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

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ABSTRACT

Objectives

Determine whether auditory brainstem response (ABR) wave I amplitude is associated with measures of auditory perception in young people with normal distortion product otoacoustic emissions (DPOAEs) and varying levels of noise exposure history.

Design

Tinnitus, loudness tolerance, and speech perception ability were measured in 31 young military Veterans and 43 non-Veterans (19-35 years of age) with normal pure tone thresholds and DPOAEs. Speech perception was evaluated in quiet using NU-6 word lists and in background noise using the words in noise (WIN) test. Loudness discomfort levels were measured using 1, 3, 4, and 6 kHz pulsed pure tones. DPOAEs and ABRs were collected in each participant to assess outer hair cell (OHC) and auditory nerve function.

Results

The probability of reporting tinnitus in this sample increased by a factor of 2.0 per 0.1 μ V decrease in ABR wave I amplitude (90% Bayesian confidence interval = 1.2 to 4.2) for males and by a factor of 2.2 (90% confidence interval = 1.1 to 5.1) for females after adjusting for sex and DPOAE level. No apparent relationship was found between wave I amplitude and either loudness tolerance or speech perception in quiet or noise.

Conclusions

Reduced ABR wave I amplitude was associated with a markedly increased risk of tinnitus, even after adjusting for DPOAEs and sex. In contrast, wave III and V amplitudes had little effect on tinnitus risk. This suggests that changes in peripheral input at the level of the inner hair cell (IHC) or auditory nerve may lead to increases in central gain that give rise to the perception of tinnitus. Although the extent of synaptopathy in the study participants cannot be measured directly, these findings are consistent with the prediction that tinnitus may be a perceptual consequence of cochlear synaptopathy.

INTRODUCTION

Tinnitus, hyperacusis, and difficulty understanding speech in background noise are three of the most common complaints reported to audiologists. These perceptual changes are often associated with elevated hearing thresholds, but most puzzling are the cases when patients with normal audiograms present with these problems (Barnea et al. 1990; Anari et al. 1999; Sanchez et al. 2005; Zhao & Stephens 2007; Sheldrake et al. 2015). Cochlear synaptopathy, the selective damage to afferent auditory nerve synapses onto the inner hair cells (IHCs), offers a potential explanation for the presence of these perceptual deficits in individuals who appear audiometrically normal. Cochlear synaptopathy was originally described in animal models in response to noise exposure and aging (Kujawa & Liberman 2009; Lin et al. 2011; Sergeyenko et al. 2013), but recent physiological data and temporal bone studies suggest that synaptopathy may also affect humans (Makary et al. 2011; Konrad-Martin et al. 2012; Viana et al. 2015;

Stamper & Johnson 2015; Bramhall et al. 2017). In animal models, the amplitude of wave I of the auditory brainstem response (ABR) is correlated with the number of IHC-afferent fiber synapses, with smaller amplitudes associated with partial loss of nerve fibers (Kujawa & Liberman 2009; Earl & Chertoff 2010; Lin et al. 2011; Sergeyenko et al. 2013; Fernandez et al. 2015). Smaller ABR wave I amplitudes have been observed in humans with normal pure tone thresholds and a significant history of noise exposure compared with individuals with less noise exposure history, which may be an indication of noise-induced synaptopathy (Stamper & Johnson 2015; Bramhall et al. 2017). However, other studies of young people with normal audiometric thresholds and varying levels of noise exposure have not shown a noise-related decrease in ABR wave I amplitude (Prendergast et al. 2017; Guest et al. 2017). Age-related reductions in ABR wave I amplitude have been demonstrated in humans (Konrad-Martin et al. 2012; Bramhall et al. 2015) and are consistent with temporal bone studies showing auditory neuronal and synaptic loss with age (Makary et al. 2011; Viana et al. 2015).

Animal and human studies suggest that the perception of tinnitus and hyperacusis may arise from excess neural activity in the central auditory system in response to decreased peripheral input, such as seen with cochlear synaptopathy (Auerbach et al. 2014; Brotherton et al. 2015). Note that the term hyperacusis used here refers specifically to loudness hyperacusis rather than pain hyperacusis (see Tyler et al. 2014 for a detailed description of the difference between these terms). A study in a mouse model of noise-induced synaptopathy found both reduced ABR wave I amplitude and hyperacusis-like behavior (Hickox & Liberman 2014). In addition, an association has been shown between decreased ABR wave I amplitude and tinnitus in humans with

normal auditory thresholds or thresholds matched to the control group (Schaette & McAlpine 2011; Gu et al. 2012). In both animal and human studies where decreased wave I amplitude was observed, wave V amplitude was either unchanged or was increased compared with animals/individuals with more normal wave I amplitudes (Schaette & McAlpine 2011; Gu et al. 2012; Sergeyenko et al. 2013; Stamper & Johnson 2015; Bramhall et al. 2017). Given that wave V of the ABR reflects contributions from central auditory nuclei, the absence of a decrease in wave V amplitude in individuals with decreased wave I amplitude has been interpreted as evidence of either central hyperactivity or loss of inhibition in response to the decreased input from the auditory nerve (Schaette & McAlpine 2011; Gu et al. 2012). Central compensatory changes resulting from cochlear synaptopathy may explain the seemingly paradoxical complaints of tinnitus and hyperacusis in patients with normal audiograms. This is supported by the fact that tinnitus and hyperacusis often occur together. An estimated 86% of patients who report hyperacusis also experience tinnitus and 27-40% of people with tinnitus report hyperacusis (Sheldrake et al. 2015). However, a recent study of young people with and without tinnitus who were matched for age, sex, and audiometric thresholds up to 14 kHz did not reveal a relationship between ABR wave I amplitude and tinnitus (Guest et al. 2017). One possible explanation for these differing results is that ABR wave I amplitude group differences observed in previous human studies were related to extended high frequency threshold differences between the groups rather than synaptopathy.

In humans, depending on age and cochlear region, approximately 5-15 auditory nerve fibers synapse with each IHC (Viana et al. 2015). In animal models, these fibers

94 vary in terms of their spontaneous firing rate and response threshold. Fibers with low
95 spontaneous rates have high thresholds (i.e. they only respond at high intensity levels),
96 whereas high spontaneous rate fibers have low thresholds (Liberman 1978). Although
97 individual auditory nerve fibers have a limited dynamic range of ~10 to 40 dB (Guinan &
98 Stankovic 1996; Taberner & Liberman 2005), the diverse range of thresholds across
99 fibers enables the auditory system to respond to sounds over a much larger dynamic
100 range. High threshold fibers appear to be particularly vulnerable to noise- and age-
101 related cochlear synaptopathy (Schmiedt et al. 1996; Furman et al. 2013). However,
102 because high threshold fibers do not respond at low stimulus levels, their loss does not
103 affect auditory thresholds (Furman et al. 2013). The high thresholds of these fibers
104 make them less susceptible to the effects of background noise than low threshold fibers
105 (Costalupes et al. 1984). An intact population of high threshold fibers is required to
106 maintain stimulus coding fidelity in the presence of any background noise that saturates
107 the responses of the low threshold fibers (Reiss et al. 2011). This may lead to
108 diminished speech-in-noise perception in individuals suffering from cochlear
109 synaptopathy. This hypothesis is supported by the finding that the combination of
110 smaller ABR wave I amplitudes and elevated pure tone thresholds are associated with
111 poorer performance on the QuickSIN (Bramhall et al. 2015). A study of young music
112 students with high levels of reported noise exposure and normal audiograms showed
113 decreased speech intelligibility in noise compared to controls with less noise exposure
114 (Liberman et al. 2016). In this study, speech-in-noise perception was correlated with the
115 ratio between the summing potential and ABR wave I amplitude, but the music

students also had significantly poorer extended high frequency thresholds than the control group, so this may have impacted the results.

In some cases, complaints of tinnitus, hyperacusis, and difficulty with speech-in-noise perception among individuals with normal audiograms may be related to sub-clinical cochlear damage. In people with normal audiograms, lower distortion product otoacoustic emission (DPOAE) levels and poorer extended high frequency thresholds have been associated with deficits such as tinnitus and difficulty with speech-in-noise perception (Badri et al. 2011; Modh et al. 2014). This highlights the importance of measuring otoacoustic emissions (OAEs) and extended high frequency thresholds in human studies of synaptopathy.

This study investigated the relationship between ABR wave I amplitude and measures of auditory perception among young military Veterans and non-Veterans with normal auditory thresholds and varying degrees of self-reported lifetime noise exposure. Lower ABR wave I amplitudes were strongly associated with the perception of tinnitus. In contrast, speech perception in quiet, performance on the words in noise (WIN) test, and loudness discomfort levels (LDLs) appeared unrelated to ABR wave I amplitude. Without temporal bone analysis, it cannot be confirmed that the study participants who reported tinnitus suffer from cochlear synaptopathy. However, the observed reduction in ABR wave I amplitude in combination with normal DPOAEs is consistent with that interpretation. These findings support the prediction that some forms of tinnitus may be associated with cochlear synaptopathy.

MATERIALS AND METHODS

Participants

One hundred sixteen participants age 19-35 were recruited as part of a larger study previously described by Bramhall et al. (2017). All participants received an audiometric evaluation from a licensed audiologist including tympanometry and air and bone conduction thresholds, screening of cognitive status with the MiniMental Status Examination (MMSE, Par Lutz, FL), and screening of DPOAE levels in response to moderate level stimuli. All participants had normal audiometric thresholds (≤ 20 dB HL) from 0.25-8 kHz, normal middle ear function, normal DPOAEs (criteria described below), and were in good general health with no significant history of otologic or neurologic disorder (including traumatic brain injury). See Bramhall et al. (2017) for additional screening criteria. Data from 10 additional participants are included in this report. A total of 74 participants were enrolled in the study (17 Veterans with a history of significant noise exposure, 14 Veterans with less noise exposure, 27 non-Veteran controls with very limited noise exposure, and 16 non-Veterans with a history of firearm use). Three participants (all non-Veterans) were excluded from the speech perception analysis because they were not native English speakers. After the screening evaluation, all subsequent study measures were taken only in a single ear. If only one ear met the study criteria (based on audiometric air and bone conduction thresholds, DPOAE screening, and tympanometry), that ear was tested. Thirty participants qualified for the study only in a single ear. The reasons for screen failing in the contralateral ear are summarized in a table in the supplemental data (see Supplemental Data Table 1). If both ears qualified for the study, the ear with higher level DPOAEs was tested to

minimize the effects of outer hair cell (OHC) loss. An overview of the participant characteristics is shown in **Table 1**.

Procedures

All study procedures were approved by the Institutional Review Board of the VA Portland Health Care System.

- **Audiometric Testing**

Pure tone thresholds for the standard audiometric frequencies (0.25-8 kHz) were assessed in all potential participants as part of the screening evaluation. In addition, audiometric thresholds from 9-16 kHz were measured in 48 out of 74 qualifying participants using Sennheiser HDA 200 headphones (Old Lyme, CT). Thresholds from 9-16 kHz were obtained from 8 additional participants (7 Veterans and 1 non-Veteran) when they participated in other research studies. Two of these participants were tested 2-4 months before the study described here and the other 6 were tested 2-2.5 years later.

- **Electrophysiological Testing**

Electrophysiological testing was completed using an Intelligent Hearing Systems SmartEP system (Miami, FL) and Etymotic Research gold foil ER3-26A tiptrode electrodes (Elk Grove Village, IL) placed in the ear canal. The reference electrode was placed on the high forehead and the ground on the low forehead. Waveforms were generated using alternating polarity 4 kHz toneburst stimuli at 80, 90, 100, and 110 dB

peak-to-peak equivalent SPL (dB p-pe SPL). The stimuli were 2 ms in duration with a rise/fall time of 0.5 ms and a Blackman envelope. The ABR response was band-pass filtered from 10-1500 Hz and averaged across 2048 presentations of the 80, 90 and 100 dB p-pe SPL stimuli and 1024 presentations of the 110 dB p-pe SPL stimuli. A stimulus repetition rate of 11.1/sec was used and 2 replications of each waveform were obtained. Electrode impedance was less than 5 kOhms, with the exception of 2 participants who had impedance values of less than 12 kOhms. The positive peak and following negative trough for waves I, III, and V were initially identified with an automated Python-based peak picking program (adapted from Buran 2015) and then evaluated by an experienced audiologist and reassigned if appropriate. Wave I and III amplitudes were defined as the difference between the voltage at the positive peak and the voltage at the following negative trough. The amplitude of wave V was calculated as the difference between the peak voltage and the average prestimulus baseline voltage calculated for the 1 ms time period before stimulus presentation. Waves I, III, and V were easily identified at the 100 and 110 dB p-pe SPL stimulus levels for all participants, and for all but 4 participants at 90 dB p-pe SPL. For some participants, wave I could not be identified at 80 dB p-pe SPL, resulting in less data at that level.

• **Otoacoustic Emissions Testing**

DPOAE testing was conducted using a custom system that includes an ER-10 B+ probe microphone and EMAN software from Boys Town National Research Hospital (Neely & Liu 1993). DPOAEs were screened in all participants as part of study candidacy using a primary frequency sweep (DP-gram) from $f_2 = 1 - 8$ kHz in 1/6-octave increments at

stimulus frequency levels of $L_1=65$ and $L_2=55$ dB SPL. Measurement based stopping rules were employed in which averaging continued until 48 seconds of artifact-free data were collected, until the noise floor was below -30 dB SPL or the signal noise ratio was ≥ 30 dB. Responses from 1.5-6 kHz were compared with the 90th and 95th percentile of a large study of DPOAEs gathered from individuals with abnormal pure tone thresholds (Gorga et al. 1997). Only individuals at or above the 90th percentile at all tested frequencies and below the 95th percentile at no more than one tested frequency were included in the study.

- **Assessment of Noise Exposure History**

All potential participants were asked several questions about their lifetime noise exposure history (occupational, military, and recreational) and use of hearing protection during a short interview (as described in Bramhall et al. 2017). The Lifetime Exposure of Noise and Solvents Questionnaire (LENS-Q) was completed by all non-Veteran participants (Gordon et al. 2016; Bramhall et al. 2017), but was completed as part of another study for many of the Veterans and the data was only available for 20 out of 31 Veterans (11 assigned to the Veteran High Noise group and 9 assigned to Veteran Low Noise group). The interview and questionnaire were scored as described previously to assign participants to noise exposure groups (Bramhall et al. 2017). An overview of the participant characteristics in each noise exposure group is shown in **Table 1**. Additional details about the noise exposure groups, such as audiometric thresholds and DPOAE levels, are described in Bramhall et al.

230 • **Speech Perception Testing**

231 Speech perception performance was assessed in quiet at both 60 and 90 dB HL
232 using recorded 50 token Northwestern University Auditory Test 6 (NU-6) word lists 2A
233 and 3A. Speech-in-noise perception was evaluated with the WIN (Wilson et al. 2007).
234 Multitalker babble was presented at 80 dB HL and the target speech varied in 4 dB
235 steps for a range of signal-to-noise ratios from 0-24 dB. WIN lists 1 and 2 were
236 presented to each participant. All speech tests were presented from the VA Speech
237 Recognition and Identification Materials, Disc 4.0 (Auditory Research Laboratory, VA
238 Medical Center, Mountain Home, Tennessee) through an audiometer.

240 • **Loudness Discomfort Level (LDL)**

241 An up-down adaptive procedure was used to measure LDL for pulsed pure tones
242 at 1, 3, 4, and 6 kHz using 2 dB steps. Participants were given the following instructions
243 adapted from the Contour Test (Cox et al. 1997): “You will hear sounds that increase
244 and decrease in volume. Pretend you are listening to the radio at that volume. Tell me if
245 the sound is comfortable or uncomfortable. Keep in mind that an uncomfortably loud
246 sound is louder than you would ever choose on your radio no matter what mood you are
247 in.” LDL was defined as the lowest level at which participants reported the volume was
248 uncomfortable at least 50% of the time on ascending trials. A minimum of two
249 responses out of three presentations was required to determine LDL.

251 • **Tinnitus Perception**

All participants completed a short hearing and health history questionnaire, which included a question about the perception of tinnitus. This question asked, “Do you have constant or frequent ringing in the ears?” Participants who responded “yes” to this question were rated as having tinnitus.

Analysis

Given that a relationship between noise exposure group and ABR wave I amplitude was previously demonstrated in this cohort (Bramhall et al. 2017), all analyses used wave I amplitude rather than noise exposure group. Comparing perceptual measures with ABR wave I amplitude, rather than noise exposure group, also offers a more direct assessment of the relationship between auditory nerve activity and any perceptual deficits. The relationship between ABR wave I and each auditory perceptual measure was plotted in an initial analysis. ABR wave I amplitude for a 4 kHz toneburst was used because a large effect of noise exposure group on ABR wave I amplitude was observed at 4 kHz in Bramhall et al. A level of 110 dB p-pe SPL toneburst was chosen because in animal models of synaptopathy and Bramhall et al., the effects of noise exposure on wave I amplitude were largest at higher stimulus levels. Based on this preliminary analysis, further investigation was completed only for the perceptual measure (tinnitus) that was observed to have a strong association with wave I amplitude.

The probability of reporting tinnitus was modeled using Bayesian logistic regression. The regression model included ABR wave I, III, and V amplitudes in response to a 110 dB p-pe SPL 4 kHz toneburst, DPOAE level averaged from 3-8 kHz,

275 and 2- and 3- way interactions of these factors (eg. the interaction between wave I and
276 wave III amplitudes). In addition, an interaction between sex and all ABR and DPOAE
277 effects was included to model the effect of sex on the probability of reporting tinnitus.
278 Although it was not expected that males and females would differ in their probability of
279 reporting tinnitus after accounting for peripheral auditory function, sex was included as a
280 factor in the model because differences in ABR wave I amplitude between males and
281 females have been reported in the literature, with smaller amplitudes for males than
282 females (Trune et al. 1988; Mitchell et al. 1989). The full equation for the model is
283 included in the supplemental data (see Text, Supplemental Digital Content 1). Average
284 DPOAE levels were used in the model rather than pure tone thresholds to specifically
285 adjust for differences in OHC function between participants. If synaptopathy in humans
286 is not confined only to low spontaneous rate fibers, but also affects a small proportion of
287 high spontaneous rate fibers, this may lead to some degree of pure tone threshold
288 elevation. Matching for pure tone thresholds or adjusting for small threshold differences
289 could prevent the detection of a synaptopathic reduction in ABR wave I amplitude. To fit
290 the model, ABR wave I, III, and V amplitudes were averaged over the 2 replicate ABR
291 runs measured on each participant. Due to the method of calculating wave V amplitude
292 (peak to prestimulus baseline), 12 participants had a negative ABR wave V amplitude
293 for 1 run of their ABR waveform. Given that a negative ABR peak amplitude is
294 meaningless and will bias the amplitude value when averaged with the replicate, in
295 instances where a negative amplitude was calculated, only the positive ABR amplitude
296 value from the replicate was used. To facilitate computation, ABR and DPOAE values

were standardized to a mean of zero and standard deviation of one. However, results are shown on the original scales.

Bayesian analysis, in contrast with classical statistical approaches, operates under the principle that all knowledge about any quantity (such as the effects of ABR wave I amplitude on the probability of reporting tinnitus) can be expressed as a probability distribution, with greater probability density concentrated around more plausible parameter values. All inferences, such as effect size estimates and confidence intervals are derived from these probability distributions. 'Knowledge' from this perspective is the combination of subject matter expertise and previous publications, collectively referred to as 'prior probabilities', and data collected in new studies. Bayesian analysis is the method of combining prior probabilities and new experimental data into revised 'posterior probabilities' via Bayes theorem. The relative weight of the priors and the experimental data on the posterior distribution depends on the amount of experimental data and the certainty of the prior belief, which is reflected in the standard deviation of the prior distribution. Priors with a tighter distribution will exert more influence on the posterior distribution, whereas those with a broader distribution will be less influential.

The published prevalence of tinnitus in the study population was used to generate priors on the intercept of the model. This prior for the prevalence of tinnitus was approximately 7.1% (Folmer et al. 2011) with a 90% prior certainty between 1.5-31.3%, which was transformed to the log-odds scale for the logistic regression model. This was chosen to reflect uncertainty about the degree of similarity between the National Health and Nutrition Examination Study (NHANES) subject pool used by

320 Folmer et al. and the current study population. The NHANES data did not include
321 females and had slightly different age groups than the current study. The prior for the
322 main effect of wave I amplitude on the probability of reporting tinnitus was chosen
323 based on published data from Guest et al. (2017) and Schaette and McAlpine (2011)
324 where wave I amplitude was measured in participants with and without tinnitus. The
325 sample mean and standard error for wave I amplitude in tinnitus and control participants
326 from each study was used to simulate 100 datasets. A logistic regression model was
327 then fit to each modeled dataset. Regression coefficients and standard errors were
328 averaged over the simulated datasets for each publication, which provided a prior mean
329 and standard deviation for the effect of wave I amplitude on the probability of reporting
330 tinnitus. This 'meta-analysis' prior induces a 68% prior probability that increasing wave I
331 amplitude decreases the probability of reporting tinnitus. As a sensitivity analysis, the
332 model was refit using a 'skeptical' prior that is centered on zero effect of wave I
333 amplitude on the probability of reporting tinnitus and allows only a 5% prior probability
334 that the effect of wave I amplitude on tinnitus is as strong as that observed by Schaette
335 and McAlpine. Further detail on the calculation of the prior for the effect of wave I
336 amplitude on probability of reporting tinnitus and plots of the meta-analysis and
337 skeptical prior distributions are included in the supplemental data (see Text,
338 Supplemental Digital Content 1). The effects of wave III and V amplitude, DPOAE
339 effects, and interaction effects were given 0-mean priors with larger standard deviations
340 reflecting greater uncertainty about the wave III, wave V, and DPOAE effects on
341 tinnitus. The female-specific effects were given Cauchy priors centered at 0 with a scale
342 parameter of 0.25, allowing for the possibility of unexpectedly large effects of sex on

tinnitus. A summary of the prior distributions used for the analysis is included in the supplemental data (see Text, Supplemental Digital Content 1).

The model was fit using the MCMC procedure in SAS software version 9.4. The posterior was evaluated using 3 chains of 1,000 iterations of the No-U-Turn sampler after a 1,000 sample burn-in period. All parameters had Gelman-Rubin convergence diagnostics below 1.01. Model fit was evaluated using replicate datasets, cumulative residuals, and binned residuals. There was no gross lack of fit of the model. The raw data used in the model can be found in the supplemental data (Supplemental Data Table 2).

RESULTS

DPOAE Levels and ABR Wave I Amplitude

There was no correlation between average DPOAE level from 3-8 kHz and ABR wave I amplitude for a 4 kHz 110 dB p-pe SPL toneburst (**Fig. 1**). This suggests that ABR wave I amplitude differences between participants were not due to differences in OHC function.

ABR Wave I Amplitude and Perceptual Measures

As tinnitus was the only perceptual measure that showed a clear relationship with ABR wave I amplitude (**Fig. 2A**), this measure will be discussed in more detail in the subsequent sections. All participants performed close to 100% for the speech perception in quiet task at both a conversational (60 dB HL) and a high intensity level

(90 dB HL) regardless of their wave I amplitude (**Fig. 2B-C**). ABR wave I amplitude did not appear correlated with speech perception in noise, as measured by the WIN test (**Fig. 2D**). WIN scores are based on the total number of correct responses and are reported as a signal-to-noise ratio threshold, with higher values indicating poorer performance. Normal performance on the WIN is defined as a score between -2 and 6 dB. Pure tone LDLs were measured as an indicator of loudness intolerance and hyperacusis. No clear association between ABR wave I amplitude and LDL was observed (**Fig. 2E**). Only LDLs for the 4 kHz stimulus are plotted because LDLs across frequencies were highly correlated.

ABR Wave I Amplitude and Perception of Tinnitus

An overview of the characteristics of participants with and without tinnitus are shown in **Table 2**. Audiograms and DPOAE levels for both groups are plotted in **Figures 3 and 4**. Extended high frequency thresholds were not obtained for 3 participants with tinnitus (2 males, 1 female) and 15 participants without tinnitus (5 males, 10 females). Only participants who reported tinnitus in the test ear were included in the tinnitus group. All of these participants reported tinnitus in both ears. Perception of constant or frequent tinnitus was reported at a very high rate in the Veteran High Noise group (82%), compared with the Veteran Low Noise group (7%), and the two Non-Veteran groups (0%). Lower ABR wave I amplitudes were strongly associated with report of tinnitus (**Fig. 5**). In contrast, wave III (**Fig. 5A**) and wave V (**Fig. 5B**) amplitudes did not appear associated with tinnitus or wave I amplitude. In response to a 4 kHz toneburst, a mean reduction in ABR wave I amplitude was observed in

participants with tinnitus, with the greatest reduction at the highest stimulus levels (**Fig. 6A**). Results from previous studies of ABR wave I amplitude in audiometrically normal young people with or without tinnitus are also plotted to show the relative effect sizes between studies (Schaette & McAlpine 2011; Guest et al. 2017). A similar reduction in mean amplitude was not observed for wave V (**Fig. 6B**). Participants with tinnitus showed a mean reduction in wave I/V ratio compared with participants without tinnitus (**Fig. 6C**). When comparing the current data with the prior studies, note that there are some differences in terms of the ABR measurements, namely the stimulus in the current study was a 4 kHz toneburst versus a click and the current study used a tiptrode rather than an electrode placed on the mastoid.

The strong relationship between ABR wave I amplitude (for a 4 kHz 110 dB p-pe SPL stimulus) and perception of tinnitus remained when using a Bayesian logistic regression model to adjust for DPOAE and sex differences between participants with and without tinnitus (**Fig. 7**). When wave III amplitude, wave V amplitude, and average DPOAE level from 3-8 kHz were set to the sample means, the probability of tinnitus was close to 0% for large wave I amplitudes and increased rapidly as wave I amplitude decreased (**Fig. 7A**). For example, when wave III amplitude, wave V amplitude, and average DPOAE level from 3-8 kHz were set to the mean values for the whole cohort and sex was set to male, a wave I amplitude of 0.25 μ V was associated with a mean risk of tinnitus of 35% (90% Bayesian confidence interval of 20-54%). In contrast, a wave I amplitude of 0.5 μ V was associated with a mean risk of tinnitus of 8% (90% confidence interval of 2-24%). This translates to a relative risk of 4.1 (90% confidence interval of 1.3-20.7) for a wave I amplitude of 0.25 μ V versus 0.5 μ V or an absolute risk

difference of 26% (90% confidence interval of 6-47%). In contrast, changes in wave III or wave V amplitude had little effect on the probability of tinnitus when DPOAE maximum amplitude at 4 kHz, and the amplitudes of the remaining 2 ABR waves were set to the mean (**Fig. 7B-C**).

Given the abundance of data (74 participants were used in the analysis), using the skeptical prior for the relationship between ABR wave I amplitude and tinnitus in the Bayesian model had little effect on the posterior inferences. Model results using the skeptical prior can be found in the supplemental data (see Text, Supplemental Digital Content 1).

The model suggests a similar relationship between ABR wave amplitude and tinnitus in both males and females, although the predicted probability of reporting tinnitus for a given ABR amplitude and DPOAE level is higher in males than females. One possible explanation for this result is that men are at greater propensity for tinnitus at any given level of peripheral auditory function. This explanation is theoretically ungrounded at present. Alternatively, men may appear at greater risk of tinnitus at a given level of peripheral auditory function as a consequence of sex-related measurement error in the ABR wave I amplitude. In this analysis, the chances of reporting tinnitus are reduced as wave I amplitude ($W1$) increases, so that:

$$\text{Expected log - odds of tinnitus given } W1 = E[\log \text{ odds} | W1] = a - b \cdot W1$$

Compared to females, the ABR wave I amplitude measurement, which is an indirect measure of auditory nerve activity (θ), is biased small in males by a factor ε :

$$\begin{aligned} \text{Male } W1 &= \theta - \varepsilon \\ \text{Female } W1 &= \theta \end{aligned}$$

Therefore, the probability of reporting tinnitus at a particular wave I amplitude can be rewritten for males and females as:

$$\begin{aligned} E[\log \text{odds} | \text{Male}, W1] &= a - b \cdot W1 = a - b \cdot (\theta - \varepsilon) = a - b \cdot \theta + b \cdot \varepsilon \\ E[\log \text{odds} | \text{Female}, W1] &= a - b \cdot W1 = a - b \cdot \theta \end{aligned}$$

The expected probability for males (top row) is bigger than the expected probability for females (bottom row) by a factor of $b \cdot \varepsilon$ since both b and ε are positive. This means that at any given level of observed wave I amplitude, males will have a higher probability of tinnitus than females due to a biased relationship between wave I amplitude and auditory nerve activity.

An alternate male-only Bayesian model reveals similar results to the male-specific analysis of the whole dataset (see Text, Supplemental Digital Content 1), confirming that the observed association between ABR wave I amplitude and tinnitus is not an artifact of sex-related differences in ABR wave I amplitude. Given that only 2 female participants in this study reported tinnitus in the test ear, additional data from females with tinnitus will be necessary to confirm the relationship between ABR wave I amplitude and the probability of reporting tinnitus in females.

DISCUSSION

Noise exposure history was associated with tinnitus probability

The high probability of reporting tinnitus in the Veteran High Noise group compared with the other lower noise exposure groups suggests an association between noise exposure history and tinnitus, with only the individuals with the highest exposures developing tinnitus. Although the relationship between noise exposure and tinnitus is not a new finding, this relationship is usually associated with abnormal pure tone

thresholds. Guest et al. found a relationship between noise exposure history and tinnitus in young people with normal audiograms who were matched for pure tone thresholds out to 14 kHz, but they did not measure OAEs (2017). The clear association between tinnitus and high intensity noise exposure in the current study is remarkable because it is observed in individuals with normal pure tone thresholds and normal DPOAEs. This suggests that the origin of tinnitus in this sample is not related to OHC dysfunction.

Perception of tinnitus was associated with reduced amplitude of ABR wave I, but not wave V

Mean ABR wave I amplitudes were reduced for study participants with tinnitus versus those without tinnitus, but this was not the consequence of an overall reduction in all ABR peak amplitudes. An increase in the gain of the central auditory system in response to reduced peripheral input has been proposed as a possible mechanism of tinnitus generation (Wang et al. 2011; Auerbach et al. 2014; Brotherton et al. 2015). Tinnitus-related central neuronal hyperactivity in response to cochlear damage has also been illustrated through computational modeling studies (Schaette & Kempster 2006; Schaette & Kempster 2009; Norena 2011). Although reduced peripheral input is generally assumed to result from outer hair cell loss and be associated with auditory threshold elevation, loss of cochlear synaptic connections would also decrease peripheral input. In the present and previous studies, individuals with tinnitus and normal auditory thresholds show a reduction in wave I amplitude compared with individuals without tinnitus, but do not demonstrate a similar reduction in wave V

amplitude (Schaette & McAlpine 2011). In fact, Gu et al. found a reduction in wave I amplitude and an increase in wave V amplitude when comparing individuals with tinnitus to age-, sex-, and threshold-matched individuals without tinnitus (2012). This suggests hyperactivity or loss of inhibition may develop in the auditory brainstem after a reduction in input from the auditory nerve and lead to the perception of tinnitus. A recent study showing increased spontaneous activity in the inferior colliculus of mice with noise-induced cochlear synaptopathy also suggests that tinnitus may be a consequence of cochlear synaptic degeneration (Hesse et al. 2016).

Although the presence of cochlear synaptopathy in the study participants with tinnitus cannot be confirmed without post-mortem histological analysis, these findings are consistent with the hypothesis that cochlear synaptic loss is associated with the perception of tinnitus. The cross-sectional nature of this study prohibited comparing ABR wave I amplitudes within subjects before and after the onset of tinnitus, but a prospective study of individuals who will be exposed to high intensity sounds would help confirm these results.

ABR wave I amplitude and speech perception appeared unrelated

No effect of ABR wave I amplitude on speech perception in quiet was observed. This is not surprising considering the relative ease of this task for individuals with normal pure tone thresholds. Additionally, even in the presence of synaptopathy, one would expect relatively good performance on this task as both low and high threshold fibers could contribute.

ABR wave I amplitude was also not correlated with performance on the WIN test. There are several possible explanations for the lack of a wave I amplitude effect on WIN performance: 1) The participants in this cohort do not have synaptopathy and therefore do not show the predicted effects on speech-in-noise perception, 2) These participants have synaptopathy and related speech perception in noise deficits, but the WIN test does not adequately assess this problem (e.g., because it is not sufficiently difficult), 3) Synaptopathy alone (i.e., in the absence of elevated pure tone thresholds) does not have an adverse impact on speech perception in noise. As suggested by previous work, the perceptual effects of synaptopathy may become more evident when combined with elevated pure tone thresholds (Bramhall et al. 2015). Further studies of synaptopathy in humans will be necessary to distinguish between these possibilities. More complex speech-in-noise perception tasks, such as those that specifically require access to temporal fine structure may yield different results.

ABR wave I amplitude was not associated with loudness tolerance

Analysis of loudness tolerance showed no clear relationship between ABR wave I amplitude and LDLs. Mean LDLs were lower than those reported in a normative sample of young people with normal audiometric thresholds from 500-6000 Hz (Sherlock & Formby 2005). This may be due to differences in the test instructions provided to the participants. LDL was measured as an indicator of hyperacusis, but recent studies suggest LDL alone is not a reliable metric for this purpose (Sheldrake et al. 2015; Zaugg et al. 2016). Therefore, it is difficult to draw any conclusions about the relationship between ABR wave I amplitude and hyperacusis from this result. In future

studies, use of hyperacusis questionnaires in combination with measures of loudness growth may help determine if hyperacusis is associated with reduced ABR wave I amplitudes.

Current clinical tests are not sensitive to all noise-related auditory changes

The results of this study in combination with previous work (Bramhall et al. 2017) indicate that high intensity noise exposure is associated with tinnitus and ABR wave I amplitude reductions even when auditory thresholds, OAEs, and clinical measures of speech perception are normal. This suggests that damage to the auditory system can occur in humans after noise exposure without showing up on a clinical audiology assessment. Although it is not clear whether this noise-induced damage adversely affects speech perception in noise or hyperacusis, the damage is clearly associated with tinnitus. The high prevalence of tinnitus highlights the importance of developing new clinical tests that are sensitive to cochlear synaptopathy.

Comparison to other studies

The relationship between reduced ABR wave I amplitude and tinnitus observed in the present study is consistent with a previous report of smaller mean ABR wave I amplitudes in individuals with normal pure tone thresholds who have tinnitus versus those without tinnitus (Schaette & McAlpine 2011). Also in agreement with this previous study is the lack of a mean decrease in wave V amplitude in the participants with tinnitus.

The absence of tinnitus in the Non-Veteran Firearms group despite the previously demonstrated reduction of ABR wave I amplitudes in this group (Bramhall et al. 2017) was surprising. This may indicate a threshold of noise exposure (and by extension reduction in ABR wave I amplitude) that must be reached before tinnitus is induced. This could translate into a percent reduction in the number of IHC-auditory nerve synapses that must be lost to initiate an increase in central gain large enough to result in the perception of tinnitus.

Guest et al. found an association between reported lifetime noise exposure history and tinnitus in young adults with normal auditory thresholds (2017). However, unlike the results presented here and in Bramhall et al. (2017), ABR wave I amplitude was not correlated with noise exposure or tinnitus. In contrast to the present study, where participants were recruited based on their noise exposure history and screened with DPOAEs to ensure relatively normal OHC function, Guest et al. recruited participants based on the presence/absence of tinnitus and a normal audiogram. Although the tinnitus and non-tinnitus groups were matched on audiometric thresholds out to 14 kHz, OAEs were not measured. Because OAEs are pre-neural responses generated by the OHCs, it seems reasonable to assert that DPOAEs, or evoked OAEs in general, are necessary to rule out the effects of noise on OHC function. In humans, OAE level shifts are observed more often than pure tone threshold shifts when the two tests are compared at corresponding audiometric frequencies after exposure to noise (Engdahl & Kemp 1996; Seixas et al. 2005; Marshall et al. 2009) or ototoxic drugs (Mulheran & Degg 1997; Ozturan & Lam 1998; Littman et al. 1998; Katbamna et al. 1999; Stavroulaki et al. 2001; Stavroulaki et al. 2002). It is possible that noise-related

OHC damage may have contributed to the perception of tinnitus in some of the Guest et al. study participants. Additionally, tinnitus is a heterogeneous disorder with many potential mechanisms other than synaptopathy (Henry et al. 2014). By recruiting based on the perception of tinnitus, they may have increased the likelihood of including a greater variety of tinnitus etiologies in their study. The presence of tinnitus unrelated to noise exposure in their sample may have obscured their results. This seems likely given that the noise exposure scores for several of the individual tinnitus participants were similar to the scores seen in the non-tinnitus controls.

Bramhall et al. (2015) investigated the relationship between speech perception in noise and ABR wave I amplitude across individuals of a variety of ages with 4 frequency pure tone averages (for 0.5, 1, 2 and 4 kHz) ranging from approximately 0 – 40 dB HL. They found that lower ABR wave I amplitudes were associated with poorer performance on the QuickSIN, but there was an interaction with pure tone average, with a greater wave I amplitude effect seen in individuals with poorer audiometric thresholds. In that study, participants with normal pure tone thresholds showed little effect of ABR wave I amplitude on their speech in noise perception. These results are consistent with the apparent lack of association between ABR wave I amplitude and the WIN in the current study.

In a study design similar to the present study, Liberman et al. divided young adults with normal pure tone thresholds from 250-8000 Hz into two groups based on their self-reported noise exposure history (2016). As in the present study, they observed similar speech perception performance in quiet for both noise exposure groups. However, they also found a significant decrease in speech-in-noise perception for males

with higher reported noise exposure compared with those with lower exposure. These contradictory findings may be due to differences in study design (both studies used NU-6 word lists, but in the Liberman study words were presented at 35 dB HL with a white noise masker versus the current study where words were presented at 80 dB HL in multitalker babble), group differences in the extended high frequency thresholds and DPOAEs for the Liberman study, or simply an artifact of sampling variability.

CONCLUSIONS

This study investigated the relationship between ABR wave I amplitude and three aspects of auditory perception (tinnitus, speech perception, and loudness discomfort levels) in young military Veterans and non-Veterans with normal auditory thresholds and DPOAEs. Perception of frequent or constant tinnitus was associated with a reduction in ABR wave I amplitude, but not wave V amplitude. The relationship between ABR wave I amplitude and tinnitus remained after adjusting for differences in sex and DPOAE levels between participants. Although the presence of cochlear synaptopathy cannot be confirmed in the participants with lower ABR wave I amplitudes, this suggests a link between synaptopathy and tinnitus. Speech perception, both in quiet and in noise, and loudness discomfort levels did not appear correlated with ABR wave I amplitude, but this should be interpreted with caution as it may be a consequence of the specific perceptual measures used in this study.

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Figure Legends

Figure 1. Relationship between average DPOAE level and ABR wave I amplitude

Auditory brainstem response (ABR) wave I amplitude for a 110 dB p-pe dB SPL 4 kHz stimulus was not correlated with average distortion product otoacoustic emission (DPOAE) level from 3-8 kHz. Mean ABR wave I amplitudes (across replications) and average DPOAE levels from 3-8 kHz are plotted for individual participants. A LOESS smooth line was fit to the data.

Figure 2. Relationship between ABR wave I amplitude and perceptual measures

Auditory brainstem response (ABR) wave I amplitude (for a 110 dB p-pe SPL 4 kHz stimulus) is associated with perception of tinnitus, but does not appear correlated with the other perceptual measures. Scatterplots show the relationship between ABR wave I amplitude and self-report of tinnitus (A), speech perception in quiet at 60 (B) and 90 (C) dB HL, performance on the words in noise (WIN) test (D), and loudness discomfort level (LDL) (E) at 4 kHz. In each subplot, a LOESS smooth line was fit to the data.

Figure 3. Audiometric pure tone thresholds by tinnitus group

Audiometric pure tone thresholds for the test ear are shown for individual study participants (thin lines) as well as the mean thresholds for the tinnitus and no tinnitus groups (thick lines). Pure tone thresholds were measured for all participants from 0.25-8 kHz (A) and in 56 participants from 9-16 kHz (B).

Figure 4. DPOAE levels across frequency by tinnitus group

DPOAE levels are shown for individual study participants (thin lines) in response to a 65/55 dB SPL stimulus at f_2 frequencies of 1-8 kHz. Mean DPOAE levels for the tinnitus and no tinnitus groups are shown with thick lines.

Figure 5. Relationship between ABR peak amplitudes for individual participants

Auditory brainstem response (ABR) wave I amplitude was reduced in participants with tinnitus, but wave III and V amplitudes appeared independent of wave I amplitude and tinnitus perception. Combined scatterplots and boxplots show individual ABR peak amplitudes for a 4 kHz 110 dB p-pe SPL stimulus from males and females with and without tinnitus. Replicate ABR runs for each participant were averaged together to generate a mean amplitude. The scatterplots show mean ABR wave I amplitude versus mean wave III (A) or wave V (B) amplitude. Wave I and III amplitudes were calculated as the voltage difference between the wave peak and the following trough. Wave V amplitude was calculated as the difference between the wave peak and the prestimulus baseline. Males are indicated with stars and females with circles. Filled symbols indicate participants who reported tinnitus. Boxplots show the relationship between wave I, III, and V amplitudes and report of tinnitus. The bottom, midline, and top of the boxes represent the 1st quartile, median, and 3rd quartile respectively, while the end of the whiskers indicate the points furthest from the box that still fall within 1.5 interquartile ranges from the edges of the box. Open circles indicate values outside of this range.

Figure 6. Relationship between ABR peak amplitudes and tinnitus across level

Auditory brainstem response (ABR) wave I amplitude was reduced in the participants with tinnitus, but a similar reduction was not observed for wave V amplitude. ABR amplitudes were measured in response to a 4 kHz toneburst stimulus at 80, 90, 100, and 110 dB p-pe SPL. Mean wave I amplitude (A), wave V amplitude (B), and wave V/I amplitude ratio (C) were calculated for study participants with and without tinnitus. Wave I amplitude was calculated as the voltage difference between the wave peak and the following trough. Wave V amplitude was calculated as the difference between the wave peak and the prestimulus baseline. Error bars indicate the standard error of the mean. The wave I amplitudes reported by Schaette and McAlpine (2011) and Guest et al. (2017) in response to a click at 90 and/or 100 dB p-pe SPL are also plotted in panels A and B (indicated by “S” and “G”) for comparison. A split axis is used in panel B to facilitate this comparison. Note that in the previous studies, mastoid electrodes were used rather than a tiptrode.

Figure 7. ABR wave I, III, and V amplitudes and the probability of reporting tinnitus

The amplitude of auditory brainstem response (ABR) wave I, but not waves III or V, can be used to predict the probability of reporting tinnitus. Results from a Bayesian logistic regression model are plotted to show the relationship between ABR wave I (A), III (B), and V (C) amplitudes (for a 110 dB p-pe SPL 4 kHz stimulus) and the posterior probability of reporting tinnitus. For each subplot, average distortion product otoacoustic emission (DPOAE) levels from 3-8 kHz and the 2 ABR waves not shown on the x-axis of the subplot are set to the mean value for the whole data set. For example, in panel A, average DPOAE level is set to 4.7 dB SPL, wave III amplitude is set to 0.14 μ V, and

wave V amplitude is set to 0.31 μ V. The dark and light shaded regions indicate the inter-quartile range and 90% Bayesian confidence interval respectively. Dots indicate the ABR wave amplitudes for participants with (top) and without (bottom) tinnitus. Dots are jittered vertically to make them easier to visualize.

884 **Figure 1**

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899 **Table 1. Participant Characteristics by Noise Exposure Group**

	Non-Veteran	Non-Veteran Firearms	Veteran Low Noise	Veteran High Noise
Age in years	25.4 (4.2)	25.8 (4.2)	29.7 (4.2)	26.7 (2.3)
Number of males	7	7	6	15
PTA (0.5, 1, & 2 kHz) – in dB HL	6.9 (4.1)	6.7 (3.0)	9.4 (4.8)	10.3 (5.6)
High frequency PTA (3, 4, & 6 kHz) – in dB HL	2.1 (4.5)	4.1 (5.0)	4.5 (3.6)	9.2 (4.9)
LENS-Q score	4.3 (0.6)	13.2 (2.4)	10.8 (3.4)	15.9 (0.8)
Speech in quiet (60 dB HL)	98.3% (1.7)	98.8% (1.4)	97.7% (2.2)	97.3% (2.4)
Speech in quiet (90 dB HL)	96.7% (2.2)	97.4% (2.0)	97.7% (1.7)	97.3% (3.5)
ABR wave I amplitude (µV)	0.41 (0.11)	0.33 (0.10)	0.38 (0.13)	0.30 (0.09)
WIN (dB SNR)	4.0 (1.1)	3.5 (1.1)	4.6 (1.4)	4.8 (1.4)
LDL – 1 kHz (dB HL)	89.3 (10.4)	88.4 (9.5)	89.9 (8.3)	88.3 (9.2)
LDL – 3 kHz (dB HL)	84.2 (9.1)	83.1 (8.2)	83.1 (5.5)	82.3 (8.8)
LDL – 4 kHz (dB HL)	81.8 (9.9)	81.1 (9.5)	81.1 (5.9)	80.2 (10.1)
LDL – 6 kHz (dB HL)	78.0 (13.7)	75.3 (10.1)	72.6 (8.6)	74.6 (10.9)
Report tinnitus	0	0	1	14
Total participants	27	16	14	17

900
901 Participant characteristics are shown for each of the 4 noise exposure groups. Except for
902 “number of males”, “report tinnitus”, and “total participants”, all values are group means with
903 standard deviations in parentheses. The pure tone average (PTA) is the average of the pure
904 tone thresholds at 0.5, 1 and 2 kHz, while the high frequency PTA consists of the thresholds at
905 3, 4, and 6 kHz. The score on the Lifetime Exposure of Noise and Solvents Questionnaire
906 (LENS-Q) provides a measure of lifetime noise exposure to occupational, military, and
907 recreational noise sources. The LENS-Q is scored on a log scale where lower scores indicate
908 less noise exposure and higher scores indicate more exposure. Auditory brainstem response
909 (ABR) wave I amplitude is reported for a 4 kHz 110 dB p-pe SPL toneburst. Perceptual
910 measures include speech in quiet at 60 and 90 dB HL, the words in noise (WIN) test, loudness
911 discomfort levels (LDLs) at 4 frequencies, and report of tinnitus. SNR is signal-to-noise ratio.

912

913

914 **Table 2. Participant Characteristics by Tinnitus Group**

	Tinnitus	
	No	Yes
Total Participants	59	15
Age		
Mean	26.7	26.3
Min	19	21
Max	35	30
Sex		
Males	22	13
Females	37	2

925 Overview of age and sex for study participants with and without tinnitus.

926

Supplemental Data

Detailed Description of Bayesian Logistical Regression

The data used for this analysis are included in Supplemental Data Table 2 below.

Equation for the model:

The log-odds of the i th subject having tinnitus (η_i) are represented by the following equation:

$$\begin{aligned}\eta_i = & a + b \cdot W1_i + c \cdot W3_i + d \cdot W5_i \\ & + e \cdot W1_i \cdot W3_i + f \cdot W1_i \cdot W5_i + g \cdot W3_i \cdot W5_i \\ & + h \cdot W1_i \cdot W3_i \cdot W5_i + j \cdot DPOAE_i \\ & + [Sex_i = female] \cdot (a^{fem} + b^{fem} \cdot W1_i + c^{fem} \cdot W3_i + d^{fem} \cdot W5_i \\ & + e^{fem} \cdot W1_i \cdot W3_i + f^{fem} \cdot W1_i \cdot W5_i + g^{fem} \cdot W3_i \cdot W5_i \\ & + h^{fem} \cdot W1_i \cdot W3_i \cdot W5_i + j^{fem} \cdot DPOAE_i)\end{aligned}$$

$W1_i$ = wave I amplitude for the i th subject

$W3_i$ = wave III amplitude for the i th subject

$W5_i$ = wave V amplitude for the i th subject

$DPOAE_i$ = average DPOAE level from 3-8 kHz for the i th subject

$a, b, c, d, e, f, g, h, j$ = coefficients for the model predictors

fem superscript = female specific adjustment to the model parameters

The first three lines of the model pertains to both males and females, while the last three lines adjust the model for effects in females only.

Prior distributions:

$a \sim \text{Normal}(-2.5, \text{sd}=1)$

b (meta-analytic prior) $\sim \text{Normal}\left(\frac{\frac{-0.01}{0.26^2 + \tau^2} + \frac{-1.11}{0.62^2 + \tau^2}}{\frac{1}{0.26^2 + \tau^2} + \frac{1}{0.62^2 + \tau^2}}, \frac{1}{\frac{1}{0.26^2 + \tau^2} + \frac{1}{0.62^2 + \tau^2}}\right) *$

b (skeptical prior) $\sim \text{Normal}(0, \text{sd} = 0.69)$

948 $c, d \sim \text{Normal}(0, \text{sd} = 0.5)$

949 $e, f, g, h, j \sim \text{Normal}(0, \text{sd} = 0.25)$

950 $(c, d, e, f, g, h, j)^{fem} \sim \text{Cauchy}(0, \text{scale} = 0.25)$

951 *The parameter τ is the average absolute difference between studies in terms of the
952 effect of ABR wave I amplitude on the risk of tinnitus (b). τ is given a half-normal prior
953 with scale parameter equal to 1, which gives 95% prior certainty that the average
954 absolute difference between studies is less than 2.5 on the log-odds scale.

955

956

Detailed description of prior distributions for b :

Meta-analytic prior:

A meta-analytic prior for the main effect of ABR wave I amplitude on the risk of tinnitus (parameter b) was generated based on published data from Schaette and McAlpine (2011) and Guest et al. (2017). One hundred datasets were simulated according to each publication's estimated mean and standard error of wave I amplitude for tinnitus and control participants. A logistic regression model was then fit to each simulated dataset after standardizing the simulated wave I amplitude to our dataset mean and standard deviation (mean=0.22, standard deviation=0.1). Regression coefficients and standard errors were averaged over the simulated datasets for each publication, which provided a prior mean and standard deviation on the regression coefficient b . For the Schaette and McAlpine study, b was estimated at -1.11 (SE = 0.62). For the Guest et al. study, b was estimated as -0.01 (SE = 0.26). These estimates were combined to give the meta-analytic prior on b shown above, where the distribution is parameterized in terms of its mean and variance (Spiegelhalter et al. 2004). This prior is shown in Supplemental Data Figure 1, with the b parameter back transformed to express the relative odds on tinnitus per 0.1 μ V increase in wave I amplitude. The vertical reference lines show the back-transformed relative odds estimates of Schaette and McAlpine and Guest et al.. This prior on b induces a 68% prior probability that increasing wave I amplitude decreases the risk of tinnitus.

Supplemental Data Figure 1. Meta-analytic prior distribution

The meta-analytic prior distribution for b is plotted to show the relative odds of tinnitus per 0.1 μ V increase in ABR wave I amplitude. A value of 1 for the relative odds of tinnitus suggest no relationship between ABR wave I amplitude and risk of tinnitus (as shown by the line indicating the Guest et al. findings). A value of less than one indicates an increased risk of tinnitus as ABR wave I decreases (as shown by the line indicating the Schaette and McAlpine findings). This prior distribution confers a 68% probability that increasing wave I amplitude reduces the risk of tinnitus. This is calculated by taking the integral of the portion of the distribution that is less than 1.

Skeptical prior:

The model was refit using a 'skeptical' prior on b that is centered on zero effect and allows only 5% prior probability that the effect of wave I is as strong as that observed by Schaette and McAlpine. This induces the prior on the odds ratio shown in Supplemental Data Figure 2.

Supplemental Data Figure 2. Skeptical prior distribution

The skeptical prior distribution for b is plotted to show the relative odds of tinnitus per 0.1 μV increase in ABR wave I amplitude. This prior distribution confers a 5% probability that the effects of ABR wave I amplitude on risk of tinnitus are at least as strong as what was reported by Schaette and McAlpine. This is calculated by taking the integral of the portion of the distribution that is below the Schaette and McAlpine line.

Supplemental Data Figure 3. Predicted relationships between ABR wave amplitudes and tinnitus using the skeptical prior

The model results using the skeptical prior show similar trends to the results using the meta-analytic prior. The amplitude of auditory brainstem response (ABR) wave I, but not waves III or V, can be used to predict the probability of reporting tinnitus. Results from a Bayesian logistic regression model are plotted to show the relationship between ABR wave I (A), III (B), and V (C) amplitudes (for a 110 dB p-pe SPL 4 kHz stimulus) and the posterior probability of reporting tinnitus. For each subplot, average distortion product otoacoustic emission (DPOAE) levels from 3-8 kHz and the 2 ABR waves not shown on the x-axis of the subplot are set to the mean value for the whole data set. For example, in panel A, average DPOAE level is set to 4.7 dB SPL, wave III amplitude is set to 0.14 μ V, and wave V amplitude is set to 0.31 μ V. The dark and light shaded regions indicate the inter-quartile range and 90% Bayesian confidence interval respectively. Dots indicate the ABR wave amplitudes for participants with (top) and without (bottom) tinnitus. Dots are jittered vertically to make them easier to visualize.

Supplemental Data Figure 4. Predicted relationships between ABR wave amplitudes and tinnitus for the male-only analysis

The male-only model results show similar trends to the male-specific results for the analysis of the whole dataset. The amplitude of auditory brainstem response (ABR) wave I, but not waves III or V, can be used to predict the probability of reporting tinnitus. Results from a Bayesian logistic regression model are plotted to show the relationship between ABR wave I (A), III (B), and V (C) amplitudes (for a 110 dB p-pe SPL 4 kHz stimulus) and the posterior probability of reporting tinnitus. For each subplot, average distortion product otoacoustic emission (DPOAE) levels from 3-8 kHz and the 2 ABR waves not shown on the x-axis of the subplot are set to the mean value for the whole data set. For example, in panel A, average DPOAE level is set to 4.7 dB SPL, wave III amplitude is set to 0.14 μV , and wave V amplitude is set to 0.31 μV . The dark and light shaded regions indicate the inter-quartile range and 90% Bayesian confidence interval respectively. Dots indicate the ABR wave amplitudes for participants with (top) and without (bottom) tinnitus. Dots are jittered vertically to make them easier to visualize.

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1140

1141 **Supplemental Data Table 1: Screen fail reasons for non-test ear**

Screen Fail Reason	Non-Veteran	Non-Veteran Firearms	Veteran Low Noise	Veteran High Noise
Tympanogram	3	1	0	0
DPOAEs	7	2	5	4
Threshold >25 dB HL	1	0	2	4
Air-bone gap >15 dB	0	0	0	1
Total	11	3	7	9

1142

1143 All study participants were required to pass an audiometric screening to qualify for study
1144 participation. Thirty participants only qualified for the study in one ear. The reasons for
1145 screen failing in the non-test ear are broken down for each noise exposure group.

1146

1147 **Supplemental Data Table 2: Data used in Bayesian logistic regression model**

1148

<i>ID</i>	<i>Tinnitus</i>	<i>Sex</i>	<i>Mean</i>			
			<i>DPOAE</i>	<i>Wave I</i>	<i>Wave III</i>	<i>Wave V</i>
1	Yes	Male	4.338	0.187	0.101	0.267
2	Yes	Male	3.540	0.332	0.244	0.279
3	Yes	Male	1.168	0.163	0.162	0.267
4	Yes	Female	3.880	0.380	0.172	0.213
5	Yes	Male	0.952	0.362	0.160	0.196
6	No	Female	-0.320	0.378	0.171	0.297
7	Yes	Male	-0.806	0.172	0.012	0.469
8	No	Female	4.416	0.212	0.040	0.225
9	Yes	Male	2.604	0.275	0.260	0.200
10	No	Male	7.054	0.326	0.307	0.519
11	No	Female	-2.384	0.334	0.165	0.290
12	No	Male	8.704	0.254	0.192	0.221
13	No	Female	10.028	0.264	0.189	0.345
14	No	Female	5.818	0.341	0.150	0.264
15	No	Female	-2.334	0.391	0.135	0.098
16	No	Female	4.084	0.334	0.226	0.291
17	No	Female	6.502	0.473	0.087	0.254
18	No	Female	4.046	0.403	0.108	0.175
19	No	Female	0.432	0.562	0.122	0.507
20	No	Female	3.368	0.276	0.289	0.582
21	No	Female	11.216	0.229	0.103	0.722
22	No	Male	6.998	0.299	0.095	0.422
23	Yes	Male	1.474	0.353	0.168	0.108
24	No	Male	1.576	0.650	0.154	0.296
25	No	Male	5.694	0.520	0.106	0.395
26	No	Male	0.140	0.239	0.082	0.273
27	Yes	Male	5.436	0.436	0.029	0.545
28	No	Female	0.192	0.345	0.084	0.293

<i>ID</i>	<i>Tinnitus</i>	<i>Sex</i>	<i>Mean</i>			
			<i>DPOAE</i>	<i>Wave I</i>	<i>Wave III</i>	<i>Wave V</i>
29	No	Female	9.958	0.352	0.038	0.436
30	No	Female	9.696	0.326	0.207	0.270
31	No	Male	5.516	0.338	0.184	0.130
32	No	Female	5.150	0.517	0.114	0.224
33	No	Male	4.782	0.391	0.247	0.172
34	No	Male	2.498	0.252	0.034	0.413
35	No	Female	5.816	0.340	0.068	0.458
36	No	Female	9.330	0.422	0.218	0.323
37	No	Female	2.672	0.417	0.162	0.474
38	No	Male	0.442	0.331	0.170	0.232
39	No	Female	6.182	0.471	0.191	0.316
40	No	Female	7.564	0.363	0.163	0.646
41	No	Male	4.600	0.274	0.160	0.066
42	Yes	Male	-0.916	0.423	0.082	0.466
43	No	Male	6.158	0.548	0.038	0.481
44	Yes	Male	2.310	0.262	0.183	0.406
45	No	Male	-2.026	0.314	0.049	0.266
46	No	Male	5.446	0.269	0.194	0.374
47	No	Female	6.468	0.468	0.126	0.470
48	No	Female	5.628	0.518	0.116	0.338
49	No	Female	7.316	0.554	0.221	0.217
50	Yes	Male	-2.736	0.358	0.078	0.404
51	Yes	Male	0.466	0.348	0.187	0.400
52	No	Female	-1.014	0.398	0.340	0.515
53	No	Female	3.602	0.471	0.142	0.137
54	No	Male	4.872	0.334	0.166	0.374
55	No	Female	12.366	0.335	0.153	0.445
56	No	Female	3.814	0.362	0.145	0.188
57	No	Female	9.426	0.445	0.094	0.340
58	No	Male	4.768	0.414	0.205	0.038

<i>ID</i>	<i>Tinnitus</i>	<i>Sex</i>	<i>Mean</i>			
			<i>DPOAE</i>	<i>Wave I</i>	<i>Wave III</i>	<i>Wave V</i>
59	No	Female	10.448	0.619	0.085	0.096
60	No	Male	5.238	0.197	0.160	0.360
61	No	Male	12.116	0.204	0.070	0.149
62	No	Female	6.882	0.299	0.141	0.305
63	No	Female	3.082	0.245	0.074	0.266
64	No	Male	6.596	0.403	0.136	0.376
65	Yes	Male	4.248	0.235	0.014	0.145
66	No	Female	11.882	0.205	0.074	0.311
67	No	Male	3.404	0.299	0.084	0.168
68	No	Female	0.336	0.247	0.183	0.126
69	No	Female	8.454	0.530	0.171	0.328
70	No	Male	8.234	0.475	0.262	0.046
71	No	Female	8.530	0.363	0.233	0.224
72	Yes	Female	2.840	0.118	0.093	0.168
73	No	Male	7.646	0.524	0.124	0.189
74	No	Female	8.328	0.540	0.041	0.595

Summary of the information used in the Bayesian logistic regression model including reporting of tinnitus, sex, mean DPOAE level (in dB SPL) from 3-8 kHz, and ABR peak amplitudes (in μ V) in response to a 4 kHz 110 dB p-pe SPL toneburst.