Basal Ganglia Neuromodulation for Tinnitus Suppression

Audiology Amplification Update XI

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Disclosure

• No personal financial or institutional interest in any of the drugs, materials, or devices discussed in this presentation.

Agenda

• Background
• New Onset Tinnitus Clinical Course
• Basal Ganglia Overview
• Target Selection for Deep Brain Stimulation (DBS)
• DBS of the Striatum: Two Experiments
• Tinnitus Conceptual Model
• Phase I Clinical Trial

Tinnitus – Auditory Phantoms

Auditory Percept Without an External Source

Pathophysiology

• Aberrant Activity Originating from the Auditory System
  • Hyperactivity; Synchronized Oscillations; Reorganized Cortical Maps
  • Brain Networks Acting in Concert

Tinnitus-Related Distress

• Auditory Phantom Qualia Uncorrelated with Tinnitus Severity
  • Loudness Level; Sound Character
• Modulators
  • Limbic System: Reinforcement, Mood, Behavior
  • Others: Eye, Facial, Cervical Movements; Sounds
Tinnitus Functional Index (0 – 100 score)

≥ 70 (very big problem), 60-69 (big problem), 40-59 (moderate problem), 30-39 (small problem), ≤ 29 (not a problem)

Therapeutic Modalities

Reduce Contrast
- Mask Phantom Percept
- Suppress Hyperactivity

Examples:
- Hearing Aids
- Cochlear Implants
- Cortical Stimulation
- Vagal N Stimulation

Reclassify Phantom Percept
- Reduce Salency
- Mitigate Emotional Distress

Examples:
- Tinnitus Retraining
- Cognitive-behavioral therapy
- Neuromonics
- Fractal tones
- Antidepressants

Disrupt Information Conveyance
- Transcranial Magnetic Stimulation
- Direct Electrical Stimulation
- Basal Ganglia Neuromodulation

Auditory-Striatal-Limbic Connectivity

Investigational Therapies

‘Natural History’ of New Auditory Phantoms

Initial Complaints (≤ 3 months)
- Unfamiliar
- Relatively loud
- Commands attention
- Intrusive and annoying

Typical Course (6 – 12 months; 80%)
- Familiar
- Much softer
- Easy to ignore
- Not particularly noticeable

Atypical Course (≥ 1 year; 20%)
- Familiar
- Remains relatively loud
- Still commands attention
- Drives associated emotional and behavioral reactions
General Role of the Basal Ganglia

A multisensory integration system that:
• Detects interpretations of sensory patterns
• Releases responses

Medial Surface of the Basal Ganglia

1. Head of Caudate Nucleus
2. Body of Caudate Nucleus
3. Caudatolenticular Grey Bridge
4. Putamen
5. Tail of Caudate Nucleus
6. External segment of Globus Pallidus
7. Internal segment of Globus Pallidus
8. Amygdaloid Body
9. Nucleus Accumbens
Functional Loops of the Basal Ganglia

- Sensorimotor
  - Sensorimotor (Auditory) and Premotor Cortices
  - Tectum (Colliculi)

- Associative
  - Dorsolateral Prefrontal Cortex
  - Lateral Orbitofrontal Cortex
  - Higher Order Auditory Cortex

- Limbic
  - Limbic and Paralimbic Cortices
  - Hippocampus
  - Amygdala

Basal Ganglia Target Selection

Corticobasal Loops and Interconnectivity

Limbic to Sensorimotor Connections

Diffuse Basal Ganglia Lesion

63 year old otolaryngologist with 40 year history of mostly constant, high-pitched tinnitus. Tinnitus was mostly louder in the left ear, with episodic increases in loudness. Audiogram showed right moderate and left moderate-to-severe sensorineural hearing losses.

Left hemispheric stroke involving 'the more dorsal part of the corona radiata.' In addition there is involvement of the neostriatum, including the body of the caudate and the caudodorsal aspect of the putamen. As such it most likely involves thalamocortical radiations and corticothalamic projection in addition to corticocortical fibers running in the superior longitudinal fasciculus.

- Tinnitus Suppressed Completely
- Hearing Remained Unchanged
A 56-year-old woman underwent deep brain stimulation (DBS) for implantation of the left subthalamic nucleus for medically refractory Parkinson’s disease. Baseline “hissing” tinnitus was reported to be reduced on the first postoperative day. Long-term data showed enduring outcomes.

![Tinnitus Suppressed Substantially](image1.png)

- Tinnitus Suppressed Substantially
- Hearing Remained Unchanged

### Caudate Nucleus (Area LC) – DBS Target

- The caudate is routinely traversed during deep brain stimulation surgery for movement disorders.
  - Opportunity to perform acute caudate stimulation experiments without altering the surgical procedure.
  - Study population with known nigrostriatal dysfunction.
- IRB approval obtained.

### Deep Brain Stimulation System

- **Anchor** Secures Probe to the skull
- **Connector** Establishes link to the Controller
- **Programmer** Communicates with the Controller to customize therapy
- **Controller** Determines parameters for brain stimulation and houses the power source

### Neuromodulation of Auditory Phantoms

- Loudness Level
- Sound Quality
Caudate Nucleus Confirmed by Stealth Trajectory and Microelectrode Recordings

Summary of Deep Brain Stimulation in Area LC Tinnitus Loudness & Sound Qualia Modulation

<table>
<thead>
<tr>
<th>Subject (age/gender)</th>
<th>Side of stimulation</th>
<th>Stimulation parameters</th>
<th>Tinnitus threshold to effect in volts (range)</th>
<th>Tinnitus baseline quality</th>
<th>Tinnitus loudness at stimulation threshold</th>
<th>Area LC Neuromodulation effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (63/m)</td>
<td>Right</td>
<td>185 Hz</td>
<td>90 µsec</td>
<td>5V (0-8) Noise-like</td>
<td>0 Left</td>
<td>2 Right</td>
</tr>
<tr>
<td>B (51/m)</td>
<td>Right</td>
<td>180 Hz</td>
<td>90 µsec</td>
<td>5V (0-8) Cricket-like</td>
<td>0 Left</td>
<td>2 Right</td>
</tr>
<tr>
<td>C (57/m)</td>
<td>Right</td>
<td>180 Hz</td>
<td>90 µsec</td>
<td>10V (0-10) Musical</td>
<td>1 Left</td>
<td>1 Right</td>
</tr>
<tr>
<td>D (67/m)</td>
<td>Right</td>
<td>150 Hz</td>
<td>60 µsec</td>
<td>4V (0-10) Musical</td>
<td>2 Left</td>
<td>2 Right</td>
</tr>
<tr>
<td>E (66/m)</td>
<td>Right</td>
<td>185 Hz</td>
<td>90 µsec</td>
<td>3V (0-8) Tonal</td>
<td>2 Left</td>
<td>2 Right</td>
</tr>
<tr>
<td>F (61/m)</td>
<td>Right</td>
<td>180 Hz</td>
<td>60 µsec</td>
<td>4V (0-10) Musical</td>
<td>0 Left</td>
<td>2 Right</td>
</tr>
<tr>
<td>G (50/f)</td>
<td>Right</td>
<td>10 Hz</td>
<td>60 µsec</td>
<td>2V (0-10) None</td>
<td>0 Left</td>
<td>2 Right</td>
</tr>
<tr>
<td>H (67/f)</td>
<td>Left</td>
<td>10 Hz</td>
<td>60 µsec</td>
<td>4V (0-10) None</td>
<td>0 Left</td>
<td>2 Right</td>
</tr>
</tbody>
</table>

Summary

Sound Quality Modulation

Loudness Level Modulation
Striatal Neuromodulation Effects on Tinnitus

- Baseline loudness of auditory phantoms was modulated, to higher and lower perceptual levels.
  - Mostly Bilateral
- New auditory phantoms may be triggered in a controllable manner.
  - Mostly Contralateral
- No changes to hearing with acute stimulation.
- No seizures up to 10V stimulation.

Tinnitus Conceptual Framework

Key Features

- Instruction on details of phantom percepts are represented in the central auditory system.
- Permission to gate candidate phantom percepts for conscious awareness is controlled by the dorsal striatum.
- Action to attend, reject or accept phantom percepts, and form perceptual habits is decided by the ventral striatum.
- Determination of tinnitus distress severity is mediated through the limbic and paralimbic system-nucleus accumbens-ventral striatum loop.

Phase I Clinical Trial

- NIH/NIDCD Funded (8 – 10 Subjects)
- Key Inclusion Criterion: TFI > 50
- Enrollment Starts Winter 2013
- Specific Aims
  - To estimate the treatment effect size of DBS in area LC on tinnitus severity (TFI score).
  - To assess preliminary safety and tolerability of DBS in area LC (neuropsychological assays).
- Enrollment Starts Winter 2013

Study Flowchart
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