Phantom Sound Tinnitus: Human Brain Imaging, Neural Plasticity, Animal Models and Therapy Web Seminar
Recorded March 28, 2014

Phantom Sound Tinnitus: Human Brain Imaging, Neural Plasticity, Animal Models and Therapy
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Tinnitus Who Gets it?
✓ ~12-14% of Adult have experienced tinnitus
✓ 1% experience significant tinnitus and seek medical treatment

Patients In Tinnitus Clinic (Nicholas-Puel 2006)
✓ Age 55 years (+/- 15); 55% males; 45% females
✓ Age Tinnitus Onset: ~48 years
✓ Presbycusis: 42%
✓ Noise Trauma: 22%
✓ Meniere’s & Meniere’s like: ~10%
✓ Sudden Hearing Loss: 2%
✓ Ototoxicity: 4%
✓ No Hearing Loss: 5.6%???

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Debilitating Tinnitus

“I remember waking up on the morning of April 12, 1994, with a high-pitched squealing in my ears, I thought it was the microwave going off downstairs, but I wasn’t able to find the sound anywhere. Ultimately, I went into a state of depression and couldn’t even work. I have spent the last four years looking for help, but I have been told to learn to live with it.”
Noise-Induced Tinnitus (90 patients)
Patients In Tinnitus Clinic (Nicholas Puel 2006)

- Amplified Music: 40%
- Firearms/Exlosions: 25%
- Alarms: 14%
- Medical treatment: 9%
- Explosion: 9%
- ~50% US combat soldiers develop tinnitus

Hyperacusis-Loudness Intolerance

- Point Prevalence: ~9% (Andersson 2001)
- Patient with primary complaint of tinnitus-40% have hyperacusis (Baguley 2003)
- Patients with hyperacusis-86% have tinnitus
- Gu, Melcher 2010-Most patients with tinnitus and clinically normal hearing had sound tolerance problems

Audiogram: does not detect damage to inner hair cells or spiral ganglion neurons

Insensitivity of the Audiogram to Carboplatin Induced Inner hair cell loss in Chinchillas, Lobarinas et al. 2013, Hearing Res
What Does Tinnitus Cost?
- VA Disability Costs Skyrocketing!

![Cost bar chart]

Traditional Hypothesis
- Tinnitus Perceived in Damage Ear
- Tinnitus Generator in Ear
- Spontaneous Hyperactivity
- Tumor-Cut Auditory Nerve
  - No spontaneous activity-tinnitus persists
  - Ototoxic drugs damage inner & outer hair cells
    - Induces Tinnitus
    - Spontaneous activity reduced
  - Maybe Tinnitus Generated in Brain

Test Hypothesis that Tinnitus Generated in Central Nervous System
- 1994 Positron Emission Tomography (PET)
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Positron Emission Tomography
- Utilizes radioisotope-isotope is unstable and breaks down into a more stable element—when this occurs positrons (positively charged electrons) are given off which are annihilated.
- Annihilation-occurs when positron (+) collides with electrons (-). Disintegration of positron gives off 2 gamma rays that move in opposite directions.
- Gamma rays are detected by PET scanner

Annihilation
1-4 mm

gamma ray → gamma ray

Positron Emission Tomography (PET)
- Functional Imaging-Sound Evoked
- $^{15}$O labeled water-estimate local blood flow a marker of neural activity
- Conditions
  - Rest-Quiet scanner
  - Tone bursts
  - SPM-Statistics

High Level Background Noise Can Mask Tinnitus
PET Scanner Noise ~70 dB SPL, Steady, Low Frequency
Ear Plug+Active Noise Reduction-Little Effect on Threshold

PET THRESHOLD - BOOTH THRESHOLD

CHAGE IN THRESHOLD (dB)

100 1000 10000

FREQUENCY (Hz)
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Normal Hearing Listeners-4000 Hz
- Tone Right Ear versus Quiet
  L & R Auditory Cortex
  L Medial Geniculate
  L Lateral Lemniscus
  L Brainstem Tegmentum
  L Parafloccular Lobe
  Note: Sound to right ear activates both left & right auditory cortex
  Right Ear 4000 Hz

Somatic Tinnitus
- Modulate Tinnitus with Oral Facial Maneuver

Conditions
- Resting Brain Activity
- 2000 Hz tone, 80 dB
- OFM-Jaw Clench

Somatic Tinnitus-Modulate Tinnitus Percept (n=45)
* 65% modulate tinnitus with jaw movement = Trigeminal Nerve (V)
* 60% modulate tinnitus with neck movement = Cervical spinal nerve 1-2
* 50% modulate tinnitus with head rotation = Accessory Nerve (XI)
Oral-Facial Maneuver & Right Ear Tinnitus
1 patient loudness increases, 2 patients loudness decreases
Loudness decrease (Rest-OFM) + Loudness increase (OFM-Rest)
• CBF Significant Change
• Left auditory cortex (BA21, BA41)
• Left hippocampus-limbic region
• Right medial geniculate

Normal Subjects—2000 Hz, 80 dB SPL Right Ear
• Monaural stimulation activates left & right auditory cortex

• L transverse temporal gyrus BA41
• L hippocampus 2000 Hz
• R superior temporal gyrus BA22
• R transverse temporal gyrus BA41
  Auditory cortex

Tone Activation Tinnitus Patients
• 2 kHz tone burst, 80 dB SPL
• Tinnitus patients greater than normal activation in left auditory cortex (BA38 and BA41)-Hyperactive
• Patients normal hearing 2 kHz
• Patients hearing loss 4 kHz

Right 4000 Hz
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- Somatosensory Invasion of Deaf Auditory Cortex
- Activation by touch to face, neck, shoulder

Auditory Cortex

Gaze-Evoked Tinnitus
• Unusual complication-Vestibular Schwannoma surgery
• Tinnitus-loudness and pitch change in lateral eye gaze
• Found 125 patients-Gaze-Evoked Tinnitus-Acoustic Neuroma Newsletters
• Gaze-evoked tinnitus is common!

Patient with Acoustic/Vestibular Schwannoma

Contrast-enhanced CT scan
✓ 44 year old woman, operated on 2/80 for 3.6 cm right acoustic schwannoma
✓ GET on right lateral gaze
✓ (Whittaker, 1982, 1983)
Single subject SPM analysis

- Left Acoustic neuroma
- Gaze to left alters tinnitus loudness

- Activation-Angular Gyrus Next to Auditory Cortex

3 Subject SPM, R Acoustic Neuroma
Activation vestibular nuclei & cochlear nuclei

Lidocaine & Tinnitus!
- Otology-Suppresses Tinnitus!
- Cardiology-Induces Tinnitus!
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Lidocaine Increases & Decreases Tinnitus Loudness
- Reduction in tinnitus decrease in rCBF
- Increases in tinnitus increase in rCBF

Right Auditory Cortex-Only region that shows a change in rCBR with change in tinnitus loudness

Model/Hypotheses
• Tinnitus-Loss of Cochlear Input
• Cochlear Damage Alters Central Auditory System
• Abnormal Plasticity
• Analogous to Phantom Limb Pain
• Gain Control: Brain Turns Up Volume Control to Compensate for Hearing Loss

Tinnitus & Hyperacusis Mechanisms
Animal Models
• Physiology
• Biochemical
• Molecular
• Behavior
Animal Model of Tinnitus (SIPAC)
- **Schedule Induced Polydipsia (SIP)**
- Deliver food pellet 1/min-drives drinking in food deprived rats
- **Avoidance Conditioning (AC)**
- Drinking (Licks) is put under stimulus control (pairing sound with foot shock)

Behavioral Model of Tinnitus
Schedule Induced Polydipsia-Avoidance Conditioning

Quiet = Lick-for-Water
Food Pellet 1/minute

![Animal Model of Tinnitus](image)

![Behavioral Model of Tinnitus](image)

![Graph](image)
Salicylate-Dose-Response Study

- Licks-in-quiet decrease with increase in salicylate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Saline</th>
<th>50mg/kg</th>
<th>100mg/kg</th>
<th>150mg/kg</th>
<th>350mg/kg</th>
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<tbody>
<tr>
<td>Lick Count</td>
<td>0</td>
<td>1000</td>
<td>2000</td>
<td>3000</td>
<td>4000</td>
<td>5000</td>
</tr>
</tbody>
</table>

Licks in Quiet

Memantine (NMDA) Antagonist-Tinnitus Treatment

- Memantine Causes Slight Increase Licks in Quiet
- Not Significant; Not Dose Dependent

Scopolamine, Anti-Cholinergic-Tinnitus Treatment

1 mg/kg-Slight Increase Licks in Quiet, Not Significant
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Potassium Channels
- Greatest Ion Channel Diversity
- Important targets for therapy
- Kv7.2-7.5 in cochlea

<table>
<thead>
<tr>
<th>Drug</th>
<th>Kv7.2-7.5</th>
<th>Kv7.1</th>
<th>BK (KCa)</th>
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<tbody>
<tr>
<td>Maxipost</td>
<td>Positive modulator (activation)</td>
<td>Negative Modulator (inhibition)</td>
<td>Positive modulator (activation)</td>
</tr>
<tr>
<td>(BMS 204342)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-Maxipost</td>
<td>Negative modulator (inhibition)</td>
<td>Negative Modulator (inhibition)</td>
<td>Positive modulator (activation)</td>
</tr>
</tbody>
</table>

**Effects of Maxipost (n=6)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Average Licks-in-Quiet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td></td>
</tr>
<tr>
<td>5 mg Maxipost</td>
<td></td>
</tr>
<tr>
<td>10 mg Maxipost</td>
<td></td>
</tr>
<tr>
<td>SS + 5 mg Maxipost</td>
<td></td>
</tr>
<tr>
<td>SS + 10 mg Maxipost</td>
<td></td>
</tr>
</tbody>
</table>

* tinnitus

**Effects of R-Maxipost (n=6)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Average Licks-in-Quiet</th>
</tr>
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<tbody>
<tr>
<td>Baseline</td>
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</tr>
<tr>
<td>Saline</td>
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</tr>
<tr>
<td>5 mg R-Maxipost</td>
<td></td>
</tr>
<tr>
<td>10 mg R-Maxipost</td>
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</tr>
<tr>
<td>SS + 1 mg R-Maxipost</td>
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<tr>
<td>SS + 3 mg R-Maxipost</td>
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<tr>
<td>SS + 5 mg R-Maxipost</td>
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<tr>
<td>SS + 10 mg R-Maxipost</td>
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</table>

* tinnitus
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What are the Neural Correlates of Tinnitus?
- Identify Neural Changes in Auditory Cortex During Salicylate Induced Tinnitus?
- Use 16 Channel Microwire Electrodes to Record from Neurons in Auditory Cortex of Awake Rats

Distortion Product Otoacoustic Emission (DPOAE) Frequency Dependent Loss in Cochlear Amplifier
- Large Loss above and below 16 kHz
- Small loss near 16 kHz

Salicylate Suppresses CAP from Inner Ear
Recording From Awake Rat

Single Unit and Evoked Potential Recorded from Same Electrode in Awake Rat

Effect of Salicylate on Evoked Response & Spike Awake Rat Treated with 300 mg/kg Salicylate

- Pre-Salicylate
- Post-Salicylate

EVP Increases
S/N Ratio Improves
Spontaneous Rate Decreases
Driven Rate Unchanged
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**Driven Spike Rate Increases after Salicylate Decreases 2 days Post-Treatment**

- Pre
- Post 60'
- Post 180'
- Post 240'
- Post 2 day

<table>
<thead>
<tr>
<th>Frequency (kHz)</th>
<th>Spikes/sec</th>
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<tr>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>100</td>
<td>120</td>
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</tbody>
</table>

- Time Post-Salicylate (250 mg/kg)

**Auditory Cortex**
Salicylate Reduces Spontaneous Discharge Rate (n=10 units)

<table>
<thead>
<tr>
<th>Time</th>
<th>Spikes/second</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>30</td>
</tr>
<tr>
<td>2 h</td>
<td>20</td>
</tr>
<tr>
<td>1 d</td>
<td>10</td>
</tr>
<tr>
<td>2 d</td>
<td>5</td>
</tr>
<tr>
<td>3 d</td>
<td>0</td>
</tr>
</tbody>
</table>

**Salicylate Increases Cortical Field Potential Greatest Effect 16-20 kHz**

- Pre
- Post SS (1 hr)
- Post-1h

<table>
<thead>
<tr>
<th>dB SPL</th>
<th>Normalized AC Amp</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.5</td>
</tr>
<tr>
<td>70</td>
<td>1.0</td>
</tr>
<tr>
<td>90</td>
<td>1.5</td>
</tr>
<tr>
<td>100</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Systemic Salicylate

*CAP reduced but little Effect on Inferior Colliculus

*Some Neural Amplification Between Auditory Nerve & Inferior Colliculus

Salicylate on Round Window-CAP Reduced

* CAP and Auditory Cortex Response Reduced

Use Startle Reflex-Behavioral Test of Hyperactivity
Startle Reflex Amplitude

Salicylate-Enhanced Startle Reflex Amplitude

Salicylate-Induced Shifts in Tuning Curve CFs

- Low CFs shift up to 16 kHz
- High CFs shift down to 16 kHz
- Tinnitus pitch: 10-20 kHz
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Jastreboff Neurophysiological Model

- Auditory and Other Cortical Areas
- Auditory Subconscious
- Limbic System
- Reactions
- Auditory Periphery
- Autonomic Nervous System

Wallhauser-Frank 2003, Exp. Brain Res.
Salicylate-Induces c-fos expression
- AI, AAF, P: auditory cortex
  - Perception
- CeA, LA: amygdala
  - Emotion, Attention

Record from Lateral Amygdala - Systemic Salicylate
- Salicylate Enhances Local Field Potentials
Salicylate Alters Tuning of Auditory Neurons in Amygdala

* Low CFs shift up to 16 kHz
* High CFs shift down to 16 kHz

One Multiunit Cluster Tuning Curve

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Tinnitus Model

* Spontaneous rate-little change
* # Neurons "tagged" with 16 kHz CF increased
* Tinnitus-Total Discharge in Quiet
  Spontaneous rate x # 16 kHz neurons

Does Amygdala Influence Response of Auditory Cortex?

* Infuse Salicylate into Amygdala; Record from Auditory Cortex
* No Change in Threshold
  *Auditory Becomes Hyperactive*
Peripheral Effects of Salicylate

- Frequency Dependent Loss
- Greatest Loss at Very Low and Very High Frequencies

Central Effects of Salicylate

- CFs Shifts to Mid-Frequencies (Peripheral + Central Effect)
- Amygdala Further Increases Gain (Hyperactive)

Symptoms Associated with Tinnitus

- Stressed Linked to Tinnitus (Niger et al., 2008)
- High Depression & Anxiety Scores (Andersson et al., 2000)

Is a High Dose of Salicylate Stressful?

- Salicylate Increases Corticosterone Stress Hormone
- Salicylate Levels Increases in dose dependent manner
- $\geq 150$ mg/kg Salicylate induces tinnitus/hyperactivity
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Corticosterone Levels Normal 24 h Post-Salicylate
- Corticosterone Stress Hormone High 2 h Post-Salicylate
- Corticosterone levels decline to baseline ~24 h

Noise Induced Hearing Loss in Left Ear
- Retain Normal Hearing in Right Ear
  - Noise Expose Left Ear
  - 126 dB, 12 kHz Narrow Band Noise, 2 hr

Noise-Induced Tinnitus Assessed with SiPIC
Unilateral Exposure 120 dB, 2 h, OBN Centered at 11 kHz
- Noise Induced Tinnitus
  - Persistent
  - Transient
**2 Alternative Forced Choice Tinnitus Paradigm**

**Behavior Schematic**

<table>
<thead>
<tr>
<th>Normal Behavior</th>
<th>Tinnitus Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Diagram" /></td>
<td><img src="image" alt="Diagram" /></td>
</tr>
</tbody>
</table>

In ‘Quiet’ the rat is trained to respond to the right feeder.

If rat has tinnitus on ‘Quiet’ trials, it shifts its response to the left feeder.

**Expose: 16 kHz, 110 dB, 40 min**

![Graphs](image)

**Expose: 16-20 kHz noise, 96 dB, 96 h**

![Graphs](image)
Current Treatments for Tinnitus
- Hearing Aids
- Sound Generator
- Cochlear Implants
  - (75-80% suppress)

• Future
- New Pharmaceuticals
- Transcranial Magnetic Stimulation
- Brain Electrical Stimulation

Frequent Comments of Tinnitus Patients
• Why Haven’t You Found a Cure Yet?

• How much funding goes to Tinnitus Research?

2006 Research Dollars for Tinnitus
• $4.3 M Abrams Tank
Thanks to my collaborators:
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