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Putting the 'Neural' Back in Sensorineural: Cochlear Neurodegeneration in Noise and Aging

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Massachusetts Eye and Ear Infirmary
Harvard Medical School

American Auditory Society-Audiology Online Webinar
December 9, 2014

Outline

Noise-Induced PTS and TTS: Basics

Cochlear Synaptic and Neural Degeneration after 'Recovery' from TTS

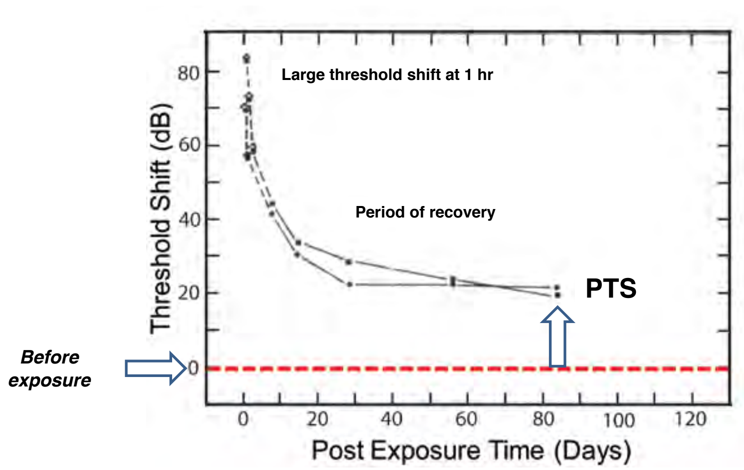
Cochlear Synaptopathy of Aging

Adding Insult to Injury: Aging after Noise

Beyond the Audiogram: 'Hidden Hearing Loss'

Noise-Induced PTS and Cochlear Injury

Threshold Shifts after Noise: Acute vs. Chronic



Miller, Watson & Covell 1963

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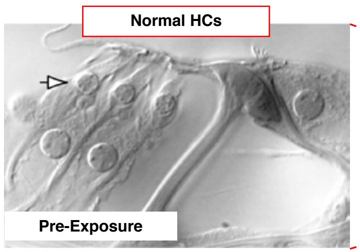
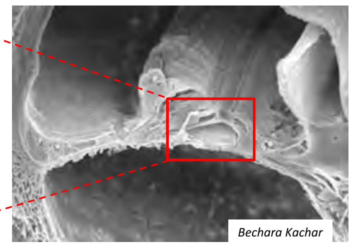
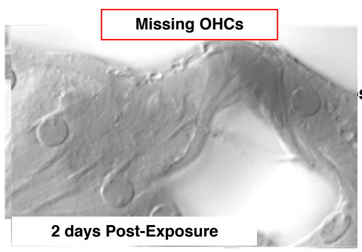
PTS: Hair Cell Loss & Stereocilia Damage







sure

Ears with PTS often have hair cell loss or stereocilia damage

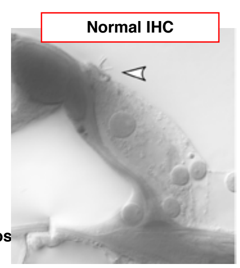
Rapid time course

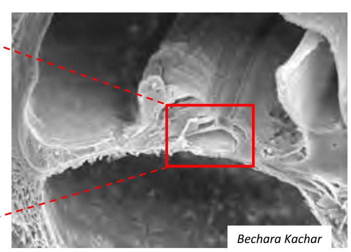
Loss of OHCs eliminates the 'amplifier' & shifts threshold

Wang et al 2002

PTS: Hair Cell Loss & Stereocilia Damage

Pre-Expos





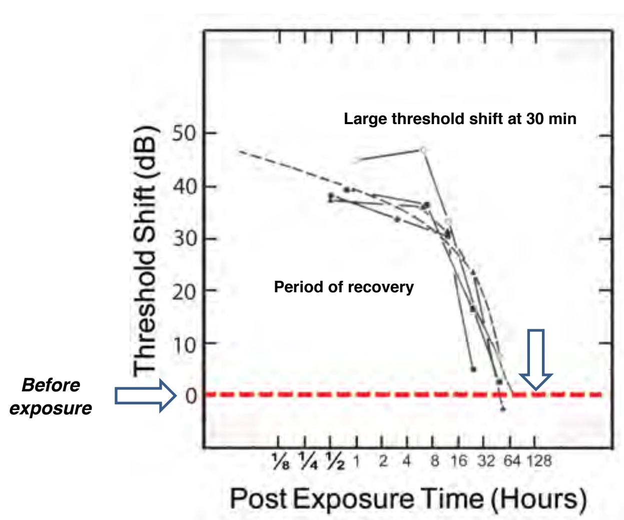
95% of cochlear afferents communicate with IHCs

Loss of IHCs makes non-responsive regions

Wang et al 2002

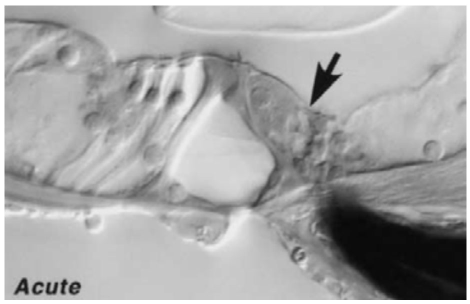
Noise-Induced TTS and Cochlear Injury

Threshold Shifts after Noise: Acute vs. Chronic



Miller, Watson & Covell 1963

TTS: Reversible Injury to Synaptic Structures?

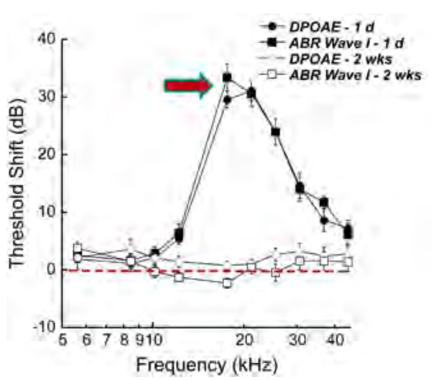


CBA Mouse: OBN 8-16 kHz 100 dB 2 hrs

Swelling (and TTS) mimicked by glutamate agonists, reduced by glutamate antagonists (Puel and colleagues)

Wang et al, 2002

TTS: Reversible Injury to Synaptic Structures?

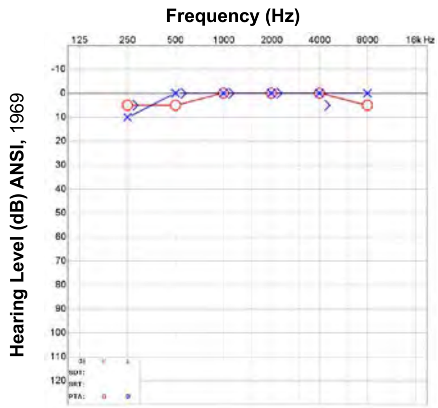


CBA Mouse: OBN 8-16 kHz 91 dB 2 hrs

But close similarity of TTS for DPOAEs and ABRs suggests that most is due to injury on the input side to the IHCs

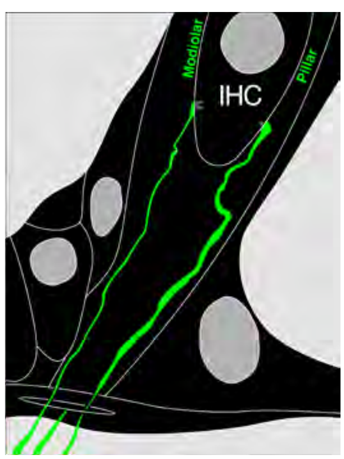
Kujawa, unpublished

TTS: Common, from Occupational and Recreational Sources



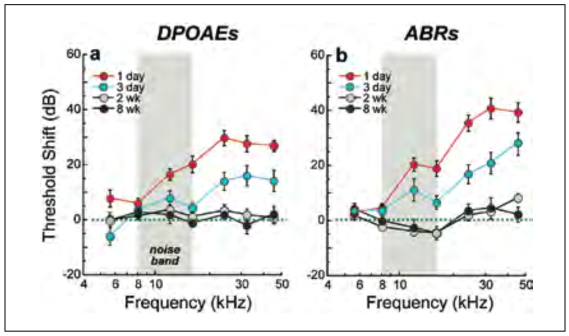
Threshold recovery taken as evidence for a recovered ear and a benign exposure….true?

Cochlear Synaptopathy & Neurodegeneration After TTS



Threshold Recovery

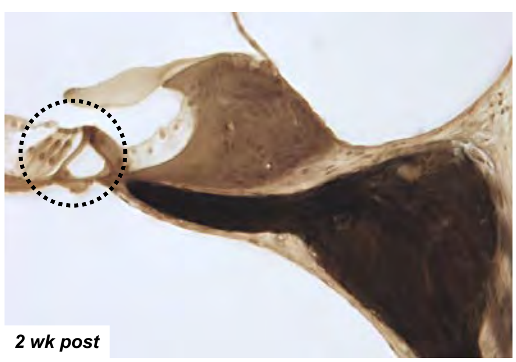
ABR and DPOAE thresholds recover from initial shift



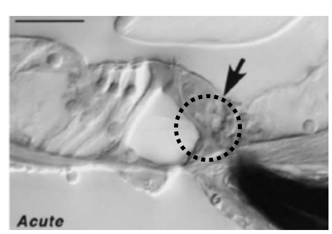
CBA/CaJ: 8-16 kHz, 100 dB SPL, 2 h @ 16 wk

Kujawa and Liberman 2009

No Hair Cell Loss



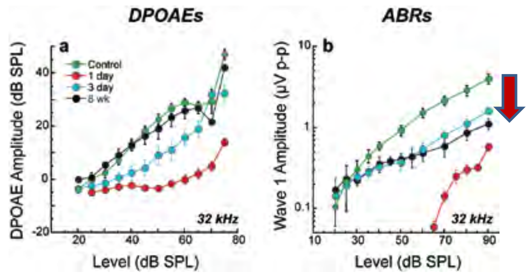
…but there is excitotoxic swelling



Kujawa and Liberman 2009

Persistent Neural Amplitude Declines

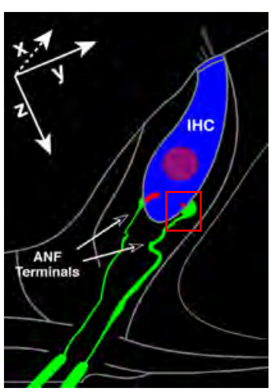
ABR amplitudes do not recover in regions of maximum TTS

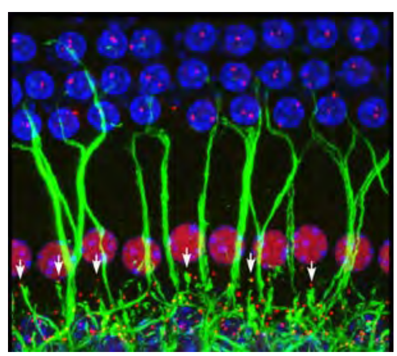


CBA/CaJ: 8-16 kHz, 100 dB SPL, 2 h @ 16 wk

Kujawa and Liberman 2009

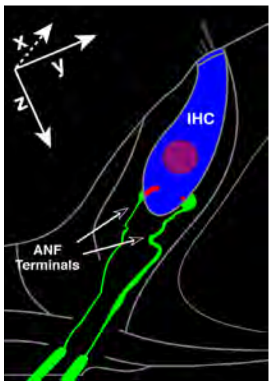
What's Happening at the Synapse?

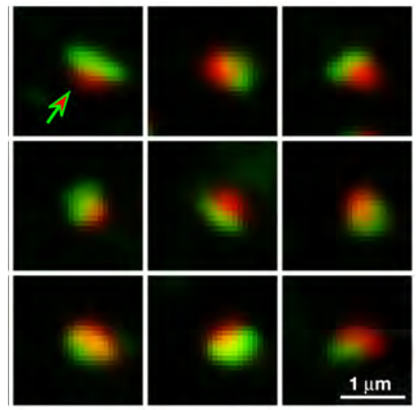




Kujawa and Liberman 2009

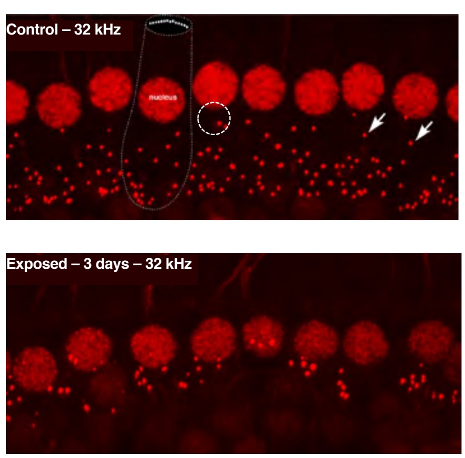
What's Happening at the Synapse?





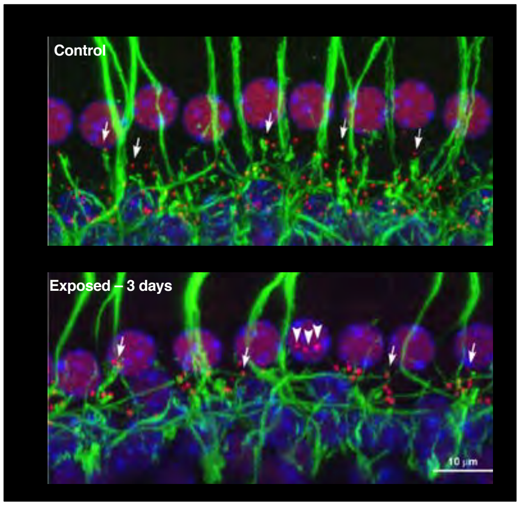
Kujawa and Liberman 2009

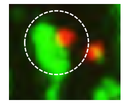
Rapid Loss of Synapses, Terminals After Noise



Kujawa and Liberman 2009

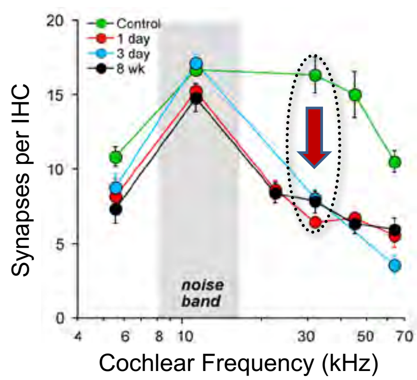
Rapid Loss of Synapses, Terminals After Noise





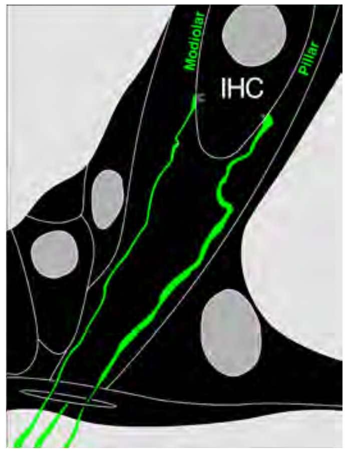
Kujawa and Liberman 2009

Rapid Loss of Synapses, Terminals After Noise

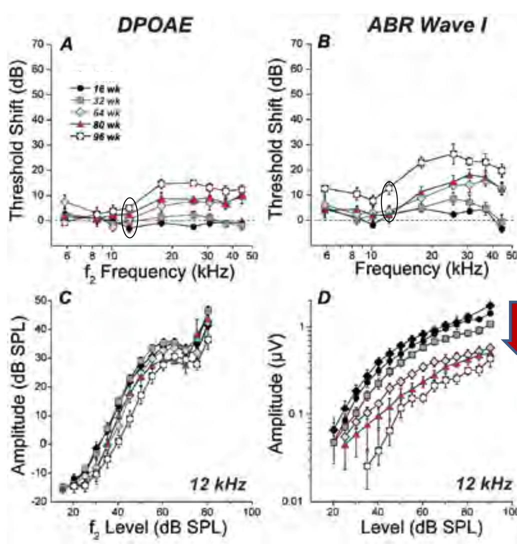


Kujawa and Liberman 2009

Cochlear Synaptopathy & Neurodegeneration in Aging



Cochlear Thresholds and Suprathreshold Response Growth



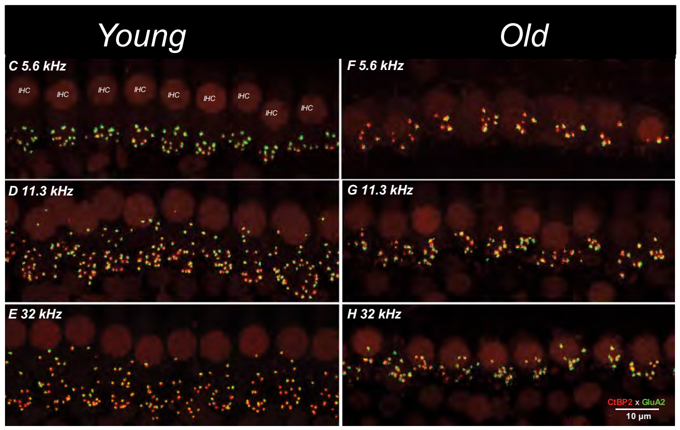
Mild threshold losses to ~2 years

Large neural amplitude declines

Sergeyenko, Lall, Liberman, Kujawa 2013

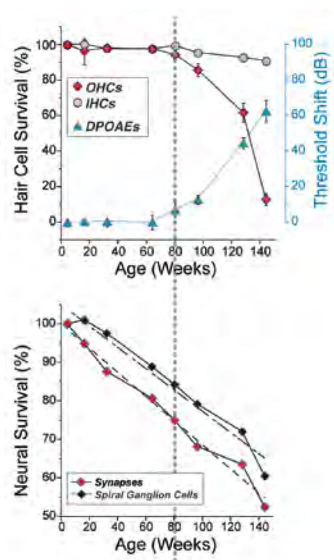
Age-Related Loss of Cochlear Synapses

Synapses are lost gradually, throughout the cochlea



Sergeyenko, Lall, Liberman, Kujawa 2013

Synapse Loss is Primary, SGN Loss is Proportional

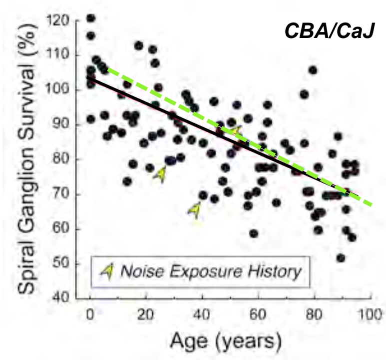


By mouse middle age, IHC-cochlear neuron communications have been reduced by ~25%, but threshold and hair cell losses are trivial.

Sergeyenko, Lall, Liberman, Kujawa 2013

Cochlear Neuropathy in Human Aging?

"Normal" Humans

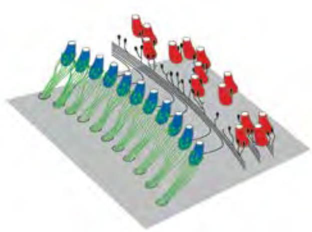


100 human temporal bones (10/decade, 0-100 yrs) with no significant HC loss

Sergeyenko, Lall, Liberman, Kujawa 2013
Makary, Shin, Kujawa, Liberman & Merchant, 2011

Summary

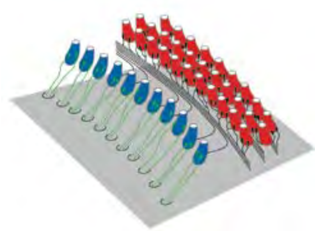
Hair Cell Loss



Hair cells (especially OHCs) are among the most vulnerable elements in the cochlea and their loss is a common cause of threshold elevations.

However, for at least two major causes of acquired SNHL (aging, noise), synapses are most vulnerable.

Synaptic Loss

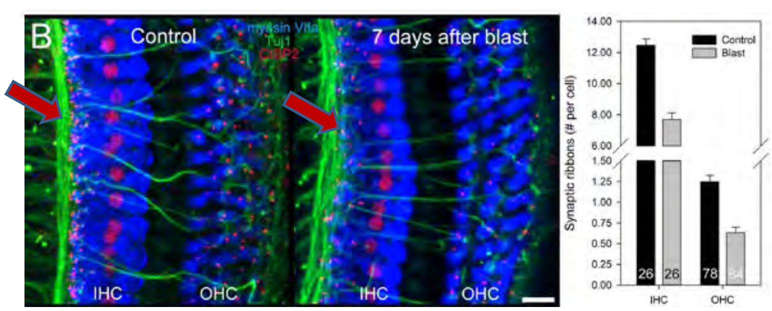


The result? Many cochlear nerve fibers become permanently disconnected from IHCs. In aging, the loss is gradual; after noise, it is sudden, then progressive.

The condition, called "hidden hearing loss" because it is not revealed by tests of threshold sensitivity, is likely a major cause of speech-in-noise difficulties and tinnitus.

Identifying 'Hidden Hearing Loss'

Post-Blast Ribbon Loss



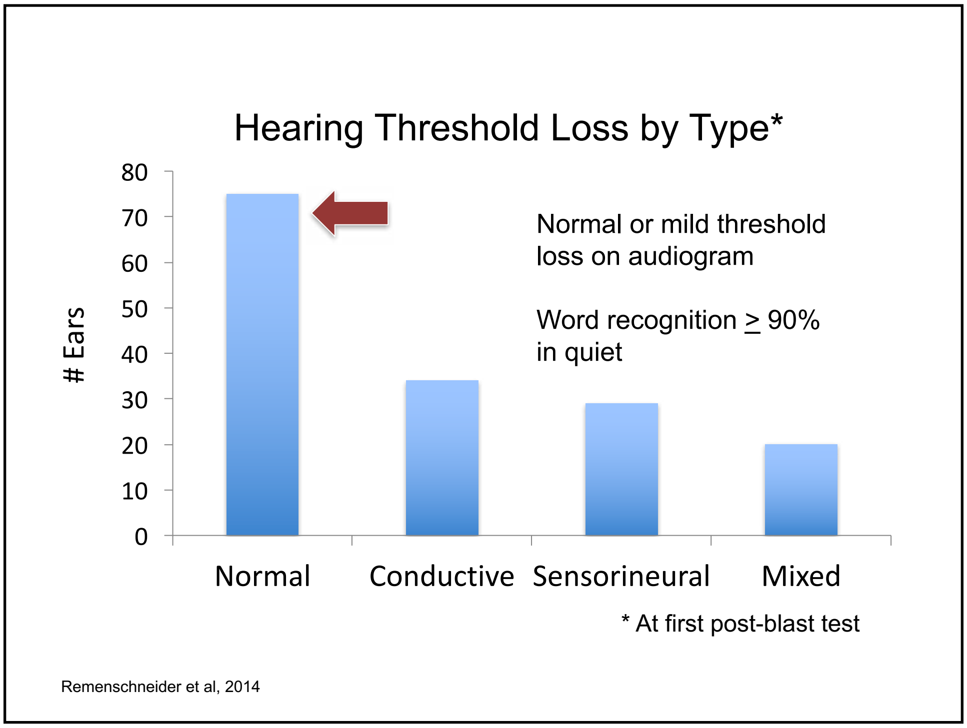
Cho SI et al Plos One 2013

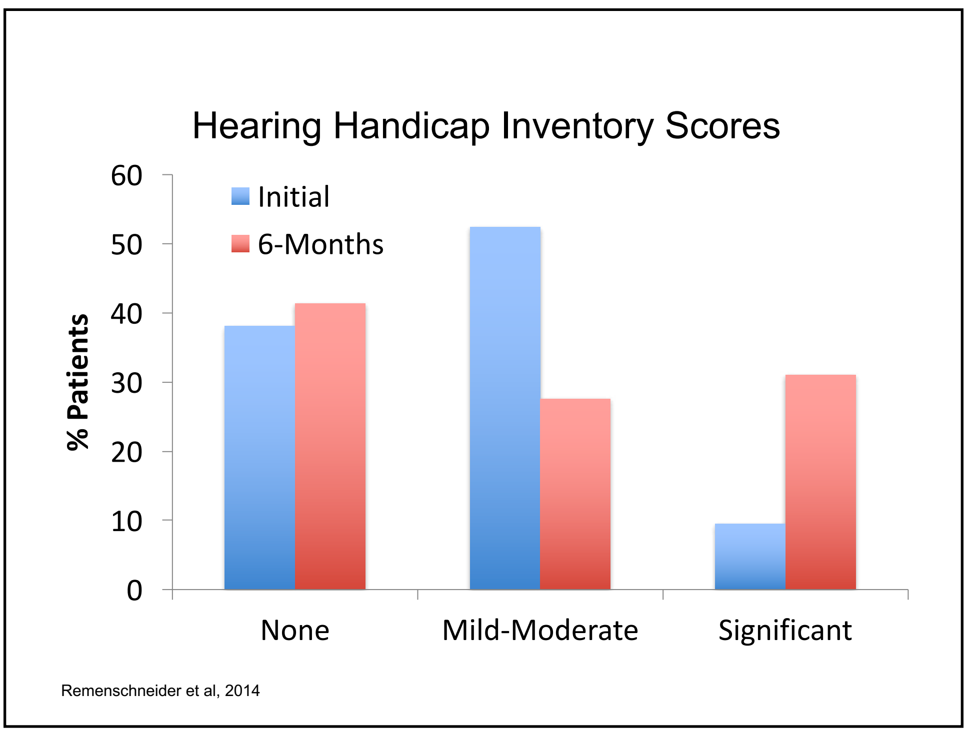
Boston Marathon 2013

Subjects	
Patients Identified	103
Patients Enrolled	94
Pre-Blast Otologic Symptoms	
Hearing "excellent/good"	91
Hearing "fair/poor"	3
No tinnitus	86
Tinnitus	8
Pre-Blast Otologic/Neurologic Problems	
Prior tympanostomy tubes	7
Prior tympanic perforation / cholesteatoma	1
Hearing aid use	0
History of concussion	10
History of contact sports	18
Firearm noise exposure, with hearing protection	4

Remenschneider et al, 2014

264 individuals received medical care in area hospitals, 3 died on the scene


Hearing Threshold Loss by Type*
Ears
80
70
60
50
40
30
20
10
0
Normal
Conductive
Sensorineural
Mixed
Normal or mild threshold loss on audiogram
Word recognition > 90% in quiet
* At first post-blast test
Remenschneider et al, 2014


Hearing Handicap Inventory Scores
% Patients
60
50
40
30
20
10
0
Initial
6-Months
None
Mild-Moderate
Significant
Remenschneider et al, 2014

Normal Thresholds, Persistent Complaints

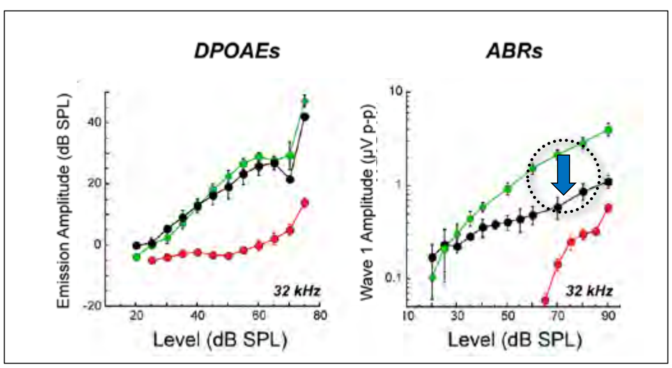
Even with normal thresholds, patient complaints of new hearing problems:

- Speech-in-noise difficulties
– Tinnitus
– Hyperacusis

Remenschneider et al, 2014

Non-Invasive Assays of Synaptic/Neural Loss

Synaptopathic Exposure: Signature pattern of OAE/neural responses (at least until OHC losses begin)

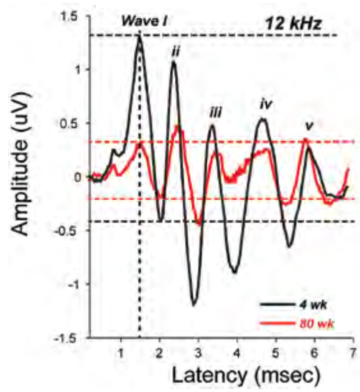


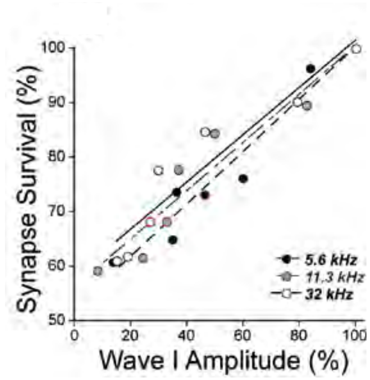
CBA/CaJ: 8-16 kHz, 100 dB SPL, 2 h @ 16 wk

Kujawa and Liberman 2009

Non-Invasive Assays of Synaptic/Neural Loss

Changes in Wave I amplitude and synapse counts are proportional (at least until OHC losses begin)

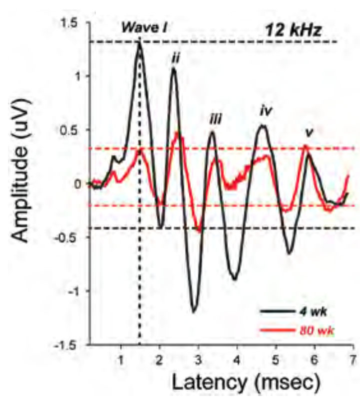


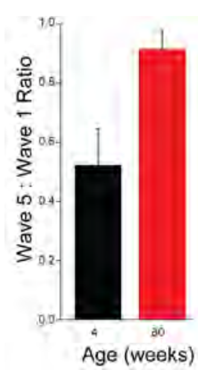


Sergeyenko, Lall, Liberman, Kujawa 2013

Non-Invasive Assays of Synaptic/Neural Loss

Wave V-I amplitude ratios are altered by noise, aging

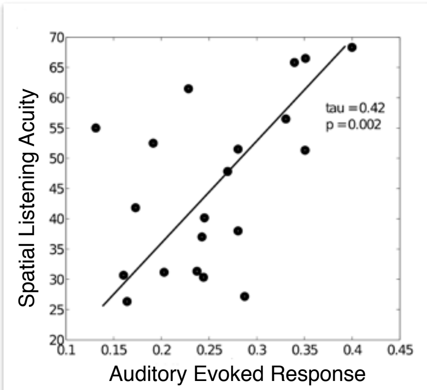




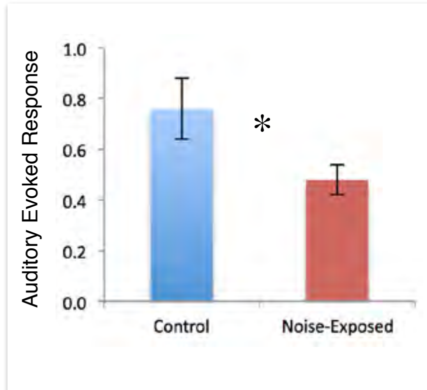
Sergeyenko, Lall, Liberman, Kujawa 2013

Non-Invasive Assays of Synaptic/Neural Loss

College students with normal audiograms

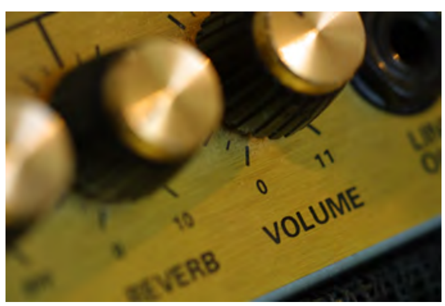


Shinn-Cunningham Lab
Boston University
(Ruggles et al 2011, 2012; Bharadwaj et al 2014)



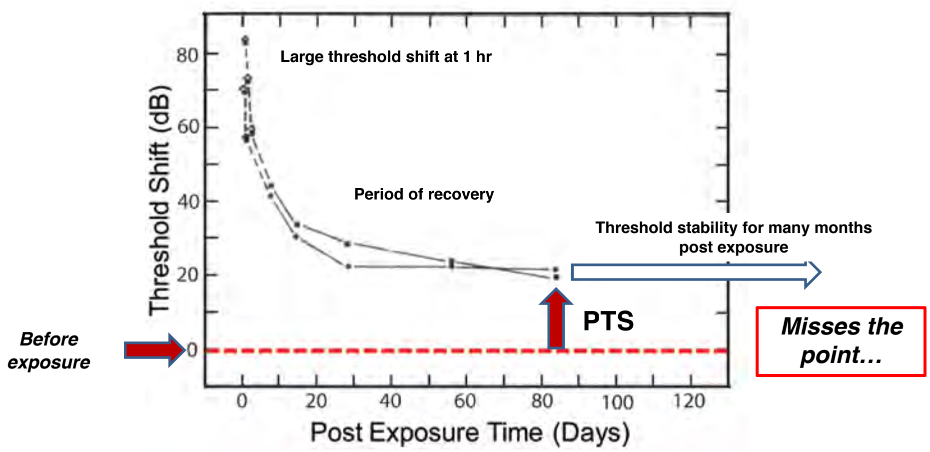
Plack Lab
University of Manchester
(Barker et al 2014; Plack et al 2014)

Implications for Public/Occupational Health and the Epidemiology of Acquired SNHL



"These Go to Eleven!"
Nigel Tufnel ('This is Spinal Tap')

Long Period of Threshold Stability



Miller, Watson & Covell 1963

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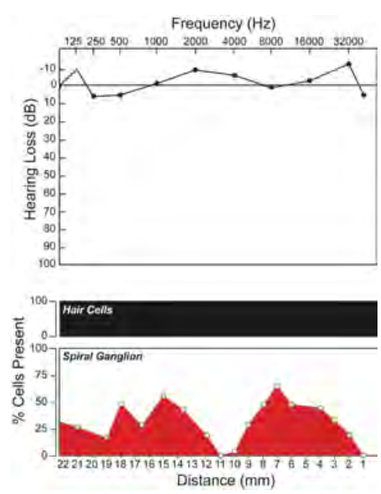
Normal Thresholds ≠ Normal Neuronal Population



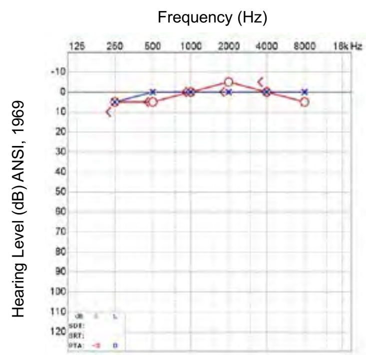
Thresholds are relatively insensitive to diffuse synaptic and neural loss

Schuknecht and Woellner, 1955

The Metric for Noise Damage is PTS

Thresholds for pure tones represent the gold standard for quantifying noise damage in humans.

…but normal thresholds can mask significant underlying neural degeneration.



"The most common protection goal is the preservation of hearing for speech discrimination". (NIOSH 1998)

Summary: Primary Cochlear Neurodegeneration in Noise and Aging

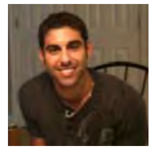
In both aging and after TTS-producing noise, IHC synapses with cochlear neurons are most vulnerable. (see also Liu et al 2013)

Noise-induced loss of synapses and SGNs can progress, changing the way ears and hearing age, long after the noise has stopped

Non-invasive assays of function are both sensitive and specific; show promise for translation to human clinical characterization

Acknowledgements

Katharine Fernandez



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Penelope Jeffers

Charlie Liberman

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