Canadian Academy of Audiology
Academie Canadienne d'audiologie

Development of Inner Ear Medicines for the Threshold and Supra Threshold indications

Speaker: Dr. Colleen Le Prell, Professor of Hearing Science Head at The University of Texas at Dallas

Host: Stephen G. Lomber, Ph.D., Professor of Physiology at McGill University, CAA Board Member

2023-05-24

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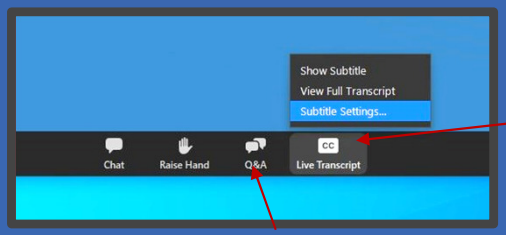

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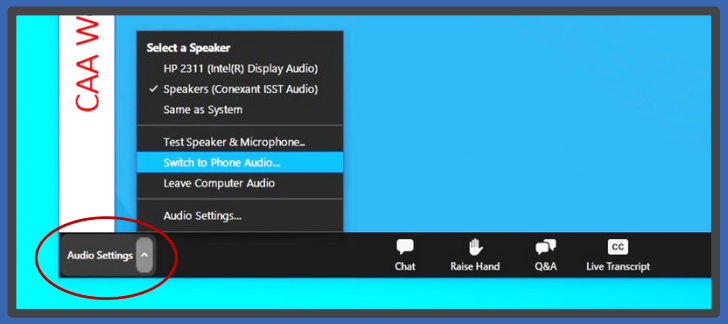

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Canadian Academy of Audiology is a professional association dedicated to enhancing the role of audiologists as primary hearing health care providers through advocacy, education and research.

Moderator – Stephen G. Lomber, Ph.D., Professor of Physiology at McGill University, CAA Board Member

Stephen G. Lomber, Ph.D. is a Professor of Physiology at McGill University and directs the Cerebral Systems Laboratory. Dr. Lomber is the Associate Editor of Hearing Research and Scientific Program Chair for the Annual Meeting of the Association for Research in Otolaryngology (ARO).

He is a past chair of the Gordon Research Conference on the Auditory System and the International Conference on Auditory Cortex, and a CAA Board Member.

Speaker: Dr. Colleen Le Prell, Professor of Hearing Science Head at The University of Texas at Dallas

Dr. Le Prell has received research funding from government, industry, and philanthropic sources for clinical, translational, and applied research in her laboratory. Programmatic research in her laboratory advances the understanding and prevention of noise-induced hearing loss.

She is currently mentoring three AuD-PhD students and six AuD students on NIHL-related research projects and interests. Dr. Le Prell has published 79 peer-reviewed articles and 21 book chapters, and she has edited or co-edited five journal special issues and three books on topics related to her research interests.

DEVELOPMENT OF INNER EAR MEDICINES FOR THRESHOLD AND SUPRA-THRESHOLD INDICATIONS

Colleen Le Prell Ph.D.
Emilie & Phil Schepps Professor of Hearing Science
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School of Behavioral and Brain Sciences
The University of Texas at Dallas

Behavioral and Brain Sciences

Disclosures

Co-inventor on patents owned by the University of Michigan

- Miller, J.M., Le Prell, C.G., and Yamashita, D. US 7,786,100 B2, Composition and method of treating hearing loss. Awarded August 31, 2010. (Delayed Treatment/Vitamin E, Salicylate)
- Miller, J.M., Le Prell, C.G., Schacht, J., and Prieskorn, D.M. US 7,951,845, Composition and method of treating hearing loss. Awarded May 31, 2011. (ACEMg)

Paid consultant on issues related to clinical trial design

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- 3M, Inc.
- AAA Foundation (Jansen, Woodford)

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- Edison Pharmaceuticals, Inc.

- **Emilie and Phil Schepps Distinguished Professorship in Hearing Science**

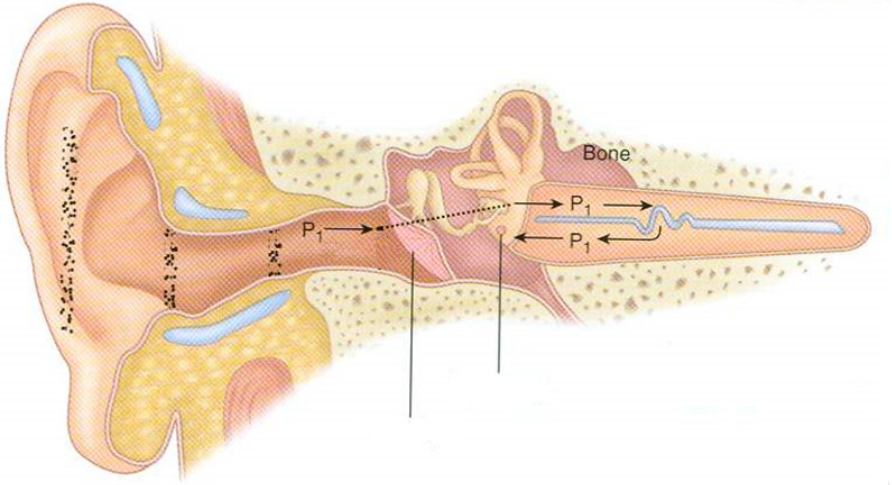
Session Overview

- This session will review patterns of cell death in the inner ear and corresponding changes in the audiogram, OAE and ABR responses, and deficits “beyond the audiogram” (supra-threshold deficits).
- Although supra-threshold deficits have been termed “hidden” because they are not captured by the audiogram, hearing-in-noise difficulties and tinnitus are common patient complaints, not-so-hidden to the patient or audiologist when the appropriate test battery is completed.
- With increasing attention to supra-threshold complaints has come interest in medicines that could protect or repair inner ear sensory cells. Inclusion of threshold and supra-threshold tests in current and recently completed clinical trials will therefore be reviewed.

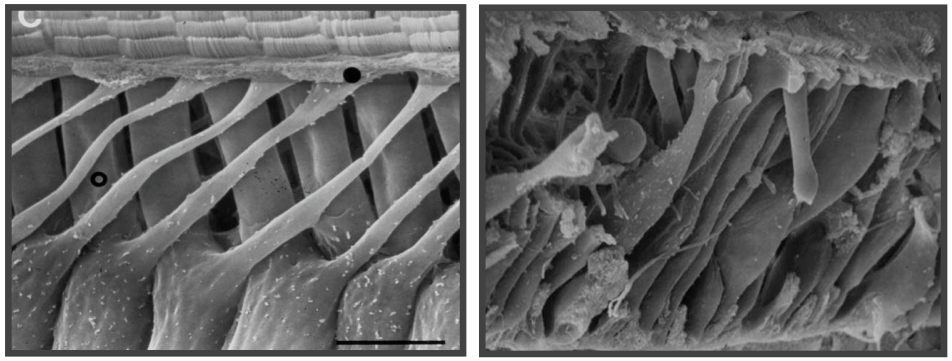
Agenda

- Noise-induced cochlear pathology
- HHL-related terms and definitions
- Some points of agreement on cochlear synaptopathy, and some open questions
- Existing use of the audiogram, tinnitus surveys, hearing in noise tests, and ABR in clinical trials
- Investigational medicines for hearing loss prevention and hearing restoration

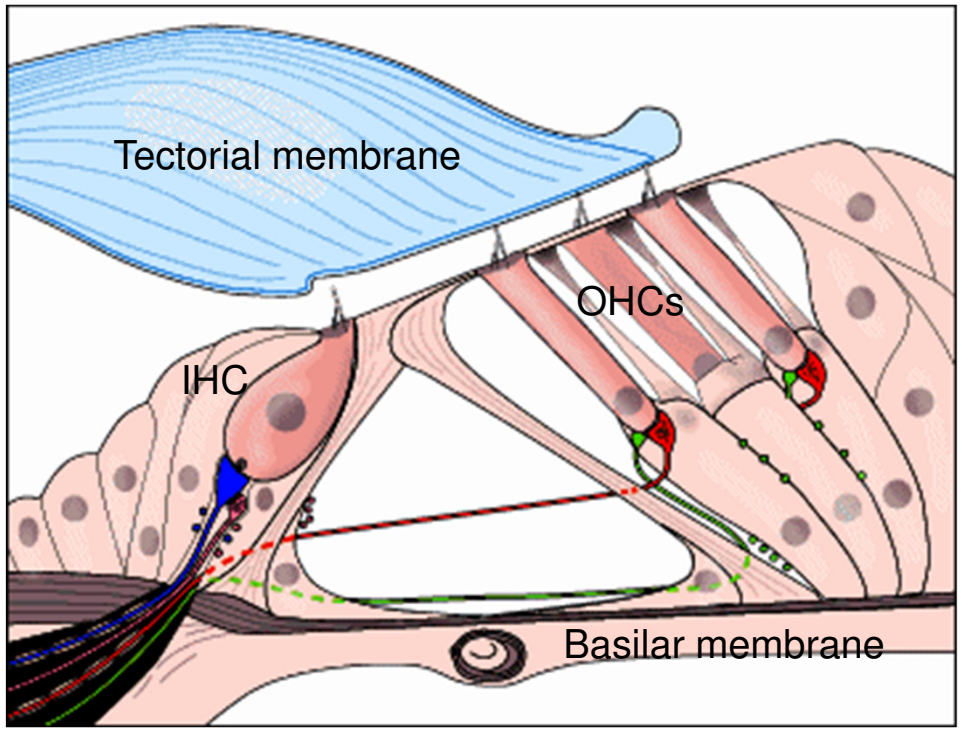
Sound is Mechanical Stimulus…….. that Causes Mechanical Response



From: Anatomy and Physiology of Hearing for Audiologists. W. W. Clark and K. K. Ohlemiller (2008). Singular.



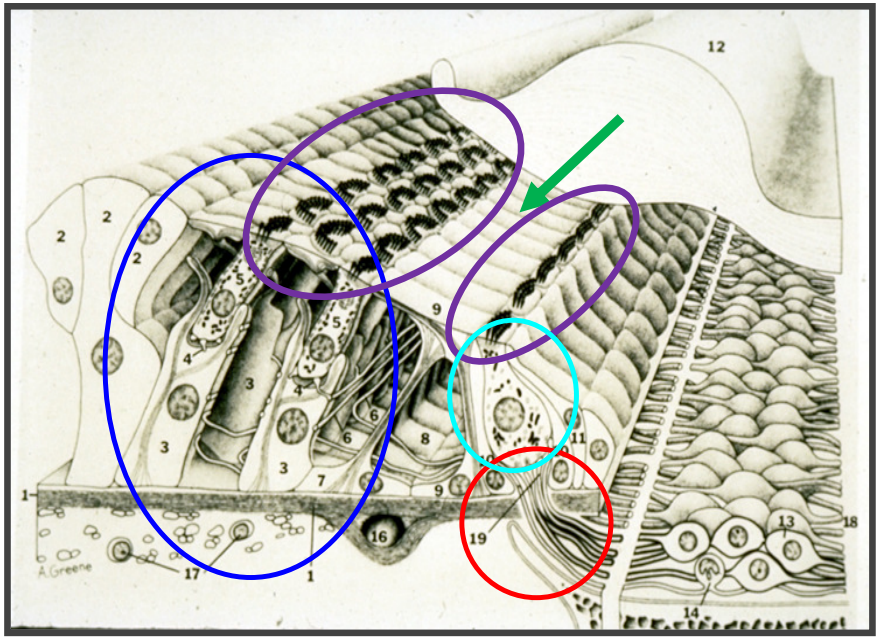
Raphael Y, Lenoir M, Wroblewski R, Pujol R. The sensory epithelium and its innervation in the mole rat cochlea. J Comp Neurol. 314:367-82, 1991.



http://www.iurc.montp.inserm.fr/cric/audition/english/ear/fear.htm

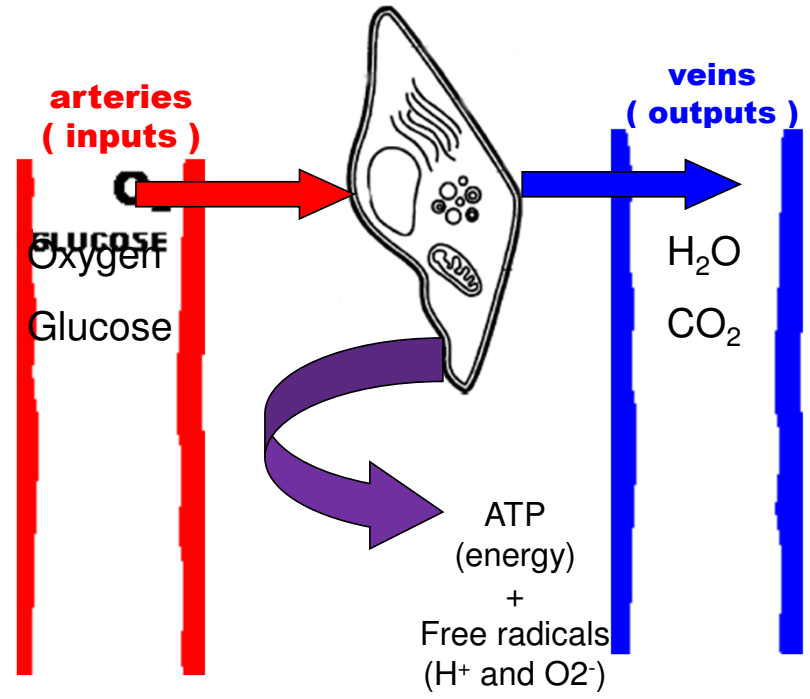
Noise-Induced Pathology

- Injury to OHCs correlated with PTS; 100% OHC loss results in ~40 dB PTS
- Sudden and profound increase in PTS above critical boundary, likely associated with breach of reticular lamina
- Shorter/less intense noise results in neural swelling, damaged stereocilia (both OHC and IHC), swollen or misshapen OHCs
- Permanent loss of synaptic connections between IHCs and auditory nerve after TTS may be associated with tinnitus, hyperacusis, hearing-in-noise deficits, and acceleration of age-related hearing changes
- BUT, pathology is not strictly mechanical – there is an active metabolic cell stress/cell death process resulting in progressive cell death over days to weeks



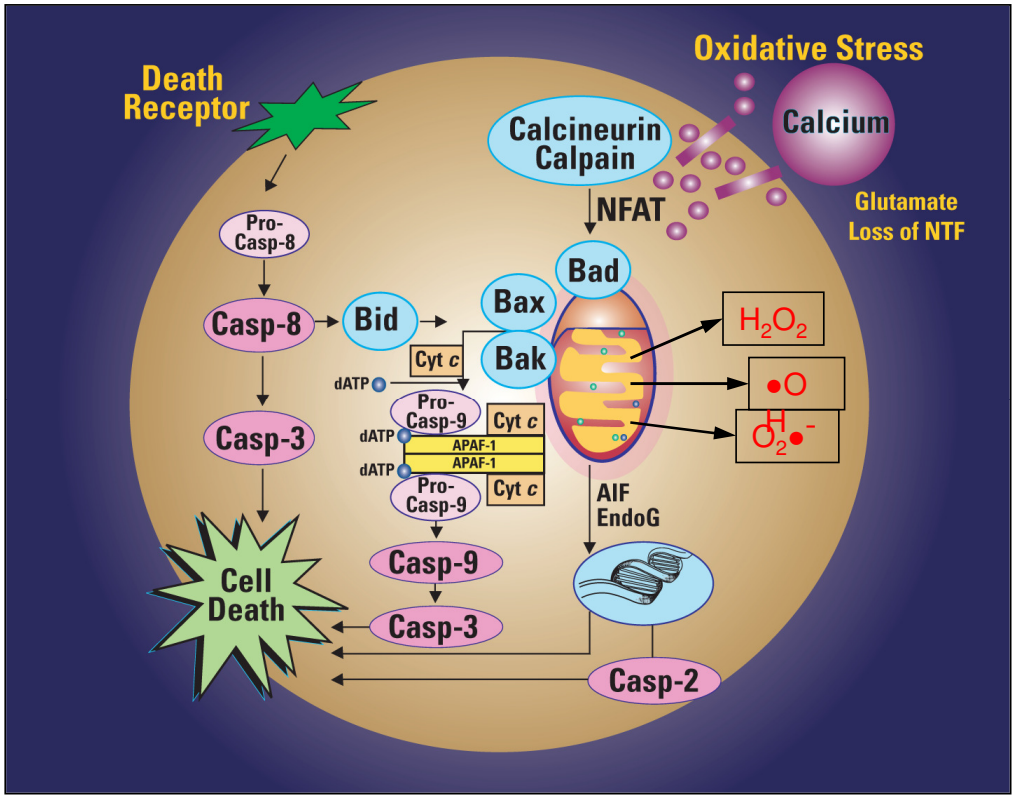
From: Bases of Hearing Science (3rd Ed.). J.D. Durrant and J.H. Lovrinic (1995).

Free radicals are normal metabolic byproduct but toxic in excess



Adapted from http://www.nadh.com/site7/GTactl35.htm#Top

- Glucose/sugar and oxygen broken down in cells
- Mitochondria convert nutrients to energy (ATP)
- This process produces waste, and leaks electrons (free radicals)
- Waste is excreted
- Leaked electrons must be neutralized, or damage to cell membranes, mitochondria, and DNA can occur, resulting in cell death



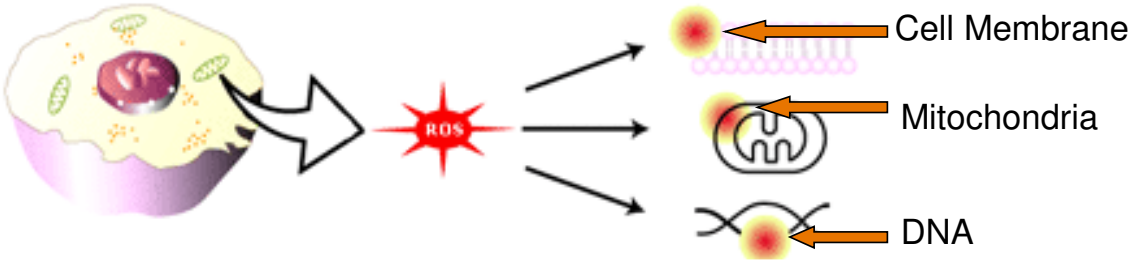
Adapted from Le Prell, C. G., Yamashita, D., Minami, S., Yamasoba, T., and Miller, J. M. (2007). "Mechanisms of noise-induced hearing loss indicate multiple methods of prevention," Hear. Res. 226, 22-43.

Oxidative stress drives cell death

Excess free radicals:

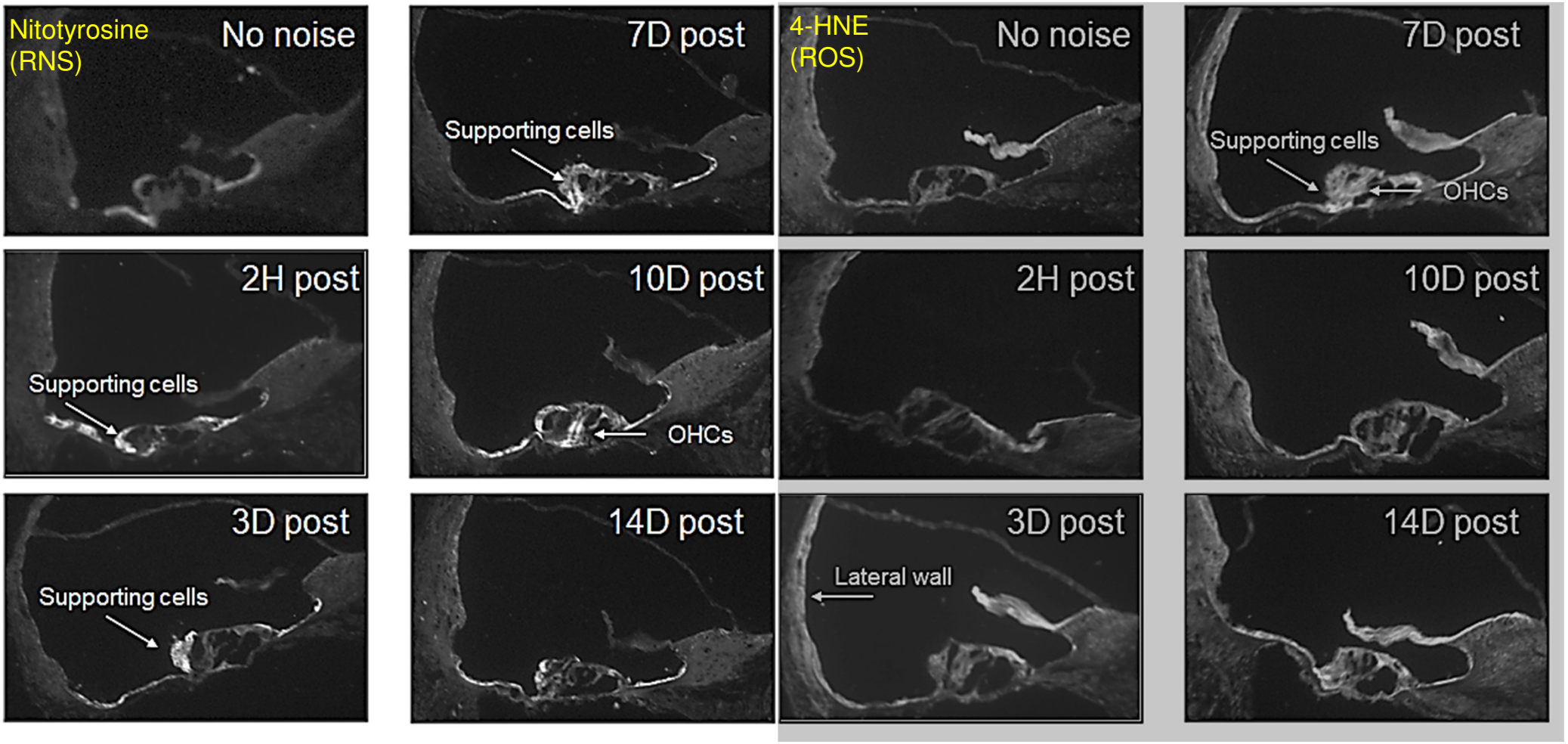
- Damage membranes, proteins, DNA
- Upregulate cell death pathways
- Drive vasoconstriction
- Induce inflammatory response

These biochemical pathways provide mechanistic targets for drugs to protect inner ear

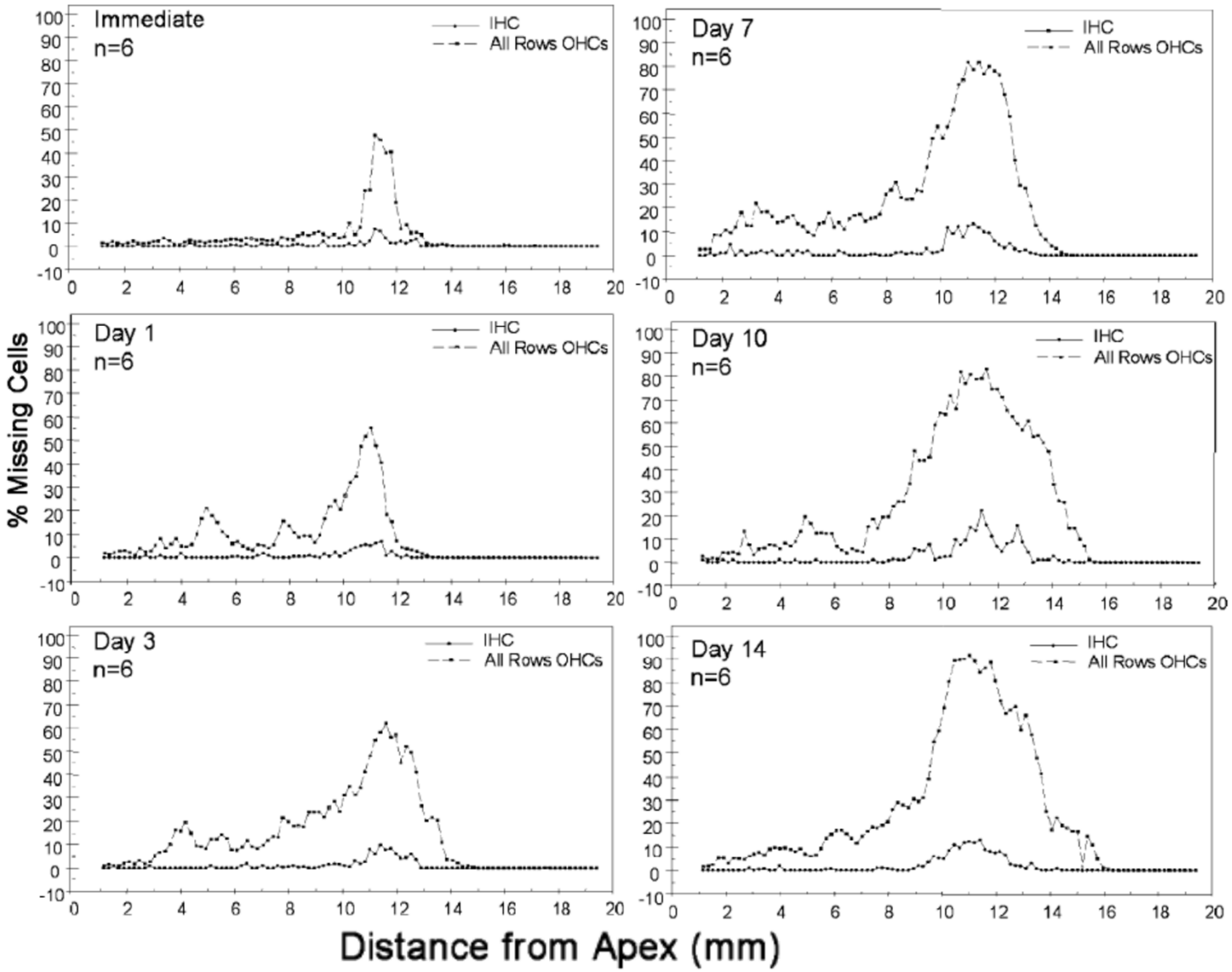


From http://www.whfoods.com/genpage.php?tname=faq&dbid=19

Oxidative stress (free radical accumulation) increases after noise insult



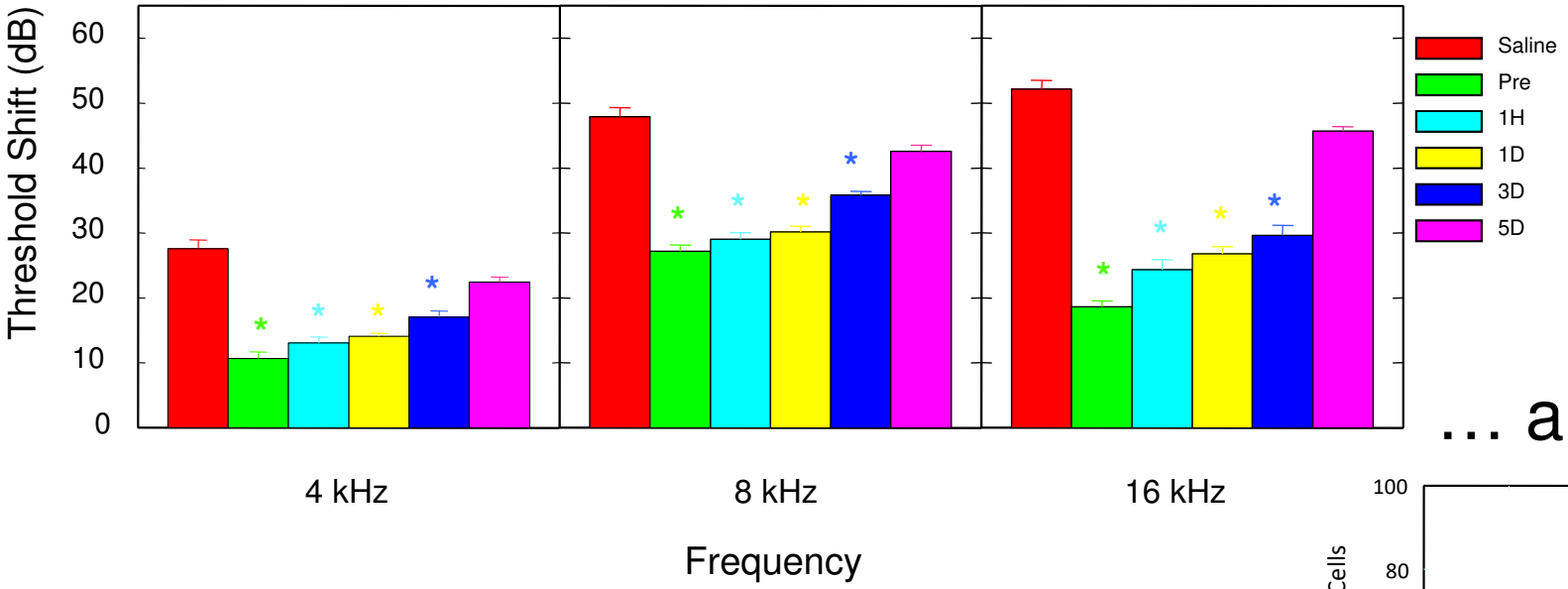
Yamashita, D., Jiang, H., Schacht, J., and Miller, J. M. (2004). "Delayed production of free radicals following noise exposure," Brain Research 1019, 201-209.



- OHC loss increases over 10-14 day window
- Stressed hair cells enter cell death process
- Multiple biochemical cascades, one of which is oxidative stress

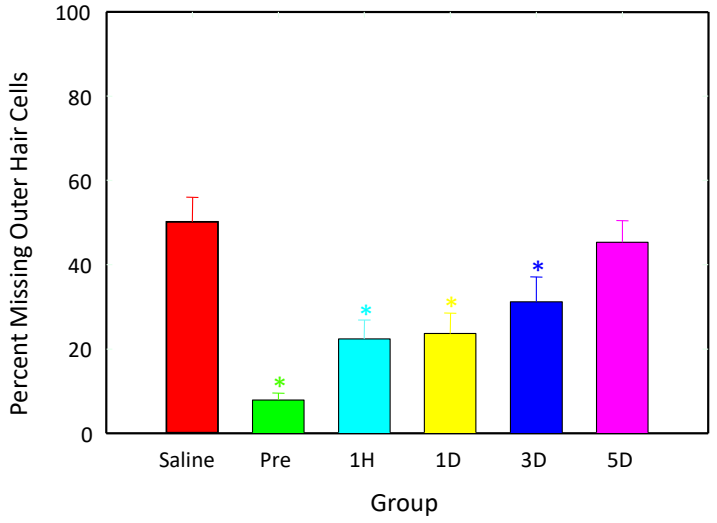
Yamashita D, Jiang HY, Schacht J, Miller JM. (2004). Delayed production of free radicals following noise exposure. Brain Res. 1019(1-2):201-9.

Antioxidants (salicylate+vit. E) reduce NIHL…



… even with post-noise treatment onset, but earlier treatment is more effective

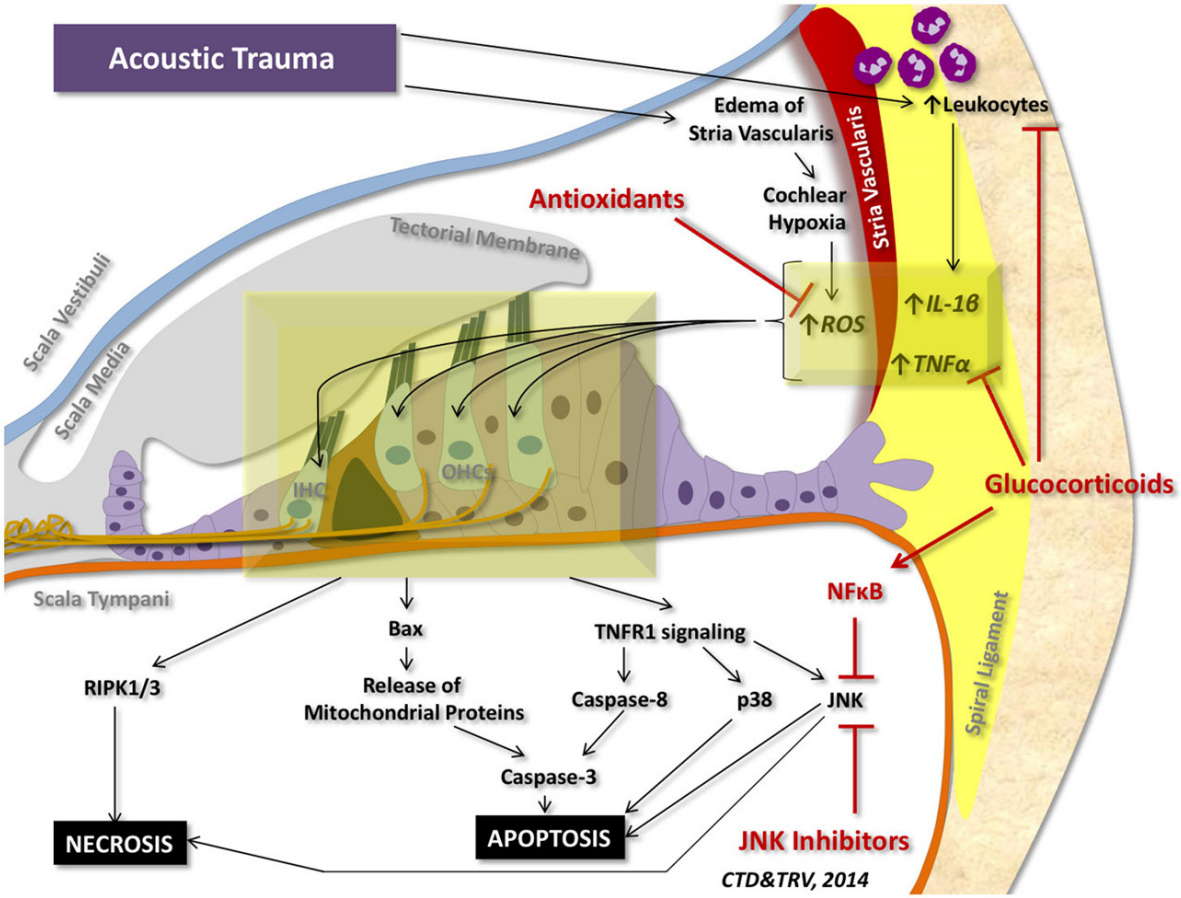
… and OHC loss…



Yamashita D, Jiang HY, Le Prell CG, Schacht J, Miller JM. Post-exposure treatment attenuates noise-induced hearing loss. *Neuroscience, 134:633-42,* 2005.

Most efforts focus on OHC protection – little emphasis on afferent neurons or their synapses

- **Antioxidants** reduce ROS, RNS, so they can be safely excreted (ebselen, D-Met, NAC, dietary antioxidants)
- **Glucocorticoids** reduce inflammation driven by TNFα and NFκB
- **JNK inhibitors** block "death receptor" activation
- **Gene therapy** is different; drives development of new cells



Dinh, C. T., Goncalves, S., Bas, E., Van De Water, T. R., & Zine, A. (2015). Molecular regulation of auditory hair cell death and approaches to protect sensory receptor cells and/or stimulate repair following acoustic trauma. Frontiers in Cellular Neuroscience, 9, 96. https://doi.org/10.3389/fncel.2015.00096

Terms and Definitions

Hearing Loss

- Measured using audiogram
- Threshold elevation
  - NIHL, ARHL
- Clinical gold standard
- **Primary outcome measure in vast majority of clinical trials to date**

Hearing Disorders

- Hearing-in-noise deficits
- Tinnitus
- Hyperacusis
  - Collectively, NIHD, when associated with noise exposure
- Temporal processing deficits
- Sound localization deficits
- **Not as well represented in clinical trials**

“Hidden Hearing Loss”

- Kujawa and Liberman (2009) documented decreased wave I amplitude in presence of normal ABR thresholds, with loss of cochlear synapses with inner hair cells (“cochlear synapthopathy”)
- Schaette and McAlpine (2011) defined decreased Wave I amplitude with normal ABR thresholds as “hidden hearing loss”
- “Hidden hearing loss” now routinely used for all of the following:
  - Cochlear synaptopathy
  - Decreased Wave I in presence of normal thresholds
  - Various supra-threshold hearing disorders not captured by the audiogram

Some points of agreement (and some questions)

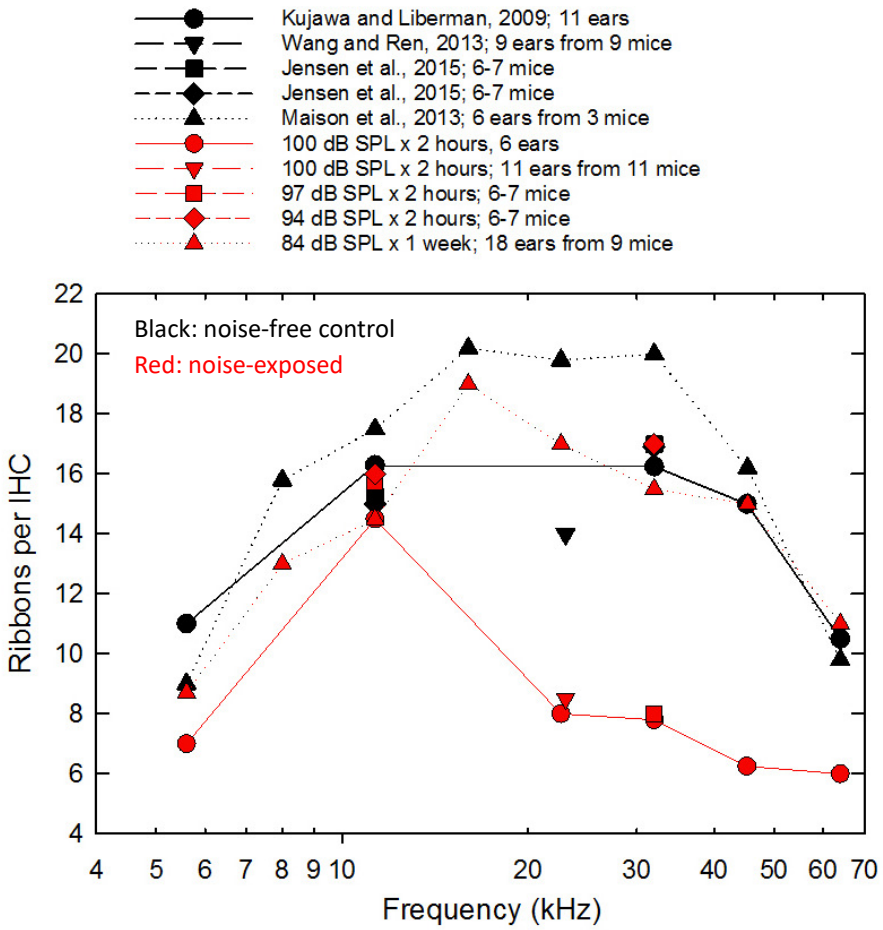
- **Not every noise exposure resulting in TTS produces synapse loss**
- There are vast differences in vulnerability across species
- Humans are at risk for cochlear synaptopathy; vulnerability to noise-induced synapse loss unclear, but age-related synapse loss documented
- Individual variability in vulnerability unknown but likely substantive
- Suprathreshold deficits are major clinical concern regardless of whether synapse loss or OHC loss is cause
- Risks for OHC loss and synapse loss during occupational noise exposure are of high interest
- Measurement of threshold and suprathreshold deficits in clinical trials is a high priority

Not every noise exposure that causes TTS is synaptopathic

Black symbols – cochlear synapses per IHC in CBA/CaJ mice without noise exposure

Red symbols - cochlear synapses per IHC in CBA/CaJ mice with different noise exposures

- All exposures caused TTS (~20 to 50 dB 24 hrs post noise) but not all exposures caused synapse loss
- Fernandez et al. 2020 have additionally explored damage/risk relationships and while damage increases with increasing exposure, risk of synaptopathy declines when exposures induce PTS and OHC loss.



Le Prell, C.G., and Brungart, D.S. (2016). Potential effects of noise on hearing: supra-threshold testing using speech-in-noise and auditory evoked potentials, *Otology & Neurotology, 37: e295-e302*.

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Synaptopathic injury across species

- Mouse: 100-dB SPL OBN x 2 hrs
  - Dose-response studies show PTS with 3 dB level increase, no pathology with 3 dB level decrease
- Chinchilla: similarly vulnerable; 98-99 dB SPL OBN x 2 hrs
  - Synaptic damage plus PTS observed at 100-101 dB SPL (2-dB increase)
- Guinea Pig: 106-dB SPL OBN x 2 hrs
  - PTS observed at 109 dB SPL x 2 hrs (3-dB increase)
- Rat: 109 dB SPL OBN x 2 hrs
  - 106-dB SPL OBN x 2 hrs produced no synaptic injury (3-dB decrease)
- Ramachandran and his team show Rhesus macaque is less vulnerable; synapse damage observed with either 108-dB SPL NBN x 4 hrs (50 Hz noise band centered at 2 kHz) or 120 dB SPL OBN x 4 hrs
- Data from humans are mixed

For review see Le Prell, C. G. (2019). "Effects of noise exposure on auditory brainstem response and speech-in-noise tasks: A review of the literature," Int. J. Audiol. 58, S3-S32.

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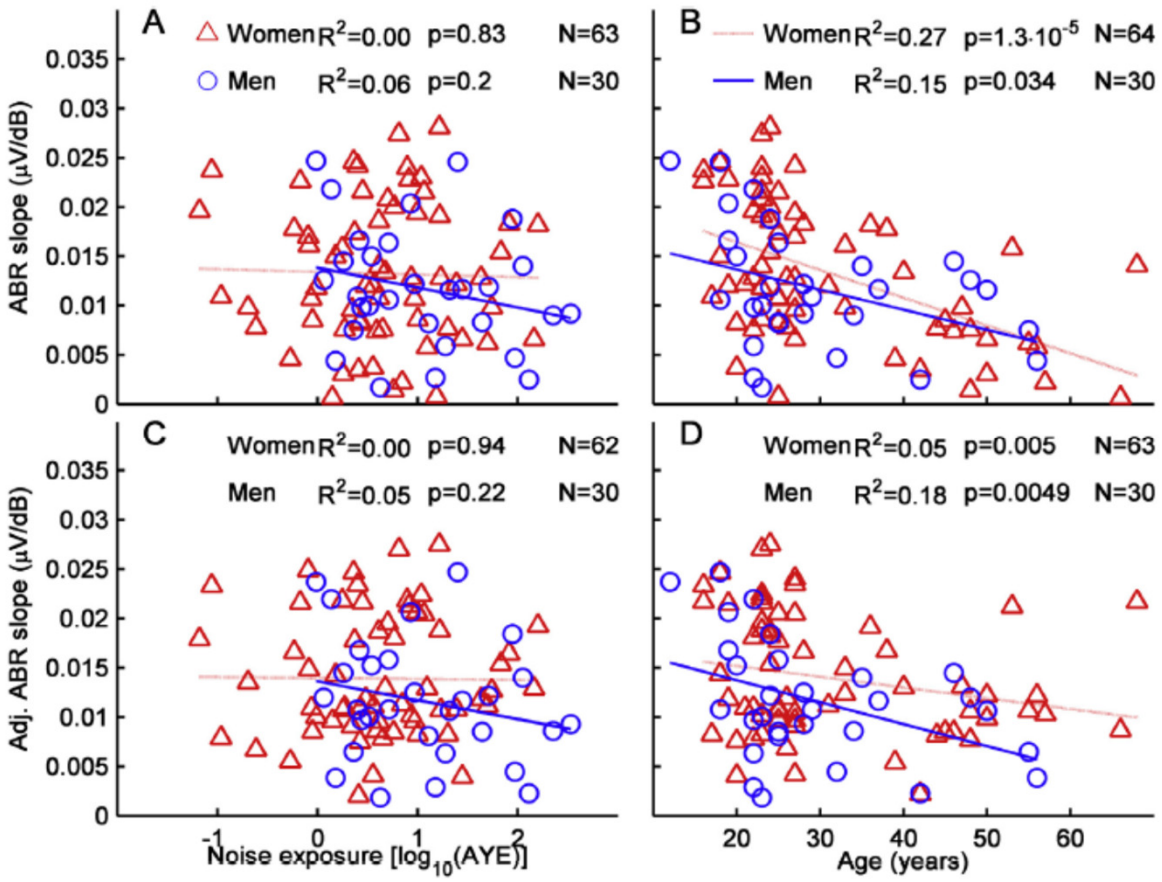
ABR amplitude associated with age but not noise history



- 94 participants (64F, 30M), 12-68 yrs of age, with ≤20 dB HL thresholds from 0.25-4kHz and ≤30 dB HL thresholds at 6 and 8kHz
- Participants had varied noise histories
- A and C: No statistically significant relationships between noise history and ABR slope (growth in amplitude with increasing sound level)
- **B and D: Statistically significant relationship between age and ABR slope (growth in amplitude with increasing sound level)**

Johannesen PT, Buzo BC, and Lopez-Poveda EA (2019). Evidence for age-related cochlear synaptopathy in humans unconnected to speech-in-noise intelligibility deficits, Hear Res 374:35-48.

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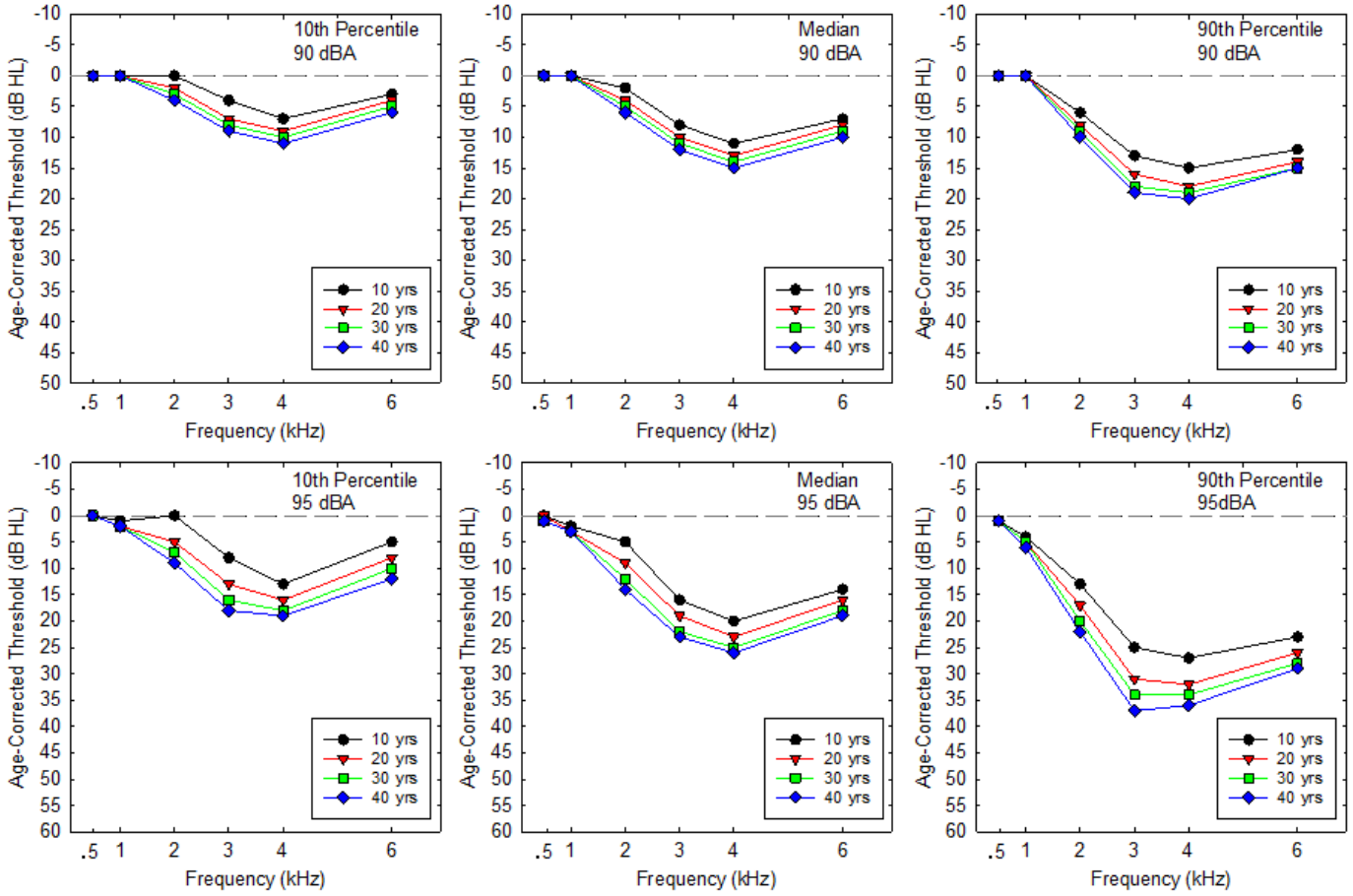
Individual variability is substantive(10th vs 90th percentile)



- Individual differences in vulnerability related to:
  - HPD use
  - Non-occupational noise exposure
  - Genetics
  - Cardiovascular health
  - Earcanal amplification
  - Middle ear power transfer
  - Diet
  - Circadian rhythm
  - Hormones
  - Gender
  - Race/ethnicity

Le Prell, C. G., Brewer, C., and Campbell, K.C.M. (2022). The audiogram: Detection of pure-tone stimuli in ototoxicity monitoring and assessments of investigational medicines for the inner ear. *Journal of the Acoustical Society of America, 151(1): 470-490, doi: 10.1121/10.0011739.*

JASA Special Issue: Noise-Induced Hearing Loss: Translating Risk from Animal Models to Real World Environments
https://asa.scitation.org/toc/jas/collection/10.1121/jas.2019.NIHLNS2019.issue-1

How much exposure is safe for everyone?

- Reviews of NIHL in adults (Fligor and Neitzel, 2019) and children (Roberts and Neitzel, 2019) suggest:
- exposure limit of **80 dB-A L_{EX}** (L_{EX}: 8-hour equivalent continuous average sound pressure level) would protect all but the most vulnerable individuals against NIHL
- **75 dB-A L_{EX}** limit would be necessary if the goal were to protect even the most vulnerable individuals

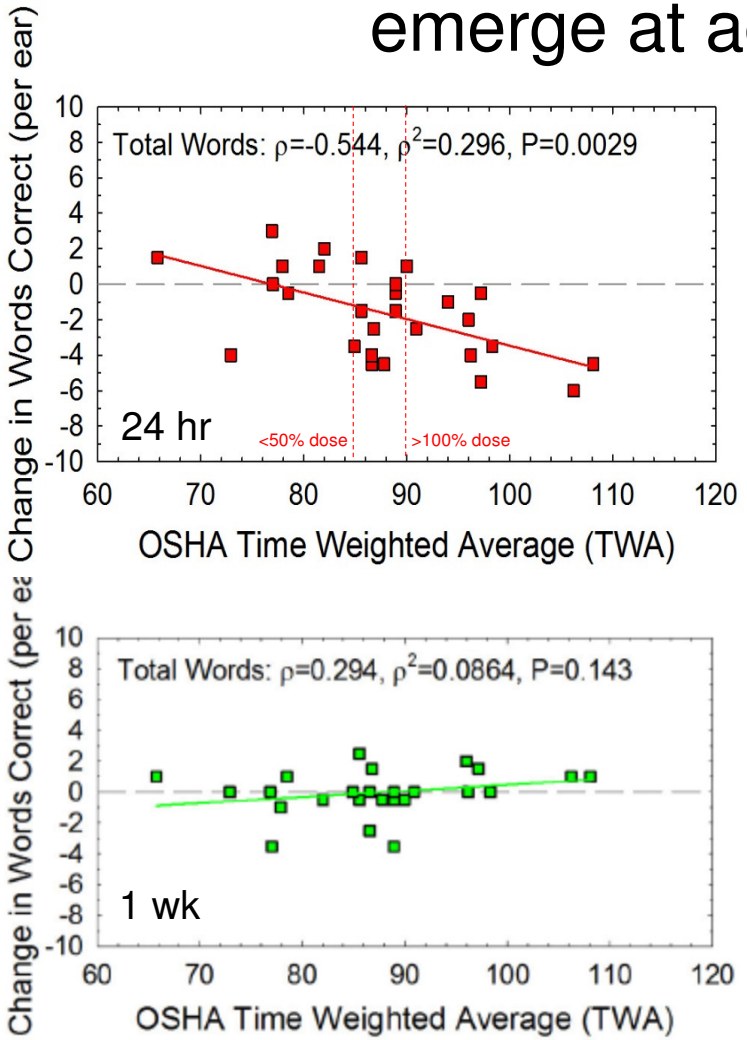
Reminders:

We do not have data that specifically address whether risk for noise-induced tinnitus and hearing-in-noise deficits begin at same exposure level

We do not yet have any way to identify who the most vulnerable individuals are in advance of noise injury

We do not have damage risk criteria for cochlear synaptopathy or OHC pathology

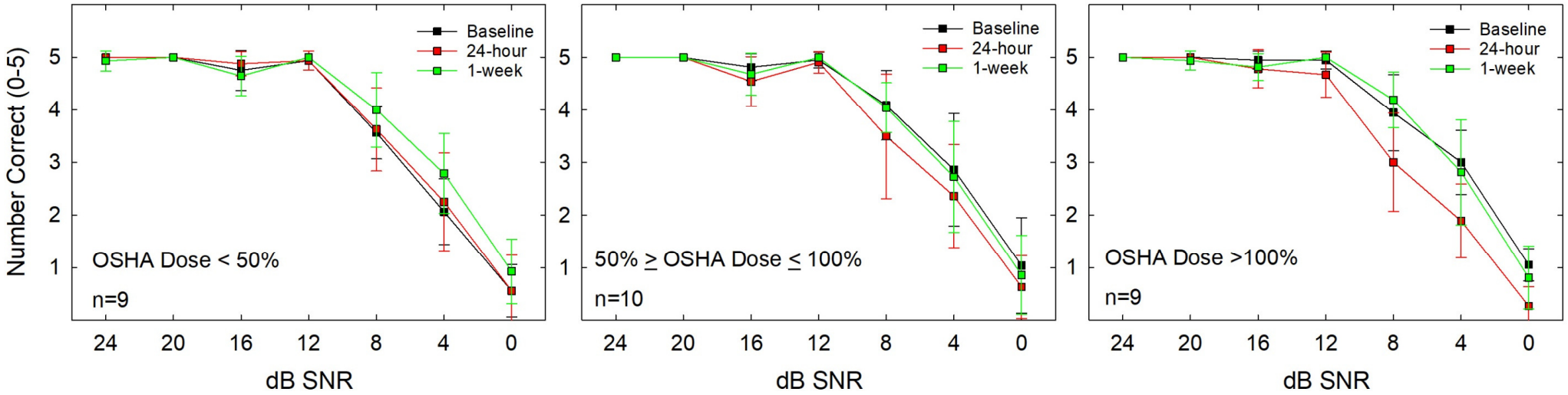
Temporary hearing-in-noise deficits the day after exposure emerge at action level of 85 dBA TWA



- 28 participants attended recreational event they deemed loud
  - Level: 93.3±7.8 dBA (range 73.1–104.2 dBA)
  - Duration: 4.2±3.5 hrs (range 1.5–16.0 hrs)
- Average dose and TWA calculated using 29 CFR 1910.95 (OSHA)
  - 168.4%±276% (range 3.5%–1,230.8%)
  - 87.8 dBA TWA±9.5 dBA (range 65.8–108.1 dBA TWA)
- No reliable threshold shift; dose-dependent hearing-in-noise shift that recovered within 1 week
- Marginally significant decrease in DPOAE amplitude at 24 hr but not 1 wk test
- No post-noise decrease in wave 1 amplitude

Grinn, S., Baker, J., Wiseman, K., and Le Prell, C. G. Hidden hearing loss? No effect of common recreational noise exposure on cochlear nerve amplitude in humans. *Frontiers in Neuroscience, 11:465;* https://doi.org/10.3389/fnins.2017.00465

Temporary hearing-in-noise deficits evident in MOST difficult listening conditions



Exposure Data:

- < 50% OSHA dose (4 male, 5 female)
- 50-100% OSHA dose (4 male, 6 female)
- > 100% OSHA dose (3 male, 6 female)

Average noise dose, calculated using 29 CFR 1910.95, was 168.4% ± 276% (range 3.5% – 1,230.8%)

Grinn, S., Baker, J., Wiseman, K., and Le Prell, C. G. Hidden hearing loss? No effect of common recreational noise exposure on cochlear nerve amplitude in humans. *Frontiers in Neuroscience, 11:465;* https://doi.org/10.3389/fnins.2017.00465

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Hearing in background noise

Difficulties hearing in noise are one of most common complaints; can occur with or without hearing loss

About 10% of patients seen for hearing-in-noise complaints with no audiometric loss at testing (Parthasarathy et al., 2020)

Rapidly emerging literature shows hearing-in-noise deficits can occur with damage to OHCs (inferred from OAE deficits, EHF deficits) or damage to synapses (inferred from evoked potential shifts)

-work by Parker, Liberman, Bramhall, Guest, Plack, Kamerer, Beach and others

Hearing-in-noise deficits are NOT diagnostic for synapse loss (although synapse loss might be inferred if OAEs are robust)

For detailed reviews, see:

Le Prell C.G. & Clavier O.H. 2017. Effects of noise on speech recognition: Challenges for communication by service members. Hear. Res., 349, 76-89.

Le Prell, C. G. (2019). Effects of noise exposure on auditory brainstem response and speech-in-noise tasks: A review of the literature. *International Journal of Audiology*, *58*(sup1), S3-S32.

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A fundamental pitfall in extrapolating rodent neuropathy data to human exposure regulations

- Rodent neuropathy occurred only after exposures that caused "pathological" TTS (TTS bordering on PTS)
- This has been recognized as an unsafe exposure for decades
- Pathological TTS does not appear to occur in humans with exposures below the OSHA PEL

"Based on what is known to date, it would be premature to conclude that noise exposures below the OSHA PEL can cause cochlear neuropathy in humans… Of course, it would be equally premature to conclude that such effects cannot occur."

Dobie RA & Humes LE (2017) Commentary on the regulatory implications of noise-induced cochlear neuropathy. International Journal of Audiology, 56:sup1, 74-78, DOI: 10.1080/14992027.2016.1255359

Systematic review of ABR data from noise-exposed workers

- Thirteen studies reported ABR data from noise-exposed worker populations
- Multiple reports that Wave I, III, and/or V latency was delayed in workers exposed to noise; a subset of studies measured Wave I, III, or V amplitude and reported smaller amplitudes
- The high prevalence of ABR waveform deficits across occupational noise groups contrasts with inconsistent deficits within leisure noise groups
- Although ABR waveform deficits were common with occupational noise exposure, most noise-exposed worker cohorts had significant hearing loss – i.e., these were not "hidden" hearing losses
- Presence of NIHL suggests OHC pathology accompanied any neuropathic change that might potentially be inferred from the atypical ABR results

Le Prell, C. G. (2019). Effects of noise exposure on auditory brainstem response and speech-in-noise tasks: A review of the literature. *International Journal of Audiology*, *58*(sup1), S3-S32.

Other questions raised by Dobie and Humes

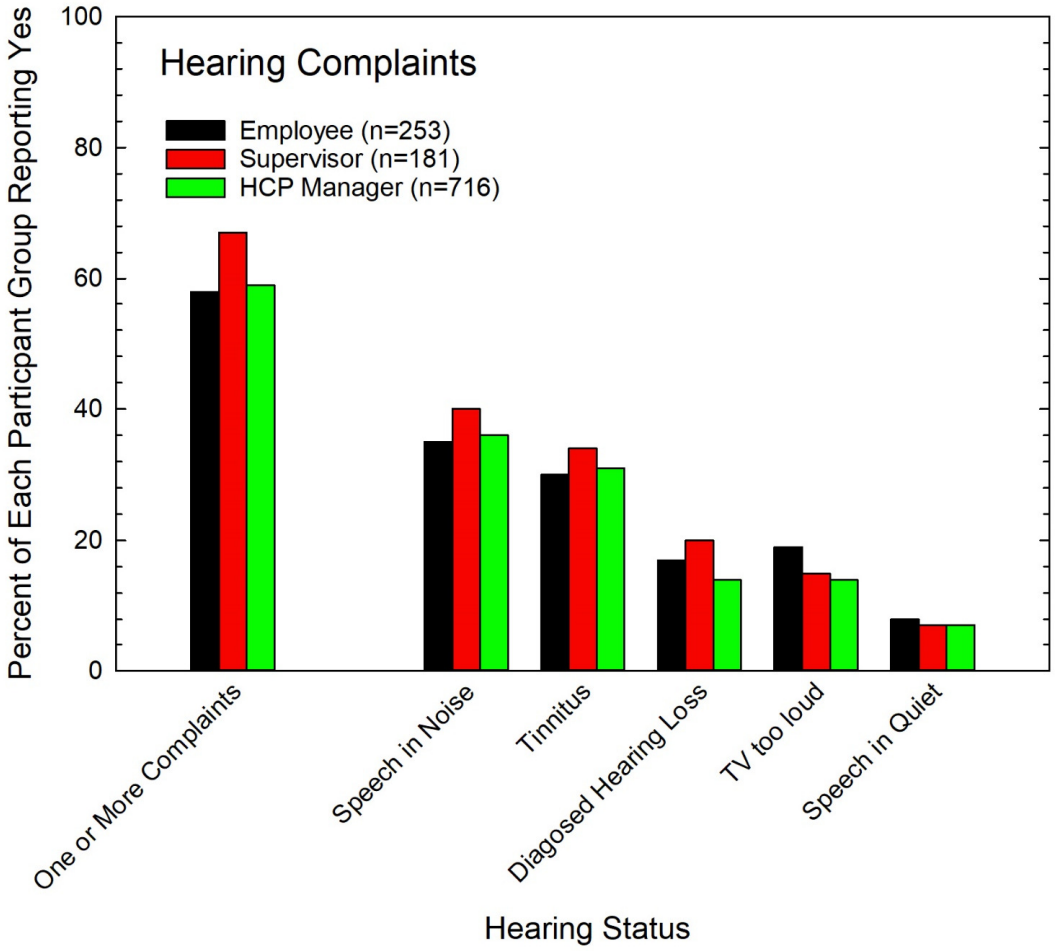
- Do noise-exposed people report poorer communication performance than audiometrically matched non-noise-exposed people (as might be expected if neuropathy were relatively more important for noise induced than for age-related hearing loss)?
- Do they have worse speech recognition scores in difficult listening situations than audiometrically matched non-noise-exposed individuals?

Dobie RA & Humes LE (2017) Commentary on the regulatory implications of noise-induced cochlear neuropathy. International Journal of Audiology, 56:sup1, 74-78, DOI: 10.1080/14992027.2016.1255359

High rate of hearing complaints with occupational noise

- Survey study recruiting workers required to wear HPDs, supervisors of workers who are required to wear HPD, and hearing conservation program managers
  - 60-65% reported one or more complaints
  - 35-40% reported hearing-in-noise issues
  - 30-35% reported tinnitus
  - 15-20% had diagnosed hearing loss

Tinnitus and hearing-in-noise difficulties were twice as common as diagnosed hearing loss; neither are monitored in occupational HCP's and there are no damage-risk criteria for these NIHD



Jansen C, Cochran A, Fallon E, Le Prell CG. In preparation.

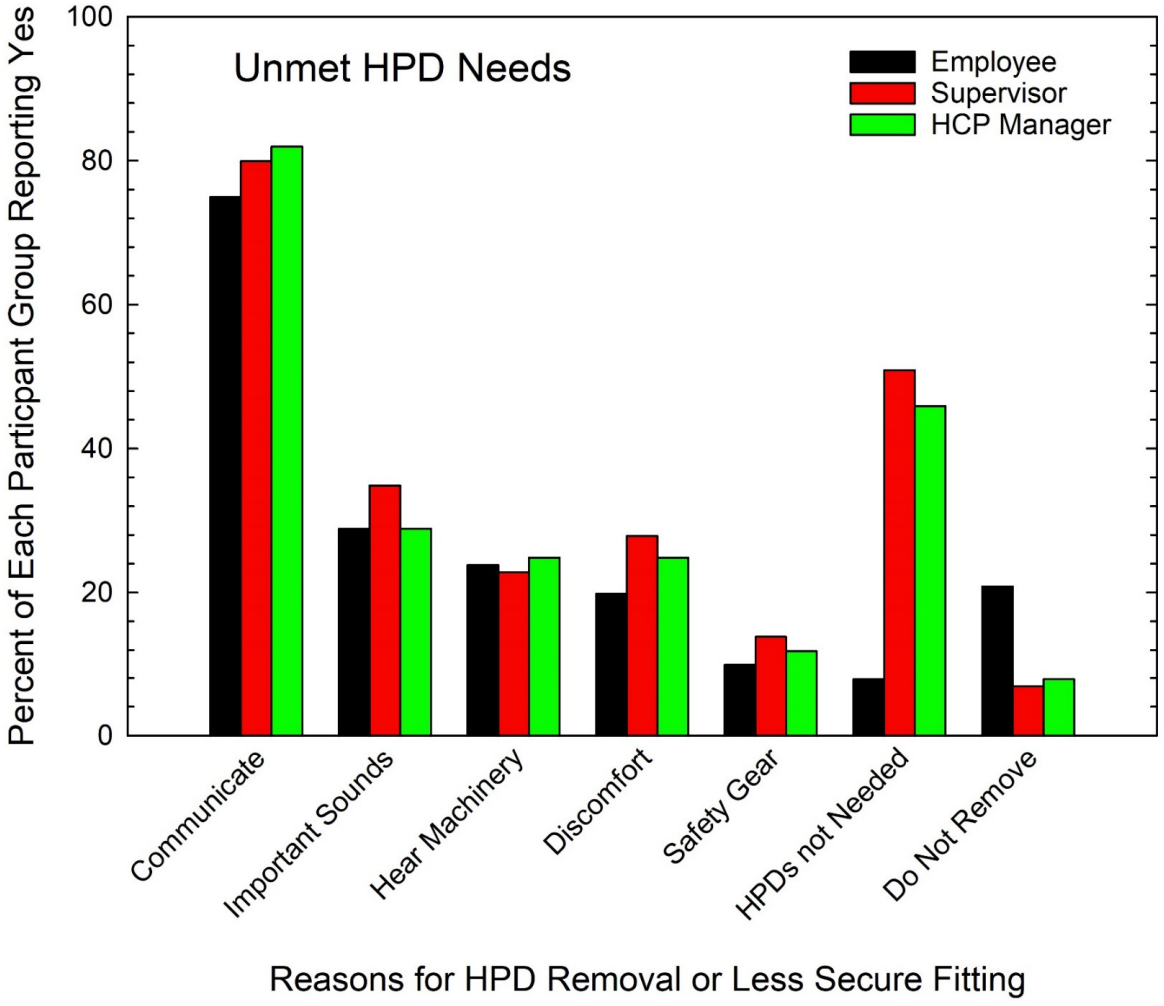
Audibility Needs

- **67% of Employees** sometimes remove HPDs to hear better while working
- **80% of Supervisors and 74% of HCP Managers** report Employees they supervise sometimes remove their HPDs to hear better while working

Statement	Agreement Levels	Employee % (n=253)	Supervisor % (n=181)	HCP Managers % (n=718)
I sometimes remove my hearing protectors to hear better while working.	**Strongly Agree**	**16% (40)**	**21% (38)**	**14% (98)**
	Agree	**21% (54)**	**31% (56)**	**30% (213)**
	Slightly Agree	**30% (77)**	**28% (52)**	**30% (213)**
	Slightly Disagree	5% (7)	3% (6)	9% (68)
	Disagree	11% (28)	11% (20)	10% (71)
	Strongly Disagree	17% (42)	6% (11)	7% (53)

Reasons reported for removing or less securely fitting HPDs

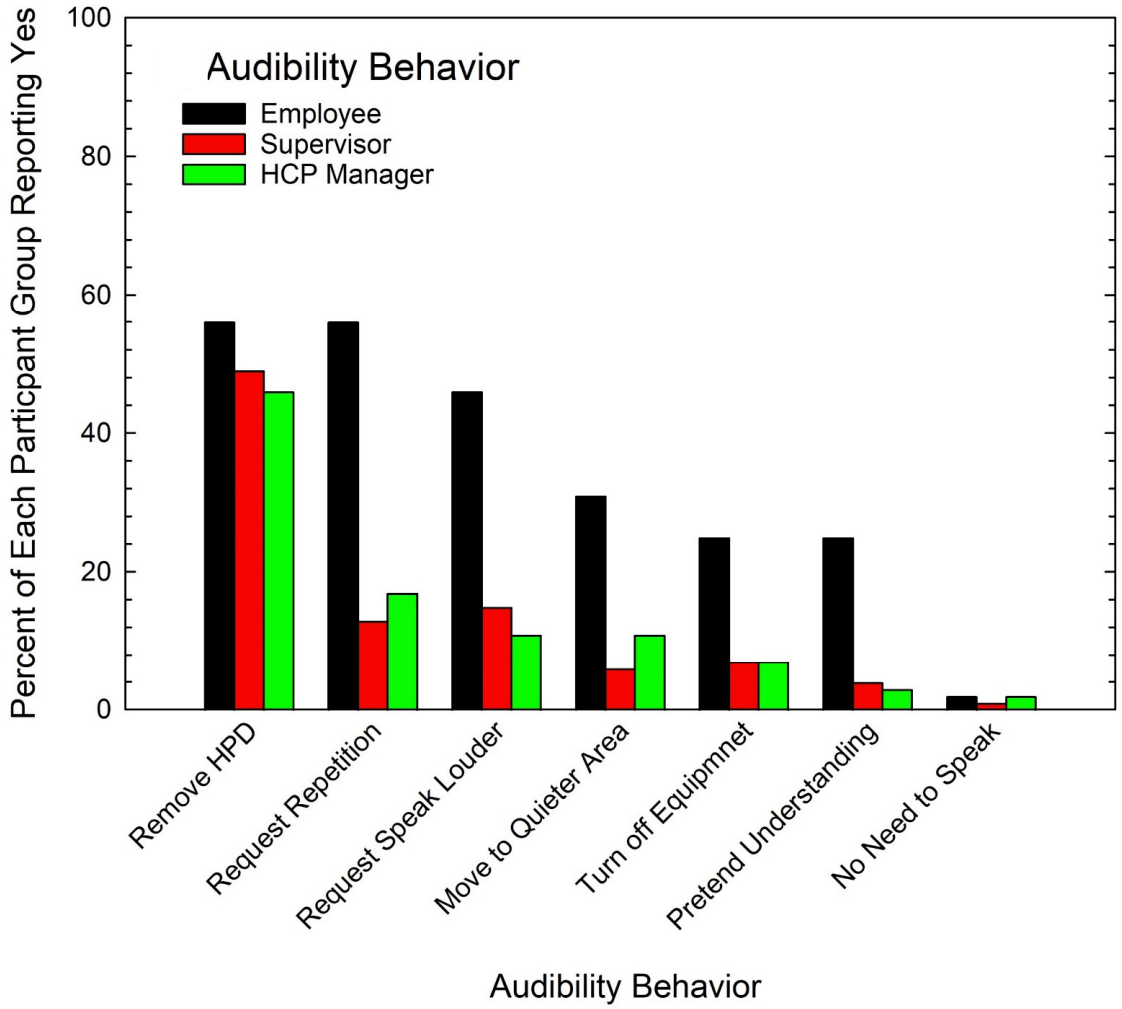
- To communicate with co-workers – 75-80%
- Can't hear important sounds when wearing HPDs – 30-35%
- To hear machinery or processes better – 25%
- Not all reasons were audibility related
  - Discomfort – 20-30%
  - Don't work with other safety equipment – 10-15%



Jansen C, Cochran A, Fallon E, Le Prell CG. In preparation.

Additional Audibility Behaviors Used to Communicate with Co-Workers

- HPD removal was the most common but workers reported additional strategies such as requesting repetition, moving to a quieter area, turning off equipment
- Pretending understanding was also reported
- Supervisors and safety managers did not recognize that employees use these additional communication strategies



Jansen C, Cochran A, Fallon E, Le Prell CG. In preparation.

Some points of agreement (and some questions)

- Not every noise exposure resulting in TTS produces synapse loss
- There are vast differences in vulnerability across species
- Humans are at risk for cochlear synaptopathy; vulnerability to noise-induced synapse loss unclear, but age-related synapse loss documented
- Individual variability in vulnerability unknown but likely substantive
- Suprathreshold deficits are major clinical concern regardless of whether synapse loss or OHC loss is cause
- Risks for OHC loss and synapse loss during occupational noise exposure are of high interest
- **Measurement of threshold and suprathreshold deficits in clinical trials is a high priority**

Clinical Trial Phases

	Phase 1	Phase II	Phase III
Description	First test of new treatment to see if it is safe	Preliminary test of safe agents to see if benefit is provided	Assessment of agents that appear to provide benefit; frequently compares new agent to standard of care
Goals	-is treatment safe -how to deliver (pills, shot) -determine dose-related side effects in healthy volunteers	-does treatment "work" -do new side effects emerge when patients are treated	-is new treatment better than, equivalent to, or poorer than standard of care
Sample Size	Typically 20-30	Often 100 or more	Typically several hundred to several thousand
What to Expect	Physical exams and multiple laboratory tests	Physical exams and multiple laboratory tests; may be open-label or may be masked	Physical exams and blood tests; randomization, placebo control, double masking

Bhowmik D, Chandira M, Maharajganj N, Pradesh U. (2010). Emerging trends of scope and opportunities Clinical trials in India. *International Journal of Pharmacy and Pharmaceutical Sciences.* 2(Suppl. 1):7-20.

Key Definitions in Clinical Trial Design

- Outcome: measured variable
  - e.g., audiometric threshold, DPOAE amplitude
- Endpoint: analyzed parameter (e.g., change from baseline)
  - Primary endpoint – typically will be the most important outcome; addresses whether a new treatment prevents disease, or is better at preventing disease than the standard therapy
  - Secondary endpoint – other relevant questions to be answered by study; can build on primary endpoint with mechanistic insights (e.g., a drug for osteoporosis with fractures as the primary endpoint could include improved bone density as a secondary endpoint)
- Indication: use of a drug for treating a particular disease (e.g., use of a drug for NIHL prevention or ARHL treatment)
  - Multiple endpoints may be used to evaluate clinical benefit when (1) there are several important aspects of a disease or several ways to assess an important aspect, (2) there is no consensus about which one will best serve the study purposes, and (3) an effect on any one will be sufficient as evidence of effectiveness to support 501 approval.

Challenges in matching “HHL” endpoints to indications

- Per FDA: A therapeutic intervention may be said to confer clinical benefit **if it prolongs life, improves function, and/or improves the way a patient feels**
  - Changes in ABR amplitude (or other evoked potentials) may be earliest outcomes of disease or injury process; however, if there are no measurable perceptual deficits associated with those changes, clinical benefit and medical indication may be difficult to establish
  - Changes in audiogram are the most common clinical trial outcome but cochlear synaptopathy by definition does not affect the audiogram
  - Hearing-in-noise and tinnitus receiving significant discussion; ultimately up to FDA what constitutes clinically significant benefit

Review of endpoints in hearing loss trials in ClinicalTrials.gov

- All clinical trials funded by NIH must be listed; many trials under FDA oversight listed
- 42 CFR 11.22 requirements broadly include registration for any U.S. clinical trial with one or more arms that (i) is interventional, (ii) is other than Phase 1, and/or (iii) studies an FDA-regulated drug product.
- The criteria for U.S. clinical trials further include (i) having at least one clinical trial location within the U.S. or one of its territories, (ii) product manufacturing in and export from the U.S. or one of its territories for study in another country, and/or (iii) the clinical trial has an FDA IND Number.
- Thus, all efficacy-based U.S. clinical trials submitted to FDA for review through IND (investigational new drug application) process and any clinical trial using drugs manufactured in the U.S. must be listed
- Not every trial listed on ClinicalTrials.gov is overseen by FDA

Audiogram is most common endpoint measure in hearing loss prevention/hearing restoration trials posted on ClinicalTrials.gov

Primary, Secondary, or Other Endpoint	NIHL (n = 9)	DIHL (n = 30)	SNHL (n = 13)	SSNHL (n = 9)
Threshold Shift	7; 78%	14; 47%	8; 62%	9; 100%
Rate of ASHA SOC	0	6; 20%	0	0
Rate of CTCAE	0	3; 10%	0	0
Rate of Brock	0	1; 3%	0	0
Rate of Boston SIOP	0	1; 3%	0	0
Rate of Tune	0	1; 3%	0	0
Other STS Rate	1; 11%	8; 27%	1; 8%	0

Le Prell CG. 2021. Investigational medicinal products for the inner ear: Review of clinical trial characteristics in ClinicalTrials.gov. J Am Acad Audiol, 32(10):670–694.

Other endpoint measures rarely used in hearing loss prevention/hearing restoration trials posted on ClinicalTrials.gov

Primary, Secondary, or Other Endpoint	NIHL (n = 9)	DIHL (n = 30)	SNHL (n = 13)	SSNHL (n = 9)
DPOAE shift	5;56%	10; 33%	1; 8%	0
EHF Threshold shift	1; 11%	5; 17%	2; 15%	0
Word Recognition Change	0	2; 7%	6; 46%	4; 44%
Hearing in Noise Change	**2; 22%**	**2; 7%**	**5; 38%**	**0**
Change in Tinnitus	**5; 56%**	**7; 23%**	**5; 38%**	**1;11%**
ABR Amplitude Shift	**0**	**0**	**2; 15%**	**0**

Le Prell CG. 2021. Investigational medicinal products for the inner ear: Review of clinical trial characteristics in ClinicalTrials.gov. J Am Acad Audiol, 32(10):670–694.

What's the current landscape for tinnitus trials?

- ClinicalTrials.gov search for "Tinnitus" on 9/22/2022 resulted in 301 Hits
- 106 Device Studies
  - repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation, masking therapy, cochlear implant, brainstem implant, trigeminal nerve stimulation, vagus nerve stimulation, jugular vein compression, neuromonics
- 41 Behavioral Interventions
  - biofeedback, cognitive behavioral therapy, coping, counseling, meditation, mindfulness, neurofeedback, tinnitus retraining therapy, yoga
- 61 Other and Procedure: Mix of behavioral and device studies
- **61 Drug studies (**40 complete, **7 enrolling participants, 1 not yet recruiting,** 5 terminated, 1 suspended, 2 withdrawn, 5 unknown)
- 7 Dietary supplement studies
- **3 Biological interventions**
- Plus other assorted diagnostic tests and other assessments not captured above

Number	Outcome measurements	Number of studies (total number of studies: 66)
1	Scaling (e.g., satisfaction, severity, loudness, distress, annoyance, and awareness)	37
2	Tinnitus Handicap Inventory (THI)	27
3	Puretone audiometry	21
4	Patient self-report (e.g., severity, seriousness, and loudness)	19
5	Tinnitus Functional Index (TFI)	13
6	Loudness measurement	10
7	Beck Depression Inventory (BDI)	6
8	Pittsburg Sleep Quality Index (PSQI)	6
9	Pitch measurement	5
10	Tinnitus Handicap Questionnaire (THQ)	5
11	Minimum Masking Level (MML)	4
12	Otoacoustic emission	4
13	World Health Organization Quality of Life (WHOQOL) questionnaire	4
14	Otoscopic examination	3
15	Beck Anxiety Inventory (BAI)	2
16	Functional magnetic resonance imaging (fMRI)	2
17	Tympanometry	2
18	Tinnitus Questionnaire (TQ)	2
19	Words in Noise test	2

Major outcome measures in clinical trials evaluating pharmaceutical interventions for tinnitus are not standardized

Jin, I.-K. and Tyler, R. S. (2022). Measuring tinnitus in pharmaceutical clinical trials. The Journal of the Acoustical Society of America 152, 3843-3849; doi: 10.1121/10.0014699

What's the current landscape for regeneration trials?

- Over 1800 human clinical trials in Ginn et al. (2013) review – no hearing loss trials
  - Ginn, S. L., Alexander, I. E., Edelstein, M. L., Abedi, M. R., and Wixon, J. (2013). "Gene therapy clinical trials worldwide to 2012 - an update," J. Gene Med. 15, 65-77.
- Ahmed et al. (2017) review noted no regeneration trials in the human inner ear yet
  - Ahmed, H., Shubina-Oleinik, O., and Holt, J. R. (2017). "Emerging gene therapies for genetic hearing loss," J. Assoc. Res. Otolaryngol. 18, 649-670.
- Over 2600 human clinical trials in Ginn et al. (2018) review – hearing loss included as part of "other diseases" (combined, 58 trials (2%) out of >2600 trials)
  - Ginn, S. L., Amaya, A. K., Alexander, I. E., Edelstein, M., and Abedi, M. R. (2018). "Gene therapy clinical trials worldwide to 2017: An update," J. Gene Med. 20, e3015.
- 10 inner ear regeneration studies in ClinicalTrials.gov search by Le Prell et al (2022), search date 2/27/2022
  - Le Prell, C. G., Brewer, C. C., and Campbell, K. C. M. (2022). "The audiogram: Detection of pure-tone stimuli in ototoxicity monitoring and assessments of investigational medicines for the inner ear," J. Acoust. Soc. Am. 152, 470-490.
  - Otonomy and Frequency programs suspended/terminated; new inner ear trials are in various stages of planning since 2022 review

Clinical Trial ID	Inclusion Criteria	Primary Outcome	Secondary Outcomes	Status (3/2/23)
NCT02132130	21-75 yrs; non-fluctuating severe-to-profound unilateral or bilateral HL	Adverse events, conventional audiometry, bone conduction audiometry	BAER, vestibular function (HIT, VEMP, SVV), speech recognition	Completed
NCT03300687	18 or older; severe to profound SNHL of 80 dB HL or poorer at 500 Hz, meets criteria for CI; has chosen CI surgery	Adverse events (tinnitus, vertigo, perforation)	plasma pharmacokinetics over 24 and 72 hours; perilymph pharmacokinetics within 24 hours	Completed
NCT04629664	18-65 yrs; acquired, non-genetic, severe sensorineural hearing loss; PTA5124 of 71-90 dB HL in ear to be injected	Number of CTCAE v5.0 adverse events; abnormal otoscopic changes; abnormal change in tympanometry; suicide risk	speech in quiet, speech in noise (BKB-SIN), conventional and high frequency audiometry, tinnitus (TFI)	Completed
NCT05086276	18-65 yrs; acquired, adult onset, SNHL (NIHL or sudden SNHL); PTA5124 of 35-85 dB HL in ear to be injected	Speech perception	standard and high frequency audiometry, tinnitus assessment, and multiple patient reported outcome measures	Completed
NCT03616223	18-65 yrs; stable hearing loss due to NIHL or sudden SNHL; PTA5124 better than 70 dB HL	Number of CTCAE v5.0 adverse events	drug concentration in plasma within first 24 hours	Completed
NCT04120116	18-65 yrs; stable hearing loss due to NIHL or sudden SNHL; PTA5124 26-70 dB HL in the injected ear	Speech in quiet, speech in noise (WIN), audiometry, CTCAE v5.0 adverse events, abnormal otoscopic changes; abnormal change in tympanometry	high frequency audiometry, tinnitus assessment (TFI), and multiple patient reported outcome measures (HHIA, HIS)	Completed
NCT04462198	66-85 yrs; age-related SNHL; PTA5124 of 26-70 dB HL in ear to be injected	Treatment emergent adverse events	pharmacokinetics Other outcomes include speech in noise, audiometry, auditory brainstem response	Completed
NCT04601909	66-85 yrs; age-related SNHL; PTA5124 of 26-70 dB HL in ear to be injected	Number of CTCAE v5.0 adverse events; abnormal otoscopic changes; abnormal change in tympanometry; suicide risk (C-SSRS)	speech in quiet, speech in noise (WIN), conventional and high frequency audiometry, tinnitus (TFI)	Completed
NCT04129775	21-64 yrs; normal or up to moderately severe hearing impairment, self-reported difficulty hearing in noise for at least 6 months and a speech-in-noise deficit in at least one ear	Number of adverse events; abnormal otoscopic changes; abnormal change in audiometry	speech in noise, auditory brainstem response, and patient global impression of change	Completed
~~NCT05061758~~ -	18-65 yrs; ≥6 months stable hearing loss and stable word recognition test for approximately 6 months; <80 dB HL through 8 kHz	Number of responders with at least 2 dB improvement in an adaptive sentence in noise test (international matrix test) compared to placebo		Withdrawn

Drugs of interest for cochlear synaptopathy?

- Neurotrophic factors are of high interest for synaptic regeneration
- Animal data suggest restored synapses and restored wave I amplitude
- What is the clinical correlate? And, is it selective for synaptopathic injury?

Summary

- Audiogram is clinical gold standard and most common outcome measure in trials investigating NIHL, DIHL, ARHL, SSNHL
- Word recognition in noise most common within biologic (regeneration) trial space, but with no consensus on test protocol
- No consensus on gold standard for tinnitus assessment
- Objective measures (ABR, DPOAE) rarely used in clinical trials
- Use of patient-reported subjective outcomes is emerging
- Tinnitus and hearing-in-noise complaints may be consequences of OHC loss or cochlear synaptopathic injury
- Prevention of NIHD and treatments for existing NIHD are urgent unmet needs - it is essential to have functional measures that document patient complaints and provide clinically significant endpoints

AuD-PhD students leading HPD, NIHL, and NIHD studies

Aaron Cochran

Conner Jansen

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https://labs.utdallas.edu/noiselab/

Many thanks to our outstanding AuD student team:

- Amanda Duren
- Vickie Hanks
- Emily Myers
- Shamine Alves

And lab alumni:

- Sarah Grinn, AuD, PhD
- Tess Zaccardi, AuD
- Sarah Gittleman, AuD
- Kaitlyn Palmer, AuD
- Kathryn Ideker, AuD
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Questions and Discussion

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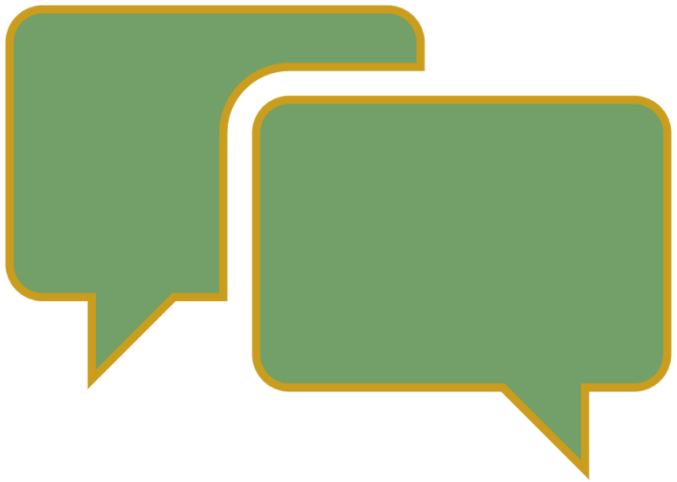

Questions?

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