Changes in the Central Auditory System Following Loss of Auditory Input

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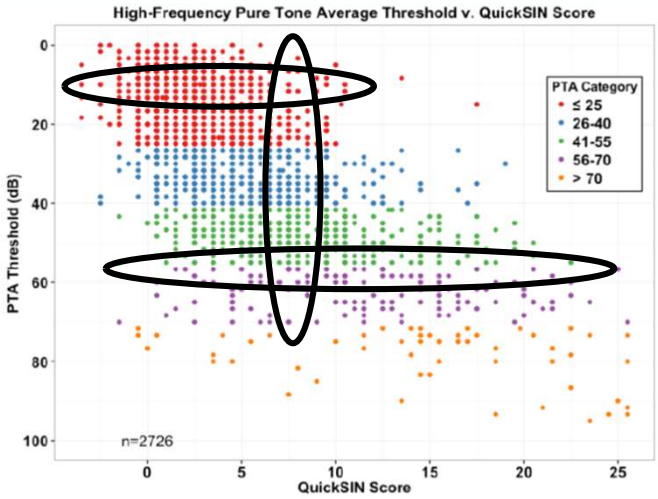
Variable outcomes in people with hearing loss



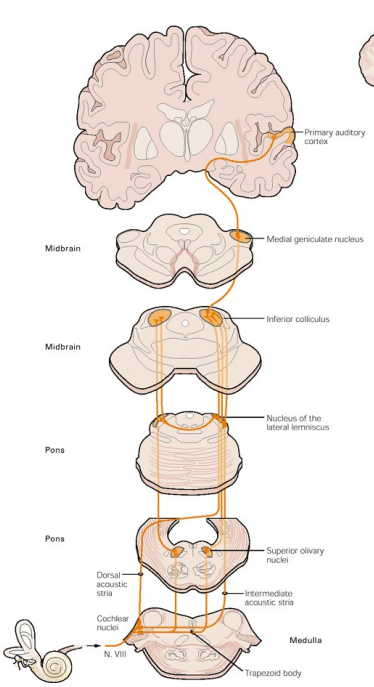
Losorelli et al., ARO 2017

- People with very similar thresholds can show very different Speech in Noise (SiN) performance
- People with very similar hearing loss can show very different speech comprehension outcomes

Hearing sounds is not the same as understanding them. The ears may hear sounds, but the brain needs to make sense of them.

2

The Central Auditory System: Ascending Auditory Pathway



- Modular: different brain regions specialized for different types of processing
- Hierarchical: ascending and descending projections. Descending connections may be particularly important for attention and learning.
- Interconnected: most complex listening abilities (e.g. Listening in noisy environments) require many different brain areas to work together (e.g. multisensory processing)
- Plastic: neural pathways/processing can be changed (e.g. following damage or experience). Changes in one brain area may lead to knock-on changes in others.

Peripheral changes (e.g. hearing loss) may cause knock-on effects throughout the brain.

3

Central Effects after Loss of Auditory Input

If peripheral input is lost, the pathways associated with this input can be either (i) weakened or (ii) strengthened and refined.

The brain can learn to either ignore damaged inputs or compensate by becoming more sensitive to damaged inputs

<u>Loss of auditory input can change:</u>

1. Numbers of neurons (e.g. cell death)
2. Neuronal preferences/selectivity (e.g. tonotopic map reorganization)
3. Neuronal transmission (e.g. excitation/inhibition balance)
4. Neuronal sensitivity (e.g. gain change)
5. Spontaneous activity in neurons (e.g. hyperactivity)

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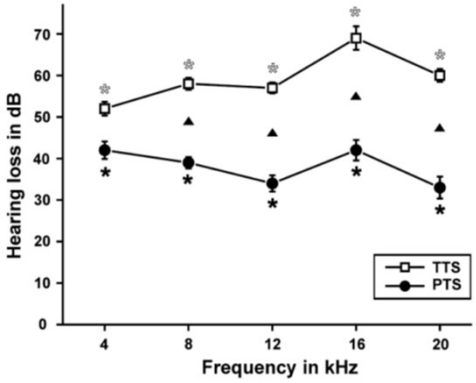
Cell Death in the Central Auditory System after Acoustic Trauma

Acoustic trauma: Anaesthetized mice exposed to loud broadband noise for 3 hours (5-20 kHz,115 dB SPL)

Hearing Loss: Noise exposure produced immediate hearing loss (temporary shifts in ABR thresholds). Hearing was slightly better 7 days later, but did not return to normal (permanent shifts in ABR thresholds).



TTS: temporary threshold shift

PTS: permanent threshold shift

Cell Death: Very little cell death was observed immediately after noise exposure, but ~30% of neurons were dead 7 days later (slightly less in cortex).

Gröschel et al. 2010

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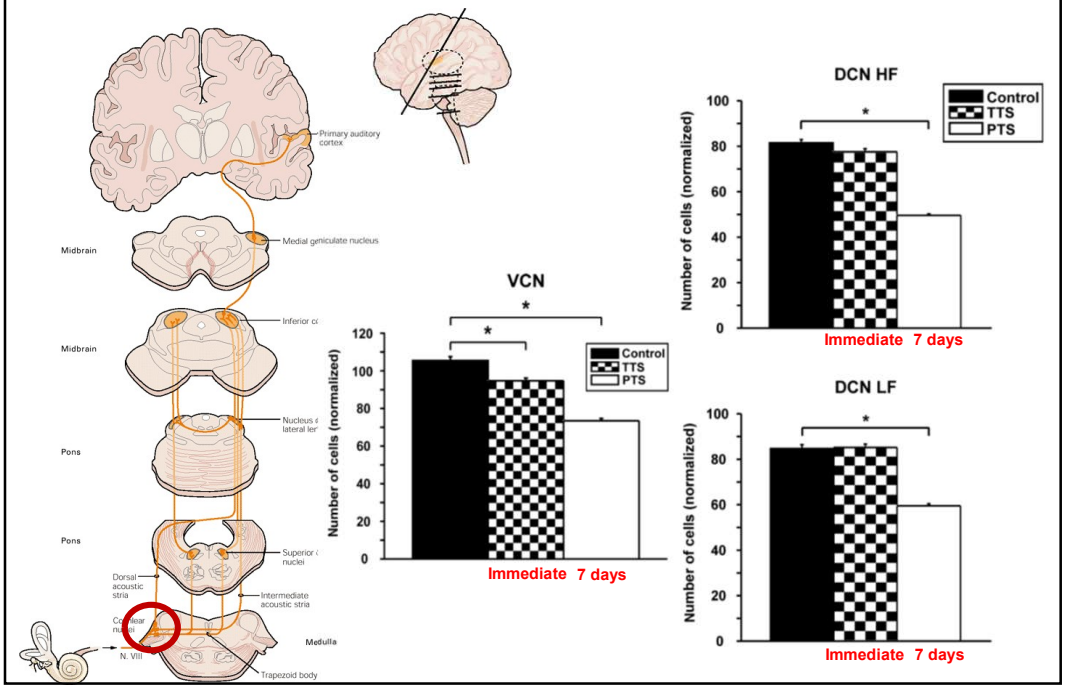
Cell Death in the Cochlear Nucleus



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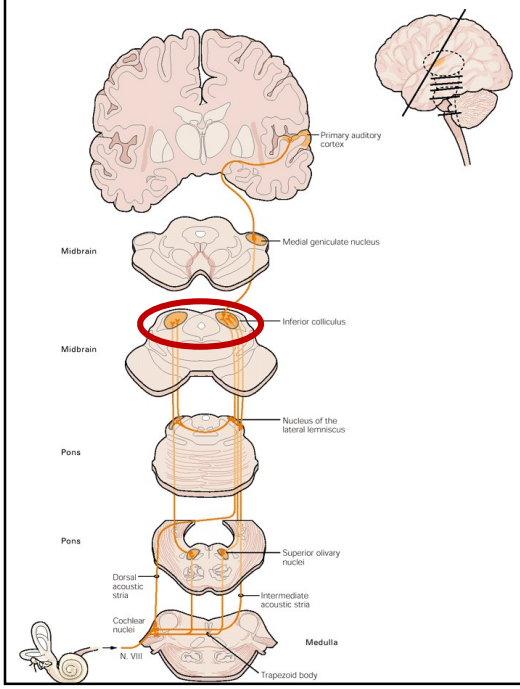
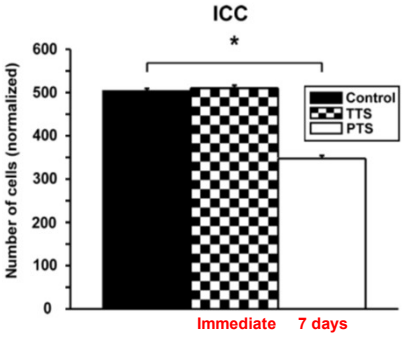
Cell Death in the Inferior Colliculus





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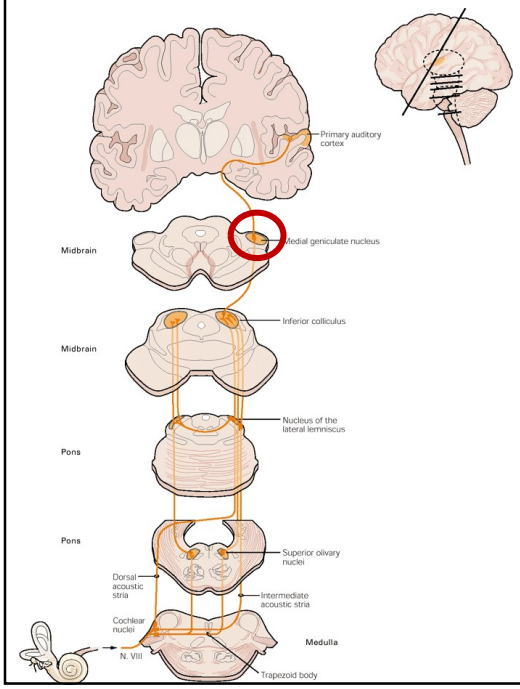
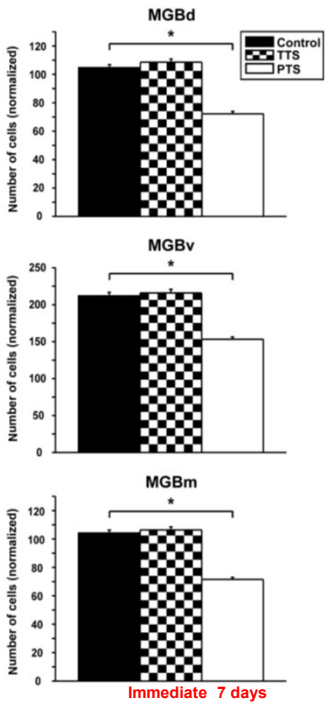
Cell Death in the Thalamus





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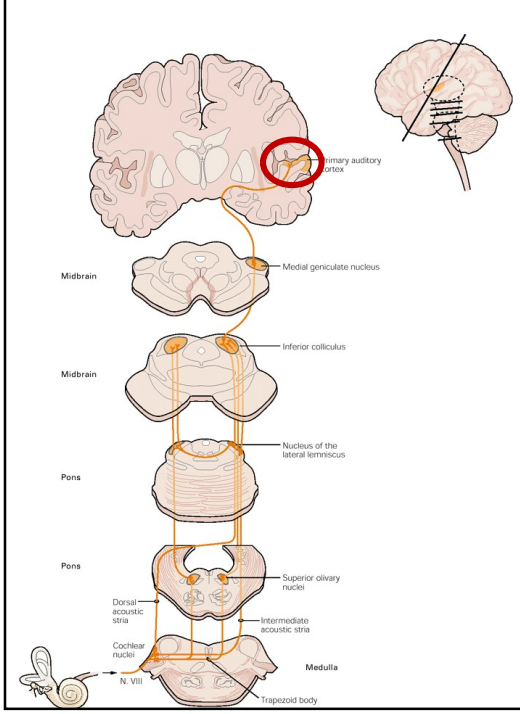
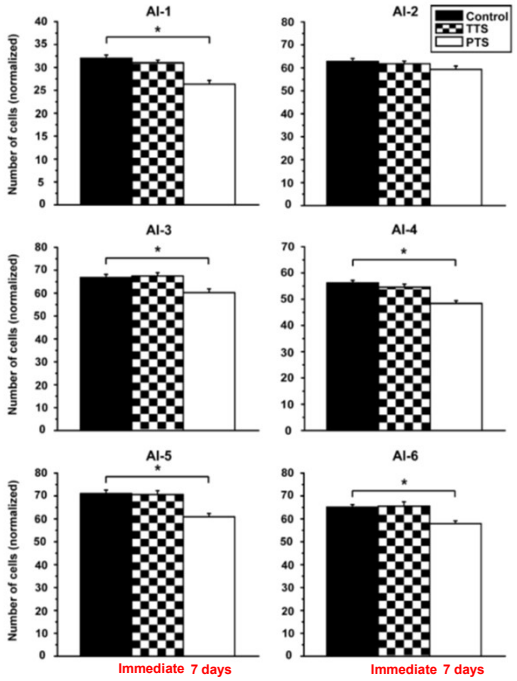
Cell Death in the Auditory Cortex





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Cell Death after Noise Exposure

Key Results:

Cell death occurs throughout the auditory system after noise exposure

Cell death ocurs imediately in more peripheral brain regions (VCN), but takes longer to occur in higher brain regions (and may be less extensive).

Open Questions:

Why do cells die following noise exposure? Is it because they are too active (excitotoxicity) or not active enough (input deprivation)?

How does cell death affect neural processing in damaged neuronal circuits? Is processing impaired or improved?

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Central Effects after Loss of Auditory Input

Peripheral damage can change:

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5. Spontaneous activity in neurons (e.g. hyperactivity)

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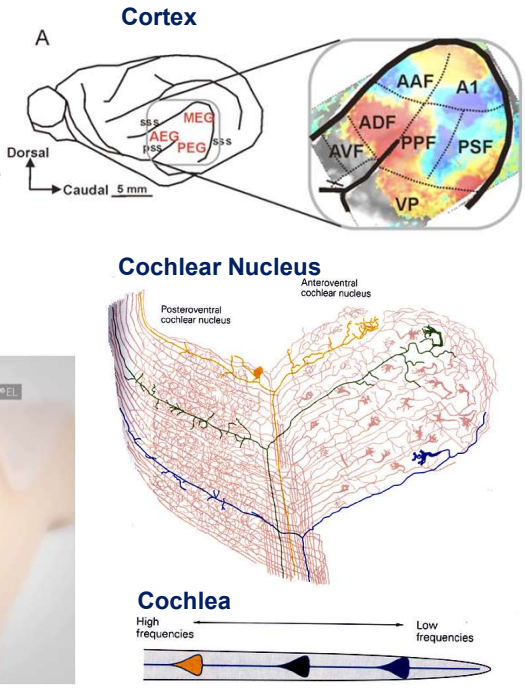
Tonotopic Maps Occur Throughout the Auditory System

Tonotopic Map: Adjacent neurons respond best to similar frequencies

Place Code: the physical location of an active neuron provides information about the stimulus

A tonotopic map occurs in the cochlea because each region of the basilar membrane is most sensitive to a specific frequency

Tonotopic organization is preserved throughout the auditory system (up to cortex)



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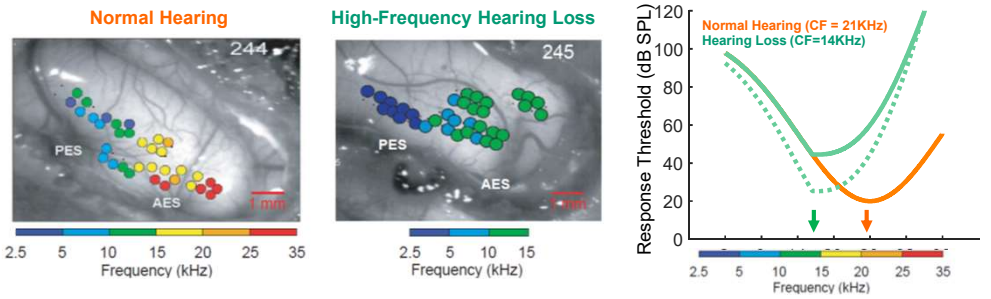
Hearing Loss Produces Changes in Cortical Tonotopic Maps

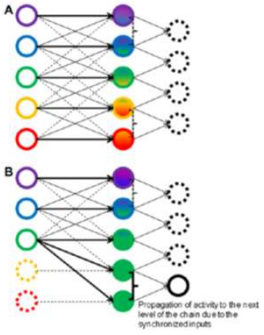


Following high-frequency noise-induced hearing loss in cats, neurons that normally prefer high frequencies switch to preferring lower frequencies

This is because high-frequency inputs are no longer able to activate these neurons

High-frequency neurons may also become more excited and/or less inhibited by low-frequency inputs

Hearing loss may lead to an over-representation of intact sensory inputs in tonotopic maps



Norena & Farley, 2013

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Changes in Excitation and Inhibition Following Unilateral Hearing Loss

Hearing Loss: Induced short-term hearing loss in one ear in rats (earplug in one ear for 24 hours)

Synaptic Strength: Quantified receptor density for excitatory and inhibitory synapses in the cochlear nucleus (using electron microscopy)

Boosting Sensitivity to Compensate for Hearing Loss: excitatory synapses were strengthened and inhibitory synapses were weakened (but changes were reversible after normal hearing was restored)

(Whiting et al., 2009)

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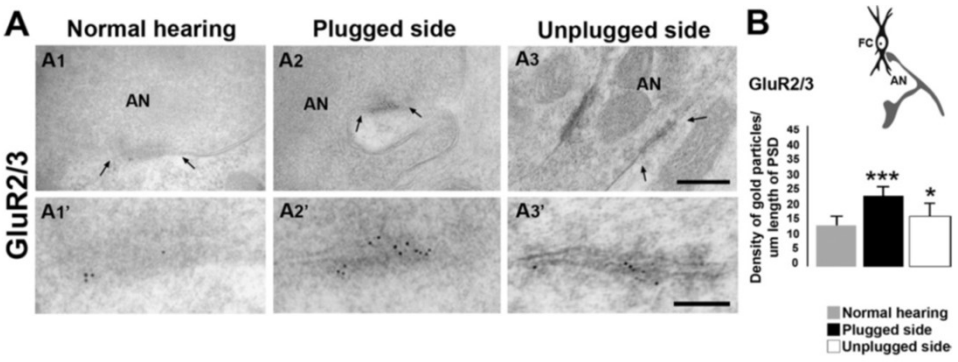
Increases in Receptor Numbers at Excitatory Synapses



Glutamate receptor density is increased following unilateral hearing loss

Hearing loss in one ear strengthens excitatory synapses in the cochlear nucleus (particularly on the side of the affected ear)

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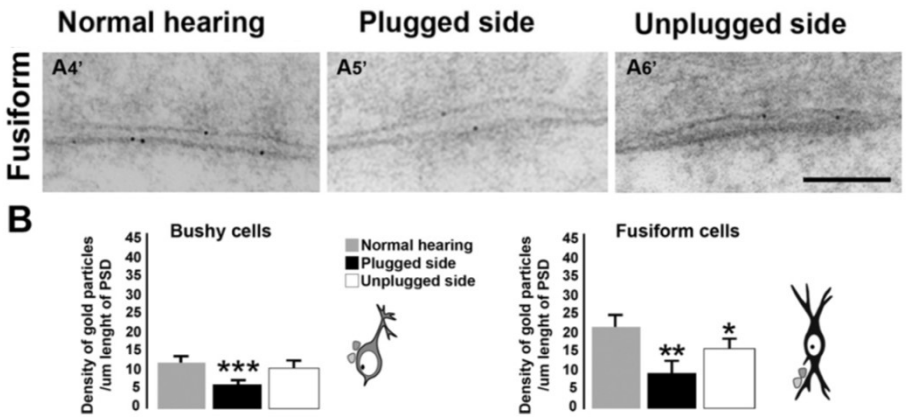
Decreases in Receptor Numbers at Inhibitory Synapses



Glycine receptor density is decreased following unilateral hearing loss

Hearing loss in one ear weakens inhibitory synapses in the cochlear nucleus (particularly on the side of the affected ear)

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Central Effects after Loss of Auditory Input

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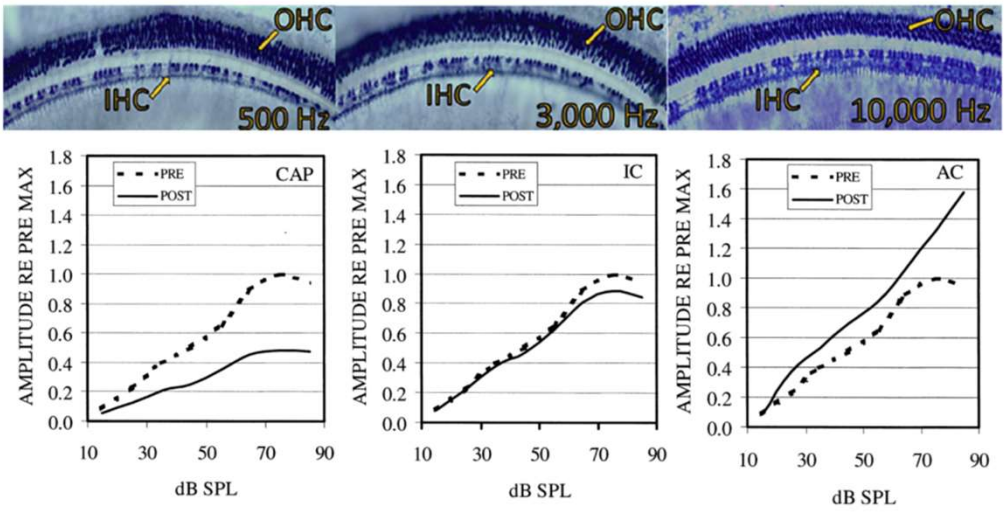
Changes in Neural Gain after Carboplatin-Induced IHC Loss

Chinchillas with ~50% IHC loss through carboplatin (Salvi et al., 2000)



Auditory cortex neurons show greater response amplitudes following hearing loss. This is because higher regions of the brain compensate for hearing loss by become more sensitive to auditory input

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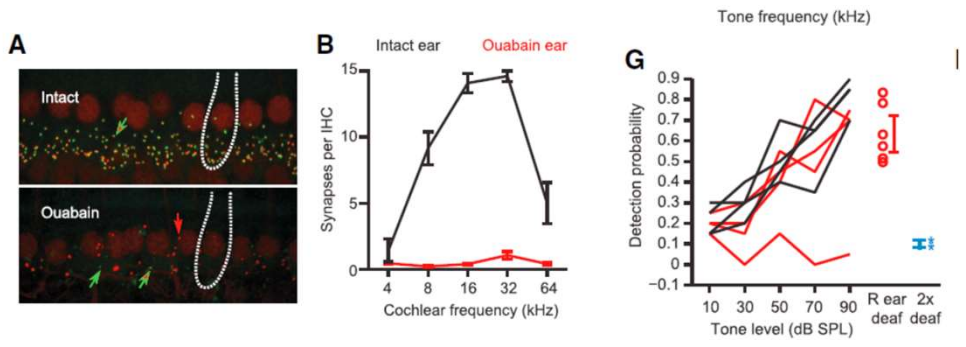
Thresholds Can Remain Normal Despite Loss of Auditory Nerve Fibres



- Ouabain used to eliminate ~90% of type-I AN fibres in mice
- Tone detection thresholds remain near-normal despite loss of AN fibres

Sound sensitivity can recover to normal levels despite massive loss of auditory input

(Chambers et al., 2016)

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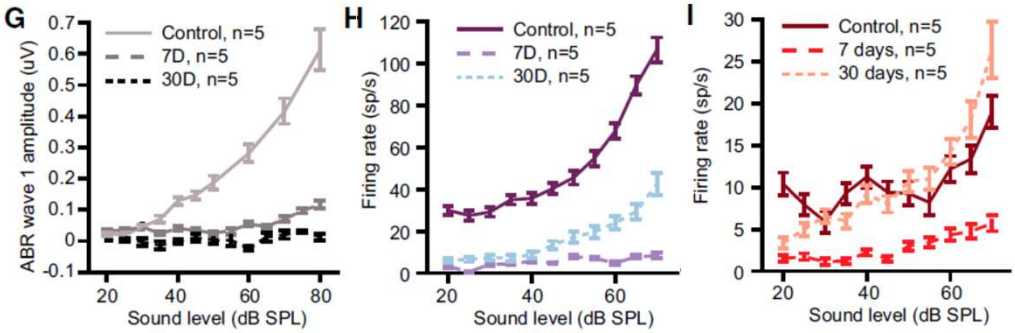
Sound Sensitivity Becomes Increasingly Normal at Higher Levels of Processing

Neural response amplitudes:

- Are permanently reduced in the auditory nerve
- Partially recover in the inferior colliculus after 30 days
- Recover to normal levels in auditory cortex after 30 days



Cortical neurons can learn to maintain normal sensitivity to sound despite reduced sound sensitivity at lower levels of processing

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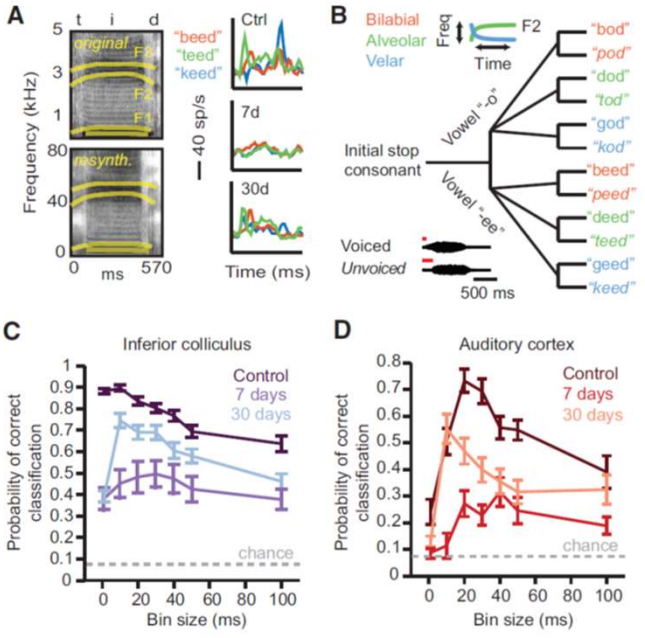
Incomplete Restoration of "Fine Structure" of Responses to Complex Stimuli



Sensitivity: ability to detect that a sound is present

Selectivity: ability to distinguish between different sounds

- Neurons' ability to distinguish between different sounds only partly recovers following loss of auditory nerve fibres
- Cortical neurons show impaired sound selectivity even though their sound sensitivity is normal (because firing patterns are abnormal).

Normal sensitivity to sound does not guarantee a normal ability to make sense of sound

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5. Spontaneous activity in neurons (e.g. hyperactivity)

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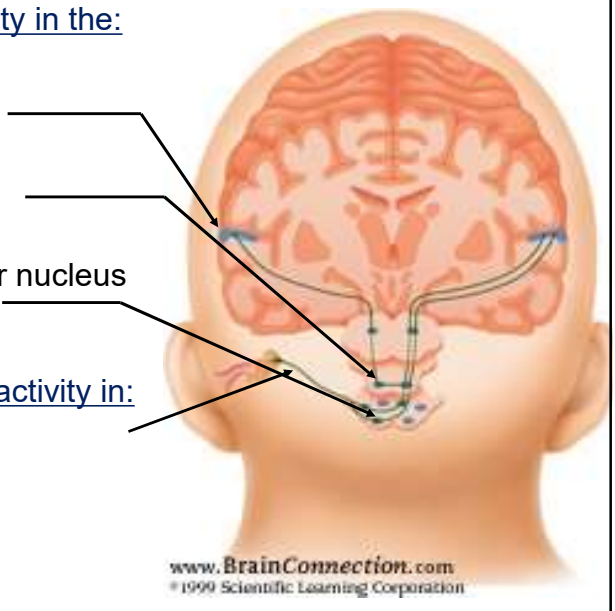
Noise Exposure Changes Spontaneous Activity Throughout the Auditory Brain

Increased spontaneous activity in the:

- auditory cortex
  (Norena & Eggermont, 2003)
- inferior colliculus
  (Mulders & Robertson, 2009; Hesse et al., 2016)
- dorsal and ventral cochlear nucleus
  (Kaltenbach et al., 1998, Vogler et al. 2011)

But decreased spontaneous activity in:

auditory nerve fibers
(Liberman et al., 1984)



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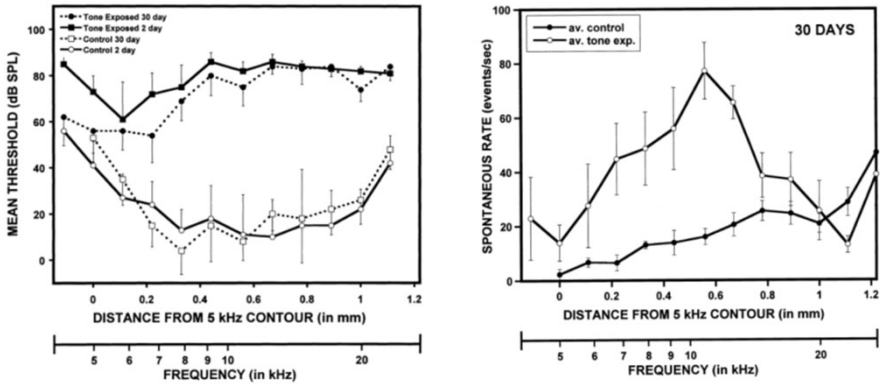
DCN Hyperactivity after Noise-Induced Hearing Loss

- Noise Exposure: 10 kHz tone,127 dB SPL for 4 hours



Following noise-induced hearing loss, neurons in the dorsal cochlear nucleus show increased spontaneous activity

Kaltenbach et al. 2000

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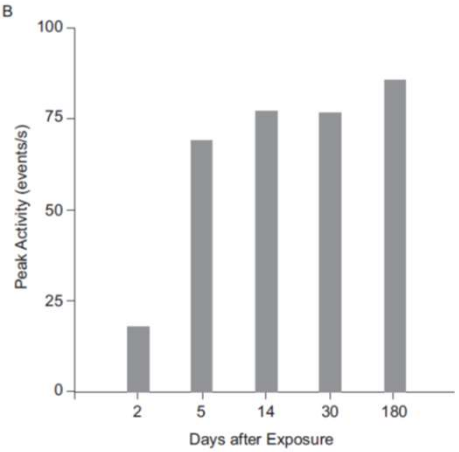
Changes in Spontaneous Activity do not Occur Immediately Following Acoustic Trauma



Hyperactivity develops between days 2 and 5 following noise exposure

Kaltenbach et al. 2000

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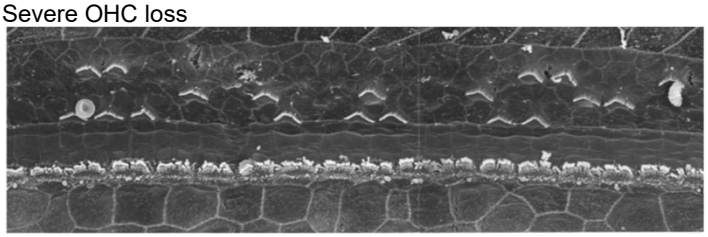
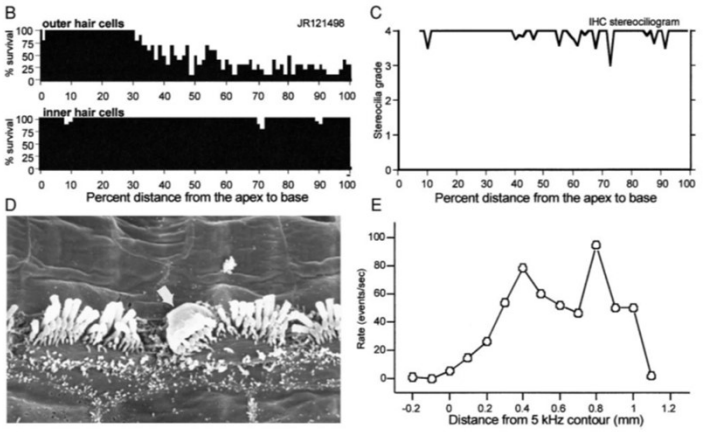
Cisplatin-Induced OHC Loss and DCN Neuronal Hyperactivity

Severe OHC loss





Increased spontaneous activity also occurs following cisplatin-induced hearing loss

Kaltenbach et al. 2002

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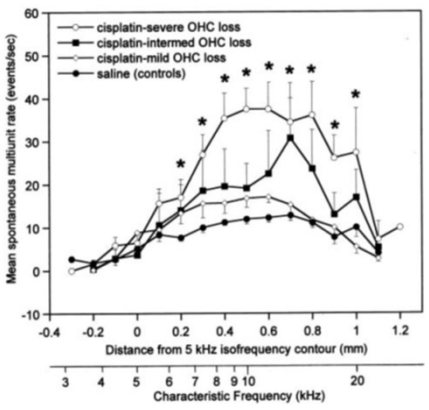
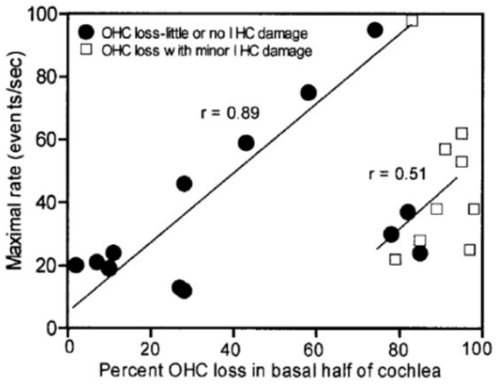
Correlation Between OHC Loss and DCN Neuronal Hyperactivity





Greater loss of OHCs is associated with greater levels of spontaneous activity in the dorsal cochlear nucleus

Kaltenbach et al. 2002

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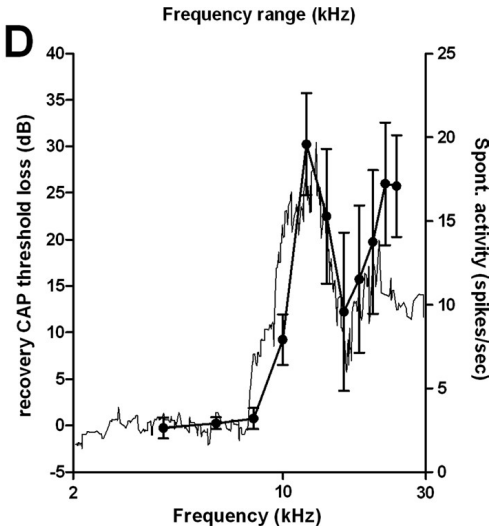
Correlation between Hyperactivity in the IC and Noise-Induced Hearing Loss



Noise Exposure: Guinea pigs exposed to 10 kHz tone, at 124 dB SPL for 2 hours

Hearing Loss: measured at different frequencies using the cochlear compound action potential

Spontaneous Activity: measured in inferior colliculus neurons tuned to different frequencies

Spontaneous activity is greater in neurons tuned to frequencies that experience greater hearing loss

Mulders et al. 2011

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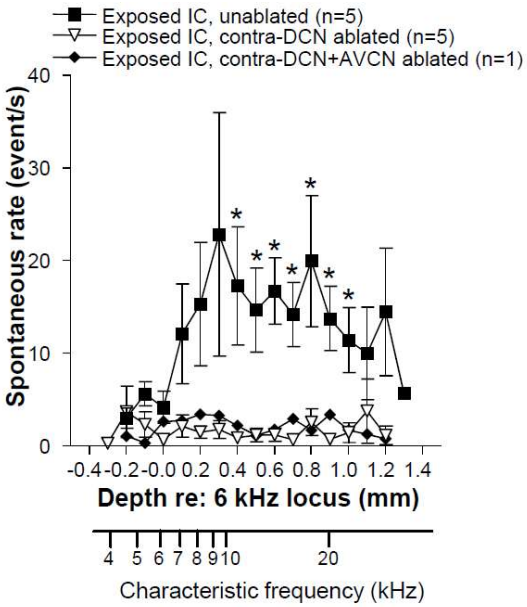
Propagation of Hyperactivity along the Auditory Pathway



- DCN ablation abolishes noise-induced neuronal hyperactivity in the IC
- Therefore, DCN hyperactivity can drive IC hyperactivity

Hyperactivity in one brain region can cause hyperactivity in other brain regions via knock-on effects

Manzoor et al. 2012

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Summary

Loss of auditory input can:

1. produce cell death throughout the auditory system, although cells in higher brain regions typically do so only after a delay
2. lead to changes in the preferred stimuli of neurons, which can alter tonotopic maps
3. Reduce sensitivity to sound, but sensitivity may be partly recovered by strengthening excitatory synapses and weakening inhibitory synapses
4. Impair selectivity for different sounds even if sensitivity to sounds returns to normal.
5. Produce subsequent changes in spontaneous activity throughout the auditory system. This may be partly because hyperactivity in one brain region may cause hyperactivity in others.

If peripheral input is lost, the pathways associated with this input can be (i) weakened or (ii) strengthened and refined.

The brain can learn to either ignore damaged inputs or compensate by becoming more sensitive to damaged inputs (but risk of becoming too sensitive!)

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Over-sensitivity in auditory neurons: hearing sounds that do not exist

Theory:

If neurons become too sensitive, they may activate even in the absence of sound. This may lead to the perception of sounds that do not exist (i.e. tinnitus).

What is tinnitus?

- Perception of a phantom sound without a corresponding acoustic stimulus
- Can be tone-like (beeping, whistling) or noise-like (hissing, roaring)

- Can be perceived in one ear, both ears, or in the head
- Prevalence:
  - Tinnitus in general: 5-10% of the population
  - Troublesome tinnitus: 1-2% of the population

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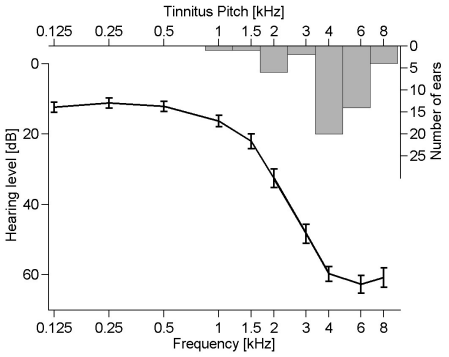
Does Hearing Loss Cause Tinnitus?

1. Hearing loss is a major risk factor for tinnitus:
   - Most people with tinnitus have hearing loss
   - Prevalence of tinnitus increases with hearing loss
2. Tinnitus can be perceived following conductive hearing loss, not just sensorineural (e.g. almost all otosclerosis patients have tinnitus)
3. Animals develop signs of tinnitus after induction of hearing loss
4. If tinnitus has a pitch-like quality, it is perceived at frequencies that have experienced hearing loss

Schaette, 2014 (Review Paper)

Tinnitus percepts following noise-induced hearing loss in the workplace



König and Schaette et al. (2006)

Hearing loss is strongly associated with tinnitus, often in a frequency-specific way

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Can you experience tinnitus if you cannot hear anything else?

- Cutting the auditory nerve usually does not abolish tinnitus (House & Brackmann, 1981)
- Complete hearing loss after surgery for vestibular schwannoma can lead to perception of tinnitus in the dead ear (e.g. Cope et al., 2011)
- Tinnitus can be experienced even in complete silence (may even be stronger)

Tinnitus can be generated entirely in the brain, even there is no auditory input

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What Neurophysiological Changes could Produce Tinnitus?

Changes in Spontaneous Activity:

- In order to perceive tinnitus, there must be neurons (mis-)firing in the brain
- However, tinnitus can occur in the absence of auditory input
- And In the absence of auditory input, auditory neurons only fire spontaneously

Therefore: Changes in spontaneous activity must be able to produce tinnitus

- However, spontaneous activity typically occurs without producing tinnitus
- But when real sounds are present, spike rates are increased and neuronal activity becomes more synchronous (multiple neurons fire together at the same time)

Therefore: Tinnitus might be produced if spontaneous activity is increased and/or becomes more synchronous

Brozoski et al., 2002; Ahlf et al., 2011, Dehmel et al., 2012; Engineer et al., 2011

Changes in Tonotopic Maps:

- Tonotopic map reorganization means that high-frequency neurons can be driven by low-frequency inputs
- But activity in high-frequency neurons might still be perceived as a high-frequency sound

Therefore: Tinnitus at one frequency might be produced by auditory input at another frequency

Engineer et al., 2011

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What might drive neurophysiological changes following hearing loss?

Homeostatic Plasticity:

- Acts to keep the mean activity of neurons constant (Turrigiano, 1999) – similar to a thermostat that acts to keep the temperature of a house constant
- Does this by altering the relative strength of excitatory and inhibitory inputs and regulating intrinsic excitability

Homeostatic Plasticity Following Hearing Loss:

- If auditory inputs are reduced following hearing loss, a neuron's mean activity may be reduced.
- However, homeostatic plasticity can restore mean activity levels to normal by making the neuron more sensitive to auditory input (e.g. by strengthening excitatory inputs and weakening inhibitory inputs)
- But increasing a neuron's sensitivity may make it too sensitive, thereby increasing rates of spontaneous activity – this may be experienced as tinnitus

Following hearing loss, homeostatic plasticity may lead to tinnitus by making neurons over-excitable

Key Prediction: tinnitus may occur following any type of prolonged auditory deprivation

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Can tinnitus occur in the absence of cochlear damage?

- Classic study - Heller and Bergman 1953:
  - Prolonged time in sound-proof booth led to perception of phantom sounds
  - Phantoms sounds disappeared after leaving the booth
- Schatte et al., 2012
  - Participants wre an earplug in one ear for 7 days
  - Majority of participants experienced phantom sounds at the frequencies most attenuated by the earplug
  - Phantom sounds disappeared after earplug was removed

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Conclusion: Curing Tinnitus by Curing Hearing Loss?

- Currently no cure for noise-induced or age-related hearing loss
- Conductive hearing loss (e.g. Otosclerosis) can often be reduced or eliminated through surgery
- Stapedectomy or stapedotomy abolish tinnitus in around 50% of otosclerosis patients (Gersdorff et al., 2000; Ayache et al., 2003; Sobrinho et al., 2004)
- Tinnitus reduction correlated with hearing loss reduction, suggesting causal relationship
- Treatment with hearing aids could be limited by severity of cochlear damage and technical limitations (Schaette et al., 2010; Kiani et al., 2013)

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