The Neuroscience of Tinnitus: Cochlea to Cortex

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“Translating Tinnitus Research Findings into Clinical Practice”
Portland, Oregon, October 4th 2017
What neurons in the hearing loss region do generates tinnitus, and stopping what they do suppresses it.
Then why do 15% of tinnitus sufferers have normal audiograms?

Adapted from Kujawa and Liberman

_Hypothesis:_
Loss of ribbon synapses on high threshold auditory nerve fibers may predispose to tinnitus

Adapted from Kujawa and Liberman

_J. Neurosci 2009_
Cochlear Modeling of the Envelope Following Response @ 5 kHz Suggests a Role for Hidden Hearing loss in Tinnitus Subjects with Normal Audiograms

(All subjects have hearing thresholds <20 dB HL to 10 kHz)

- Severe high-threshold fiber loss at 5 kHz will reproduce the EFRs of control subjects with poor AM coding ability;
- An additional loss of ~30-60% of low-threshold fibers was needed to reproduce the EFRs of tinnitus subjects
- Why are these fibers important for tinnitus? (Because they have high rates of spontaneous firing in quiet - will return to this topic)

Animal models of Tinnitus

Gap-Startle Method (GPIAS)

If tinnitus fills the gap, the startle response returns (gap/no gap ratio = 1)

Conditioning Methods (one example)

Low-pitched sound (<3 kHz): go to black to avoid foot shock

High-pitched sound (>4 kHz): go to white to avoid foot shock

Shuttle box

After tinnitus induction, test preference in silence; if the animal hears tinnitus (which is a high-pitched sound), it will prefer the white box

Yang & Bao et al. PNAS 2011

Jeremy Turner et al. (2006)

*Behav. Neurosci.* 120, 188–195.
Tinnitus neural activity begins in the cochlear nucleus

James Kaltenbach (Wayne State University, now the Cleveland Clinic)


Susan Shore (University of Michigan)

Results from the Susan Shore Laboratory

More bimodal intervals give LTP than LTD in animals with tinnitus

Spontaneous and synchronous neural activity is increased in tinnitus animals

Fusiform cell spontaneous activity is increased or decreased depending on the order and timing of bimodal inputs

Wu, Martel and Shore (J. Neurosci 2016)
Koehler and Shore (J Neurosci 2013)
Why is the loss of low threshold fibers important for tinnitus?

Because the **high rates of spontaneous firing of these fibers** may preserve the balance of excitation and inhibition in the DCN

Possible mechanisms:

Homeostatic plasticity downregulates inhibition to compensate for decreased ANF activity*
Decreased feedforward inhibition unleashes STDP on apical dendrites
Other inhibitory cell types or circuits in the DCN may be affected
Neuromodulation

*Driven responses also increase: “Central gain”*
A PUZZLE:
Decreased GABAergic and glycinergic inhibition in the VCN, DCN, and IC should be expressed in the thalamus

Instead Sametsky et al (2016) found:

(1) *Increased* tonic inhibition in a *subset* of MGB neurons, mediated by extrasynaptic GABA$_A$ receptors;

(2) These neurons switched to a burst firing mode

Bursting of MGB neurons may drive oscillations over the cortex:

Delta oscillations (< 4 Hz) recorded over auditory, temporal, parietal, sensorimotor, and limbic cortex of human tinnitus patients


Synaptic rescaling:

Salient features of sensory information are represented in interlaminar (layer to layer) interactions. Sensory codes of lesser salience activate these interactions weakly and are thus "deleted" by inhibition ascending from neurons in deep layers bursting at delta frequencies.

(Paraphrase of Carracedo et al 2013)

Applied to Tinnitus:

Low frequency oscillations distribute over several brain regions, disinhibiting local networks and integrating the tinnitus signal within these networks.

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**Trace recorded from layer 5**
(Somatosensory/parietal slice)

Neuromodulation affects whether one sees interlaminar interactions and delta rhythms

Rat and human slice preparations
Deafferentation

Reduced inhibition increases SFRs and aberrant synchrony in subcortical auditory pathways

Low frequency oscillations distribute over several brain regions, disinhibiting local networks and integrating the tinnitus signal within these networks

Aberrant tinnitus signal (neural synchrony) evokes hyperpolarization and low-frequency bursting activity in a subset of thalamic MGB neurons

Tinnitus may provide a window on normal auditory information processing

Omissions:
- Downstream processing
- Olivocochlear Pathway
- Neuromodulation
- Time course
- Centralization
Changes in Primary Auditory Cortex

Tinnitus brain network activity affects electrocortical responses evoked by sound

(1) Diminished tonic intracortical inhibition alters tonotopic frequency organization in the hearing loss region

(2) Changes in the 40-Hz ASSR track residual inhibition depth

Roberts et al 2015 *Hearing Research*

(3) Modulation of ASSR and N1 responses by attention is attenuated in tinnitus

(4) Effects of auditory training are modified

Paul Bruce and Roberts 2014 *Neural Plasticity*


Roberts Bosnyak & Thompson (2012) *Frontiers in Systems Neuroscience*
Why is hidden hearing loss important?

Can explain tinnitus without audiometric threshold shift

Might explain threshold shift without tinnitus

Tinnitus in adolescents

28.8 % of 170 adolescents in a private school in São Paulo Brazil experienced a psychoacoustically verified persistent tinnitus

Their audiograms (0.25 – 16 kHz) and otoacoustic emissions (to 12 kHz) were completely normal

But their sound level tolerance was reduced by 11.3 dB

Scientific Reports 2016
(Sanchez, Moraes, Casseb, Cota, Freire & Roberts)

Loss of inhibition in central auditory pathways?
Homeostatic plasticity triggered by hidden hearing loss?
Fear of sound?
One-year follow-up (n = 54)
(Sanchez & Roberts ARO 2018 Submitted)

<table>
<thead>
<tr>
<th>Loudness Discomfort Level</th>
<th>dB SPL</th>
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<tbody>
<tr>
<td>1</td>
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<tr>
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<td>105</td>
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<tr>
<td>3</td>
<td>110</td>
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<td>4</td>
<td>115</td>
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Main effect p = 0.0086

1 = repeaters (6/14, 42.9%)
2 = no tinnitus either test
3 = recovered tinnitus (8/14, 57.1%)
4 = new tinnitus

There was a high prevalence of risky listening habits in these adolescents (Study 1 data):

Study 2 parties and raves:
42.3% (Groups 2,3)
62.5% (Groups 1,4)

(but n.s.)
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