Towards a differential diagnosis of cochlear synaptopathy as a contributor to sensorineural hearing loss.

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SALUS UNIVERSITY
Osborne College of Audiology

CAA Canadian Academy of Audiology
Heard. Understood.

Academie canadienne d'audiologie ACA
Entendus. Compris.

Outline

Cochlear synaptopathy in animal studies
(primary noise- and age-related inactivation and degeneration of auditory nerve fibers)

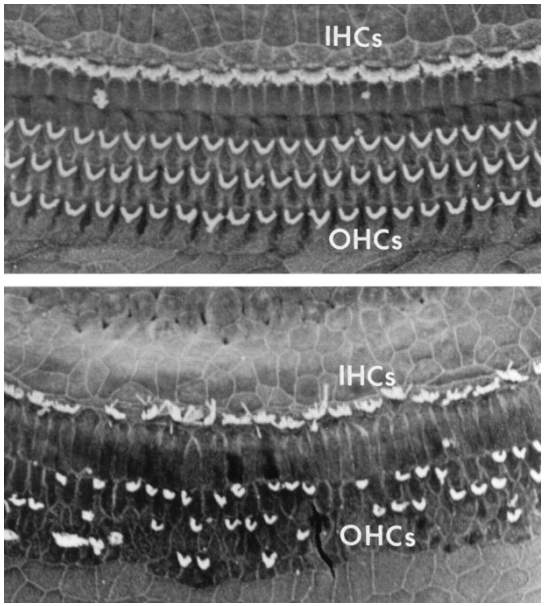
Do such acquired auditory nerve losses drive speech-in-noise difficulties, and tinnitus and hyperacusis, in people with normal or near-normal audiograms?

Case study

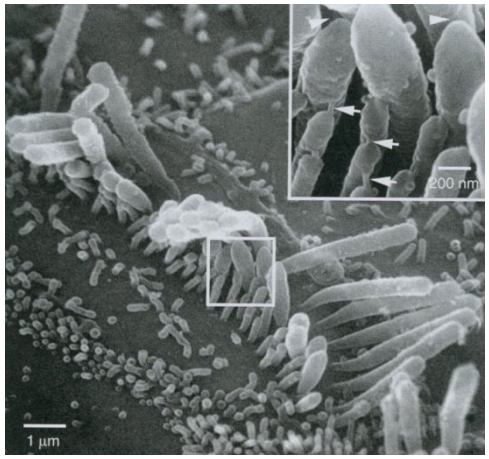
Considerations for future research

Pathophysiology of noise-induced sensorineural hearing loss circa 2008

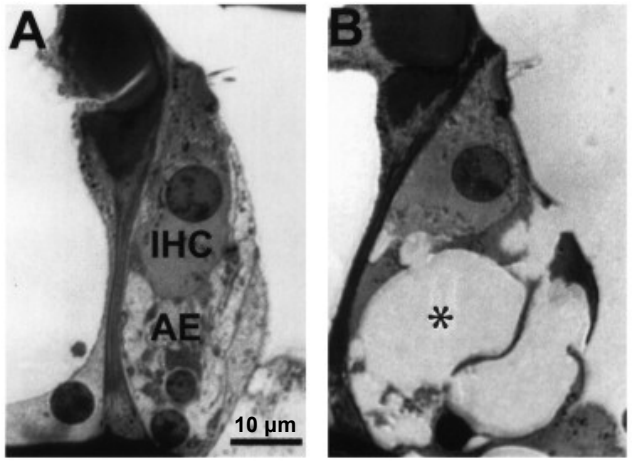
Even brief exposures to very loud noise can permanently destroy cochlear hair cells, particularly the OHCs, causing PTS.



At lower noise doses, TTS can occur without PTS.
TTS had been associated with disrupted OHC stereocilia (left), swollen IHC synaptic terminals (* right), reduced cochlear blood flow, bent cochlear pillar cells, etc. Presumably, these things can be fixed, leading to a full reversal of the TTS and avoiding PTS.



Pickles et al 1987 (Hear Res)



Puel et al 1998 (Neuroreport)

Note that the cilia damage is the direct result of mechanical stress, whereas the swelling of IHC synaptic terminals is due to glutamate excitotoxicity. Puel et al subsequently showed that infusion of glutamate (without noise exposure) also produced IHC synaptic swelling.

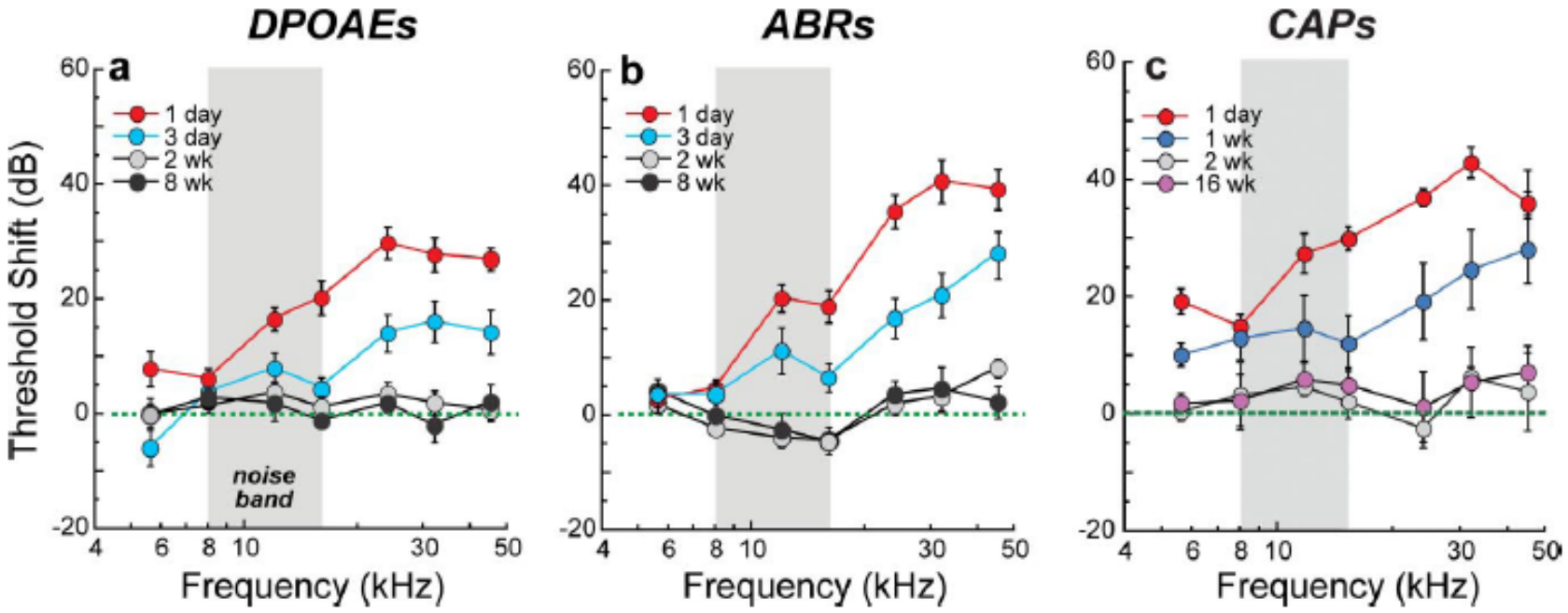
Adding Insult to Injury: Cochlear Nerve Degeneration after "Temporary" Noise-Induced Hearing Loss

Sharon G. Kujawa[1,2,3,4] and M. Charles Liberman[1,2,4]

The Journal of Neuroscience, November 11, 2009 • 29(45):14077–14085 • 14077

Showed that noise could irreparably damage IHC synapses, causing a degeneration of the disconnected nerve fibers, even in the absence of hair cell loss and PTS.

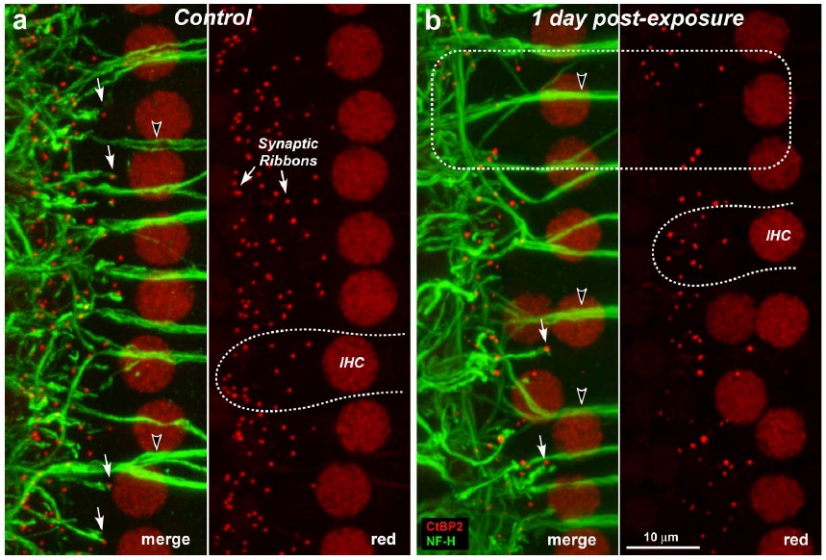
Temporary DPOAE, ABR, and CAP threshold shifts of **up to 40 dB,** measured in **CBA mice** after a **2 h** exposure to **8–16 kHz** octave-band noise at **100 dB SPL**. Note: **no PTS**

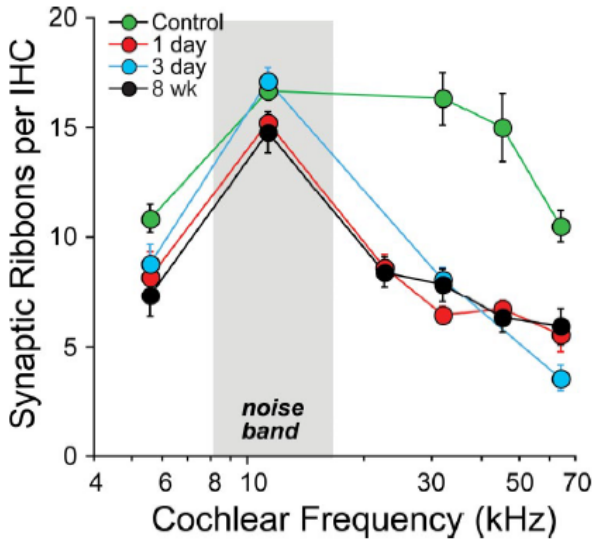


Adding Insult to Injury: Cochlear Nerve Degeneration after "Temporary" Noise-Induced Hearing Loss

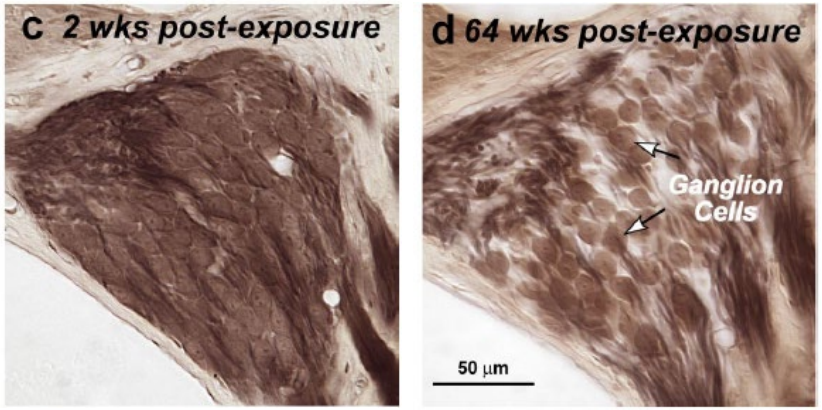
In high-frequency regions of the cochlea (above the 8–16 kHz noise band), there was a partial loss of IHC synapses with ANFs.

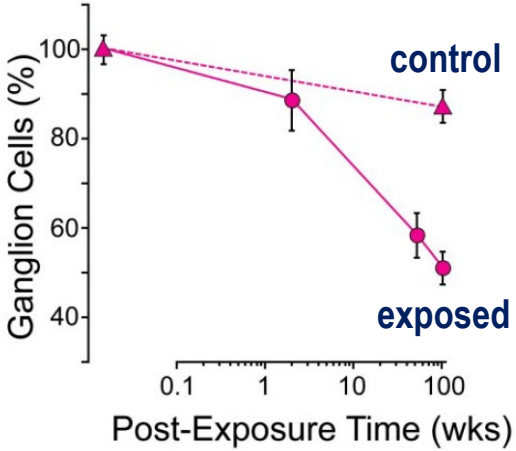
Although DPOAE/ABR/CAP thresholds all recovered, up to 50% of synapses were lost.





Auditory nerve fibers slowly degenerated after synapse loss while IHCs and OHCs remained intact.

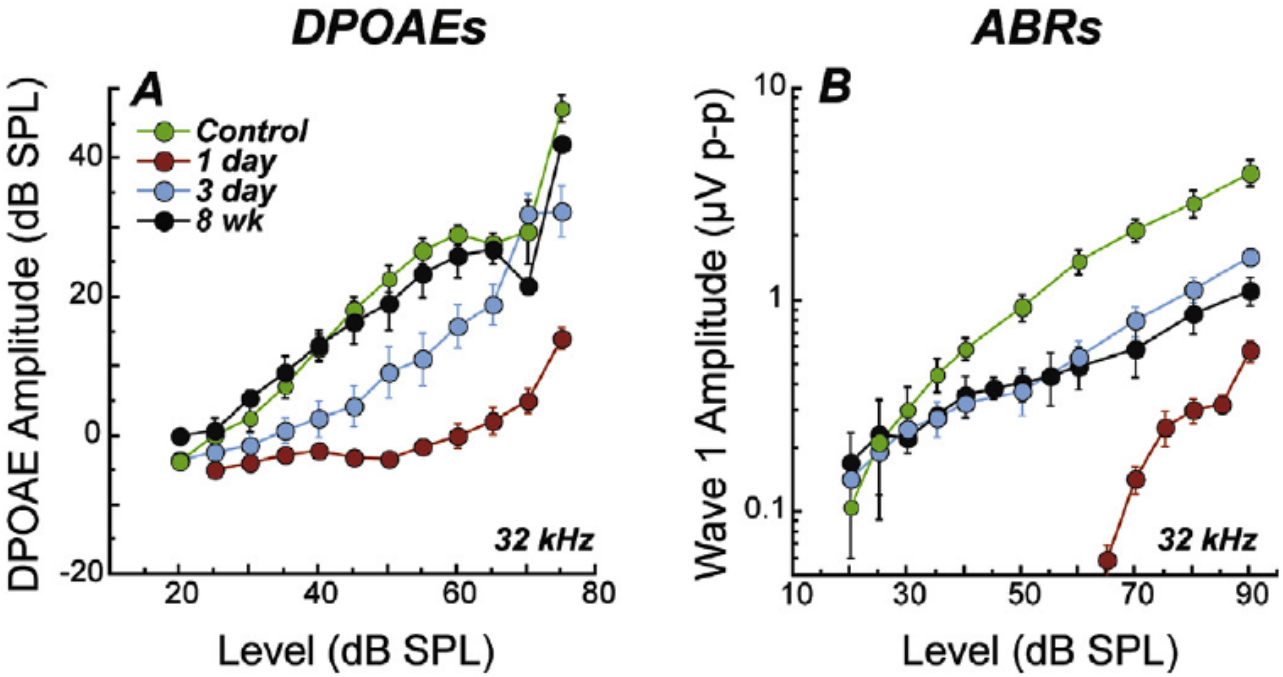




Adding Insult to Injury: Cochlear Nerve Degeneration after "Temporary" Noise-Induced Hearing Loss

DPOAEs recovered at all SPLs, consistent with little or no OHC loss.

ABR thresholds also recovered, but ABR wave 1 amplitudes remained reduced at mid to high stimulus levels, suggesting a potential non-invasive test of synaptopathy.



However, the amplitudes of surface-recorded ABR wave Is (and tiptrode-recorded CAPs) are smaller and more variable between human subjects than in subcutaneous animal recordings, due to higher electrode impedances, variable head size, etc.

How can ABR wave I thresholds remain unaffected by synaptopathy, while wave I amplitudes at mid-high SPLs are reduced?

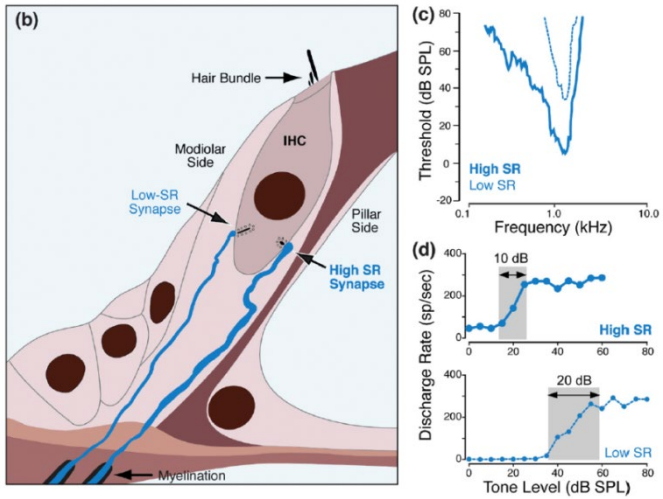
It has long been known that cats could retain normal hearing sensitivity after a nearly complete bilateral sectioning of the auditory nerve, despite ANF losses of up to 80% (Schuknecht & Woellner 1953).

More recently, Lobarinas et al (2013) found normal behavioral audiograms in chinchillas with carboplatin-induced IHC losses of up to 80%, and Chambers et al (2016) reported the same in ouabain-treated mice with up to 90% ANF loss.

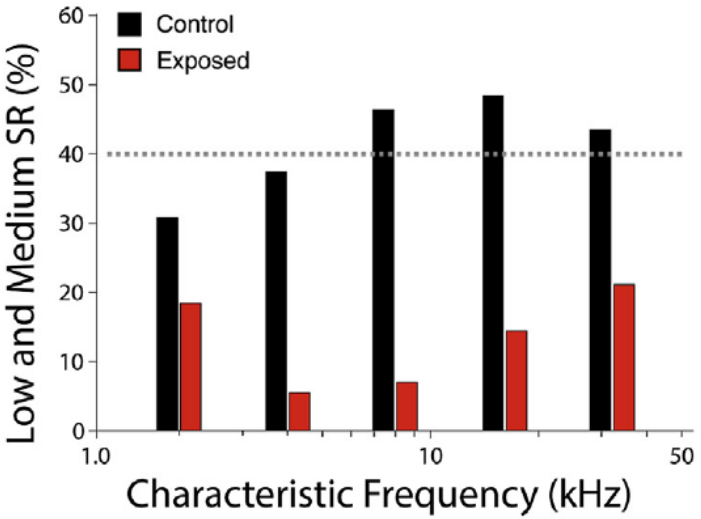
In the above studies, the IHC/ANF losses were distributed more or less evenly along the cochlea, i.e., **there were no "dead regions"**. This indicates that only a small percentage of surviving IHCs/ANFs is required for normal tone sensitivity in quiet, providing that the OHCs remain mostly intact (can lose 20–40% of OHCs before tone thresholds go up; e.g., Clark et al 1987 JASA).

A hallmark of auditory neuropathy is that speech intelligibility is substantially poorer than expected on the basis of the audiogram, which can remain in the clinically normal range.

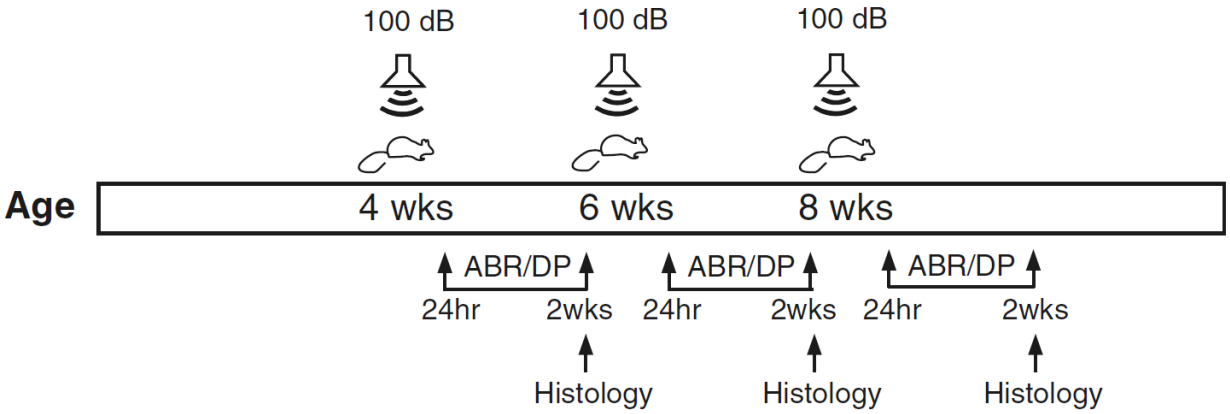
Low-threshold (high SR) and high-threshold (low SR) ANFs

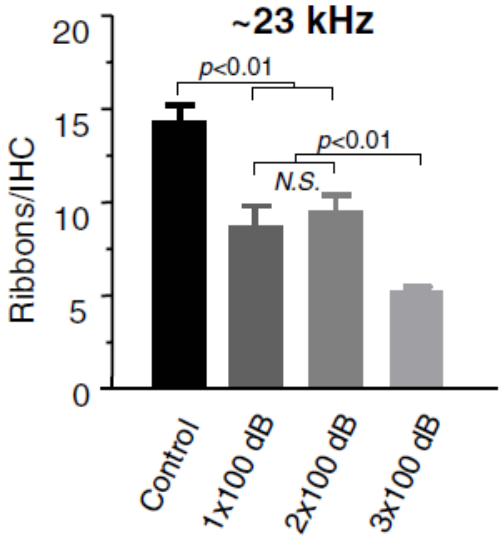


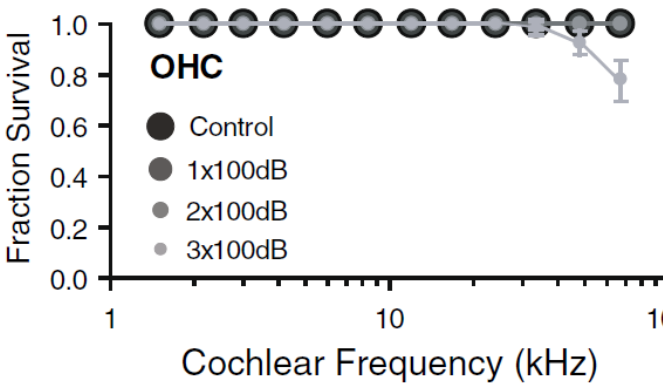
Synapses with high-threshold ANFs appear more vulnerable to both noise and aging, whereas low-threshold fibers appear better preserved (e.g. Furman et al 2013)

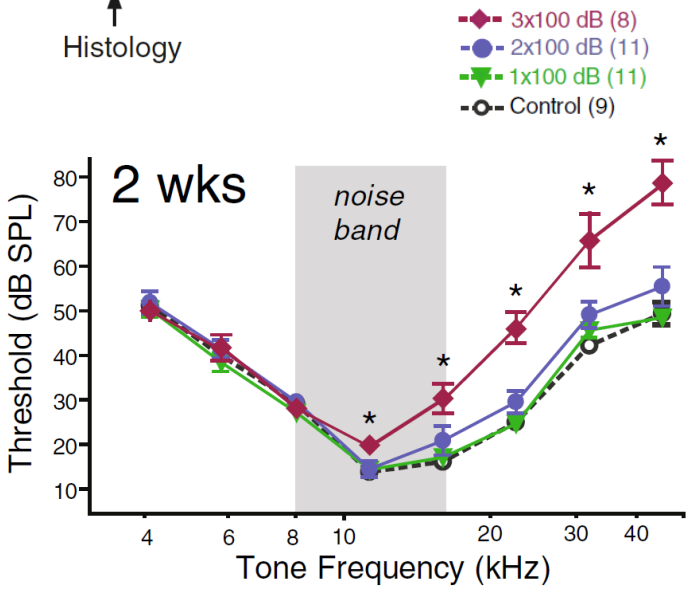


What about a series of 2 h, 100 dB SPL exposures? (Wang & Ren, 2012)



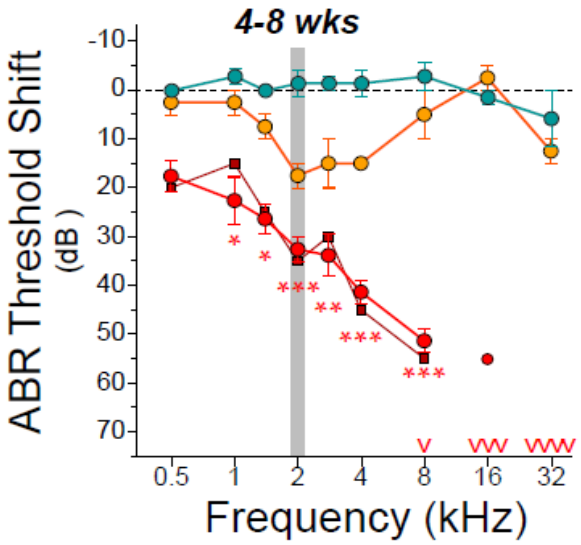


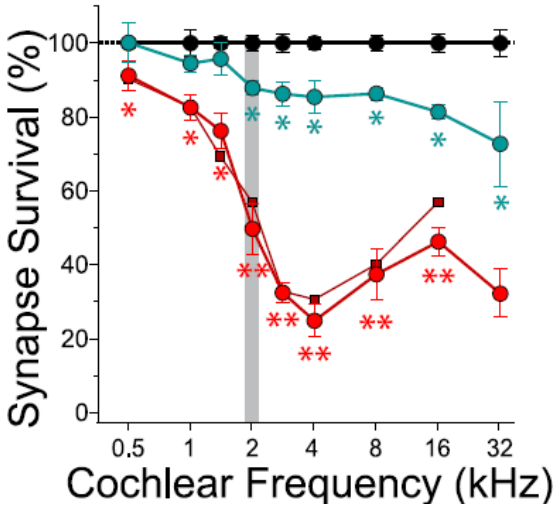


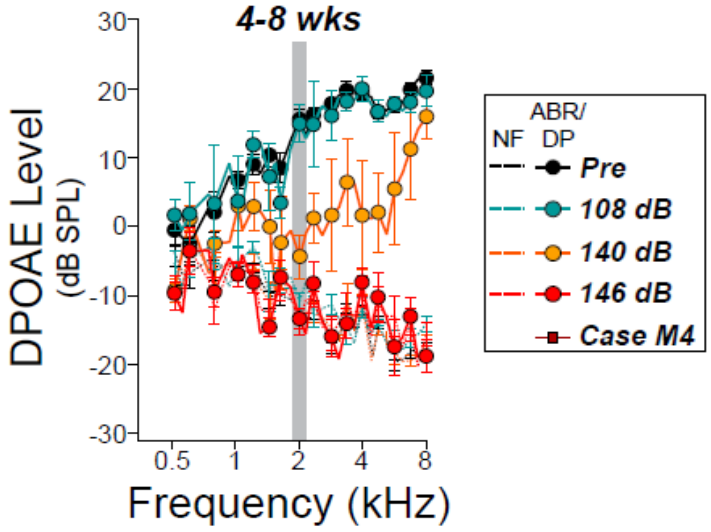


If enough synapses are lost (about 2/3 in the study of Wang & Ren), ABR thresholds begin to increase, although after 3 exposures some high-frequency OHC loss was also observed.

Cochlear synaptopathy in primates (rhesus monkeys) after a 4 h exposure to 2 kHz narrowband noise at 108 dB SPL (Valero et al, 2017)







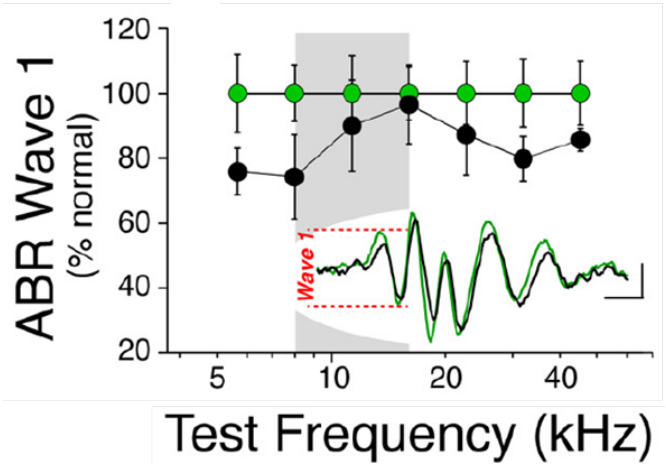
In primates, synaptopathy can also occur in the absence of hair cell loss, although rodents are clearly more vulnerable to noise trauma: 108 dB SPL for 4 h caused less synaptopathy in primates than did 100 dB SPL for 2 h in mice.

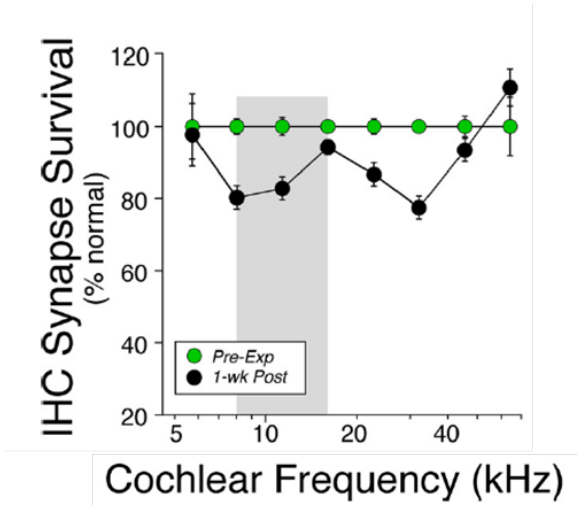
Noise doses that destroy OHCs (140–146 dB SPL) also cause massive synaptopathy. **Thus, there is little doubt that synaptopathy is a major contributor to human sensorineural hearing loss, and likely explains why people with similar audiograms can vary widely in SIN scores.**

Longer-term exposures cause synaptopathy in CBA mice at “moderate” SPLs (also without PTS or OHC/IHC losses)

Such findings have implications for noise exposure regulations, which were intended to prevent PTS, not TTS.

1 week of 8–16 kHz noise at 84 dB SPL (ABRs at 2 weeks post-exposure)

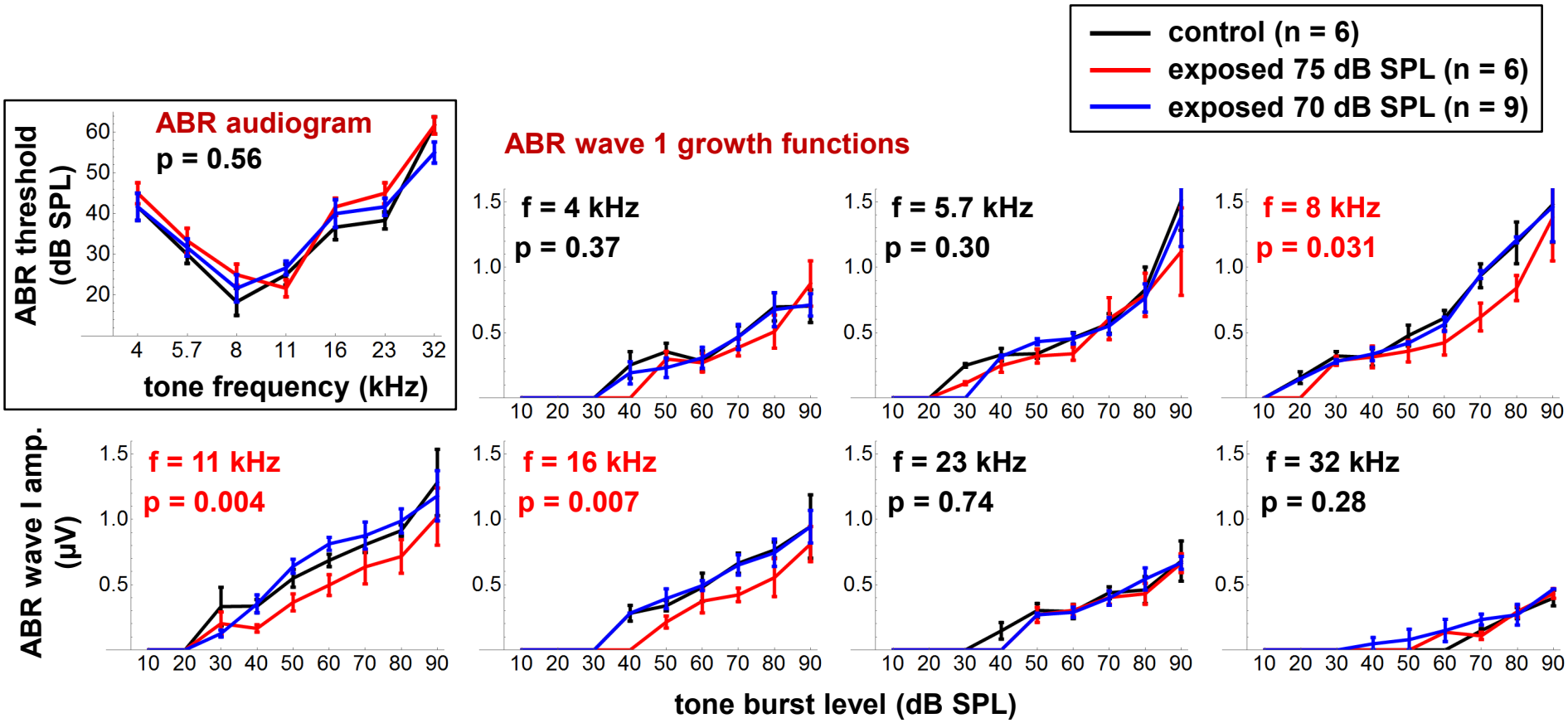




Maison et al 2013 (J Neurosci)

Longer-term exposures cause synaptopathy in CBA mice at “moderate” SPLs (also without PTS or OHC/IHC losses)

2 months of 8–16 kHz noise at 75 dB SPL (ABRs at 3 weeks post-exposure)



Pienkowski 2018 (Trends in Hearing)

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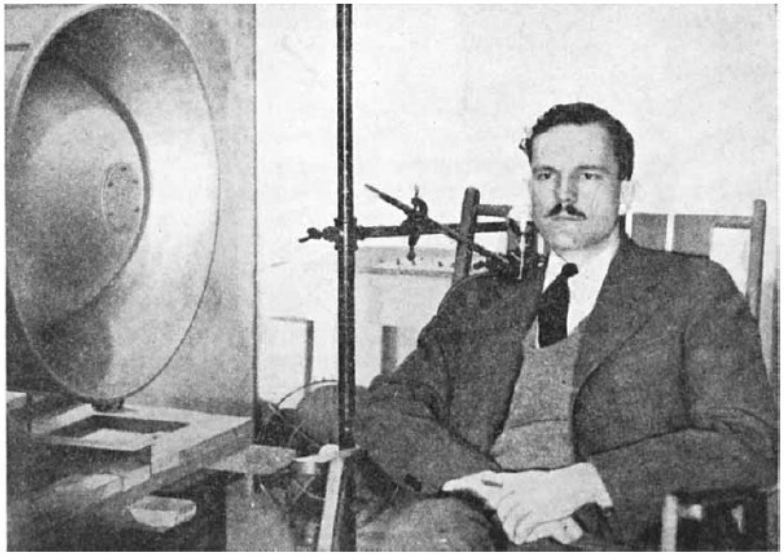
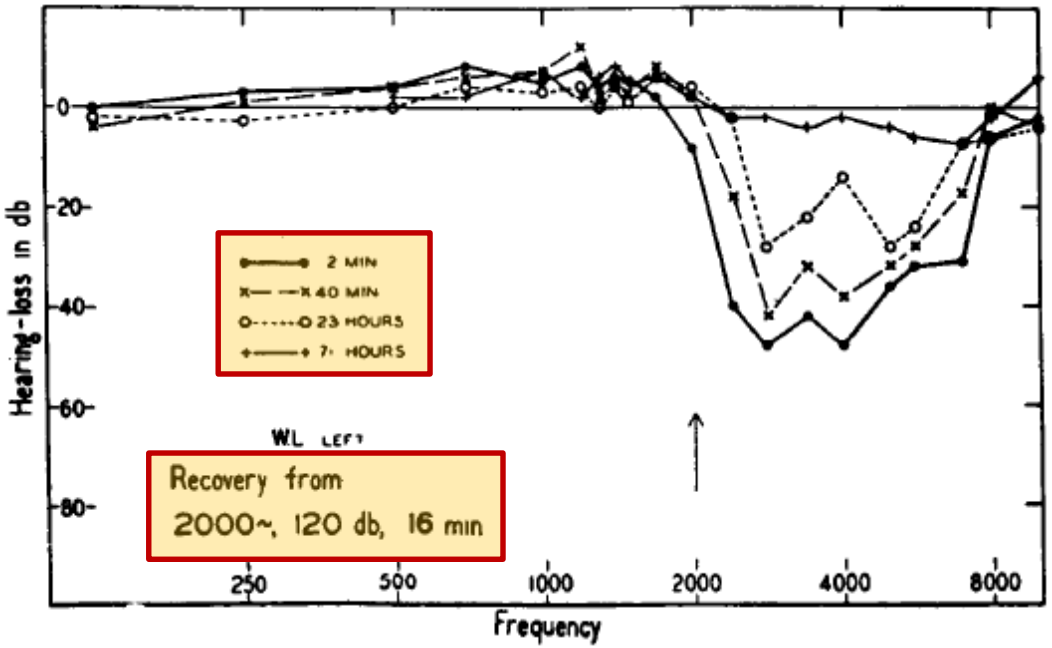
Early human laboratory studies of noise-induced temporary threshold shifts





Davis et al 1950 (Acta Otolaryngol Suppl)

Davis and colleagues repeatedly subjected themselves to noise doses that caused a 40 dB TTS, same as in the mouse studies. While humans are less vulnerable to noise trauma than mice, Davis anecdotally reported that his ability to hear in noise deteriorated as a consequence of these experiments, in spite of the fact that thresholds always recovered.

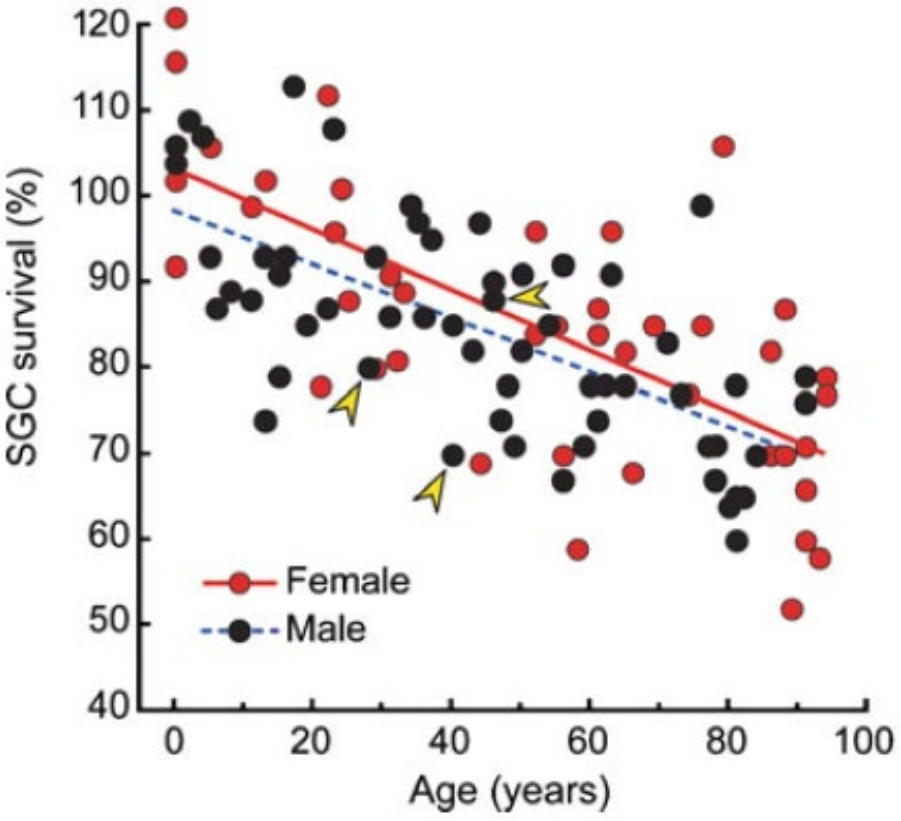
Many people with a history of exposure to loud music or noise report difficulties understanding speech in noisy settings, even if their audiograms remain clinically normal (≤20 dB HL up to 8 kHz). Some develop tinnitus, hyperacusis, or both. Eventually, they appear to acquire larger audiometric losses with age than peers who avoided loud noise (although more longitudinal studies are needed).

Age-Related Primary Cochlear Neuronal Degeneration in Human Temporal Bones

Chadi A. Makary[1,2], Jennifer Shin[1,2], Sharon G. Kujawa[1,2,3], M. Charles Liberman[1,2,3], and Saumil N. Merchant[1,2,3]

JARO
Journal of the Association for Research in Otolaryngology
JARO 12: 711–717 (2011)

Spiral ganglion cell (SGC) survival vs. age at death from 100 people ***without* IHC or OHC losses**.



There is a progressive loss of SGCs with age *that is independent of hair cell loss* (~1,000 SGCs per decade from ~30,000 at birth). *Thus, synaptopathy is an important component of presbycusis.*

This age-related loss of SGCs likely underestimates the degree of neural loss in presbycusis, because human SGCs can survive for years or even decades after the loss of their synapses with IHCs.

Does the large scatter in the plot suggest a noise-induced component to human synaptopathy?

Arrows point to 3 males with a known history of noise exposure (more data would be great):

- 28 year old carpenter

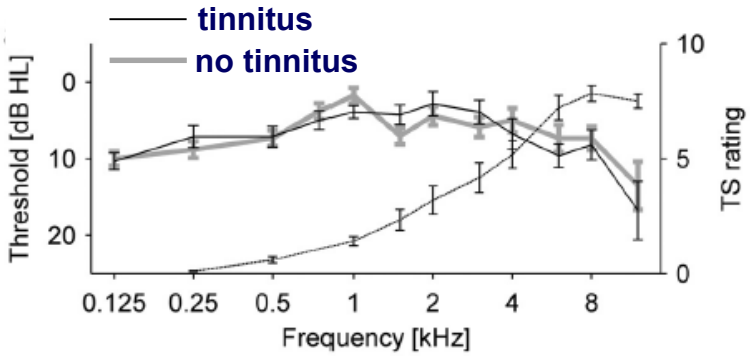
- 40 year old who suffered TTS but no PTS after an accidental gun discharge near his ears 5 years prior to death

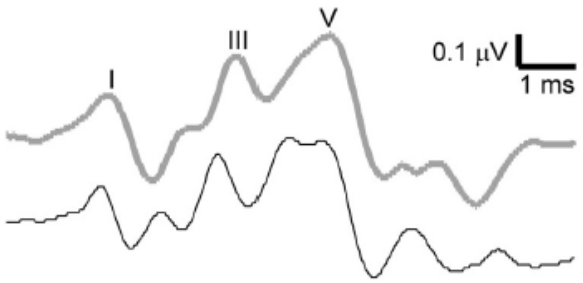
- 46 year old printing press operator

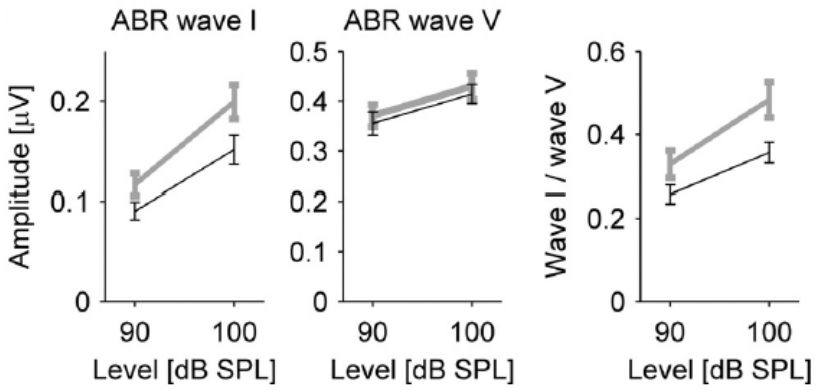
Tinnitus with a Normal Audiogram: Physiological Evidence for Hidden Hearing Loss and Computational Model

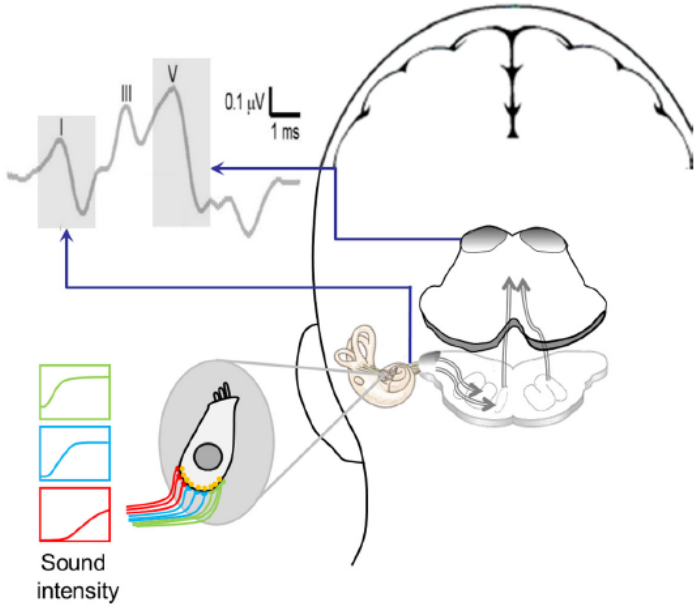
Roland Schaette and David McAlpine

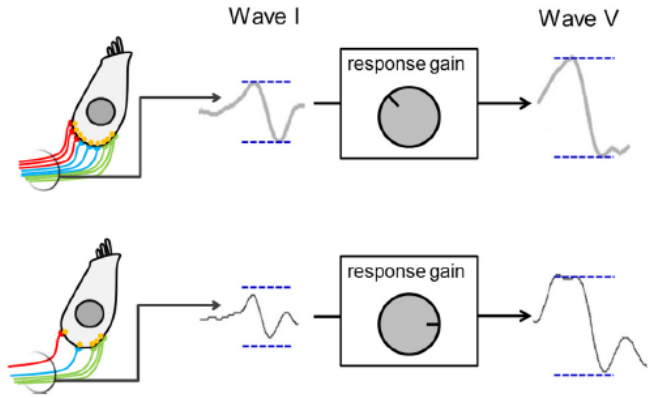
The Journal of Neuroscience, September 21, 2011 • 31(38):13452–13457







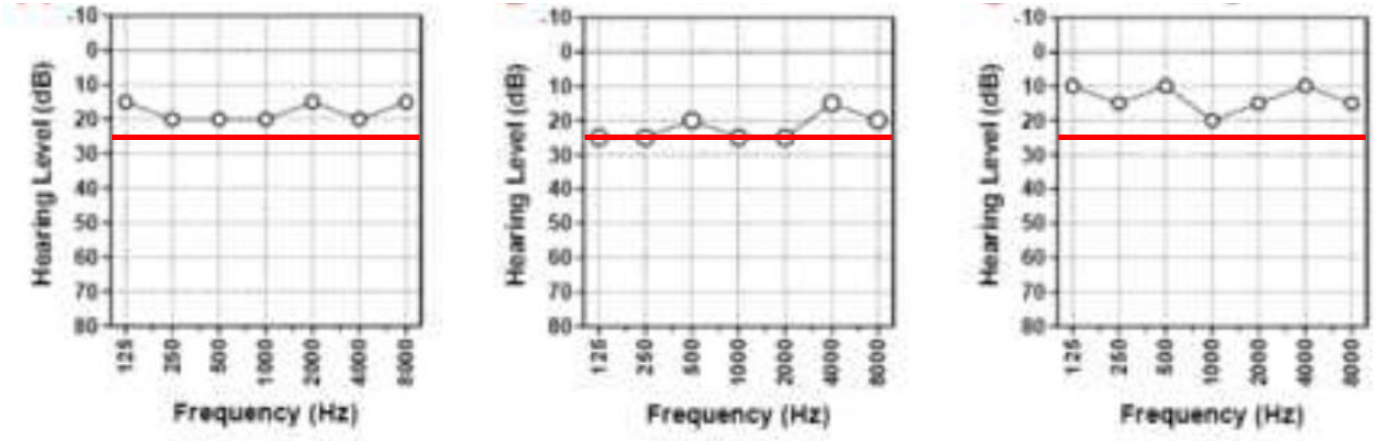




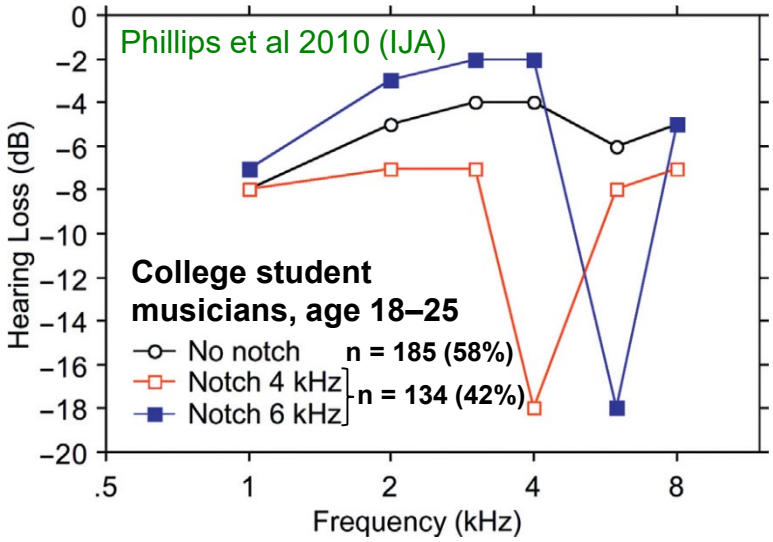
Average hearing thresholds of "normal-hearing" young adults are **defined as 0 dB HL**.

95% CIs are within -10 to 10 dB HL up to 8 kHz, and within -20 to 20 dB HL at 16 kHz.

Three tinnitus patients with "clinically normal" audiograms.



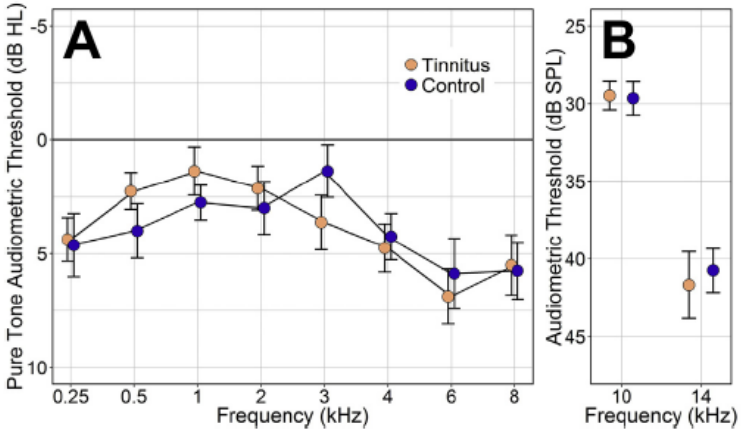
Even a person with 10 dB HL hearing may have a 20 dB hearing loss if they started at -10 dB HL.
Baseline measures are important in audiology, and in medicine in general…

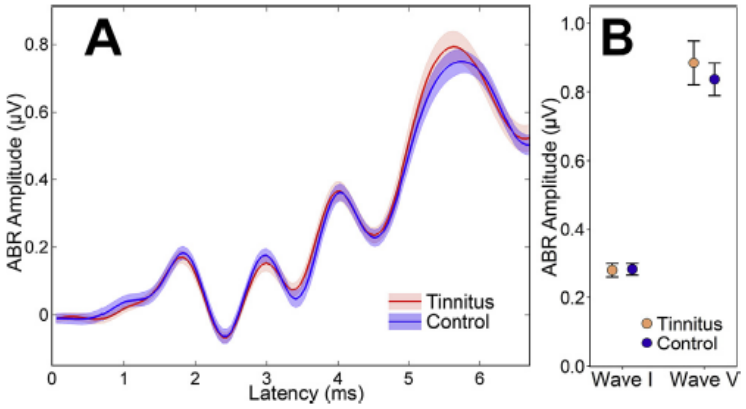


Tinnitus with a normal audiogram: Relation to noise exposure but no evidence for cochlear synaptopathy

Hannah Guest [a, *], Kevin J. Munro [a, c], Garreth Prendergast [a], Simon Howe [b], Christopher J. Plack [a, d]

Hearing Research 344 (2017) 265–274



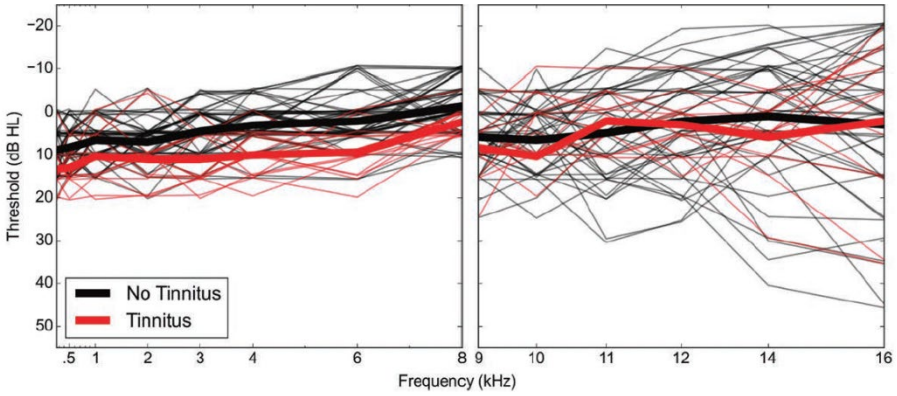


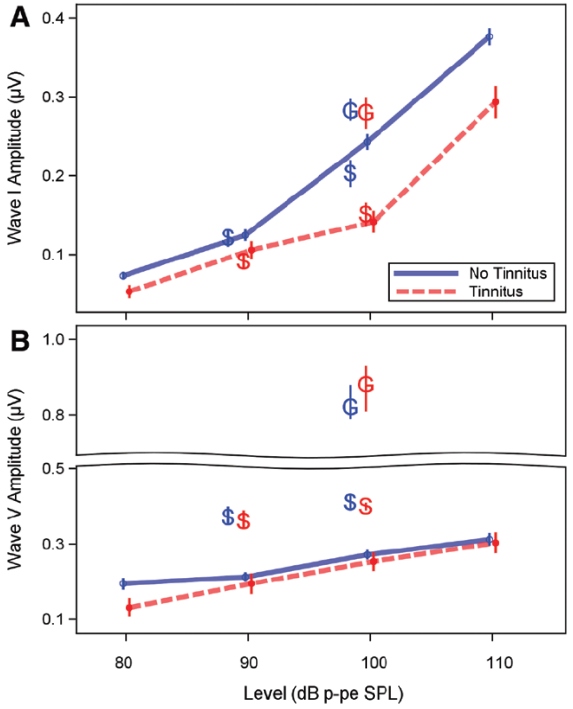
ABR wave I amplitudes are unlikely to be sensitive enough to reliably detect synaptopathy in individual tinnitus patients, **unless perhaps baseline measures are available.**

Tinnitus and Auditory Perception After a History of Noise Exposure: Relationship to Auditory Brainstem Response Measures

Naomi F. Bramhall,[1,2] Dawn Konrad-Martin,[1,2] and Garnett P. McMillan[1,2]

(Ear & Hearing 2018;XX;00–00)

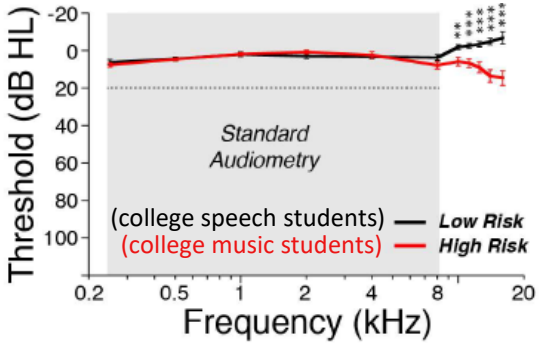


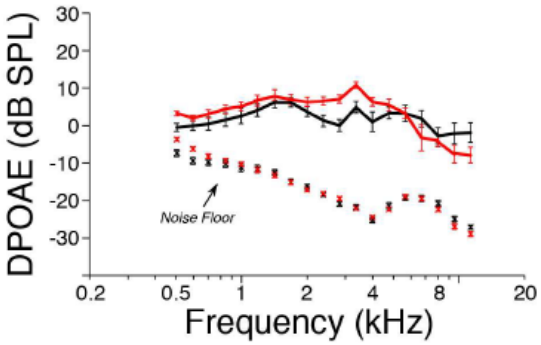


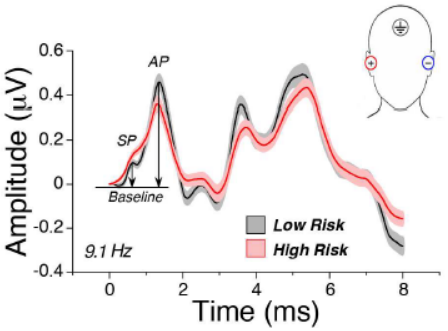
Toward a Differential Diagnosis of Hidden Hearing Loss in Humans

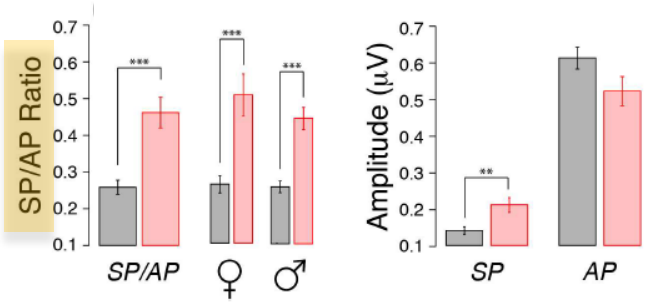
M. Charles Liberman[1,2,3], Michael J. Epstein[4], Sandra S. Cleveland[4], Haobing Wang[2], Stéphane F. Maison[1,2,3]*

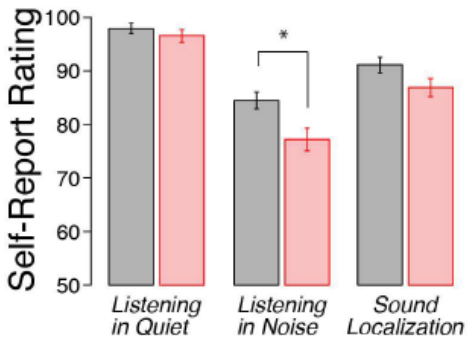
PLOS ONE | DOI:10.1371/journal.pone.0162726 September 12, 2016

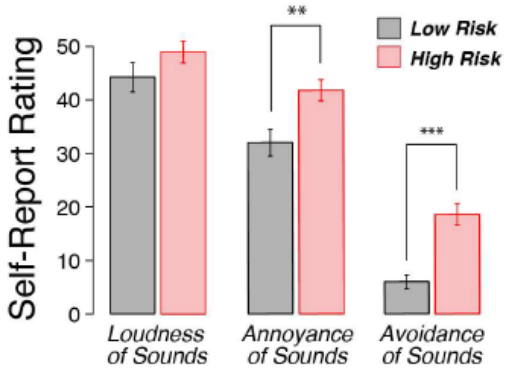


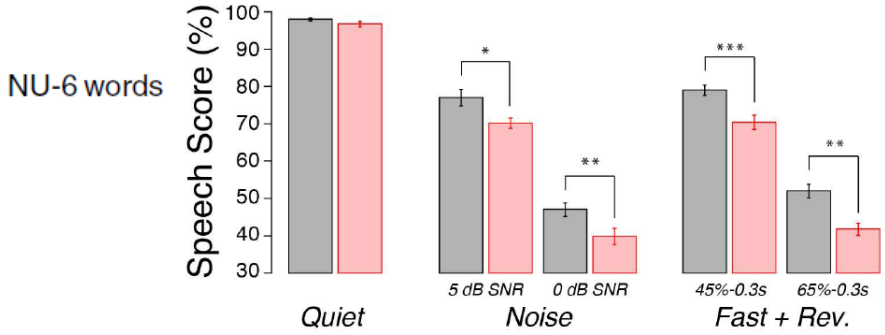


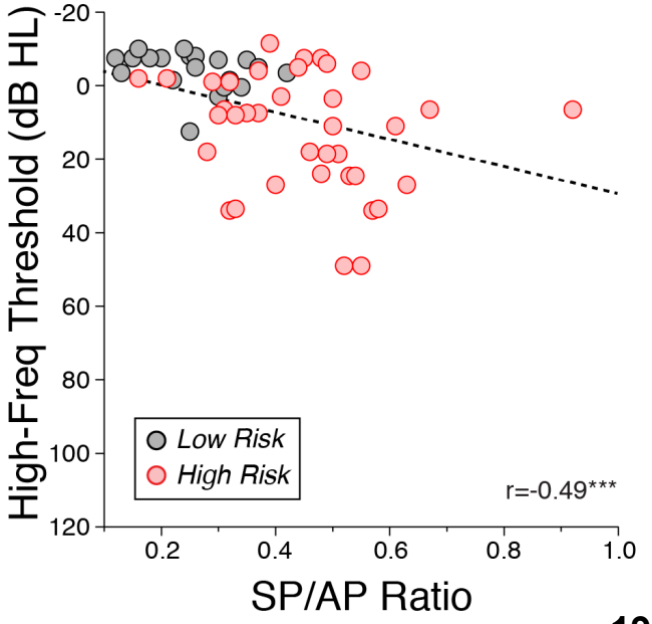




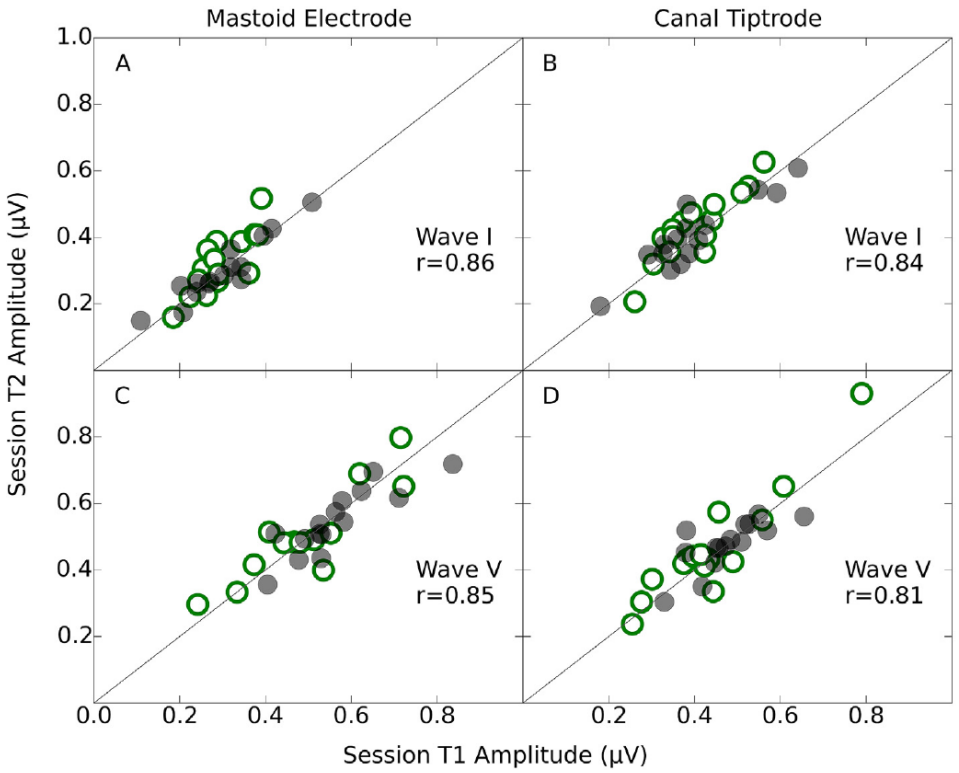


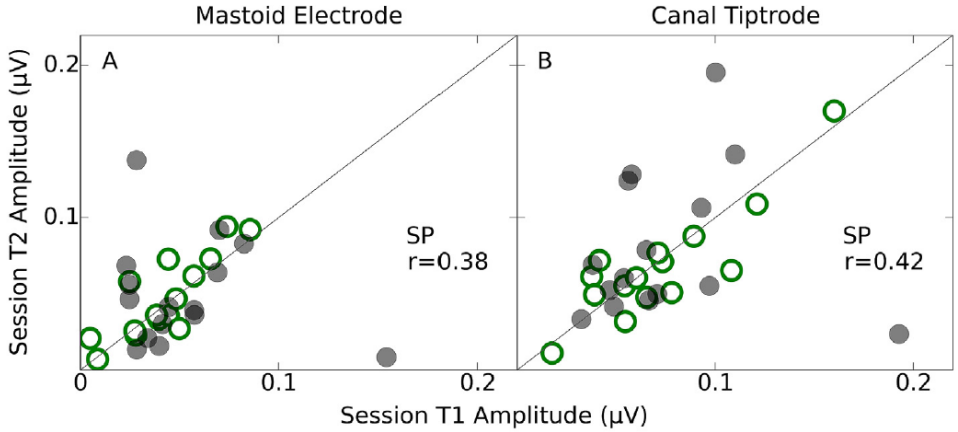






Test-retest reliability of wave I and wave V amplitudes, and of the SP





Low Noise

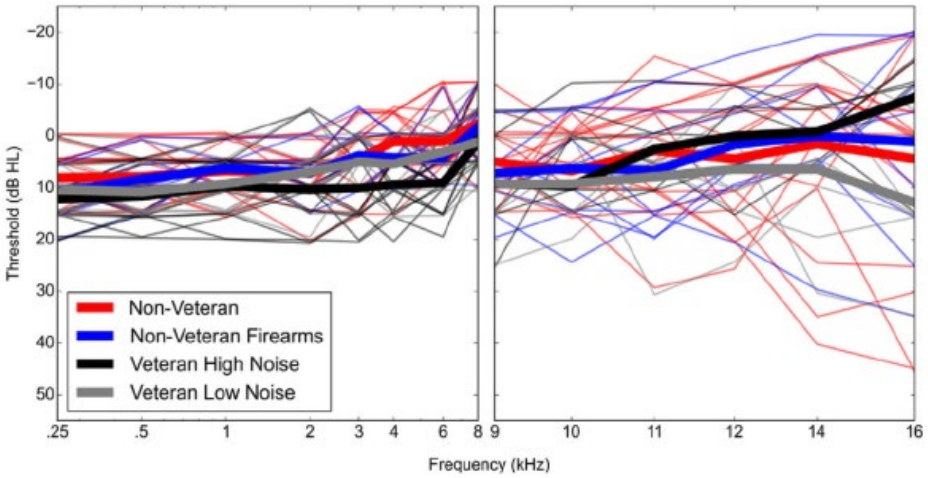
High Noise

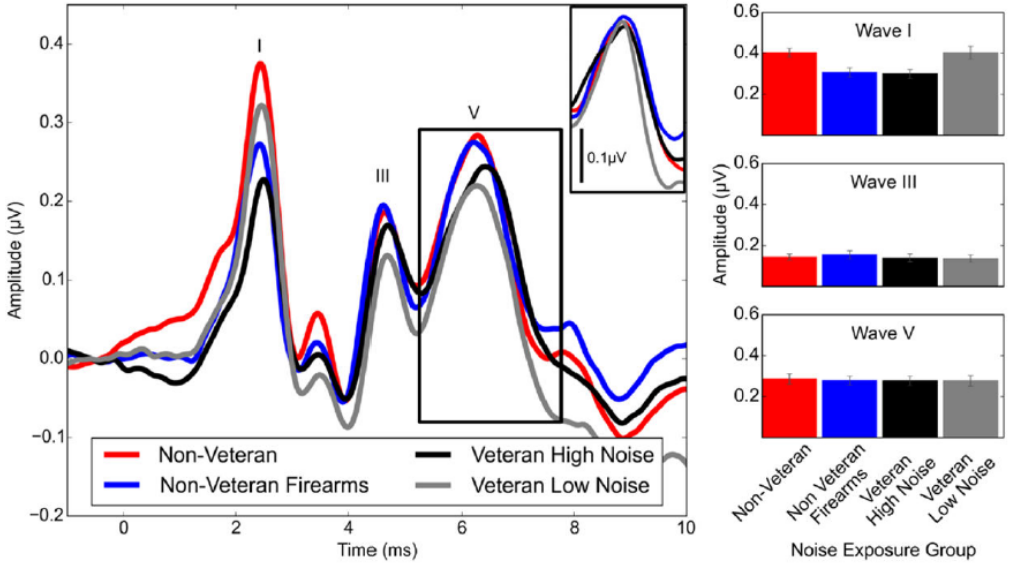
Prendergast et al 2018 (Hear Res)

Ear Hear. 2017 ; 38(1): e1–e12. doi:10.1097/AUD.0000000000000370.

Auditory Brainstem Response Altered in Humans With Noise Exposure Despite Normal Outer Hair Cell Function

Naomi F. Bramhall[1], **Dawn Konrad-Martin**[1,2], **Garnett P. McMillan**[1], and **Susan E. Griest**[1,2]



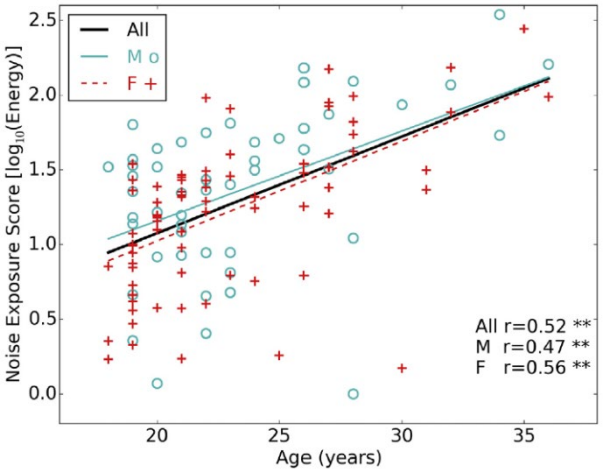


Effects of noise exposure on young adults with normal audiograms I: Electrophysiology

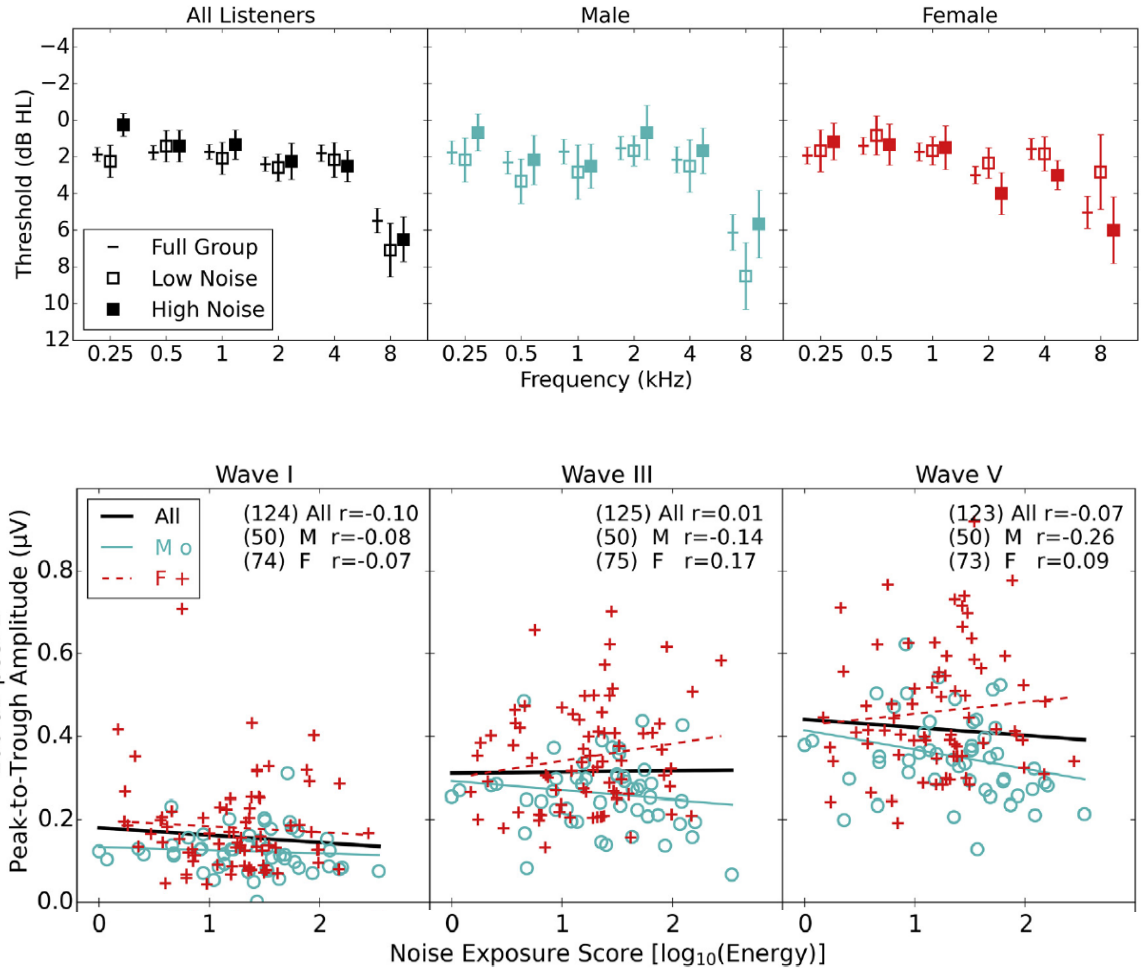
Garreth Prendergast [a, *], Hannah Guest [a], Kevin J. Munro [a, b], Karolina Kluk [a], Agnès Léger [a], Deborah A. Hall [c, d], Michael G. Heinz [e], Christopher J. Plack [a, f]

Hearing Research 344 (2017) 68–81

lifetime noise dose
(note $\log_{10}$ units so more than a 100x range)



People who have accumulated a high lifetime recreational noise dose might have genetically "tougher" ears, which sustain less damage than the more "tender" ears of people who have learned to avoid loud settings. Or perhaps noise that is loud but not damaging "conditions" the ear, improving resistance to very loud exposures.



Outline

Cochlear synaptopathy in animal studies
(primary noise- and age-related inactivation and degeneration of auditory nerve fibers)

Do such acquired auditory nerve losses drive speech-in-noise difficulties, and tinnitus and hyperacusis, in people with normal or near-normal audiograms?

Case study

Considerations for future research

Case study: 44 year old Caucasian male

primary complaint: difficulty hearing speech in noise (good speech in quiet)
secondary complaint: mild bilateral tinnitus and hyperacusis

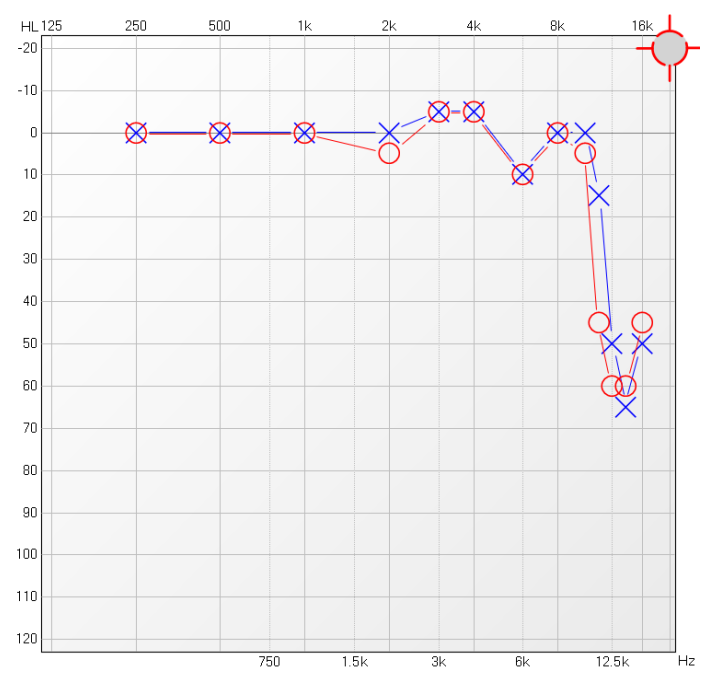
- At age 24, experienced a series of about a half dozen loud music exposures over the course of a few weeks; each exposure was up to 120 dB SPL, and lasted up to a half hour. Transient tinnitus and TTS of up to 40 dB recovered completely within 24 h after each exposure, as did DPOAEs, which would temporarily disappear into the noise floor.

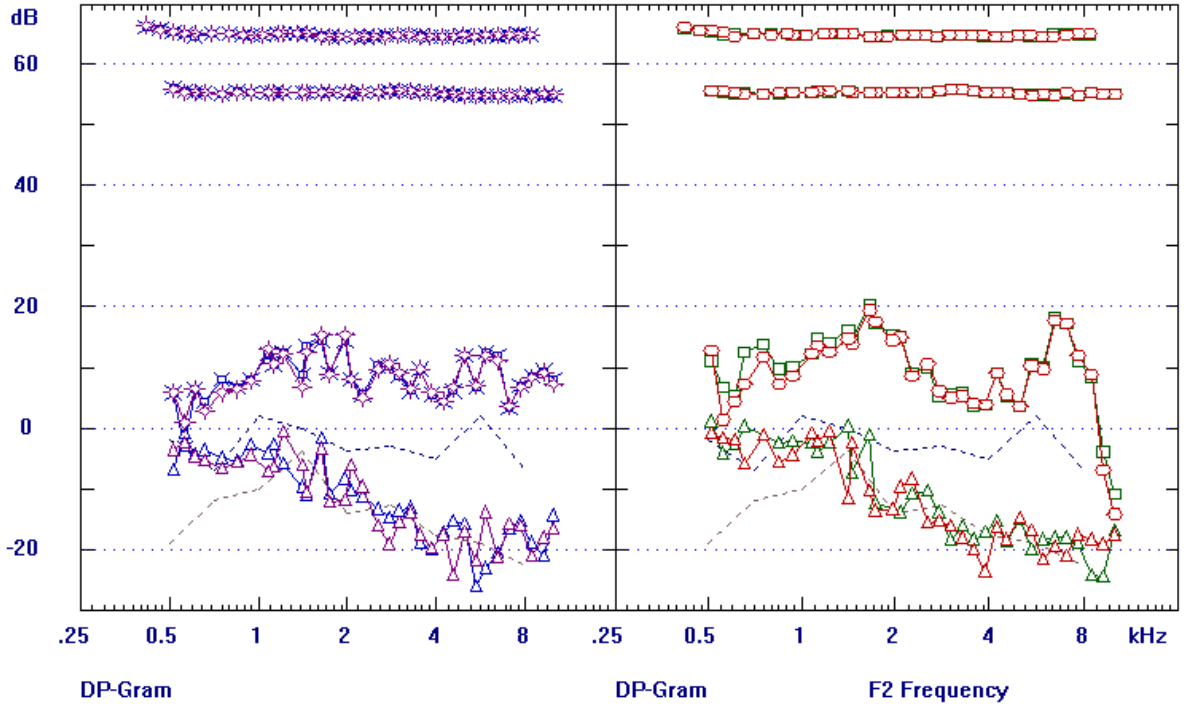
- Within a year of loud music exposures, noticed a dramatic and at the time scary drop-off in ability to hear in noise (at conference poster halls and other places). Audiometry remained 0 dB HL or better at all frequencies up to 8 kHz.

- Since then, developed a mild (non-bothersome so far), bilateral, high-pitched tinnitus, and mild hyperacusis, but these took much longer to emerge than the speech-in-noise issues.

- Also since then, became more vulnerable to loud noise in that transient tinnitus is louder and longer-lasting after an exposure; therefore, protects ears when mowing lawn, vacuuming, etc., and tries to avoid loud music and noise.

Audiogram to 16 kHz, and DPgram (65/55 dB SPL) to 10 kHz





Pure tone thresholds are -5 to 5 dB HL bilaterally up to 10 kHz (**average about 0 dB HL**), except at 6 kHz = 10 dB HL. Above 10 kHz, both ears show a hearing loss averaging about 50 dB, which starts at a lower frequency in the right ear, just above 10 kHz.

DPOAEs average nearly 10 dB SPL up to 10 kHz in the left ear, and up to 8 kHz in the right ear. Above 8 kHz, the right DPgram steeply falls into the noise floor by 10 kHz.

DPOAEs can be more sensitive to OHC losses than the audiogram

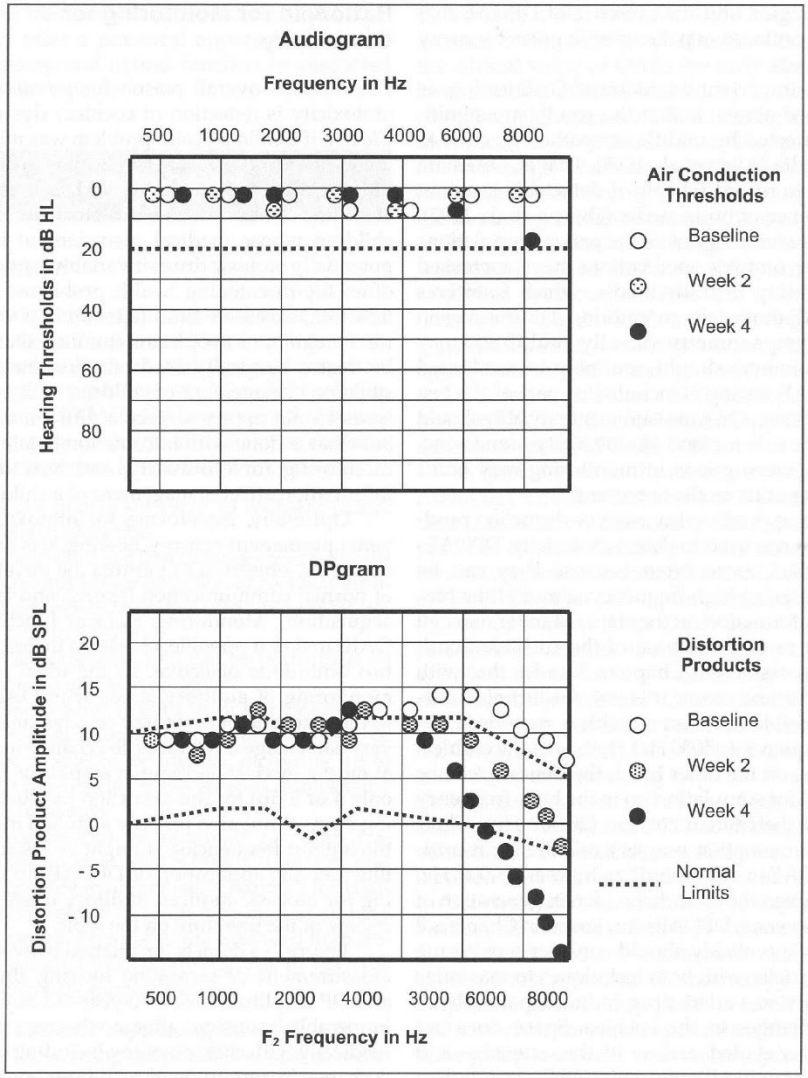
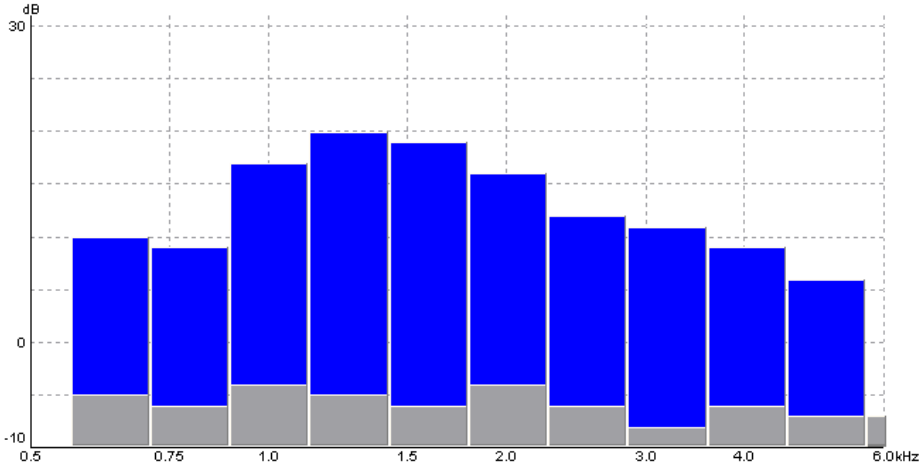
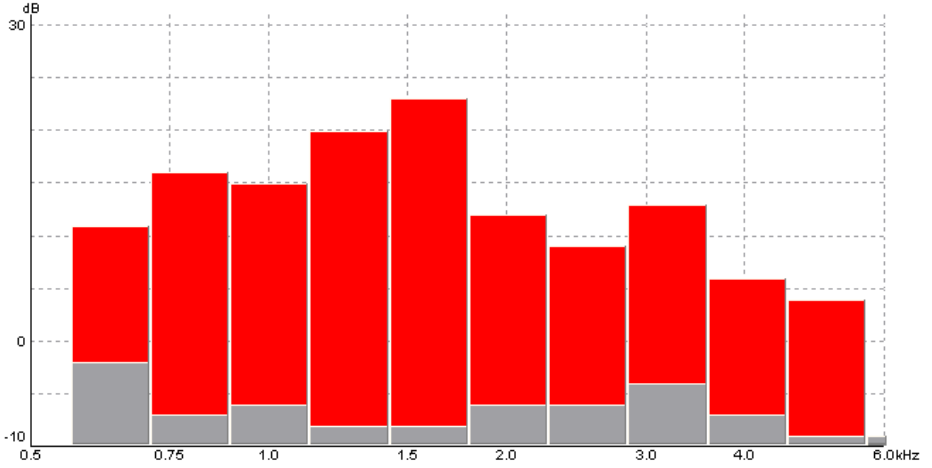


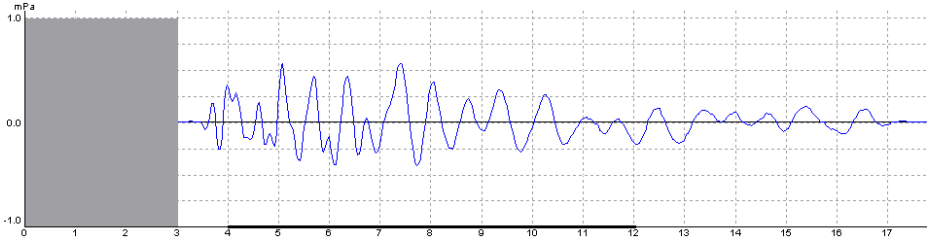
FIGURE 7–4. Pure-tone hearing thresholds and distortion product otoacoustic emissions (DPOAEs) in a 7-year-old boy with a brainstem tumor undergoing medical management with chemotherapy that included cisplatin. Findings are described in the text.

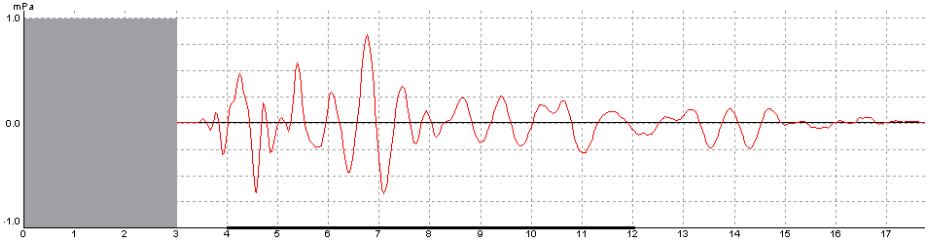
Dhar & Hall 2018 (OAEs: Principles, Procedures, and Protocols, 2nd Ed)

TEOAEs (Clicks at 80 dB peSPL)

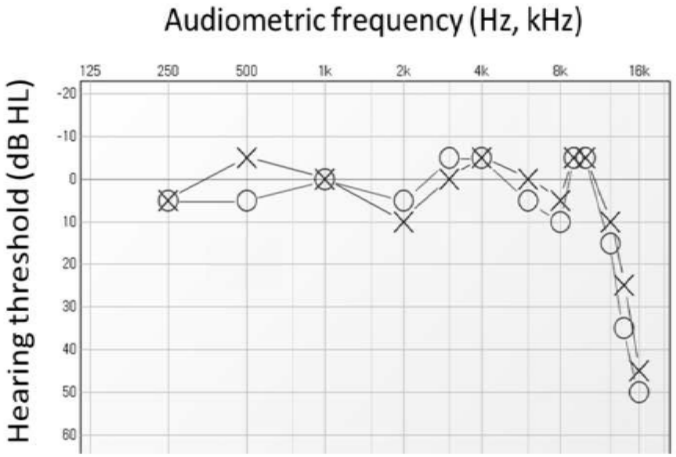








The “extended high frequencies” or EHFs (8–20 kHz)



35 year old female, ex-college musician, with thresholds within 10 dB HL up to 11.5 kHz, sloping to a loss of 45–50 dB at 16 kHz. She has mild, bilateral tinnitus which reliably pitch-matches to 9 kHz.

There is very little acoustic power in speech above 8 kHz. How much do audiometric EHF losses directly contribute to SIN deficits?

Audiograms at even conventional frequencies (within the speech range) correlate poorly with clinical SIN scores, for thresholds in the normal to mild-impaired range (e.g., Phatak et al 2018; Ear Hear). What about more moderate EHF losses, as in the two audios shown? Regardless of their potential contribution to SIN deficits, EHF losses are a sure sign that basal OHCs have been damaged.

Could EHF losses point to synaptopathy in lower cochlear frequency regions where thresholds remain normal? Could synaptopathy explain tinnitus with a pitch that lies within the audiometrically normal range? Could synaptopathy explain SIN deficits in some adults (and children) with normal conventional audiograms? Or are tinnitus and SIN deficits a direct consequence of the EHF losses?

EHF losses as early indicators of cochlear damage:

Is the cochlear base even more vulnerable to noise than the 3–6 kHz frequency region, where hearing sensitivity is normally greatest due to ear canal & pinna resonances?

Might depend on the noise type, bandwidth, intensity, etc.

A 4-year longitudinal study of Australian teenagers found that occasionally attending discos resulted in significant audiometric losses only at 14 and 16 kHz (Serra et al 2005; IJA).

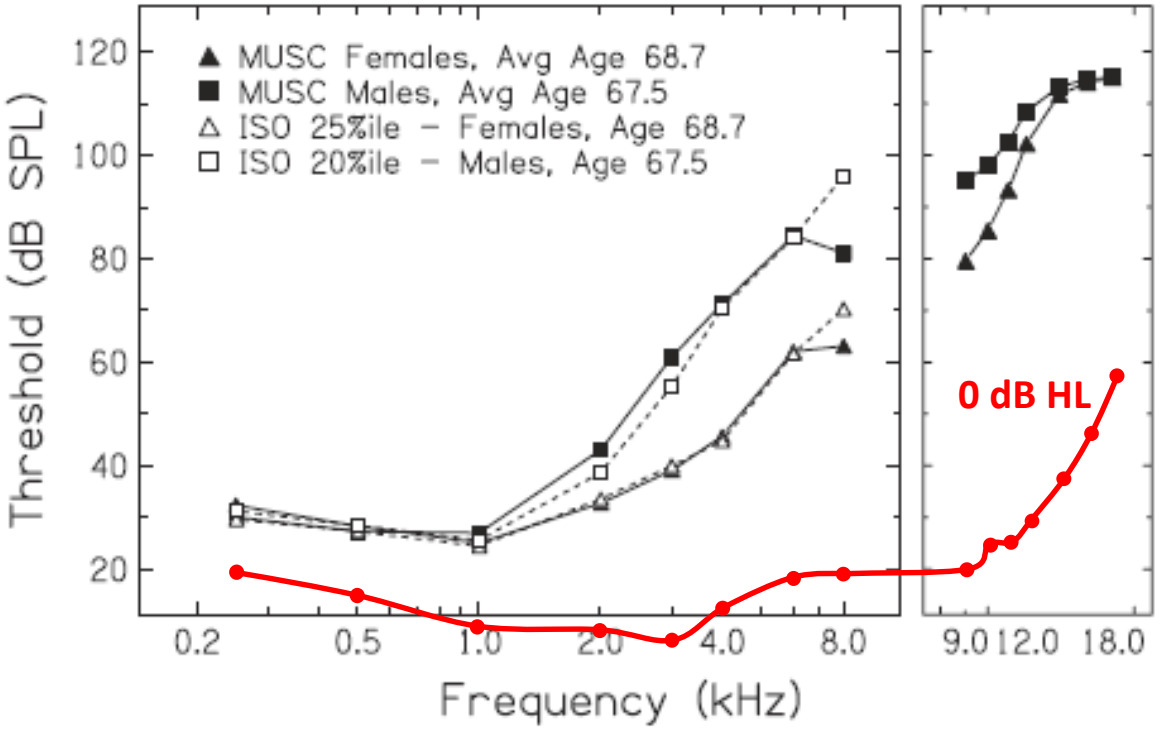
Chinese college students who used personal music players had significantly increased thresholds above 3 kHz compared to controls, but the losses were greatest above 6 kHz. In the music player group, subjects with clinically normal thresholds up to 8 kHz nevertheless had significantly elevated EHF thresholds (Peng et al 2007; J Otolaryngol).

Young adult Americans with clinically normal audiograms to 8 kHz, who reported long-term music player use at loud volumes, had significantly elevated EHF thresholds (Le Prell et al 2013; JAAA)

Although the EHF losses in all of these studies were significant, they were small. Given the higher variability of EHF thresholds between subjects with "normal hearing" (-20 to 20 dB HL), it is unclear whether EHF thresholds will be sensitive enough to reliably detect early-stage cochlear damage in individual patients, unless baseline measures are available. If you are measuring someone's baseline audiogram, do it to 16 kHz!

Average hearing loss in 68 year olds

Losses are up to 20 dB greater in senior males than females **between 2 and 12 kHz**.
In both sexes, losses are greatest above 8 kHz.



Lee et al 2005 (Ear & Hear)

44 year old male: click ABRs in quiet and in ipsilateral broadband masking noise

No ABR at an SNR of +5 dB in the left ear, and +15 dB in the right ear…

Clinical speech-in-noise testing (all speech presented at 65–70 dB SPL)

QuickSIN SNR loss was 1.5 dB in the right ear and 0.3 dB in the left ear.

QuickSIN was not sensitive to the patient's SIN difficulties, which again were "dramatic and scary" at the time they were first noticed about 20 years ago. Many people with self-reported SIN issues, especially musicians, have normal QuickSINs.

QuickSIN sentences are quite redundant, e.g., "A toad and a frog are hard to tell apart." When sentences were less redundant, the patient sometimes made mistakes at higher SNRs, e.g., 15 dB SNR: "Down that road is the way to the grain farmer."
10 dB SNR: "The black trunk fell from the landing."

AZBio sentences in noise (presented free-field) are even more redundant. Patient scored 95% words correct at an SNR of +10 dB, and 92% words correct at +5 dB.

WIN test (monosyllabic NU-6 words): 50% correct at SNR of +6.8 dB in the right ear, and +5.6 dB in the left ear (mild-impaired)

SPRINT test (US army; NU-6 words presented binaurally at a fixed SNR of +9 dB): scored 88% correct (mild-impaired). Normal listeners score 95–100%. 88% correct is 72nd percentile among "H-3" soldiers, who face "significant" challenges in performing military duties because of difficulties hearing.

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Speech-in-noise problems despite normal or near-normal audiograms could be due to central auditory processing disorders or to issues with attention, working memory, or language. Another possibility is damage to the cochlea, such as noise- and age-related cochlear synaptopathy/neuropathy.

Can we effectively identify people who are especially vulnerable to loud noise, or who have already incurred some cochlear damage, so as to counsel them to avoid loud noise?

Which tests could be most sensitive to cochlear damage, especially if individual baselines are available?

- extended high frequency audiometric losses (10–20 kHz)
- audiometric "noise notches" (3–6 kHz)
- tone-in-noise thresholds
- DPOAEs or TEOAEs (up to 16 kHz with ER-10X probe?)
- ABR wave Is or CAPs (in quiet, or in masking noise)
- strength of the middle ear muscle reflex (MEMR; aka acoustic reflex)
- strength of the medial olivocochlear (MOC) efferent reflex (OAE suppression)
- severity of TTS or transient tinnitus following a loud noise exposure (unfortunately, not likely)

We are beginning a longitudinal study, obtaining baselines and continuing to gather auditory (and cognitive) test data as subjects live their lives – in relative quiet or with exposures to loud noise.

Guinea pigs that are more resistant to NIHL showed greater baseline DPOAE suppression due to a stronger MOC efferent reflex (Maison & Liberman 2000)

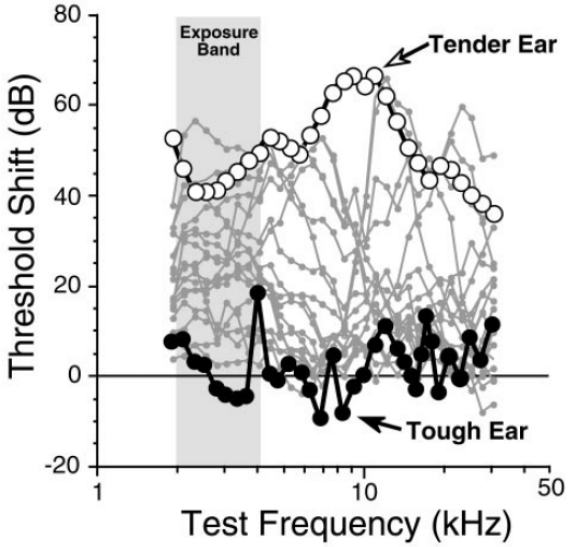
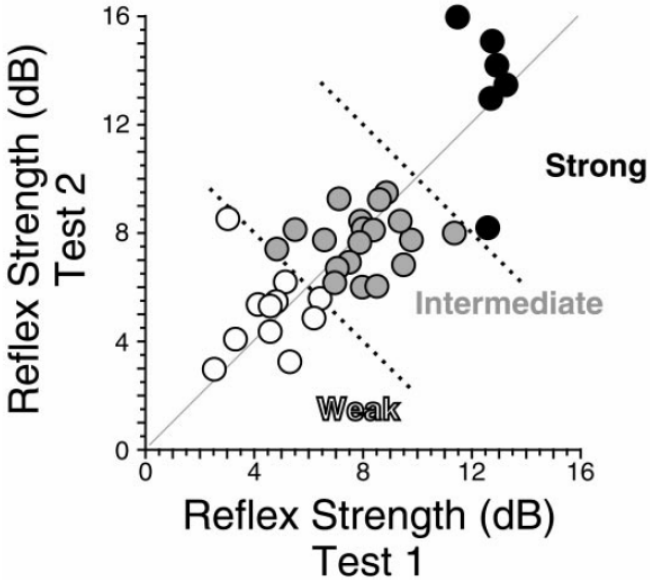


Figure 4. Variability in PTSs in 12 guinea pigs identically exposed to the 2–4 kHz noise band at 109 dB for 4 hr. PTS is computed by subtracting the average CAP thresholds in seven control (unexposed animals) from the CAP thresholds in each of the 12 animals in this group. Threshold shift curves for two of the 12 animals are highlighted: one particularly vulnerable is shown by the *open symbols*, and one particularly resistant is shown by the *filled symbols*. All others are shown in *gray*.



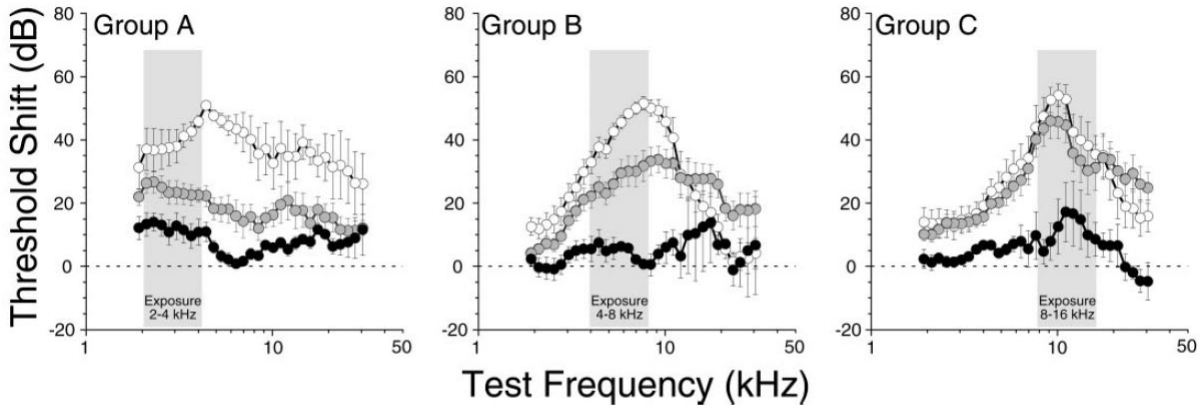


Figure 5. Mean values of noise-induced permanent threshold shift in three sets of animals, when grouped according to the pre-exposure strength of their MOC reflex: animals with the strongest reflexes suffer the least threshold shift. The three panels show results from different sets of animals exposed to different noise bands: 12 animals exposed at 2–4 kHz (*A*), 12 animals exposed at 4–8 kHz (*B*), and 12 animals exposed at 8–16 kHz (*C*). Error bars indicate SEM. CAP data were obtained from both ears of each experimental animal.

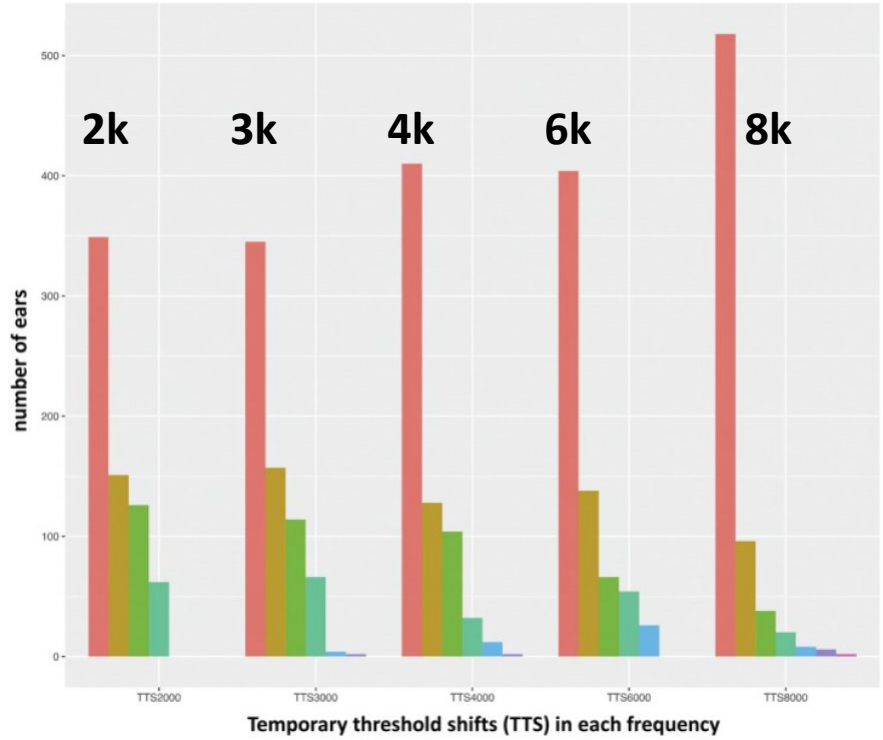
Noise Health. 2018 May-Jun; 20(94): 101–111.
doi: 10.4103/nah.NAH_61_17
PMCID: PMC5965001
PMID: 29785975

Utility of Otoacoustic Emissions and Olivocochlear Reflex in Predicting Vulnerability to Noise-Induced Inner Ear Damage

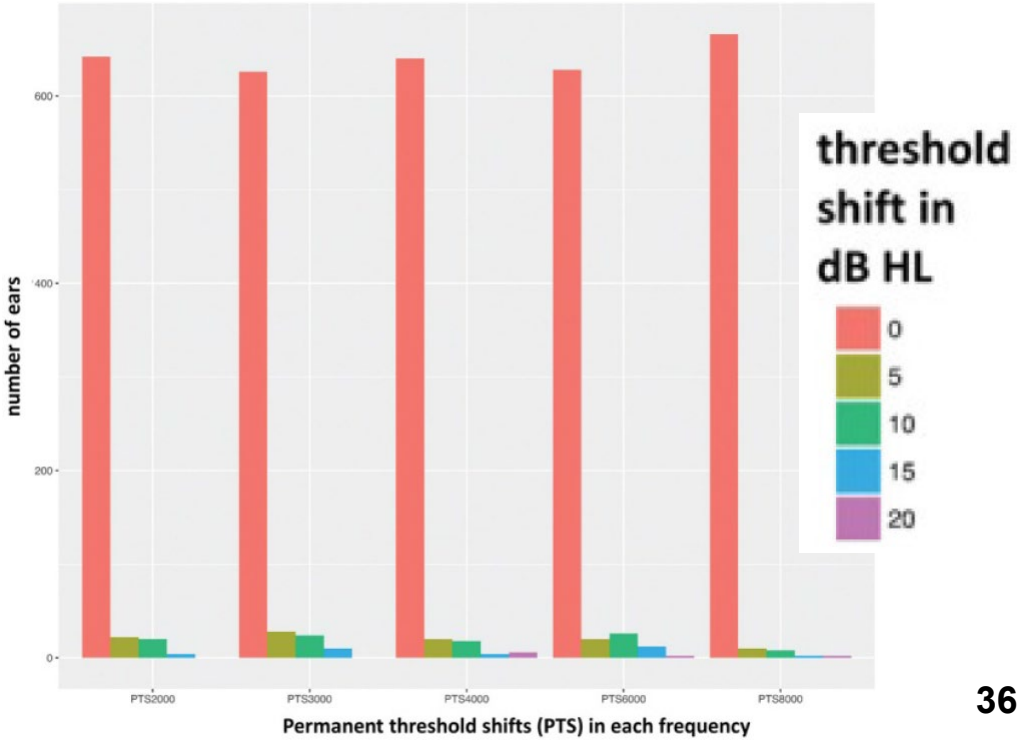
Sarantis Blioskas,[1] Miltiadis Tsalighopoulos,[2] George Psillas,[2] and Konstantinos Markou[2]

344 young military cadets (188 male; 156 female) with normal-hearing (<20 dB HL at all frequencies) were tested at the beginning of basic training. They fired 10 rounds from an assault rifle while wearing army standard disposable earplugs, each shot generating 155 dB peSPL, and had measurements repeated within 8 h (TTS), and after 30 days (PTS), before further rifle training (want to identify vulnerable ears).

Audiometric TTS (≥ 5 dB at ≥ 2 freqs)
405 ears (59%)



Audiometric PTS (≥ 5 dB at ≥ 2 freqs)
57 ears (8.2%)



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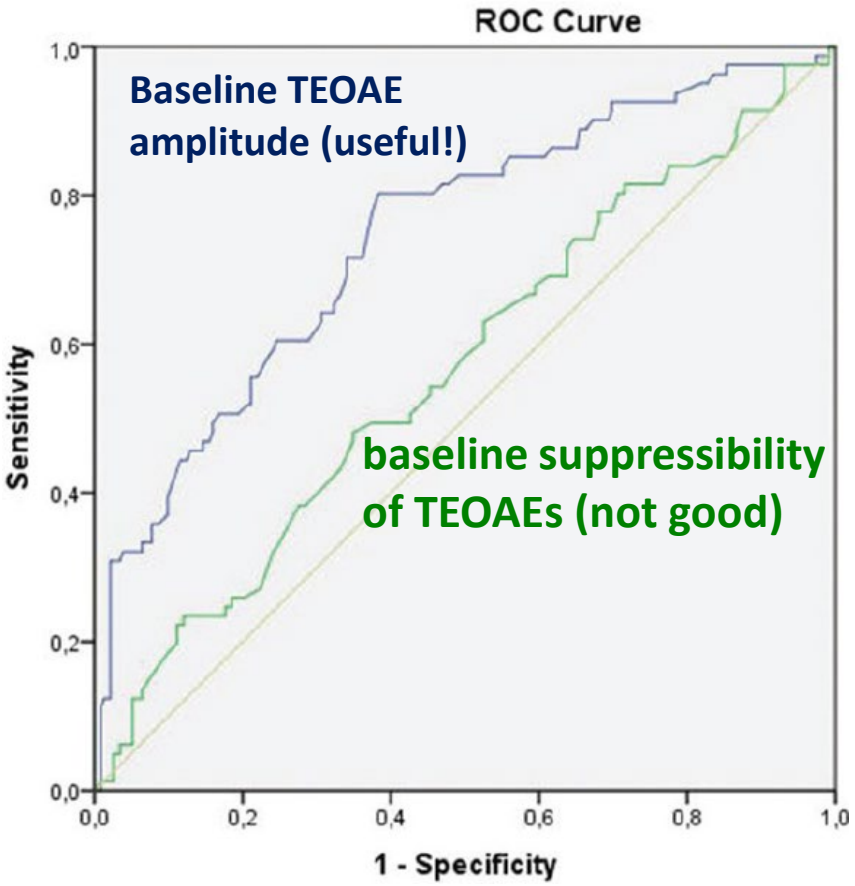
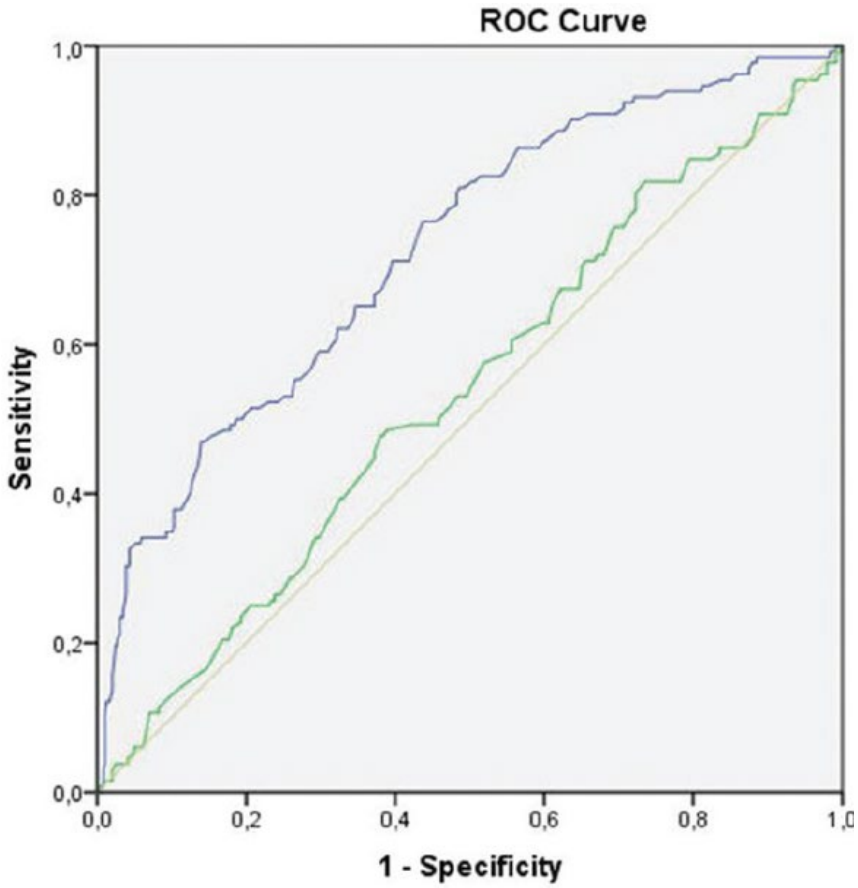
Power to predict TTS



Power to predict PTS



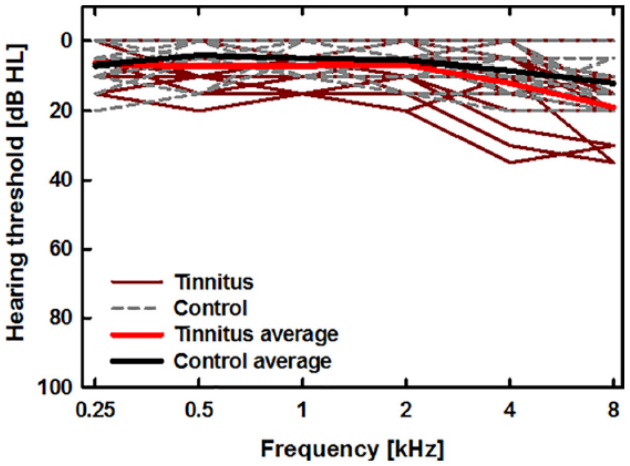
eNeuro

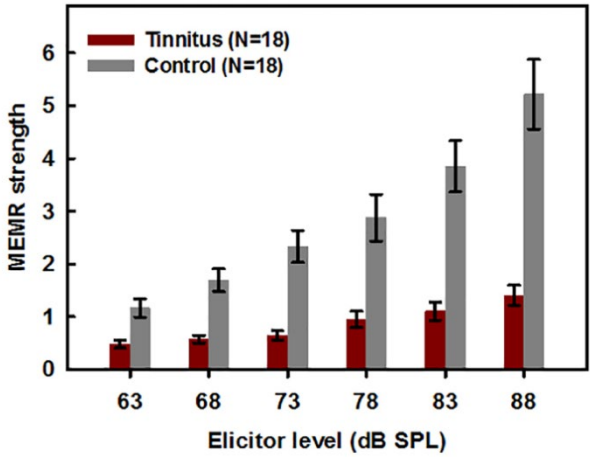
New Research

Sensory and Motor Systems

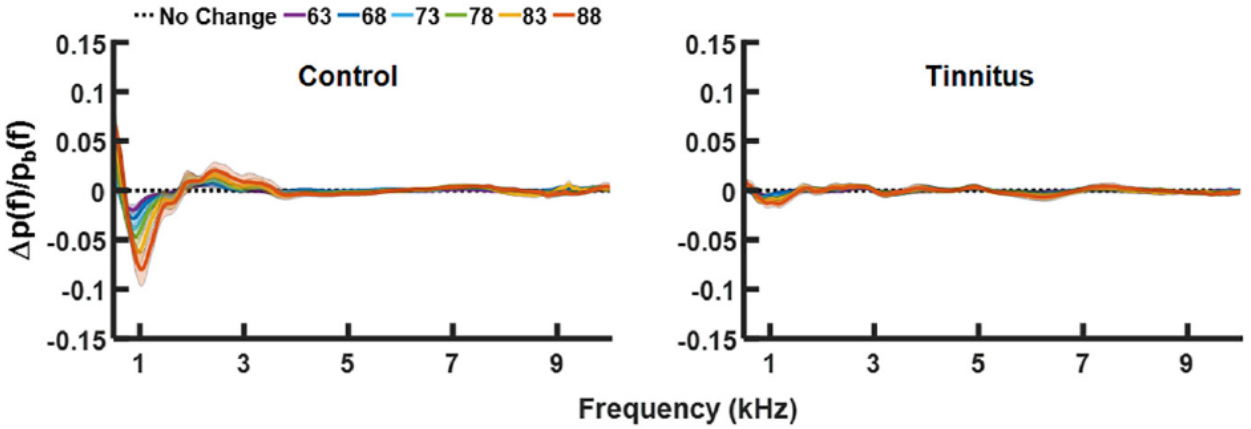
Weak Middle-Ear-Muscle Reflex in Humans with Noise-Induced Tinnitus and Normal Hearing May Reflect Cochlear Synaptopathy

Magdalena Wojtczak, Jordan A. Beim, and Andrew J. Oxenham





Relative changes in click-evoked ear canal sound pressure (as a function of frequency) with a contralateral MEMR activator at levels indicated



Summary

The main focus of recent human work has been the detection of cochlear synaptopathy in adults with a history of noise exposure, but with clinically normal audiograms, and often with difficulties hearing in noise, and with tinnitus and/or hyperacusis. This has proven to be a challenging task, in spite of the clear-cut results obtained in many animal studies!

The full impact of acquired synaptopathy/neuropathy as a contributor to hearing loss might only be revealed when it can be differentially diagnosed in individuals with significant OHC (audiometric) loss.

One of the holy grails of audiology has always been to differentiate OHC from IHC/ANF losses, which are presently lumped together as sensorineural hearing loss. There is little doubt that such differential diagnosis would prove useful in improving hearing aid fitting, and better predicting cochlear implantation outcomes. It is also a prerequisite for future inner ear regenerative medicine.

NEUROSCIENCE

INTERNATIONAL BRAIN IBRO RESEARCH ORGANIZATION

RESEARCH ARTICLE

M. Pienkowski / Neuroscience xxx (2018) xxx–xxx

Rationale and Efficacy of Sound Therapies for Tinnitus and Hyperacusis

Martin Pienkowski