The Neuroscience of Tinnitus from Cochlea to Brain

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

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Ottawa, October 14th 2017

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

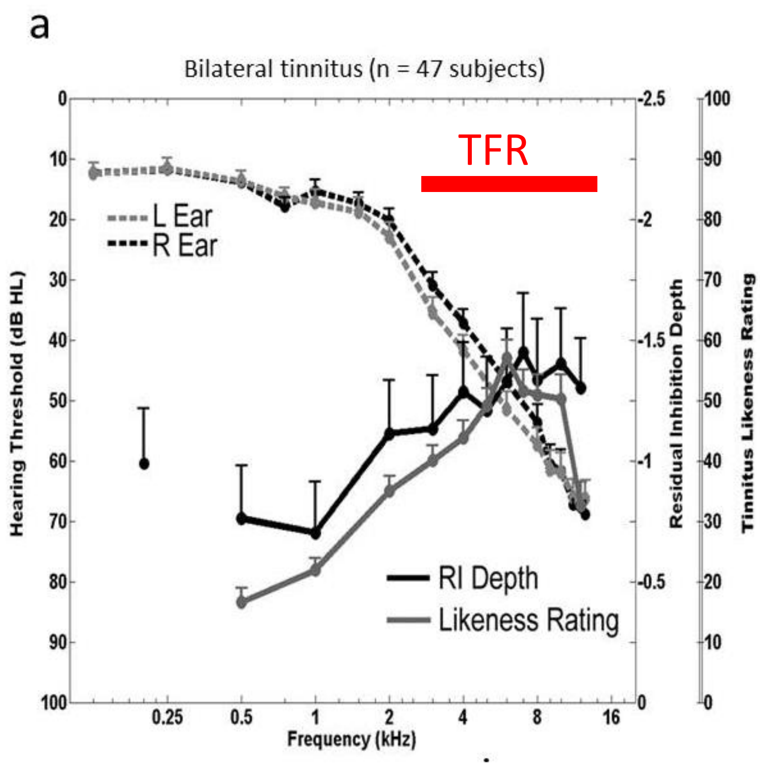
NSERC CRSNG

AMERICAN TINNITUS ASSOCIATION

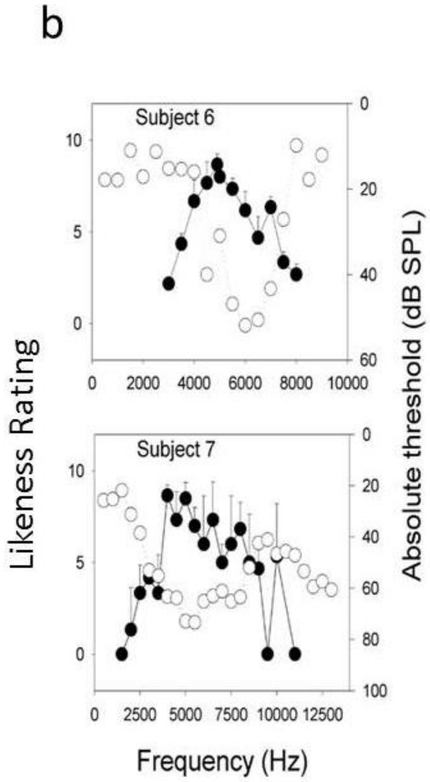
TINNITUS
RESEARCH
INITIATIVE

European Commission
ERASMUS MUNDUS

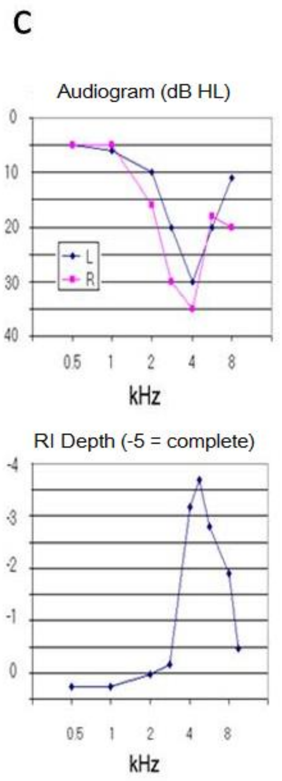
Initiating Condition: Deafferentation



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



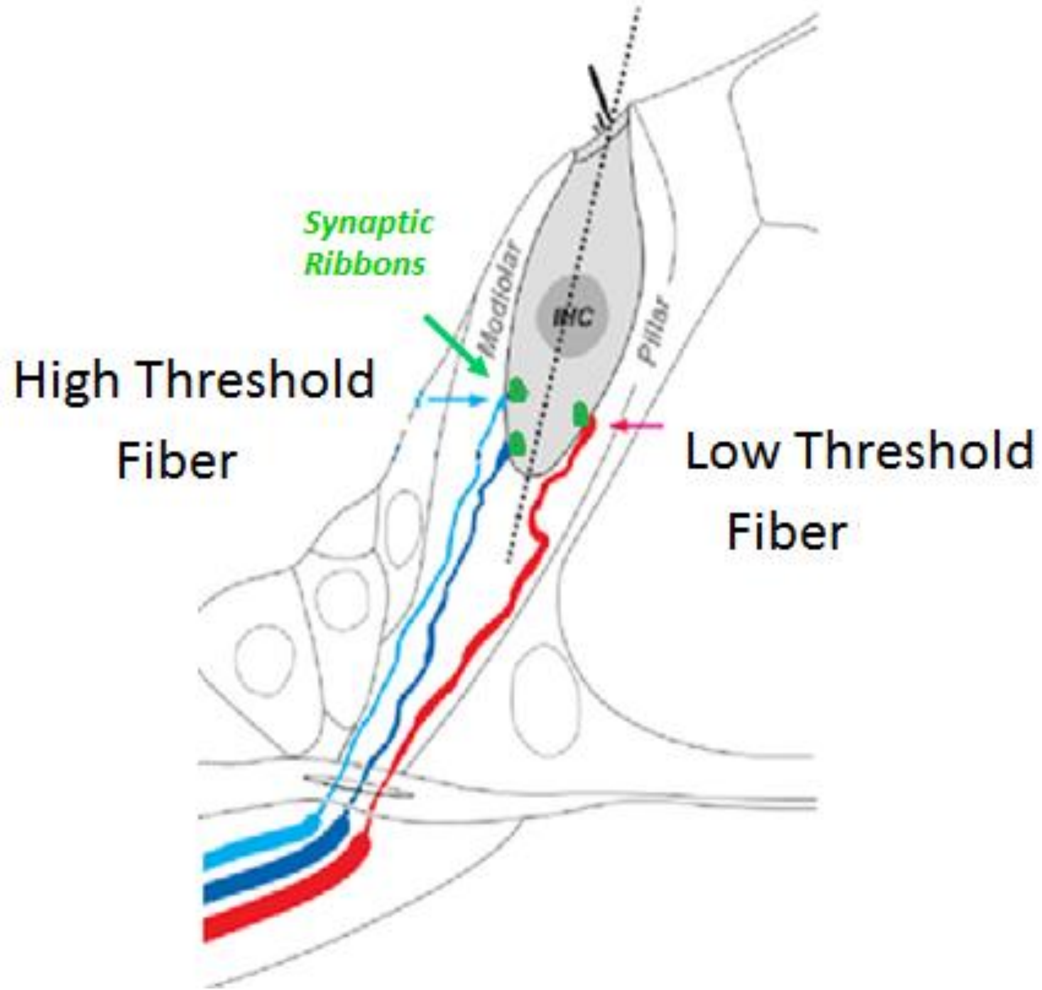
Noreña, A., Micheyl, C., Chery-Croze,
S., & Collet, L. (2002). *Audiology and
Neurootology, 7,* 358–369.



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?

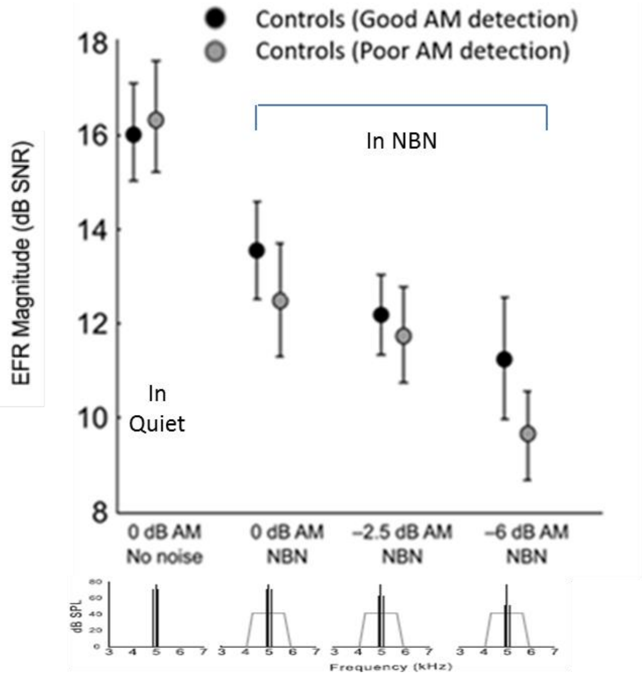


Hypothesis:
Loss of ribbon synapses on high threshold auditory nerve fibers may predispose to tinnitus

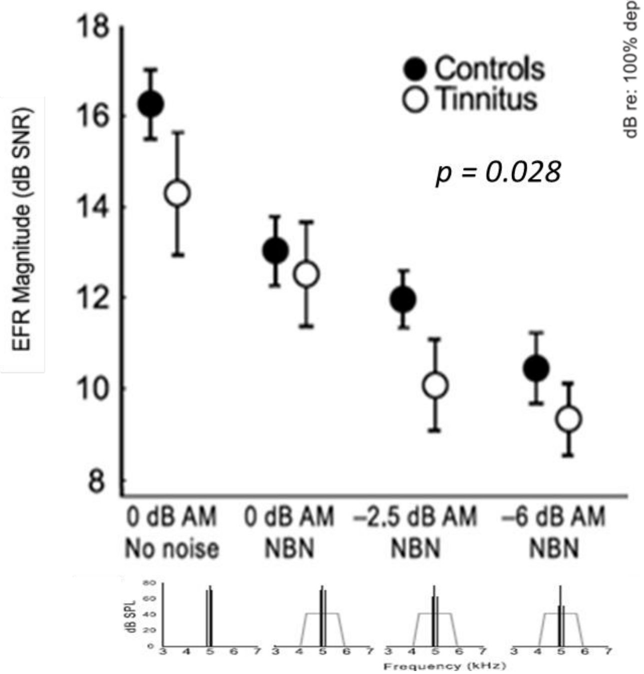
Adapted from Kujawa and Liberman
J. Neurosci 2009

Cochlear Modeling of the Envelope Following Response in Audiometrically Normal Hearing

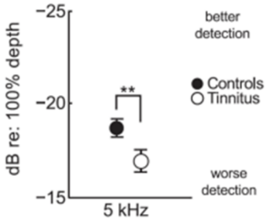
5 kHz AM @ 85 Hz



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



p = 0.016

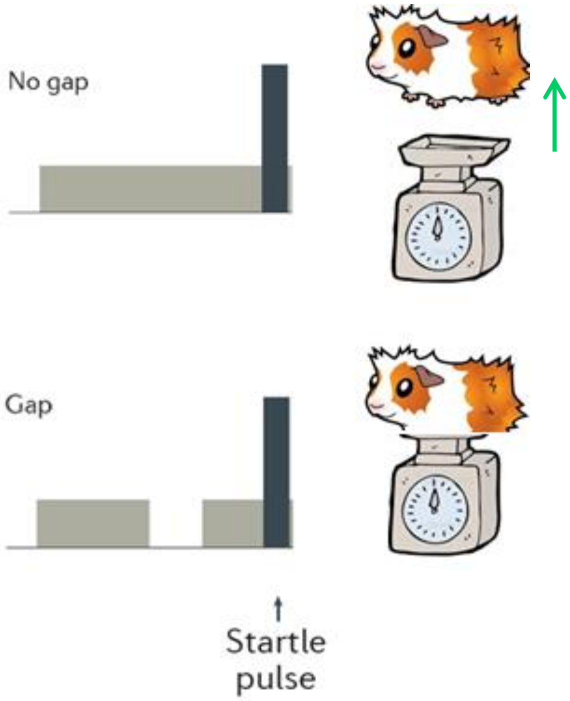


- Severe high-threshold fiber loss at 5 kHz will reproduce the EFRs of control subjects with poor AM coding ability;
- **An additional loss of ~30-60% of *low-threshold fibers wa*s needed to reproduce the EFRs of tinnitus subjects**
- *Why are these fibers important for tinnitus*? (will return to this 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)

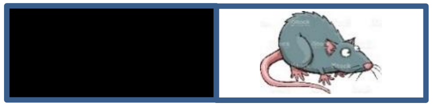
Jeremy Turner et al. (2006)
Behav. Neurosci. 120, 188–195.

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

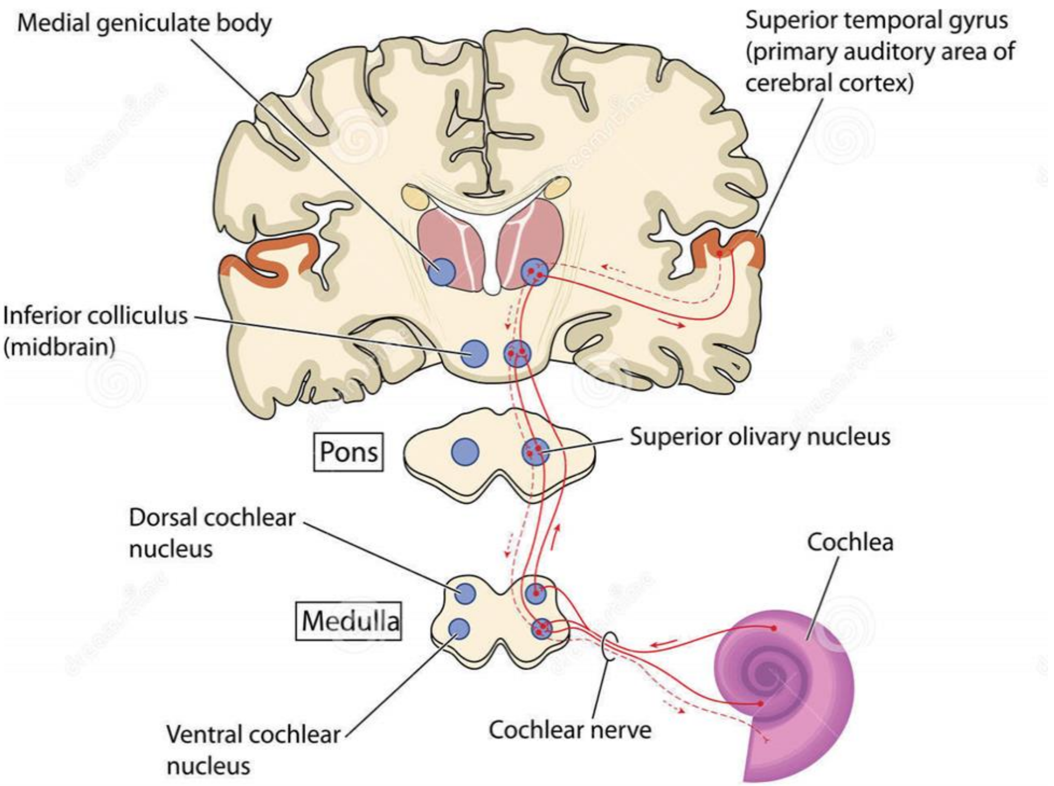
Yang & Bao et al. PNAS 2011

Tinnitus neural activity begins in the cochlear nucleus

James Kaltenbach (Wayne State University and the Cleveland Clinic)

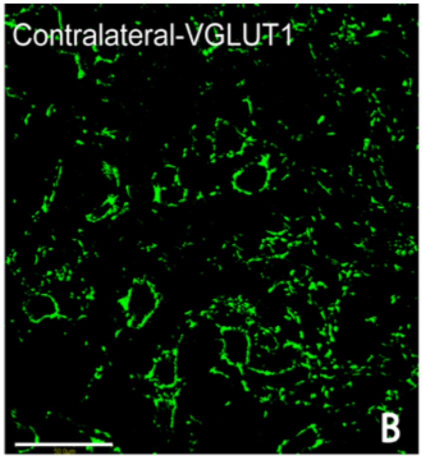
Susan Shore (University of Michigan)

Neural Plasticity is strongly expressed in the cochlear nucleus (two examples

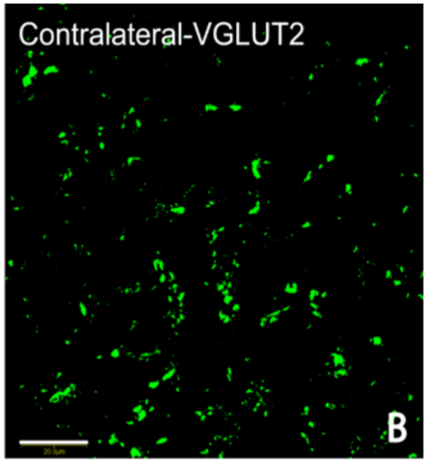


Homeostatic Plasticity in the Ventral Cochlear Nucleus

Normal Hearing



Auditory Inputs
VGULT1



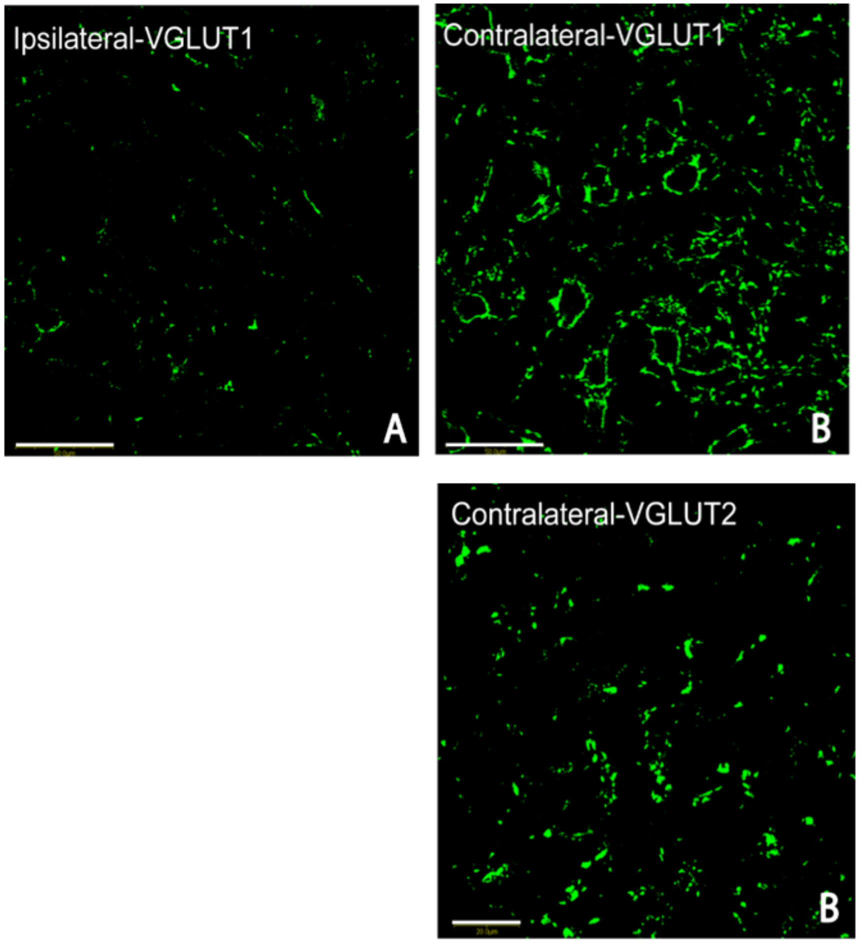
Somatosensory Inputs
VGULT2

Results from the Susan Shore Laboratory
Zeng, Nannapaneni, Zhou, Hughes, & Shore (J. Neurosci, 2009)
(Glutamate transporters are tagged with antibodies for immunolabeling)

Homeostatic Plasticity in the Ventral Cochlear Nucleus

Deafened Ear

Normal Hearing



Auditory Inputs
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Somatosensory Inputs
VGULT2

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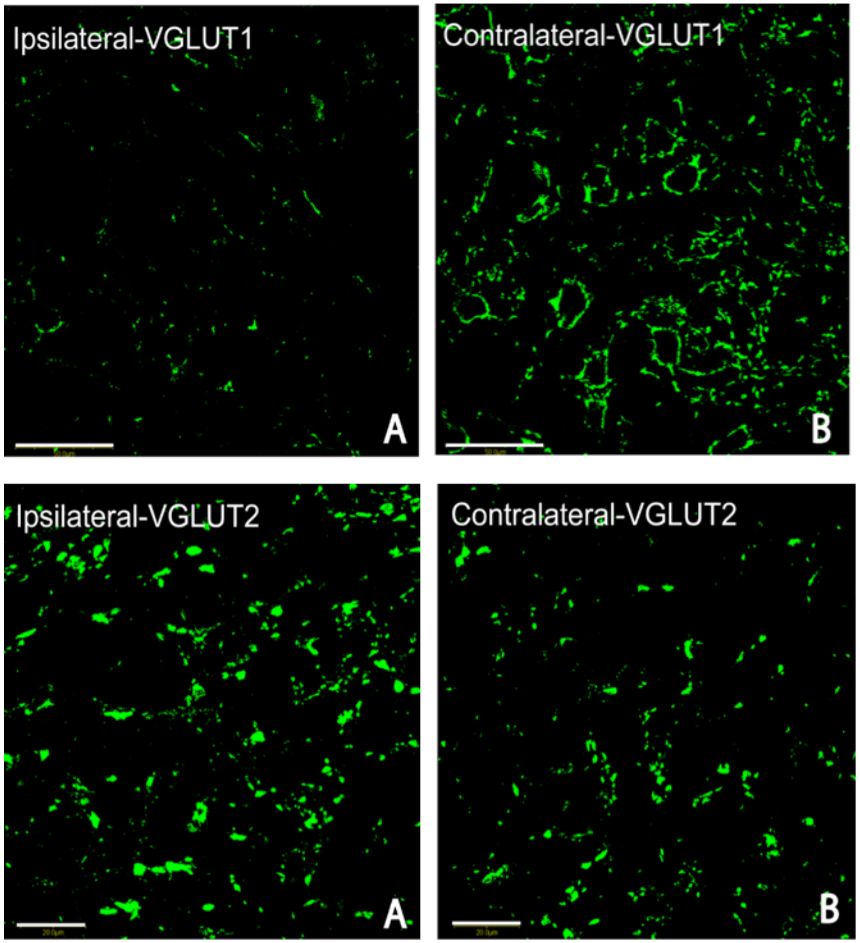

Auditory Inputs
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Somatosensory Inputs
VGULT2

Results from the Susan Shore Laboratory
Zeng, Nannapaneni, Zhou, Hughes, & Shore (J. Neurosci, 2009)
(Glutamate transporters are tagged with antibodies for immunolabeling)

Stimulus timing dependent plasticity (STDP) in the Dorsal Cochlear Nucleus

(Results from the Susan Shore Laboratory)

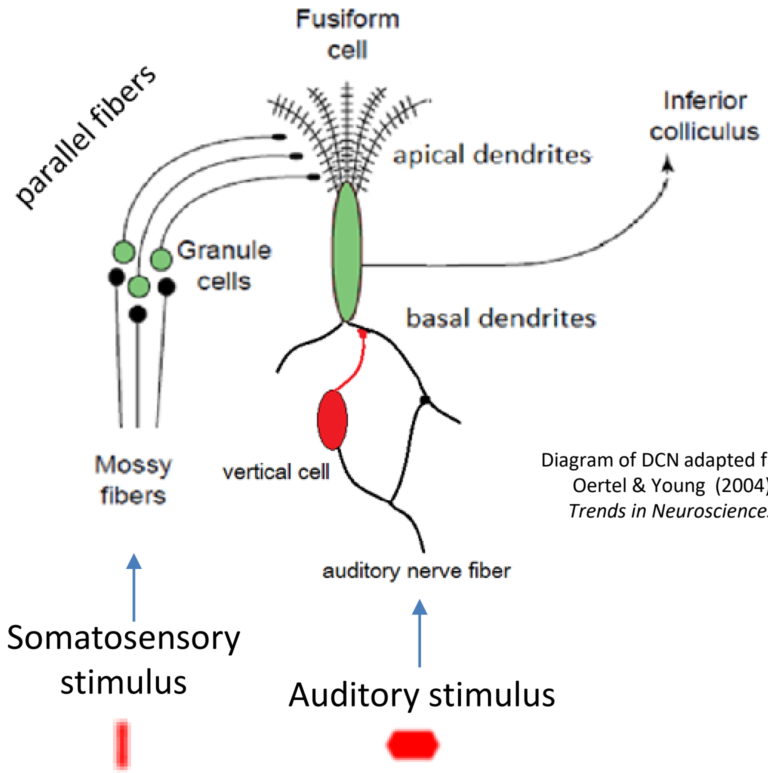
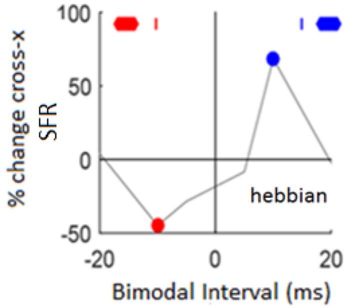


Diagram of DCN adapted from Oertel & Young (2004) *Trends in Neurosciences*

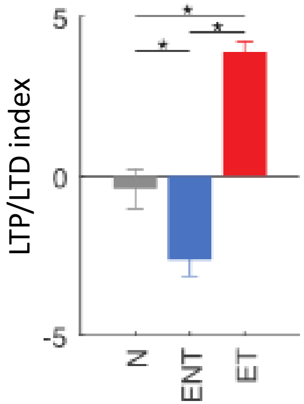
Fusiform cell excitability is increased or decreased depending on the order and timing of bimodal inputs

Timing rule

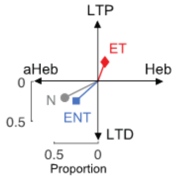


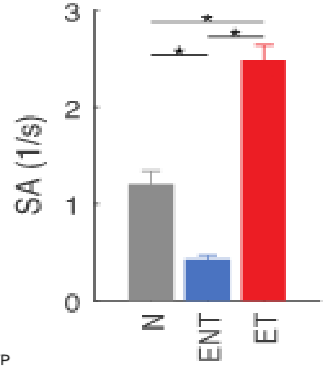
Wu, Martel and Shore (*J. Neurosci* 2016)
Koehler and Shore (*J Neurosci* 2013)

More bimodal intervals are potentiating than depressing in animals with tinnitus

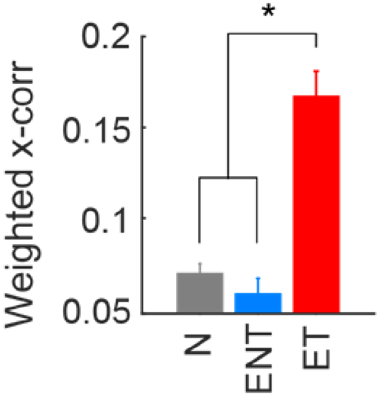


Spontaneous and synchronous neural activity is increased in tinnitus animals





Spontaneous activity



Neural Synchrony

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

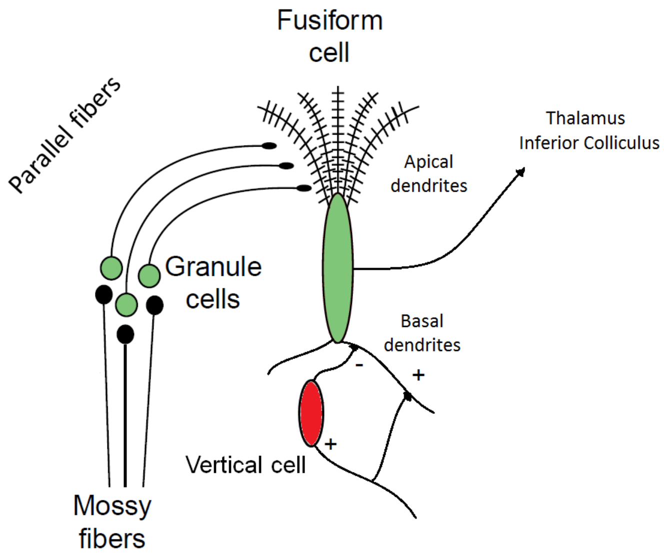
LT fibers have much higher rates of spontaneous firing in quiet (50-90 spikes/sec) than do HT fibers (1-10 spikes/sec)

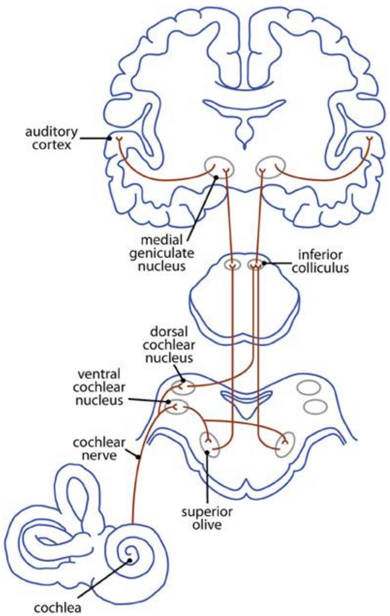
This attribute of LT fibers may preserve the balance of excitation and inhibition in the cochlear nucleus

When such fibers are lost:

Homeostatic plasticity may downregulate inhibition to compensate for decreased ANF activity*
Decreased feedforward inhibition may unleash STDP on apical dendrites of DCN fusiform cells
Other inhibitory cell types or circuits in the DCN may be involved
Further changes occur at higher levels of the auditory pathway

*Sound-driven responses also increase: "Central gain"





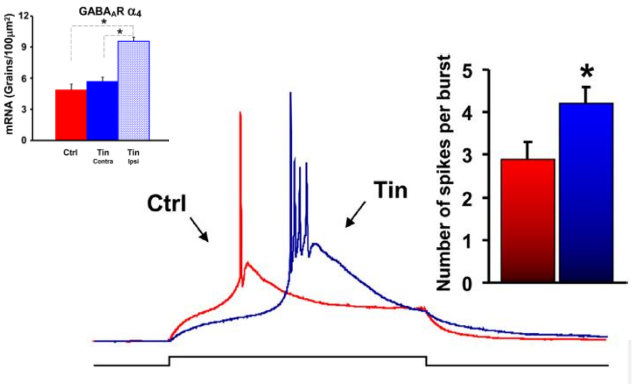
A PUZZLE:

Decreased GABAergic and glycinergic inhibition in the VCN, DCN, and IC should be expressed in the thalamus; Consistent with this, some neurons in the auditory thalamus (MGB) show increased excitability in tinnitus animals.

But 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

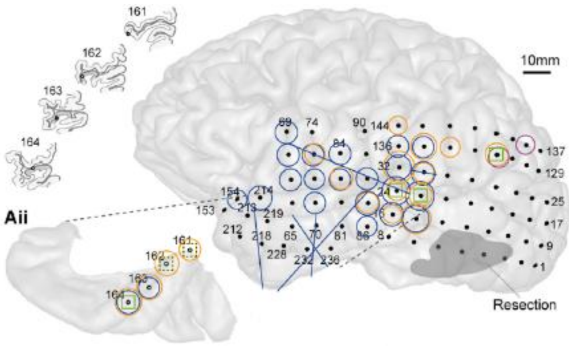


Time shift arbitrary (for viewing)

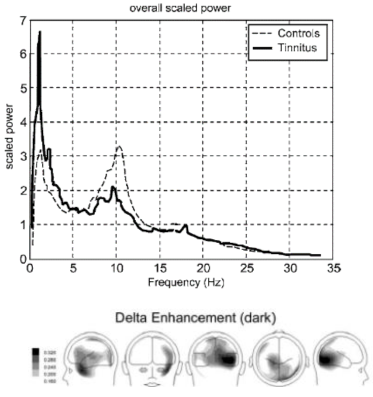
Sametsky, Turner, Larsen, Ling, & Caspary (2015). *J. Neurosci 35*, 9369–9380.

Low frequency oscillatory activity is distributed over the cortex in tinnitus:

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



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



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

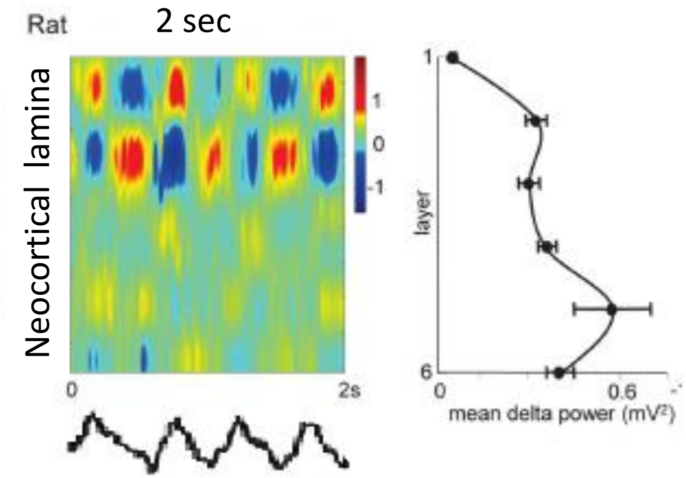
One *hypothesis* is that bursting firing in MGB neurons may drive this activity

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)



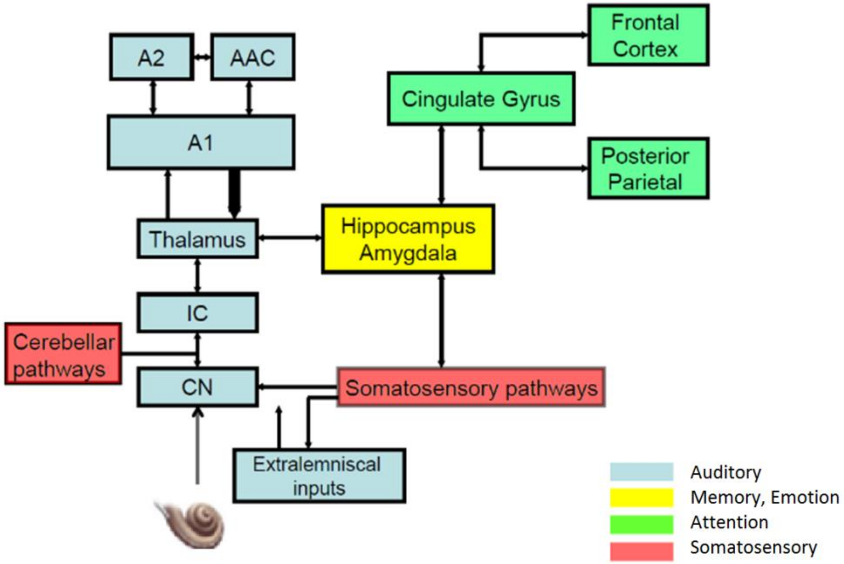
Oscillation in layer 5
(Somatosensory/parietal slice)

Neuromodulation affects whether one sees interlaminar interactions and delta rhythms

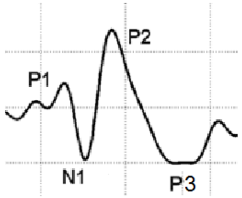
Carracedo et al (2013*) J. Neurosci* 33:10750-10761
Rat and human slice preparations

Applied to Tinnitus:

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



Auditory evoked potential

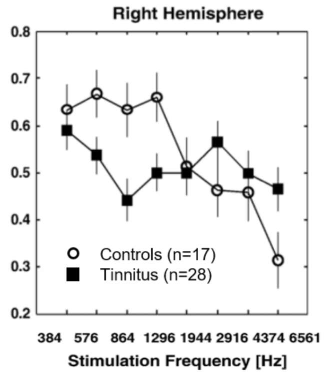


Tinnitus could reveal the time course of normal auditory processing

Changes in Primary Auditory Cortex

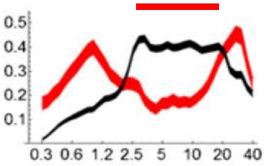
Tinnitus neural changes affect electrocortical responses evoked by sound

(1) Frequency organization of the 40-Hz ASSR is modified in tinnitus

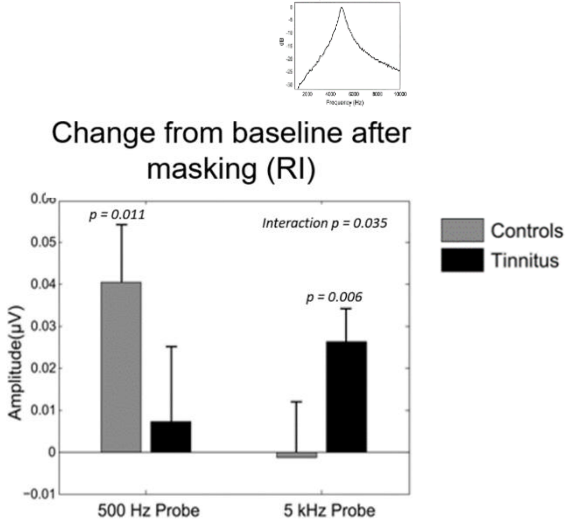


Wienbruch, Paul, Weisz, Elbert & Roberts (2006) *NeuroImage* 33:180-194

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

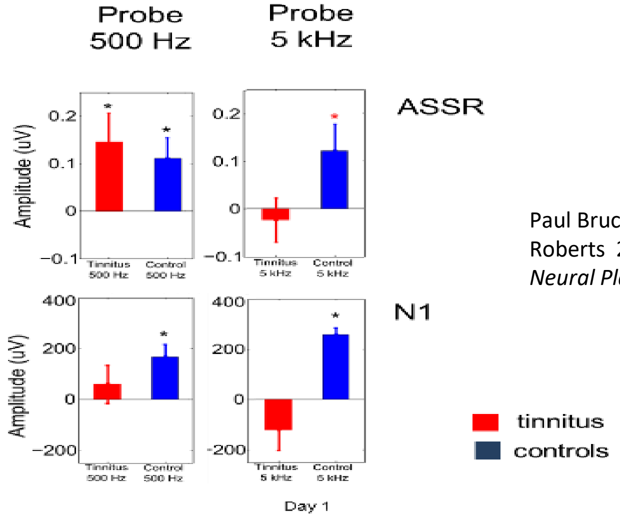


Pienkowski & Eggermont Hearing Research 2011



Roberts et al 2015 *Hearing Research*

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

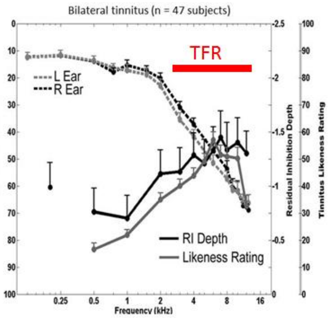


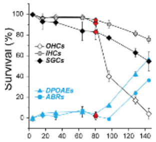
Paul Bruce and Roberts 2014 *Neural Plasticity*

Is this all there is to tinnitus?

Hi-spont fiber loss

Alters the balance of excitation and inhibition in the CN





Sergeyenko et al 2013

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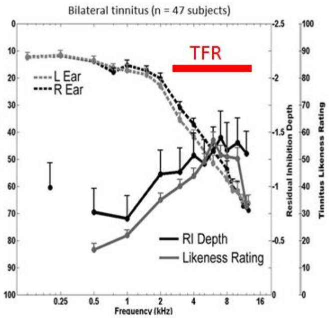
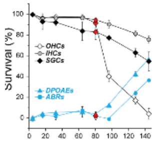
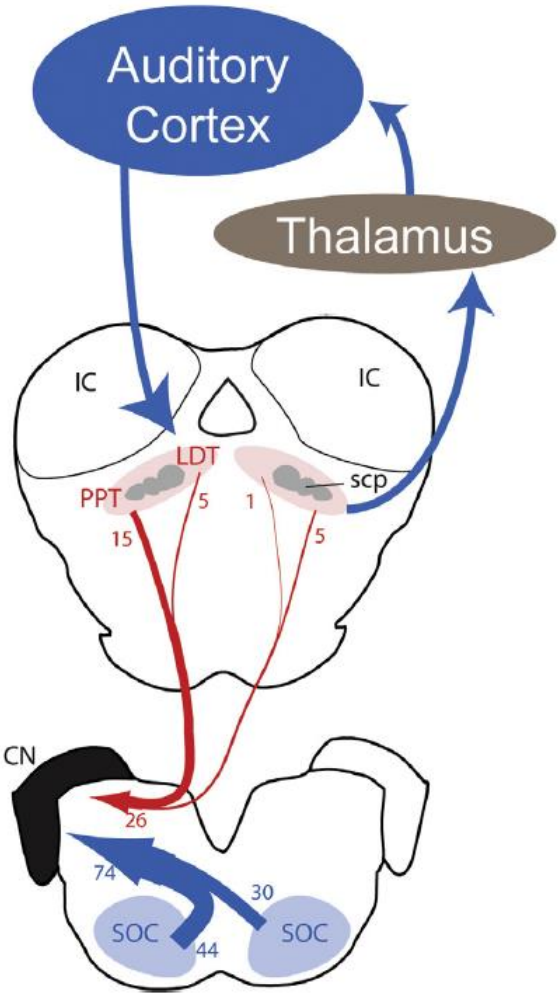




Sergeyenko et al 2013

Neuromodulatory systems
(example: PMT cholinergic system)



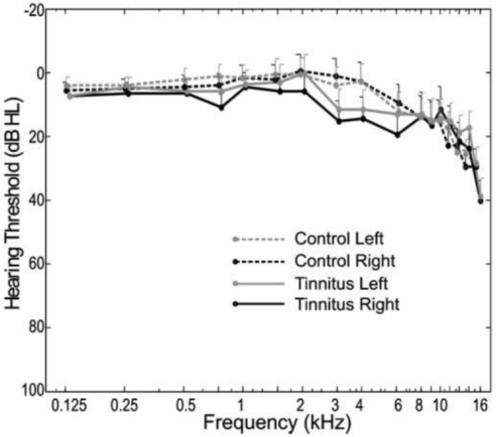
Other Omissions:
Olivocochlear Pathway
Centralization

Why is hidden hearing loss important?

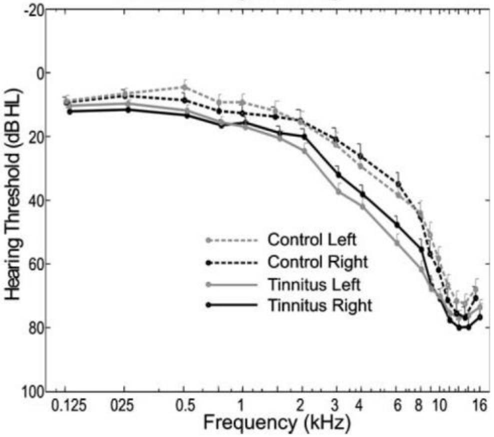
May be sufficient to explain tinnitus without audiometric threshold shift

Might also explain cases of threshold shift without tinnitus

< 50 years old



> 50 years old



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

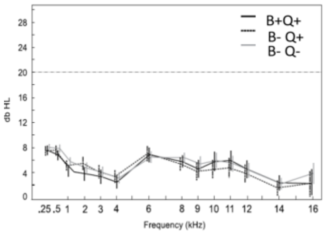
Tinnitus in adolescents

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

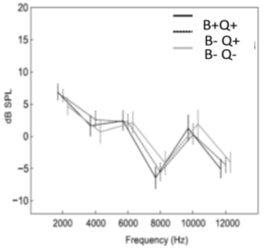
High Prevalence of risky listening habits (~90%) in all adolescents

Audiograms (0.25 – 16 kHz) and otoacoustic emissions (to 12 kHz) were normal

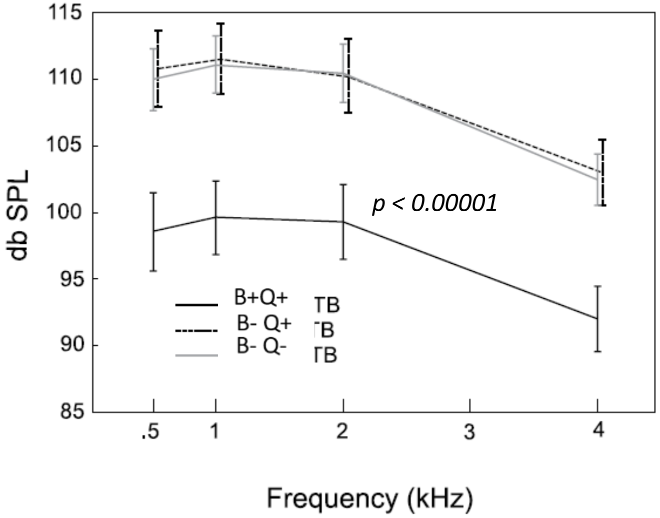
Sound Level Tolerance was reduced by 11.3 dB in adolescent with tinnitus



audiogram



DPOAE



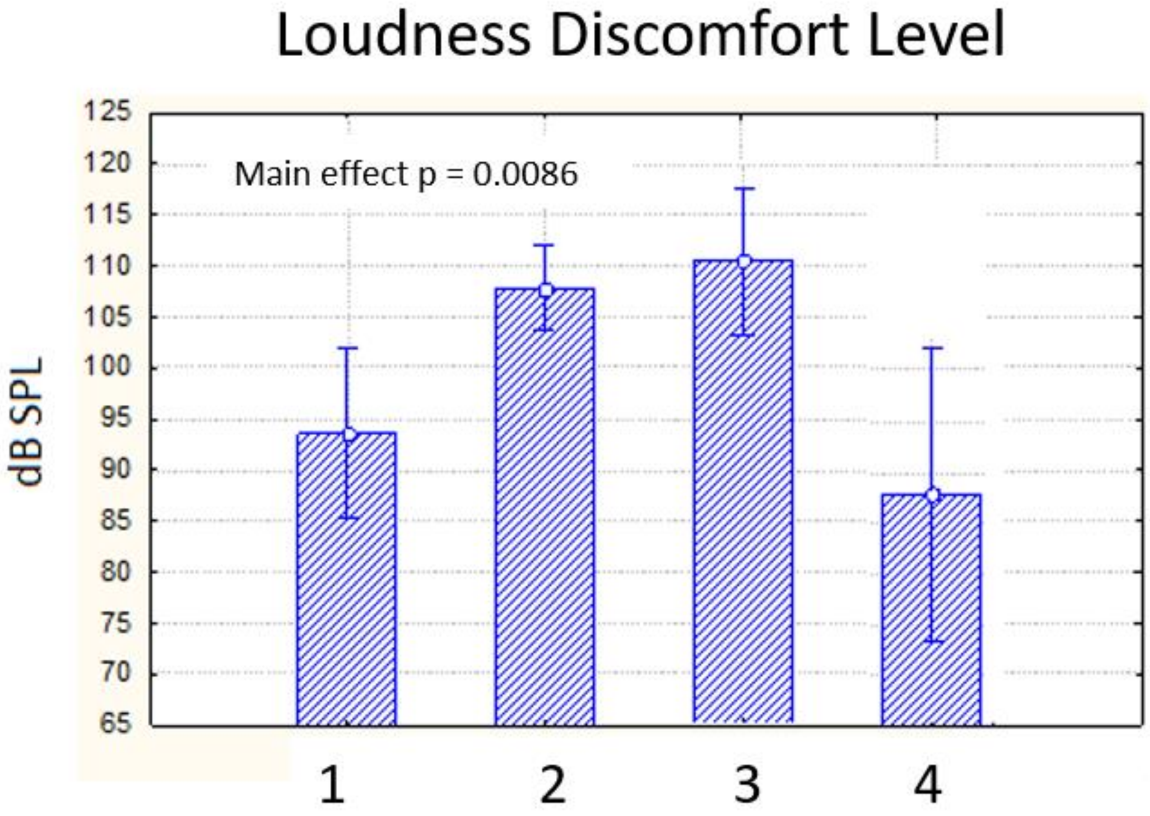
Loudness Discomfort Level

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

Loss of inhibition in auditory pathways?
Increased central gain triggered by hidden hearing loss?
Fear of sound?

One-year follow-up (n = 54)

(Sanchez & Roberts ARO 2018 Submitted)



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

How do we explain tinnitus persistence and remission?

1. Intracochlear changes?
   Suprathreshold ABRs
   EFRs
   Other temporal processing

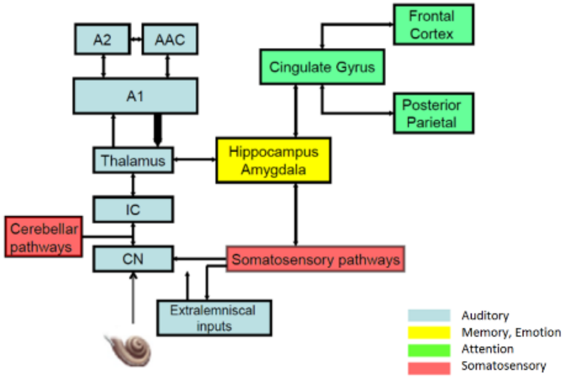
2 Risk Behaviors?

Study 1 vs 2 parties and raves:
82.1% Study 1
53.7% Study 2
(p = 0.001)

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

Some take home messages

1. Loss of high-SR auditory nerve fibers may be crucial for tinnitus;
2. Such losses appear to add tinnitus to deficient temporal processing putatively caused by Low-SR fiber synaptopathy;
3. Eliminating the tinnitus sound by neuroplastic remodeling will be difficult, because deafferentation is its initiating condition;
4. Neuromodulation plays an undetermined role;
5. *Reactions to having tinnitus are modifiable;*
6. Pharmaceutical shotguns not bullets;



7. Prevention of hearing injuries is the key to the problem of tinnitus

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