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Hidden Hearing Loss in Humans

Chris Plack

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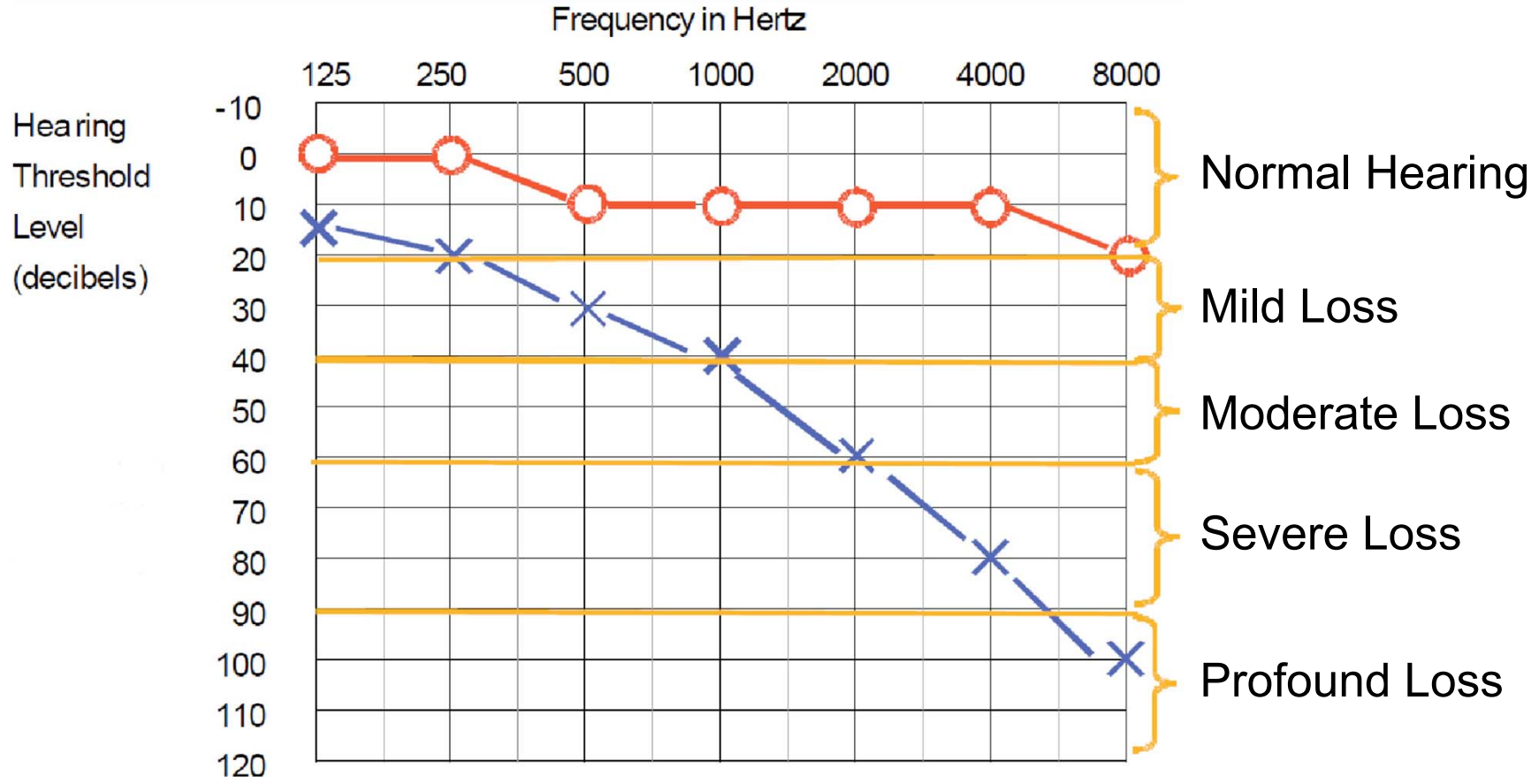
The Audiogram

Hearing loss as measured by pure tone audiometry is primarily a result of hair cell (particularly **outer hair cell**) dysfunction:



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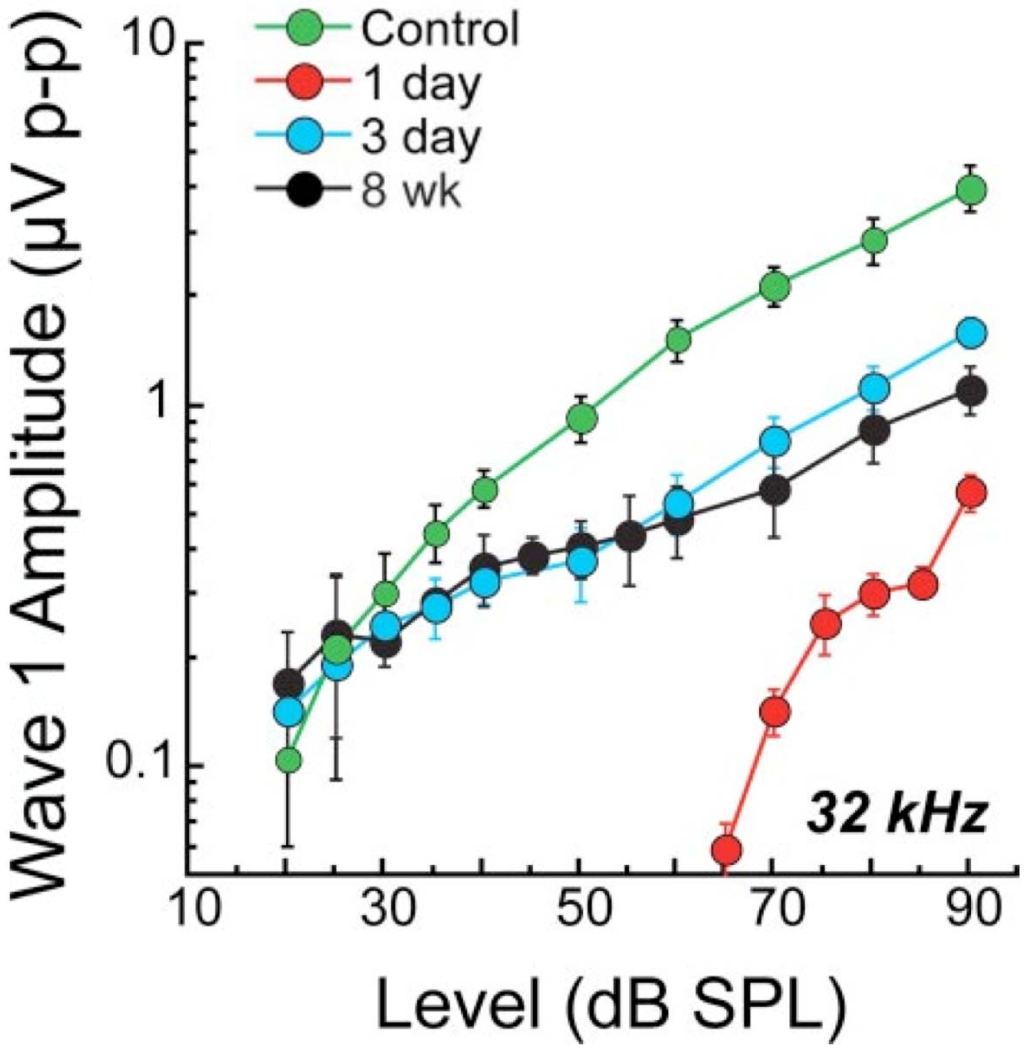
Noise-Induced Cochlear Synaptopathy in Rodents

Kujawa and Liberman (2009). Mice exposed to 100 dB SPL, 8-16 kHz, noise for 2 hours. ABR wave I at threshold recovered after a few days, but permanent **reduction in ABR amplitude at high levels** (low-SR fibers?):



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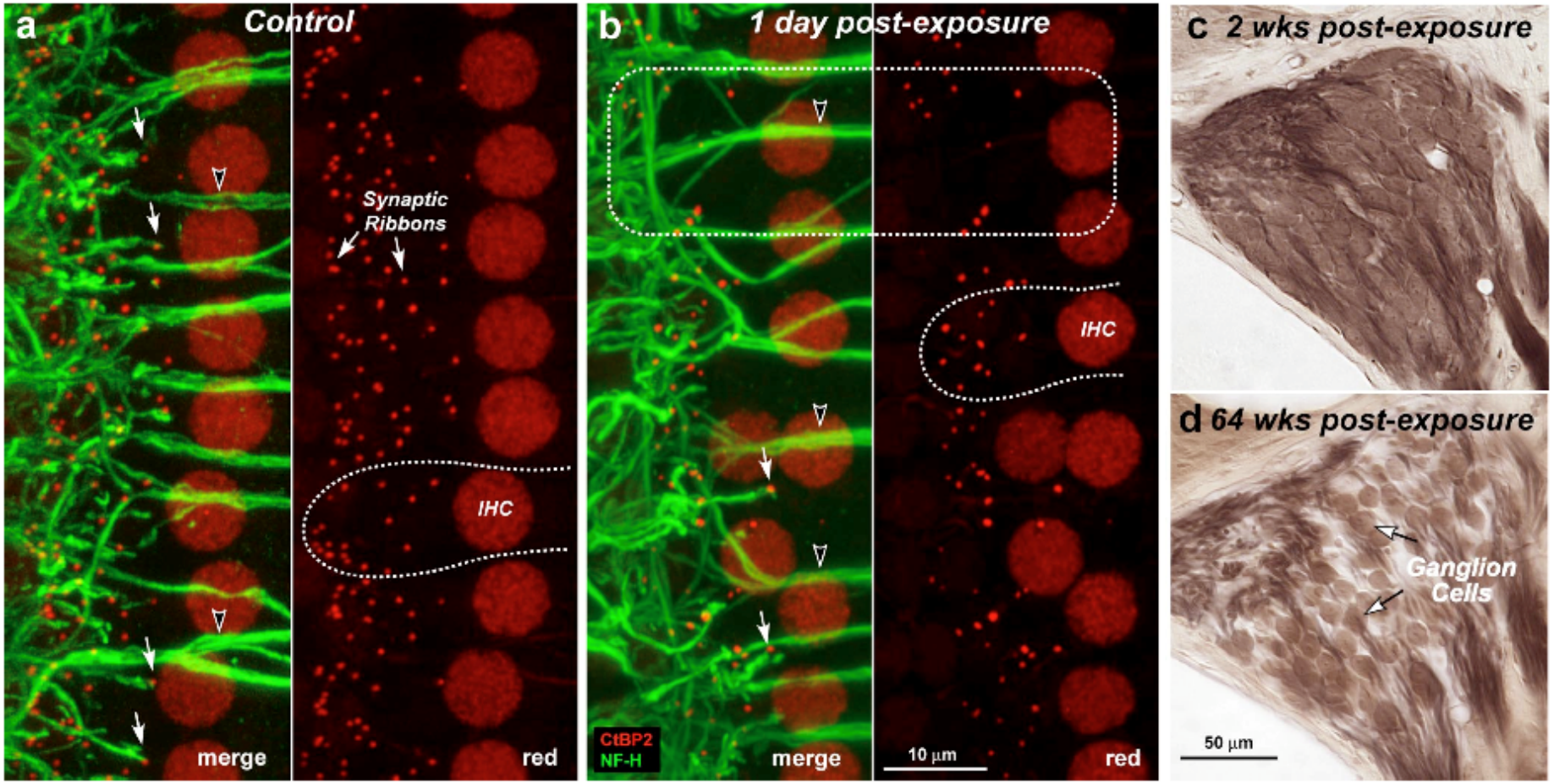
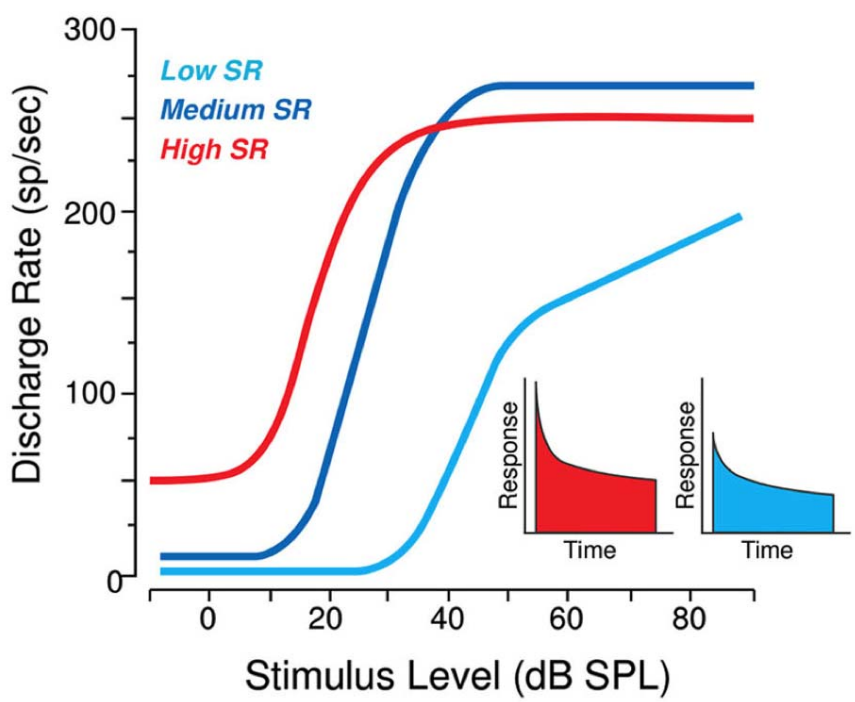
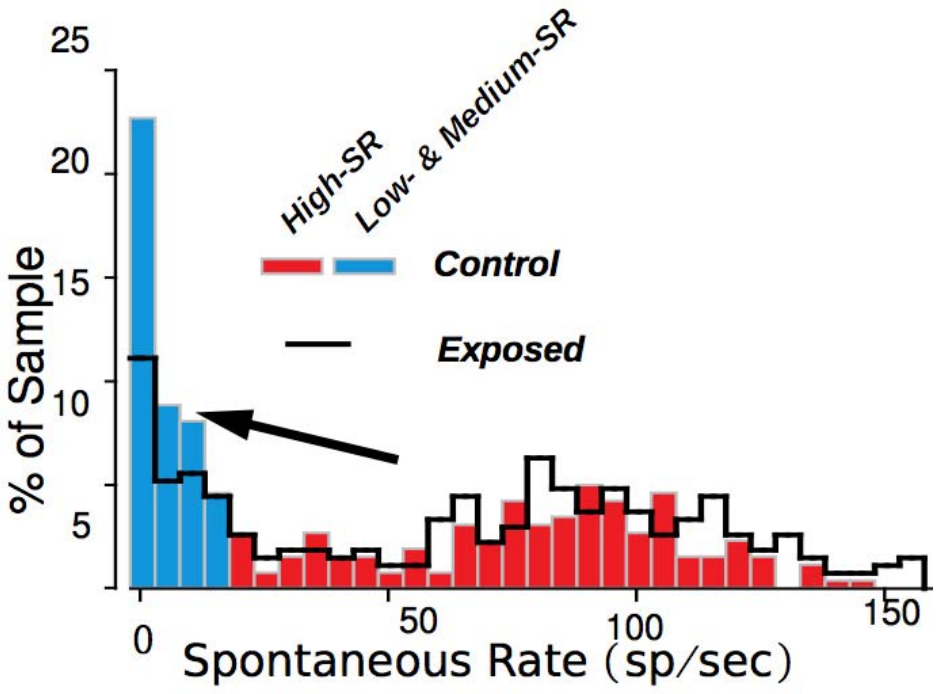
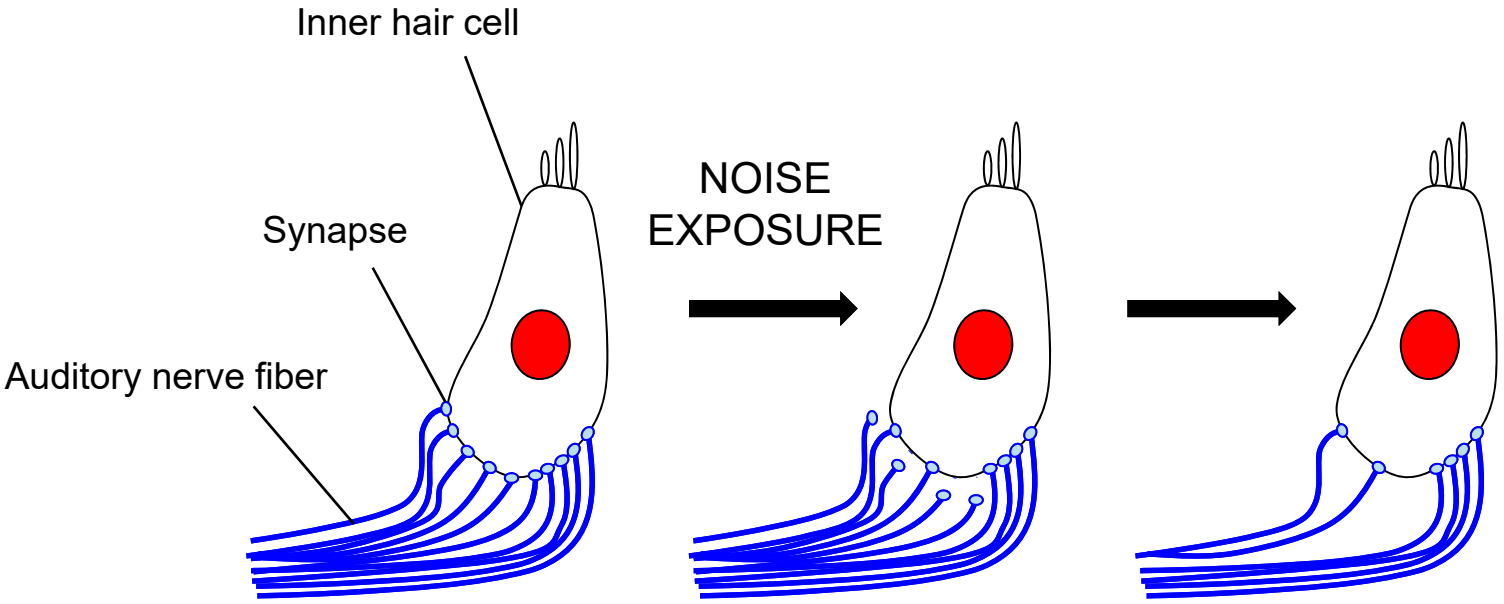
Noise exposure produced loss of synaptic ribbons and, after 64 weeks, **50% ganglion cell loss** at high characteristic frequencies:



Furman et al. (2013). Guinea pigs exposed to 106 dB SPL for two hours. Single unit recordings confirm **damage selective to low and medium spontaneous-rate (high-threshold) fibers** (possibly why ABR reduction not seen at low levels):







1. Synapses intact

2. Synapses lost

3. Nerve fibers degenerate

Cochlear Synaptopathy

- In rodent models, noise exposure can cause substantial loss of the connections between inner hair cells and low-SR auditory nerve fibers which may code information at moderate-to-high sound levels.

- The disorder has been termed cochlear synaptopathy, or **“hidden hearing loss”** (Schaette and McAlpine, 2011) because it is not thought to be detectable using pure-tone audiometry.

- Crucial question: **Is noise-induced cochlear synaptopathy an important cause of hearing impairment in humans?**

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Noise-Induced Cochlear Synaptopathy in Humans?

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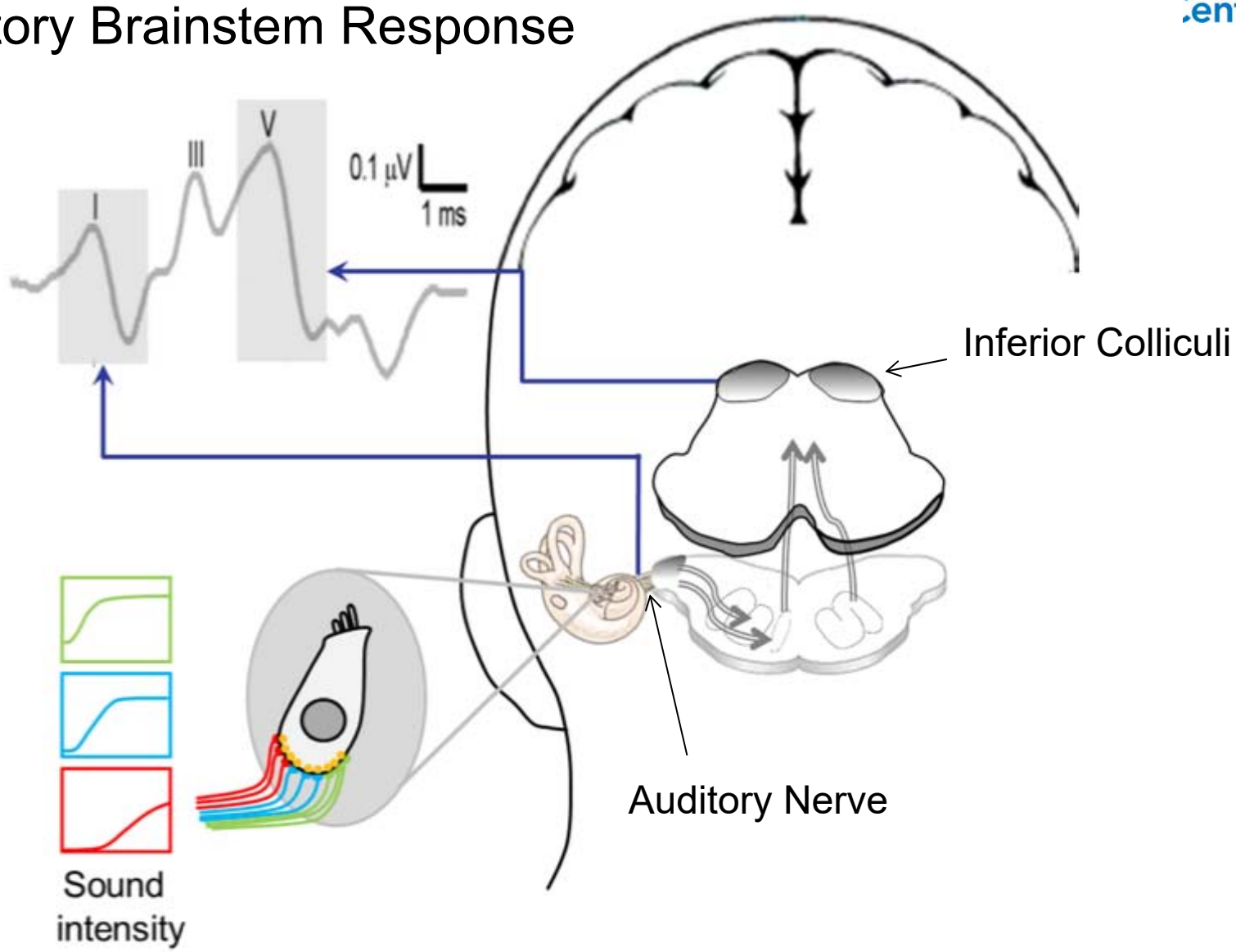
Auditory Brainstem Response



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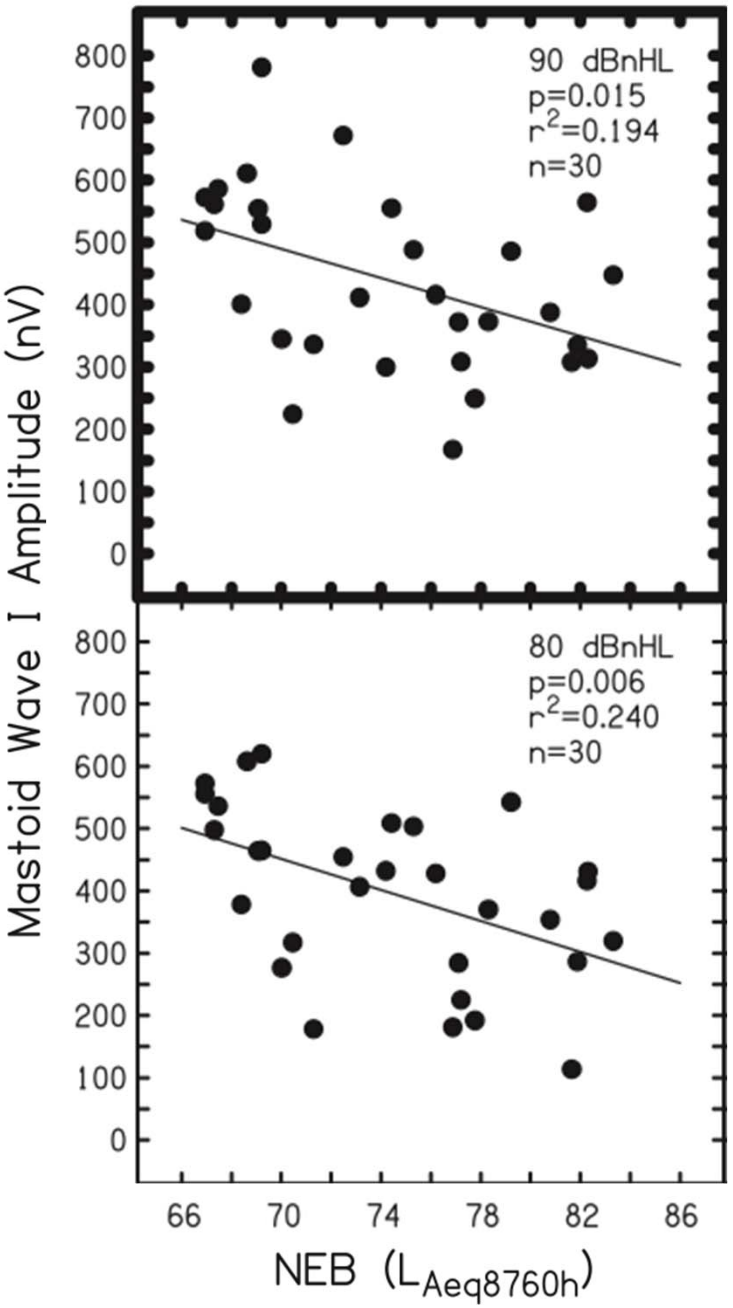
Stamper and Johnson (2015a). **Reduction in ABR wave I** for normal hearing listeners with high noise exposure (NEB = noise exposure background, measured over previous year):



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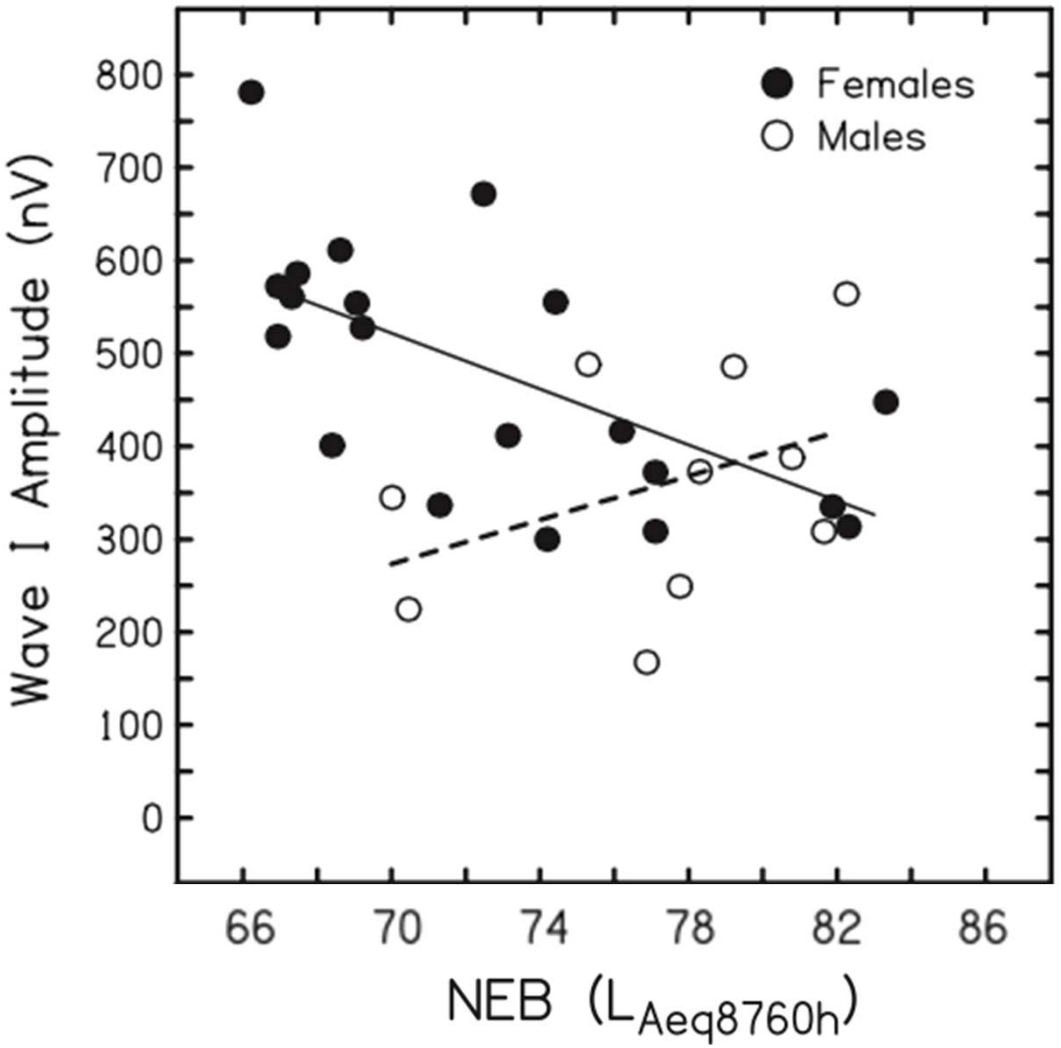
However, Stamper and Johnson (2015b) subsequently **separated data by sex** (but only for 90 dB nHL), and effect is **only present for females** (in general, males tend to have higher noise exposures and also lower ABR amplitudes):



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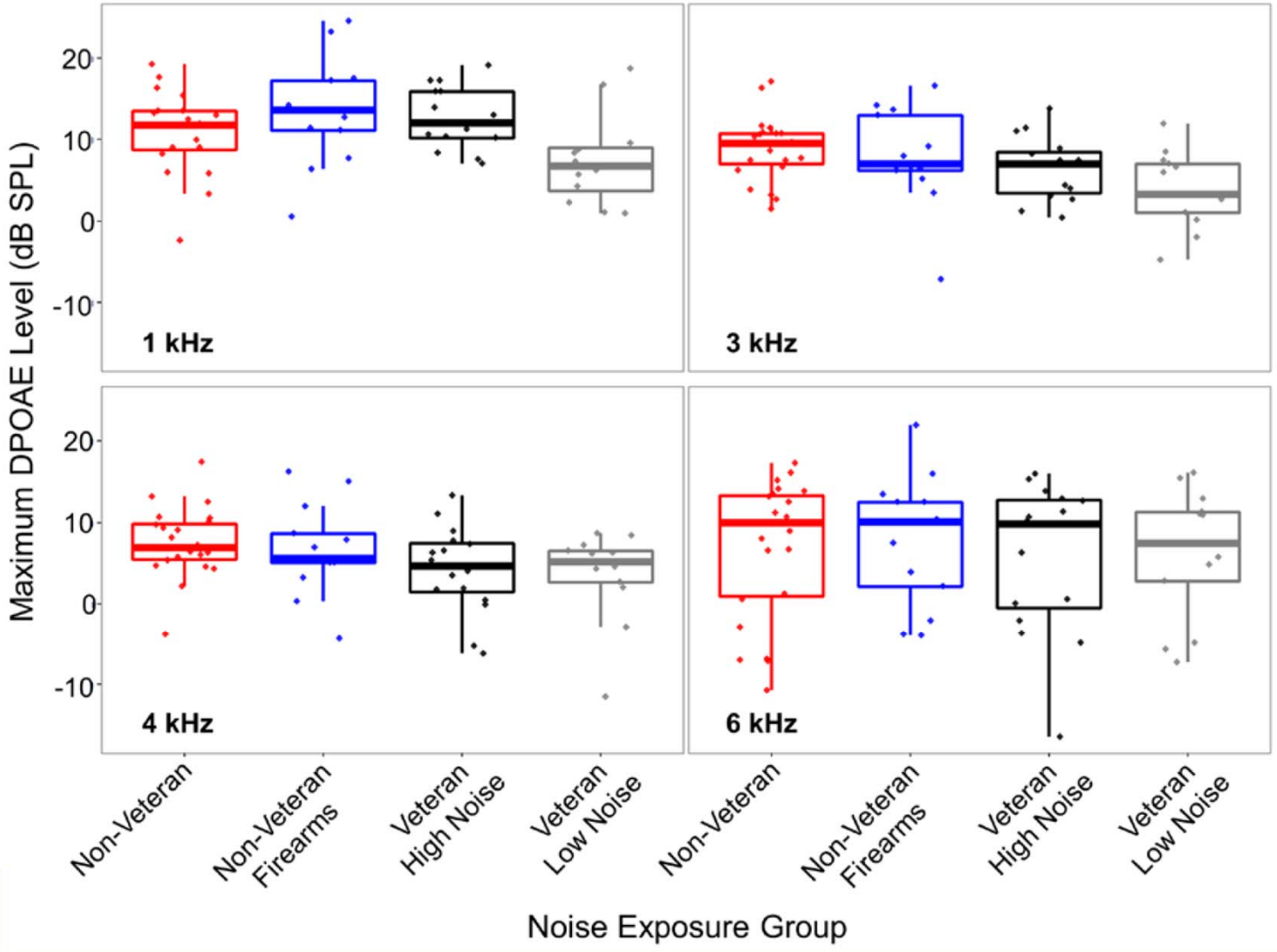
Bramall et al. (2017). Noise-exposed veterans and firearms users. **No difference in DPOAEs** (outer hair cells) between exposed and controls:



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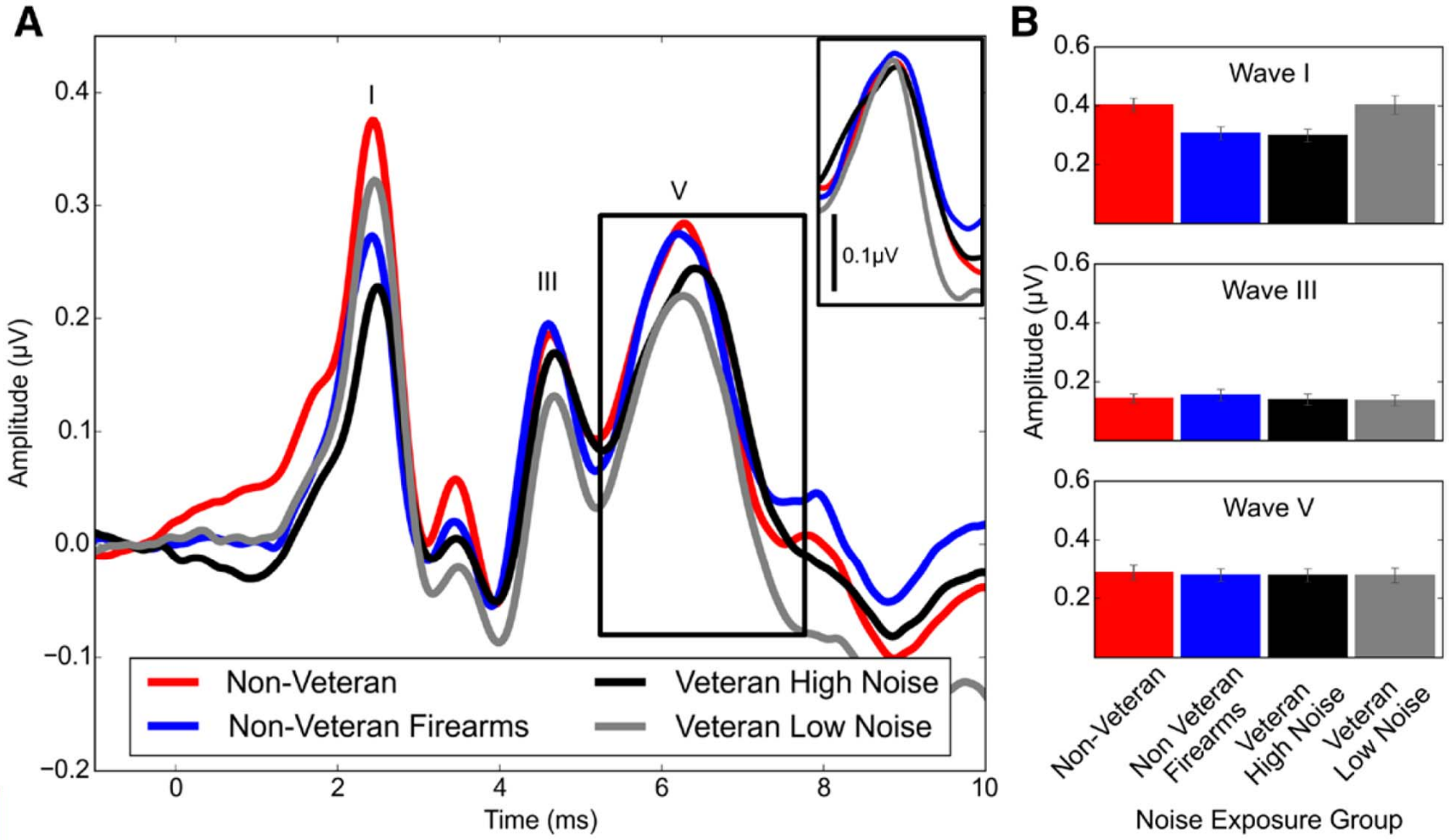
Bramall et al. (2017). **Noise-exposed groups had lower ABR wave I amplitudes**. However, audiograms were not closely matched and there were sex differences between groups (noise-exposed more males).



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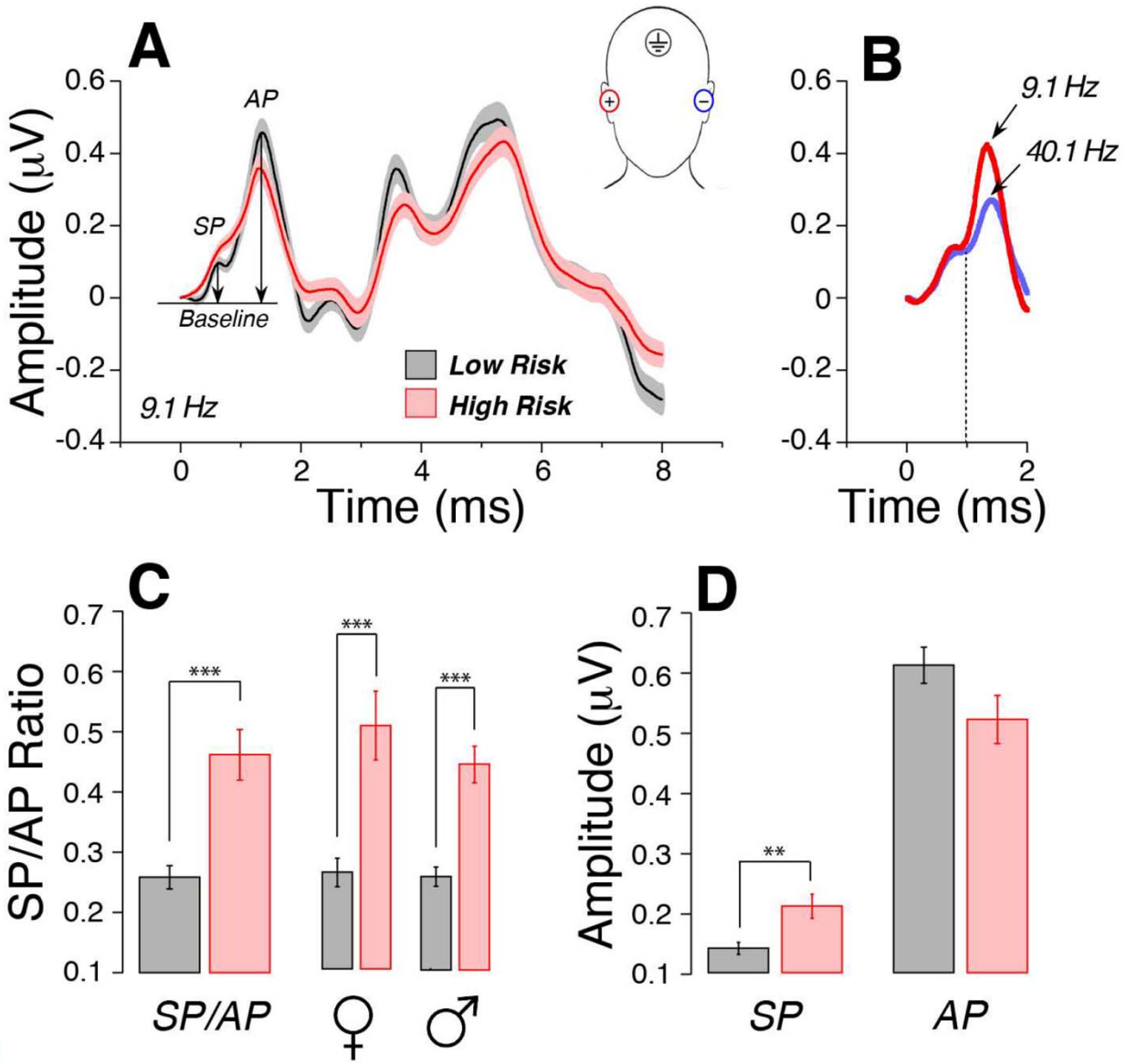
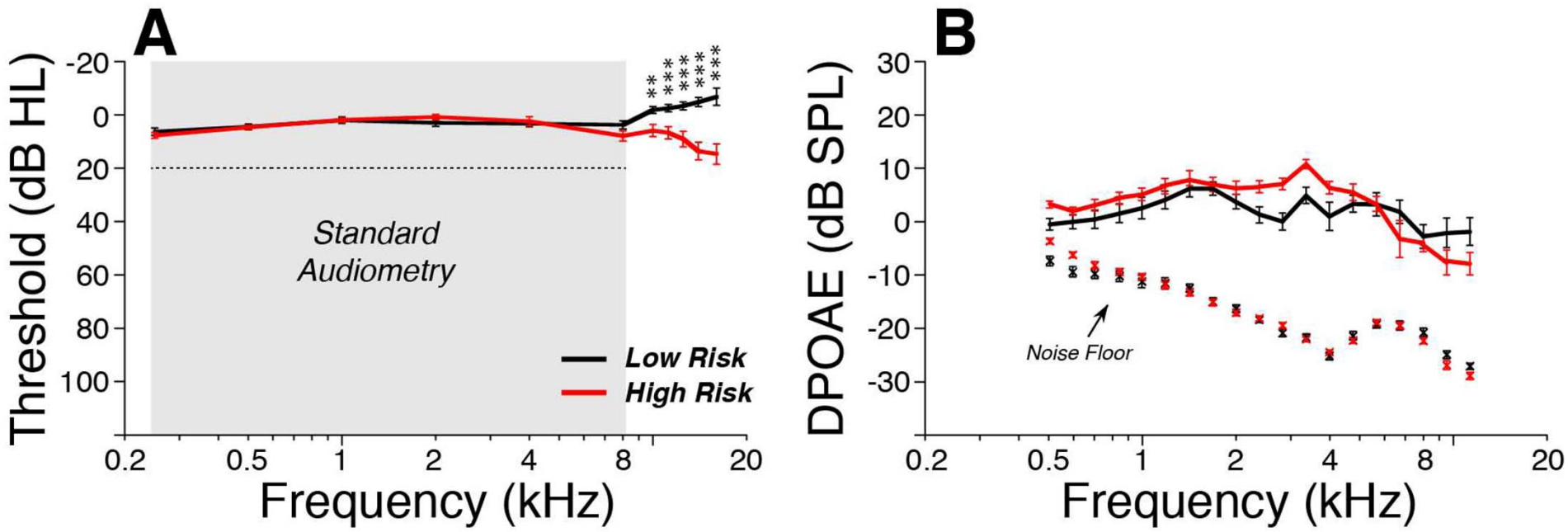
Liberman et al. (2016). ABR wave I (AP) for noise-exposed group not significantly different from controls, but significant effect on **SP/AP ratio** consistent with synaptic loss (but not clear why SP should increase):



Liberman et al. (2016). However, **high-frequency hearing loss** in noise-exposed group *may* have affected electrophysiological results (outer hair cell damage has been associated with increased SP):



ABR Wave I & High-Frequency Sensitivity

- Studies reporting noise effects on ABR have either also reported high-frequency audiometric loss related to exposure, or have not measured extended high frequency thresholds.
- Wave I is largely produced by basal generators (e.g., Don and Eggermont, 1978), and hence may be quite sensitive to high-frequency hearing loss.
- So the ABR effects *may* be due to high-frequency hair cell damage, rather than synaptopathy.

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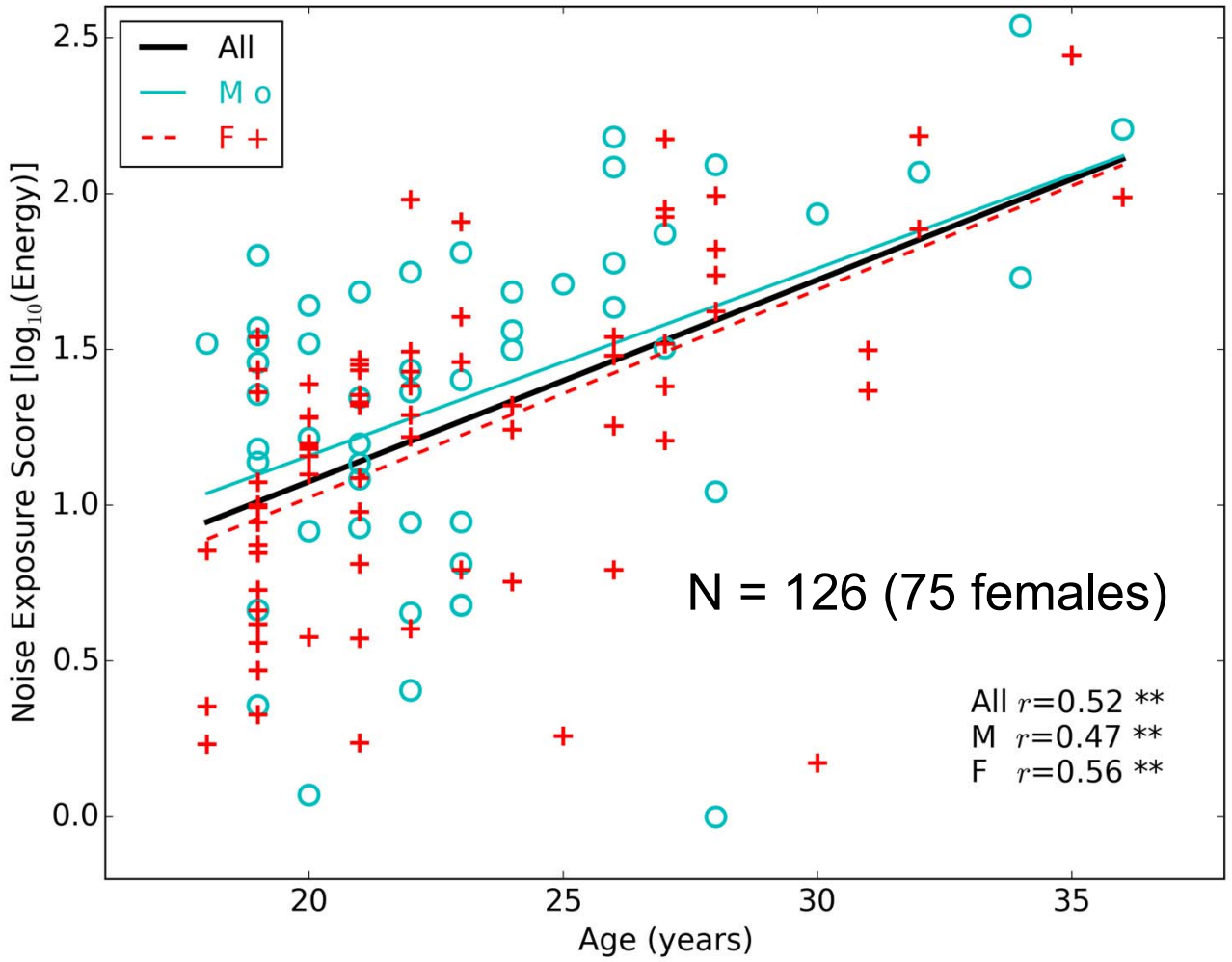
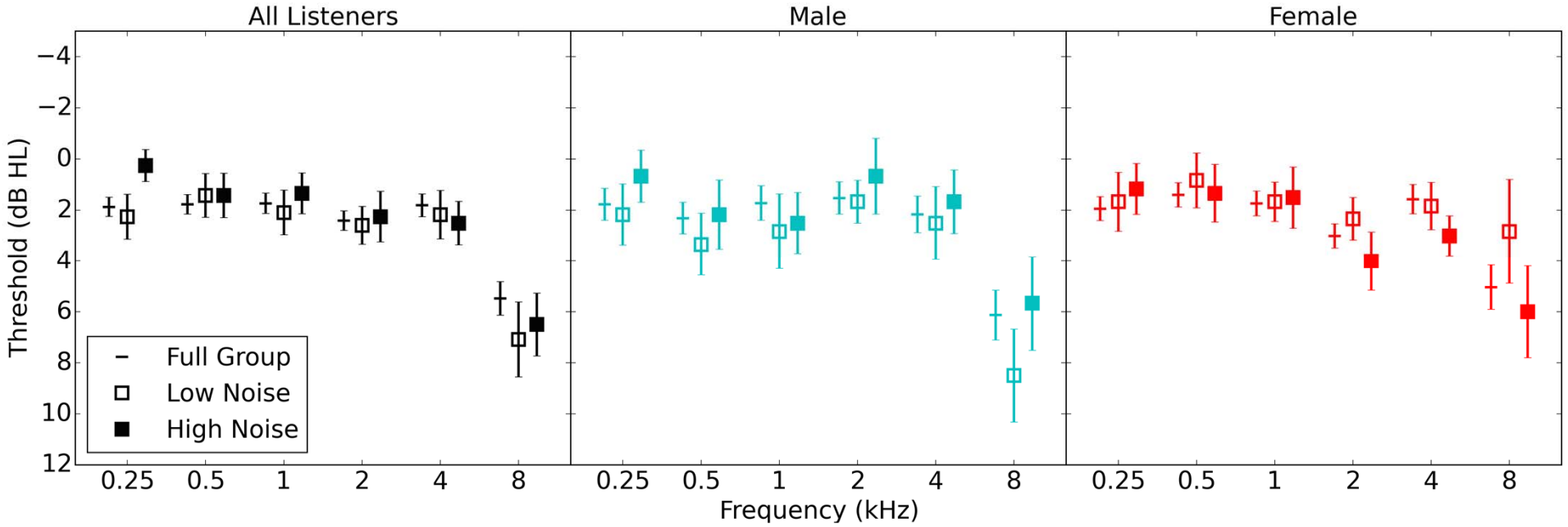
Manchester MRC Study (Garreth Prendergast PDRA)

Participant Age & Lifetime Noise Exposure



Prendergast et al. (2017a)

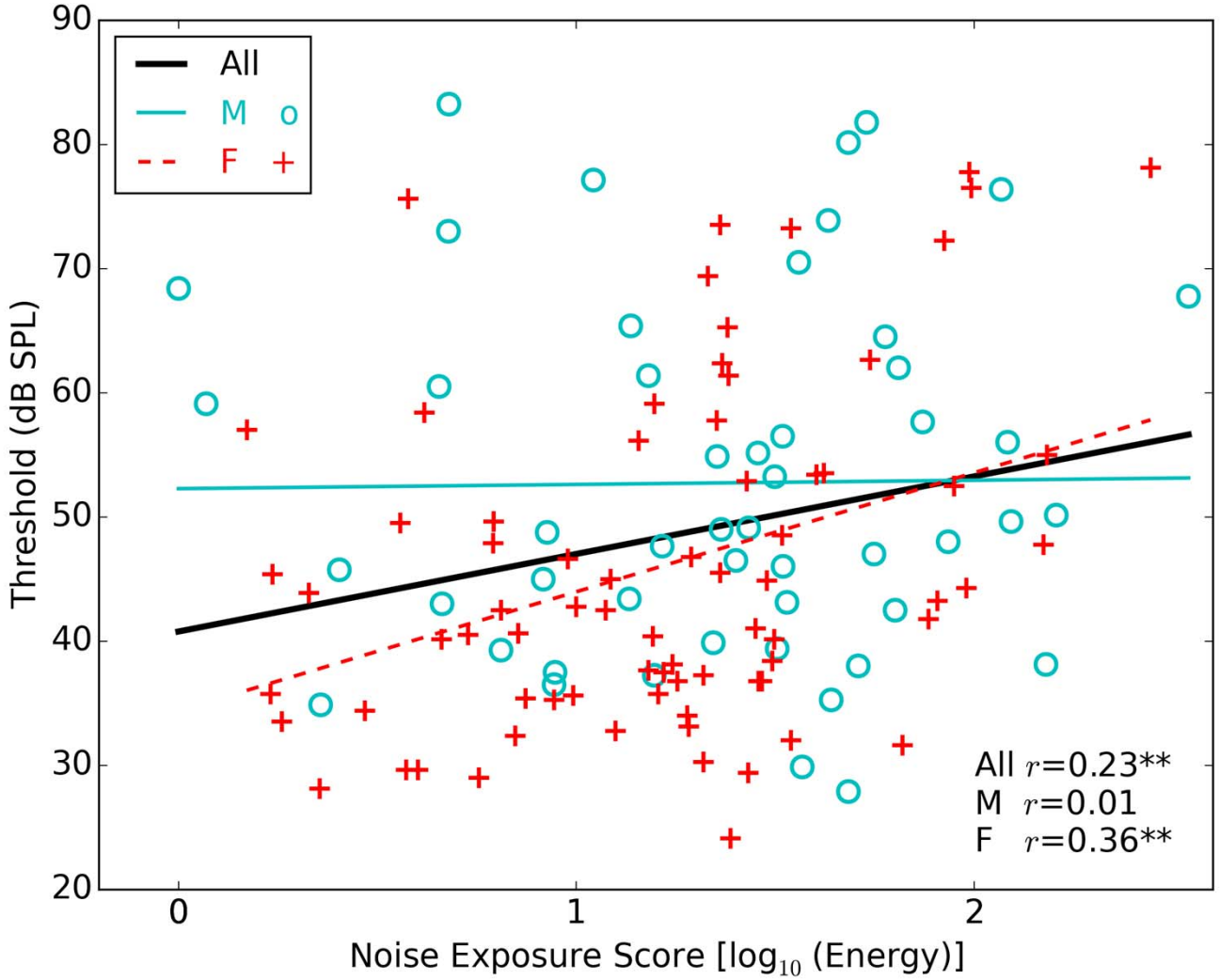
Pure Tone Audiometry



Note: low / high noise exposure groups are **lowest / highest 30** for **All** and **lowest / highest 15** for **Male** and **Female**.

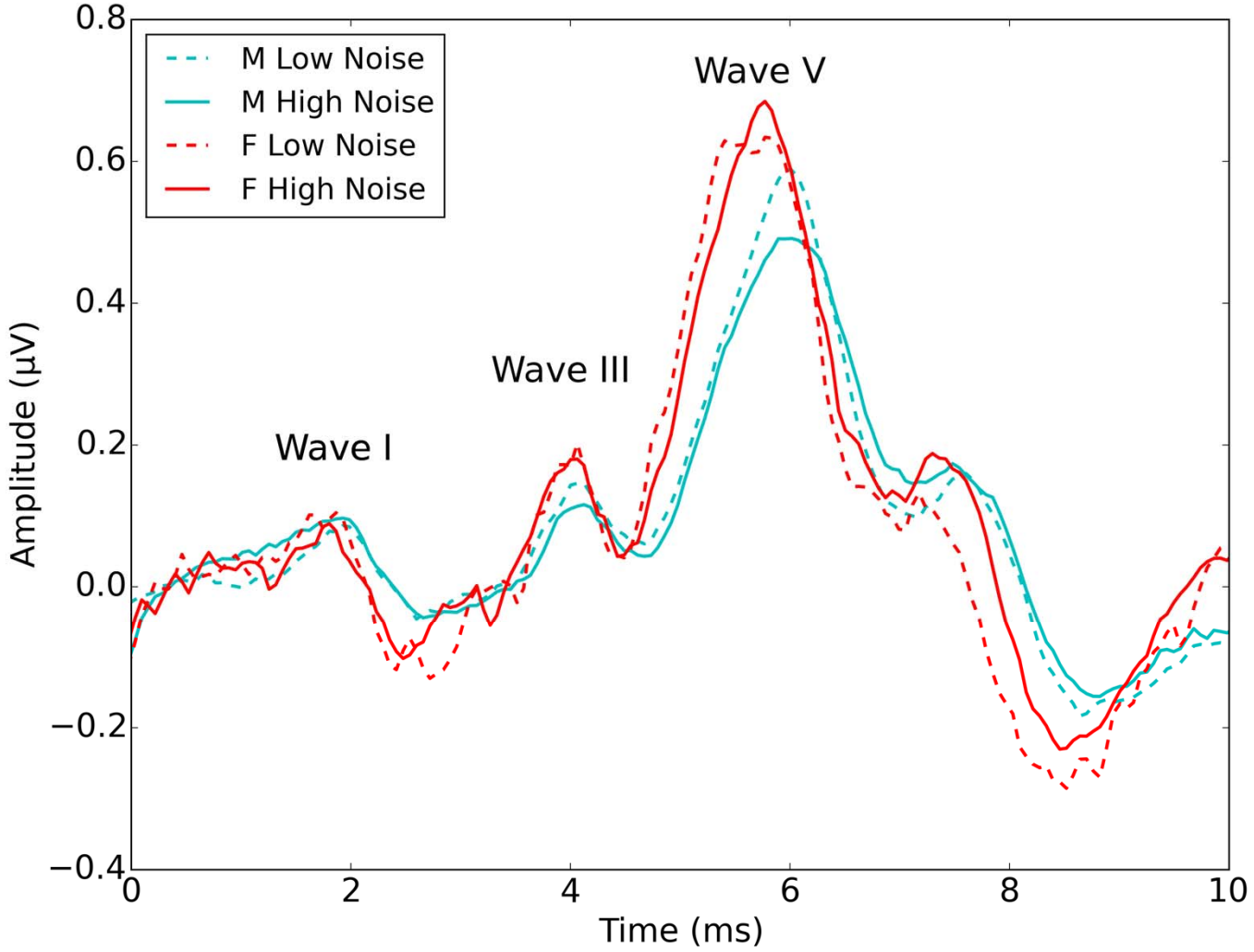
Prendergast et al. (2017a)

16-kHz Thresholds



Prendergast et al. (2017a)

100 dB peSPL Mean ABRs



Prendergast et al. (2017a)

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ABR Wave I

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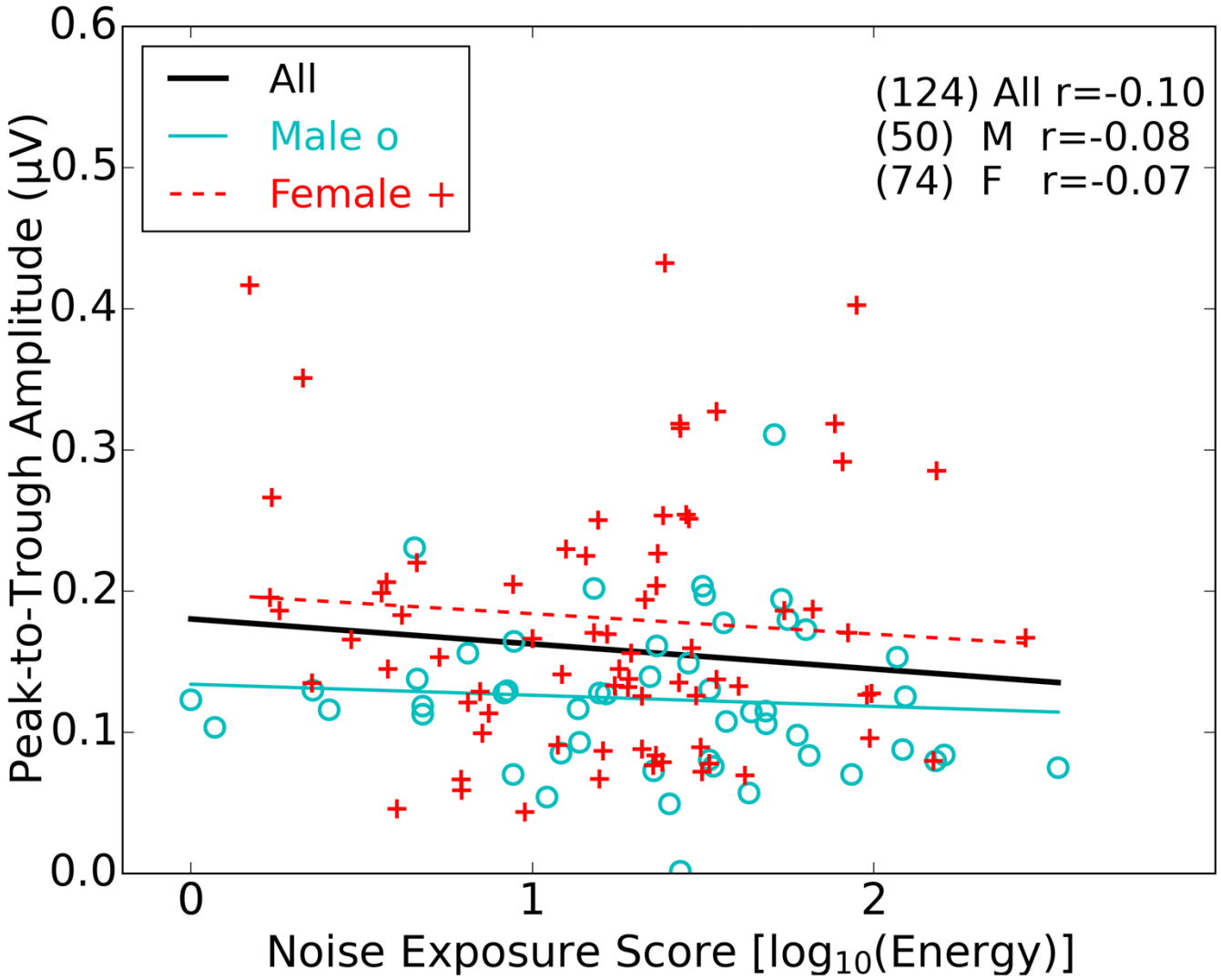
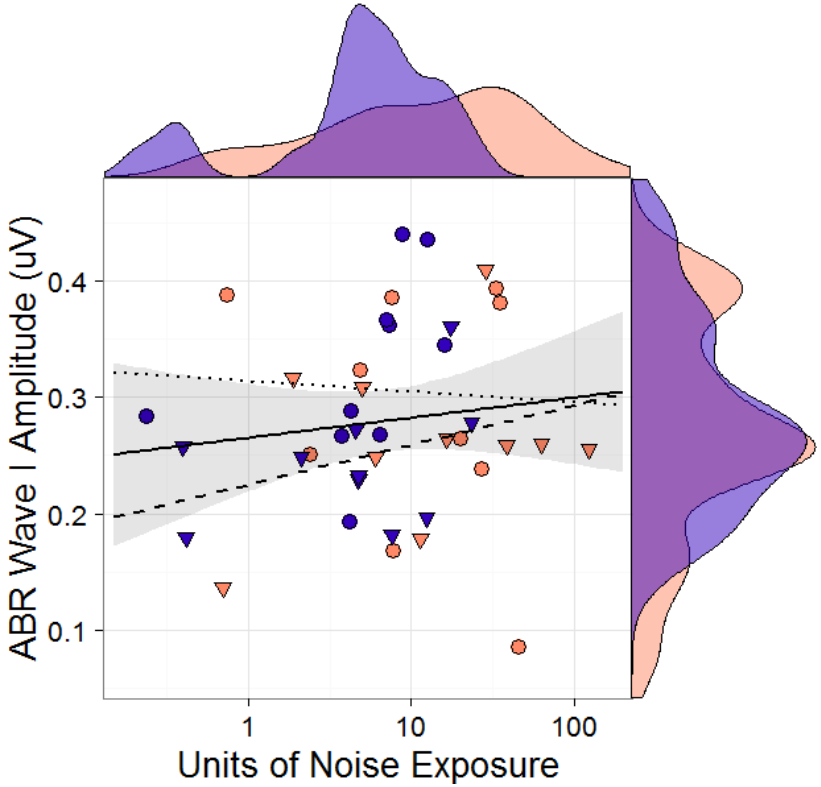
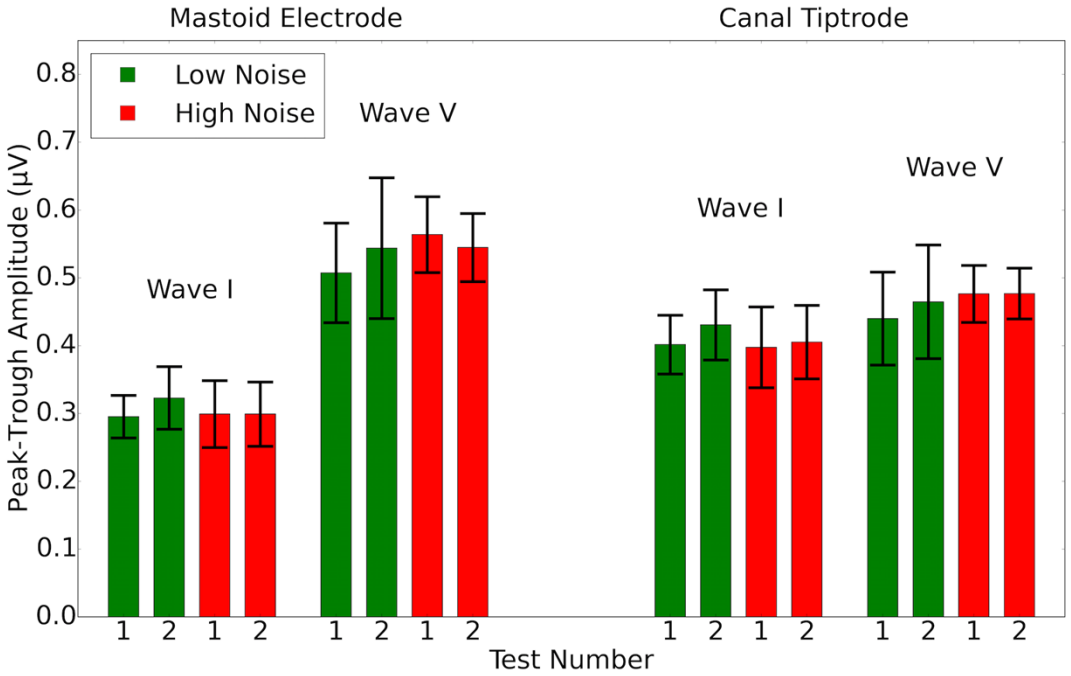


Prendergast et al. (2017a)

ABR Wave I

These results have been replicated in two subsequent studies from our laboratory:



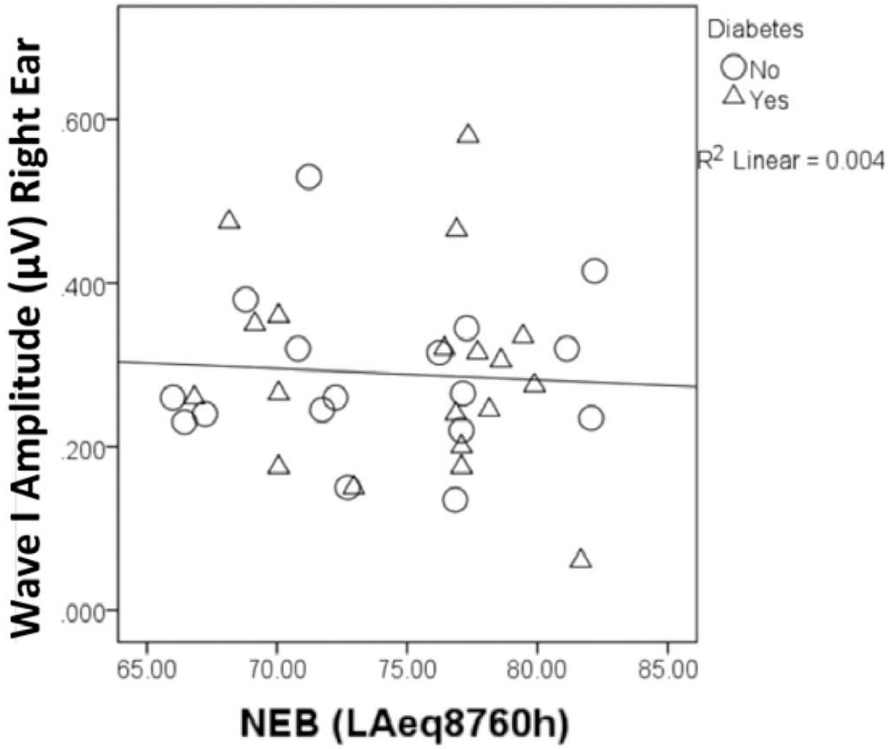


Guest et al. (2017a)

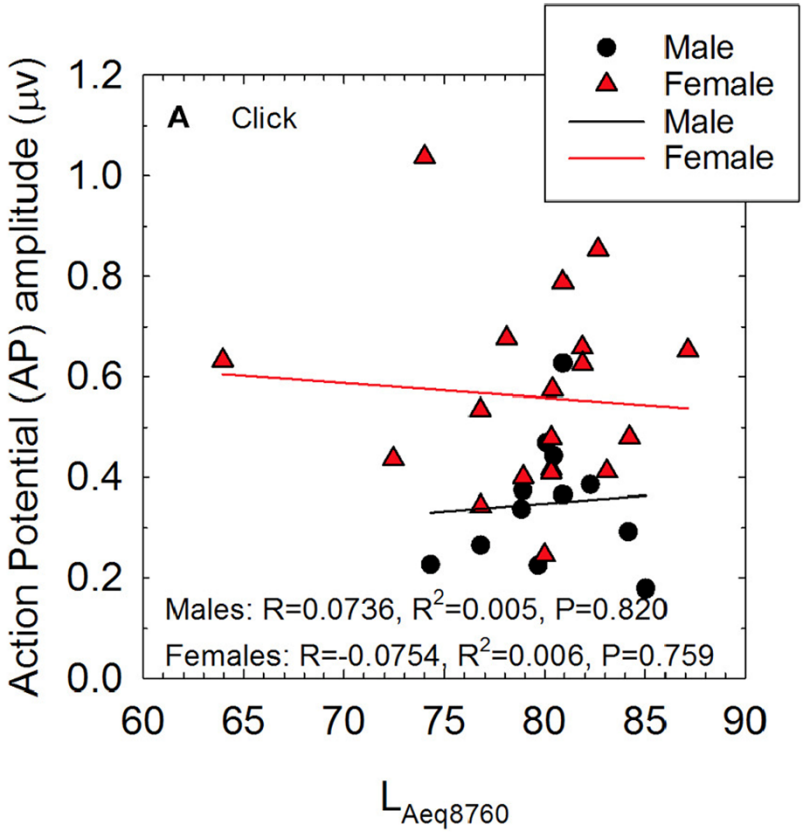
Prendergast et al. (2017c)

ABR Wave I

Two recent studies from other laboratories confirm these findings:



Spankovich et al. (2017)



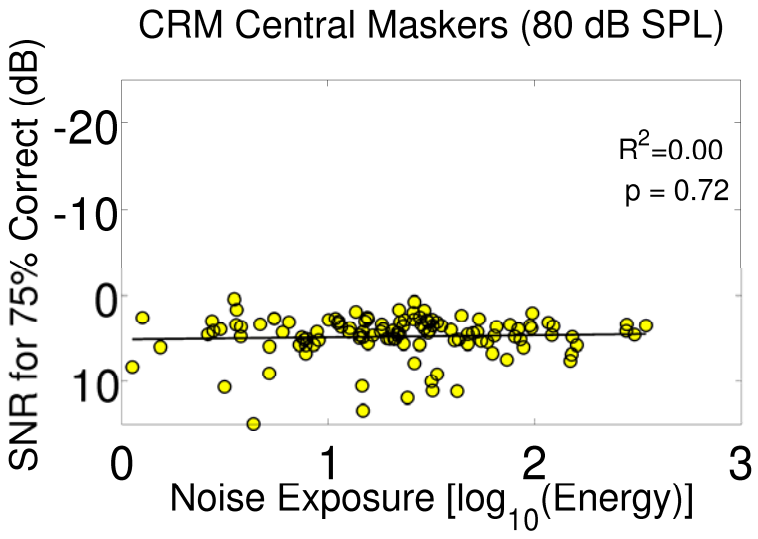
Grinn et al. (2017)

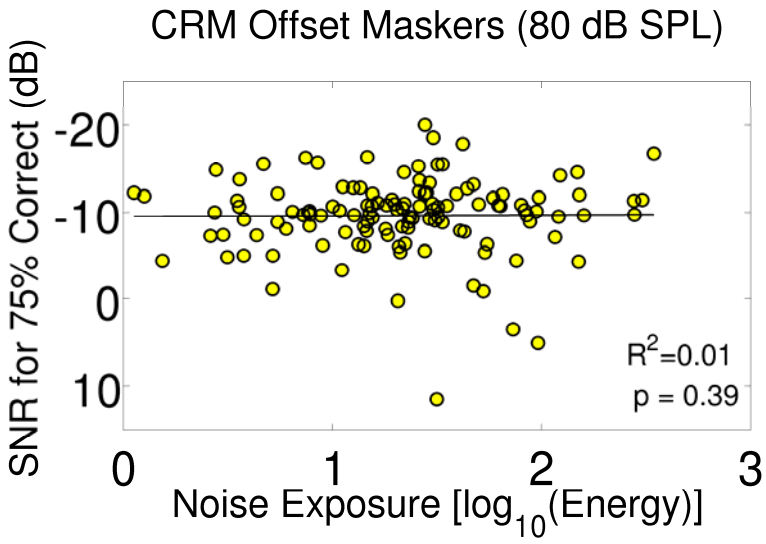
Speech in Noise

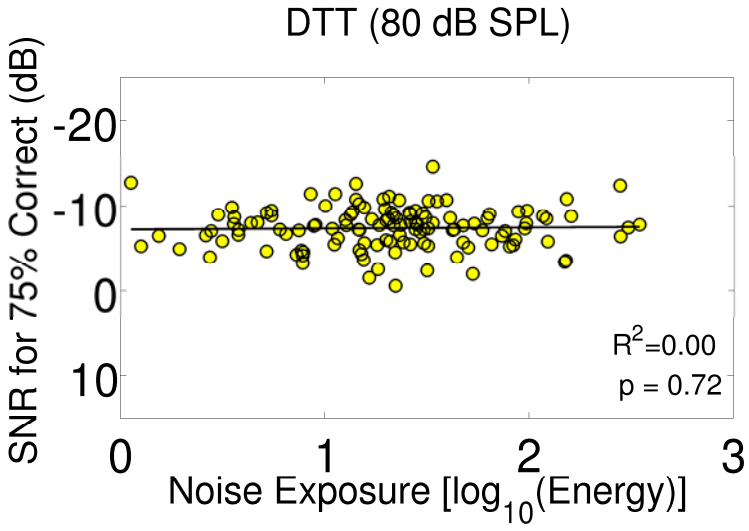
- Co-ordinate response measure (CRM, three speaker) with spatially co-located and spatially offset maskers.
- Digit triplet task (DTT), diotic presentation.
- Stimuli presented at 80 dB SPL.

Prendergast et al. (2017b)

Speech in Noise



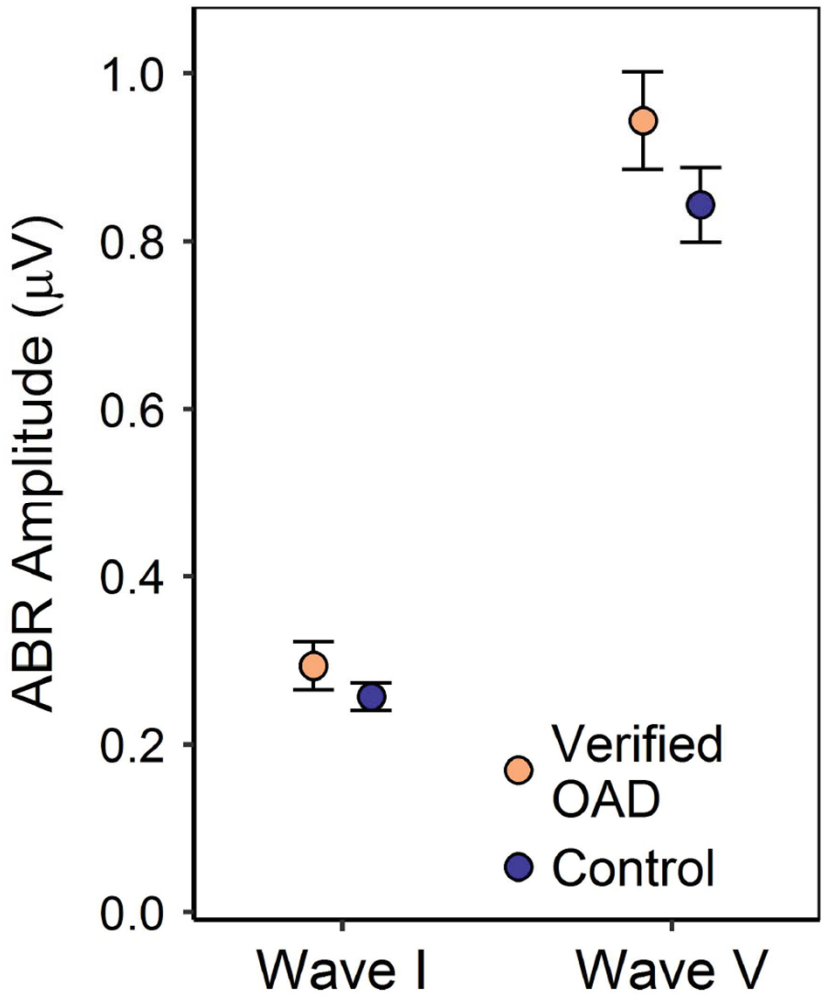




Prendergast et al. (2017b)

ABR Wave I & OAD

In another recent study, we found **no evidence for a wave I reduction in listeners with obscure auditory dysfunction** (listening difficulties with normal audiogram):



Guest et al. (2017b)

Noise-Induced Cochlear Synaptopathy in Humans

- The majority of recent studies suggest that **common recreational noise exposure has little permanent effect on auditory function**.
- Humans may be less vulnerable to noise-induced synaptopathy than rodents, and synaptopathy may always co-occur with a high-frequency audiometric loss.

Panic Over?

- So should we all stop worrying about hidden hearing loss?

- **No**, for three reasons:

(i) We may not yet have a sensitive measure of synaptopathy in humans. Negative results may be due to problems in measurement rather than an absence of synaptopathy.

(ii) Even if it turns out that humans are less susceptible than rodents, it is quite possible (likely?) that synaptopathy co-occurs with hair cell damage, revealed in the audiogram.

(iii) There is increasing post-mortem histological evidence that ageing in humans is associated with substantial synaptopathy.

Summary

- In rodent models, noise exposure can result in substantial cochlear synaptopathy without affecting sensitivity to soft sounds (“hidden hearing loss”).

- However, recent human studies suggest that noise-induced cochlear synaptopathy is either not very prevalent in young adults, or is not revealed by current electrophysiological or behavioral tests.

- It remains quite possible that noise-induced cochlear synaptopathy contributes to listening difficulties for patients with an audiometric loss. There is then the diagnostic challenge of distinguishing hair cell loss and synaptopathy.

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Agnès Léger
Becky Millman
Kevin Munro
Garreth Prendergast
Wenhe Tu

Funders:

MRC Medical Research Council

BBSRC bioscience for the future

ACTION ON HEARING LOSS
A national charity since 1911

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The End

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Additional Figures

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Tinnitus and Cochlear Synaptopathy

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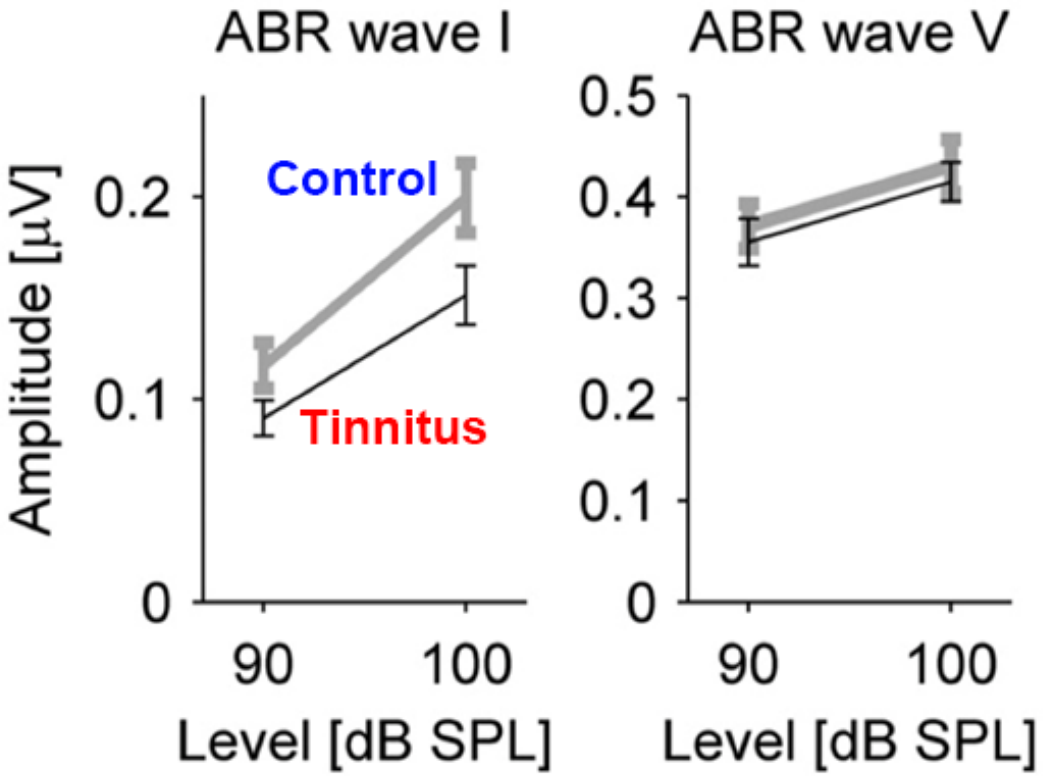
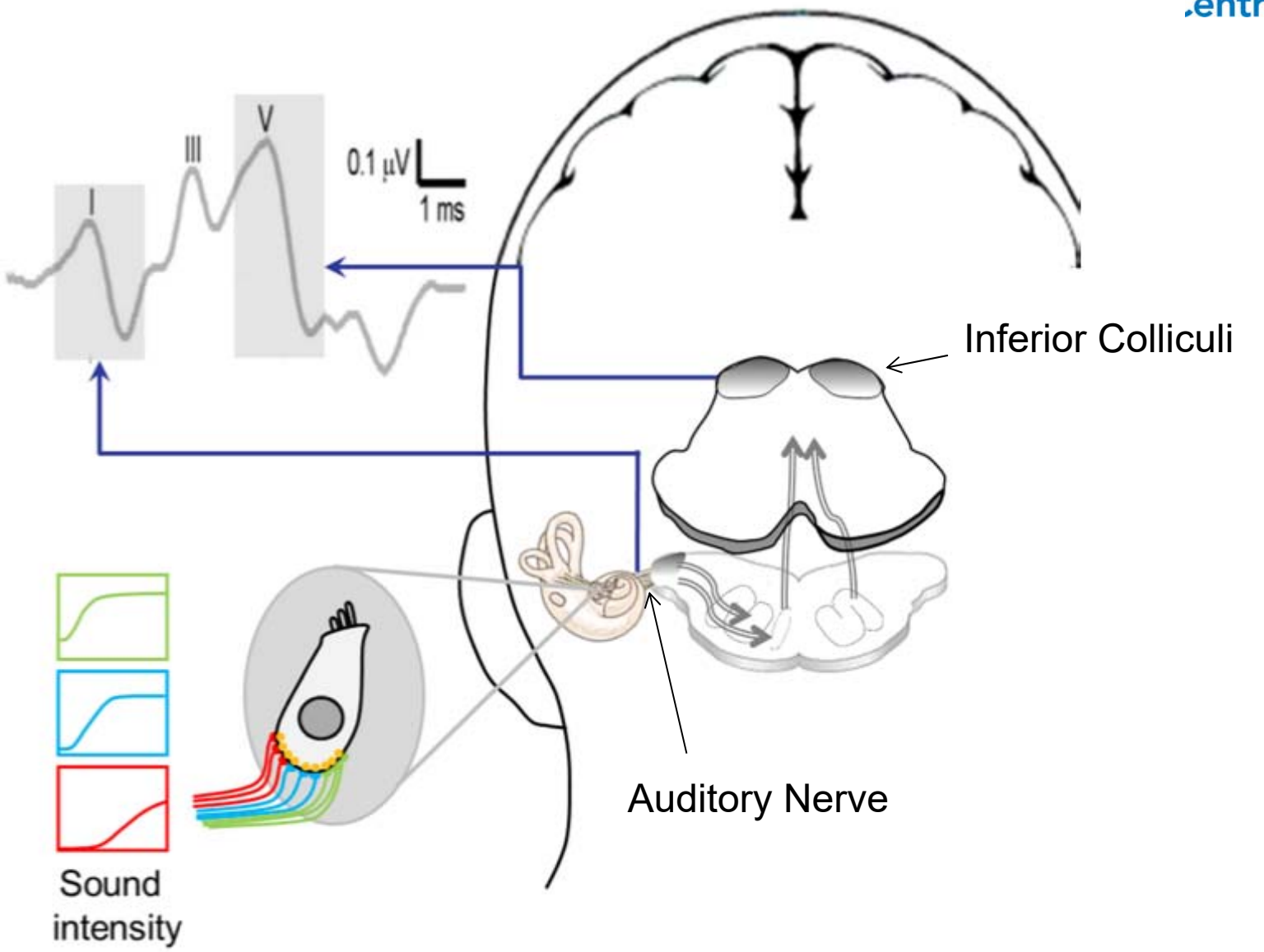
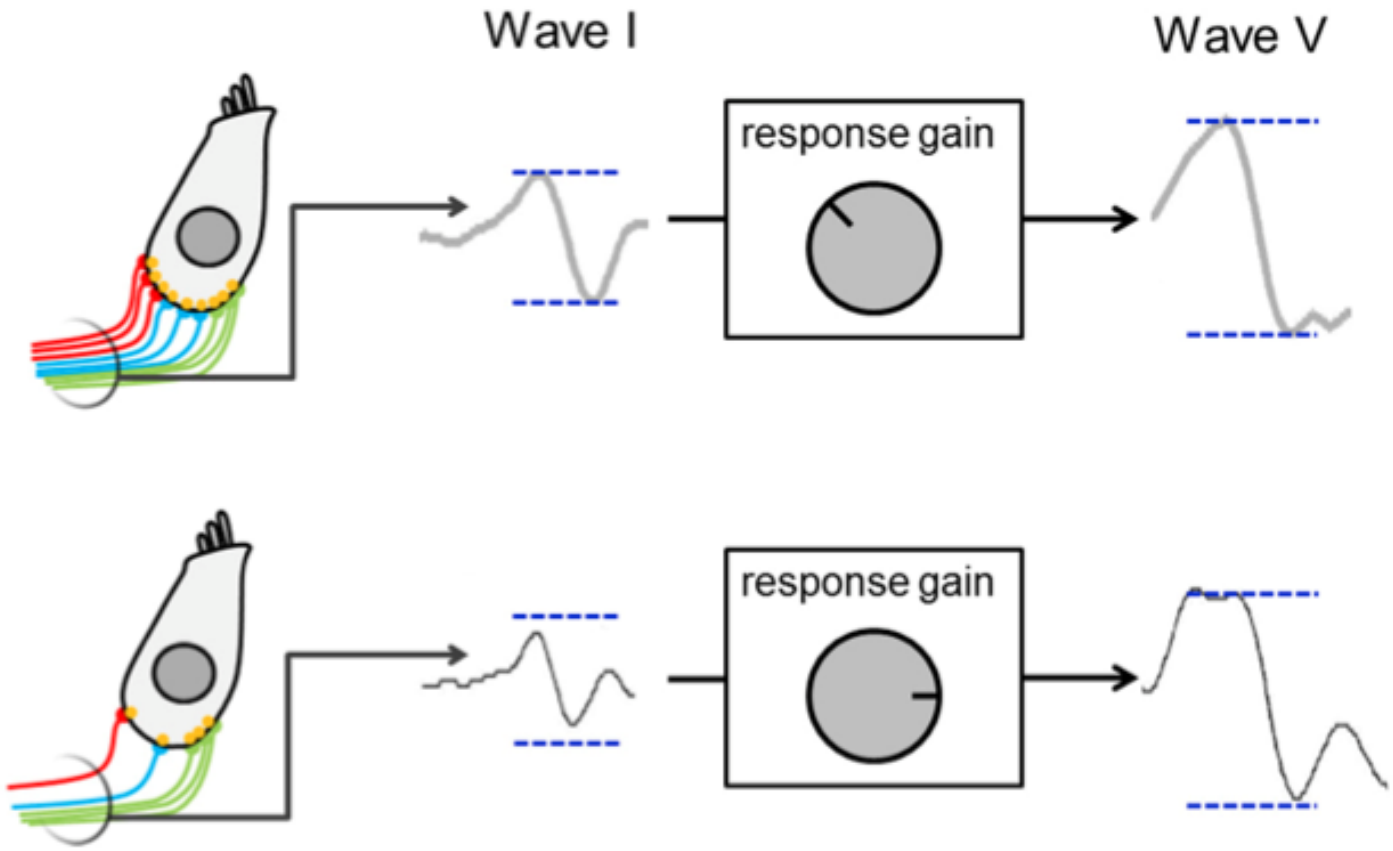
Cochlear Synaptopathy and Tinnitus

Schaette and McAlpine (2011). Tinnitus with normal audiogram associated with reduced Wave I of ABR, but normal Wave V:




I
III
V
0.1 µV
1 ms
Inferior Colliculi
Auditory Nerve
Sound intensity

Tinnitus may be caused by increased **central gain** following deafferentation:



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Manchester AoHL Study (Hannah Guest PhD project)

Participants

Tinnitus

n = 20 (female = 10), mean age = 25.7 ± 1.3 years

Controls

n = 20 (female = 10), mean age = 25.5 ± 1.3 years

Individually matched with tinnitus participants for age and sex, group matched for PTA

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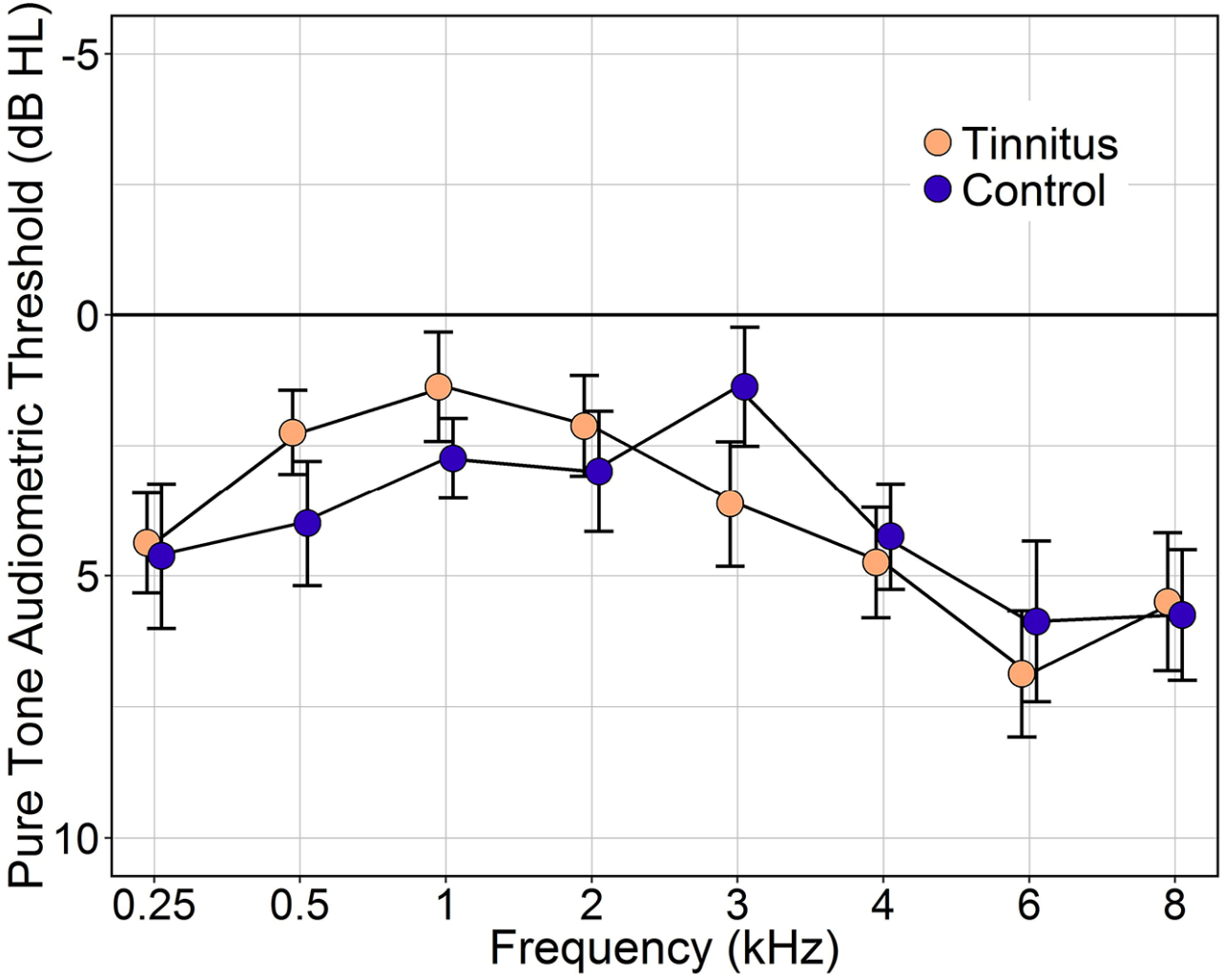
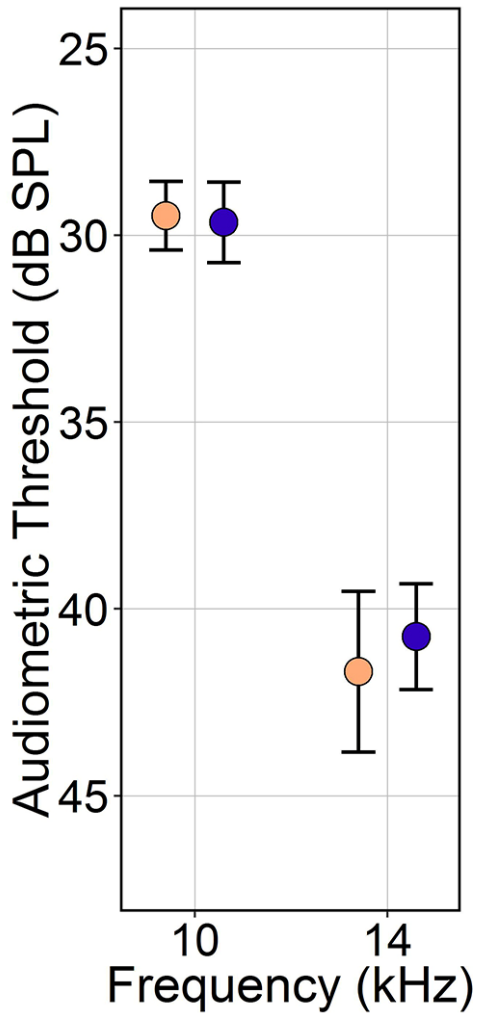
Audiometry





Guest et al. (2017)

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Noise Exposure History

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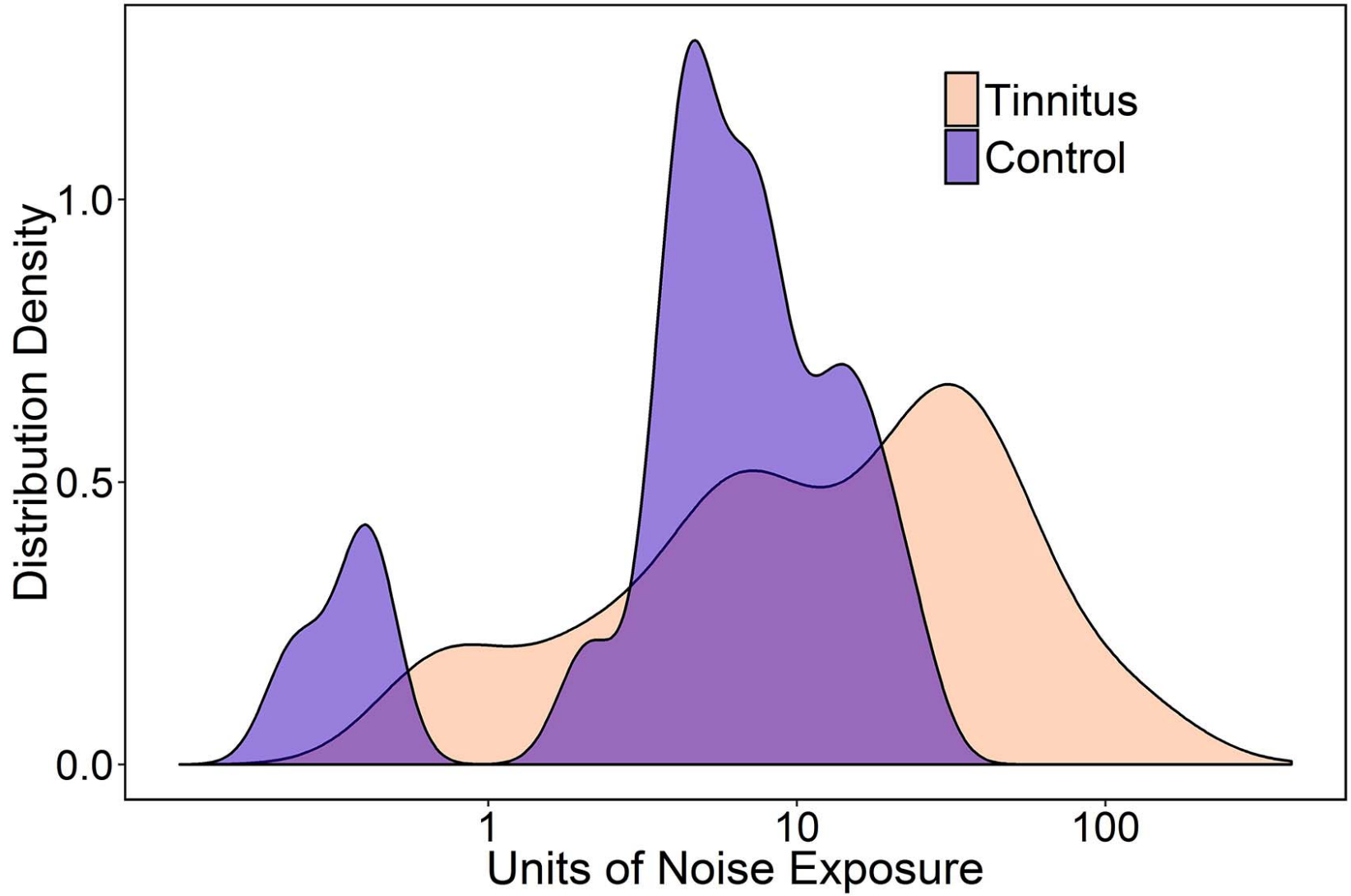
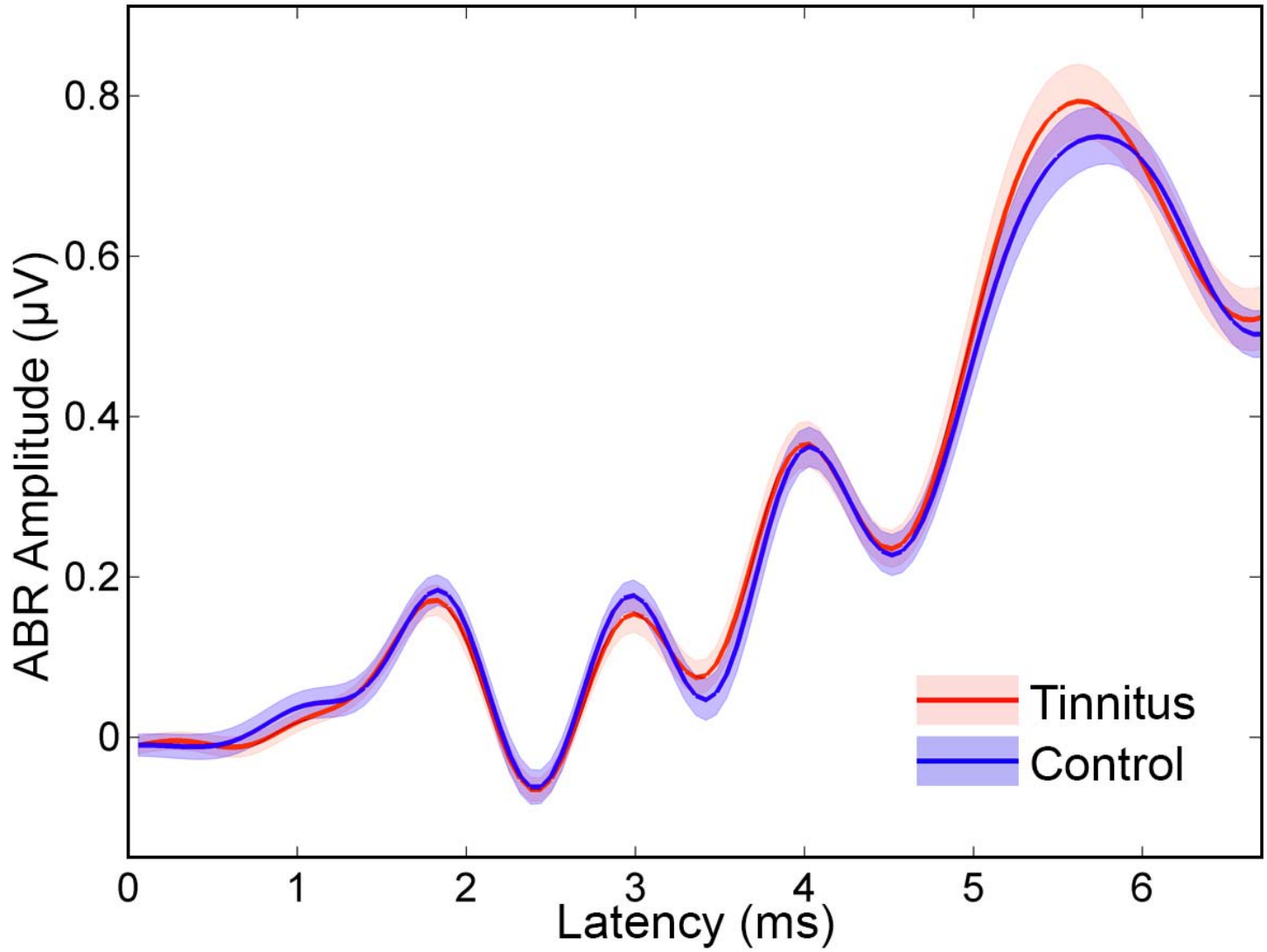


Guest et al. (2017a)

102 dB peSPL Mean ABRs



Guest et al. (2017a)

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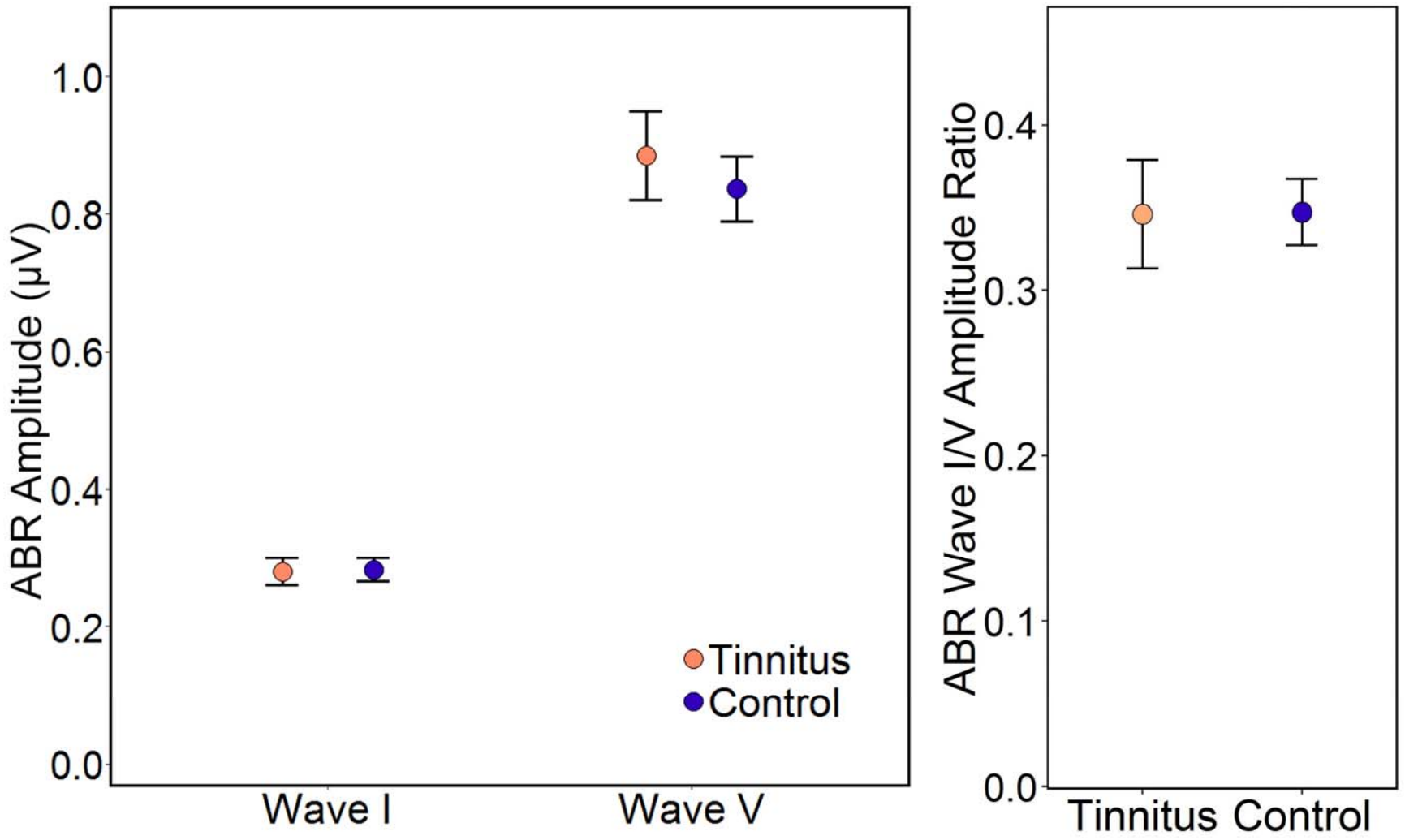
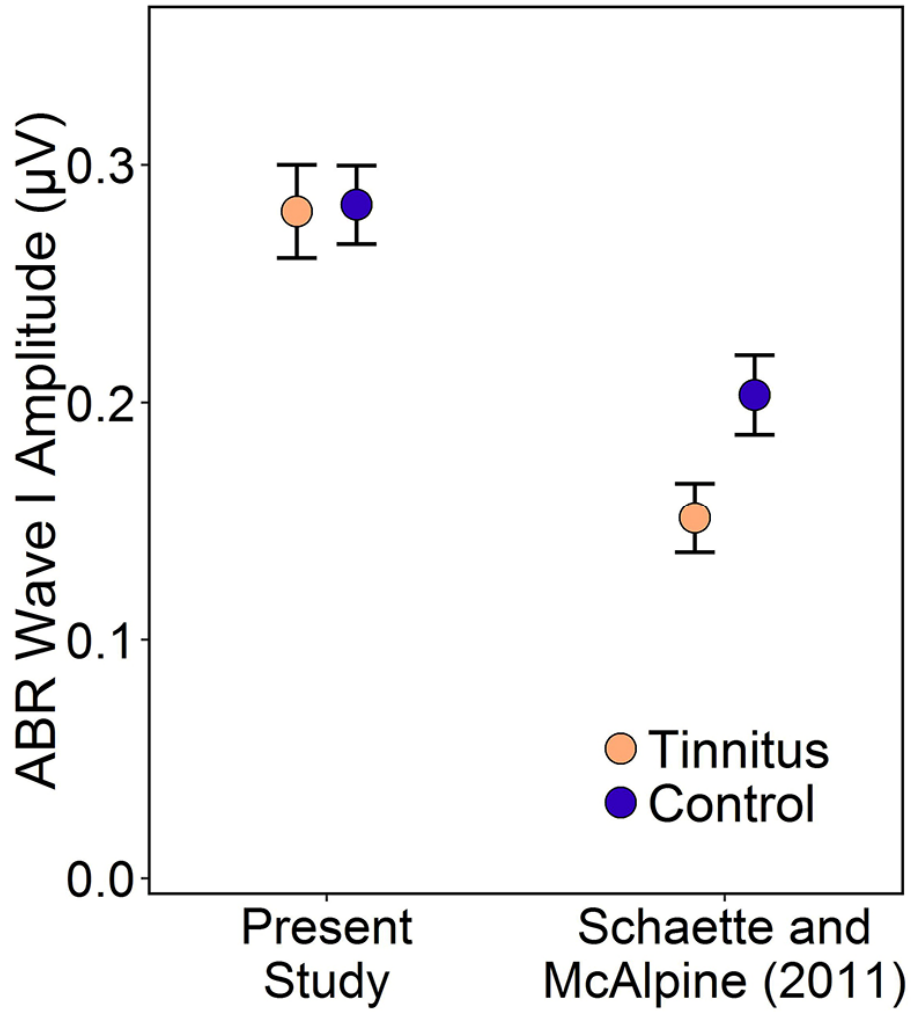
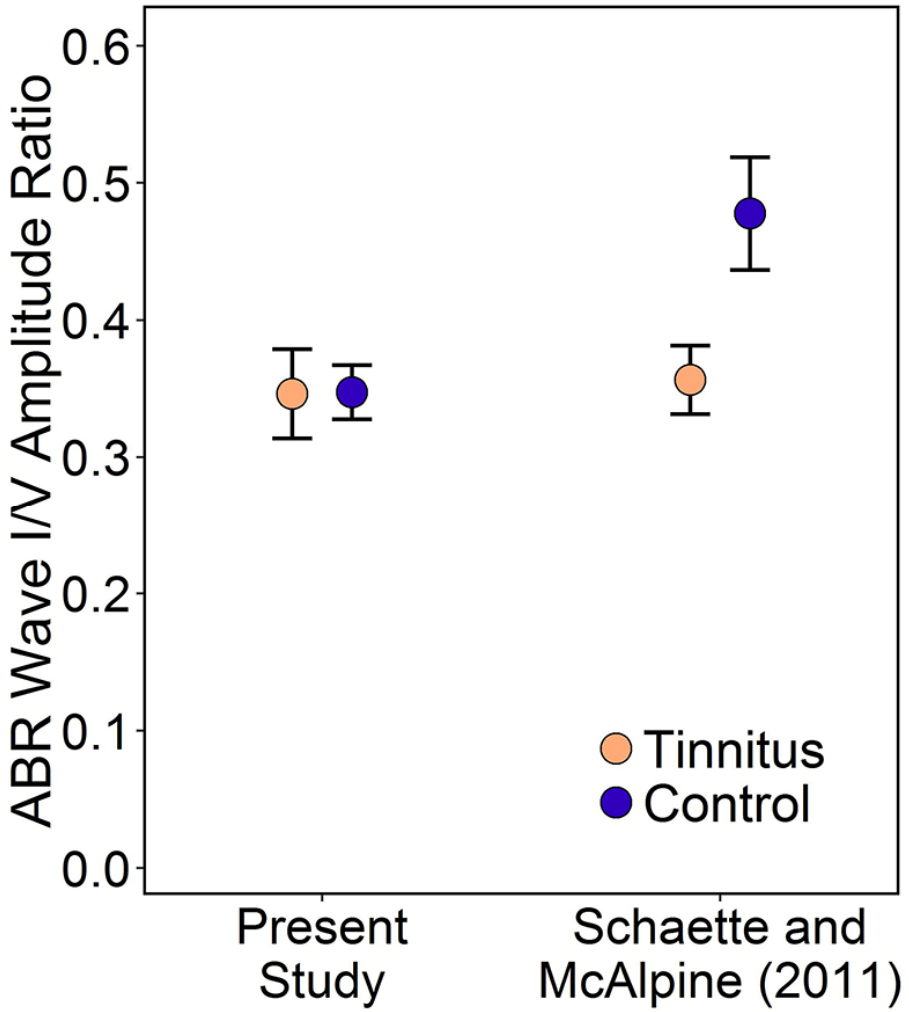
ABR Amplitude



Guest et al. (2017a)

…vs. Schaette & McAlpine





Guest et al. (2017a)

Failure to Replicate

- S&M used headphones with a slightly wider bandwidth (TDH 49 vs. our ER3As).
- S&M's 12-kHz audiometric thresholds in the tinnitus group worse than controls by ~3.5 dB.
- S&M's mean age higher: tinnitus mean 36, control mean 33. Our mean age was 25.
- Cochlear synaptopathy perhaps one cause among several of tinnitus with normal audiogram. Other causes dominant in younger group?

Summary

- Tinnitus with a normal audiogram is associated with a history of high noise exposure.
- No evidence from our ABR data that tinnitus with a normal audiogram is associated with cochlear synaptopathy, or an increase in central gain.

Tinnitus Characteristics

- Prolonged spontaneous tinnitus.
- Non-pulsatile, stable percept (> 4 months).
- 95% have tinnitus that is constant in quiet.
- Consciously aware of tinnitus during 41% of waking hours (± 4%).
- 95% bilateral tinnitus.

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Auto-Interpreted ABRs

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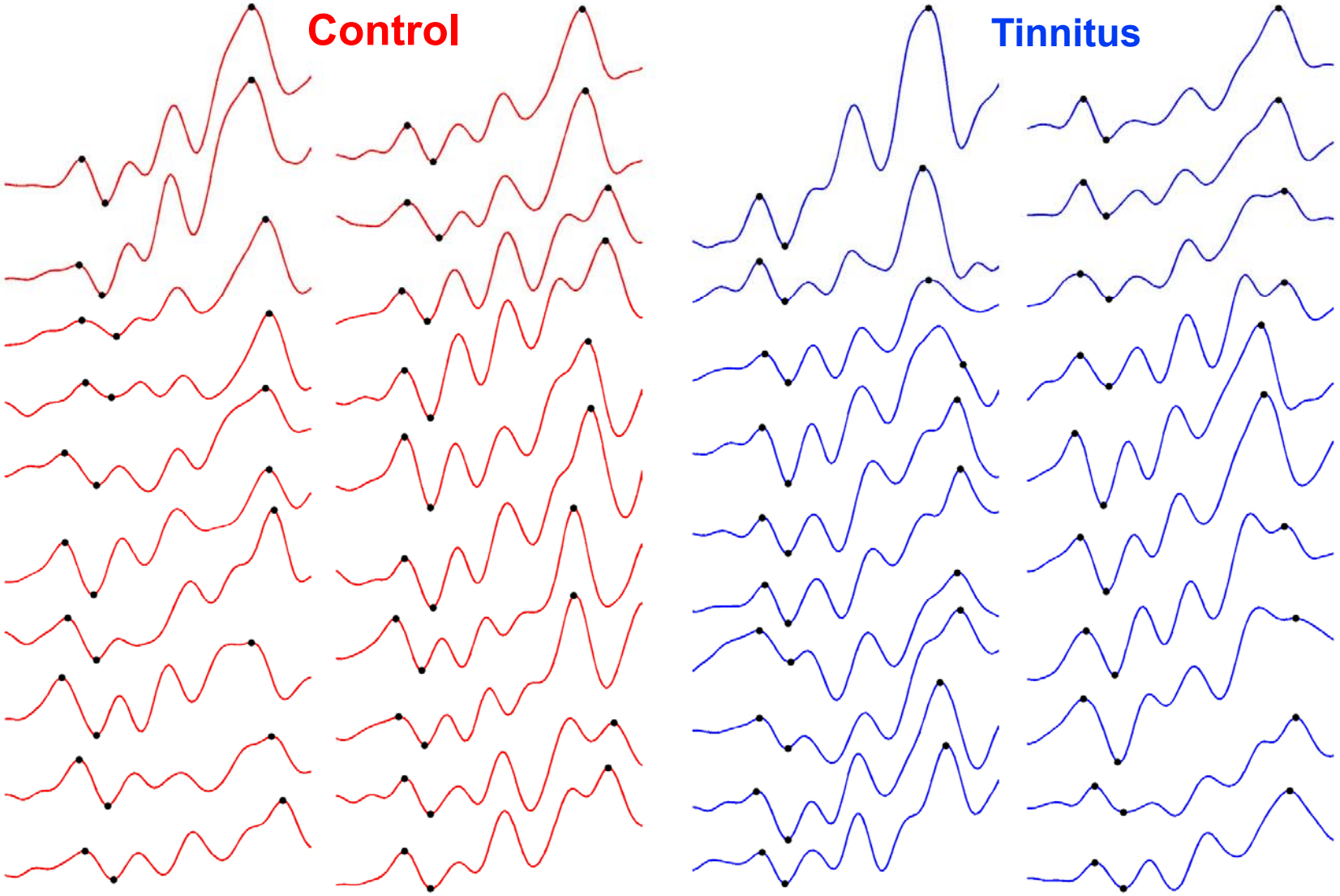

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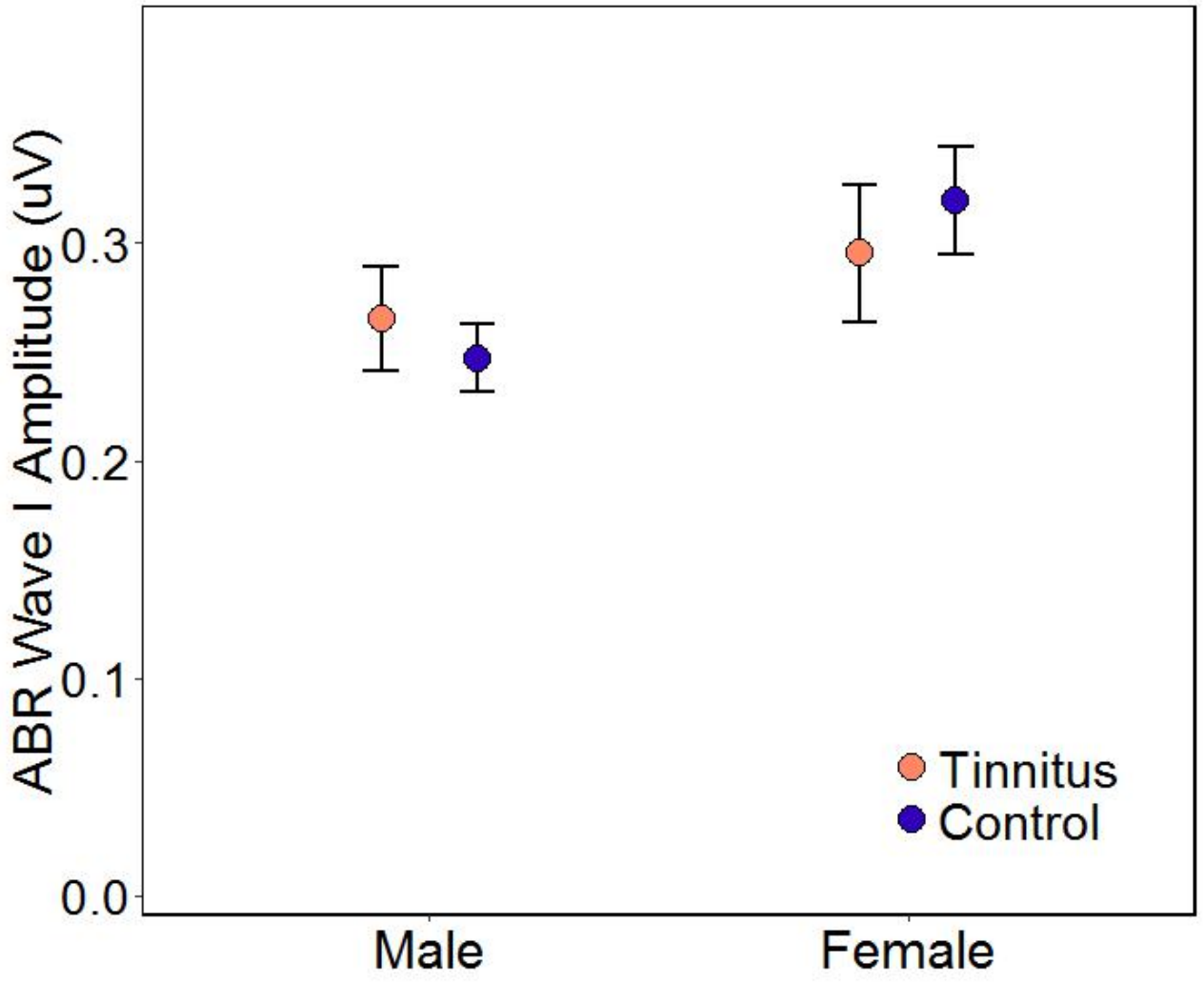
Sex & ABR Wave I



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Envelope Following Response (EFR)

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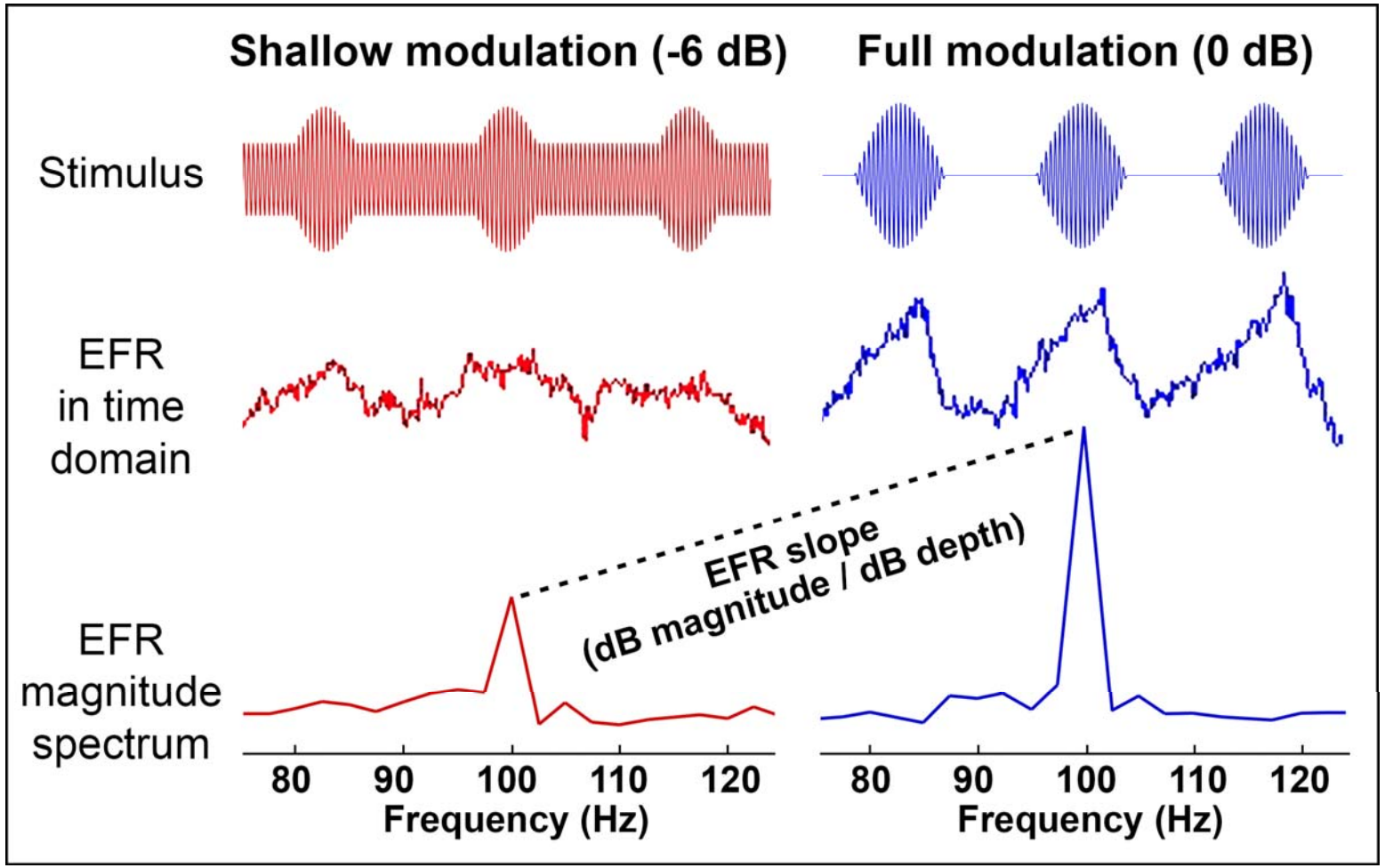

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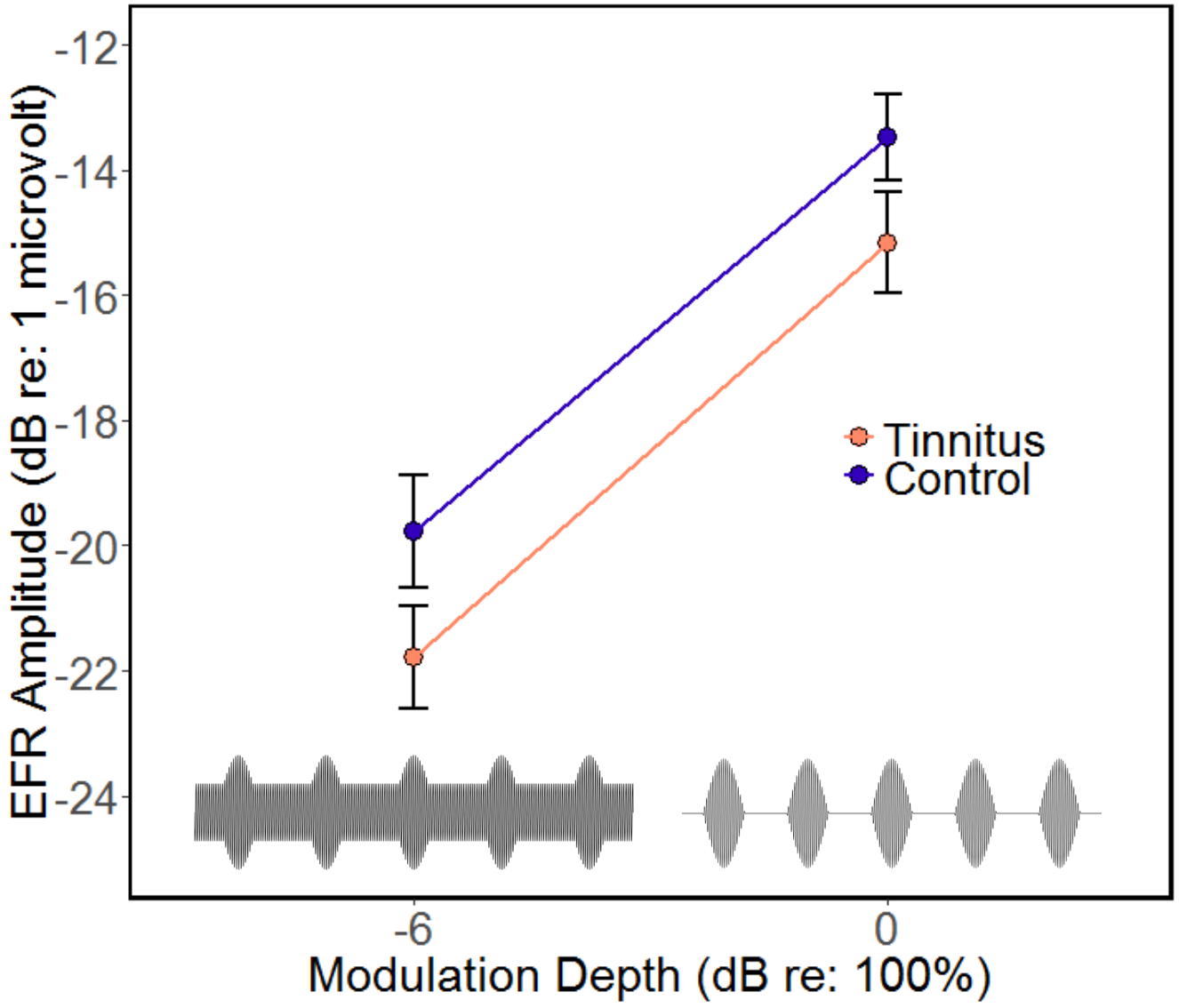
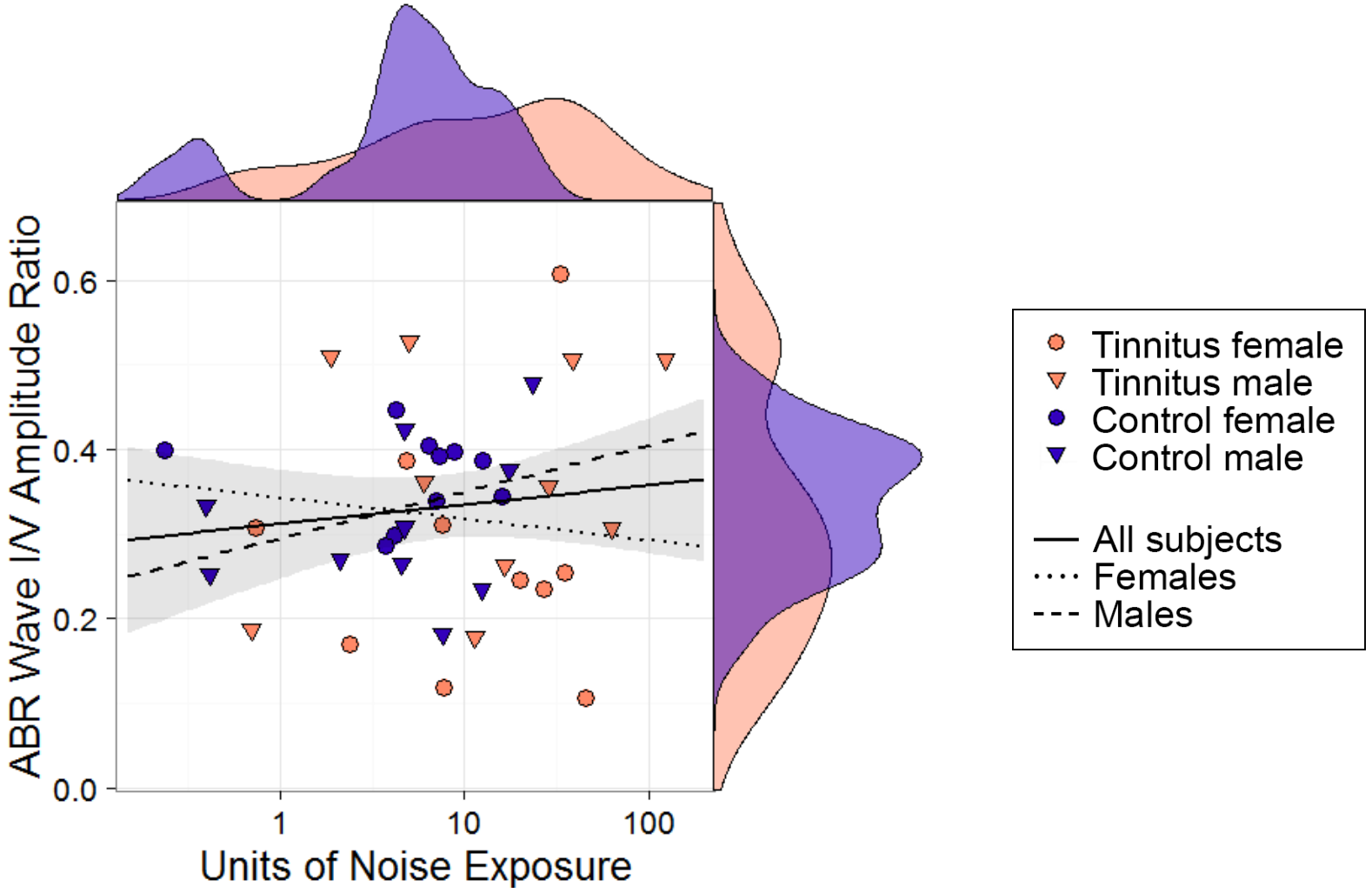
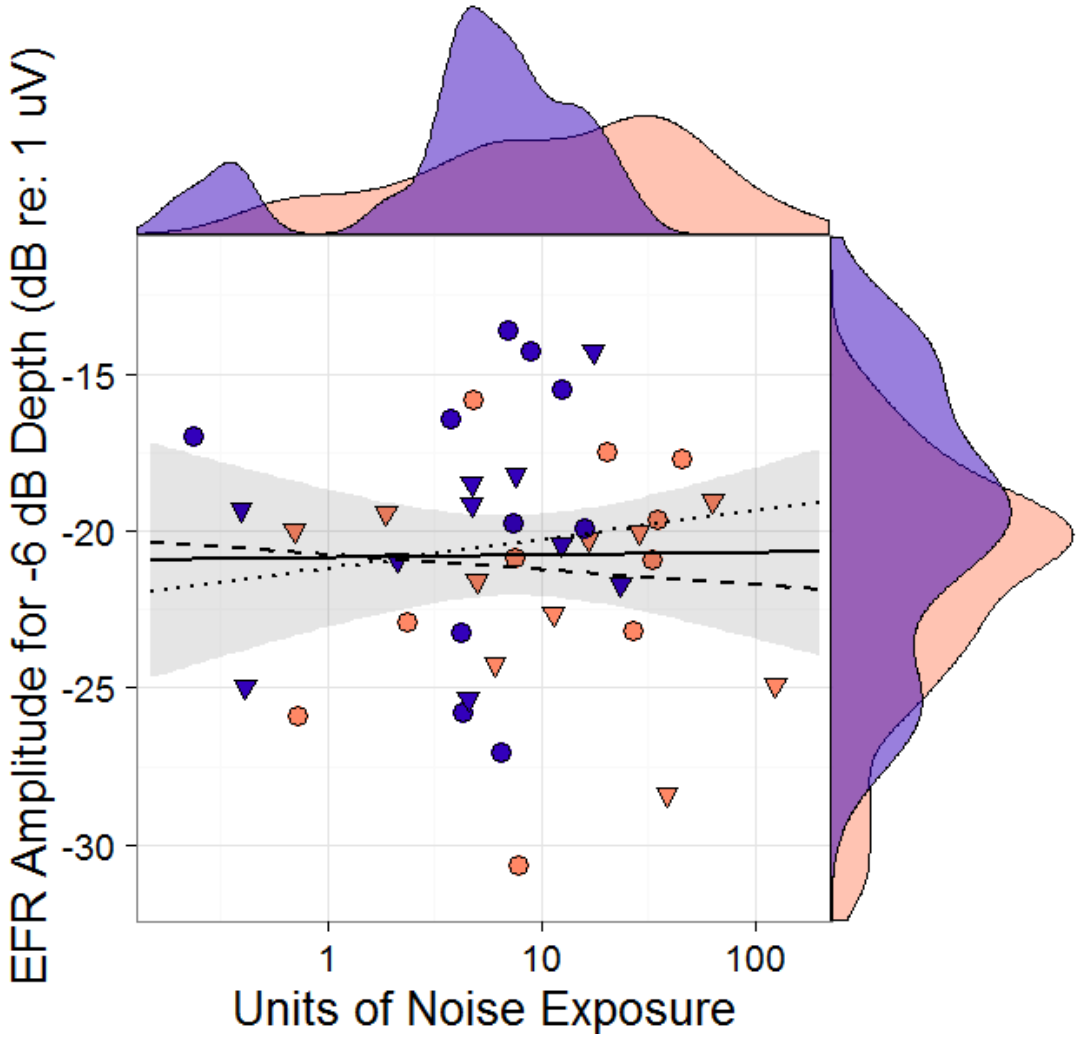
EFR Amplitude

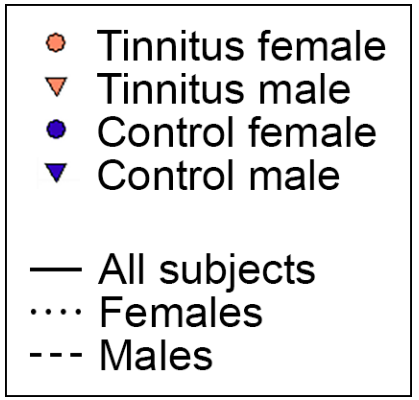


Wave I/V Ratio vs. Noise Exposure

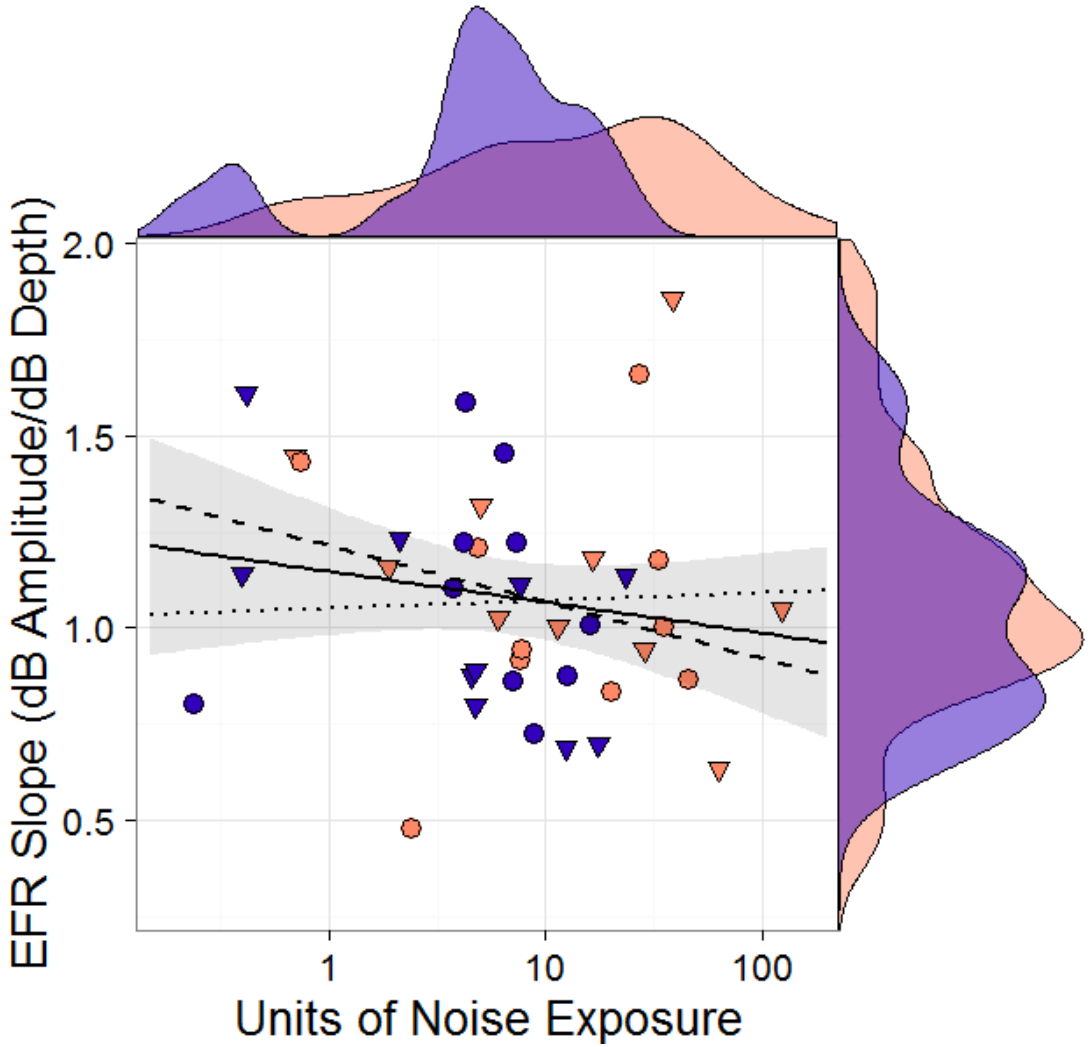


EFR Amplitude vs. Noise Exposure



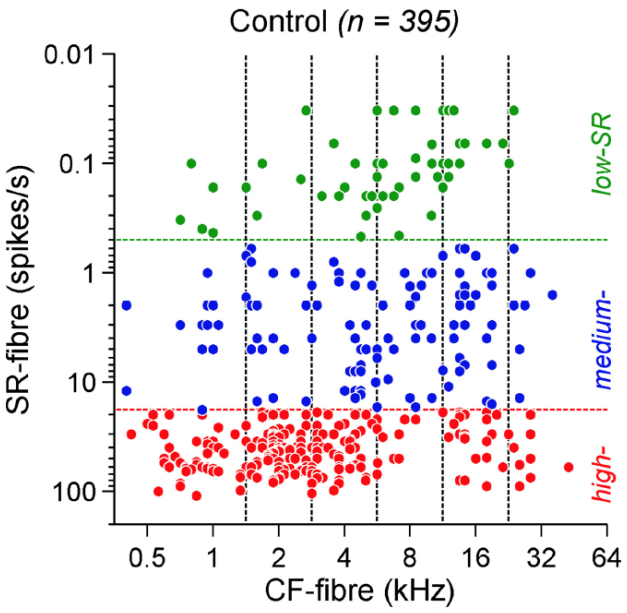


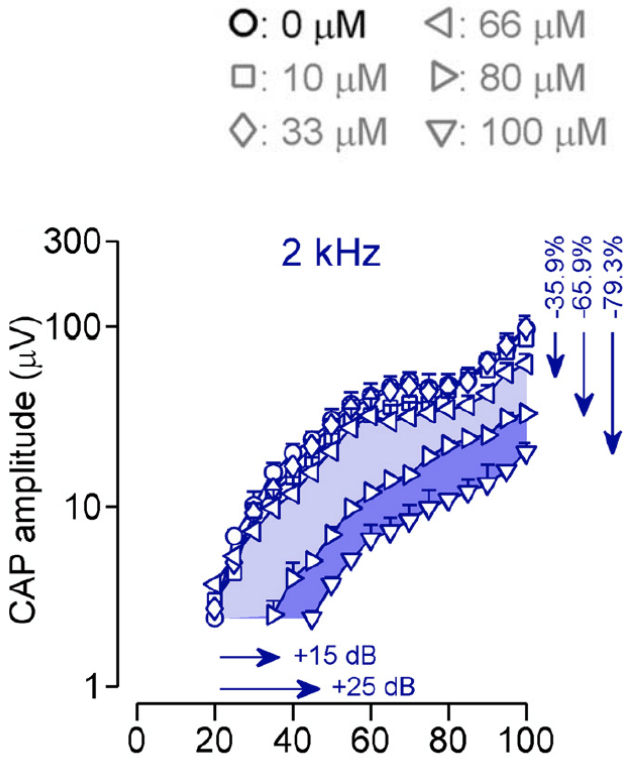
EFR Slope vs. Noise Exposure

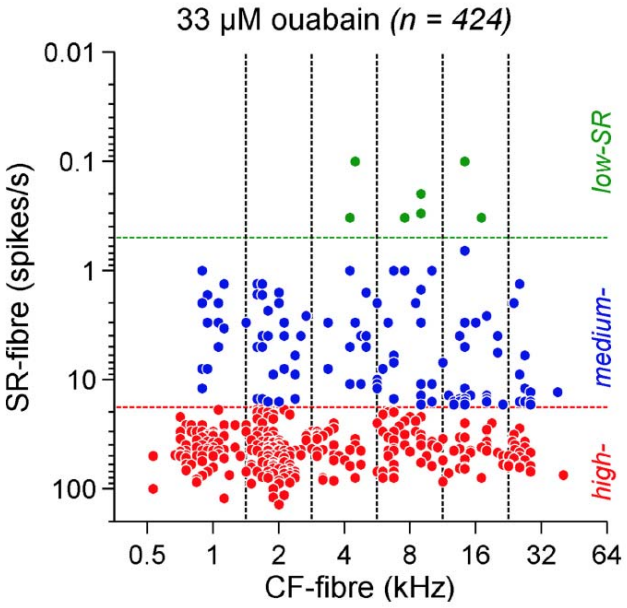


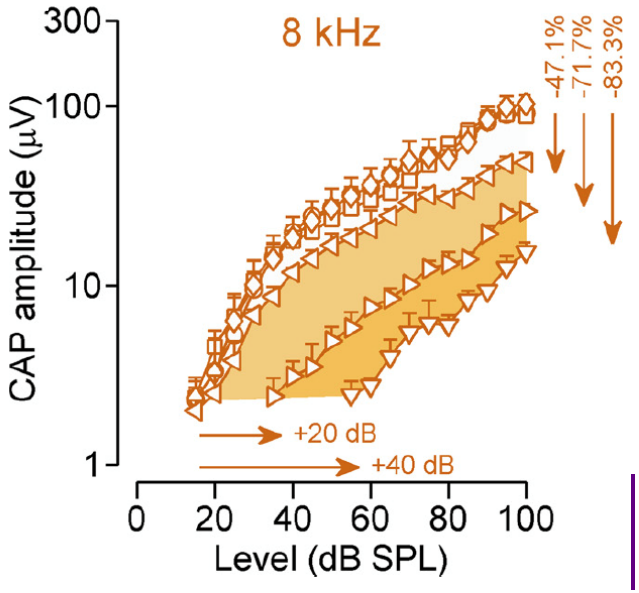
CAP Unaffected by Loss of Low-SR Fibers

Bourien et al. (2014, gerbil). 33 μM ouabain selectively destroys low-SR fibers but does not reduce CAP amplitude:

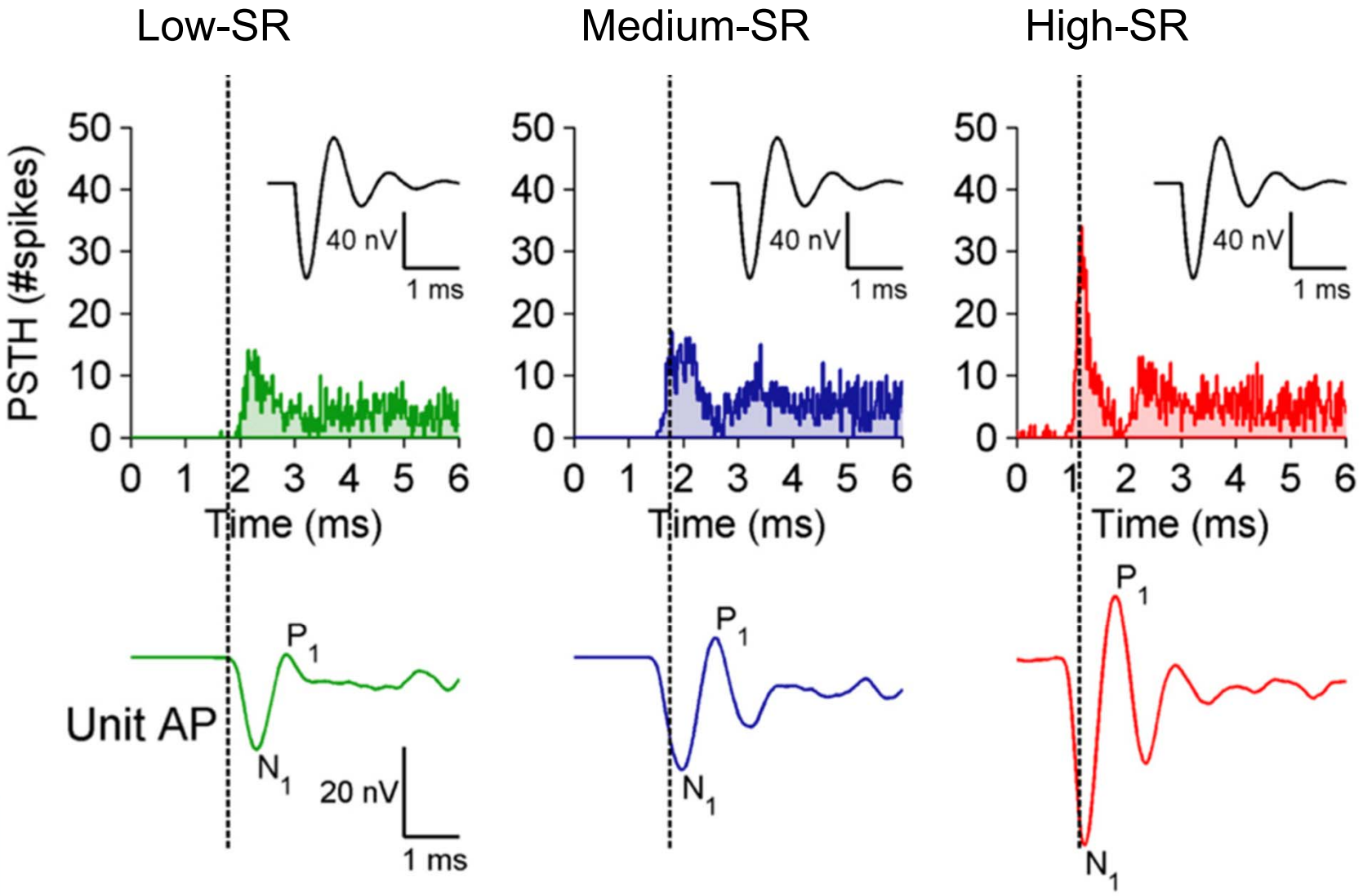








Low-SR fibers have delayed and broad first spike latency distribution, leading to reduced unit action potential (Bourien et al., 2014):

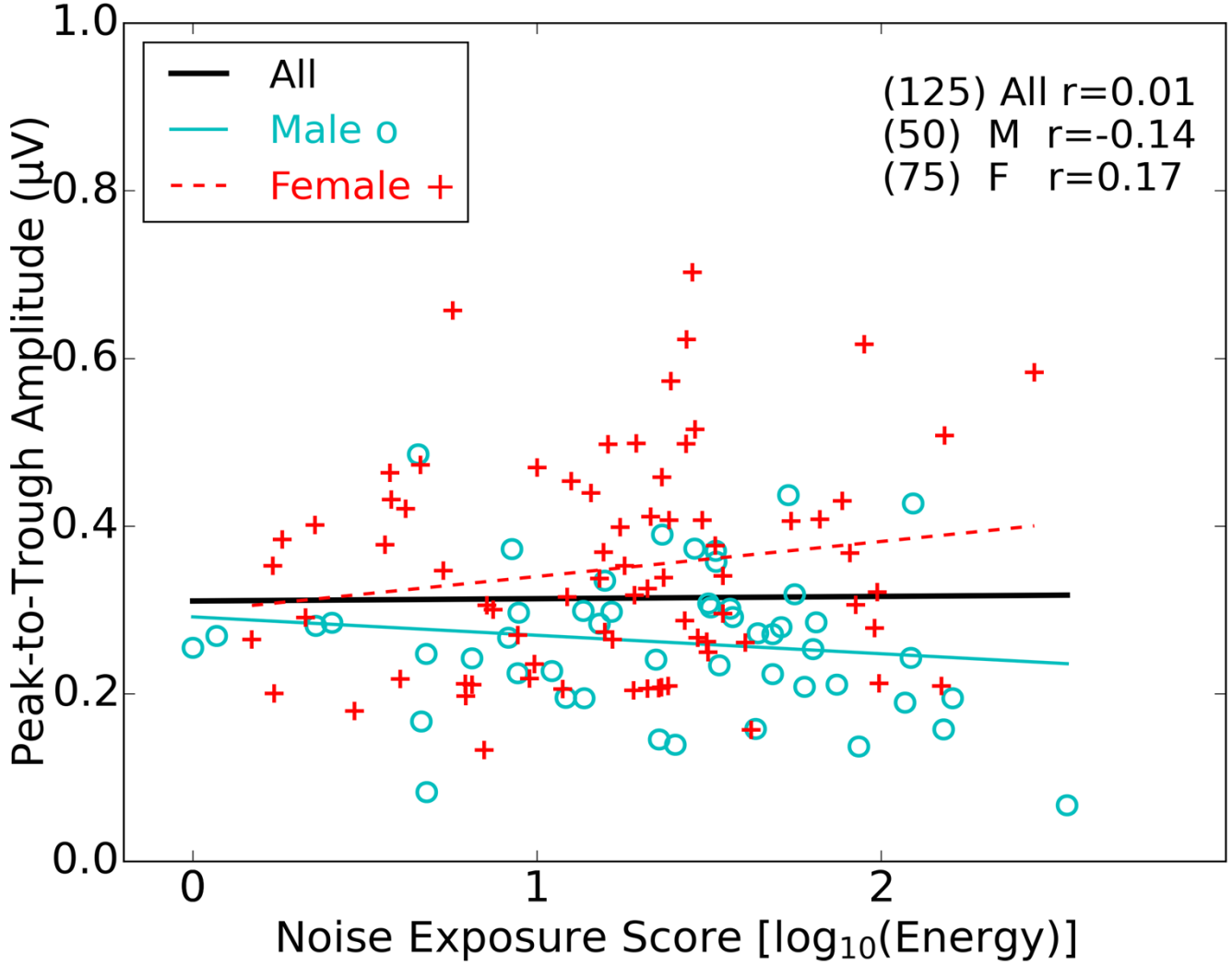


MANCHESTER 1824

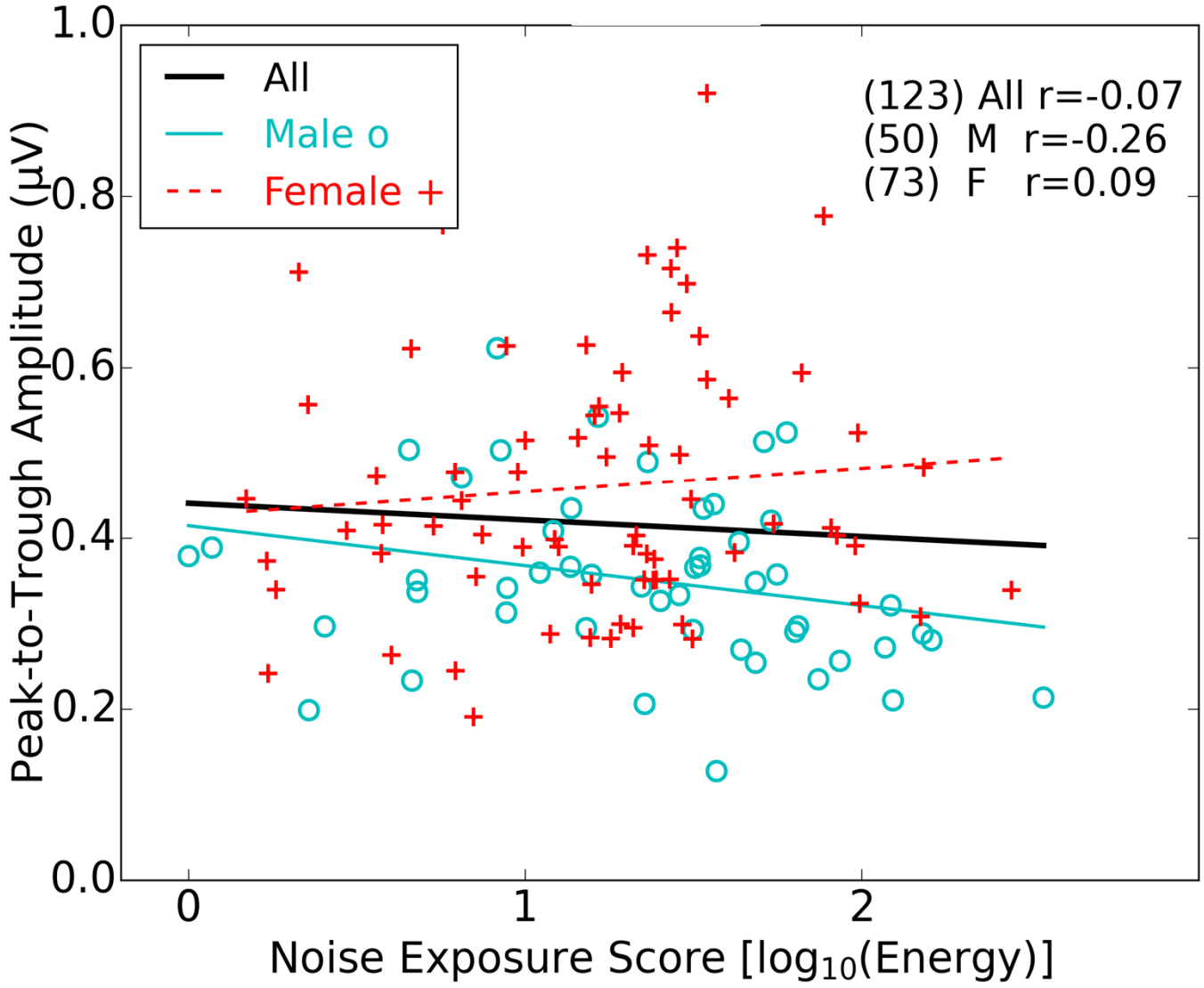
The University of Manchester

ABR Wave III

Manchester Academic Health Science Centre



ABR Wave V


All
Male o
Female +
(123) All r=-0.07
(50) M r=-0.26
(73) F r=0.09
Peak-to-Trough Amplitude (μV)
Noise Exposure Score [log10(Energy)]
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2