The Neuroscience of Tinnitus: Cochlea to Cortex

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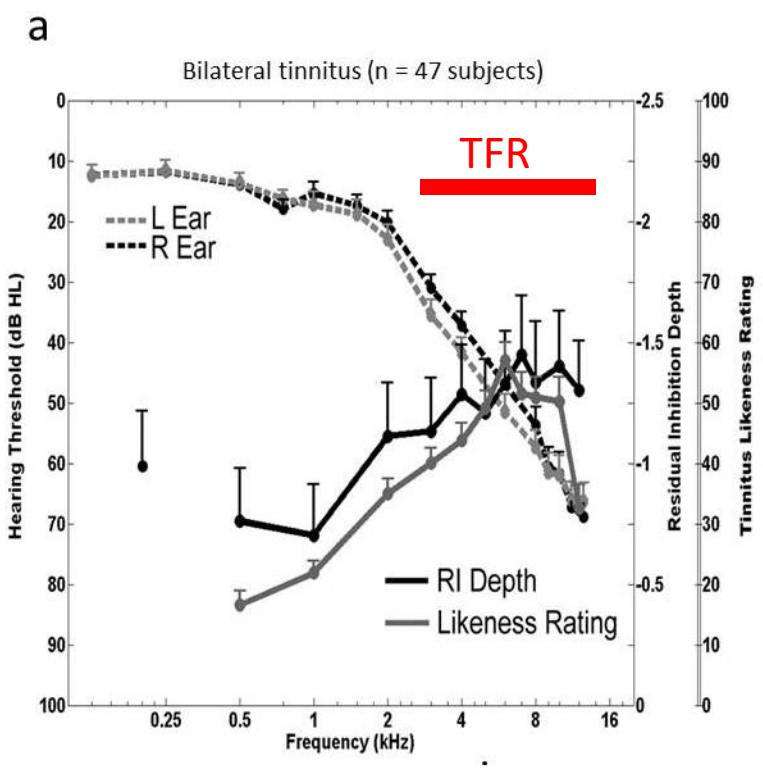
Jos Eggermont - Arnaud Noreña - Susan Shore - Donald Caspary
Nathan Weisz- Tim Griffiths – Tanit Sanchez

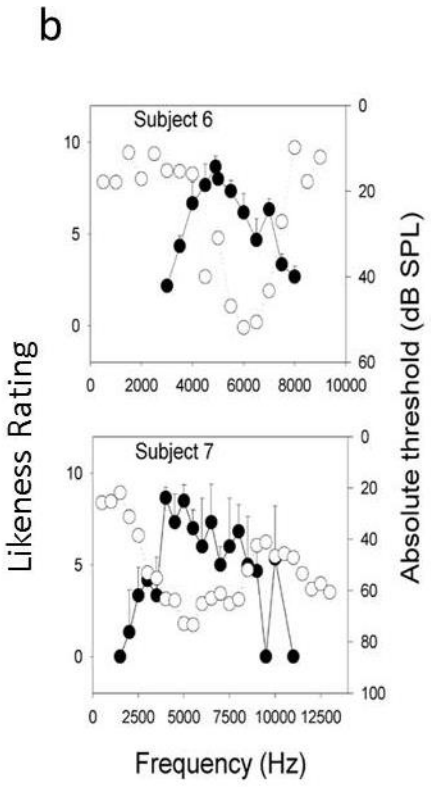
NCRAR Conference
"Translating Tinnitus Research Findings into Clinical Practice"
Portland, Oregon, October 4th 2017

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada
NSERC CRSNG
AMERICAN TINNITUS ASSOCIATION
TINNITUS RESEARCH INITIATIVE
European Commission ERASMUS MUNDUS

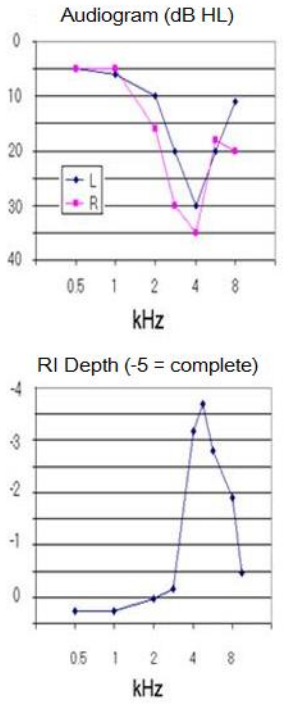
Initiating Condition: Deafferentation



Roberts, Moffat, Baumann, Ward, & Bosnyak (2008) *JARO* 9:417-435



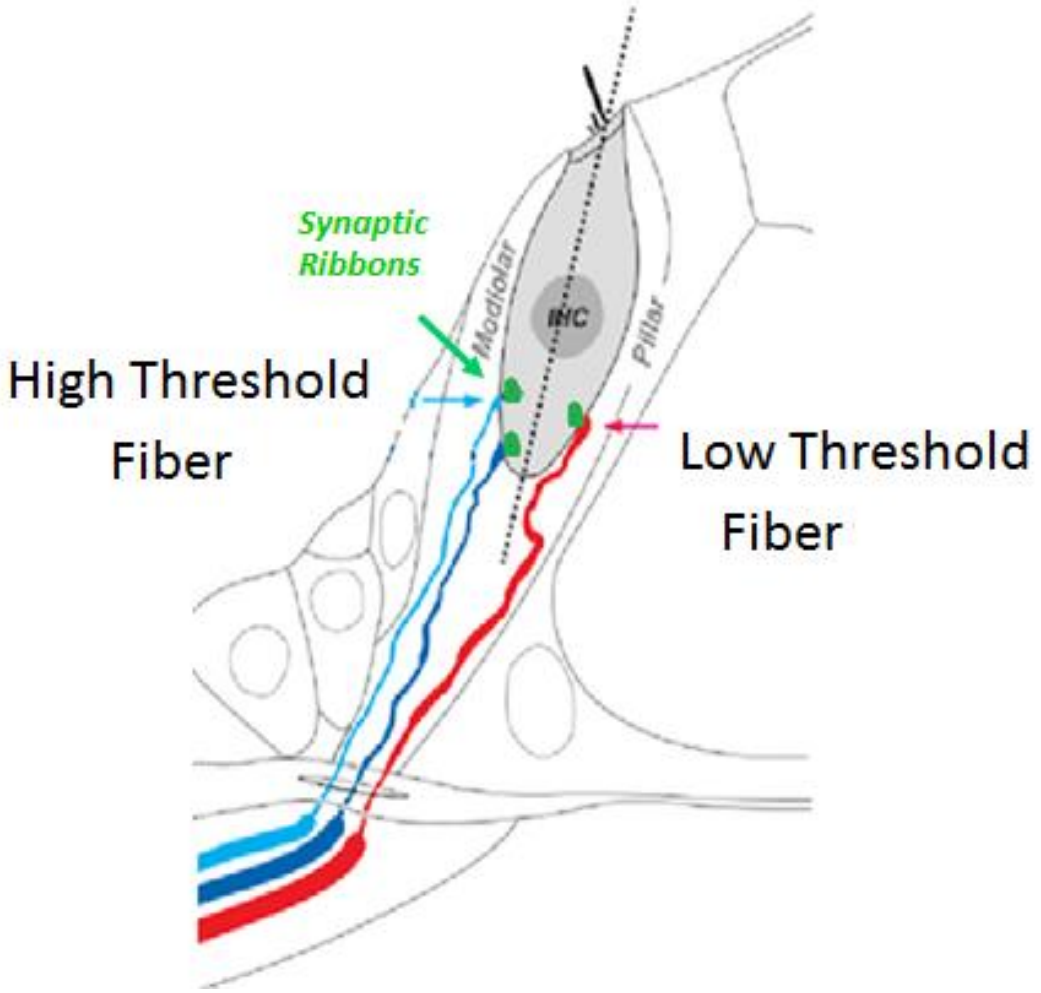
Noreña, A., Micheyl, C., Chery-Croze, S., & Collet, L. (2002). *Audiology and Neurootology, 7,* 358–369.



Roberts and Platt (1998)
(From Roberts et al, 2010)

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?

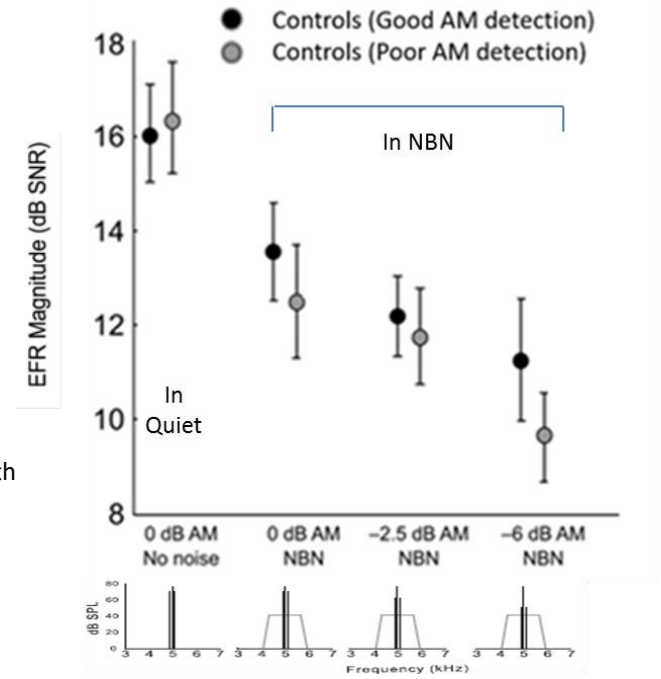


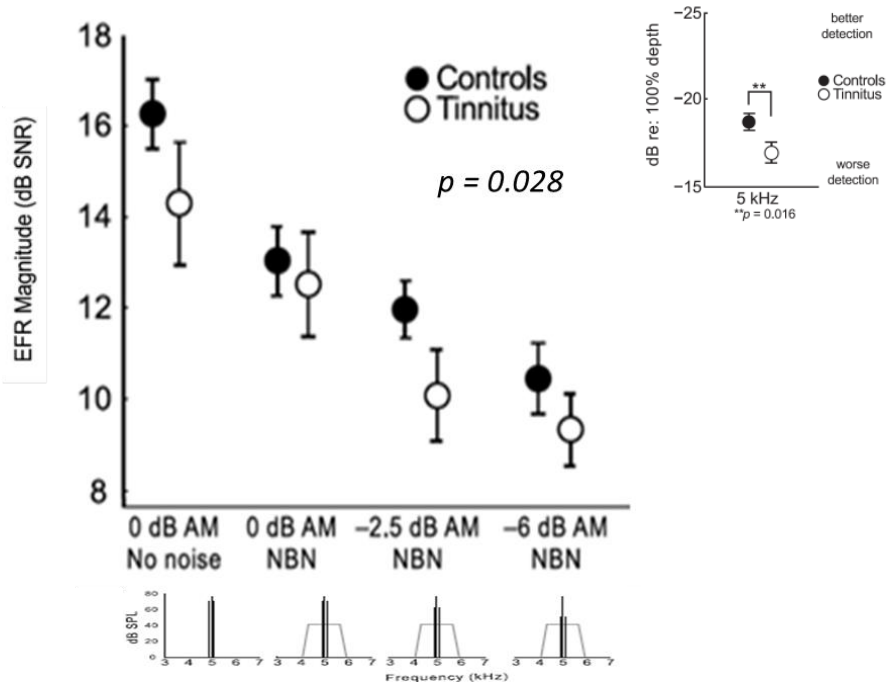
Hypothesis:
Loss of ribbon synapses on high threshold auditory nerve fibers may predispose to tinnitus

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)





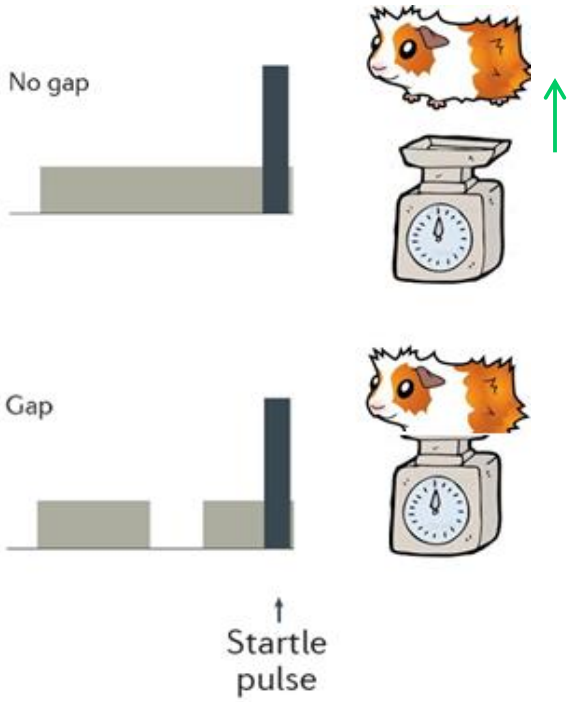
Drop correlates with AM detection (r=0.45, p=0.027)

- 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)

Paul, Bruce & Roberts (2017) *Hearing Research*, *344*, 170–182.

Animal models of Tinnitus

Gap-Startle Method (GPIAS)



If tinnitus fills the gap, the startle response returns

(gap/no gap ratio = 1)

Jeremy Turner et al. (2006)
Behav. Neurosci. 120, 188–195.

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

Tinnitus neural activity begins in the cochlear nucleus

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

Kaltenbach JA & McCaslin DL (1996). Increases in spontaneous activity in the dorsal cochlear nucleus following exposure to high intensity sound: A possible neural correlate of tinnitus. Aud. Neurosci 3, 57-78.

Susan Shore (University of Michigan)

Shore SE. (2011). Plasticity of somatosensory inputs to the cochlear nucleus – implications for tinnitus. Hear Res. 2011 Nov;281(1-2):38-46

Results from the Susan Shore Laboratory

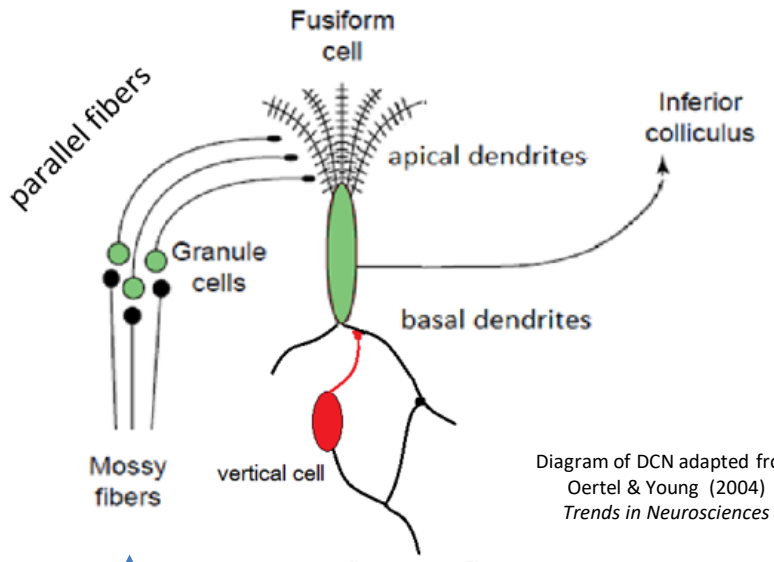
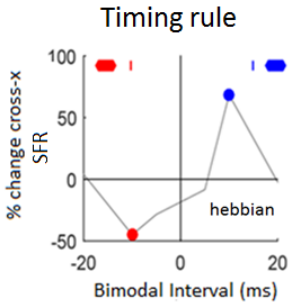


Diagram of DCN adapted from Oertel & Young (2004) *Trends in Neurosciences*

Somatosensory stimulus

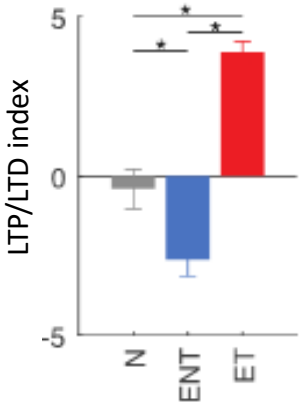
Auditory stimulus

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

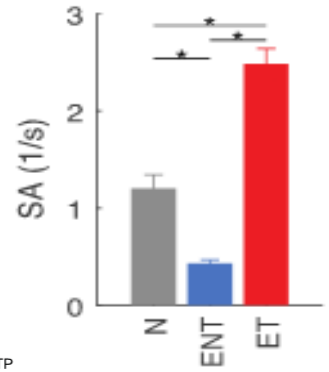


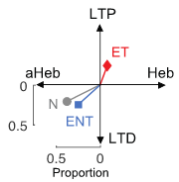
Wu, Martel and Shore (*J. Neurosci* 2016)
Koehler and Shore *(J Neurosci* 2013*)*

More bimodal intervals give LTP than LTD in animals with tinnitus

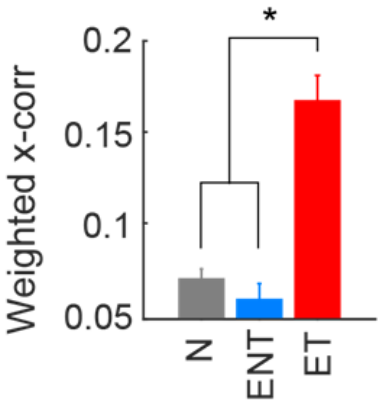


Spontaneous and synchronous neural activity is increased in tinnitus animals





Spontaneous activity



Neural Synchrony

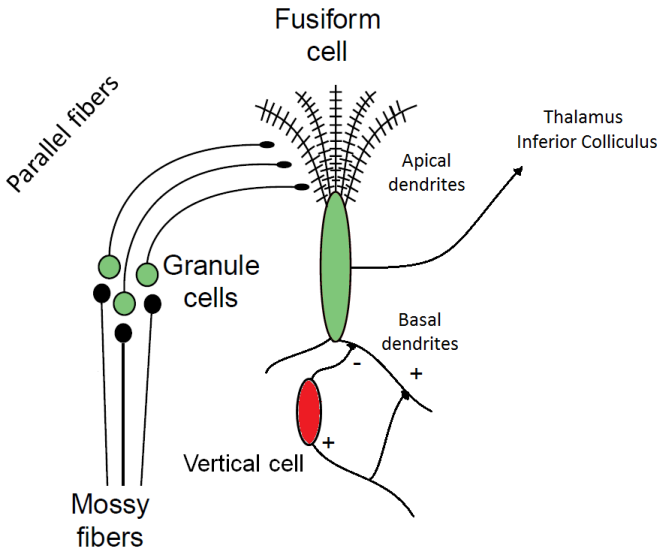
Why is the loss of low threshold fibers important for tinnitus?

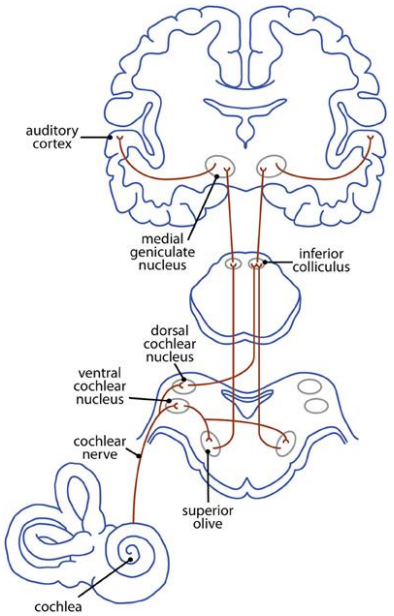
*Because the **high rates of spontaneous firing of these fibers** may preserve the balance of excitation and inhibition in the DCN*

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"





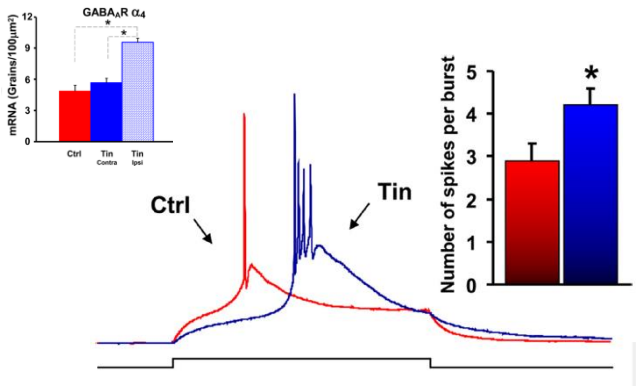
A PUZZLE:

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

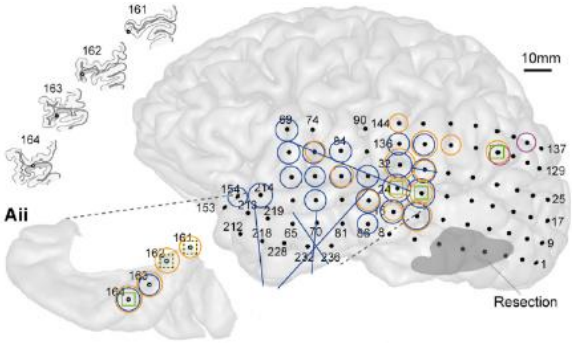


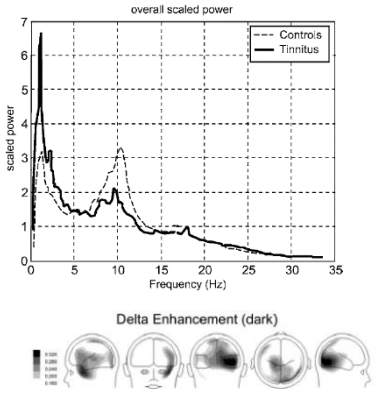
Time shift arbitrary (for viewing)

Sametsky, Turner, Larsen, Ling, & Caspary (2015). *J. Neurosci 35*, 9369–9380.

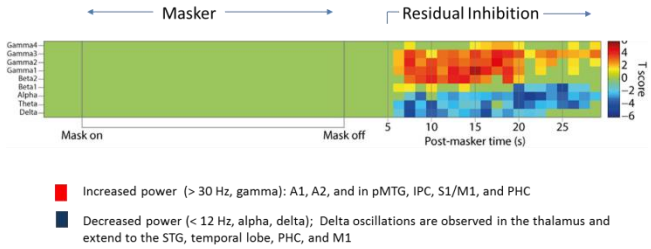
Bursting of MGB neurons may drive oscillations over the cortex:

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





Weisz, Moratti, … & Elbert (2005) PLoS Med 2:153.



Llinas et al., (2005) Trends in Neurosciences

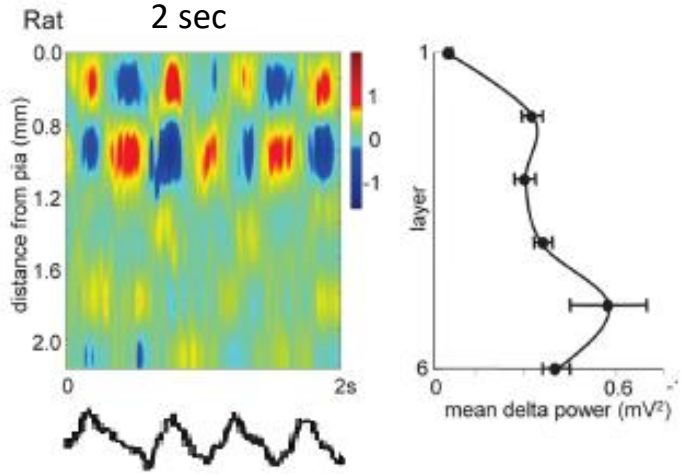
Sedley, Gander, …Griffiths (2015) *Current Biology*, *25*, 1–7.

What are the oscillations doing (reflecting)?

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)



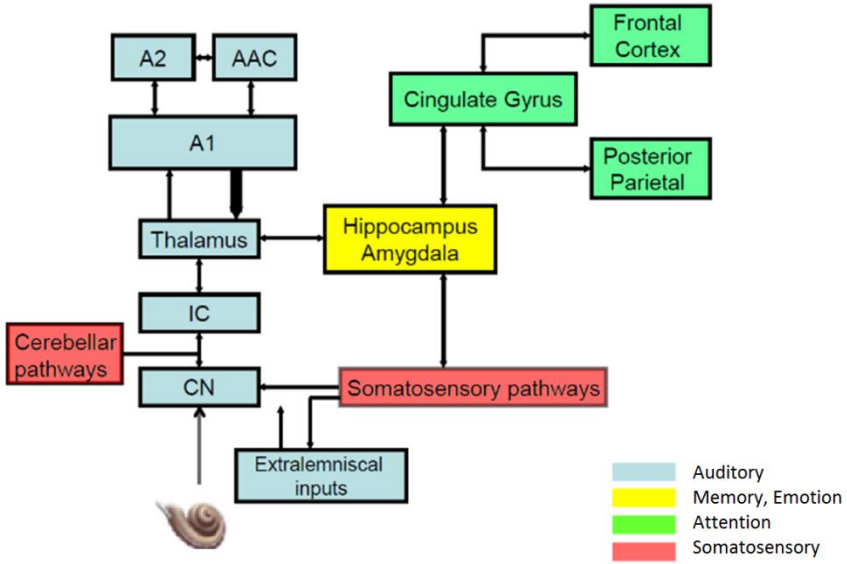
Trace recorded from layer 5
(Somatosensory/parietal slice)

Neuromodulation affects whether one sees interlaminar interactions and delta rhythms

Carracedo et al (2013*) J. Neurosci* 33:10750-10761
Rat and human slice preparations

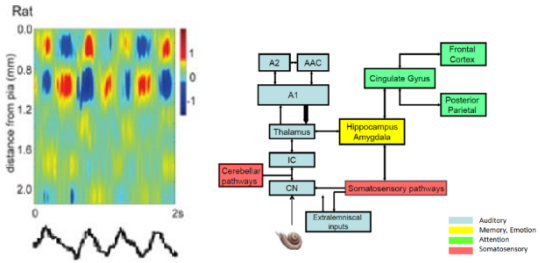
Applied to Tinnitus:

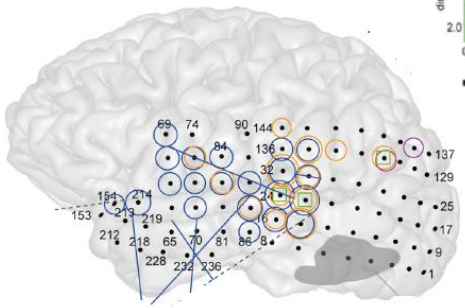
Low frequency oscillations distribute over several brain regions, disinhibiting local networks and integrating the tinnitus signal within these networks



Summary Picture

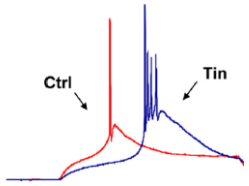
Low frequency oscillations distribute over several brain regions, disinhibiting local networks and integrating the tinnitus signal within these networks

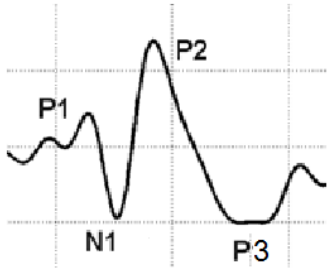




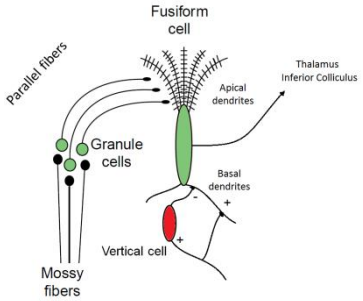
Omissions:
Downstream processing
Olivocochlear Pathway
Neuromodulation
Time course
Centralization

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





Reduced inhibition increases SFRs and aberrant synchrony in subcortical auditory pathways



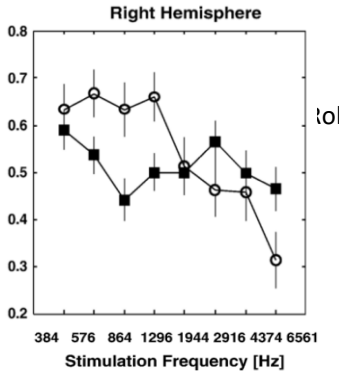
Deafferentation

Tinnitus may provide a window on normal auditory information processing

Changes in Primary Auditory Cortex

Tinnitus brain network activity affects electrocortical responses evoked by sound

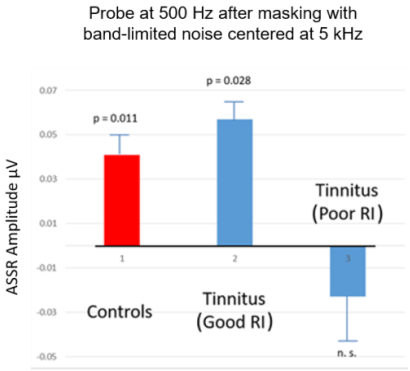
(1) Diminished tonic intracortical inhibition alters tonotopic frequency organization in the hearing loss region



Wienbruch, Paul, Weisz, Elbert & Roberts (2006) *NeuroImage* 33:180-194

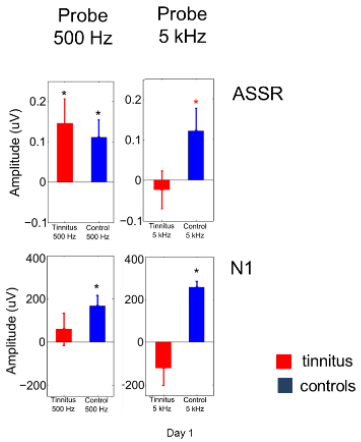
(2) Changes in the 40-Hz ASSR track residual inhibition depth

Roberts et al 2015 *Hearing Research*

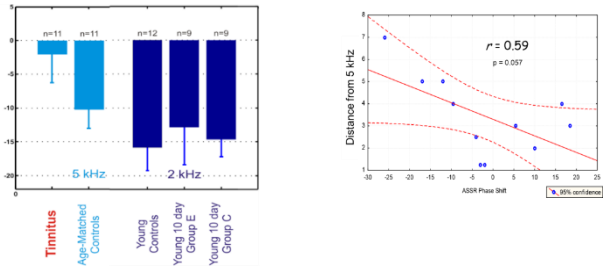


(3) Modulation of ASSR and N1 responses by attention is attenuated in tinnitus

Paul Bruce and Roberts 2014 *Neural Plasticity*



(4) Effects of auditory training are modified

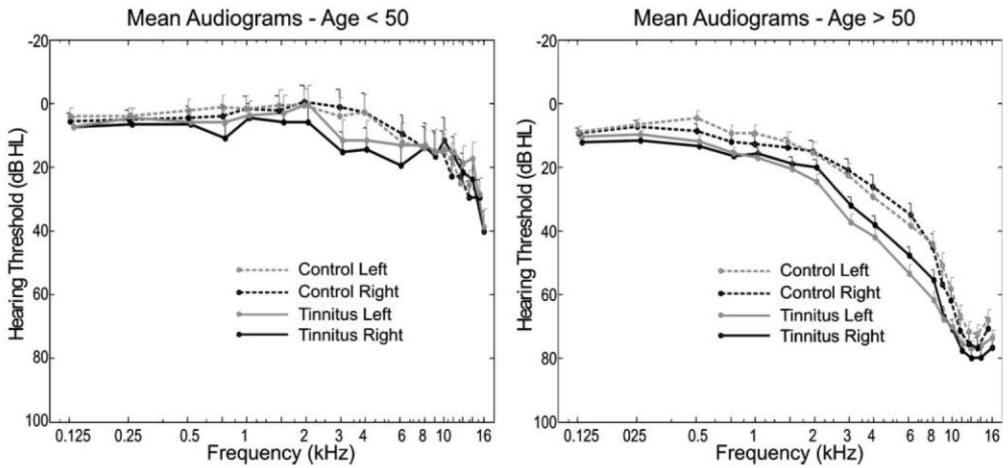


Roberts Bosnyak & Thompson (2012) *Frontiers in Systems Neuroscience*

Why is hidden hearing loss important?

Can explain tinnitus without audiometric threshold shift

Might explain threshold shift without tinnitus



Roberts, Moffat, Baumann, Ward, & Bosnyak (2008) *JARO* 9:417-435

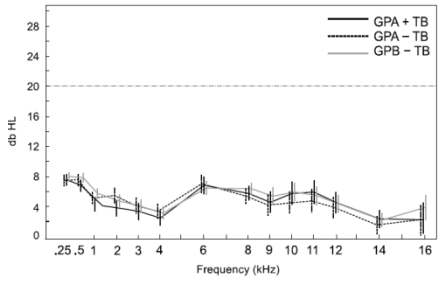
Tinnitus in adolescents

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

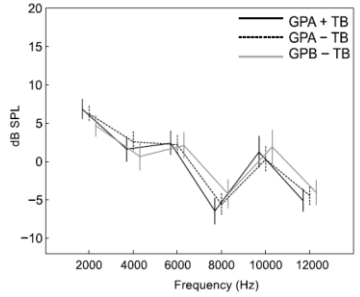
Their audiograms (0.25 – 16 kHz) and otoacoustic emissions (to 12 kHz) were completely normal

But their sound level tolerance was reduced by 11.3 dB

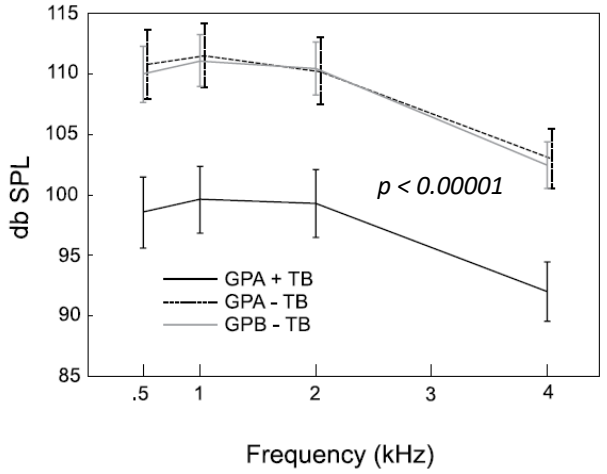
audiogram



DPOAE



Loudness Discomfort Level



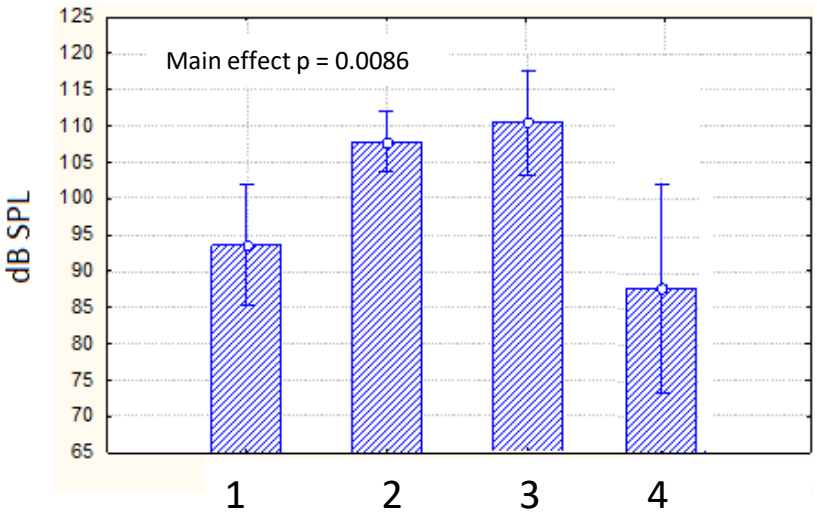
Scientific Reports 2016
(Sanchez, Moraes, Casseb, Cota, Freire & Roberts)

Loss of inhibition in central auditory pathways?
Homeostatic plasticity triggered by hidden hearing loss?
Fear of sound?

One-year follow-up (n = 54)

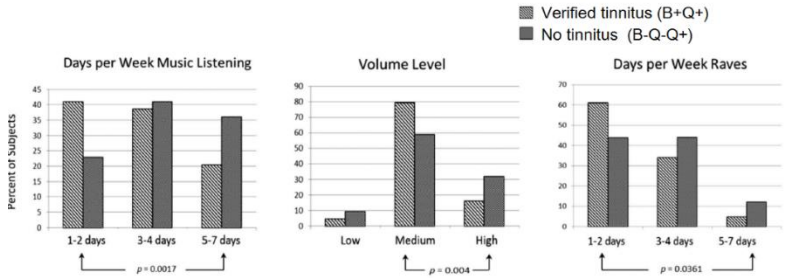
(Sanchez & Roberts ARO 2018 Submitted)

Loudness Discomfort Level



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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Jos Eggermont
Univ. Calgary


Tanit Ganz Sanchez
Univ of São Paulo

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