Understanding Cochlear Synaptopathy: From Animal Models to Veterans

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*The contents of this presentation do not represent the views of the U.S. Department of Veterans Affairs or the United States Government

Assumptions about noise-induced hearing loss (prior to 2009)

- Outer hair cells are the most vulnerable part of the auditory system to noise.
- If auditory thresholds are not permanently changed, no permanent damage to the auditory system.
- Hearing conservation programs can detect early signs of noise damage with an annual audiogram.

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

Behavioral/Systems/Cognitive

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

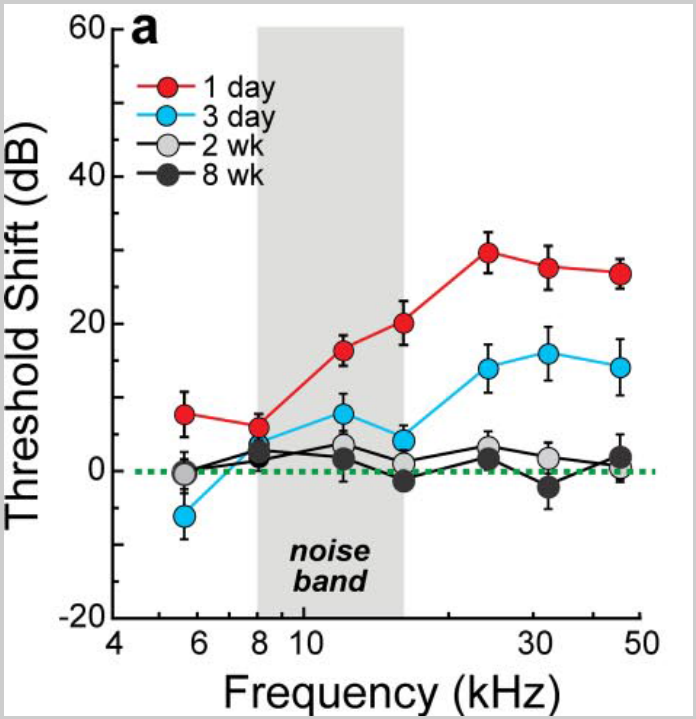
Sharon G. Kujawa[1,2,3,4] **and M. Charles Liberman**[1,2,4]

[1]Department of Otology and Laryngology, Harvard Medical School, Boston, Massachusetts 02115, [2]Eaton-Peabody Laboratory and [3]Department of Audiology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts 02114, and [4]Program in Speech and Hearing Bioscience and Technology, Division of Health Science and Technology, Harvard–Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

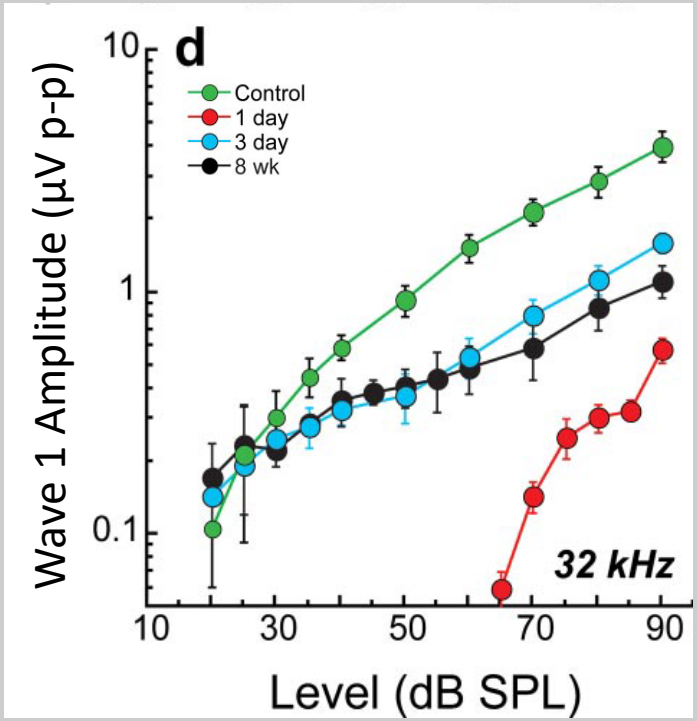
Mice were exposed to an 8-16 kHz band of noise at 100 dB SPL for 2 hours

Physiology suggests noise-induced auditory nerve dysfunction

DPOAEs - Assessment of outer hair cell (OHC) function



ABR wave 1 amplitude - Assessment of auditory nerve function



Auditory thresholds are normal, but input to central auditory system is reduced – "hidden hearing loss"

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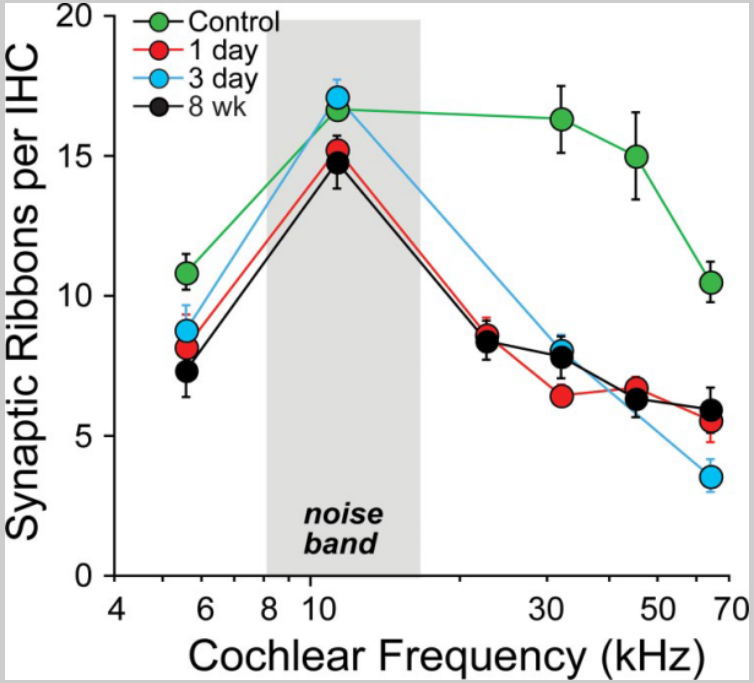
Kujawa and Liberman 2009, Journal of Neuroscience

Histology shows loss of cochlear synapses



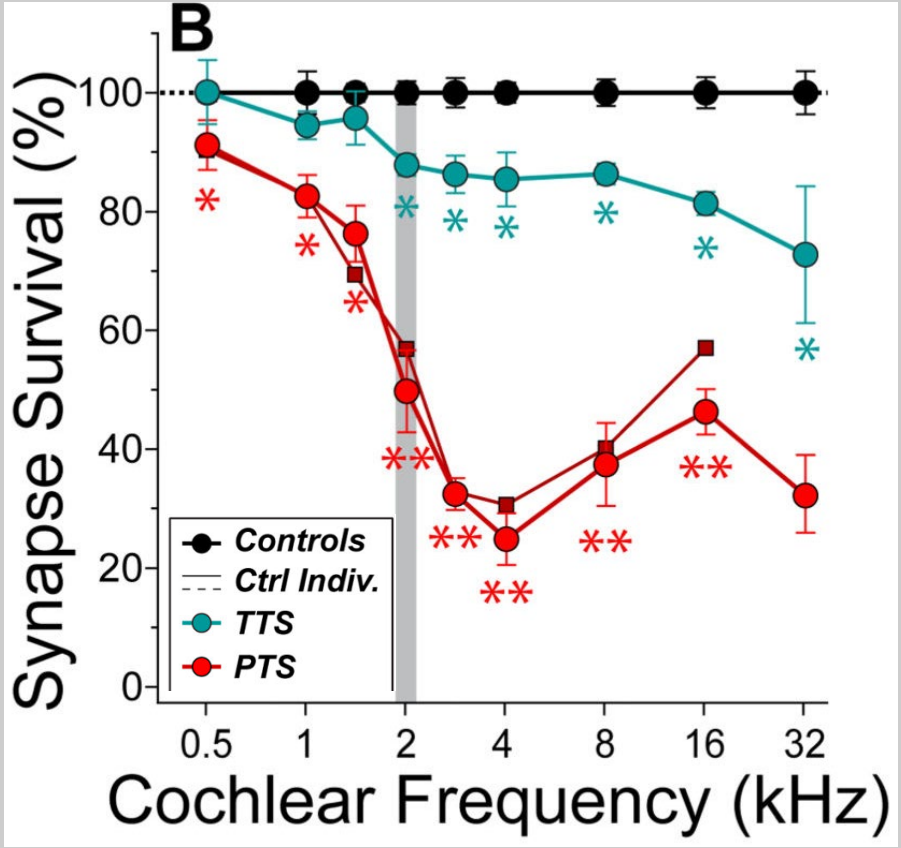
Kujawa and Liberman 2009, Journal of Neuroscience

Noise exposure results in an immediate loss of IHC/auditory nerve fiber synapses

Primates may be less susceptible to noise-induced synaptopathy than mice

Mouse:
Exposure to a 100 dB SPL band of noise for 2 hours resulted in a temporary threshold shift (TTS) and synaptic loss.

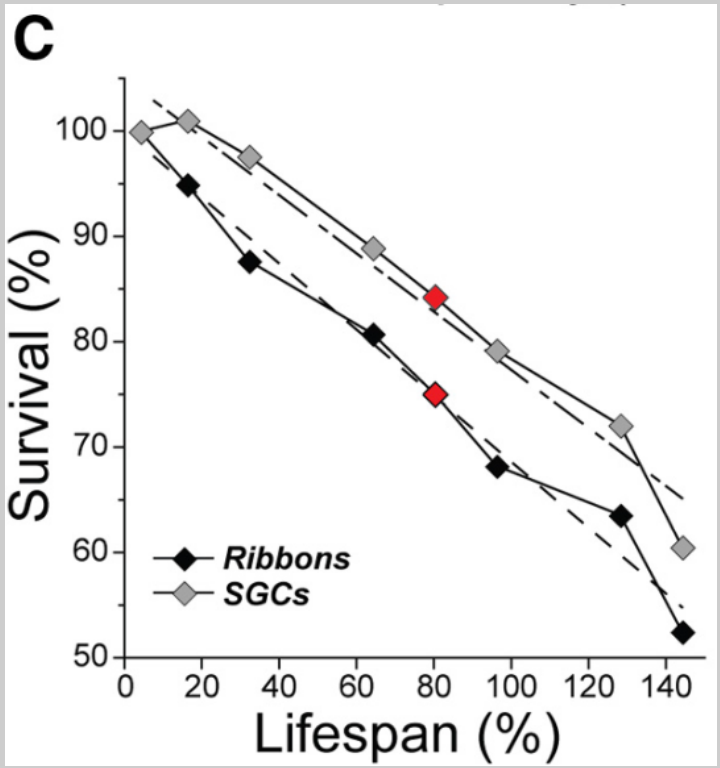
Rhesus monkey:
Exposure to a 108 dB SPL band of noise for 4 hours resulted in a TTS and synaptic loss.



Valero et al. 2017, Hearing Research

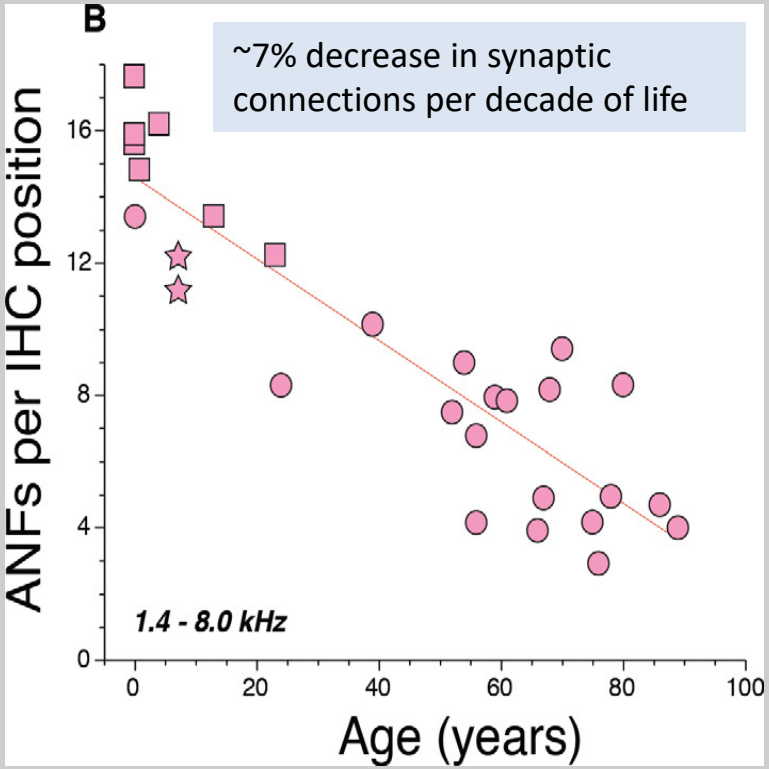
Aging leads to synaptopathy

Mouse



Sergeyenko et al. 2013, Journal of Neuroscience

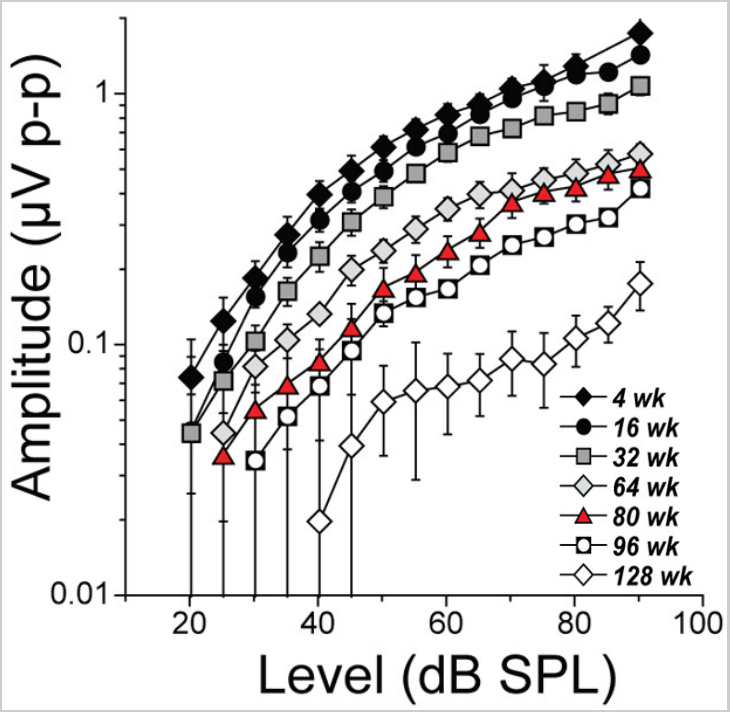
Human



Wu et al. 2019, Neuroscience

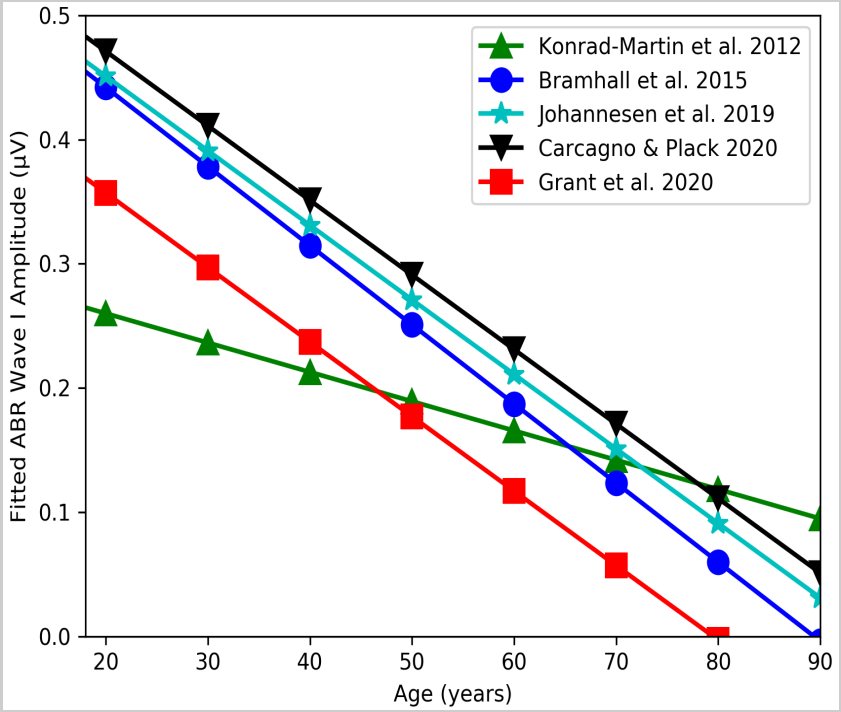
ABR wave I amplitude decreases with age

Mouse



Sergeyenko et al. 2013, Journal of Neuroscience

Human



Bramhall (In Press), JASA.

Overview of cochlear synaptopathy

- Cochlear synaptopathy refers to loss of the synaptic connections between the inner hair cells and the afferent auditory nerve fibers.
- In animal models, synaptopathy occurs in response to noise exposure, aging, and ototoxic drugs.
- While auditory thresholds appear relatively insensitive to cochlear synaptopathy, suprathreshold ABR wave I amplitude is sensitive to synaptopathy in animal models.
- Noise-induced cochlear synaptopathy has been demonstrated in multiple animal models, including non-human primates.
- However, vulnerability to noise-induced synaptopathy varies between species and primates appear less vulnerable.
- Temporal bone and physiology studies indicate that age-related synaptopathy occurs in humans.

Unanswered questions

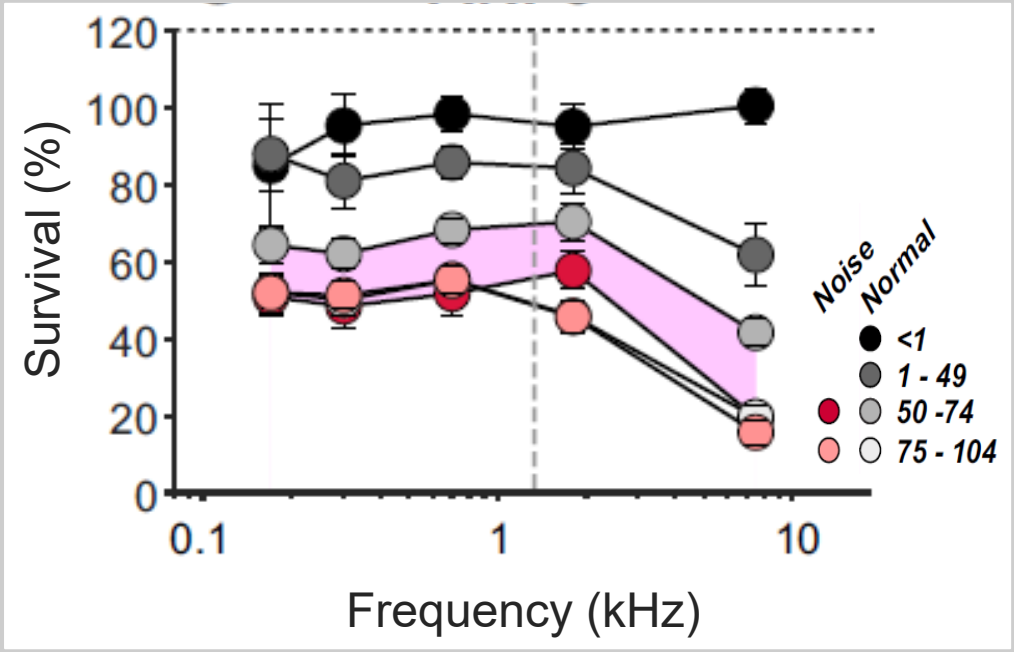
- Does noise-induced cochlear synaptopathy occur in humans?
- What are the perceptual consequences of synaptopathy?
- Can non-invasive physiological measures be used to diagnose synaptopathy?

Does noise-induced cochlear synaptopathy occur in humans?

Challenges of investigating noise-induced synaptopathy in humans:

- No current method of confirming synaptopathy in live humans
- It isn't ethical to noise expose humans for a research study
- Humans are not very reliable at reporting their noise exposure and are exposed to a lot of different types of noise
- Unlike mice, humans are not genetically identical – may have differences in susceptibility to noise damage
- Physiological measures of synaptopathy, such as ABR wave I amplitude, may be impacted by outer hair cell loss

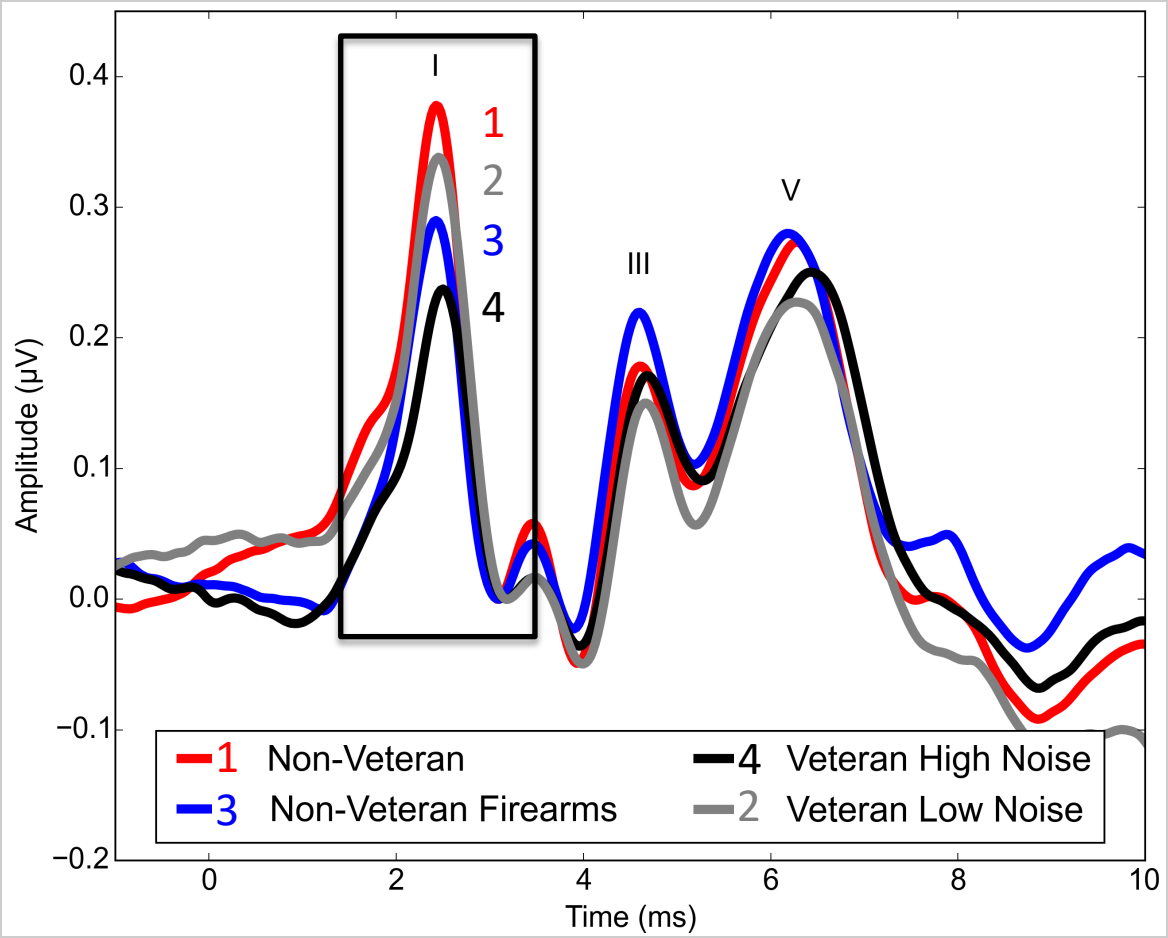
Temporal bone data suggest decreased synapse survival with noise exposure



Wu et al. 2021, J. Neuroscience

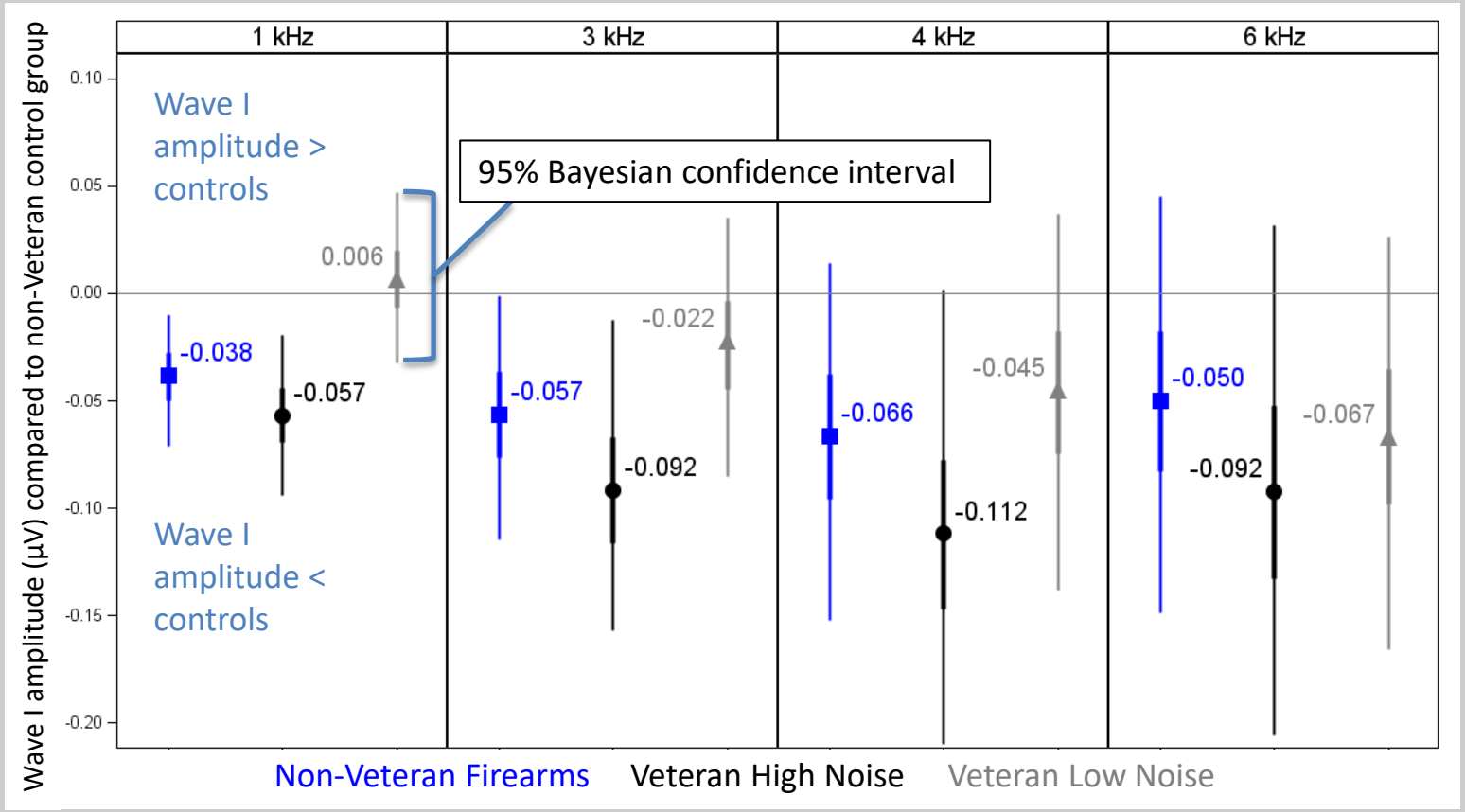
Sex	Age	Side	Exposure
M	43	L	Military service
M	52	R, L	Ship engine room
M	58	R, L	Ship builder
M	59	R, L	Pipeline worker
M	60	L	Truck driver
M	61	R, L	Military service, coppersmith
M	62	R, L	Foundry worker
M	63	R	Military service
M	66	L	Subway conductor
M	68	R, L	Military service: jet engines
M	69	R, L	Noisy machine
M	70	R	Carpenter
M	71	R, L	Steel worker
M	72	R	Construction worker

ABR wave I amplitude reduced for Veterans and non-Veterans with firearm use



Adapted from Bramhall et al. 2017, Ear and Hearing

Wave I differences persist after adjusting for DPOAEs and sex



Noise exposure-related reductions in wave I amplitude are consistent with animal models of cochlear synaptopathy

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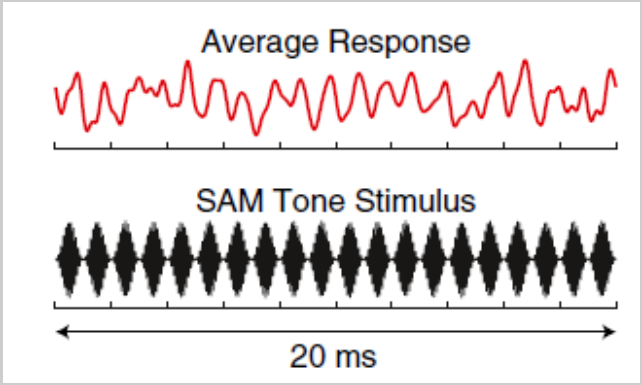
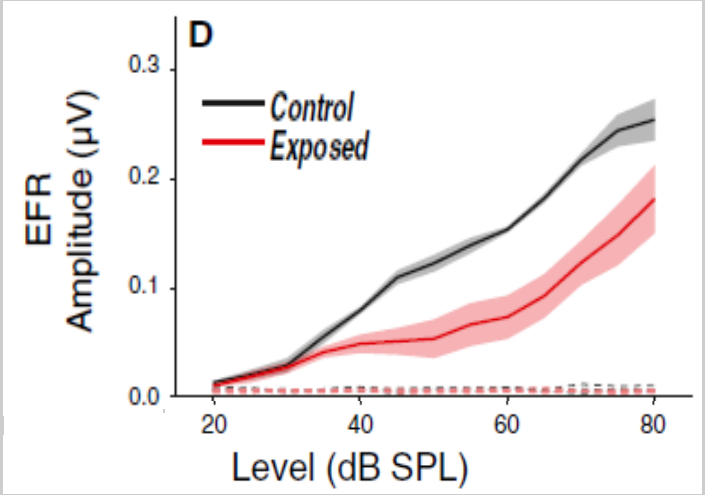
Bramhall et al. 2017, Ear and Hearing

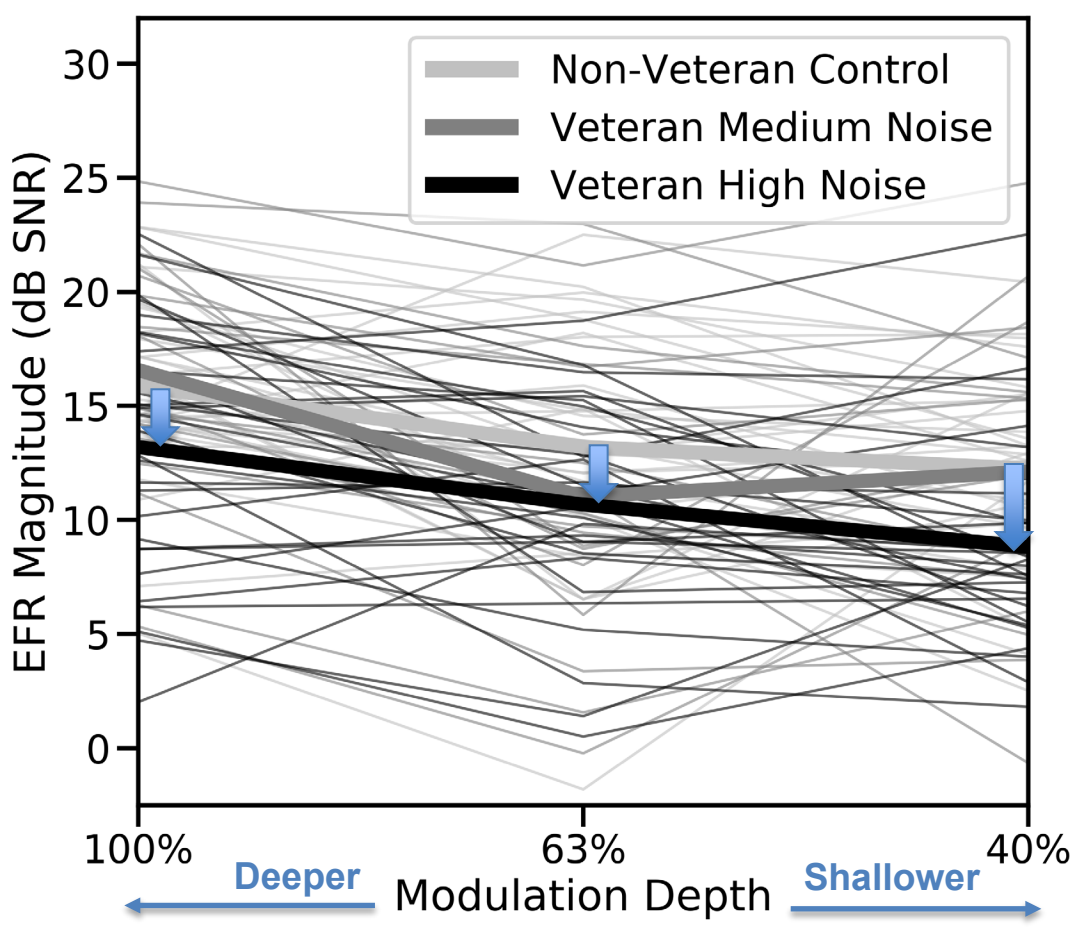
Envelope following response (EFR) reduced in mice with synaptopathy





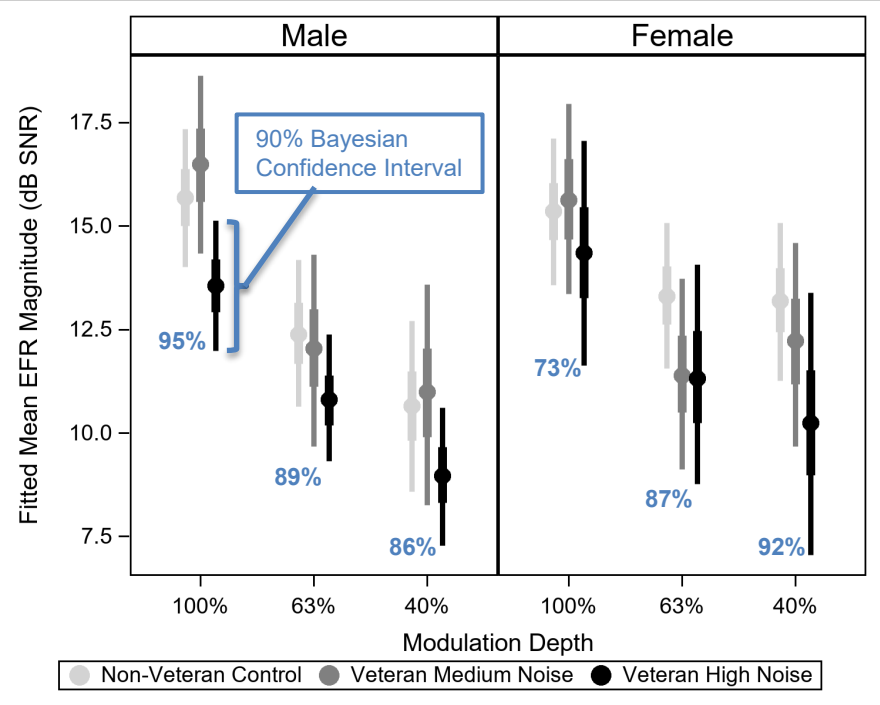
Shaheen et al. 2015, JARO

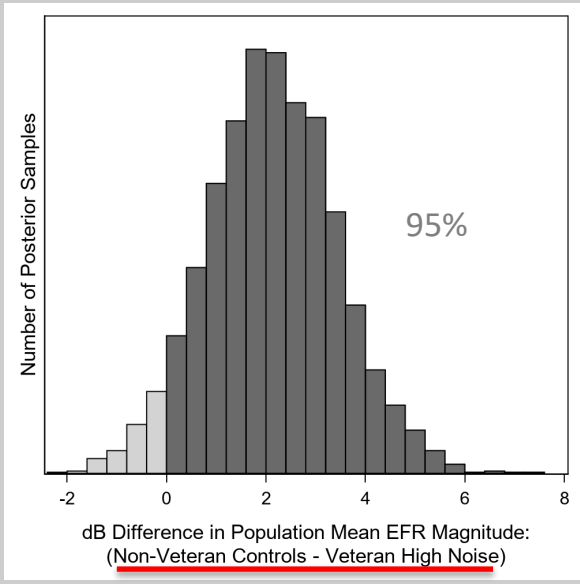
EFR strength reduced among Veterans with high noise exposure



Bramhall et al. 2021, Hearing Research

Model-based mean EFR magnitudes adjusted for sex and DPOAEs

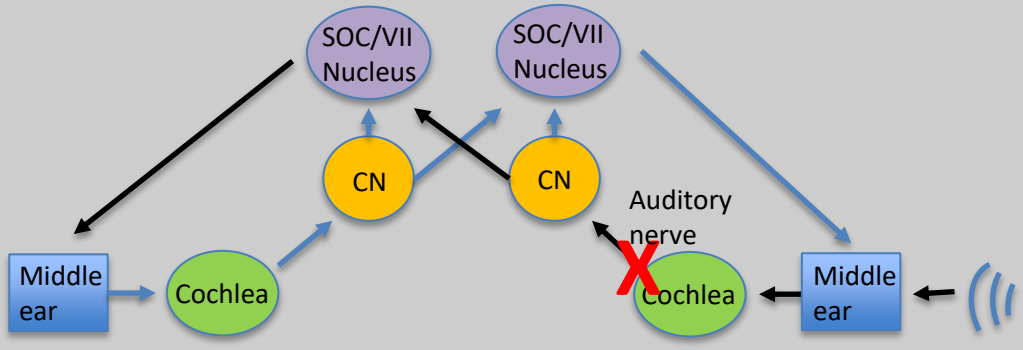


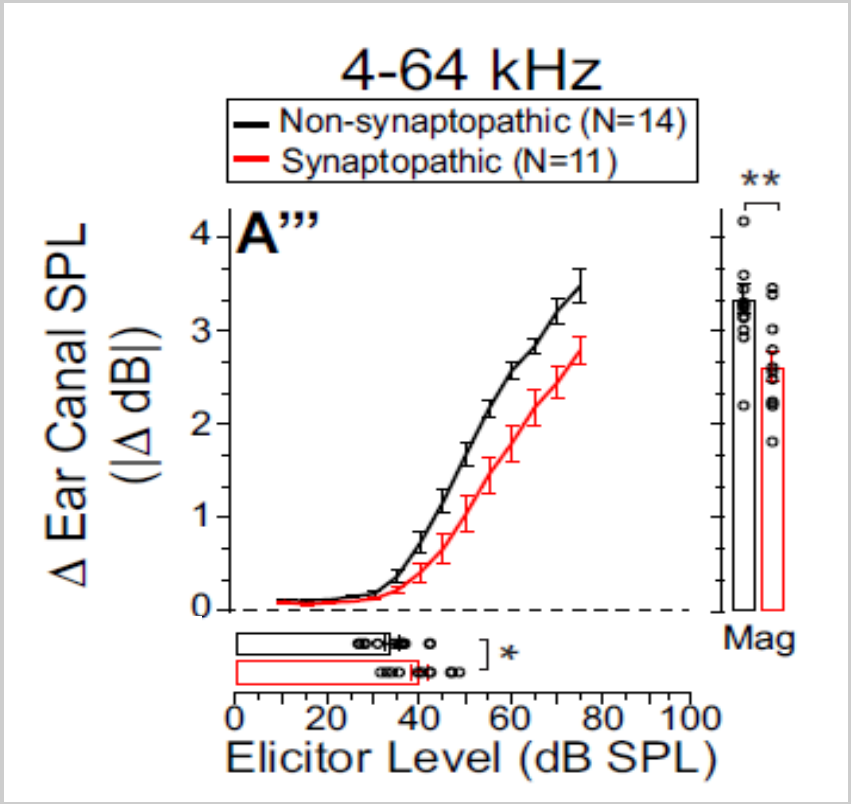


Bramhall et al. 2021, Hearing Research

Noise exposure-related reductions in EFR magnitude are consistent with animal models of cochlear synaptopathy

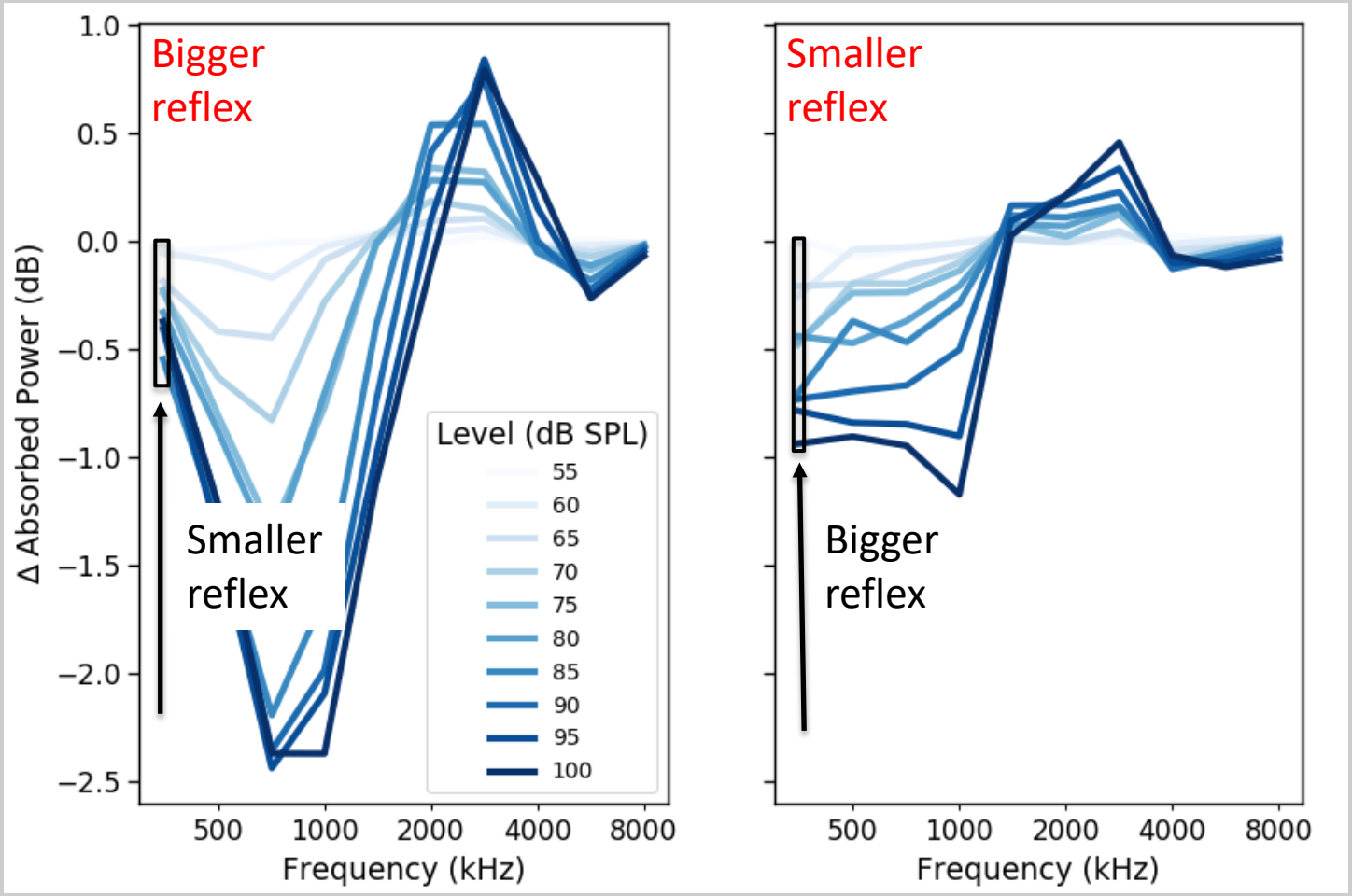
Middle ear muscle reflex (MEMR) weaker in mice with synaptopathy



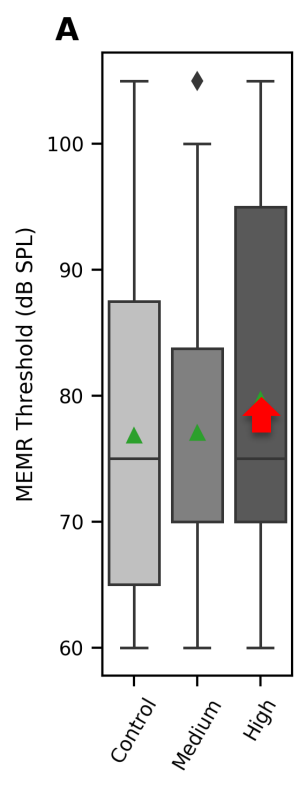


Valero et al. 2018, Hearing Research

MEMR with a wideband vs. 226 Hz probe

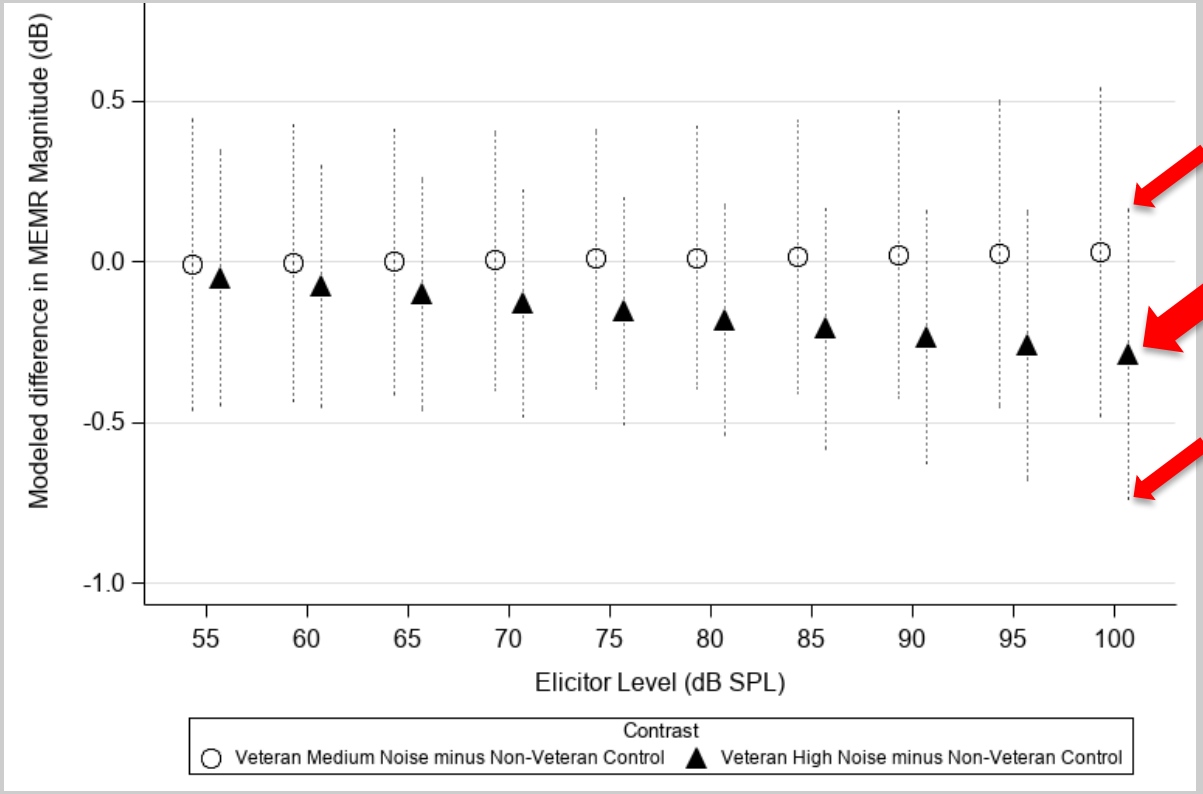


Wideband MEMR magnitude smallest for the Veteran High Noise group



Bramhall et al. (In Press), American Journal of Audiology

Modeled MEMR magnitude contrasts



Bramhall et al. (In Press), American Journal of Audiology

Model estimates indicate a reduction in MEMR magnitude for Veterans with high noise exposure compared with controls, but confidence intervals are broad.

Recreational noise exposure not associated with physiological indicators of synaptopathy

Several human studies of noise-induced synaptopathy have not found a clear relationship between physiological indicators of synaptopathy (ABR, EFR, and MEMR) and noise exposure history.

Most of these studies consisted of noise exposure groups with a history of recreational noise exposure, including frequent attendance of live music events, attending nightclubs, and playing in bands.

Potential reasons for differing results

- Humans may be less vulnerable to noise-induced synaptopathy than rodents.
- ABR and EFR measurements are more variable in humans than in rodents.
- ABR wave I amplitude, EFR, and MEMR may not be as sensitive to human synaptopathy, especially when OHC dysfunction is also present.
- Noise exposure metrics are variable and don't predict susceptibility to noise damage.
- Control groups may differ across studies – some control groups may include individuals with synaptic or OHC loss.
- Clinical MEMR may be less sensitive to synaptopathy than the wideband MEMR.

Summary of evidence for noise-induced synaptopathy in Veterans

- After adjusting for differences in DPOAEs and sex, non-Veterans with firearm use and Veterans who report high levels of military noise exposure show reduced ABR wave I amplitudes and EFR magnitudes compared to non-Veteran controls.

- Model estimates suggest that Veterans with high self-reported noise exposure have weaker wideband MEMRs than non-Veteran controls with minimal noise exposure, but confidence intervals indicate that stronger MEMRs for Veterans with high noise exposure are also possible given the data.

- Overall, these results are consistent with animal models of synaptopathy and suggest that noise-induced synaptopathy occurs in humans.

What are the perceptual consequences of synaptopathy/deafferentation?

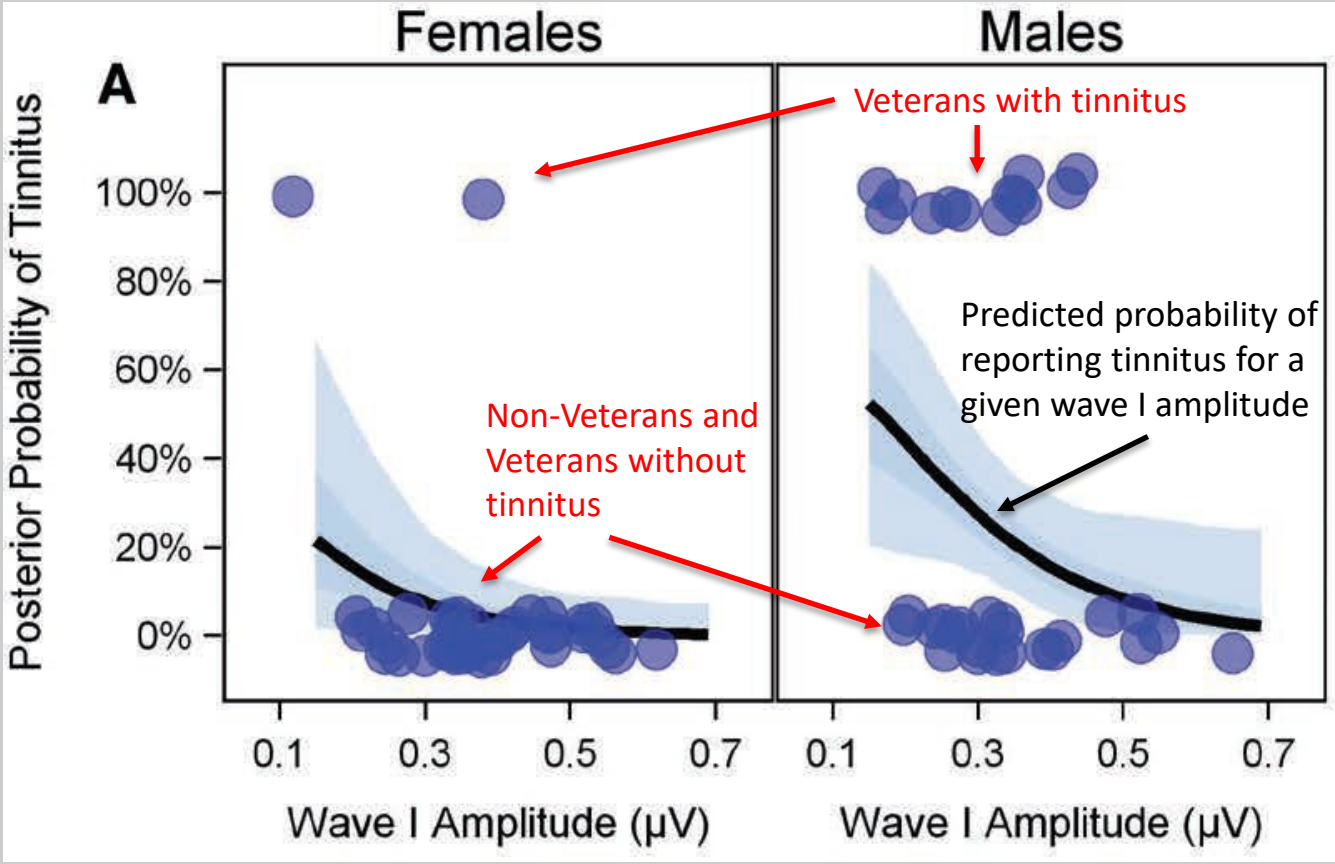
Deafferentation – loss of afferent input to the central auditory system through damage to inner hair cells, cochlear synapses, or spiral ganglion cells (the cell bodies of the auditory nerve).

These 3 types of damage cannot be differentiated physiologically and they should have similar functional impacts, so we will refer to them collectively as deafferentation.

Predicted perceptual consequences of deafferentation include:

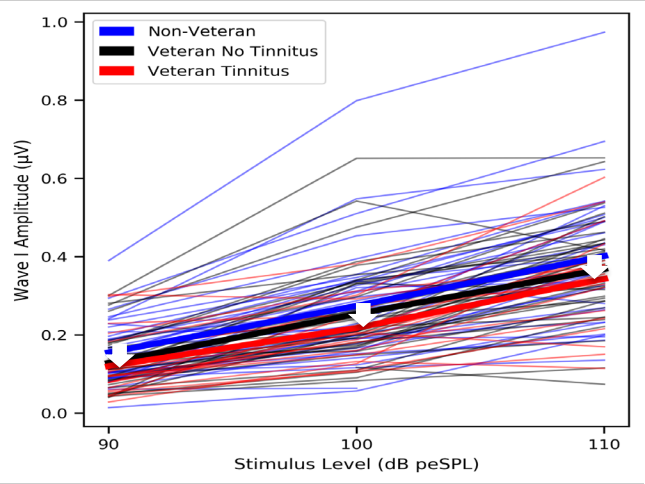
- Tinnitus
- Problems with speech-in-noise perception
- Hyperacusis

Lower ABR wave I amplitudes are associated with an increased probability of tinnitus

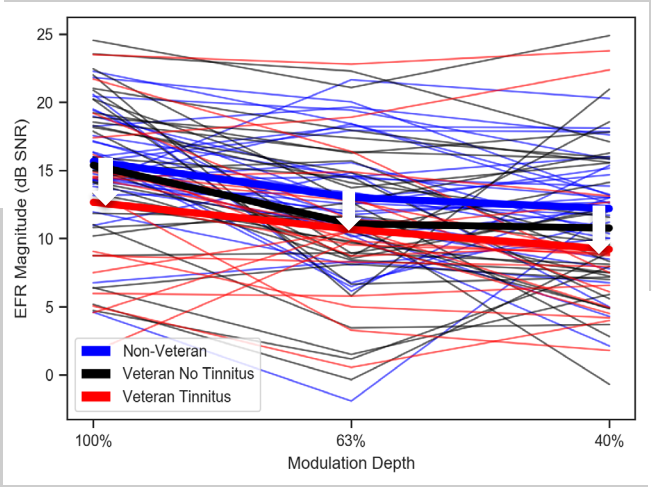


Bramhall et al. 2018, Ear and Hearing

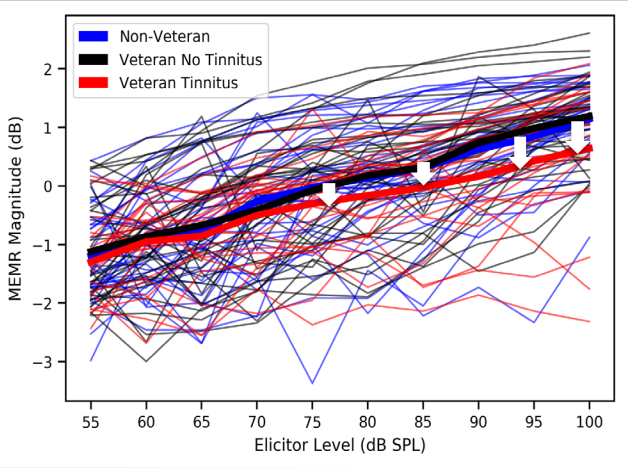
ABR, EFR, and MEMR magnitude reduced among Veterans with tinnitus



ABR



EFR



MEMR

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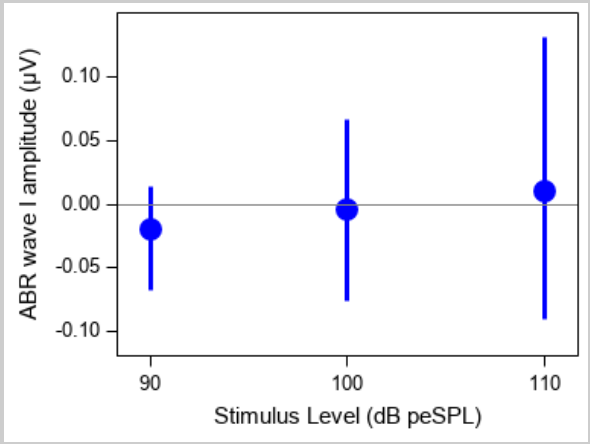
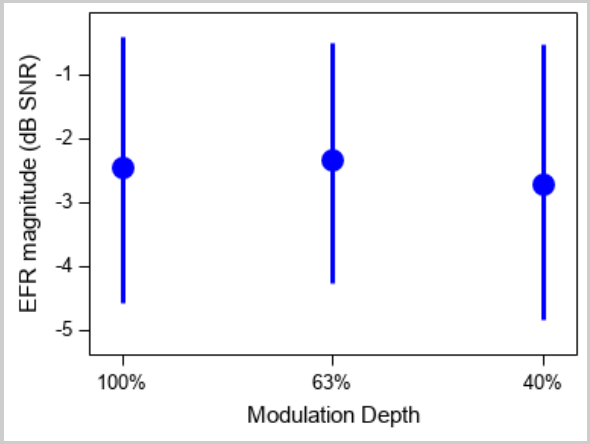
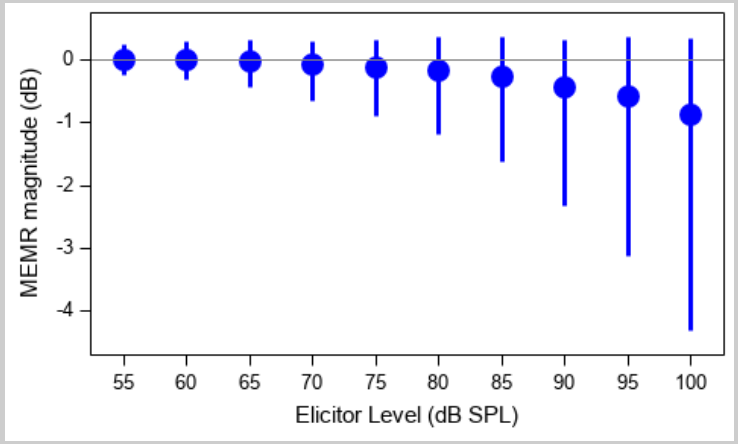
ABR, EFR, and MEMR magnitude contrasts adjusted for OHC function and sex

Magnitude contrast for Veteran Tinnitus – Non-Veteran Control

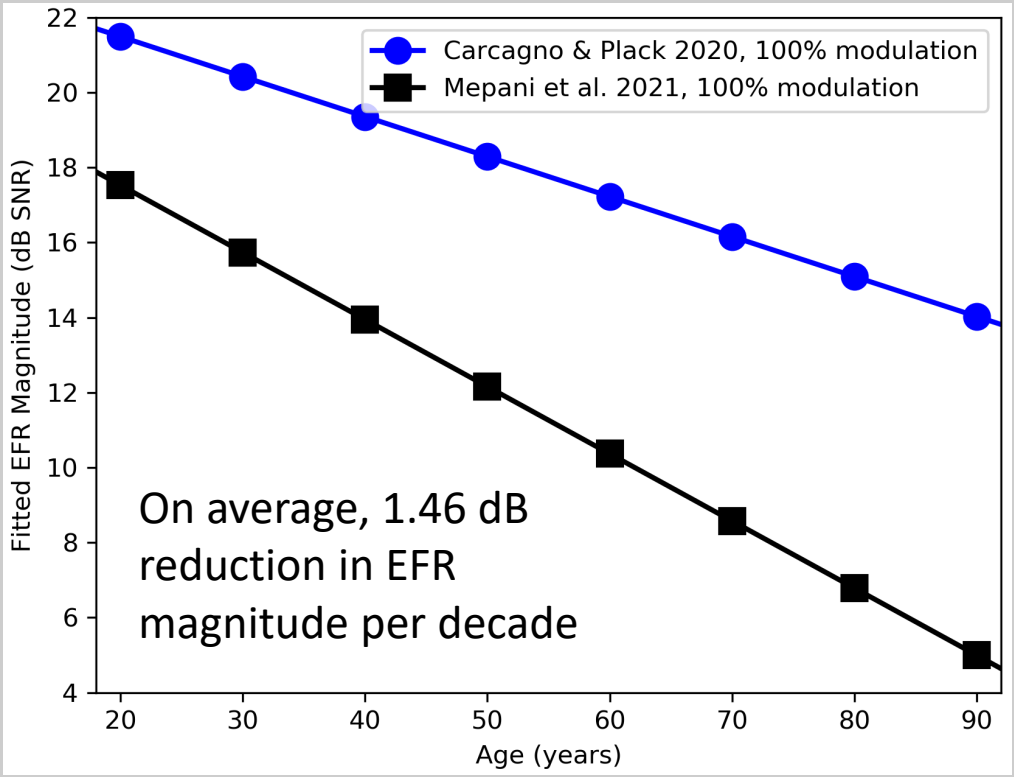






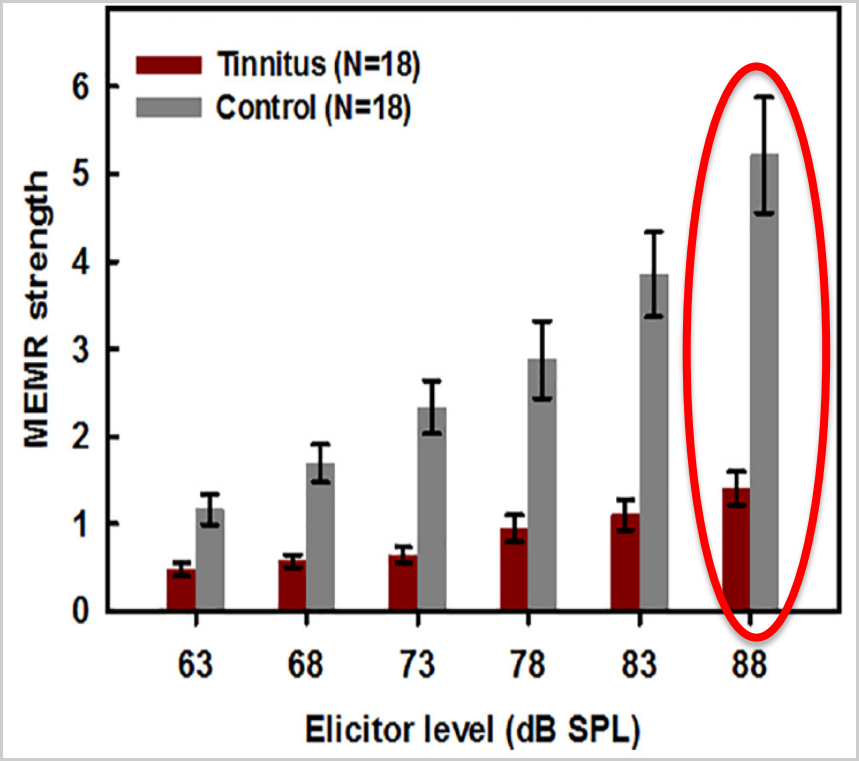
Tinnitus-related reductions in ABR, EFR, and MEMR measures suggest that some forms of tinnitus are a perceptual consequence of synaptopathy/deafferentation

Age-related change in EFR magnitude

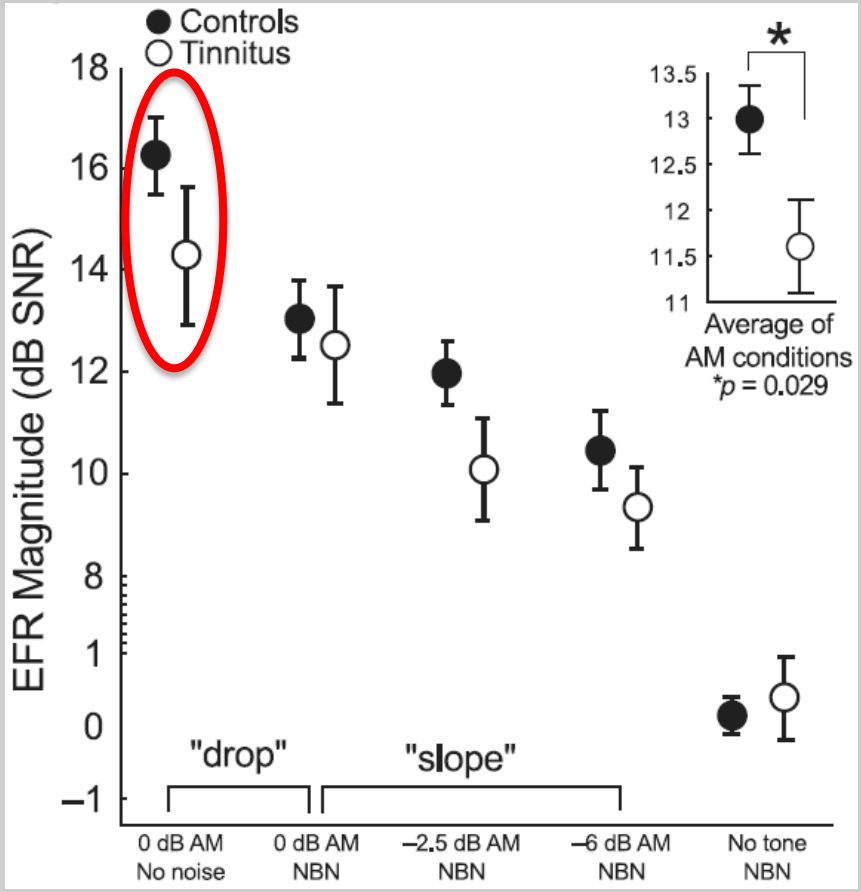


- Model results suggest a mean reduction in EFR magnitude for Veterans with tinnitus of 2.4 dB compared with non-Veteran controls
- This suggests that the change in EFR magnitude for Veterans with tinnitus is roughly equivalent to 16 years of aging.

Other studies have found similar relationships

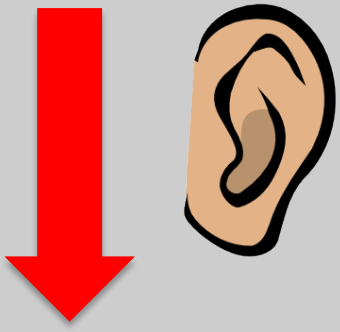


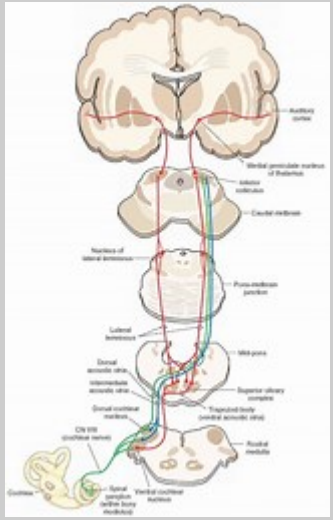
Wojtczak et al. 2017, eNeuro



Paul et al. 2017, Hearing Research

Central gain hypothesis





Decreased peripheral auditory input (due to middle ear issues, OHC loss, IHC loss, synaptic loss, neuronal loss)

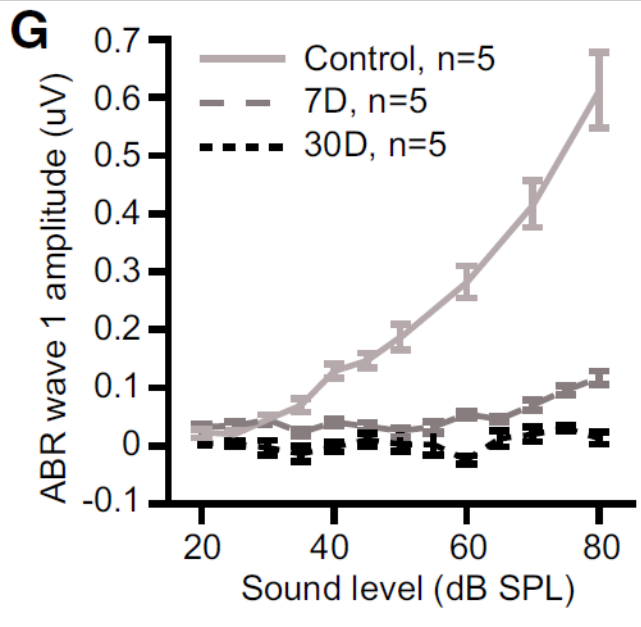
Hyperactivity in the central auditory system

Perception of tinnitus and/or hyperacusis

Central gain in mouse model of drug-induced deafferentation

Chambers et al. (2016) treated mice with the neurotoxic drug ouabain, resulting in ~95% loss of spiral ganglion cells. Damage increased with time - more damage 30 days after treatment than at 7 days post.

Auditory Nerve



Deafferentation leads to central gain, which can exceed normal levels of activity

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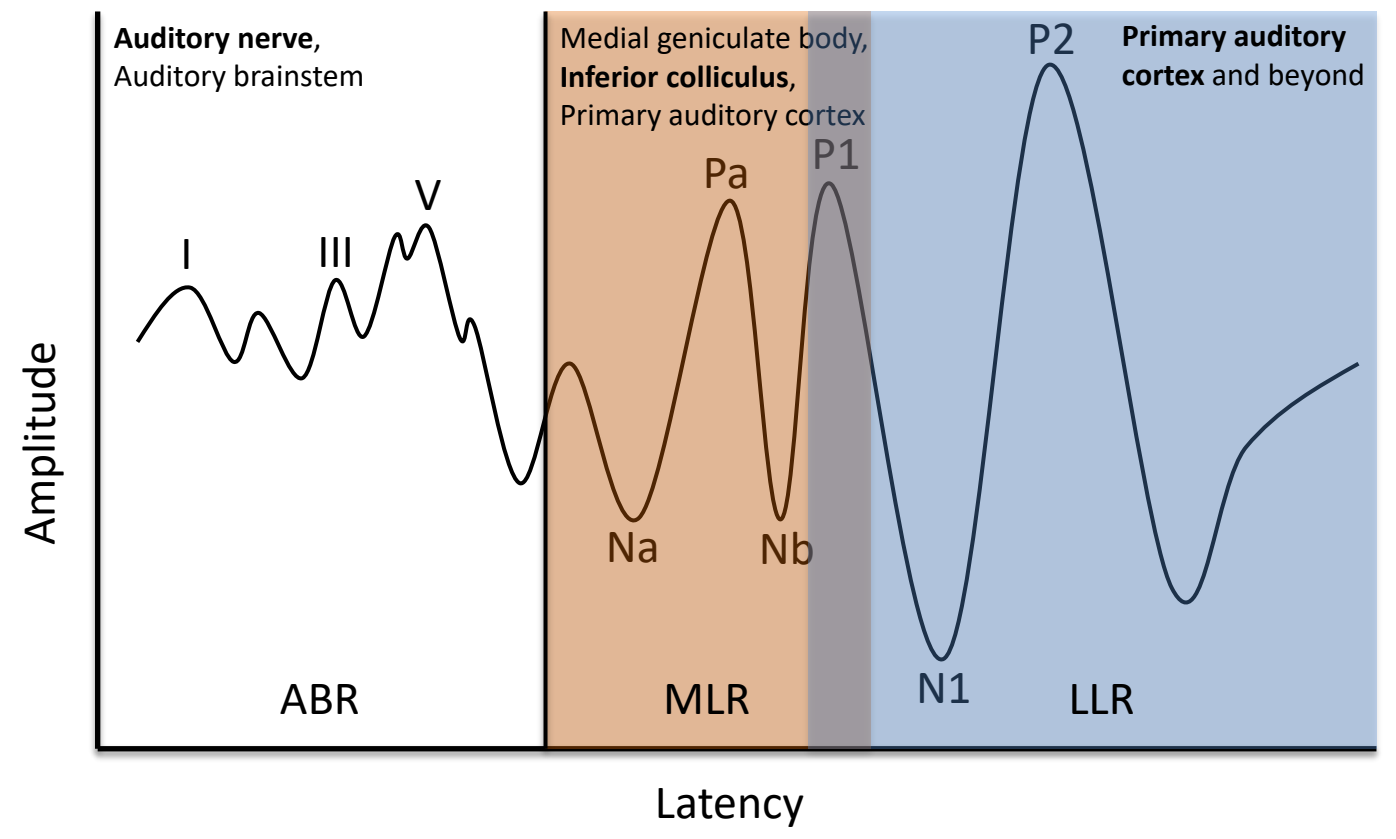
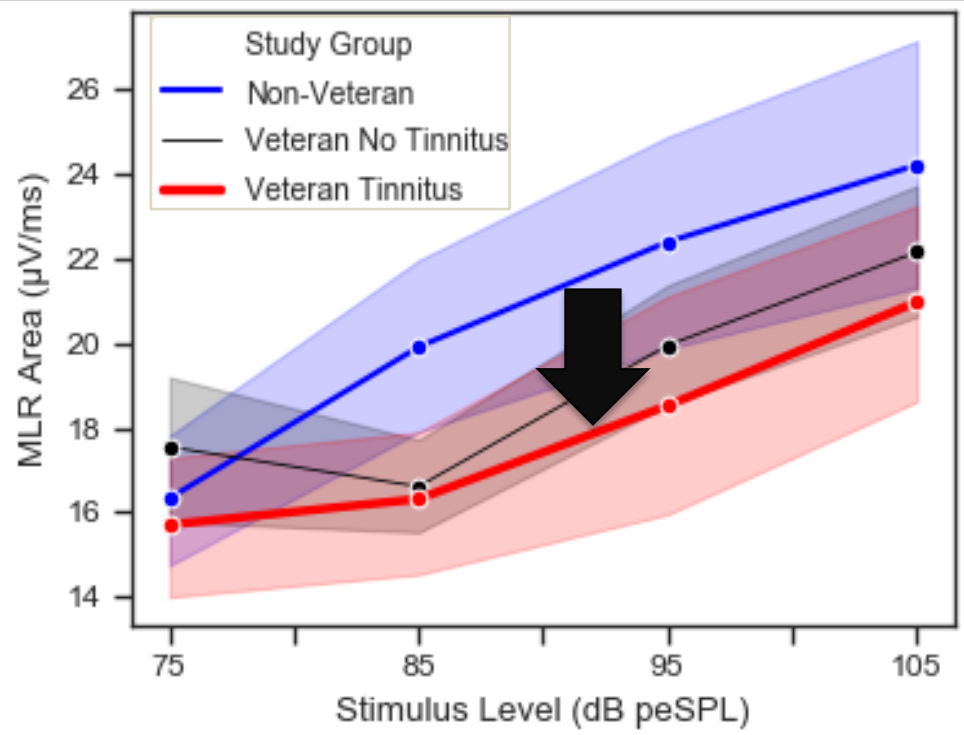
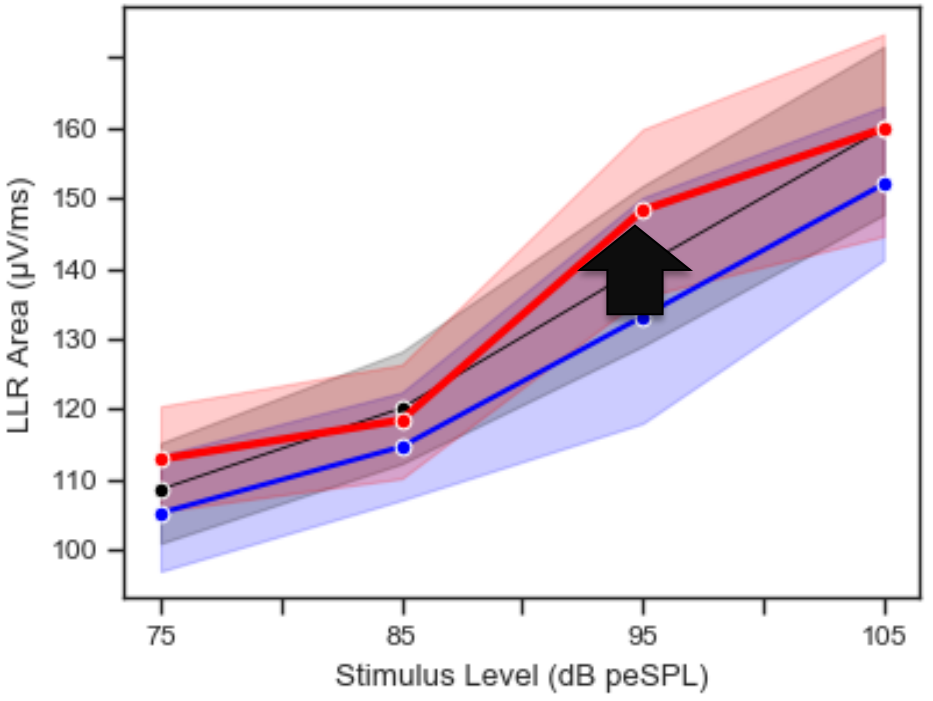
Chambers et al. 2016, Neuron

Electrophysiological measurement of central auditory function



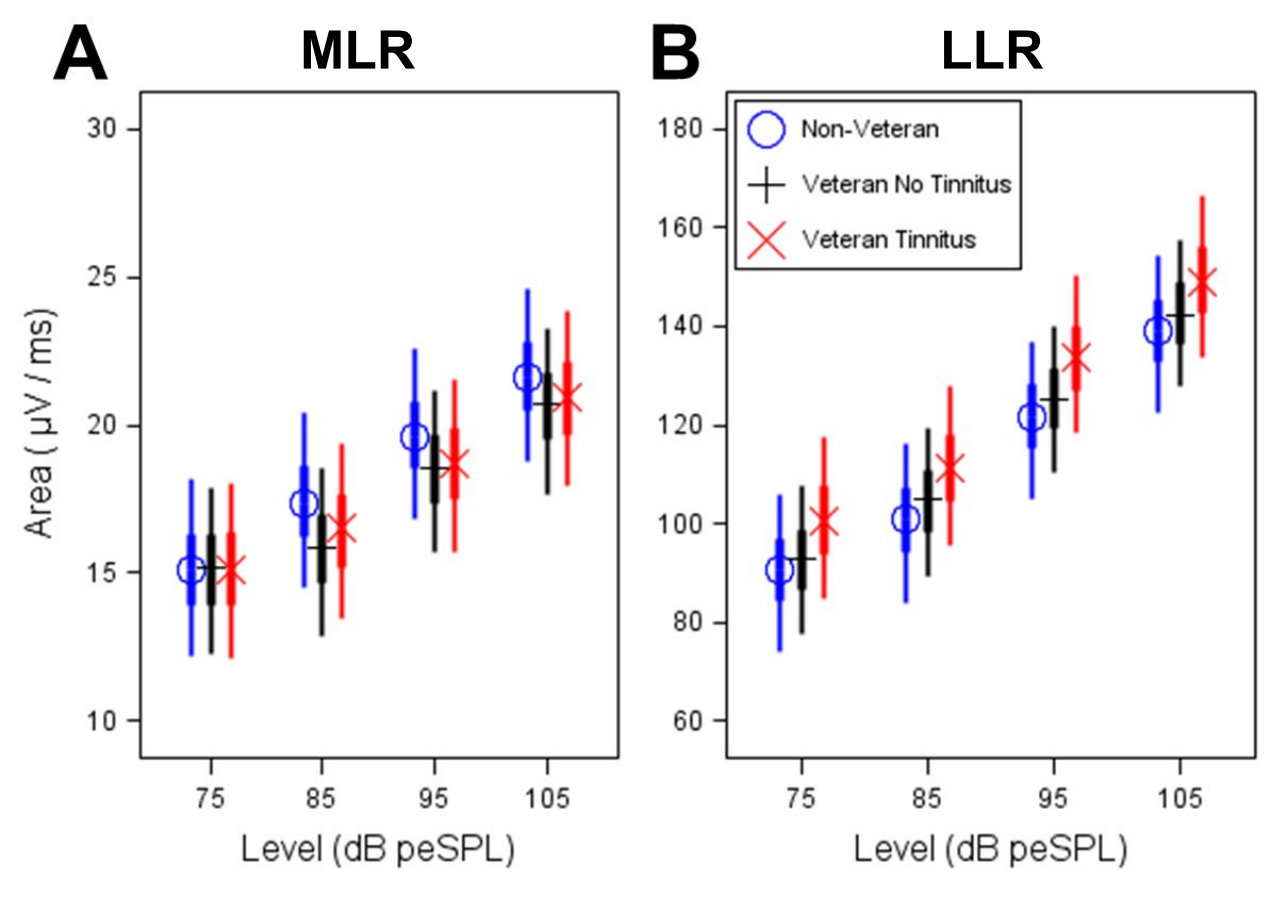
MLR area, but not LLR area, reduced for Veterans with tinnitus





Bramhall et al. 2020, American Journal of Audiology

Pattern remains after statistical adjustment for sex and DPOAE level

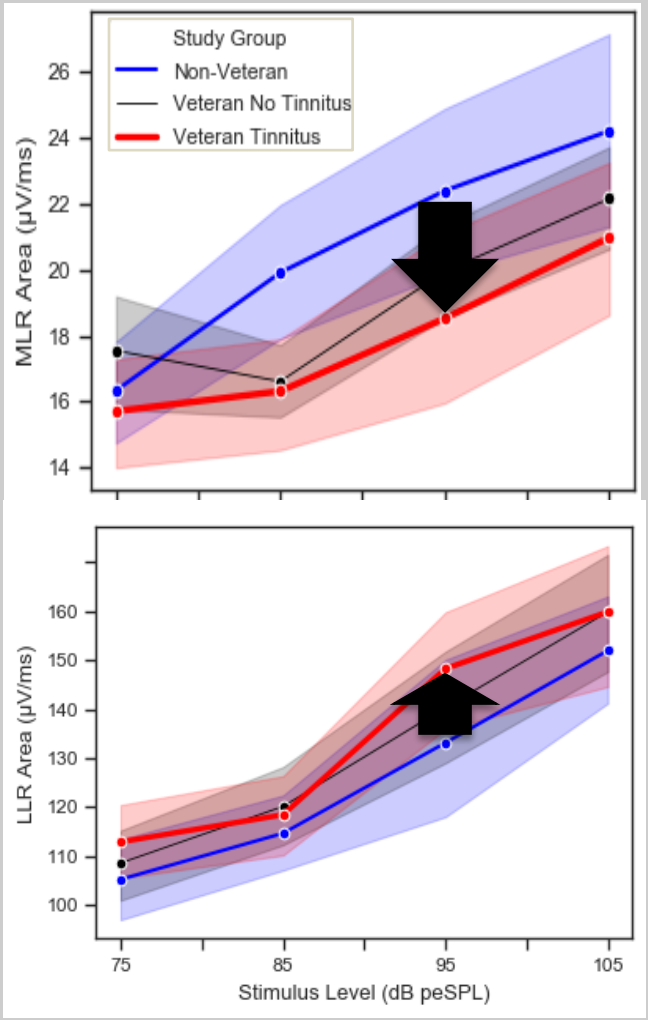


Bramhall et al. 2020, American Journal of Audiology

MLR and LLR results similar to Chambers et al. (2016) deafferentation mouse model

Inferior Colliculus: At 30 days post-treatment, firing rates were reduced compared to controls.

Auditory Cortex: At 30 days post-treatment, firing rates were similar to controls for lower stimulus levels and surpassed controls at higher stimulus levels, indicating excessive central gain developing over time.



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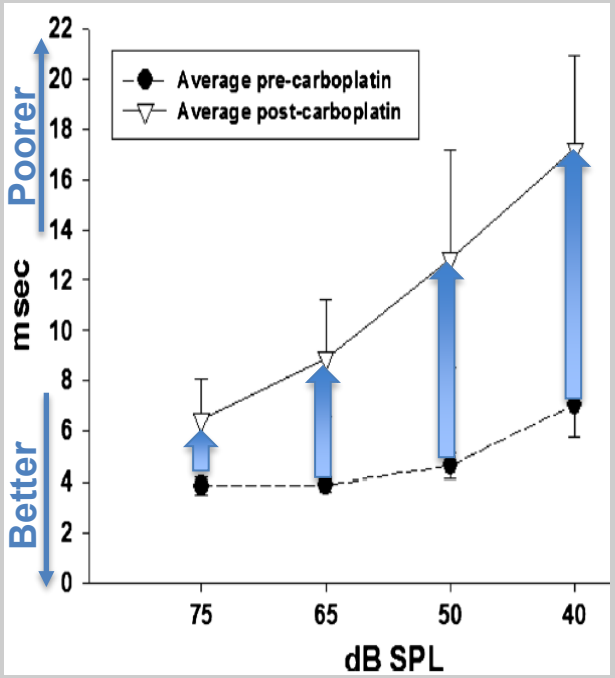
Bramhall et al. 2020, American Journal of Audiology

Summary of perceptual consequences of deafferentation: Tinnitus and central gain

- Reductions in ABR wave I amplitude, EFR magnitude, and MEMR strength among individuals with tinnitus suggest that deafferentation is associated with tinnitus.
- MLR area in response to a click is reduced in Veterans with tinnitus, while LLR area is increased, even after adjusting for sex and DPOAEs.
- These results suggest that noise-related deafferentation among individuals with clinically normal hearing impacts the central auditory system, eventually resulting in hyperactivity (central gain) at the level of the auditory cortex - in some people this central gain is associated with tinnitus.

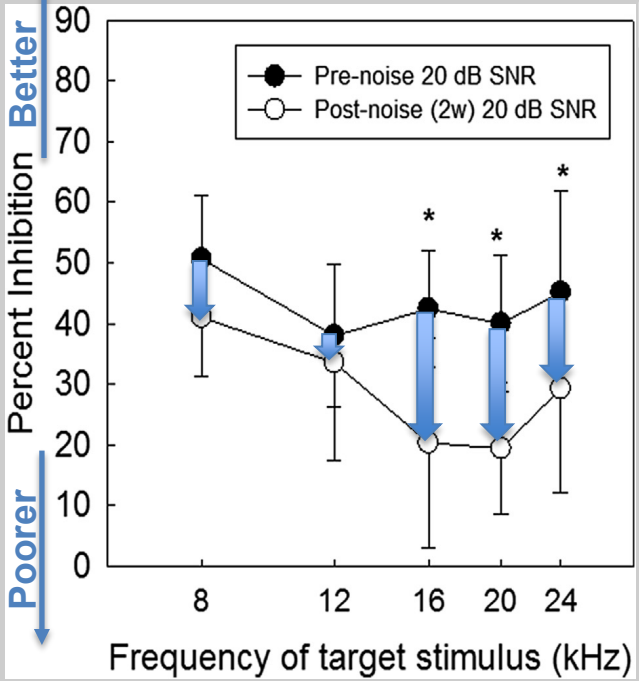
Perceptual impacts of deafferentation: speech perception in noise – animal studies

Gap detection in chinchillas with ~70% drug-induced IHC loss



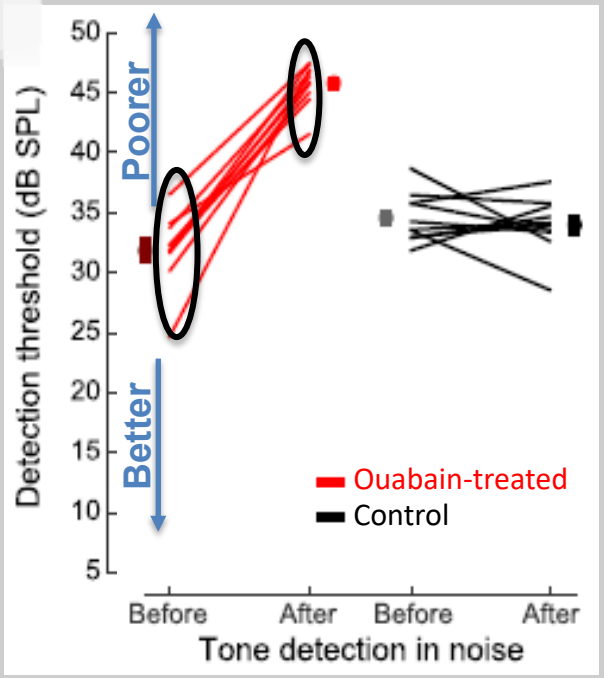
Lobarinas et al. 2020, JARO

Signal-in-noise detection for rats with presumed noise-induced synaptopathy



Lobarinas et al. 2017, Hearing Research

Tone-in-noise detection for mice with ~ 70% drug-induced spiral ganglion cell loss



Resnik and Polley 2021, Neuron

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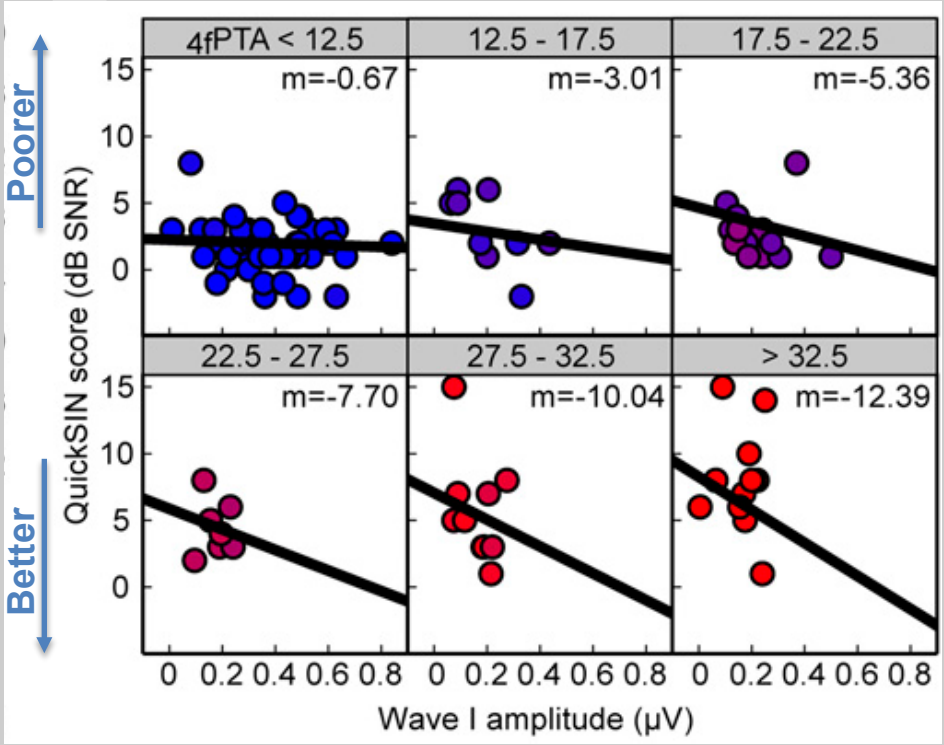
Summary of human studies of deafferentation and speech-in-noise perception

Author	Physiological Measure	Speech measure	Result
Bramhall et al. 2015	ABR wave I amplitude	QuickSIN (sentences)	Interaction effect of wave I amplitude and PTA on performance
Liberman et al. 2016	ABR SP/AP amplitude ratio	Words in noise or time compressed (w/ or w/o reverberation)	Lower SP/AP ratio associated with poorer performance
Fulbright et al. 2017	ABR wave I amplitude	Words in Noise (WIN) test	No relationship
Prendergast et al. 2017	ABR wave I/V amplitude ratio, EFR	Digit triple test, coordinated response measure	No relationship
Guest et al. 2018; 2019	ABR wave I amplitude, EFR, acoustic reflex threshold (226 Hz probe)	Coordinated response measure	No relationship
Bramhall et al. 2018	ABR wave I amplitude	Words in Noise (WIN) test	No relationship
Mepani et al. 2020	ABR SP/AP amplitude ratio, wideband acoustic reflex threshold/magnitude	Words in noise or time compressed (w/ or w/o reverberation)	Weaker MEMR and lower SP/AP ratio associated with poorer performance
Shehorn et al. 2020	ABR wave I amplitude, wideband acoustic reflex	CNC word recognition at high intensity level (104 dBA)	Weaker MEMR associated with poorer performance

Interaction effect between wave I amplitude and pure tone thresholds on speech perception in noise



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Bramhall et al. 2015,
Journal of the American Academy of Audiology

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Relationships between physiological indicators of deafferentation and speech perception may be more likely when there is some OHC dysfunction

Summary: Deafferentation and speech perception in noise

- Animal models of cochlear deafferentation suggest that speech-in-noise detection may be negatively impacted.
- Several human studies have suggested a relationship between speech-in-noise perception and physiological indicators of deafferentation, while others have not.
- It would be premature at this point to assume that synaptopathy/deafferentation has no impact on complex speech perception.
- It's possible that careful test selection is necessary to detect the effects of deafferentation on complex speech perception.
- Deafferentation may impact complex speech perception more when there is also outer hair cell damage.

Can non-invasive physiological measures be used to diagnose synaptopathy?

- Observed relationships between physiological measurements (ABR, EFR, MEMR) and proposed risk factors (e.g., noise exposure) and perceptual consequences (e.g., tinnitus) among Veterans suggest these measurements may be useful for diagnosing deafferentation.
- These measurements cannot distinguish between inner hair cell, cochlear synapse, and spiral ganglion cell loss. However, studies of animals and human temporal bones suggest synapse loss will be the most common type of cochlear deafferentation.
- In addition, the extent to which these physiological measures are impacted by outer hair cell damage needs to be explored further.
- More than one test measure may be necessary to differentially diagnose deafferentation (e.g., ABR plus DPOAEs).
- Normative values for ABR, EFR, and MEMR measurements will be necessary for diagnosing deafferentation in individual patients.

Conclusions

- Physiological measures (ABR, EFR, and MEMR) are consistent with deafferentation among Veterans reporting high noise exposure and non-Veterans with a history of firearm use, suggesting that noise-induced synaptopathy occurs in humans.
- Tinnitus is associated with reductions in physiological indicators of deafferentation and young Veterans with tinnitus show electrophysiological evidence of increased central gain in the auditory cortex, suggesting that deafferentation has perceptual consequences.
- There is some evidence that speech perception in noise may be impacted by deafferentation, particularly when outer hair cell function is abnormal, but there is a lack of consensus across studies.
- The ABR, EFR, and MEMR show promise as possible future diagnostic indicators of deafferentation, but further work is necessary before they can be used clinically.

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