Auditory brainstem response demonstrates that reduced peripheral auditory input is associated with self-report of tinnitus

Auditory brainstem response and tinnitus

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Abstract

Tinnitus is one of the predicted perceptual consequences of cochlear synaptopathy, a type of age-, noise-, or drug-induced auditory damage that has been demonstrated in animal models to cause homeostatic changes in central auditory gain. Although synaptopathy has been observed in human temporal bones, assessment of this condition in living humans is limited to indirect non-invasive measures such as the auditory brainstem response (ABR). In animal models, synaptopathy is associated with a reduction in ABR wave I amplitude at suprathreshold stimulus levels. Several human studies have explored the relationship between wave I amplitude and tinnitus, with conflicting results. This study investigates the hypothesis that reduced peripheral auditory input due to synaptic/neuronal loss is associated with tinnitus. ABR wave I amplitude data from 193 individuals (43 with tinnitus (22%), 150 without tinnitus (78%)), who participated in up to three out of four different studies, were included in a logistic regression analysis to estimate the relationship between wave I amplitude and tinnitus at a variety of stimulus levels and frequencies. Statistical adjustment for sex and distortion product otoacoustic emissions was included in the analysis. The results suggest that smaller ABR wave I amplitudes are associated with an increased probability of reporting tinnitus.

Keywords

Tinnitus; auditory brainstem response; cochlear synaptopathy; hidden hearing loss
I. INTRODUCTION

Tinnitus is one of the predicted perceptual consequences of cochlear synaptopathy, a loss of the synaptic connection between the inner hair cells (IHCs) and the afferent auditory nerve fibers (Kujawa & Liberman 2009, 2015). The central gain hypothesis, initially proposed by Jastreboff (1990), suggests that tinnitus results from hyperactivity or lack of inhibition in the central auditory system in response to a reduction in input from the peripheral auditory system, such as from damage to the cochlear hair cells, afferent fibers and/or synapses. This hypothesis is strengthened by observations of plastic changes in the brain, altered neurochemistry, and increased spontaneous and/or sound-evoked neuronal firing rates in the central auditory pathway of rodents with behavioral evidence of tinnitus following noise- or age-related cochlear injury (e.g., Kaltenbach et al. 2004; Wang et al. 2011; for review also see Auerbach et al. 2014). The central gain hypothesis is also supported by computational studies showing that homeostatic gain control could explain observed changes in spontaneous firing rate in the central auditory system after peripheral damage (Schaette & Kempter 2006; Chrostowski et al. 2011; Norena 2011). The prediction that decreased auditory input, specifically in the form of deafferentation, can lead to hyperactivity in the central auditory system and the perception of tinnitus is supported by several animal studies. In a mouse model with near complete (>95%) drug-induced loss of Type-I spiral ganglion neurons, but normal outer hair cell (OHC) function, Chambers et al (2016) found decreased tone-induced firing in the inferior colliculus compared with controls, but the firing rate in the auditory cortex exceeded that of controls at higher stimulus levels. In mice with histologically confirmed noise-induced synaptopathy, Hesse et al. (2016) also
observed decreased tone-evoked firing in the inferior colliculus, but spontaneous firing rates were elevated compared to controls. Although these animals were not assessed for tinnitus, this suggests that compensatory central gain changes induced by synaptic/neuronal loss can lead to spontaneous and evoked firing rates at later stages of the auditory pathway in excess of those observed in control animals.

A simple graphical presentation of how reduced peripheral auditory input is predicted to relate to increased gain in the central auditory system is shown in Figure 1. This plot illustrates that both OHC loss and deafferentation could lead to central auditory hyperactivity by reducing peripheral auditory input. At a given level of deafferentation (a combination of reduced IHC, synaptic, and neuronal function), the degree of hyperactivity increases as OHC function decreases. For a set level of OHC function, central hyperactivity is higher for greater levels of deafferentation and lower for less deafferentation. Note that the shapes of the functions used to illustrate these relationships are speculative, although it seems reasonable to assume that the relationships are monotonic. The central gain hypothesis predicts that as the degree of central hyperactivity increases, regardless of the underlying etiology of the reduced peripheral input, the probability of reporting tinnitus increases.

Cochlear synaptopathy has been demonstrated in animal models in response to aging, noise exposure, and ototoxic drug exposure (Kujawa & Liberman 2009; Sergeyenko et al. 2013; Ruan et al. 2014). Remarkably, up to 50% synaptic loss has been observed in the absence of any permanent threshold shift (Kujawa & Liberman 2009; Sergeyenko et al. 2013). This has led to concern about the effects of synaptopathy on human auditory perception that may be “hidden” from the audiogram.
Unfortunately, this perceptual impact has proved difficult to study. Although human temporal bone studies confirm that auditory neuronal and synaptic loss occur in humans with age (Makary et al. 2011; Viana et al. 2015), studies of synaptopathy in living humans are complicated by the lack of a reliable non-invasive metric of cochlear synaptic number and the large degree of measurement error associated with self-reported noise exposure. In animal models of synaptopathy, the amplitude of wave 1 of the auditory brainstem response (ABR) is highly correlated with synaptic survival (Kujawa & Liberman 2009; Lin et al. 2011; Sergeyenko et al. 2013). This makes ABR wave I amplitude a good candidate measure for studying synaptopathy in humans, although care must be taken when interpreting ABR results as wave I amplitude may also be impacted by factors such as electrode impedance, head size and anatomy, sex, and OHC function. For example, reduced ABR wave I amplitudes in males compared to females have been demonstrated previously, related at least in part to differences in head size (Trune et al. 1988; Mitchell et al. 1989).

Several human studies have used ABR wave I amplitude as an indirect measure of synaptic number in individuals of varying age or noise exposure history, with differing results, some showing a reduction in ABR wave I amplitude with age (Konrad-Martin et al. 2012; Bramhall et al. 2015) or noise exposure history (Stamper & Johnson 2015; Bramhall et al. 2017; Valderrama et al. 2018) and others showing no relationship between recreational noise exposure and wave I amplitude (e.g., Grinn et al. 2017; Guest et al. 2017b; Prendergast et al. 2017). Among these studies, differences in how the noise-exposed and control groups were defined, the magnitude and type of noise exposure experienced by the noise-exposed groups, and how possible effects of
cochlear damage on ABR wave I amplitude were addressed may account for the variability in results.

Several human studies have investigated the relationship between the perception of tinnitus and ABR wave I amplitude in individuals with normal or matched audiograms (Schaette & McAlpine 2011; Gu et al. 2012; Guest et al. 2017b; Shim et al. 2017; Bramhall et al. 2018). One advantage of directly investigating the relationship between tinnitus and ABR wave I amplitude is that this relationship can be evaluated independently of self-reported noise exposure history, which is inherently imprecise. In three out of five previous studies of tinnitus and ABR wave I amplitude, tinnitus was associated with a reduction in ABR wave I amplitude and either no reduction or an increase in wave V amplitude (Schaette & McAlpine 2011; Gu et al. 2012; Bramhall et al. 2018), suggesting that some forms of tinnitus may be associated with increased central gain related to deafferentation. However, two of the studies (Guest et al. 2017a; Guest et al. 2017b; Shim et al. 2017) did not find a significant difference in wave I amplitude between the tinnitus and control groups.

Previous studies of the relationship between ABR wave I amplitude and tinnitus have used either toneburst (4 kHz) or click stimuli at a variety of levels ranging from 90 dB peSPL to 90 dB nHL (~125 dB peSPL). Animal models of synaptopathy suggest that higher ABR stimulus levels make it easier to differentiate animals with synaptopathy from controls based on wave I amplitude (e.g., Kujawa & Liberman 2009; Lin et al. 2011; Furman et al. 2013). This may be due to the activation of high threshold, low spontaneous rate auditory nerve fibers at high stimulus levels, the subtype of fibers that appear most vulnerable to noise-induced synaptopathy (Furman et al. 2013).
models also show frequency specific effects of acute noise-induced synaptopathy on ABR wave I amplitude, related to the frequency content of the noise exposure (e.g., Kujawa & Liberman 2009; Lin et al. 2011; Furman et al. 2013), although as the time post-noise exposure increases, ABR wave I amplitude is reduced across a broader range of frequencies (Fernandez et al. 2015). However, animal models demonstrating the relationship between synaptopathy and ABR wave I amplitude have focused on animals with good OHC function, so it is unclear how the combination of OHC loss and synaptopathy might impact ABR wave I amplitude. On the one hand, reduced ABR wave I amplitude might be expected in the presence of high frequency OHC dysfunction due to reduced stimulation of high frequency auditory nerve fibers that contribute to wave I amplitude (Verhulst et al. 2016). However, computational modeling shows that the loss of cochlear non-linearity associated with OHC damage leads to steepening of the ABR amplitude growth function, so that wave I amplitudes at high stimulus levels are increased in individuals with high frequency OHC dysfunction compared to individuals with normal OHC function (Verhulst et al. 2018). Therefore, the presence of OHC dysfunction complicates the interpretation of the relationship between wave I amplitude and deafferentation, particularly at high stimulus levels. These findings suggest that there may be an optimal ABR stimulus that best describes the relationship between noise-induced deafferentation and tinnitus in humans who have a combination of OHC loss and deafferentation. We hypothesize that the optimal stimulus would stimulate 3-6 kHz, the frequency region most impacted by noise exposure (Wilson & McArdle 2013), and be presented at a level that is high enough to activate low
spontaneous rate fibers, but not so high that ABR wave I amplitude is dominated by the altered response of the basilar membrane in individuals with OHC dysfunction.

Verification of the relationships between OHC dysfunction, deafferentation, and the perception of tinnitus is difficult to achieve in humans because OHC loss and synaptic/neuronal loss cannot be experimentally manipulated. This report takes the approach of compiling a cross-sectional sample of individuals with varying degrees of noise- and/or age-related OHC dysfunction and deafferentation and using statistical modeling to evaluate how distortion product otoacoustic emission (DPOAE) and ABR wave I amplitude measures relate to self-reported tinnitus. This relationship is described in 193 individuals who took part in up to three out of four studies conducted at the VA RR&D National Center for Rehabilitative Auditory Research (NCRAR) in Portland, Oregon. These four studies consisted of three studies investigating the relationship between noise exposure and ABR wave I amplitude in young military Veterans and non-Veterans with normal to near normal hearing thresholds and one study of the relationship between aging and ABR wave I amplitude in Veterans and non-Veterans varying in age and pure tone thresholds. Data from two of these studies have been described previously (Gallun et al. 2014; Bramhall et al. 2017; Bramhall et al. 2018). Across the four studies included in this report, ABR data were collected in response to a variety of stimuli (1, 3, 4, and 6 kHz tonebursts, 4 kHz tonebursts with notched noise, and a multi-toneburst) collected at levels ranging from 90-110 dB peSPL. These measurements were incorporated into a single Bayesian logistic regression analysis that included statistical adjustment for sex and average DPOAE level. The results indicate that tinnitus is more likely to occur in ears with low suprathreshold ABR wave I
amplitudes, and that the effect of wave I amplitude on tinnitus depends on average
DPOAE level.

II. METHODS

A. Participants

Participants were military Veterans and non-Veterans 19-76 years of age, with
hearing status ranging from clinically normal hearing to moderate hearing loss. Inclusion
criteria differed from study to study (see below for study-specific details). None of the
participants were recruited based on their perception of tinnitus. Several participants
were included in more than one study: 28 were included in two different studies and 10
were included in three studies, for a total of 193 participants measured under up to
three out of four test protocols. Participants who took part in more than one study were
linked across studies and the data from the additional study(ies) treated as replicate
data (see Statistical analysis for more detail). The participant characteristics for the
whole sample are summarized in Table I.

1. Study 1

Seventy-four participants, aged 19-35, were included in study 1. All participants
had normal audiometric thresholds (≤ 20 dB HL) from .25-8 kHz, normal middle ear
function, and were in good general health with no significant history of otologic or
neurologic disorder (including traumatic brain injury (TBI)). DPOAEs from all participants
were screened to ensure good OHC function. DPOAE response amplitudes 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. This study was described previously by Bramhall et al. (2018). Data were collected from 2014-2016.

2. Study 2

Sixty-five participants, aged 21-35, were included in study 2. Inclusion criteria were as described for study 1, although the DPOAE criteria were slightly less restrictive. Only individuals with DPOAEs at or above the 90th percentile from 1.5-6 kHz were included in this sample. Data were collected from 2016-2019.

3. Study 3

Sixty-three participants, aged 19-76 years, were included in study 3. Potential participants were excluded who had more than a moderate hearing loss (pure tone threshold average for 3, 4, and 6 kHz of > 50 dB HL) in the better ear. Individuals with any indication of a conductive component (as demonstrated by abnormal tympanometry and/or air-bone gaps greater than 10 dB at two or more frequencies) were excluded. Additionally, individuals were excluded who had a failing score (< 24) on the Mini Mental State Examination (MMSE), a history of neurologic dysfunction, or used medication that could impact assessment of auditory function (e.g., cause drowsiness). An attempt was made to balance the numbers of younger and older males/females and Veterans/non-Veterans recruited for participation in the study. DPOAEs were measured, but were not exclusionary. Participant recruitment and audiometry methods are described in detail elsewhere (Gallun et al. 2014). Data were collected from 2011-2014.

4. Study 4
Seventy-one participants, aged 19-40 years, were included in study 4. No individuals with any pure tone thresholds (from .25-8 kHz) > 40 dB HL in the better ear were included. Individuals with any indication of a conductive component (as demonstrated by abnormal tympanometry and/or air-bone gaps greater than 10 dB at two or more frequencies) were excluded. All participants had normal otologic and neurologic history, with no reported history of TBI or concussion. DPOAEs were measured, but were not exclusionary. Data were collected from 2015-2018.

B. Procedures

All testing was completed in a double-walled sound-treated booth by a licensed audiologist. All participants consented to take part in the studies described following the guidelines of the VA Portland Health Care System's Institutional Review Board (IRB) and were compensated for their time.

1. Auditory brainstem response (ABR)

ABR data were obtained in each participant’s better hearing ear if applicable. All reported data are for the ABR test ear. During ABR testing, participants sat in a recliner and were encouraged to nap. Calibration of ABR stimuli was performed using a Brüel and Kjær (B&K) Head and Torso Simulator type 4128C (HATS). The earphone was seated in the artificial ear of the HATS while digitizing the output of the HATS using a B&K type 3160-A-042 LAN-xi high performance digitizer. The digitized waveforms were analyzed for their dB peSPL using Matlab software (Mathworks, Natick, Massachusetts) as described in IEC 60645-3. ABR stimuli included: 1) alternating polarity 1, 3, 4 and 6 kHz tonebursts at levels of 90, 100, and 110 dB peSPL for 1, 4, and 6 kHz and 110 dB peSPL for 3 kHz. Stimulus durations were 4 msec for 1 kHz (4 cycles), 2.5 msec for
3000 Hz (7.5 cycles), 2 msec for 4 kHz (8 cycles), and 1.5 msec (9 cycles) for 6 kHz; 2) a 1.4 ms bandlimited stimulus created by summing sinewaves of 1/12-octave frequencies ranging from 698-3946 Hz with zero starting-phase shift. The stimulus onset and offset was tapered using 0.12 msec cosine squared ramps. This stimulus will be referred to as a “multi-toneburst” and was presented at levels of 95, 100, and 105 dB peSPL; and 3) 4 kHz rarefaction tonebursts (2 msec) presented at 90, 100, and 105 dB peSPL in notched noise at 30 dB below the presentation level of the tonebursts. See Table II for a summary of the number of ABR measurements for each stimulus and level. ABR wave I amplitudes were measured as the voltage difference between the peak of wave I and the following trough\(^1\).

2. Audiometry

Air-conduction thresholds were obtained using a GSI-61 audiometer (Grason-Stadler, Inc.) and ER3A insert earphones (Etymotic Research, Inc.) from .25-8 kHz. Extended high frequency thresholds (9-16 kHz) were also measured, using Sennheiser HDA 200 headphones, in all but 18 participants. Bone conduction thresholds were obtained at octave frequencies from .5-4 kHz. The audiometers and earphones used for air and bone conduction measurements were calibrated annually by e3 MSR West.

3. Distortion product otoacoustic emissions (DPOAEs)

DPOAE testing was conducted using a custom system that includes an ER-10 B+ probe microphone and EMAV software from Boys Town National Research Hospital (Neely & Liu 1993). DPOAEs were measured in all participants using a primary frequency sweep (DP-gram) from \(f_2 = 1 \text{ – 8 kHz}\) in 1/3-octave increments at stimulus

\(^1\) See supplementary material at ... for study-specific details on the ABR measurements.
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 or until the noise floor was below -30 dB SPL. Participants with DPOAE levels below -20 dB SPL or a DPOAE signal-to-noise ratio of less than 3 dB (if the noise floor was $\geq$ -20 dB SPL) at any frequency from 3-8 kHz were excluded from the analysis due to the questionable validity of their DPOAE measurements. Twenty-five individuals were excluded for this reason. DPOAE levels were averaged within participants who took part in more than one study because the DPOAE measurement protocols were identical across the four studies.

4. Report of tinnitus

All participants completed a short hearing and health history questionnaire, which included a question about the perception of tinnitus. This question either asked, “Do you have constant or frequent ringing in the ears?” or “Do you have constant or frequent tinnitus?” Participants who responded “yes” to this question were rated as having tinnitus. Participant report of tinnitus was consistent across studies for those individuals who participated in multiple studies.

B. Statistical analysis

1. Model overview

The relationship between ABR wave I amplitude and report of tinnitus was evaluated previously using a Bayesian logistic regression model (Bramhall et al. 2018). The purpose of that model was to determine whether ABR amplitudes were predictive of
self-reported tinnitus. By treating self-report of tinnitus as the dependent variable, the data was analyzed in a manner consistent with the hypothesis that reduced peripheral auditory input leads to the perception of tinnitus. The model consisted of ABR wave I, III, and V amplitudes for a single stimulus frequency and level (4 kHz toneburst at 110 dB peSPL), as well as adjustments for sex and average DPOAE level from 3-8 kHz due to the known impacts of sex and OHC dysfunction on wave I amplitude. The results of that analysis indicated that wave I amplitude in response to a 4 kHz 110 dB peSPL toneburst was predictive of tinnitus, but not wave III and V amplitudes.

The Bayesian logistic regression model used in this study is similarly constructed to determine the relationship between ABR wave I amplitude and self-reported tinnitus, while adjusting for sex, average DPOAE level from 3-8 kHz, and the interaction between wave I amplitude and average DPOAE level. In a model consisting of ABR wave I amplitude for a single stimulus, the observed wave I amplitude for each participant is entered as a single number into the logistic regression model. The current sample, however, is composed of 193 participants who participated in up to three of four studies that obtained ABR measurements with 15 different ABR stimulus type/level combinations (listed in Table II). Given that there is currently no consensus on the optimal ABR stimulus for detecting noise-induced deafferentation and/or tinnitus in humans, wave I amplitudes for all 15 ABR stimuli were included in the analysis. This adds an additional layer of complexity to the model because none of the participants took part in all four studies, but 38 participants took part in more than one study.

One approach is to fit 15 separate models, identical in every way except the stimulus used to elicit the ABR and the sample data to which the model is fit. This
approach is unsatisfactory for several reasons. First, it ignores the fact that the same participant will be used in multiple analyses, resulting in correlation across analyses in the outcome measure. Second, ABR measures obtained from the same participant are likely to be correlated with one another, meaning the results of each analysis can’t be interpreted independently. Third, sample sizes vary by an order of magnitude from the smallest dataset (31 observations for the multi-toneburst at 95 dB peSPL) to the largest (301 observations for the 4kHz toneburst stimulus at 110 dB peSPL), which will result in marked variability across estimated effect sizes even if the true underlying effect is identical. We feel it is preferable to develop a single model of all the data that accounts for correlation across ABR stimuli.

The approach used in this report is to consider wave I amplitude elicited across different stimulus types and levels as a “response surface”, with the height of the surface representing a wave I amplitude (in µV) that varies systematically from person-to-person due to factors such as age and noise exposure. If all participants’ response surfaces are parallel, a single parameter $\alpha_i$, indexed by participant $i$, that measures the $i^{th}$ participants’ wave I amplitude relative to what is expected in the population for each stimulus can be identified. A positive value of $\alpha_i$ indicates a larger than expected wave I amplitude, given the ABR stimuli presented to the $i^{th}$ participant, while a negative value indicates a weaker than expected wave I amplitude. This concept is demonstrated visually in Figure 2. Deviation from the parallel response surface assumption is evaluated by regression diagnostics (see Model computation).

The parameter $\alpha_i$ is entered into the logistic regression model, taking the role of the ABR wave I amplitude predictor used by Bramhall et al. (2018). Estimating each $\alpha_i$
requires additional work. Replicate ABR measurements are available for many of the
participants, dependent on the studies that they participated in. Averaging is commonly
used in this situation, but replication differed between studies, meaning that the amount
of ABR data available from each participant varies. This requires a formal model of the
ABR response surface within the logistic regression model of the probability of reporting
tinnitus. In addition, weak ABRs were sometimes unscoreable, meaning that the wave I
amplitude could only be identified as below a visual detection limit. Referring to these
observations as missing is incorrect since we know that they are small, but are
uncertain as to how small. Instead, these observations can be treated as censored
(Klein & Moeschberger 2003) at a detection limit of 0.03 µV. This nomenclature
identifies these observations as somewhere below 0.03 µV, with no further identification
of their exact amplitudes. This approach uses all of the available ABR measurements,
including those with unscorable wave I amplitudes, to estimate each participant’s
deviation from the expected wave I amplitude, given the stimulus used to elicit each
measurement.

2. Model equations

A total of 193 participants, indexed \( i = 1 \) to 193, were observed on up to three out
of four possible measurement occasions, over which ABR wave I amplitude was elicited
by up to 15 distinct stimuli (listed in Table II). The deviation of a participant’s wave I
amplitude response surface from the sample mean \( \alpha_i \) was estimated by fitting a normal
errors regression model to the collection of log wave I amplitudes for each participant.
Specifically, \( j \) denotes a single log wave I amplitude \( y_j \) out of the 2,256 wave I amplitude
measurements gathered from the 193 participants, with the expected value \( \mu_j \)
composed of the stimulus effects and subject-specific effects on the mean log wave I amplitude. This model of the population mean response surface and the subject-specific deviation from the population mean is written as

\[ \mu_j = \beta_0 + \varphi_{s[j]} + \left( \beta_1 + \lambda_{s[j]} \right) \cdot L_j + \theta_{S-L[j]} + \beta_2 \cdot G_{i[j]} + \alpha_{i[j]}, \quad (1) \]

where \( \varphi_{s[j]} \) is the effect of the \( s^{th} \) stimulus type (toneburst (1, 3, 4, or 6 kHz); toneburst with notched noise; multi-toneburst) used to elicit the \( j^{th} \) ABR wave I amplitude. The \( \left( \beta_1 + \lambda_{s[j]} \right) \cdot L_j \) portion of equation (1) is the linear relationship between the mean log wave I amplitude and stimulus level \( L_j \) used to elicit the \( j^{th} \) ABR with stimulus type \( s \).

This is the population mean growth function for the \( s^{th} \) stimulus. The parameter \( \theta_{S-L[j]} \) models stimulus-specific deviations from linear growth. A subject-specific effect of sex \( \beta_2 \) on the mean response is also included due to sex differences in wave I amplitude.

The parameter \( \alpha_i \) is the \( i^{th} \) participant’s residual log wave I amplitude from expectation, given the ABR stimulus condition and the participant’s sex \( G_i \). Alternatively, \( e^{\alpha_i} \) can be defined as the \( i^{th} \) participant’s mean wave I amplitude relative to the population expected value for any given stimulus and sex. For \( e^{\alpha_i} = 0.5 \), the \( i^{th} \) participant’s wave I amplitude is half that expected for someone of that individual’s sex in response to any stimulus. For \( e^{\alpha_i} = 1.5 \), the \( i^{th} \) participant’s wave I amplitude is 50% bigger than expected in response to any stimulus for that individual’s sex.

The likelihood contribution of each observation in the dataset must be defined in order to model the unscorable ABR wave I amplitudes. The likelihood, denoted \( L \), for a collection of observations is a mathematical function of all unknown parameters in the model that measures the extent to which different parameter values are supported by
the observations. Each observation $j$ contributes $\mathcal{L}(\mu_j, \sigma^2; y_j, c_j)$ to the likelihood, where

$\mu_j$ is all of the parameters in equation (1), $\sigma^2$ is the Normal residual variance of the log wave I amplitudes $y_j$, and $c_j$ is a censoring indicator for the $j$th observation taking a value of 0 if the $j$th wave I amplitude is scorabale and a value of 1 if the $j$th wave I amplitude is known to lie below the detection limit of 0.03 µV. $\mathcal{L}(\mu_j, \sigma^2; y_j, c_j = 0)$ is the Gaussian probability density function evaluated at the observed $y_j$. $\mathcal{L}(\mu_j, \sigma^2; y_j, c_j = 1)$ is the Gaussian cumulative distribution function evaluated at the detection limit 0.03 µV. The likelihood contributions are multiplied over all observations in the dataset to give the full likelihood. In maximum likelihood analysis the full likelihood is maximized with respect to the parameters to identify parameter values best supported by the data. In Bayesian analysis the full likelihood is multiplied times the prior probability density over all the parameters to give a function proportional to the posterior distribution over all parameters.

The $i$th participant’s probability of reporting tinnitus $p_i$ was modeled as a function of their average DPOAE level from 3 to 8 kHz $D_i$, the deviation of their wave I amplitude response surface from the population mean $\alpha_i$ (see equation 1), the interaction between $D_i$ and $\alpha_i$, and sex $G_i$ (0 for males, 1 for females) using logistic regression, so that

$$\log \left( \frac{p_i}{1-p_i} \right) = \eta_0 + \eta_1 \cdot \alpha_i + \eta_2 \cdot D_i + \eta_3 \cdot D_i \cdot \alpha_i + \eta_4 \cdot G_i \quad (2)$$

By exponentiating a parameter in equation (2), an odds ratio for that effect can be obtained. For example, $e^{\eta_4}$ is the relative odds on reporting tinnitus for females compared to males. If $e^{\eta_4} > 1$ then females have elevated odds on reporting tinnitus compared to males, while $e^{\eta_4} < 1$ indicates the converse.
Interpretation is more nuanced for continuous effects such as $D_i$ and $\alpha_i$ in equation (2). We can compute $e^{\eta_1 + \eta_3 \cdot D_i}$ as the odds ratio for a unit change in residual log wave I amplitude at a given $D_i$. In addition to odds ratios, a risk difference can be identified as the difference in the probability that the $i^{th}$ participant reports tinnitus if their $\alpha_i$ is set to a particular low or high value. Gelman and Pardoe (2007) proposed using posterior predictive comparisons in this manner for describing effects in a Bayesian framework. The participant's probability of reporting tinnitus (from equation 2) can be defined as $p_i^{\text{low}}$ and $p_i^{\text{high}}$ with $\alpha_i^{\text{low}}$ set to log (0.5), corresponding to a wave I amplitude that is 50% below expectation, and $\alpha_i^{\text{high}}$ set to log (1.5), corresponding to a wave I amplitude that is 50% greater than expected. The difference $p_i^{\text{low}} - p_i^{\text{high}}$ is the estimated tinnitus risk difference as a consequence of "inducing" a low or high $\alpha$ for the $i^{th}$ participant. The logistic regression model of the probability of reporting tinnitus, and the censored data model of ABR wave I amplitude are fit jointly, meaning that the ABR data is not modeled first and then the tinnitus probability modeled subsequently. Rather, these sets of outcomes are tied together by the fact that the parameter $\alpha_i$ occurs in both equations (1) and (2). This approach recognizes uncertainty in the true values of $\alpha_i$, and allows information about their values to “flow” between the ABR model and the tinnitus model.

3. Model priors

Parameters in the logistic regression model were given weakly informative Normal priors, denoted $N(\text{mean}, \text{variance})$,

$$\eta_0 \sim N(-1, 0.5^2) \quad \eta_1, \eta_3, \eta_4 \sim N(0, 1^2) \quad \eta_1 \sim N(-0.25, 0.5^2)$$
corresponding to the belief that tinnitus will occur at a rate of less than 50% in a sample composed of Veterans and non-Veterans, and that, consistent with experience, the probability of reporting tinnitus decreases as DPOAE levels increase. The \( N(0,1) \) priors on the remaining parameters correspond to our ignorance about the effects of the residual log wave I amplitude \( \alpha_i \), its interaction with average DPOAE level \( D_i \), and sex \( G_i \) on the probability of reporting tinnitus. Priors for the ABR model parameters were identified using mean ABR wave I amplitude data from study 2 for males and females in response to a 4 kHz toneburst stimulus at levels of 100 and 110 dB peSPL. The expected wave I amplitudes for males and females are 0.2 µV and 0.25µV for a 100 dB peSPL stimulus and 0.3µV and 0.375µV for a 110 dB stimulus. A mean wave I amplitude of 1 µV or more was judged to be highly unlikely. The intercept \( \beta_0 \), overall level effect \( \beta_1 \), and sex effect \( \beta_2 \) were estimated from standardized, log transformation of these values, giving

\[
\beta_0 \sim N(1.74, 1^2) \quad \beta_1 \sim N(0.41, 0.2^2) \quad \beta_2 \sim N(0.299, 0.15^2).
\]

The stimulus effects on mean wave I amplitude were given zero-mean hierarchical priors, such that

\[
\phi_s \sim N(0, \tau_\phi) \quad \lambda_s \sim N(0, \tau_\lambda) \quad \theta_{s,L} \sim N(0, \tau_\theta)
\]

\[
\tau_\phi, \tau_\lambda, \tau_\theta \sim HN(0.15^2)
\]

\( HN(\cdot) \) denotes the Half-Normal distribution. The residual variance of the ABR wave I amplitudes \( \sigma^2 \) was also given a Half-Normal prior \( \sigma^2 \sim HN(0.35^2) \). The parameters \( \alpha_i \), which are the subject-specific residual ABR wave I amplitude from expectation given stimulus condition and sex, were given a one degree-of-freedom Student’s \( t \) distribution
centered at zero with scale parameter $\tau_\alpha$, in turn given a Half-Normal distribution $\tau_\alpha \sim HN(1^2)$. A Student’s $t$ distribution was used since a normal distribution for the $\alpha_i$ fit poorly to some of the participant’s observed wave I amplitudes, particularly those elicited using a multi-toneburst. Simulated data from these prior distributions corresponded well to the overall scale of the actual data.

4. Model computation

The continuous independent variables $D_i$ and $L_j$, and the continuous dependent variable $y_j$, were standardized to a mean of zero and standard deviation of 1 to facilitate computation, though final results are shown on the original scale. Analyses were conducted with SAS software, version 9.4, MCMC procedure. The joint posterior distribution of all parameters was evaluated using the No-U-Turn sampler. Three separate chains with random starting values were run for 2,000 iterations each. Gelman-Rubin convergence diagnostics, measuring the variability of the posterior samples across chains relative to the variability within each chain were below 1.02 for all parameters in the model. The model fit was evaluated by predicting ABR wave I amplitudes for each participant for the ABR stimuli they were presented and comparing these predictions to the observed wave I amplitudes. Posterior predictive distributions closely matched the observed wave I amplitudes and there was no gross deviation from the parallel response surface assumption. Calibration plots of observed tinnitus against predicted probability of tinnitus also showed excellent model fit for males and to a lesser
extent for females, where there were too few participants with tinnitus to formally evaluate model fit².

III. Results

A. Characteristics of tinnitus and control groups

Although the combined sample is made up of roughly half Veteran and half non-Veteran participants, the tinnitus group consists primarily of Veterans (90.7%). The tinnitus group is also predominantly male (79%), likely related, at least in part, to the high proportion of Veterans. However, the tinnitus and control groups are similar in age, with means of 31.9 and 29.5 years, respectively.

Audiometric thresholds and DPOAE levels differ systematically between the tinnitus and control groups, with poorer pure tone thresholds and lower DPOAE levels in the tinnitus group. This is most apparent for the extended high frequency thresholds where the tinnitus group has a mean average (from 9-16 kHz) of 11.6 dB HL, while the control group has a mean of 5.7 dB HL. This is expected based on the central gain hypothesis as illustrated in Figure 1, since OHC loss and deafferentation can lead to loss of pure tone sensitivity. These differences also highlight the necessity of statistically adjusting for DPOAE level to differentiate synaptic/neuronal contributions to any observed relationship between wave I amplitude and tinnitus from OHC dysfunction.

B. Unadjusted relationship between ABR wave I amplitude and report of tinnitus

Figure 3 shows the raw difference in mean ABR wave I amplitude between the control and tinnitus groups for the different stimulus types and levels used across the

² See supplementary material at...for plot comparing predicted probability of tinnitus vs. observed tinnitus.
four studies. For comparison, data from four published studies of the relationship between ABR wave I amplitude and tinnitus are plotted (Schaette & McAlpine 2011; Gu et al. 2012; Guest et al. 2017b; Shim et al. 2017). With the exception of the Guest et al. data, the Gu et al. data at 65.5 dB peSPL, the NCRAR 4 kHz toneburst with notched noise data at 105 dB peSPL, and the NCRAR 6 kHz toneburst at 90 dB peSPL, the plot shows greater mean wave I amplitudes for the control groups as compared to the tinnitus groups. The largest differences in mean ABR wave I amplitude between the two groups were obtained when using a broadband stimulus (multi-toneburst and click), but this may not be meaningful because the broadband stimuli were used with separate samples from the frequency-specific stimuli and the results are therefore difficult to compare.

The effect of stimulus level on wave I amplitude differences can be evaluated more easily because in many cases different levels of the stimulus were used in the same sample. Generally, where multiple stimulus levels are available for a single stimulus type, an increase in the wave I amplitude difference between the tinnitus and control groups can be observed as the level increases from ~65 to 100 dB peSPL. However, the NCRAR data for several different stimulus types (multi-toneburst, 4 kHz toneburst, and 4 kHz toneburst with notched noise) show a non-monotonic relationship for the wave I amplitude difference between the tinnitus and control groups at the highest stimulus levels. This is particularly apparent for the multi-toneburst and the 4 kHz toneburst with notched noise where the wave I amplitude difference between groups drops precipitously at 105 and 110 dB peSPL, respectively.
Overall, these results suggest a reduction in ABR wave I amplitude in individuals with tinnitus. However, the results should be interpreted with caution due to the potential for confounding effects of differences in sex and OHC function between the groups.

**C. Modelled relationship between ABR wave I amplitude and report of tinnitus**

Each of the 193 participants provided ABR and DPOAE data for one to three out of the four possible studies. The stimuli used to elicit the ABR varied across studies, with a total of 15 stimuli. All ABR data, sex, average DPOAE level from 3-8 kHz, and the interaction between ABR wave I amplitude and average DPOAE level were entered as predictors into a Bayesian logistic regression model of the probability of reporting tinnitus. This approach allowed for the inclusion of all 193 participants and all ABR stimulus types and levels in the logistic regression model. Based on the fitted model, it is estimated that, in response to any given ABR stimulus, a 50% reduction in wave I amplitude is associated with a 1.4-fold increase in the odds on reporting tinnitus (90% Bayesian credible interval 0.8-2.3) among individuals with average DPOAE levels from 3-8 kHz that are equal to the sample mean (2.7 dB SPL). For individuals with average DPOAE levels that are one standard deviation below the sample mean (-2.3 dB SPL) the effect is smaller (odds ratio = 1.1; 90% credible interval 0.7-1.8), while those with average DPOAE levels one standard deviation above the mean (7.7 dB SPL) have a bigger effect of reduced wave I amplitude (odds ratio=1.7; 90% credible interval 0.8-3.8).

**Figure 4** shows the results of the analysis using the posterior predictive comparison framework. The fitted probability of reporting tinnitus was calculated for each participant using their sex and average DPOAE level, and by setting their residual
log wave I amplitude $\alpha_i$ to 1) a value 50% below expectation and 2) a value corresponding to a wave I amplitude that is 50% greater than expected. The difference in the estimated probability of reporting tinnitus between these two values of $\alpha_i$, or the risk difference, is plotted for each participant. Figure 4 effectively displays the interaction between average DPOAE level and wave I amplitude on tinnitus risk. Above the mean average DPOAE level (2.7 dB SPL, indicated by the dashed reference line), the average risk difference among males is a 13% elevated risk (90% Bayesian credible interval of -3% to 31%), while below the mean, the risk differences are smaller and much less precisely estimated (Risk difference = 6%; 90% Bayesian credible interval = -16% to 24%). Among females, the risk differences average to 5% elevated risk among those with average DPOAE levels above the mean (90% Bayesian credible interval = -1% to 15%), and 3% among those with DPOAE levels below the mean (90% Bayesian credible interval = -15% to 14%).

The modeled data can also be plotted in a similar format to Figure 1 to determine the relative impacts of deafferentation and OHC dysfunction on the report of tinnitus. This is shown in Figure 5, where the relationship between average DPOAE level and report of tinnitus is plotted for a high and low value of $\alpha$, corresponding to 50% larger and 50% smaller wave I amplitudes relative to expected. The dotted line, (representing a high wave I amplitude relative to expected and less deafferentation) indicates how decreasing OHC function affects the probability of reporting tinnitus, while the solid line (representing a low value of $\alpha$ and more deafferentation) shows how the combination of deafferentation and OHC dysfunction impact report of tinnitus. At a high
average DPOAE level, the difference between these two lines illustrates how report of
tinnitus increases with deafferentation.

IV. DISCUSSION

A. High proportion of Veterans in tinnitus group suggests noise-induced tinnitus

The large variety of tinnitus etiologies make it difficult to pinpoint the mechanisms
that induce tinnitus. In this report, the high proportion of participants with tinnitus who
are Veterans suggests that the majority of the tinnitus reported is related to noise
exposure rather than other causes. This result is broadly consistent with the view that
tinnitus often occurs following cochlear injury from noise and other causes of hearing
loss that lead to central gain changes (Jastreboff 1990). Using population-based data
from the National Health and Nutrition Examination Survey, Folmer et al. (2011) showed
that male Veterans had double the prevalence of self-reported tinnitus compared with
male non-Veterans. The paucity of epidemiological studies on hearing deficits in
Veterans makes it difficult to determine risk factors for tinnitus. These likely include male
sex (through its association with high-risk combat exposures and comorbidities that can
increase the prevalence of age-related hearing loss), as well as characteristics of the
initial auditory injury and post-traumatic stress disorder (PTSD), according to a recent
systematic review (Theodoroff et al. 2015). In order to better understand the prevalence
and risk factors for tinnitus, future studies ideally will use a longitudinal study design and
assessments of the precipitating damage (e.g., noise) that are more precise than those
currently available.
One benefit of the analytic approach described here, is that by using tinnitus self-report as the dependent variable, we can test a predicted mechanism of damage (the central gain hypothesis), and assess evidence for a synaptic/neuronal contribution to the underlying cochlear injury. An additional strength of this study is the inclusion of individuals with mild hearing loss to provide insight into how suprathreshold ABR measures predict tinnitus in ears with OHC dysfunction.

**B. Level is an important factor in determining the optimal ABR stimulus**

The raw ABR wave I amplitude data (Figure 2) suggest that higher stimulus levels, up to 100 dB peSPL, yield larger mean wave I amplitude differences between tinnitus and control groups. These results may indicate that 100 dB peSPL stimuli, regardless of the specific stimulus type, hit a wave I amplitude “sweet spot”. Lower intensity stimuli (i.e. 90 dB peSPL) may be less sensitive to synaptic/neuronal differences between groups. This is consistent with animal models of synaptopathy that show greater reductions in ABR wave I amplitude at higher stimulus levels (e.g., Kujawa & Liberman 2009; Lin et al. 2011; Furman et al. 2013) and model simulations of ABR wave I amplitude growth in humans with synaptopathy (Verhulst et al. 2018). Peak picking is also more difficult at 90 dB peSPL, particularly in individuals with reduced wave I amplitudes and/or elevated hearing thresholds. This is clear from the number of participants providing ABR wave I amplitude data at 90 dB peSPL compared to higher stimulus levels (Table II). This could result in increased measurement error.

Above 100 dB peSPL, wave I is easily identified, but a reduction in ABR wave I amplitude due to synaptic or neuronal loss may be counteracted by increased wave I amplitude due to high frequency OHC damage and the associated loss of cochlear non-
linearity (Verhulst et al. 2018). This would weaken the relationship between wave I amplitude and the report of tinnitus at those stimulus levels. Given that across samples, the individuals with tinnitus displayed lower average DPOAE levels from 3-8 kHz, it is reasonable to assume they had high frequency OHC dysfunction. This is consistent with the observation that the two stimuli that showed a steep drop above 100 dB peSPL in the mean ABR wave I amplitude difference between the tinnitus and control groups (multi-toneburst and 4 kHz toneburst with notched noise) were used in studies where the participants were not required to have normal audiograms (studies 3 and 4) and were therefore more likely to have OHC dysfunction. In contrast, the 1, 4, and 6 kHz tonebursts either showed an increase in mean wave I amplitude difference at 110 dB peSPL or a modest drop. These stimuli were used in studies that required clinically normal audiograms and good DPOAEs for study inclusion (studies 1 and 2). These observations are further supported by Verhulst et al. (2016) who found that model simulations of varying degrees of cochlear gain loss had limited impact on ABR wave I amplitude for a click with a stimulus level of 100 dB peSPL. Given these results, including a stimulus level of 100 dB peSPL in future ABR protocols for assessing deafferentation is recommended.

C. Model results indicate increased probability of reporting tinnitus with decreased wave I amplitude when OHC function is good

The results of the Bayesian logistic regression model indicate a reduction in the probability of reporting tinnitus as ABR wave I amplitude increases. This suggests that cochlear deafferentation, whether through IHC, synaptic, or neuronal loss, is associated with some forms of tinnitus. However, the results also show that both deafferentation
and OHC dysfunction are associated with the perception of tinnitus. As a consequence, in individuals with poorer DPOAEs, ABR wave I amplitude is less predictive of tinnitus. This may explain the conflicting results in previous studies of the relationship between ABR wave I amplitude and tinnitus, particularly if otoacoustic emissions were not assessed. The model results plotted in Figure 5 closely resemble the graphical representation of the central gain hypothesis shown in Figure 1. This supports the prediction that reduced peripheral auditory input, either through deafferentation or OHC dysfunction, leads to hyperactivity in the central auditory system and the perception of tinnitus.

D. Relationship of findings to published studies

It is not surprising that the results of this analysis are in agreement with those described in Bramhall et al. (2018) because the sample described in Bramhall et al. was included in this analysis. In addition, Figure 2 shows that the raw data from the other three NCRAR studies as well as several other published studies are also consistent with this result. The results of this analysis are also consistent with the statistical analyses of Schaette et al. (2011), who used 90 and 100 dB peSPL click stimuli, and Gu et al. (2012), who used an 80 dB nHL click (115.5 dB peSPL according to the international standard reference level for clicks (ISO 389-6, 2007)). These studies both found a statistically significant reduction in ABR wave I amplitude among individuals reporting tinnitus. Wojtczak et al. (2017) observed a reduction in the strength of the middle ear muscle reflex (MEMR) growth curve in participants with tinnitus as compared to those without, even after statistical adjustment for sex, age, and average pure tone thresholds at 4 and 8 kHz. Although ABR wave I amplitude was not measured, mouse models
suggest that both ABR wave I amplitude and the MEMR are sensitive to cochlear synaptopathy (Valero et al. 2016; Valero et al. 2018). The association of both reduced ABR wave I amplitude and weaker MEMR with tinnitus in humans suggest it may be related to synaptic/neuronal damage.

Guest et al. (2017a; 2017b) used a click stimulus at a level of 102 dB peSPL to compare young tinnitus and non-tinnitus groups who both had clinically normal hearing and mean thresholds matched out to 14 kHz. They did not observe any mean ABR wave I amplitude difference between the groups. However, tinnitus is multifactorial and may result from a variety of etiologies in addition to synaptopathy, including cardiovascular disease, head and neck trauma, thyroid disorders, medications, and OHC damage (Henry et al. 2014). Guest et al. specifically recruited participants based on the presence or absence of tinnitus, which could lead to greater variability in the underlying tinnitus etiology and contribute to the differing results between studies. In the present analysis, perception of tinnitus was very highly correlated with Veteran status, suggesting a noise exposure-related etiology for the tinnitus. In addition, although Guest et al.’s tinnitus and control groups were matched for pure tone thresholds, no otoacoustic emissions were reported, so it’s unclear how the groups compare in terms of OHC function. Shim et al. (2017) found no difference in ABR wave I amplitude for a 90 dB nHL (125.5 dB peSPL) click stimulus between a group with unilateral tinnitus and a group without tinnitus. This stimulus level is considerably higher than the highest stimulus level (110 dB peSPL) used in the present analysis, which suggests it may not be optimal for predicting tinnitus, particularly in the presence of OHC dysfunction. In addition, similar to Guest et al., the participants were recruited based on the presence
or absence of tinnitus. Efforts were made to exclude individuals with other tinnitus etiologies such as diagnosed retrocochlear lesions, otitis media, or endolymphatic hydrops. However, neither Veteran status nor noise exposure history was evaluated, so it is unclear whether the tinnitus participants had noise-induced tinnitus. Limiting participation only to individuals with unilateral tinnitus may have encouraged recruitment of participants with non-noise-related tinnitus, such as individuals with undiagnosed retrocochlear lesions or Menière’s disease. In addition, otoacoustic emissions and extended high frequency hearing thresholds were not evaluated, so individual differences in OHC function that were not accounted for in the analysis may have confounded the results.

**E. Future directions for studying synaptopathy and tinnitus in humans**

These findings suggest that new diagnostic tools, beyond the conventional audiogram and otoacoustic emissions, may be necessary to more completely assess and treat the cochlear injury related to tinnitus. The results presented here highlight the importance of sample population characteristics, stimulus level, and accounting for sex and DPOAE differences when interpreting ABR wave I amplitudes. Other important factors to consider when evaluating the relationship between synaptopathy and noise-induced tinnitus include ruling out tinnitus etiologies unrelated to noise exposure. Given the confounding effects of sex and OHC dysfunction on the ABR, use of other physiological measures, such as the MEMR, that have been shown to be sensitive to synaptopathy in animal models, may help clarify the relationship between synaptic loss and tinnitus.
V. Conclusions

The findings of this study indicate that tinnitus is associated with reductions in ABR wave I amplitude, particularly when the ABR is measured with a stimulus level of 100 dB peSPL (approximately 65 dB nHL). This relationship between wave I amplitude and tinnitus persists after accounting for sex and OHC function, suggesting that the reductions in wave I amplitude may be related to synaptic and/or neuronal loss. This supports predictions that reduced peripheral input due to cochlear synaptopathy may lead to increased central gain and the perception of tinnitus. The large number of participants and the variety of stimulus types and levels included in this analysis help to clarify the conflicting results of previous smaller studies and shed new light on the importance of stimulus level when measuring ABR wave I amplitude.

Acknowledgements

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Wilson, R. H., McArdle, R. (2013). Characteristics of the audiometric 4,000 Hz notch (744,553 veterans) and the 3,000, 4,000, and 6,000 Hz notches (539,932 veterans). *J Rehabil Res Dev*, 50, 111-132.

Table I. Summary of the demographic and hearing characteristics of the sample, broken down by tinnitus group. Measurements for individual participants that were acquired for more than one study (age, average DPOAE level, and pure tone averages (PTAs)) are averaged across studies.

<table>
<thead>
<tr>
<th>Tinnitus?</th>
<th>No</th>
<th>Yes</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total participants</strong></td>
<td>150</td>
<td>43</td>
<td>193</td>
</tr>
<tr>
<td><strong>Non-Veteran</strong></td>
<td>101</td>
<td>4</td>
<td>105</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>67.3</td>
<td>9.3</td>
<td>54.4</td>
</tr>
<tr>
<td><strong>Veteran</strong></td>
<td>49</td>
<td>39</td>
<td>88</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>32.7</td>
<td>90.7</td>
<td>45.6</td>
</tr>
<tr>
<td><strong># Female</strong></td>
<td>78</td>
<td>9</td>
<td>87</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>52</td>
<td>20.9</td>
<td>45.1</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td><strong>Mean</strong></td>
<td>29.5</td>
<td>31.9</td>
</tr>
<tr>
<td><strong>Min</strong></td>
<td>19</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td><strong>Max</strong></td>
<td>64</td>
<td>58</td>
<td>64</td>
</tr>
<tr>
<td><strong>Avg DPOAE (3-8 kHz)</strong></td>
<td><strong>Mean</strong></td>
<td>3.5</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Min</strong></td>
<td>-11</td>
<td>-13</td>
<td>-13</td>
</tr>
<tr>
<td><strong>Max</strong></td>
<td>15.8</td>
<td>8.0</td>
<td>15.8</td>
</tr>
<tr>
<td><strong>PTA (.5, 1, &amp; 2 kHz)</strong></td>
<td><strong>Mean</strong></td>
<td>7.2</td>
<td>9.3</td>
</tr>
<tr>
<td><strong>Min</strong></td>
<td>-3.3</td>
<td>0.0</td>
<td>-3.3</td>
</tr>
<tr>
<td><strong>Max</strong></td>
<td>18.3</td>
<td>23.3</td>
<td>23.3</td>
</tr>
<tr>
<td><strong>PTA (3, 4, &amp; 6 kHz)</strong></td>
<td><strong>Mean</strong></td>
<td>4.5</td>
<td>9.6</td>
</tr>
<tr>
<td><strong>Min</strong></td>
<td>-10</td>
<td>-1.7</td>
<td>-10</td>
</tr>
<tr>
<td><strong>Max</strong></td>
<td>23.3</td>
<td>31.7</td>
<td>31.7</td>
</tr>
<tr>
<td><strong>PTA (9-16 kHz)</strong></td>
<td><strong>Mean</strong></td>
<td>5.7</td>
<td>11.6</td>
</tr>
<tr>
<td><strong>Min</strong></td>
<td>-13</td>
<td>-10</td>
<td>-13</td>
</tr>
<tr>
<td><strong>Max</strong></td>
<td>36.0</td>
<td>51.0</td>
<td>51.0</td>
</tr>
</tbody>
</table>
Table II. Summary of the available ABR wave I amplitude data. The observed wave I amplitudes (including replicates) used in the analysis are broken down by ABR stimulus type and level used.

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Level (dB peSPL)</th>
<th>#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-toneburst</td>
<td>95</td>
<td>31</td>
</tr>
<tr>
<td>Multi-toneburst</td>
<td>100</td>
<td>35</td>
</tr>
<tr>
<td>Multi-toneburst</td>
<td>105</td>
<td>38</td>
</tr>
<tr>
<td>4 kHz toneburst w/notched noise</td>
<td>90</td>
<td>110</td>
</tr>
<tr>
<td>4 kHz toneburst w/notched noise</td>
<td>100</td>
<td>116</td>
</tr>
<tr>
<td>4 kHz toneburst w/notched noise</td>
<td>105</td>
<td>108</td>
</tr>
<tr>
<td>1 kHz toneburst</td>
<td>100</td>
<td>72</td>
</tr>
<tr>
<td>1 kHz toneburst</td>
<td>110</td>
<td>129</td>
</tr>
<tr>
<td>3 kHz toneburst</td>
<td>110</td>
<td>142</td>
</tr>
<tr>
<td>4 kHz toneburst</td>
<td>90</td>
<td>291</td>
</tr>
<tr>
<td>4 kHz toneburst</td>
<td>100</td>
<td>292</td>
</tr>
<tr>
<td>4 kHz toneburst</td>
<td>110</td>
<td>301</td>
</tr>
<tr>
<td>6 kHz toneburst</td>
<td>90</td>
<td>151</td>
</tr>
<tr>
<td>6 kHz toneburst</td>
<td>100</td>
<td>150</td>
</tr>
<tr>
<td>6 kHz toneburst</td>
<td>110</td>
<td>290</td>
</tr>
</tbody>
</table>
Figure 1. Graphical representation of the predicted relationship between OHC function, deafferentation, and hyperactivity in the central auditory system.

Central auditory system hyperactivity is predicted to increase in response to any source of reduced peripheral auditory input. The amount of central auditory hyperactivity is shown on the y-axis, plotted against OHC function on the x-axis. Hyperactivity is predicted to increase as OHC function decreases. In addition, at a set level of OHC function (vertical dotted line), the level of hyperactivity is expected to be higher in individuals with more deafferentation and lower in individuals with less deafferentation.
Figure 2. Illustration of how ABR wave I amplitudes across stimulus conditions are represented by \( \alpha \). The fitted mean wave I amplitude is plotted as a function of stimulus level for a 4 kHz toneburst (shaded region shows the 90% posterior interval). Also plotted are replicate wave I amplitude measurements from two male and two female participants, one with amplitudes above the sample mean, the other with amplitudes below the mean. The \( \alpha \) values for these participants are also shown, demonstrating that low values of \( \alpha \) reflect wave I amplitudes below the mean and high values of \( \alpha \) represent wave I amplitudes above the mean.
Raw data suggest ABR wave I amplitude is reduced in individuals with tinnitus. The difference in mean ABR wave I amplitude between the control and tinnitus groups is plotted for the different stimulus types and levels used in the current sample. Previously published results (Schaette & McAlpine 2011; Gu et al. 2012; Guest et al. 2017b; Shim et al. 2017) are also plotted for comparison. A click stimulus was used for the 4 published studies. Note that all NCRAR studies used a tiptrode, while the published studies either used a mastoid electrode, frontal electrode, or did not specify. Data that were published with stimulus intensity levels in dB nHL were converted to peSPL for plotting purposes, assuming the international reference standard for a click. (Color online)
Figure 4. Modeled risk differences in the probability of reporting tinnitus as a function of average DPOAE level. The regression model indicates an increase in the probability of reporting tinnitus when ABR wave I amplitudes are reduced, particularly among individuals with good DPOAEs. The fitted probability of reporting tinnitus was calculated for each participant using their sex and average DPOAE level, and by setting their residual log wave I amplitude to a low value $\alpha_{i}^{\text{Low}} = \log(0.5)$, corresponding to wave I amplitude that is 50% below expectation, and $\alpha_{i}^{\text{High}} = \log(1.5)$, corresponding to wave I amplitude that is 50% greater than expected. The difference in the estimated probabilities of reporting tinnitus using these values of $\alpha_i$, the risk difference, are plotted for each participant, shown as distinct bars in the figure. Risk differences above 0 indicate elevated probability of reporting tinnitus with weaker wave I amplitude, while risk differences below 0 indicate the converse. The thin lines indicate the 90% Bayesian confidence interval and the thick lines indicate the interquartile range. Model predictions are plotted separately for males and females, with females showing a similar, but
smaller, effect than males. The vertical dashed line shows the sample mean average DPOAE level of 2.7 dB SPL.

Figure 5. Modeled relationship between average DPOAE level, ABR wave I amplitude, and the probability of reporting tinnitus. Model predictions suggest that both OHC dysfunction and deafferentation are associated with the perception of tinnitus. The probability of reporting tinnitus is plotted against standardized average DPOAE level for a high $\alpha$ (dashed line, double the expected value of wave I amplitude) versus a low $\alpha$ (solid line, half the expected value of wave I amplitude). The dotted line (high $\alpha$) shows how decreasing OHC function impacts the probability of reporting tinnitus. The solid line (low $\alpha$) indicates how the combination of deafferentation and OHC dysfunction effect the probability of reporting tinnitus. For both values of $\alpha$, the probability of reporting tinnitus increases as average DPOAE level decreases. The impact of
deafferentation on report of tinnitus can be gleaned by contrasting the solid and dotted lines at a high average DPOAE level. This indicates an increase in the probability of reporting tinnitus for a low value of $\alpha$ (more deafferentation). Shaded regions illustrate the 90% Bayesian confidence intervals about the predicted probability of tinnitus. Gray circles indicate the raw average DPOAE level (from 3-8 kHz) for participants with (at top) and without tinnitus (at bottom).