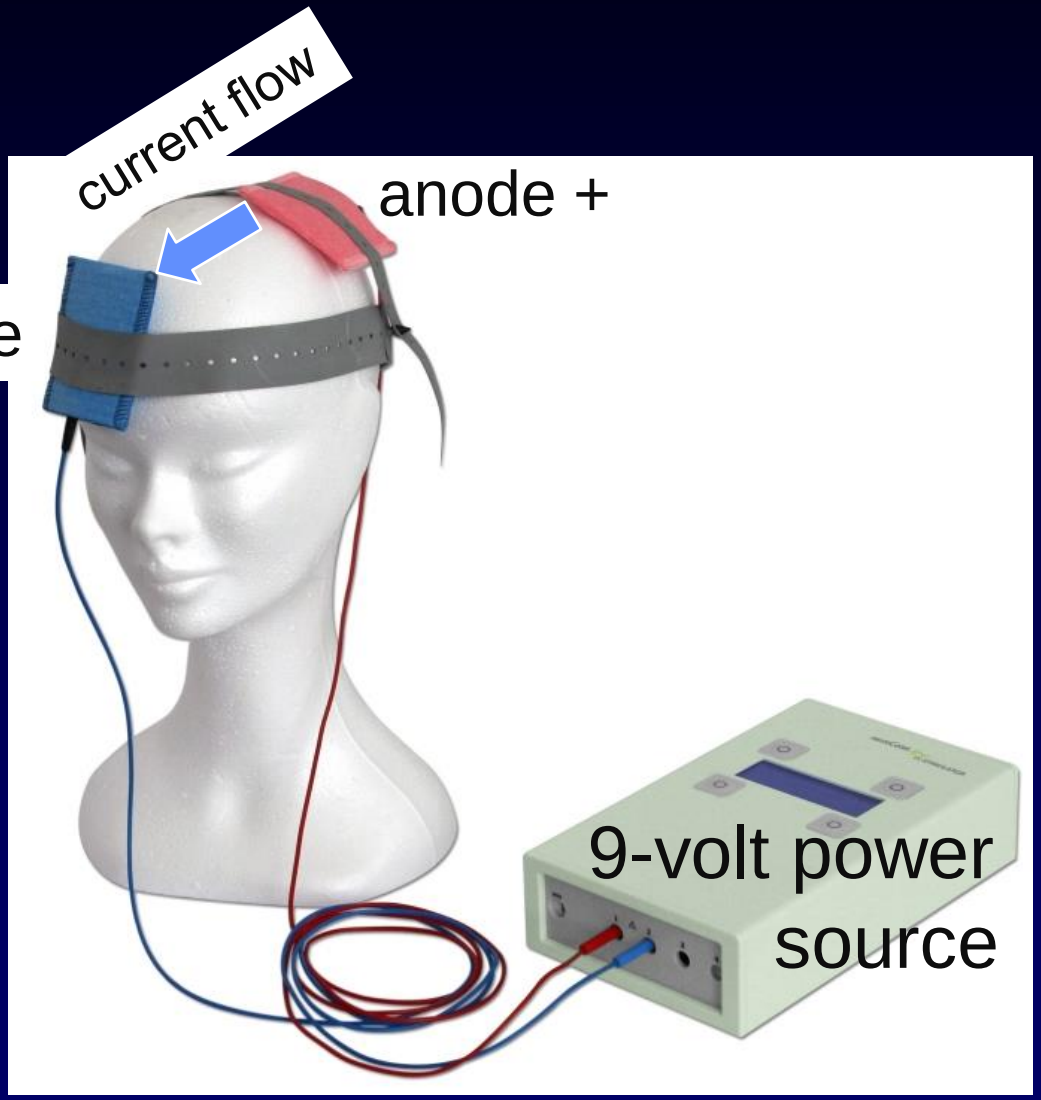


Transcranial Direct Current Stimulation (tDCS)



Used Experimentally To Treat

Depression
Chronic Pain
Headaches
Tinnitus
Cognitive Disorders
Movement Disorders

tDCS for Tinnitus

Rabau et al., *Frontiers in Aging Neuroscience*, 2017

Claim: this electrode configuration stimulates the dorsolateral prefrontal cortex and the hippocampus

32 participants received
2 sessions of tDCS weekly for 4 weeks
Each session lasted 20 minutes

Outcome measures: TFI, VAS for tinnitus loudness

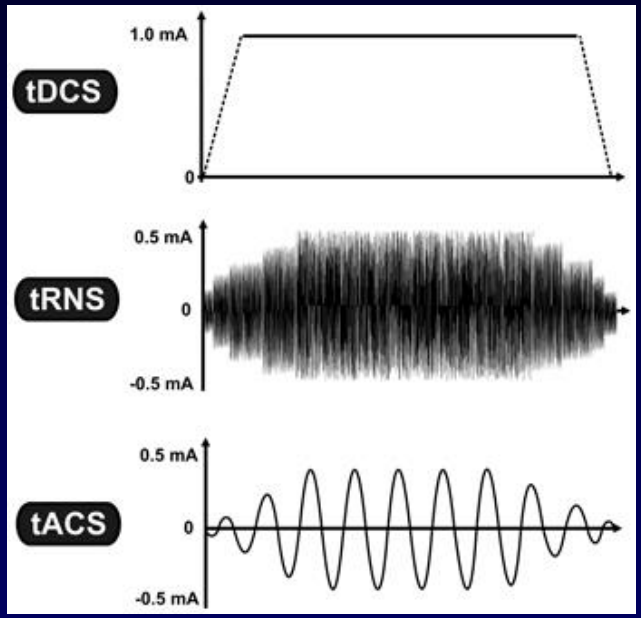
Results: Small improvements in these for the group

tDCS for Tinnitus

Other researchers have used different electrode configurations and stimulation parameters, but their results are equivocal

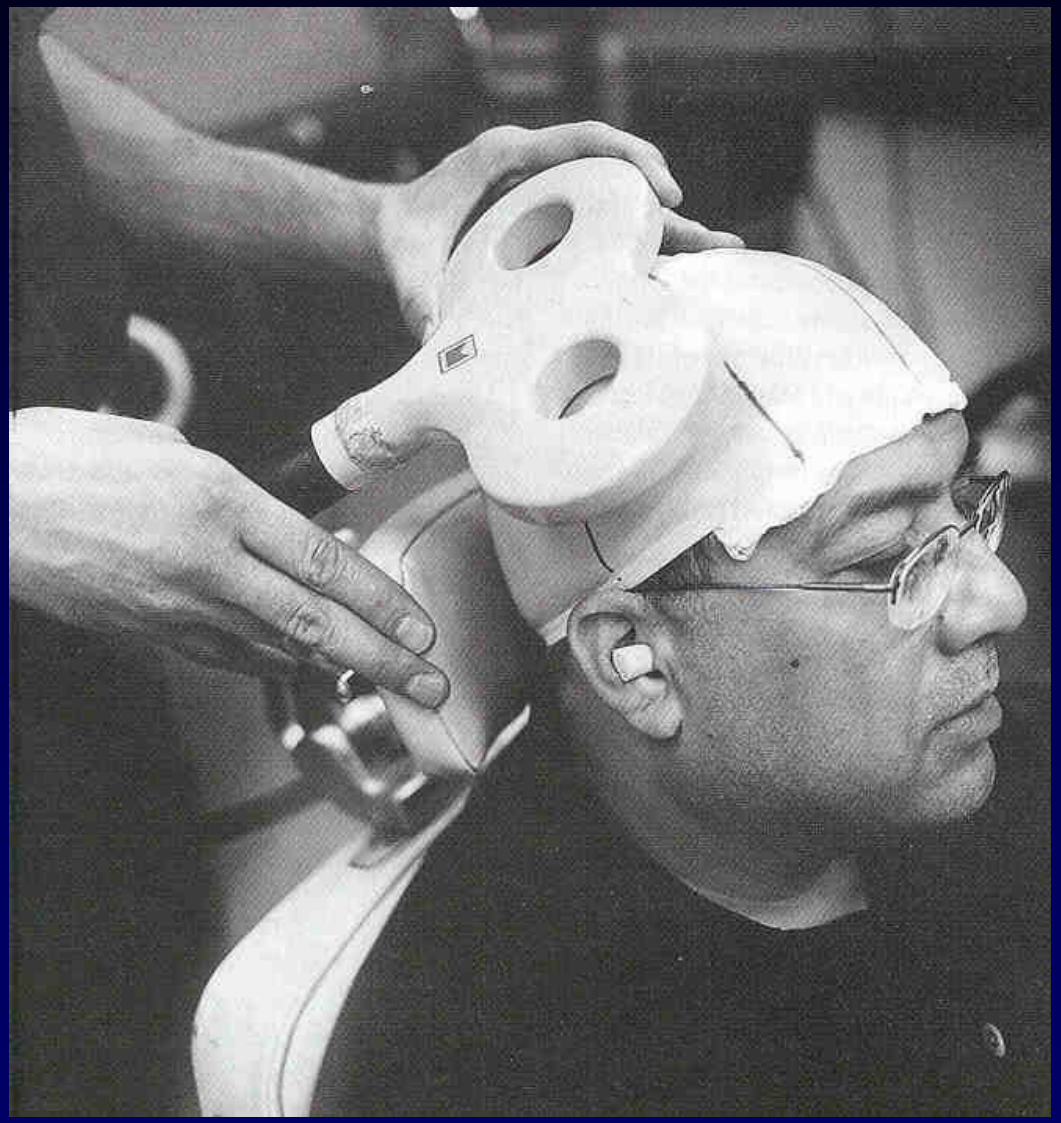
Transcranial random noise stimulation

Transcranial alternating current stimulation



Problem: it is difficult to know where the current travels in (or around) the brain and which structures it might be stimulating

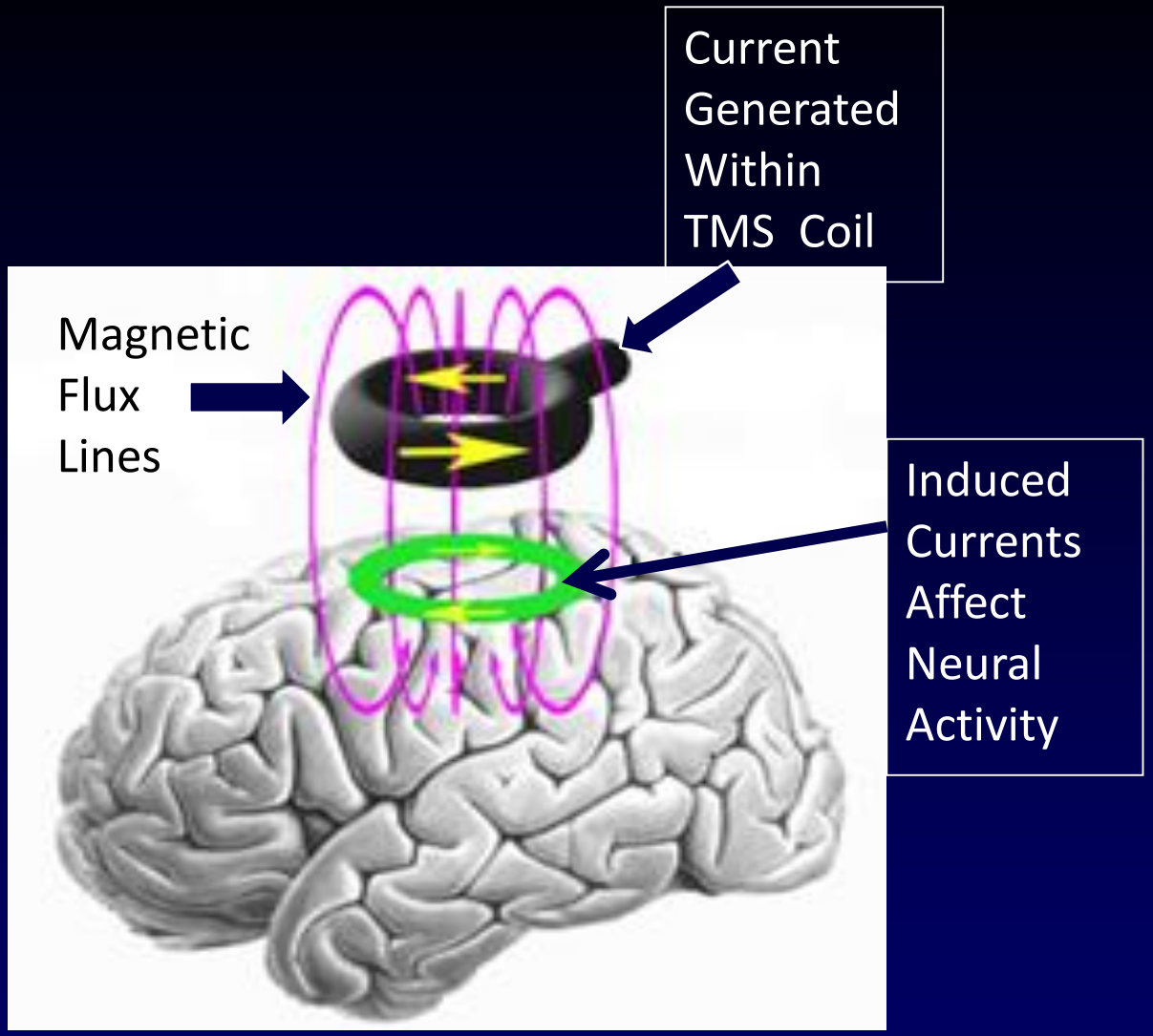
Transcranial Magnetic Stimulation (TMS)



FDA-approved for treatment of Depression

Experimental Applications:

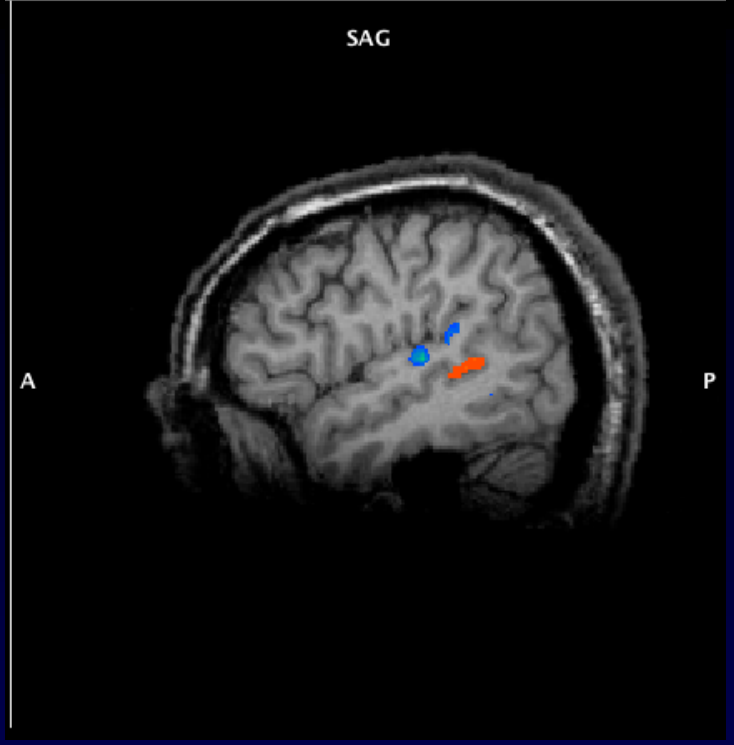
Movement Disorders
Chronic Pain
Tinnitus
Cognitive Impairment
Stroke/TBI Recovery
PTSD

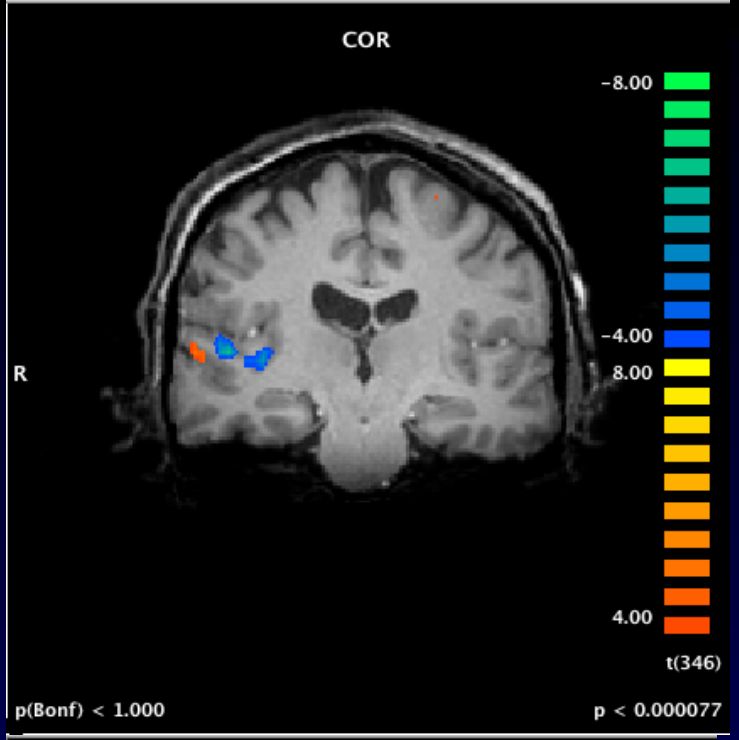

Current Generated Within TMS Coil
Magnetic Flux Lines
Induced Currents Affect Neural Activity

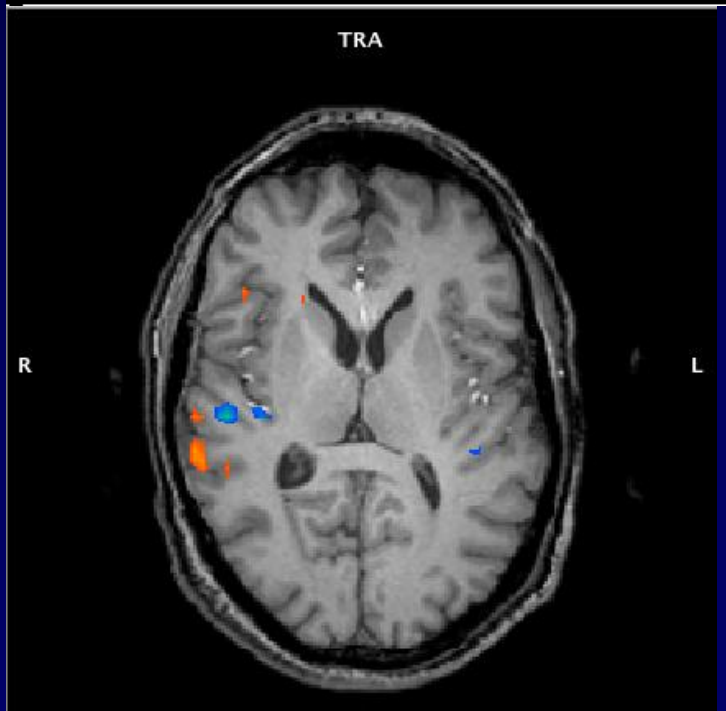
Why use TMS for tinnitus?

Imaging studies (PET and fMRI) demonstrated that tinnitus is often associated with superfluous activity in the auditory system (including aud. cortex)

Repetitive transcranial magnetic stimulation (rTMS) can suppress cortical activity and sensory perception in humans non-invasively and without serious adverse effects







from: R. Folmer *Neuroradiology* 2007;49(8):689-691.

Functional MRI of brain activity associated with tinnitus (this patient perceived 12,000 Hz tinnitus on the right side only)
Blue: masking sounds (white noise) played through headphone to the left ear activate auditory cortex primarily on the right side of the brain.
Orange: this brain area (secondary auditory cortex) is active when the patient hears tinnitus (and the masking sound is OFF)

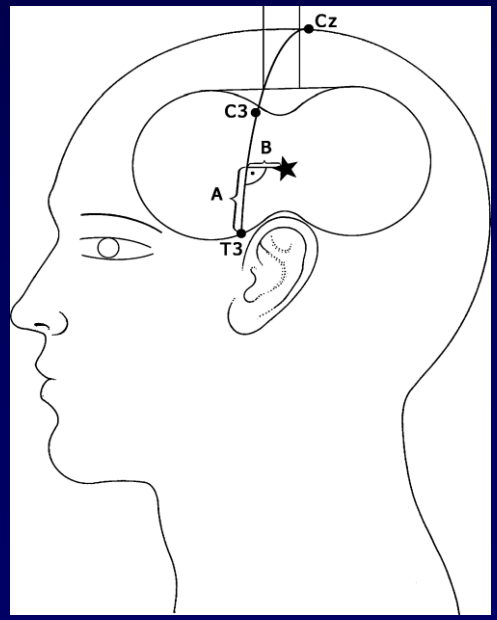
Studies of **TMS for Tinnitus**

• Early studies of rTMS for tinnitus used higher stim rates (10 Hz) during one treatment session.

• More recent studies use 1 Hz rTMS during 5-10+ treatment sessions.

• Initial scalp target: temporal lobe overlying auditory cortex

• More recent studies: either temporal lobe or temporoparietal junction
-- some add 10 Hz rTMS to DLPFC



See: Theodoroff & Folmer, 2013
Otology & Neurotology
for a review

4-year Study at NCRAR VA RR&D Clinical Trial #C7448I

n = 64 participants (all wore earplugs during TMS)

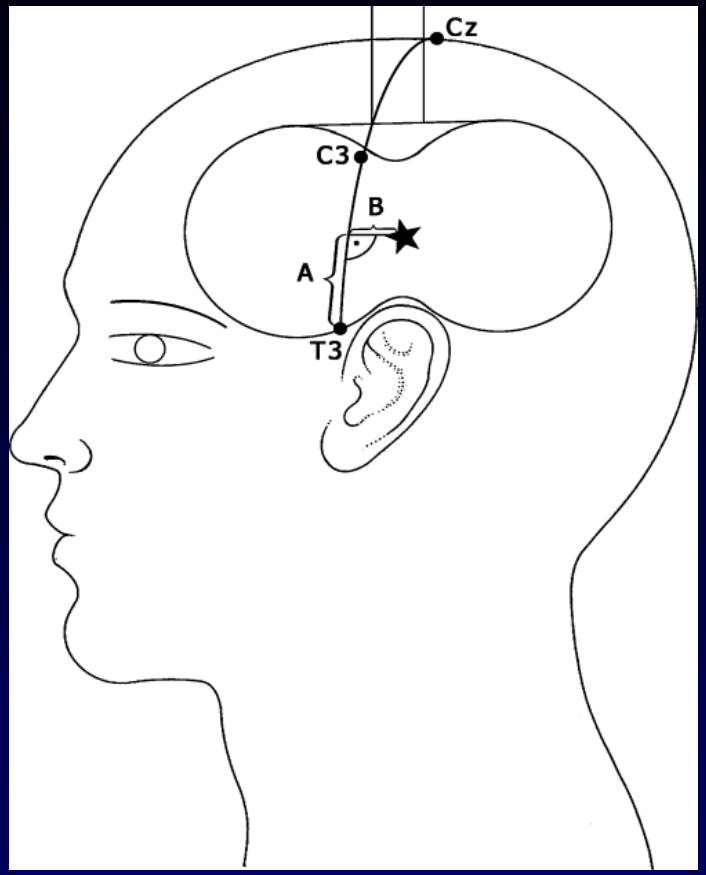
Active Left n=16	Placebo Left n=16	Active Right n=16	Placebo Right n=16

- Double-blind design

2000 pulses of 1 Hz rTMS daily for 10 days
- intensity: 60% of TMS system capacity

Main Outcome: Tinnitus Functional Index (TFI) questionnaire
Others: Tinnitus Handicap Inventory (THI), 0-to-10 scale of self-rated tinnitus loudness, matched loudness, Beck Depression Inventory, State Anxiety Index
Follow-up: 1, 2, 4, 13 and 26 weeks after last TMS session

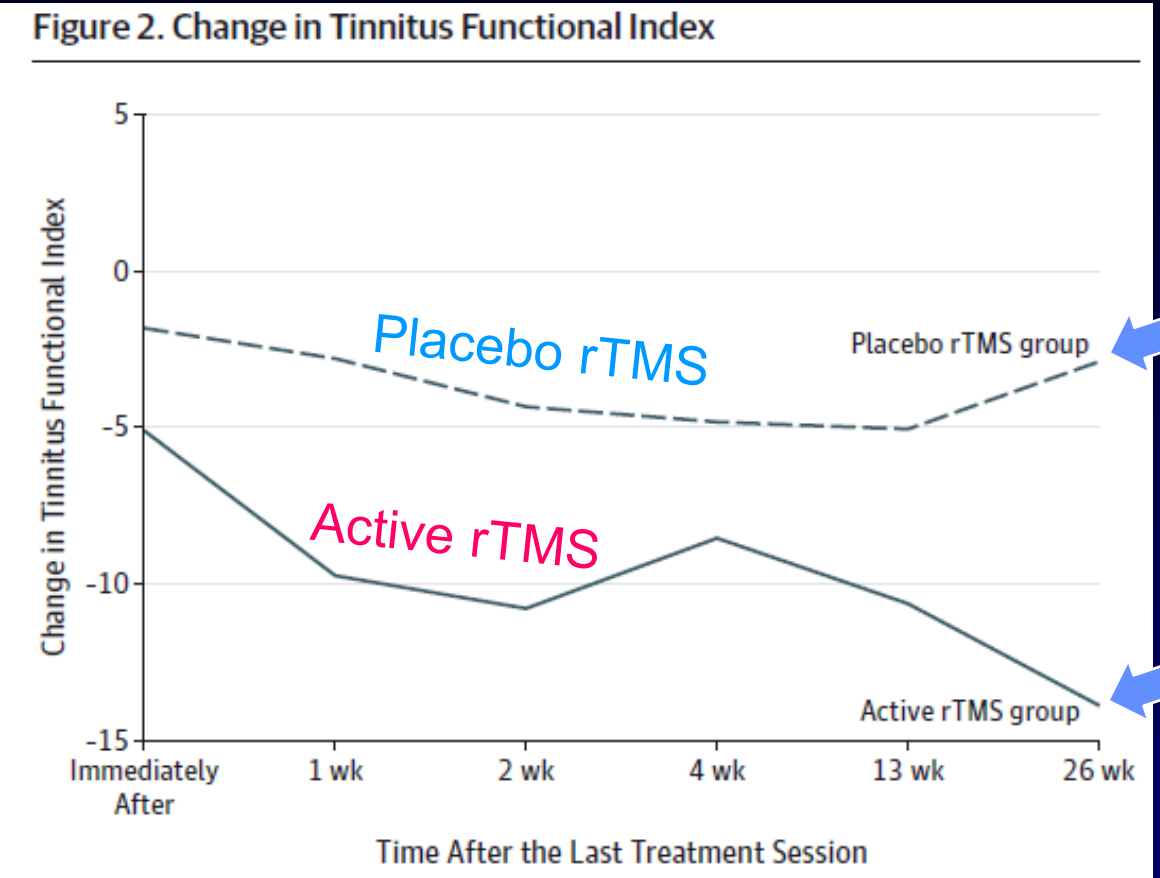
active and placebo Air Film coils



Adapted from: Langguth et al. *Brain Topography* 2006;18(4):241-247.
Method for positioning the rTMS coil over auditory cortex based on MRI data. T3, C3 and Cz are EEG electrode sites defined by the International 10-20 system. From the center of the coil, a line is drawn perpendicularly to the line between T3 and Cz. The distance (2.5 cm) from T3 to the line intersection represents coordinate A, the distance (1.5 cm) from the line T3-Cz to the enter of the coil represents coordinate B. ★ = location of maximum rTMS intensity

Results of Clinical Trial: from Folmer et al., 2015 *JAMA Otolaryngology-Head & Neck Surg*

Change in TFI Score Relative to Baseline



7% decrease;
Effect size= 0.18

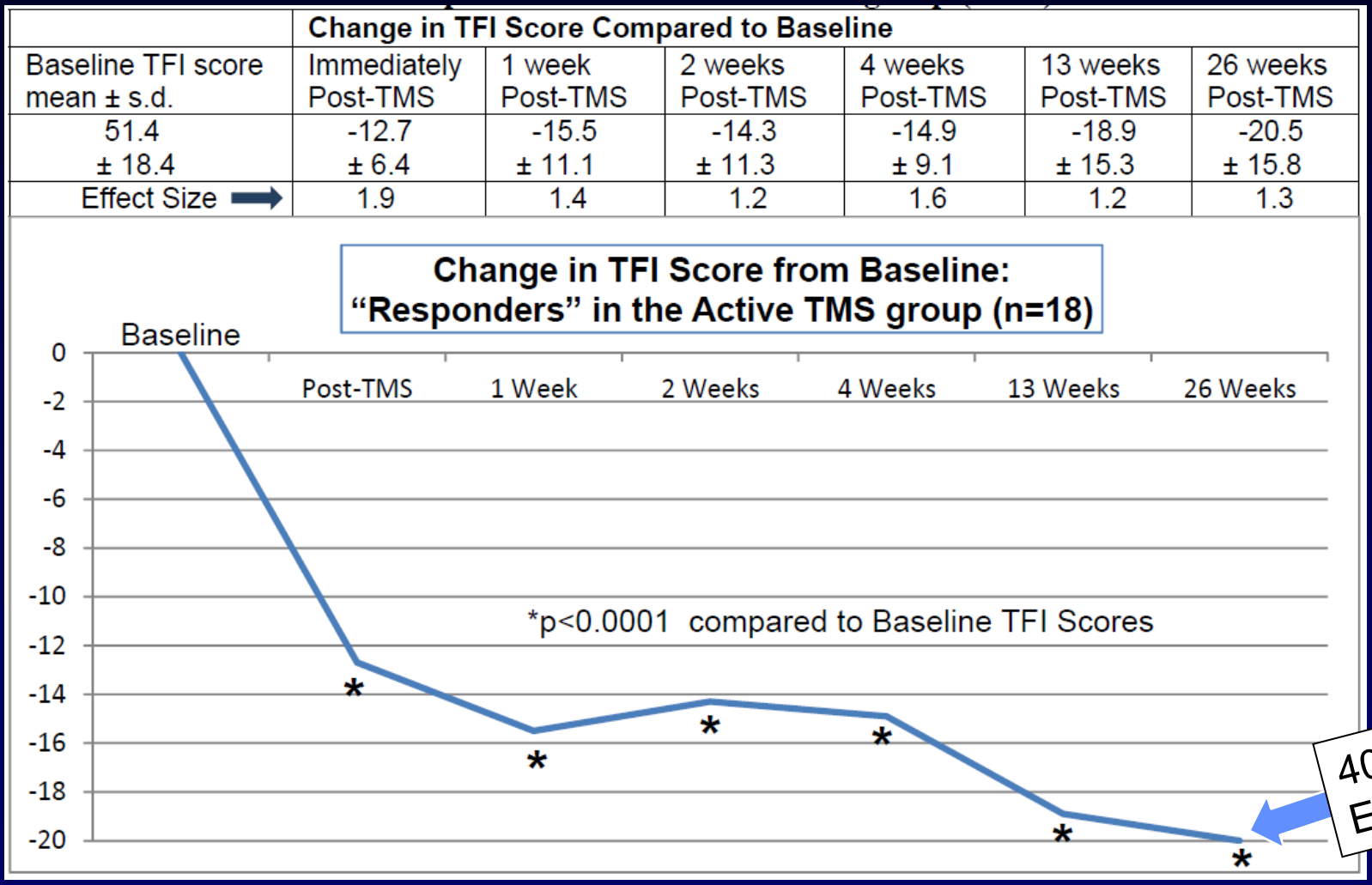
31% decrease;
Effect size= 0.92

Active rTMS Group

18 "Responders" to TMS Treatment out of 32 in group

(Responder = post-TMS improvement of >7 TFI points compared to baseline)

	Change in TFI Score Compared to Baseline					
Baseline TFI score mean ± s.d.	Immediately Post-TMS	1 week Post-TMS	2 weeks Post-TMS	4 weeks Post-TMS	13 weeks Post-TMS	26 weeks Post-TMS
51.4 ± 18.4	-12.7 ± 6.4	-15.5 ± 11.1	-14.3 ± 11.3	-14.9 ± 9.1	-18.9 ± 15.3	-20.5 ± 15.8
Effect Size →	1.9	1.4	1.2	1.6	1.2	1.3

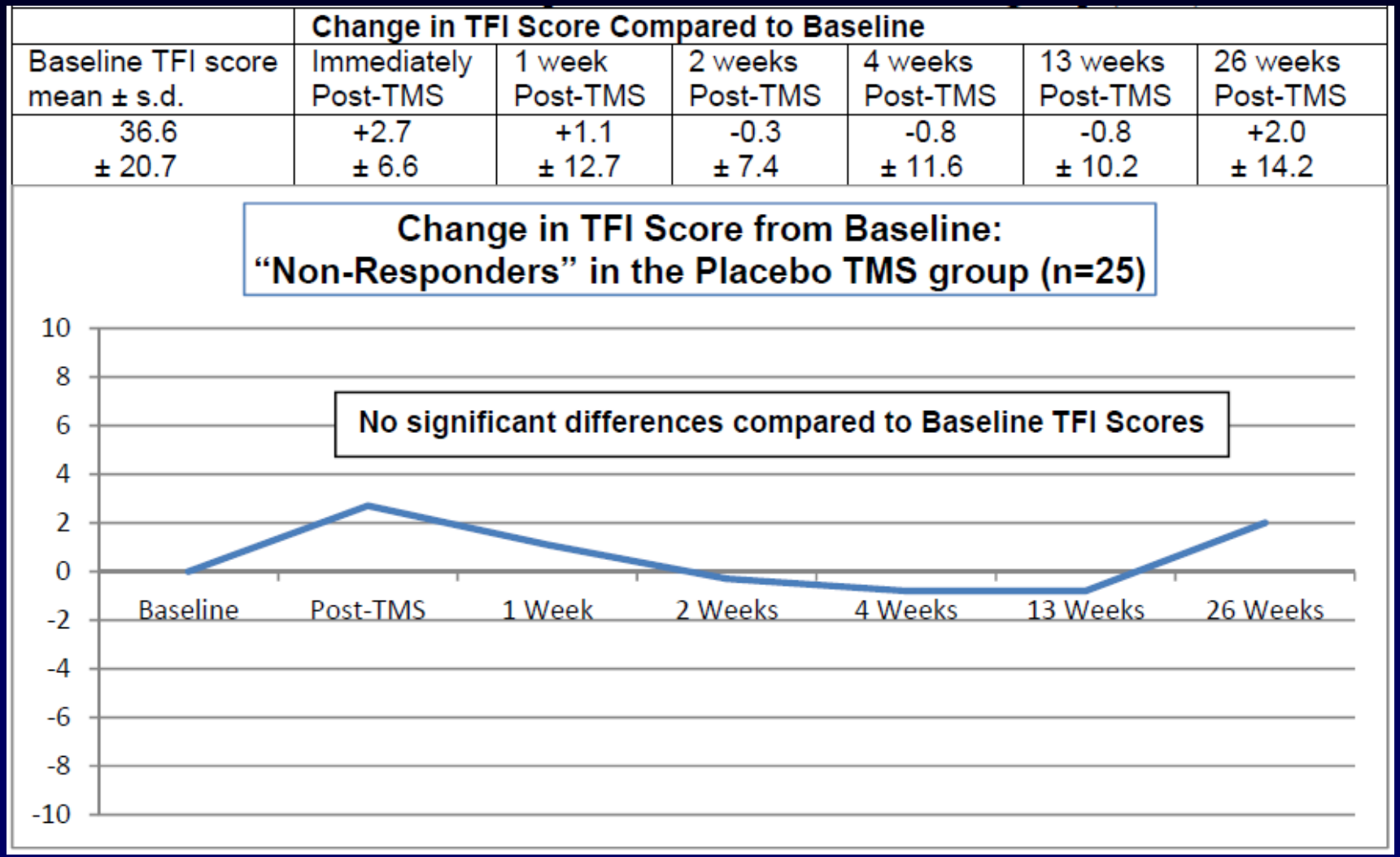


Placebo rTMS Group

25 "Non-Responders" to TMS Treatment out of 32 in group

(Responder = post-TMS improvement of >7 TFI points compared to baseline)

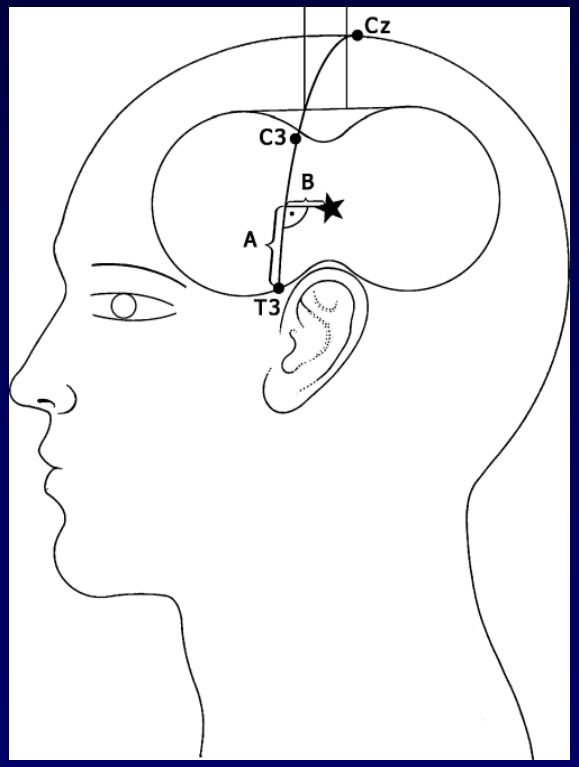
	Change in TFI Score Compared to Baseline					
Baseline TFI score mean ± s.d.	Immediately Post-TMS	1 week Post-TMS	2 weeks Post-TMS	4 weeks Post-TMS	13 weeks Post-TMS	26 weeks Post-TMS
36.6 ± 20.7	+2.7 ± 6.6	+1.1 ± 12.7	-0.3 ± 7.4	-0.8 ± 11.6	-0.8 ± 10.2	+2.0 ± 14.2



At the end of their 6-month follow-up period, subjects who received placebo rTMS were given the option to return for 10 sessions of active rTMS

TMS for Tinnitus - Question

- Why did some participants experience reductions in tinnitus severity, even if their perception of tinnitus did not change very much?



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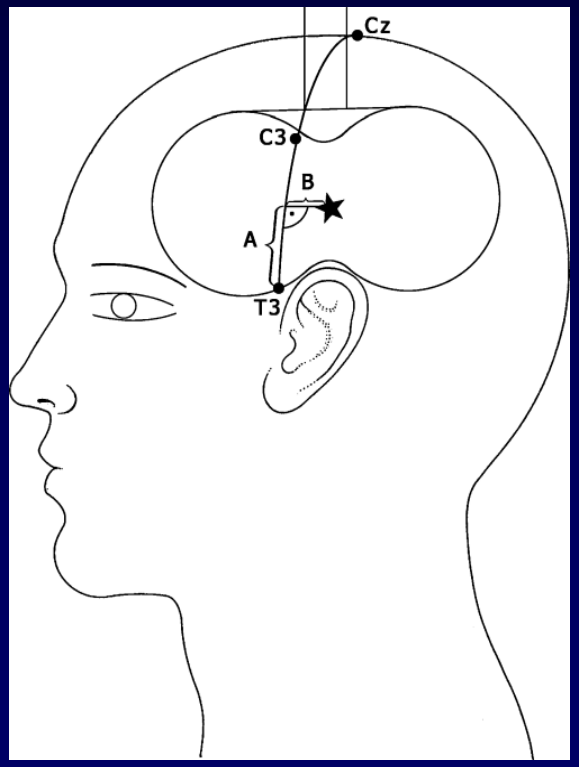

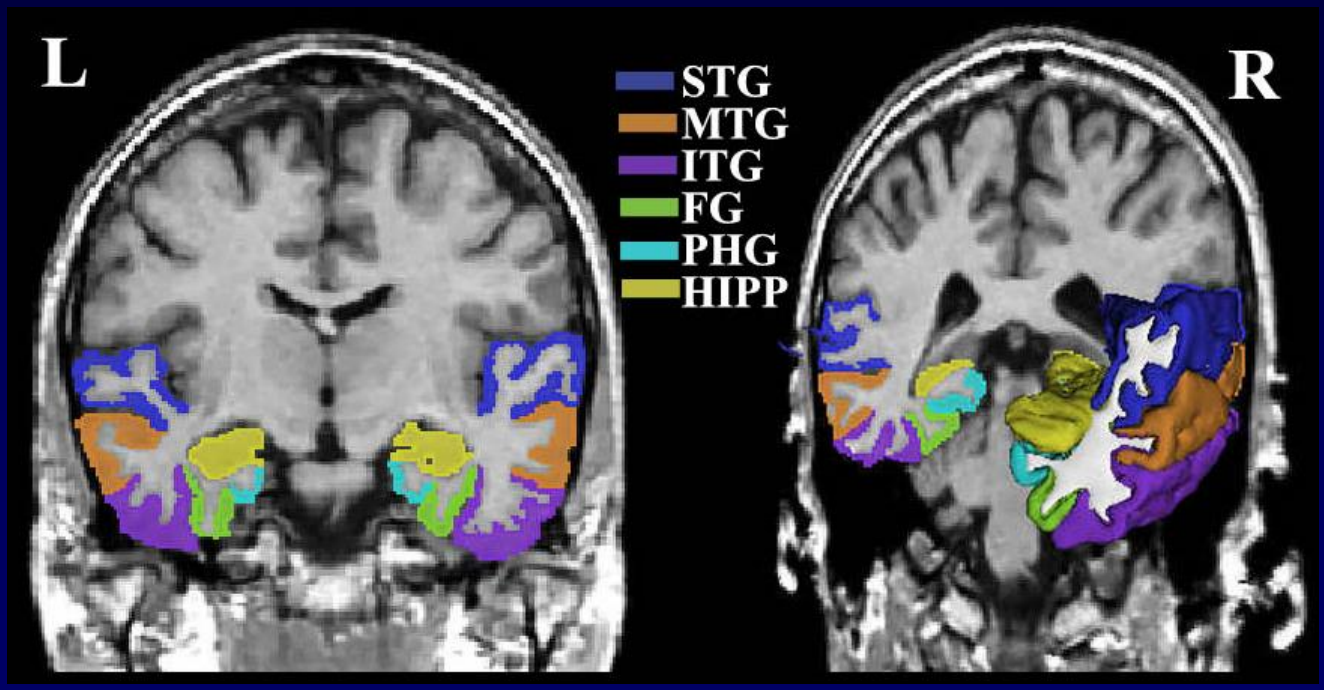

TMS for Tinnitus - Conclusions

- TMS can reduce tinnitus severity for some patients
- Several procedural questions need to be addressed before rTMS should be applied clinically for tinnitus treatment

Conclusions: Neuromodulation Therapies

- Particular neuromodulation therapies affect tinnitus in some individuals.
- The mechanism of the therapeutic action is unknown in most cases.
- If the benefits of a therapy clearly outweigh the associated risks, use it.
- Be cautious and skeptical regarding surgical interventions for tinnitus.
- Obviously, additional research should be conducted on the most promising therapies.

Thank you !