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
r = 0.57  \quad p < 0.0001
Case Report

Chronic Tinnitus following Electroconvulsive Therapy

Robert L. Folmer,¹,² Yongbing Shi,² and Sarah Theodoroff¹

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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.
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


- 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”)*
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
in 5 patients, the electrode was paused within the caudate nucleus to deliver electrical stimulation
in 5 patients, the electrode was paused within the caudate nucleus to deliver electrical stimulation
DBS for Tinnitus - Results

Self-Rated Tinnitus Loudness on 0-to-10 Scale

Pre-stim  During stim

Patient 1  Patient 2  Patient 3  Patient 4  Patient 5

Pre-Stim  During Stim
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

Tyler et al., Scientific Reports, 2017

Used the “Serenity System” that “pairs” VNS with tones

30 patients implanted

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.
# Vagus Nerve Stimulation for Tinnitus

## Surgical Method – Results (change from baseline)

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<td>-7.5</td>
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Vagus Nerve Stimulation for Tinnitus
Surgical Method

- BENEFITS
- RISKS
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
Activate Relief From the Outside In™

With gammaCore® (non-invasive vagus nerve stimulator), there’s a new way to treat pain associated with episodic cluster headache.
“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
Transcranial Direct Current Stimulation (tDCS)

1800 - Alessandro Volta developed the first battery
Transcranial Direct Current Stimulation (tDCS)

9-volt power source

- anode +
- cathode

current flow

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.

**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 induces magnetic flux lines that 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.
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)

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<tr>
<th>Group</th>
<th>Side</th>
<th>n</th>
</tr>
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<tbody>
<tr>
<td>Active Left</td>
<td>Left</td>
<td>16</td>
</tr>
<tr>
<td>Active Right</td>
<td>Right</td>
<td>16</td>
</tr>
<tr>
<td>Placebo Left</td>
<td>Left</td>
<td>16</td>
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<td>Placebo Right</td>
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- 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
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**

**Figure 2. Change in Tinnitus Functional Index**

- **Placebo rTMS**: 7% decrease; Effect size = 0.18
- **Active rTMS**: 31% decrease; Effect size = 0.92

Shown is the change from baseline for the repetitive transcranial magnetic stimulation (rTMS) groups at all posttreatment assessment time points among 64 participants (32 in the active rTMS group and 32 in the placebo rTMS group).
Active rTMS Group

18 “Responders” to TMS Treatment out of 32 in group

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

<table>
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<tr>
<th>Baseline TFI score mean ± s.d.</th>
<th>Immediately Post-TMS</th>
<th>1 week Post-TMS</th>
<th>2 weeks Post-TMS</th>
<th>4 weeks Post-TMS</th>
<th>13 weeks Post-TMS</th>
<th>26 weeks Post-TMS</th>
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<tbody>
<tr>
<td>51.4 ± 18.4</td>
<td>-12.7 ± 6.4</td>
<td>-15.5 ± 11.1</td>
<td>-14.3 ± 11.3</td>
<td>-14.9 ± 9.1</td>
<td>-18.9 ± 15.3</td>
<td>-20.5 ± 15.8</td>
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Effect Size

Change in TFI Score Compared to Baseline

Change in TFI Score from Baseline:
“Responders” in the Active TMS group (n=18)

* p<0.0001 compared to Baseline TFI Scores

40% decrease; Effect size=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)
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.
Why did some participants experience reductions in tinnitus severity, even if their perception of tinnitus did not change very much?
TMS for Tinnitus - Question

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