Predicting synapse counts in living humans by combining computational models with auditory physiology

Running title: Predicting synapse counts in living humans

Brad N. Buran^{1a)}, Garnett P. McMillan^{2b)}, Sarineh Keshishzadeh^{3c)}, Sarah Verhulst^{3d)},
Naomi F. Bramhall^{2e)}

¹Oregon Hearing Research Center, Department of Otolaryngology – Head & Neck Surgery, Oregon Health & Science University, Portland, Oregon, USA

²VA RR&D National Center for Rehabilitative Auditory Research (NCRAR), VA Portland Health Care System, Portland, Oregon, USA

³Hearing Technology @ WAVES, Department of Information Technology, Ghent University, Belgium

Corresponding author: Brad Buran

a) Email: buran@ohsu.edu

b) Email: garnett.mcmillan@va.gov

c) Email: sarineh.keshishzadeh@ugent.be

d) Email: s.verhulst@ugent.be

e) Email: naomi.bramhall@va.gov

Declarations of interest: None

Abstract

Aging, noise exposure, and ototoxic medications lead to cochlear synapse loss in animal models. As cochlear function is highly conserved across mammalian species, synaptopathy likely occurs in humans as well. Synaptopathy is predicted to result in perceptual deficits including tinnitus, hyperacusis, and difficulty understanding speech-in-noise. The lack of a method for diagnosing synaptopathy in living humans hinders studies designed to determine if noise-induced synaptopathy occurs in humans, identify the perceptual consequences of synaptopathy, or test potential drug treatments. Several physiological measures are sensitive to synaptopathy in animal models including auditory brainstem response (ABR) wave I amplitude. However, it is unclear how to translate these measures to synaptopathy diagnosis in humans. This work demonstrates how a human computational model of the auditory periphery, which can predict ABR waveforms and distortion product otoacoustic emissions (DPOAEs), can be used to predict synaptic loss in individual human participants based on their measured DPOAE levels and ABR wave I amplitudes. Lower predicted synapse numbers were associated with advancing age, higher noise exposure history, increased likelihood of tinnitus, and poorer speech-in-noise perception. These findings demonstrate the utility of this modeling approach in predicting synapse counts from physiological data in individual human subjects.

I. INTRODUCTION

In humans, approximately 40% of the synapses between inner hair cells (IHCs) and afferent auditory nerve fibers (ANFs) are lost by 50 years of age (Wu et al. 2019). Animal models suggest that noise exposure and ototoxic medications can also result in synapse loss (Kujawa & Liberman 2009; Ruan et al. 2014). Given the high conservation of cochlear processing across mammalian species, studies demonstrating synaptopathy in mouse (e.g., Kujawa & Liberman 2009), guinea pig (e.g., Lin et al. 2011), gerbil (e.g., Bourien et al. 2014), chinchilla (e.g., Hickman et al. 2018), and non-human primates (Valero et al. 2017) suggest that noise- and ototoxin-induced cochlear synaptopathy is likely to occur in humans. However, there is currently no means of diagnosing synaptopathy in living humans. Cochlear synaptopathy is predicted to result in perceptual deficits including tinnitus, hyperacusis, and difficulty with speech-in-noise perception (Kujawa & Liberman 2015). However, human studies that have attempted to evaluate relationships between physiological indicators of synaptopathy and risk factors (e.g., noise exposure) or perceptual deficits (e.g., tinnitus or speech perception difficulty), have resulted in mixed findings (Bramhall et al. 2019a; Le Prell 2019). A means of diagnosing synaptopathy will help determine if noise-induced synaptopathy occurs in humans, identify the perceptual consequences of synaptopathy, and test potential drug treatments.

Synaptopathy is difficult to detect with standard audiological measurements because it has little impact on auditory thresholds (e.g., Kujawa & Liberman 2009). In addition, a mix of synaptic and OHC loss is likely common in adults, as demonstrated by human temporal bone studies (Otte et al. 1978; Felder & Schrott-Fischer 1995; Viana et

al. 2015; Wu et al. 2019) and noise exposure studies in mice (Fernandez et al. 2020), making differential diagnosis difficult. A number of physiological measures are sensitive to synaptopathy in animal models (Kujawa & Liberman 2009; Shaheen et al. 2015; Valero et al. 2018). These measures include: 1) the auditory brainstem response (ABR) wave I amplitude, a far-field response produced by the synchronous firing of auditory nerve fibers (Hashimoto et al. 1981); 2) the envelope following response (EFR), a far-field measure of the synchronization in multiple auditory nuclei to amplitude modulated stimuli (Dolphin & Mountain 1992); and 3) the middle ear muscle reflex (MEMR), a bilateral change in middle ear impedance in response to suprathreshold stimulation that is dependent on auditory nerve function (Margolis 1993). However, the extent to which these measures are effective in detecting synaptopathy in humans remains unclear (Bramhall et al. 2019a) and thus far these measures have mainly been used to test for group differences, not to assess synaptopathy in individual human subjects. Some combination of these measures may be more effective at diagnosing synaptopathy than a single measure, particularly in the presence of OHC dysfunction (Garrett & Verhulst 2019; Keshishzadeh et al. 2021), which could impact some physiological measures of synaptopathy (Verhulst et al. 2018; Fernandez et al. 2020). Despite recent studies that have explored the sensitivity of these measures for predicting synaptopathy in the presence of OHC deficits (Verhulst et al. 2016; Keshishzadeh et al. 2020; Keshishzadeh et al. 2021; Vasilkov et al. 2021), there is no consensus on how to combine these measurements to predict synaptopathy.

This report outlines a computational modeling approach to assess synaptopathy in living humans. An existing human computational model of the auditory periphery

(CMAP; Verhulst et al. 2018) can predict otoacoustic emissions (OAEs), ABRs, and EFRs for any combination of OHC and synaptic loss, providing a framework for relating these physiological measurements to synapse counts. As a proof of concept, the CMAP was fit using Bayesian regression to predict individual synapse counts in two separate datasets. The first dataset is from a study of young military Veterans and non-Veterans (Bramhall et al. 2017; Bramhall et al. 2018) and the second dataset is from a study of adults that vary in age from 18 to 73 years (Carcagno & Plack 2020, 2021). This report demonstrates how to: 1) use the CMAP to infer OHC function from OAEs or audiograms, 2) incorporate prior knowledge to inform synapse predictions (e.g., synapse counts from human temporal bones, Wu et al. 2019), 3) incorporate multiple ABR stimuli to inform synapse predictions (e.g., six different level/frequency combinations), and 4) model the frequency-specific distribution of synapses using a small number of coefficients. In addition, relationships between predicted synapse counts and risk factors for synaptopathy (noise exposure and age) and two expected perceptual consequences of synaptopathy (tinnitus and performance on a speech-in-noise perception task) are presented to demonstrate the utility of this computational approach. The results of those additional analyses illustrate the expected relationships between predicted synapse counts and age, noise exposure, tinnitus, and speech-in-noise perception and are consistent with previous analyses of relationships with ABR wave I amplitude using the same datasets (Bramhall et al. 2017; Bramhall et al. 2018; Carcagno & Plack 2020). These results provide the framework of a biologically motivated approach to assessing synaptopathy in humans. In addition, this approach will facilitate future analyses that incorporate additional physiological measures (e.g.,

more ABR levels/frequencies and the EFR), combine results across multiple studies, and/or include participants with greater degrees of OHC dysfunction.

II. MATERIALS AND METHODS

A. Study samples

The computational algorithm was tested against two separate datasets. Each dataset was processed separately, but treated identically in terms of model fitting. A brief outline of each dataset follows. For additional detail, please see the relevant publication.

The first dataset consists of 74 young adults drawn from a study of young military Veterans and non-Veterans, aged 19-35 years. Details on the dataset as well as the data collection methods have been described previously (Bramhall et al. 2017; Bramhall et al. 2018). All participants had normal audiometric thresholds (≤ 20 dB HL) from 0.25-8 kHz, normal tympanograms, and robust distortion product otoacoustic emissions in at least one ear. ABR wave I amplitudes were collected using alternating polarity 4 kHz tonebursts presented at four levels (80, 90, 100, and 110 dB peak-equivalent SPL; peSPL) and 3 kHz and 6 kHz tonebursts presented at 110 dB SPL. Participants were grouped into one of four noise exposure groups (Non-Veteran Control, Non-Veteran Firearms, Veteran Low Noise, and Veteran High Noise) based on their Veteran status and their self-reported noise exposure history, including military noise exposure and recreational firearm use. All participants completed a questionnaire that included the question, “Do you have constant or frequent ringing in the ears?” Participants who responded “yes” were marked as having tinnitus. Speech-in-noise perception was assessed using the words in noise test (WIN; Wilson et al. 2007). Multi-

talker babble was presented at 80 dB HL with target speech that was varied in 4 dB steps for a range of signal-to-noise ratios (SNRs) from 0-24 dB. The score on this test represents the SNR required to reach 50% correct, with a higher score indicating poorer performance. Each participant was tested twice, using two different test lists.

The second dataset consists of 102 adults spanning 18 to 73 years of age. ABR wave I amplitudes in this sample were measured using bandpass filtered clicks in quiet and in high-pass noise. Details on the dataset as well as the data collection methods have been described previously (Carcagno & Plack 2020, 2021). All participants had audiometric thresholds for both ears < 20 dB HL for frequencies between 0.125 and 2 kHz, < 40 dB HL at 4 kHz, and no selection criteria for frequencies above 4 kHz.

DPOAEs were not measured as part of this dataset. ABR wave I amplitudes were collected using 80 or 105 dB ppeSPL (peak-to-peak equivalent SPL) clicks that were bandpass filtered between 0.35 and 3 kHz. Clicks were presented either in quiet or embedded in a 20 ms burst of pink noise filtered between 3.5 and 8 kHz (Carcagno & Plack 2020). A separate study reports the participants' performance on a variety of psychophysical tasks including the digit triplets test (DTT; Carcagno & Plack 2021). For the DTT, participants were presented with three monosyllabic digits embedded in 45 or 80 dB SPL noise that was low-pass filtered at 3 kHz. Digits were initially presented at 10 dB SNR and the level was adjusted using a maximum likelihood adaptive procedure to determine the participant's psychometric function. Threshold was defined as the midpoint of the psychometric function.

C. Model fitting

1. Overview of computational approach

A computational approach was used that allows DPOAE and ABR measurements to be combined to generate a prediction of the number of ANF synapses per IHC in individual human participants. Detailed explanations of each step described here are provided in subsequent sections. Table 1 summarizes the model parameters and coefficients. Throughout the manuscript, **bold** symbols represent vectors. Thus, θ represents a vector and $\theta_{[0]}$ represents an element of that vector. See Supplemental Data[§] for a table summarizing all symbols used.

Although the ABR is typically viewed as a readout of auditory nerve function, ABR responses can also be affected by decreased cochlear gain (due to OHC dysfunction). For this reason, the computational approach needs to account for potential OHC dysfunction when generating predictions of synaptic loss. The CMAP is a multi-stage model that includes middle ear filtering, cochlear mechanics, synaptic transmission from the IHC to ANF synapse, and spiking activity of ANFs. By altering the parameters of the cochlear mechanics stage, the CMAP can simulate ANF responses in an ear with OHC dysfunction. Since the ABR response is the summed activity of all ANFs, the simulated ABR can be generated by multiplying the simulated ANF responses by the predicted number of synapses per IHC at each characteristic frequency (CF; i.e., synaptogram) and then summing ANF responses across the entire population. To ensure that the model generates realistic predictions of the synaptogram, synapse count data from human cadavers were used in the Bayesian analysis to set reasonable bounds on the predictions.

The CMAP can generate predictions of the number of low, medium and high spontaneous rate (SR) fibers, enabling incorporation of these predictions into the ABR

simulations. Based on data from animal studies (Schmiedt et al. 1996; Furman et al. 2013), the model assumes first low, then medium, then high SR fibers are lost. To successfully segment the overall predicted synaptogram for an individual participant into SR-specific synaptograms, an exemplar synaptogram (i.e., the number of synapses per IHC in a pristine cochlea) is necessary for comparison. If the exemplar synaptogram has 16 synapses per IHC at 1 kHz and the participant is predicted to have 15 synapses per IHC at 1 kHz, the model will remove one low SR fiber from the pool and then simulate the ABR using the remaining fibers. Since the human cadaver data includes neonates (Wu et al. 2019), the exemplar synaptogram was estimated by assuming that the samples from the youngest cadavers represent a pristine cochlea.

Only the first two stages of the CMAP, middle ear filtering and cochlear mechanics, are required to predict DPOAEs. Thus, the model fitting was split into two stages. The first stage predicted the participant-specific parameters required by the cochlear mechanics stage based on measured audiograms (Keshishzadeh et al. 2021) or DP-grams (Keshishzadeh & Verhulst In Press). The approach for inferring OHC function differs between the two datasets since only audiograms, not DPOAEs, were available for the Carcagno & Plack dataset. The second stage of the model used the CMAP to simulate participant-specific ANF responses for each of the ABR stimuli and then used Bayesian regression analysis to estimate the average number of synapses per IHC as a function of cochlear frequency. For simplicity, all other model parameters (e.g., synaptic transmission) were assumed to be identical across participants.

2. Correcting for DPOAE and pure tone threshold measurements

The CMAP does not directly model OHCs, but simulates basilar membrane (BM) vibration using a series of 1001 longitudinally coupled cochlear mechanical filters. Each filter is centered at a given cochlear frequency indexed by k with a frequency-specific tuning parameter α_k (i.e., the double pole of the cochlear admittance). The effects of OHC dysfunction (i.e., broader cochlear filtering and reduced sensitivity) can be simulated by reducing the gain of these filters. Thus, the pole function, α , can be adjusted in a CF-dependent manner to reflect frequency-specific OHC damage in individual human participants (Verhulst et al. 2012; Verhulst et al. 2016; see Fig. 1A-B for examples).

Here, α represents the pole function corresponding to low stimulus levels where cochlear tuning is sharpest (i.e., α_A^* in Eq. 5 of Verhulst et al. 2018). As stimulus level increases, α is adjusted as described in Verhulst et. al (2018) to simulate cochlear compression and widening of cochlear filters with stimulus level. For this study, only the baseline α was adjusted to simulate OHC damage. Even though the level-dependent changes in the pole function were not altered, modifying the baseline tuning at low stimulus levels still results in reduced sensitivity and less compressive basilar membrane input-output functions at higher stimulus levels. However, the decrease in sensitivity and compression at high stimulus levels is smaller than at lower levels. Therefore, changes in the pole function will have a smaller effect on ABR wave I amplitudes collected at high stimulus levels as compared to low stimulus levels.

The parameters of the CMAP were previously calibrated using human Q_{ERB} estimates, stimulus-frequency and click-evoked OAE data (Verhulst et al. 2012; Verhulst et al. 2018). Because the model simulates the level-dependence of BM

processing, it also simulates distortion-product OAEs (DPOAEs), which were used to predict the individual pole functions. Because the shape of the nonlinearity was not specifically tailored to match experimental DPOAEs, the current iteration of the CMAP overestimates OAE amplitude for a pole function representing a normal hearing participant (Fig. 1C,D). To circumvent this limitation, the modeling approach captures changes in cochlear gain driven by OHC dysfunction. During the fitting process, the individual pole functions are adjusted to match the difference in DPOAE amplitude relative to a hypothetical participant with no OHC damage (i.e., an exemplar participant). The simulated DP-gram, $\mathbf{DP}_s$, for a participant with no OHC damage can be computed by measuring the amplitude of DPOAEs simulated using a normal-hearing pole function. The measured DP-gram, $\mathbf{DP}_M$, for the exemplar participant was estimated by taking the maximum DPOAE amplitude across all participants, where ξ_{if} is the DPOAE amplitude for the primary frequency f of participant i :

$$\mathbf{DP}_{Mf} = \max_{i=1,\dots,74} \xi_{if}$$

Then, the vector of values, δ_i , representing the difference between each participant's measured DP-gram and the exemplar measured DP-gram (i.e., $\delta_i = \mathbf{DP}_M - \xi_i$), was used as the input into a trained neural network which maps $\mathbf{DP}_s - \delta_i$ to α_i (arrows in Fig. 1C,D). The neural network was trained using methods first described in Keshishzadeh et al. (2021) and Keshishzadeh & Verhulst (In Press).

Simulated DPOAEs for 26 randomly generated pole functions were used to train a four-layer neural network. The j th randomly generated pole function, α_j , was a vector of 1001 pole values that mapped onto the k th cochlear frequency. Values for each α_{jk} were

randomly chosen from the range of 0.036 to 0.302, which covers the Q_{ERB} associated with both normal and hearing-impaired populations. The neural network was implemented in Keras (Chollet & others 2015). The four-layer network consists of an input layer of 11 neurons, two hidden layers of 200 neurons each, and an output layer of 1001 neurons. A standard sigmoid function was used for the hidden layers, while the output layer used a sigmoid designed to yield values within the range of 0.036 to 0.302. A learning rate of 0.001 was used with the ADAM optimizer to minimize mean squared error. After the network was trained on the simulated data, individual $\mathbf{DP}_S - \delta_i$ values (normalized by the mean and standard deviation of the training data) were input to predict participant specific pole functions, α_i .

The participant-specific pole functions, α_i , were then used to generate the simulated DP-grams, Ξ_i , for participant i . Since the model fit the change in cochlear gain (rather than the absolute DPOAE level), the simulated DP-gram, Ξ_i , needs to be converted to a value, $\hat{\xi}_i$, that can be compared with the measured DP-gram, ξ_i . Since $\mathbf{DP}_S - \Xi_i = \mathbf{DP}_M - \hat{\xi}_i$, $\hat{\xi}_i = \mathbf{DP}_M - (\mathbf{DP}_S - \Xi_i)$. The corrected DP-gram, $\hat{\xi}_i$, will be referred to as predicted DP-gram in the text to distinguish it from the raw model output, Ξ_i .

To generate individual pole-functions, α_i , from measured audiograms, we followed the methods described in Verhulst et al. (2016) and Keshishzadeh et al. (2021). In this approach, basilar membrane velocity impulse responses are simulated for pole values between 0.036 and 0.302. For a given pole-value at specific CF, the spectral peak dB-difference between the impulse response of this pole-value and the pole-value of a normal-hearing model is calculated. By repeating this procedure for each pole-value at each CF, a lookup table is generated that maps a particular

audiometric hearing loss to the associated pole-value. This lookup table is then used to determine the pole-values for each measured audiogram frequency. The pole values at the audiometric frequencies are then interpolated to estimate the pole function across all CFs. Using the predicted pole functions, α_i , individual audiograms were simulated based on equal-level contour differences in ANF firing rates (Keshishzadeh et al. 2021; Keshishzadeh & Verhulst In Press).

3. Priors for Synapse Counts

Based on experimental observations of synapse counts in human temporal bones (Wu et al. 2019), the average synapse counts per IHC, $N(g)$, were assumed to follow a parabola where g is fractional distance along the cochlear axis. The Greenwood equation, $G(g)$, (Greenwood 1990) was used to convert between g and the cochlear frequency corresponding to that position. To simplify parameter interpretation, the vertex form of the parabola was used. The exponent of the parabola was taken since the average number of synapse counts per IHC can never be less than 0. Let i denote the i th participant in the sample, then the predicted synapse count for participant i at position g is:

$$N_i(g) = \exp(-\exp(\theta_{i[0]})(g - \theta_{i[1]})^2 + \theta_{i[2]}). \quad \text{Eq. 1}$$

This formulation allows for a simple interpretation of parameters. For example, participant i 's maximum number of synapses per IHC, the height of the parabola at its vertex is $\exp(\theta_{i[2]})$, the vertex is positioned at cochlear frequency $g = G(\theta_{i[1]})$, and the curvature of the parabola is defined by $2 \cdot \exp(\theta_{i[0]})$. Taking the negative of the curvature ensures the parabola is always inverted regardless of the value of $\theta_{i[0]}$. The

vector of participant-specific parabola coefficients, θ_i , were assumed to be normally distributed around a population mean vector, Θ , with covariance matrix, Σ . Specifically, $\theta_i \sim MVN(\Theta, \Sigma)$ where MVN is a multivariate normal distribution. Average synapse counts per IHC from a set of 19 human cadaver ears (Wu et al. 2019) were fit with Bayesian regression to generate the priors for Θ and Σ and then used to predict synapse counts in living humans. Although this requires the assumption that the Wu et al. dataset is representative of the range of synaptograms one might expect in the population represented by the participants in this study, it provides a reasonable starting point for the analysis (see Discussion).

Given the assumption that low SR fibers are more likely to be lost in synaptopathy than high SR fibers (Schmiedt et al. 1996; Furman et al. 2013), it is necessary to establish an expected range of fibers for a pristine human cochlea to determine, given a predicted synapse count $N(g)$ per IHC, what fibers to remove. To do this, Equation 1 was reformulated to include an age effect, a , where the average number of synapses per IHC at position g is:

$$A_i(g, a_i) = \exp(-\exp(v_{[0]} + a_i \cdot Y_{[0]})(g - v_{[1]} - a_i \cdot Y_{[1]})^2 + v_{[2]} + a_i \cdot Y_{[2]}) \quad \text{Eq. 2}$$

Here, a_i is the age at death of cadaver i , $\mathbf{Y}$ is a vector of age-specific coefficients that determine the linearly modeled effect of age on the shape of the parabola, and $\mathbf{v}$ is a vector representing the parameters of the parabola. In this formulation, $\theta_i \sim MVN(\mathbf{v} + a_i \cdot \mathbf{Y}, \Psi)$ where Ψ is the covariance matrix for $\mathbf{v} + a_i \cdot \mathbf{Y}$.

4. Predicting Synapse Counts

Individualized CMAPs were used to predict the instantaneous firing rate (in spikes/s) for high, medium and low SR auditory nerve fibers distributed equally at 401 points along the tonotopic axis of the human cochlea (see Fig. 2 for schematic). The ABR response, $ABR_{ip}(t, f, l)$, for replicate p from participant i is calculated as the summed response of the average number of ANFs per IHC.

$$\exp(c_0 + c_1 \cdot S_i) [\sum_{k=1}^{401} N_{ik}^H \cdot R_{ik}^H(t, f, l) + N_{ik}^M \cdot R_{ik}^M(t, f, l) + N_{ik}^L \cdot R_{ik}^L(t, f, l)] \quad Eq. 3$$

N_{ik}^H is the average number of high SR fibers at the characteristic frequency indexed by k for participant i . $R_{ik}^H(t, f, l)$ is the instantaneous firing rate of a high SR auditory nerve fiber for participant i with characteristic frequency indexed by k responding to an ABR tone pip of frequency f and level l where t is time since onset of the ABR tone pip. Medium (M) and low (L) SR fibers are similarly represented. A scaling constant is needed to correct for differences between the simulated and measured ABR waveforms. Since there may be a sex-specific difference in ABR wave I amplitude (e.g., Trune et al. 1988), a sex-specific scaling constant (identical across all participants of a given sex), $\exp(c_0 + c_1 \cdot S_i)$, was included. S_i is 1 if participant i is female, 0 otherwise. Based on initial simulations of ABR wave I amplitude with a normal complement of fibers, c_0 was assigned a Normal prior with a mean of -10 and standard deviation of 1. For the difference between females and males, c_1 , a Normal prior with mean of 0 and standard deviation of 1 was used.

Since the distribution of low, medium and high SR fibers per IHC cannot be determined from human cadaver data, it was assumed that 10%, 16% and 74% of the normal complement of fibers per IHC at each CF were low, medium and high SR,

respectively, based on results from cat and gerbil (Liberman 1978; Tsuji & Liberman 1997). When modeling synaptopathy, it was assumed that low, then medium, then high SR fibers were preferentially lost, based on Furman et al. (2013). Let F_k represent the average number of synapses per IHC in an exemplar cochlea as determined by Equation 2, where age is set to 0 (i.e., a neonate). Although we introduce an age effect in Equation 2, this is only used when fitting the temporal bone data to establish priors for a newborn's synaptogram. The participant's age is not used when generating predictions of their synaptogram. The number of low SR fibers per IHC F_k^L can be calculated as $0.10F_k$. Since N_{ik} represents the full complement of fibers per IHC in participant i , the breakdown of low, medium and high SR fibers is calculated as follows:

$$\begin{aligned}
 N_{ik}^L &= \max(0, 0.10 \cdot F_k - \max(0, F_k - N_{ik})) \\
 N_{ik}^M &= \max(0, 0.16 \cdot F_k - \max(0, (1 - 0.10)F_k - N_{ik})) \\
 N_{ik}^H &= \max(0, 0.74 \cdot F_k - \max(0, (1 - 0.10 - 0.16)F_k - N_{ik}))
 \end{aligned}
 \tag{Eq. 4}$$

Modeled wave I amplitude was defined as the maximum value of $ABR_{ip}(t, f, l)$.

D. Statistical analysis of relationships between predicted synapse counts and age, noise exposure, tinnitus, and speech-in-noise perception

To assess the predicted synapse counts, they were evaluated for relationships with risk factors (age and noise exposure history) and predicted perceptual consequences of synaptopathy (tinnitus and difficulty with speech-in-noise perception). See Supplemental Data[§] for a table summarizing all coefficients used.

The ABR model predicted the synaptogram for each of the individual participants in the two datasets. In the Bramhall et al. dataset, synaptograms were generated for

each of the 74 participants from individual ABR wave I amplitudes for two replicates of six combinations of ABR frequency and level. In the Carcagno & Plack dataset, synaptograms were generated for each of the 102 participants from individual ABR wave I amplitudes for four combinations of ABR click level (80 and 105 dB ppeSPL) and masking noise (quiet vs. masked).

We then evaluated relationships between predicted synapse counts and age, noise exposure, tinnitus, and speech perception in noise. Although the synaptogram is a continuous function of cochlear frequency, the analysis was simplified by using the maximum predicted synapse count per IHC (i.e., the vertex) in our evaluation of synaptopathy risk factors and predicted perceptual consequences. The maximum predicted synapse count per IHC for each participant, ζ_i , is defined as $\exp(\theta_{i[2]})$. Details on how synapse count uncertainty was incorporated into each model as well as information about how the priors for the model coefficients were formulated can be found in the Supplemental Data[§].

To assess whether a participant's age was predictive of the number of synapses per IHC, Bayesian regression was used to fit $\zeta_i = \Lambda_0 + \Lambda_1 \cdot a_i/10$. Here, Λ_0 represents the mean number of synapses for a neonate, Λ_1 is the change in the mean number of synapses per decade of life, and a_i is the age, in years, of participant i .

To assess whether a participant's noise exposure group was predictive of the number of synapses per IHC, Bayesian regression was used to fit $\zeta_i = \exp(\beta_0 + \beta_1 \cdot \text{VLN}_i + \beta_2 \cdot \text{NVF}_i + \beta_3 \cdot \text{VHN}_i)$ where β_0 , β_1 , β_2 , and β_3 are model coefficients and VLN_i , NVF_i , and VHN_i are indicator variables for membership in the Veteran Low Noise, Non-

Veteran Firearms, or Veteran High Noise groups. Expanding using exponential identities results in $\exp(\beta_0) \cdot \exp(\beta_1 \text{VLN}_i) \cdot \exp(\beta_2 \text{NVF}_i) \cdot \exp(\beta_3 \text{VHN}_i)$, which gives an intuitive formulation for interpreting the coefficients of the model. In this formulation, $\exp(\beta_0)$ is the number of synapses for the non-Veteran control group and $\exp(\beta_1)$, $\exp(\beta_2)$, $\exp(\beta_3)$ are the fraction of synapses in the other noise exposure groups relative to the non-Veteran control group.

For tinnitus, it was assumed that the log-odds of the i^{th} participant reporting tinnitus was a function of the synapse count, $\gamma_0 + \gamma_1 \cdot \zeta_i$. As with many log-odds models of probability, the interpretation of the coefficients is not necessarily intuitive. For example, γ_0 is the log-odds probability of reporting tinnitus for a participant with 0 synapses and γ_1 is the change in log-odds of reporting tinnitus for each additional synapse. The probability of tinnitus given synapse number can be calculated as $\exp(\gamma_0 + \gamma_1 \cdot \zeta_i) / (1 + \exp(\gamma_0 + \gamma_1 \cdot \zeta_i))$.

Relationships with two different measures of speech-in-noise perception were evaluated, the WIN (for the Bramhall et al. dataset) and the DTT (for the Carcagno & Plack dataset). The WIN was measured twice for each participant. If WIN_{im} is the score on repeat m of the WIN for participant i , then performance can be predicted as a linear function of synapse number, $\eta_0 + \eta_1 \cdot \zeta_i$. Here, η_0 represents the expected WIN score for a participant with 0 synapses and η_1 is the change in mean WIN score for each additional synapse.

DTT thresholds were assessed twice, first using a background masker level of 45 dB SPL and again using a masker level of 80 dB SPL. In addition, cognitive

performance was assessed using a reading span task. Since cognitive function was available for this study and cognitive performance may affect performance on some psychophysical tasks, performance on the reading span test was included as a predictor. Note that cognitive ability was not evaluated as part of the Bramhall et al. dataset. The threshold for participant i on repeat r , D_{ir} , was predicted as a linear function of synapse number, $d_0 + d_1 \cdot \zeta_i + d_2 \cdot \text{HN}_{ir} + d_3 \cdot \zeta_i \cdot \text{HN}_{ir} + d_4 \cdot \check{\delta}_i$. Here, d_0 , d_1 , d_2 , d_3 , and d_4 are model coefficients, HN_{ir} is an indicator variable indicating whether repeat r for participant i used the high masker level (80 dB SPL), and $\check{\delta}_i$ is the performance of participant i on a reading span task. To expand on the meaning of these coefficients, d_0 is the expected DTT threshold with a 45 dB SPL masker for a participant with 0 synapses, d_1 is the change in mean DTT threshold with a 45 dB SPL masker for each additional synapse, $d_0 + d_2$ is the expected DTT threshold with an 80 dB SPL masker for a participant with 0 synapses, and $d_1 + d_3$ is the change in mean DTT threshold with an 80 dB SPL masker for each additional synapse.

E. Statistical analysis of relationships between ABR wave I amplitude, age, and speech-in-noise perception

Relationships between ABR wave I amplitude, noise exposure, and tinnitus for the Bramhall et al. dataset have been described previously (Bramhall et al. 2017, 2018). and are also presented in the Supplemental Data[§]. Because the relationships between ABR wave I amplitude and both age and speech-in-noise perception were not previously reported for the Bramhall et al. dataset, analyses of those relationships are presented here for comparison with the predicted synapse count analyses of age and speech-in-noise perception described above.

For the Bramhall et al. dataset, two replicates for each of six different ABR stimuli were collapsed into a single measure which represents the sex and DPOAE-corrected ABR wave I amplitude averaged across all three frequencies at 110 dB peSPL. There are 810 measurements gathered from 74 participants. The expected value for ABR wave I amplitude from measurement n is written as μ_{WI_n} and is the sum of several effects:

$$\omega_{if[n]} + \lambda_{i[n]} \cdot \frac{l_n - 110}{30} + \psi \cdot S_{i[n]} + \Pi \cdot \overline{\xi_{i[n]}}$$

Where l_n is the stimulus level, in dB pe SPL, used for ABR measurement n , $S_{i[n]}$ is the sex of the subject for ABR measurement n , and $\overline{\xi_{i[n]}}$ is the average DPOAE amplitude between 3 and 8 kHz of the subject for ABR measurement n . The subject-specific effect of ABR stimulus frequency f (3, 6, or 8 kHz) is represented by $\omega_{if[n]}$ and the subject specific effect of ABR stimulus level on ABR wave I amplitude is represented by $\lambda_{i[n]}$. Coefficients representing the difference in ABR wave I amplitude between males and females (ψ) and the relationship between ABR wave I amplitude and average DPOAE level (Π) are included. Additional details regarding how the models were formulated and the priors for each parameter can be found in the Supplemental Data[§].

The subject-specific average of the neural generator across the three frequencies is represented as $\overline{\omega_i}$. The relationship between each participant's age, a_i , and ABR wave I amplitude is modeled as $\Lambda_0^* + \Lambda_1^* \cdot a_i/10$. If WIN_{im} is the score on repeat m of the WIN for participant i , then performance can be predicted as a linear function of the average of the neural generator across the three frequencies, $\eta_0^* + \eta_1^* \cdot$

$\overline{\omega}_i$. This formulation parallels that used for analyzing the relationship between predicted synapse counts and speech-in-noise perception.

F. Bayesian regression

Bayesian regression was used to generate predicted synapse counts as well as analyze the statistical relationship between predicted synapse count and age, noise exposure, tinnitus, and speech-in-noise perception. In contrast to conventional model fitting, Bayesian analysis allows for simple calculations of credible intervals on parameters that are mathematical functions of fitted coefficients, offers simple construction of realistic hierarchical models (Gelman et al. 2013), and determines the probability that model coefficients take on a particular value or range of values (McMillan & Cannon 2019). In addition to these advantages, the ability to incorporate prior knowledge (e.g., synapse counts from human temporal bones) is crucial for successful model fitting.

Each model was fit four times for 1000 samples following a 1000 sample burn-in period using the pyMC3 implementation of the No-U-Turn Sampler (Hoffman & Gelman 2014; Salvatier et al. 2016). Posterior samples were combined across all fits (i.e., chains) for inference. Gelman-Rubin statistics were computed to ensure that the four fits, each of which started with a random estimate for each parameter, converged to the same final estimate ($\hat{R} < 1.1$). 90% Bayesian credible intervals (CIs) are reported throughout the Results section (see Supplemental Data[§] for 95% CIs). The CI is the central interval in which an unobserved parameter falls with the given probability. The choice of a 90% vs. 95% CI is arbitrary and, when correctly interpreted, does not alter the conclusion.

III. Results

1. Individualization of the CMAP and predicted synapse counts

Predicted synapse counts were generated for each of the 74 participants in the Bramhall et al. dataset by modeling ABR responses to six different ABR stimuli and for each of the 102 participants in the Carcagno & Plack dataset by modeling ABR responses to four different combinations of click level and the presence/absence of highpass masking noise. Since loss of OHC function leads to altered cochlear mechanics such as broader cochlear tuning and a loss of compressive nonlinearities (Robles & Ruggero 2001), the cochlear mechanics stage of the CMAP was individualized for each participant. Since DP-grams were not collected in the Carcagno & Plack dataset, pure tone thresholds were used instead to individualize the cochlear mechanics stage as described in Keshishzadeh et al. (2020; 2021).

Given each participant's measured DP-gram or pure tone thresholds, the gain and tuning of the cochlear mechanics stage of the CMAP were adjusted using the described neural network algorithm. The individualized CMAP was then used to generate a predicted DP-gram. For the Bramhall et al. dataset, the neural network approach was particularly effective in calculating parameters for the cochlear mechanics stage that resulted in predicted DP-grams that closely matched the measured DP-grams (Fig. 3A). The difference between measured and predicted DP-grams was less than ± 5 dB for all primary frequencies in 62% of participants and less than ± 10 dB in 80% of participants (Fig. 3B). The average correlation coefficient for the measured and predicted DP-gram, calculated for each participant, was 0.70 (median correlation coefficient was 0.75; Fig. 3C). For the Carcagno & Plack dataset, the average

correlation coefficient for the measured and predicted audiogram, calculated for each participant, was 0.79 (median correlation coefficient was 0.84; Fig. 3D-F).

The DP-gram-individualized, or audiogram-individualized, CMAP was then used to simulate participant-specific ANF responses for three different SRs (low, medium and high) and 401 different CFs for a total of 1203 simulated ANFs for each participant. The total number of fibers remaining at each CF were then predicted using Bayesian regression assuming low, then medium, then high SR fibers are lost in that order. The predicted synaptograms fell within a biologically plausible range as shown by comparison with previously published data from human cadavers (Wu et al. 2019, Fig. 4A,B). For the purpose of this analysis, the maximum number of synapses (i.e., the number of synapses at the vertex of the synaptogram) were used. Although the predicted number of synapses, spanning a mean value of 5.7 to 16.0 synapses per ANF, largely recapitulates the mean ABR wave I amplitude across all three toneburst frequencies at 110 dB SPL for the Bramhall et al. dataset (Fig. 4C) or the ABR wave I amplitude in response a 105 dB ppeSPL click in quiet for the Carcagno & Plack dataset (Fig. 4D), there are differences in synapse predictions across participants with similar mean ABR wave I amplitude (see arrow in 4C as an example). This indicates that incorporating multiple sources of information, including DP-grams and ABR wave I amplitudes for multiple frequencies and levels may provide additional information that can be used to improve the ability to estimate synapse counts. Indeed, a test of predictive power indicated that using the participant's DP-gram to adjust the cochlear gain stage slightly improved the predictive power of the model as compared to a model

that assumed that all participants had normal cochlear gain (i.e., no DP-gram adjustment; see Supplemental Data[§]).

2. Relationship between predicted synapse counts and age, noise exposure, tinnitus, and speech-in-noise perception

Advancing age was correlated with a decrease in predicted synapse count. In the Bramhall et al. dataset, consisting of young military Veterans and non-Veterans spanning 19 to 34 years of age, an average of 1.0 synapses per IHC (90% CI 0.5 to 1.5) were lost per decade of life (Fig. 5A). In the Carcagno & Plack dataset, consisting of a larger age range spanning 18 to 73 years, an average of 0.7 synapses per IHC (90% CI 0.5 to 0.9) were lost per decade of life (Fig. 6A). Given that age is not a predictor in the algorithm that predicts the synaptograms, these numbers are remarkably consistent with human temporal bone data that show an average of 0.8 synapses per IHC lost per decade of age from 0.2 to 1 kHz and an average of 1.3 synapses per IHC lost per decade of life from 1.4 to 8 kHz (Wu et al. 2019).

In the Bramhall et al. sample, the Non-Veteran Control group had the highest average predicted synapse count (mean 9.4, 90% CI 8.7 to 10.1), followed by the Veteran Low Noise (mean 8.5, 90% CI 7.7 to 9.4), Non-Veteran Firearms (mean 8.1, 90% CI 7.3 to 8.8) and Veteran High Noise groups (mean 7.4, 90% CI 6.7 to 8.1; Fig. 5B). Relative to the Non-Veteran Control group, the Non-Veteran Firearms group was predicted to have 14% (90% CI 5% to 25%) fewer synapses and the Veteran High Noise group was predicted to have 22% fewer synapses (90% CI 13% to 32%). This is consistent with the idea that greater levels of noise exposure, as determined by Veteran status and lifetime noise exposure history, leads to a greater degree of synaptopathy.

Lower predicted synapse counts were associated with a higher probability of reporting tinnitus in the Bramhall et al. dataset (Fig. 5C). The log-odds of reporting tinnitus for a participant with a synapse count at the upper end of the range of predicted synapses (16.0) was -4.29 (90% CI -6.15 to -2.33). This reflects a 2% (90% CI 0 to 5%) probability of reporting tinnitus. The log-odds probability of reporting tinnitus increases at a rate of 0.37 (90% CI 0.14 to 0.60) for each lost synapse. Due to the logit transform, the log-odds cannot directly be translated into a percentage change in the probability of reporting tinnitus for each synapse lost. However, at the lower end of the range of predicted synapses (5.7), the probability of reporting tinnitus is 39% (90% CI 23% to 54%).

Synapse count was also weakly predictive of performance on the WIN test in the Bramhall et al. dataset, which assesses speech-in-noise perception (Fig 5D). Higher scores indicate worse performance on the task. Predicted baseline performance on the WIN test with a full complement of synapses (16.0) was 3.19 dB SNR (90% CI 2.41 to 4.07 dB SNR) increasing to 4.56 dB SNR (90% 4.17 to 4.97 dB SNR) at the lower end of the range of synapses. Each synapse lost increases WIN score (i.e, decreases performance) by 0.13 dB (90% CI 0.02 to 0.24 dB). These results indicate that, based on these data, our best estimate is that the loss of one synapse increases WIN score by 0.13 dB and we are 90% certain that the true size of the effect is somewhere between 0.02 and 0.24 dB.

Synapse count was also weakly predictive of speech-in-noise performance on the DTT in the Carcagno & Plack dataset at both masker levels (45 and 80 dB SPL). Higher DTT thresholds indicate worse performance on the task. Predicted performance

on the DTT task for a participant with a full complement of synapses (16.0) was -10.06 dB SNR (90% CI -10.69 to -9.45) at 45 dB SPL and -9.14 dB SNR (90% CI -9.80 to -8.51) at 80 dB SPL. For a participant at the lower end of the range of synapses (5.7), predicted performance was -8.69 dB SNR (90% CI -9.09 to -8.24) at 45 dB SPL and -8.17 dB SNR (90% CI -8.58 to -7.73) at 80 dB SPL. Each synapse lost increases the DTT threshold (i.e., decreases performance) by 0.13 dB (90% CI 0.04 to 0.22) at 45 dB SPL (Fig. 6B) and 0.10 dB (90% CI 0.00 to 0.19) at 80 dB SPL (Fig. 6C). These results indicate that for an 80 dB SPL masker level, our best estimate is that loss of one synapse increases (i.e. worsens) DTT threshold by 0.10 dB and we are 90% certain that the true size of the effect is somewhere between 0 and 0.19 dB.

3. Relationship between ABR wave I amplitude and age, noise exposure, tinnitus, and speech-in-noise perception

For comparison with the results of analyses that used predicted synapse counts (Section 3.2), the relationship between ABR wave I amplitude and noise exposure history, tinnitus, and performance on the WIN test was assessed for the Bramhall et al. dataset. The results for the noise exposure history and tinnitus analyses are presented in the Supplemental Data[§] because similar analyses using this dataset have been published previously (Bramhall et al. 2017; Bramhall et al. 2018). The results of the age and WIN analyses are presented here because these analyses were not reported previously for this dataset.

After accounting for differences in sex and DPOAE amplitude, the average wave I amplitude at 110 dB peSPL shows a decline of 0.02 μ V (90% CI -0.01 to 0.06 μ V) per decade of life and a weak correlation with WIN score (see Supplemental Data[§] for

additional detail). Each 1 μ V decrease in wave I amplitude increases WIN score (decreases performance) by 2.07 dB (90% CI -0.27 to 4.55 dB). Although coefficients from models generated using different predictors (predicted synapse count versus ABR wave I amplitude) cannot be directly compared, the direction of the relationships are consistent (i.e., aging is associated with reductions in both ABR wave I amplitude and predicted synapse count, while lower wave I amplitudes and predicted synapse counts are both associated with poorer WIN scores).

IV. Discussion

A. Individual synaptogram predictions can be obtained from ABR measurements

The results presented here indicate that fitting of the CMAP can be used to generate synaptogram predictions for individual human participants based on their DP-grams, or audiograms, and ABR wave I amplitude measurements. These predictions fall within the range of synapse counts observed in human temporal bones (Wu et al. 2019, Fig. 4A), which is expected given that the human temporal bone data was used as priors for the synaptogram.

In developing and testing the model, we made several key assumptions. First, we assumed that the human cadaver data from Wu et al. (2019) is representative of the populations in the Bramhall et al. and Carcagno & Plack datasets. Second, we assumed that human cochleograms, including those with a high degree of synaptopathy, are well approximated by a parabola (Equation 1). Third, we assumed that low, then medium, then high SR fibers are lost in that order. Fourth, we assumed that the maximum number of synapses, regardless of the corresponding cochlear frequency, is most

closely associated with potential risk factors and perceptual consequences of synaptopathy. We further expand on these assumptions in the Supplemental Data[§] and explain how these can be adjusted as our knowledge of synaptopathy advances.

B. Synapse predictions show expected relationships with synaptopathy risk factors and predicted perceptual consequences

Predicted synapse counts decreased at a rate of 0.7 (Carcagno & Plack dataset) to 1.0 (Bramhall et al. dataset) synapses per decade of life. Given that the prediction of each participant's synaptogram did not include age as a predictor, these results are remarkably consistent with data from human temporal bones that show a loss of 0.8 (0.2 to 1 kHz) to 1.3 (1.4 to 8 kHz) synapses per decade of life (Wu et al. 2019).

In the Bramhall et al. dataset, predicted synapse counts were lower for the groups with higher noise exposure histories (Veteran High Noise and Non-Veteran Firearms) than for the Non-Veteran Control group, consistent with animal models of noise-induced synaptopathy (e.g., Kujawa & Liberman 2009; Lin et al. 2011; Hickox et al. 2017; Valero et al. 2017). This is also consistent with similar analyses of the relationship between ABR wave I amplitude and noise exposure group in the same sample (Supplemental Data; Bramhall et al. 2017, Table 2).

Report of tinnitus in the Bramhall et al. dataset, a predicted consequence of synaptopathy (Kujawa & Liberman 2015), was also associated with lower synapse counts. This is consistent with a number of reports of relationships between reductions in physiological indicators of synaptopathy (ABR wave I amplitude, EFR magnitude, and MEMR magnitude) and tinnitus perception in humans (Schaette & McAlpine 2011; Gu et

al. 2012; Paul et al. 2017; Wojtczak et al. 2017; Bramhall et al. 2018; Roberts et al. 2018; Bramhall et al. 2019b). Analyses of the relationship between ABR wave I amplitude and tinnitus for this dataset yield similar results (Supplemental Data; Bramhall et al. 2018, Fig. 7A).

In addition, lower predicted synapse counts were weakly correlated with poorer speech-in-noise perception, as measured by the WIN test (Bramhall et al. dataset) and the DTT (Carcagno & Plack dataset), another expected perceptual impact of synaptopathy (Kujawa & Liberman 2015). This result is consistent with the findings of a parallel analysis of the relationship between ABR wave I amplitude and WIN score in the Bramhall et al. dataset (Section III.3). Some studies have shown a relationship between physiological indicators of synaptopathy and complex speech perception (Bramhall et al. 2015; Liberman et al. 2016; Grant et al. 2020; Mepani et al. 2020; Shehorn et al. 2020), while others have not (Fulbright et al. 2017; Bramhall et al. 2018; Guest et al. 2018). Note that the dataset presented in Bramhall et al. (2018) is the same dataset used for this analysis. In addition, the observed relationship between synapse count and speech-in-noise perception is consistent with several animal models of cochlear deafferentation that show auditory perceptual deficits that would be expected to impact speech-in-noise perception. These animal models include: a chinchilla model of cisplatin-induced deafferentation (IHC loss) that results in gap detection deficits (Lobarinas et al. 2020), a rat model of noise-induced synaptopathy that results in poorer signal-in-noise detection (Lobarinas et al. 2017), and a mouse model of ouabain-induced spiral ganglion cell loss that results in poorer tone-in-noise detection (Resnik & Polley 2021). Because IHC, spiral ganglion cell, and synapse loss all lead to

deafferentation, the functional impacts should be similar. Therefore, these findings suggest that synapse loss may lead to auditory perceptual deficits that could negatively impact speech perception.

Although the predicted synapse count 90% credible interval for each participant may appear fairly large (e.g., gray bars in Fig. 4C and D), this illustrates a key advantage of using Bayesian analysis, which provides a probability distribution of the predicted synapse count for each participant. From that probability distribution, we can calculate the probability that an individual's synapse loss is greater than a particular threshold of synapse loss determined to be clinically significant based on the relationship with perceptual complaints such as tinnitus. For example, our data from Fig. 5C suggest that individuals with tinnitus tend to have 10 or fewer predicted synapses. For each patient, we can calculate the probability that the number of synapses is ≤ 10 . This probability would be $\geq 90\%$ for 26 out of the 74 individuals shown in Fig. 5C, indicating clinically significant synapse loss is likely.

C. Future directions

The results presented here lay the groundwork for using the CMAP to predict individualized synaptograms from noninvasive measures of auditory function. Because the human physiological datasets used in this report were drawn from previously-published work, the participant exclusion/inclusion criteria and stimulus design (e.g., ABR frequencies and levels) were not optimized for demonstrating the benefits of this modeling approach. However, this report highlights several key points that should be considered in the design of future studies to further evaluate the utility of the CMAP as a

means for diagnosing cochlear synaptopathy in individual humans. These points are discussed in the following paragraphs.

Comparing synapse count predictions to synaptopathy risk-factors as well as predicted perceptual consequences offers only a limited means of validating this approach in humans. However, despite our inability to directly validate the model predictions of synapse count in living humans, model predictions can be corroborated with various perceptual measures. If model-based synapse predictions are correlated with auditory perceptual complaints such as tinnitus, hyperacusis, and difficulty with speech-in-noise perception, they can be used clinically to identify peripheral auditory damage that is unrelated to OHC function. This may be useful for developing new treatment approaches that target cochlear deafferentation rather than OHC dysfunction.

In this dataset, the predicted synapse counts recapitulate information that can be derived from ABR wave I amplitude in terms of relationships with age, noise exposure history, tinnitus, and speech perception in noise ability, verifying that the CMAP modeling approach can perform at least as well as a basic linear regression model. Superior performance by the CMAP approach is not expected in this case because the study populations consisted of either young adults with normal audiograms (Bramhall et al. dataset) or adults with no more than a mild high frequency hearing loss (Carcagno & Plack dataset). Given that these populations are expected to have minimal OHC damage and the high stimulus levels used (e.g., 110 dB peSPL tonebursts or 105 dB ppeSPL clicks) are dominated by passive cochlear mechanics, simple regression models examining the relationship of ABR wave I amplitude with synaptopathy risk factors and perceptual consequences work well. However, using the CMAP has

advantages over use of ABR wave I amplitudes that may yield superior results in future analyses.

For example, basic linear regression models may not adequately capture complex nonlinearities in cochlear mechanics, inner hair cell transduction, and auditory nerve firing rates. Accounting for such nonlinearities will likely become more important in future studies that incorporate additional physiological data (e.g., other ABR frequencies and levels, EFR measurements, ABR peak latencies, ABR wave III and wave V amplitudes). It's also reasonable to expect that the predicted synapse count metric, as derived from the CMAP, may be more robust than ABR wave I amplitude in studies which include participants with a more diverse range of hearing thresholds.

Decisions regarding how to combine DPOAE (or pure tone threshold) and ABR wave I amplitudes at multiple stimulus levels into a single analysis can vary across studies. For example, many studies will pick a single ABR frequency for further analysis based on which frequency shows the highest correlation with the outcome of interest. The CMAP modeling approach offers a biologically-plausible means for incorporating all DPOAE (or pure tone threshold) and ABR wave I amplitude measurements into a single metric, the predicted synaptogram, regardless of variation in ABR stimuli used across studies (e.g., frequency, level, number of cycles and rise-fall ramp). There are notable differences between the methods in the Bramhall et al. and Carcagno & Plack datasets. In the Bramhall et al. dataset, ABRs were acquired using tonebursts presented at multiple levels and frequencies and DPOAE data was available. In contrast, the Carcagno & Plack dataset used band-pass filtered clicks embedded in high-pass masking noise and only pure tone threshold data was available to infer OHC function.

Despite these varying measurement approaches, we were able to combine the metrics obtained by each study to generate synaptograms for all participants, thereby facilitating a meta-analysis that allows us to make inferences across studies and demonstrate a similar effect of age on predicted synapse counts as well as predicted synapse count on speech-in-noise perception.

This approach could be applied to other studies. For example, as long as the presence of tinnitus was defined similarly, data from all previous studies that evaluated the relationship between a physiological indicator of synaptopathy and tinnitus could be combined to increase the sample size, even if the studies differ in the physiological metric and stimuli used. Similar meta-analyses could be used to evaluate associations between physiological indicators of synaptopathy and noise exposure history or complex speech perception. These types of meta-analyses could be very helpful for generating consensus in a research area plagued by uncertainty due to a large number of previous studies with varied results.

The range of predicted synapse counts is only as good as current knowledge of actual synapse counts. This analysis assumes the human cadaver dataset is drawn from the same population as the participants in this study. However, this is unlikely to be the case. For example, the human cadaver dataset is expected to include a larger range of otologic pathologies that may include more severe auditory damage than found in this experimental cohort. As additional temporal bone data that includes audiometry and etiology becomes available, predictions of synapse counts can be refined. This approach will also allow inclusion of population-specific prior knowledge (e.g., temporal bone data from human cadavers that underwent cisplatin therapy), thereby allowing

incorporation of non-physiological factors that may improve diagnosis of synaptopathy. In addition, the ability to model the tonotopic distribution of synapse counts using a parabola, defined by three parameters, that captures the range of pathologies observed in human temporal bone data (see Supplemental Data[§]) will facilitate future work that attempts to differentiate between diffuse and focal (i.e., high-frequency) loss of synapses. Although the current temporal data is well modeled by a parabola, alternate synaptopathy profiles can easily be accommodated if future studies suggest they exist.

It may be an oversimplification to assume that all low SR fibers, followed by all medium SR fibers, and then finally high SR fibers are lost with synaptopathy. Although the study by Furman et al. (2013) suggests that low and medium SR fibers are preferentially impacted by noise-induced synaptopathy, a reanalysis their data suggests a loss of 26% of high SR fibers as well (Marmel et al. 2015). Further, recent data from EFR studies suggest that high SR fibers may also be vulnerable to noise-induced synaptopathy (Paul et al. 2017; Encina-Llamas et al. 2019; Bramhall et al. 2021). As additional data on the vulnerability of different SR fiber populations becomes available, the model can be updated in terms of how it handles loss of low, medium and high SR fibers. In addition, the IHC transduction stage of the CMAP model can also be updated to simulate decreases in SR due to stereocilia damage (e.g., Liberman & Dodds 1984).

Despite an emphasis on predicting synaptograms with this computational model, this approach cannot currently differentiate between deafferentation due to IHC loss, spiral ganglion cell loss, or cochlear synaptic loss. Although these three types of deafferentation are expected to have similar perceptual impacts, the inability to differentiate between them does pose limitations for determining the appropriate target

for therapeutic treatments (e.g., hair cell regeneration vs. spiral ganglion dendrite repair). However, data from animal models and human temporal bone studies indicate that age- and noise exposure-related synapse loss exceeds IHC loss and occurs prior to loss of spiral ganglion cells (Kujawa & Liberman 2009; Sergeyenko et al. 2013; Viana et al. 2015; Wu et al. 2019; Fernandez et al. 2020). Despite the challenges of pinpointing the exact location of the damage, an individualized measure of deafferentation – regardless of whether it reflects IHC or ANF damage, has utility for differential diagnosis of peripheral auditory dysfunction and assessment of treatment efficacy.

There are additional forms of cochlear damage that were not considered in developing this model. For example, surviving IHCs may have some dysfunction (e.g., stereocilia damage) that contributes to audiometric threshold shifts (Moore et al. 1999; Wu et al. 2020) and may alter auditory nerve responses (Liberman & Dodds 1984; Liberman & Kiang 1984). This subclinical dysfunction may affect the ability of the model to account for altered cochlear gain as well as predict synapse count. Future work can account for IHC dysfunction by adjusting the IHC transduction stage.

V. Conclusions

The modeling approach presented here offers a means for predicting synapse counts in humans from non-invasive physiological data. Not only does it account for the impacts of OHC function on physiological measurements, it also allows for multiple ABR measurements to inform predicted synapse counts. Until a method for imaging cochlear synapses and OHCs in living humans is developed, there will be no direct means of validating OHC or synapse predictions. In the meantime, a model that can use non-

invasive physiological measurements to generate synapse predictions that show relationships with both expected risk factors and perceptual consequences of synaptopathy is a valuable tool.

Acknowledgements

The research described here was supported by the the Department of Veterans Affairs, Veterans Health Administration, Rehabilitation Research and Development Service - Awards #C1484-M (to NFB), #C2104-W (to NFB), and #C2361-C (to NCRAR), the National Institutes of Health National Institute on Deafness and Other Communication Disorders (NIDCD) – R21 CD01696 (to BNB), Fonds Wetenschappelijk Onderzoek - Award #G068621N (to SV and SK), and the European Research Council – Award #678120 (to SV). The opinions and assertions presented are private views of the authors and are not to be construed as official or as necessarily reflecting the views of the Veterans Administration. The authors would like to thank Samuele Carcagno for making the data from Carcagno and Plack (2020, 2021) publicly available as well as answering inquiries about the dataset.

§ See supplementary material at [URL will be inserted by AIP] for additional details regarding statistical methods and a table summarizing all coefficients used.

References

Altoe, A., Pulkki, V., Verhulst, S. (2018). The effects of the activation of the inner-hair-cell basolateral K(+) channels on auditory nerve responses. *Hear Res*, 364, 68-80.

- Bourien, J., Tang, Y., Batrel, C., Huet, A., Lenoir, M., Ladrech, S., Desmadryl, G.,
Nouvian, R., Puel, J. L., Wang, J. (2014). Contribution of auditory nerve fibers to
compound action potential of the auditory nerve. *J Neurophysiol*, 112, 1025-
1039.
- Bramhall, N., Beach, E. F., Epp, B., Le Prell, C. G., Lopez-Poveda, E. A., Plack, C. J.,
Schaette, R., Verhulst, S., Canlon, B. (2019a). The search for noise-induced
cochlear synaptopathy in humans: Mission impossible? *Hear Res*, 377, 88-103.
- Bramhall, N., Ong, B., Ko, J., Parker, M. (2015). Speech Perception Ability in Noise is
Correlated with Auditory Brainstem Response Wave I Amplitude. *J Am Acad
Audiol*, 26, 509-517.
- Bramhall, N. F., Konrad-Martin, D., McMillan, G. P. (2018). Tinnitus and Auditory
Perception After a History of Noise Exposure: Relationship to Auditory Brainstem
Response Measures. *Ear Hear*, 39, 881-894.
- Bramhall, N. F., Konrad-Martin, D., McMillan, G. P., Griest, S. E. (2017). Auditory
Brainstem Response Altered in Humans With Noise Exposure Despite Normal
Outer Hair Cell Function. *Ear Hear*, 38, e1-e12.
- Bramhall, N. F., McMillan, G. P., Gallun, F. J., Konrad-Martin, D. (2019b). Auditory
brainstem response demonstrates that reduced peripheral auditory input is
associated with self-report of tinnitus. *J Acoust Soc Am*, 146, 3849.
- Bramhall, N. F., McMillan, G. P., Kempel, S. D. (2021). Envelope following response
measurements in young veterans are consistent with noise-induced cochlear
synaptopathy. *Hear Res*, 408, 108310.

- Carcagno, S., Plack, C. J. (2020). Effects of age on electrophysiological measures of cochlear synaptopathy in humans. *Hear Res*, 396, 108068.
- Carcagno, S., Plack, C. J. (2021). Effects of age on psychophysical measures of auditory temporal processing and speech reception at low and high levels. *Hear Res*, 400, 108117.
- Chollet, F., others, a. (2015). Keras. *GitHub*. Available from:
<https://github.com/fchollet/keras>
- Dolphin, W. F., Mountain, D. C. (1992). The envelope following response: scalp potentials elicited in the Mongolian gerbil using sinusoidally AM acoustic signals. *Hear Res*, 58, 70-78.
- Encina-Llamas, G., Harte, J. M., Dau, T., Shinn-Cunningham, B., Epp, B. (2019). Investigating the Effect of Cochlear Synaptopathy on Envelope Following Responses Using a Model of the Auditory Nerve. *J Assoc Res Otolaryngol*, 20, 363-382.
- Felder, E., Schrott-Fischer, A. (1995). Quantitative evaluation of myelinated nerve fibres and hair cells in cochleae of humans with age-related high-tone hearing loss. *Hear Res*, 91, 19-32.
- Fernandez, K. A., Guo, D., Micucci, S., De Gruttola, V., Liberman, M. C., Kujawa, S. G. (2020). Noise-induced Cochlear Synaptopathy with and Without Sensory Cell Loss. *Neuroscience*, 427, 43-57.
- Fulbright, A. N. C., Le Prell, C. G., Griffiths, S. K., Lobarinas, E. (2017). Effects of Recreational Noise on Threshold and Suprathreshold Measures of Auditory Function. *Semin Hear*, 38, 298-318.

- Furman, A. C., Kujawa, S. G., Liberman, M. C. (2013). Noise-induced cochlear neuropathy is selective for fibers with low spontaneous rates. *J Neurophysiol*, 110, 577-586.
- Garrett, M., Verhulst, S. (2019). Applicability of subcortical EEG metrics of synaptopathy to older listeners with impaired audiograms. *Hear Res*, 380, 150-165.
- Gelman, A., Carlin, J. B., Stern, H. S., Dunson, D. B., Vehtari, A., Rubin, D. B. (2013). *Bayesian Data Analysis*. (3rd edition ed.). London: CRC Press.
- Grant, K. J., Mepani, A. M., Wu, P., Hancock, K. E., de Gruttola, V., Liberman, M. C., Maison, S. F. (2020). Electrophysiological markers of cochlear function correlate with hearing-in-noise performance among audiometrically normal subjects. *J Neurophysiol*, 124, 418-431.
- Greenwood, D. D. (1990). A cochlear frequency-position function for several species-- 29 years later. *J Acoust Soc Am*, 87, 2592-2605.
- Gu, J. W., Herrmann, B. S., Levine, R. A., Melcher, J. R. (2012). Brainstem auditory evoked potentials suggest a role for the ventral cochlear nucleus in tinnitus. *J Assoc Res Otolaryngol*, 13, 819-833.
- Guest, H., Munro, K. J., Prendergast, G., Millman, R. E., Plack, C. J. (2018). Impaired speech perception in noise with a normal audiogram: No evidence for cochlear synaptopathy and no relation to lifetime noise exposure. *Hear Res*, 364: 142-151.
- Hashimoto, I., Ishiyama, Y., Yoshimoto, T., Nemoto, S. (1981). Brain-stem auditory-evoked potentials recorded directly from human brain-stem and thalamus. *Brain*, 104, 841-859.

- Hickman, T. T., Smalt, C., Bobrow, J., Quatieri, T., Liberman, M. C. (2018). Blast-induced cochlear synaptopathy in chinchillas. *Sci Rep*, 8, 10740.
- Hickox, A. E., Larsen, E., Heinz, M. G., Shinobu, L., Whitton, J. P. (2017). Translational issues in cochlear synaptopathy. *Hear Res*, 349, 164-171.
- Hoffman, M. D., Gelman, A. (2014). The No-U-Turn Sampler: Adaptively Setting Path Lengths in Hamiltonian Monte Carlo. *J Mach Learn Res*, 15, 1593-1623.
- Keshishzadeh, S., Garrett, M., Vasilkov, V., Verhulst, S. (2020). The derived-band envelope following response and its sensitivity to sensorineural hearing deficits. *Hear Res*, 392, 107979.
- Keshishzadeh, S., Garrett, M., Verhulst, S. (2021). Towards Personalized Auditory Models: Predicting Individual Sensorineural Hearing-Loss Profiles From Recorded Human Auditory Physiology. *Trends Hear*, 25, 2331216520988406.
- Keshishzadeh, S., Verhulst, S. (In Press). Individualized Cochlear Models Based on Distortion Product Otoacoustic Emissions. *Conf Proc IEEE Eng Med Biol Soc*.
- Kujawa, S. G., Liberman, M. C. (2009). Adding insult to injury: cochlear nerve degeneration after "temporary" noise-induced hearing loss. *J Neurosci*, 29, 14077-14085.
- Kujawa, S. G., Liberman, M. C. (2015). Synaptopathy in the noise-exposed and aging cochlea: Primary neural degeneration in acquired sensorineural hearing loss. *Hear Res*, 330, 191-199.
- Le Prell, C. G. (2019). Effects of noise exposure on auditory brainstem response and speech-in-noise tasks: a review of the literature. *Int J Audiol*, 58, S3-S32.

- Liberman, M. C. (1978). Auditory-nerve response from cats raised in a low-noise chamber. *J Acoust Soc Am*, 63, 442-455.
- Liberman, M. C., Dodds, L. W. (1984). Single-neuron labeling and chronic cochlear pathology. III. Stereocilia damage and alterations of threshold tuning curves. *Hear Res*, 16, 55-74.
- Liberman, M. C., Epstein, M. J., Cleveland, S. S., Wang, H., Maison, S. F. (2016). Toward a Differential Diagnosis of Hidden Hearing Loss in Humans. *PLoS One*, 11, e0162726.
- Liberman, M. C., Kiang, N. Y. (1984). Single-neuron labeling and chronic cochlear pathology. IV. Stereocilia damage and alterations in rate- and phase-level functions. *Hear Res*, 16, 75-90.
- Lin, H. W., Furman, A. C., Kujawa, S. G., Liberman, M. C. (2011). Primary neural degeneration in the Guinea pig cochlea after reversible noise-induced threshold shift. *J Assoc Res Otolaryngol*, 12, 605-616.
- Lobarinas, E., Salvi, R., Ding, D. (2020). Gap Detection Deficits in Chinchillas with Selective Carboplatin-Induced Inner Hair Cell Loss. *J Assoc Res Otolaryngol*, 21(6): 475-483.
- Lobarinas, E., Spankovich, C., Le Prell, C. G. (2017). Evidence of “hidden hearing loss” following noise exposures that produce robust TTS and ABR wave-I amplitude reductions. *Hearing research*, 349, 155-163.
- Margolis, R. H. (1993). Detection of hearing impairment with the acoustic stapedius reflex. *Ear Hear*, 14, 3-10.

- Marmel, F., Rodríguez-Mendoza, M. A., Lopez-Poveda, E. A. (2015). Stochastic undersampling steepens auditory threshold/duration functions: implications for understanding auditory deafferentation and aging. *Front Aging Neurosci*, 7, 63.
- McMillan, G. P., Cannon, J. B. (2019). Bayesian Applications in Auditory Research. *J Speech Lang Hear Res*, 62, 577-586.
- Mepani, A. M., Kirk, S. A., Hancock, K. E., Bennett, K., de Gruttola, V., Liberman, M. C., Maison, S. F. (2020). Middle Ear Muscle Reflex and Word Recognition in "Normal-Hearing" Adults: Evidence for Cochlear Synaptopathy? *Ear Hear*, 41, 25-38.
- Moore, B. C., Vickers, D. A., Plack, C. J., Oxenham, A. J. (1999). Inter-relationship between different psychoacoustic measures assumed to be related to the cochlear active mechanism. *J Acoust Soc Am*, 106, 2761-2778.
- Otte, J., Schunknecht, H. F., Kerr, A. G. (1978). Ganglion cell populations in normal and pathological human cochleae. Implications for cochlear implantation. *Laryngoscope*, 88, 1231-1246.
- Paul, B. T., Bruce, I. C., Roberts, L. E. (2017). Evidence that hidden hearing loss underlies amplitude modulation encoding deficits in individuals with and without tinnitus. *Hear Res*, 344, 170-182.
- Resnik, J., Polley, D. B. (2021). Cochlear neural degeneration disrupts hearing in background noise by increasing auditory cortex internal noise. *Neuron*, 109, 984-996 e984.
- Roberts, L. E., Paul, B. T., Bruce, I. C. (2018). Erratum and comment: Envelope following responses in normal hearing and in tinnitus. *Hear Res*, 361, 157-158.

- Robles, L., Ruggero, M. A. (2001). Mechanics of the mammalian cochlea. *Physiol Rev*, 81, 1305-1352.
- Ruan, Q., Ao, H., He, J., Chen, Z., Yu, Z., Zhang, R., Wang, J., Yin, S. (2014). Topographic and quantitative evaluation of gentamicin-induced damage to peripheral innervation of mouse cochleae. *Neurotoxicology*, 40, 86-96.
- Salvatier, J., Wiecki, T., Fonnesbeck, C. (2016). Probabilistic programming in Python using PyMC3. *PeerJ Comput Sci*, 2, e55.
- Schaette, R., McAlpine, D. (2011). Tinnitus with a normal audiogram: physiological evidence for hidden hearing loss and computational model. *J Neurosci*, 31, 13452-13457.
- Schmiedt, R. A., Mills, J. H., Boettcher, F. A. (1996). Age-related loss of activity of auditory-nerve fibers. *J Neurophysiol*, 76, 2799-2803.
- Sergeyenko, Y., Lall, K., Liberman, M. C., Kujawa, S. G. (2013). Age-related cochlear synaptopathy: an early-onset contributor to auditory functional decline. *J Neurosci*, 33, 13686-13694.
- Shaheen, L. A., Valero, M. D., Liberman, M. C. (2015). Towards a Diagnosis of Cochlear Neuropathy with Envelope Following Responses. *J Assoc Res Otolaryngol*, 16, 727-745.
- Shehorn, J., Strelcyk, O., Zahorik, P. (2020). Associations between speech recognition at high levels, the middle ear muscle reflex and noise exposure in individuals with normal audiograms. *Hear Res*, 392, 107982.
- Trune, D. R., Mitchell, C., Phillips, D. S. (1988). The relative importance of head size, gender and age on the auditory brainstem response. *Hear Res*, 32, 165-174.

- Tsuji, J., Liberman, M. C. (1997). Intracellular labeling of auditory nerve fibers in guinea pig: central and peripheral projections. *J Comp Neurol*, 381, 188-202.
- Valero, M. D., Burton, J. A., Hauser, S. N., Hackett, T. A., Ramachandran, R., Liberman, M. C. (2017). Noise-induced cochlear synaptopathy in rhesus monkeys (*Macaca mulatta*). *Hear Res*, 353, 213-223.
- Valero, M. D., Hancock, K. E., Maison, S. F., Liberman, M. C. (2018). Effects of cochlear synaptopathy on middle-ear muscle reflexes in unanesthetized mice. *Hear Res*, 363, 109-118.
- Vasilkov, V., Garrett, M., Mauermann, M., Verhulst, S. (2021). Enhancing the sensitivity of the envelope-following response for cochlear synaptopathy screening in humans: The role of stimulus envelope. *Hear Res*, 400, 108132.
- Verhulst, S., Altoe, A., Vasilkov, V. (2018). Computational modeling of the human auditory periphery: Auditory-nerve responses, evoked potentials and hearing loss. *Hear Res*, 360, 55-75.
- Verhulst, S., Dau, T., Shera, C. A. (2012). Nonlinear time-domain cochlear model for transient stimulation and human otoacoustic emission. *J Acoust Soc Am*, 132, 3842-3848.
- Verhulst, S., Jagadeesh, A., Mauermann, M., Ernst, F. (2016). Individual Differences in Auditory Brainstem Response Wave Characteristics: Relations to Different Aspects of Peripheral Hearing Loss. *Trends Hear*, 20.
- Viana, L. M., O'Malley, J. T., Burgess, B. J., Jones, D. D., Oliveira, C. A., Santos, F., Merchant, S. N., Liberman, L. D., Liberman, M. C. (2015). Cochlear neuropathy

- in human presbycusis: Confocal analysis of hidden hearing loss in post-mortem tissue. *Hear Res*, 327, 78-88.
- Wilson, R. H., Carnell, C. S., Cleghorn, A. L. (2007). The Words-in-Noise (WIN) test with multitalker babble and speech-spectrum noise maskers. *J Am Acad Audiol*, 18, 522-529.
- Wojtczak, M., Beim, J. A., Oxenham, A. J. (2017). Weak Middle-Ear-Muscle Reflex in Humans with Noise-Induced Tinnitus and Normal Hearing May Reflect Cochlear Synaptopathy. *eNeuro*, 4.
- Wu, P. Z., Liberman, L. D., Bennett, K., de Gruttola, V., O'Malley, J. T., Liberman, M. C. (2019). Primary Neural Degeneration in the Human Cochlea: Evidence for Hidden Hearing Loss in the Aging Ear. *Neuroscience*, 407, 8-20.
- Wu, P. Z., O'Malley, J. T., de Gruttola, V., Liberman, M. C. (2020). Age-Related Hearing Loss Is Dominated by Damage to Inner Ear Sensory Cells, Not the Cellular Battery That Powers Them. *J Neurosci*, 40, 6357-6366.

Figure Captions

Figure 1: Schematic illustrating the parameter predictions for the cochlear gain

stage of the CMAP. A. OHC dysfunction is reflected by changes in cochlear tuning.

The cochlear tuning in the CMAP is defined by a vector of parameters known as the pole function. Changes to the parameters of the pole function alter cochlear tuning and gain. The black line represents the pole function of a cochlea with no OHC damage (i.e., the exemplar). The other lines are pole functions, as predicted by the machine learning algorithm, for four participants in the Bramhall et al. dataset. Pole values range from 0.036 to 0.302. Larger pole values (relative to the exemplar for the same CF) represent more severe OHC damage. **B.** The sharpness of tuning (Q_{ERB}), can be directly calculated from the pole function. The black line represents the Q_{ERB} of an exemplar cochlea and the other lines show the estimated Q_{ERB} for the four participants shown in

panel A. **C.** Measured DP-grams for each of the 74 participants in the Bramhall et al. dataset (gray lines) are shown. Colored lines show the DP-grams for the four participants from panels A-B. The exemplar DP-gram for the measured data is shown by the thick black line with circles. **D.** Simulated DP-grams for an exemplar (black line) and the four participants shown in A-C. Since simulated DP-grams are higher in amplitude than measured DP-grams, the goal is to match the change in DPOAE level (black arrows in C and D) rather than the absolute DPOAE level. The online version of the paper shows data from each participant in color to facilitate comparing data across plots.

Figure 2: Schematic of ABR model illustrating how the CMAP prediction of ANF response is fitted to the participant's wave I amplitude. The first column shows the predicted response of low, medium and high ANF units as a function of time in response to an 80 dB SPL, 4 kHz toneburst. Each row of the heatmap is the instantaneous firing rate of a unit with the corresponding CF. Predictions are generated using the individualized CMAP (i.e., the CMAP after adjusting for the participant's DP-gram). The second column is the synaptogram, which represents the number of low, medium and high SR fibers as a function of CF. The synaptogram is a free parameter in the model. The third column is the summed instantaneous firing rate of all ANF fibers of a given CF (i.e., first column multiplied by second column). Given the small numbers of low and medium SR fibers in a cochlea as well as their low firing rates, the summed instantaneous firing rates of the low and medium SR fibers may be difficult to see in the figure. However, this highlights their relative contribution to the ABR. The predicted ABR response is generated by summing across the third column. Predicted wave I amplitude is the maximum value of the predicted ABR response. The text on each panel indicates the corresponding component in Equation 3. The color scale is the same for all panels within a column; however, the color scale for the summed firing rate covers a larger range than the color scale for the ANF firing rate.

Figure 3: Individualizing the cochlear mechanics stage of the CMAP for each participant. **A.** Comparison of predicted DP-grams from the individualized CMAP with the measured DP-gram for each of four different participants from the Bramhall et al. dataset. **B.** Measured DPOAE level vs. predicted DPOAE level at $f_2 = 4$ kHz. Gray line indicates unity. **C.** Distribution of correlation coefficients between the measured and predicted DP-gram for each participant in the Bramhall et al. dataset. **D.** Comparison of predicted audiograms from the individualized CMAP with the measured audiogram for each of four different participants from the Carcagno & Plack dataset. **E.** Measured threshold vs. predicted threshold for a 4 kHz pure tone. Gray line indicates unity. **F.** Distribution of correlation coefficients between the measured and predicted audiograms for each participant in the Carcagno & Plack dataset.

Figure 4: Predicted synapse counts. **A, B.** Predicted synaptogram for each individual participant from the Bramhall et al. (A) and Carcagno & Plack (B) datasets. Data from Wu et al. (2019) are overlaid to demonstrate that the synaptograms fall within a reasonable range of predicted values. Measured ABR frequencies in the Bramhall et al. dataset are shown with vertical dotted lines (A) and the frequency spectrum of the filtered click in the Carcagno & Plack dataset is shown by a solid gray rectangle (B). **C, D.** For all subsequent analyses, the maximum number of synapses from each participant's synaptogram (i.e., the vertex) was used. Maximum number of predicted synapses per IHC is plotted against the ABR wave I amplitude for a toneburst at 110 dB peSPL (mean of 3, 4 and 6 kHz) for the Bramhall dataset (C) or for a 105 dB ppeSPL click in quiet for the Carcagno & Plack dataset (D). Gray bars indicate 90% CI for

predictions. Arrow in C indicates a cluster of participants with similar wave I amplitudes, but differing synapse counts.

Figure 5: Relationship between predicted synapse count and synaptopathy risk factors/perceived perceptual consequences in the Bramhall et al. dataset. A.

Predicted synapse count by age for each participant. **B.** Range of predicted synapse counts for each noise exposure group. The filled gray band is the 90% CI for the Non-Veteran Control group and is shown for reference. **C.** Probability of reporting tinnitus given the predicted synapse count. Individual participants are shown by gray circles and are plotted at 0% (the participant didn't report tinnitus) or 100% (the participant reported tinnitus). Data is jittered along the y-axis to facilitate visualization of individual data points. **D.** WIN score given the predicted synapse count. For all panels, gray circles

show predicted synapse counts for individual participants and the black line and shaded region indicate the mean and 90% CI of the model prediction.

Figure 6: Relationship between predicted synapse count and synaptopathy risk factors/predicted perceptual consequences in the Carcagno & Plack dataset. A. Predicted synapse count by age for each participant. **B, C.** DTT threshold given the predicted synapse count for low (45 dB SPL) and high noise (80 dB SPL) conditions, respectively. For all panels, gray circles show predicted synapse counts for individual participants and the black line and shaded region indicate the mean and 90% CI of the model prediction.

Supplement for Buran et al. 2021

1 Greenwood equation

The Greenwood equation (Greenwood, 1990), $G(g)$ maps fractional position, g , along the basilar membrane to the corresponding cochlear frequency, in Hz:

$$G(g) = 1.65 \cdot (10^{2.1 \cdot g} - 0.88)$$

To map frequency in Hz, f , to fractional position, g , along the basilar membrane:

$$G^{-1}(f) = \frac{\log_{10}(f/1.65 + 0.88)}{2.1}$$

2 Incorporating uncertainty of estimates in synapse count

In Bayesian regression, it's common to use log transforms for parameters that cannot take on negative values (such as the number of synapses) to simplify defining priors. Thus, although predicted synapse count is the parameter of interest, the logarithm of synapse count (represented by $\theta_{i[2]}$) is the estimated parameter.

An intrinsic outcome of fitting unobserved parameters using Bayesian regression is that a posterior distribution is produced for each parameter. The posterior distribution reflects the probability that the parameter takes on a particular value or range of values. Fitting the ABR model (Eq. 3 in the manuscript) gives a posterior distribution for each $\theta_{i[2]}$ (Supplemental Fig. 1A). The mean value of the posterior distribution for $\theta_{i[2]}$ (i.e., the expected value) can be used as the measure of the logarithm of the predicted synapse count for subject i . This would be a very simple approach for subsequent analysis of predicted synapse count vs. age, noise exposure, tinnitus, and speech-in-noise perception. However, this approach assumes that there's no uncertainty in the predicted

synapse count. This is certainly not the case (even when using conventional regression approaches). The standard deviation of the posterior distribution for $\theta_{i[2]}$ is a measure of certainty of the predicted synapse count. Smaller standard deviations indicate greater certainty whereas larger standard deviations reflect greater uncertainty.

This measure of certainty can be incorporated into analyses of the relationship between predicted synapse count and age, noise exposure, tinnitus, and speech-in-noise perception. One approach is to use a meta-analytical technique that is commonly used when comparing results across multiple studies where only means and standard deviation (or standard error) are reported. This ensures that statistical analysis of the relationship between predicted synapse count and age, noise exposure group, tinnitus and speech-in-noise perception correctly accounts for certainty (or uncertainty) in estimates of each subject's predicted synapse count.

Since the posterior on $\theta_{i[2]}$ is reasonably normal (Supplemental Fig. 1B), the predicted synapse count, ζ_i , can be described based on the mean, $\hat{\theta}_i$, and standard error, $\text{sd}(\hat{\theta}_i)$, of the posterior for $\theta_{i[2]}$. Uncertainty in the estimate of synapse count is then modeled as:

$$\begin{aligned} \hat{\theta}_i &\sim \text{Normal}(\mu_i, \text{sd}(\hat{\theta}_i)) \\ \zeta_i &= \exp(\mu_i) \end{aligned} \tag{1}$$

Exact details of how this was incorporated for each model are provided in the appropriate section.

3 Relationship between predicted synapse count and age

Given the participant's age, a_i , a linear relationship between age and predicted synapse number, ζ_i , is as-

Supplemental Figure 1: The posterior of $\theta_{i[2]}$ gives an expected value (mean) and measure of uncertainty (standard deviation). **A.** Mean and standard deviation of $\theta_{i[2]}$ for all subjects in the Bramhall et al. dataset. The blue and orange markers correspond to the examples shown in B. **B.** Posterior distributions of $\theta_{i[2]}$ for two subjects.

sumed.

$$\zeta_i = \Lambda_0 + \Lambda_1 \cdot \frac{a_i}{10} \quad (2)$$

Supplemental Eq. 1, which defines ζ_i , is incorporated into this model to allow us to incorporate uncertainty regarding predicted synapse counts. The priors for Λ_0 and Λ_1 are derived from published synapse counts from human temporal bone data (Wu et al., 2019) which demonstrate a mean intercept of 17 synapses per IHC with a loss of 1.1 synapses per decade of life.

$$\Lambda_0 \sim \text{Normal}(17, 3.8)$$

$$\Lambda_1 \sim \text{Normal}(-1.1, 0.4)$$

4 Relationship between predicted synapse count and noise exposure

VLN_i , NVF_i , and VHN_i are indicator variables for the i th subject's membership in the Veteran low noise, non-Veteran firearms, and Veteran high noise groups, respectively.

$$\mu_i = \beta_0 + \beta_1 \cdot \text{VLN}_i + \beta_2 \cdot \text{NVF}_i + \beta_3 \cdot \text{VHN}_i \quad (3)$$

Supplemental Eq. 1, which defines μ_i , is incorporated into this model. The prior for β_0 is based on the mean and standard deviation of $\theta_{[2]}$ as derived from

the age model (Eq. 2 in the manuscript) fit to the human cadaver dataset (Wu et al., 2019) when age, a , is set to 0. The remaining coefficients are set to weakly-informative priors.

$$\beta_0 \sim \text{Normal}(2.8, 0.2)$$

$$\beta_1 \sim \text{Normal}(0, 1)$$

$$\beta_2 \sim \text{Normal}(0, 1)$$

$$\beta_3 \sim \text{Normal}(0, 1)$$

The relationship between noise exposure and predicted synapse count can be derived by taking the exponent of both sides of Supplemental Eq. 3.

$$\zeta_i = \exp(\beta_0 + \beta_1 \cdot \text{VLN}_i + \beta_2 \cdot \text{NVF}_i + \beta_3 \cdot \text{VHN}_i) \quad (4)$$

In this formulation $\exp(\beta_0)$ is the mean number of synapses in the non-Veteran control group. Since a subject can only belong in one noise exposure group, $\exp(\beta_1)$, $\exp(\beta_2)$, and $\exp(\beta_3)$ represent the ratio of the number of synapses in the corresponding noise exposure group relative to the non-Veteran control group. This is illustrated by looking at a subject in the Veteran high-noise group. For this subject, VHN_i is 1 and both VLN_i and NVF_i are 0. Thus, β_1 and β_2 drop out of the equation, leaving $\exp(\beta_0 + \beta_3)$. Expanding using exponential identities gives $\exp(\beta_0) \cdot \exp(\beta_3)$.

5 Relationship between predicted synapse count and tinnitus

Given the tinnitus status, T_i , for the i th subject ($T_i = 1$ when the subject has tinnitus, 0 otherwise), a linear relationship between predicted synapse number, ζ_i , and the log-odds of having tinnitus is assumed.

The log-odds of subject i having tinnitus is then defined as:

$$\begin{aligned} \text{logit}^{-1}(x) &= \frac{\exp(x)}{\exp(x) + 1} \\ p_{T_i} &= \text{logit}^{-1}(\gamma_0 + \gamma_1 \cdot \zeta_i) \\ T_i &\sim \text{Bernoulli}(p_{T_i}) \end{aligned} \quad (5)$$

Supplemental Eq. 1, which defines ζ_i , is incorporated into this model. A conditional means prior approach (Bedrick et al., 1996), where priors are placed on two values of p_{T_i} , was used. A young, non-Veteran subject was assumed to have 16 synapses (the maximum of the range of predicted synapses observed in the dataset) while Veterans would have 8.5 synapses (the mean of the range of predicted synapses observed in the dataset). A large-scale study of tinnitus among male Veterans and non-Veterans in the United States showed a low probability of having tinnitus in young, non-Veterans of 1.5% (Folmer et al., 2011). In contrast, only 27.6% of military Veterans reported having no tinnitus (Henry et al., 2019) with 44.3% reporting constant tinnitus. Since the probability of reporting tinnitus can depend on the exact question asked (e.g., intermittent vs. constant), relatively broad priors on the probability of tinnitus were used (Fig. 2A), which induced a joint prior on γ_0 and γ_1 (Fig. 2B):

$$\begin{aligned}\text{logit}^{-1}(\gamma_0 + \gamma_1 \cdot 8.5) &\sim \text{Beta}(\alpha = 2, \beta = 5) \\ \text{logit}^{-1}(\gamma_0 + \gamma_1 \cdot 16) &\sim \text{Beta}(\alpha = 16, \beta = 1)\end{aligned}$$

6 Relationship between predicted synapse count and speech-in-noise perception

Given the m th words in noise (WIN) score for the i th subject, WIN_{im} , a linear relationship between predicted synapse number, ζ_i , and WIN_{im} , was assumed.

$$\begin{aligned}\mu_{\text{WIN}_i} &= \eta_0 + \eta_1 \cdot \zeta_i \\ \sigma_{\text{WIN}} &\sim \text{HalfCauchy}(1) \\ \text{WIN}_{im} &\sim \text{Normal}(\mu_{\text{WIN}_i}, \sigma_{\text{WIN}})\end{aligned}\tag{6}$$

Supplemental Eq. 1, which defines ζ_i , is incorporated into this model. A conditional means prior approach (Bedrick et al., 1996) where priors are placed on two values of μ_{WIN_i} was used. This allows for specifying prior knowledge in terms of the expected range of WIN scores for a subject with a particular synapse count. Considering the difficulty of placing a reasonable prior directly on η_0 , which is the expected WIN score when the auditory nerve is completely missing,

Supplemental Figure 2: Use of conditional means priors for probability of tinnitus. **A.** Prior and posterior distributions for probability of tinnitus given the expected synapse count, ζ . **B.** Although no priors were directly set on γ_0 and γ_1 , the priors from A induce a joint prior on γ_0 and γ_1 as shown by the bivariate distribution. The univariate distribution of γ_0 and γ_1 are shown in the margins. The bivariate and univariate posterior distributions are also shown.

the conditional means approach has some advantages despite the increased computational complexity.

A young, non-Veteran subject was assumed have approximately 16 synapses (the maximum of the range of predicted synapses observed in the dataset) while Veterans would have approximately 8.5 synapses (the mean of the range of predicted synapses observed in the dataset). Young, non-Veteran subjects have a mean WIN score of 2.7 dB SNR (standard deviation 1.5 dB) and military Veterans have a mean WIN score of 8 dB SNR (standard deviation 3.5 dB), giving the following priors:

$$\begin{aligned}\eta_0 + \eta_1 \cdot 16 &\sim \text{Normal}(2.7, 1.5) \\ \eta_0 + \eta_1 \cdot 8.5 &\sim \text{Normal}(8, 3.5)\end{aligned}$$

Placing these priors on values of the function (Fig. 3A) induced a joint prior on η_0 and η_1 (Fig. 3B).

Supplemental Figure 3: Use of conditional means priors for WIN score. **A.** Prior and posterior distributions for WIN score, WIN, given the expected synapse count, ζ . **B.** Although no priors were directly set on η_0 and η_1 , the priors from A induce a joint prior on η_0 and η_1 as shown by the bivariate distribution. The univariate distribution of η_0 and η_1 are shown in the margins. The bivariate and univariate posterior distributions are also shown to illustrate that the prior had a very weak influence, relative to the likelihood of the data, on the overall model prediction.

7 Relationship between ABR wave I amplitude and age, noise exposure, tinnitus, and speech-in-noise perception

Although the relationships between ABR wave I amplitude and both noise exposure and tinnitus have been reported previously (Bramhall et al., 2017, 2018), there are some differences in model design. For example, the noise exposure model in Bramhall et al. (2017) includes wave III and V amplitudes and the tinnitus model in Bramhall et al. (2018) is a meta-analysis that incorporates data from multiple studies. To facilitate comparison with the CMAP, the data is re-analyzed using the exact set of subjects and physiological measurements that were also used for generating predicted synapse counts.

Since there are two replicates for six different ABR stimuli, these measures need to be first collapsed into a single measure which represents the sex and DPOAE-corrected ABR wave I amplitude averaged

across all three frequencies at 110 dB peSPL. Specifically, WI_n represents the ABR wave I amplitude from measurement n . There are 810 measurements gathered from 74 participants. The expected value for ABR wave I amplitude, μ_{WI_n} , is the sum of several effects:

$$\mu_{WI_n} = \omega_{if[n]} + \lambda_{i[n]} \cdot \frac{l_n - 110}{30} + \psi \cdot S_{i[n]} + \Pi \cdot \overline{\xi_{i[n]}}$$

$$WI_n \sim \text{Normal}(\mu_{WI_n}, \sigma_{WI})$$

Where l_n is the stimulus level, in dB peSPL, used for ABR measurement n , $S_{i[n]}$ is the sex of the subject for ABR measurement n , and $\overline{\xi_{i[n]}}$ is the average DPOAE amplitude between 3 and 8 kHz of the subject for ABR measurement n . ω_{if} is the subject-specific effect of ABR stimulus frequency f (3, 6 or 8 kHz) and λ_i is the subject-specific effect of ABR stimulus level on ABR wave I amplitude. Both ω_{if} and λ_i are hierarchical parameters centered around their respective group means:

$$\omega_{if} \sim \text{Normal}(\mu_{\omega_f}, \sigma_{\omega})$$

$$\lambda_i \sim \text{Normal}(\mu_{\lambda}, \sigma_{\lambda})$$

ψ is a coefficient representing the difference in ABR wave I amplitude between males and females and Π is the coefficient representing the relationship between ABR wave I amplitude and average DPOAE level. Priors for the coefficients are as follows:

$$\mu_{\omega_f} \sim \text{Normal}(0.35, \sigma_{\mu_{\omega_f}})$$

$$\mu_{\lambda} \sim \text{Normal}(0, 1)$$

$$\psi \sim \text{Normal}(0, 1)$$

$$\Pi \sim \text{Normal}(0, \sigma_{\Pi})$$

All σ parameters were set to HalfCauchy(1).

In this formulation, ω_{if} is the subject and frequency-specific ABR wave I amplitude at 110 dB peSPL after correcting for DPOAE and sex (i.e., the ABR wave I amplitude at 110 dB peSPL assuming the subject is male and has a DPOAE amplitude of 0). The average across all three frequencies is represented as $\overline{\omega_i}$. The relationship between predicted synapse count (ζ_i) and age (Supplemental Eq. 2),

noise exposure (Supplemental Eq. 4), tinnitus (Supplemental Eq. 5), and speech in noise perception (Supplemental Eq. 6) have already been defined. Substituting $\bar{\omega}_i$ for ζ_i generates an equivalent model that uses average ABR wave I amplitude instead of synapse count as the predictor. Model coefficients are denoted with an asterisk to differentiate them from the coefficients used for describing the relationship between synapse count and age, noise exposure, tinnitus, and speech-in-noise discrimination.

Specifically, the relationship between age and ABR wave I amplitude is modeled as:

$$\bar{\omega}_i = \Lambda_0^* + \Lambda_1^* \cdot \frac{a_i}{10}$$

Priors for Λ_0^* and Λ_1^* were averaged from two previous studies on the relationship between age and ABR wave I amplitude (Bramhall et al., 2015; Konrad-Martin et al., 2012).

$$\begin{aligned}\Lambda_0^* &\sim \text{Normal}(0.56, 0.23) \\ \Lambda_1^* &\sim \text{Normal}(-0.006, 0.022)\end{aligned}$$

The relationship between ABR wave I amplitude and noise exposure is modeled as:

$$\mu_{\bar{\omega}_i} = \exp(\beta_0^* + \beta_1^* \cdot \text{VLN}_i + \beta_2^* \cdot \text{NVF}_i + \beta_3^* \cdot \text{VHN}_i)$$

The relationship between ABR wave I amplitude and expected probability of reporting tinnitus is modeled as:

$$p_{T_i} = \text{logit}^{-1}(\gamma_0^* + \gamma_1^* \cdot \bar{\omega}_i)$$

The relationship between ABR wave I amplitude and expected WIN score is:

$$\mu_{\text{WIN}_i} = \eta_0^* + \eta_1^* \cdot \bar{\omega}_i$$

Conditional means priors were placed on p_{T_i} and μ_{WIN} using the same rationale described for the corresponding analysis of predicted synapse count, ζ_i (see supplemental sections 5 and 6). Specifically, a young, non-Veteran subject would have an average ABR wave I amplitude of $0.6 \mu V$ and Veterans would

have a wave I amplitude of $0.35 \mu V$ (the mean of the range of wave I amplitudes at 110 dB peSPL observed in the dataset). Therefore, the conditional means priors for the tinnitus model were:

$$\begin{aligned}\text{logit}^{-1}(\gamma_0^* + \gamma_1^* \cdot 0.35) &\sim \text{Beta}(\alpha = 2, \beta = 5) \\ \text{logit}^{-1}(\gamma_0^* + \gamma_1^* \cdot 0.60) &\sim \text{Beta}(\alpha = 16, \beta = 1)\end{aligned}$$

The conditional means priors for the speech in noise model were:

$$\begin{aligned}\eta_0^* + \eta_1^* \cdot 0.35 &\sim \text{Normal}(8, 3.5) \\ \eta_0^* + \eta_1^* \cdot 0.60 &\sim \text{Normal}(2.7, 1.5)\end{aligned}$$

The modeled relationships between ABR wave I amplitude and age, noise exposure, tinnitus, and speech-in-noise perception are shown in Supplemental Fig. 4.

Supplemental Figure 4: Relationship between ABR wave I amplitude and synaptopathy risk factors/predicted perceptual consequences. **A.** Mean wave I amplitude given the participant's age. **B.** Range of wave I amplitudes for each noise exposure group. The mean and 90% CI for each noise exposure group are shown with the black bars. The filled gray band is the 90% CI for the Non-Veteran Control group and is shown for reference. **C.** Probability of reporting tinnitus given mean wave I amplitude. Individual participants are plotted at 0% (the participant did not report tinnitus) or 100% (the participant reported tinnitus). Data is jittered along the y-axis to facilitate visualization of individual data points. **D.** WIN score given mean wave I amplitude. For all panels, gray circles show data from individual participants. The black line and shaded region indicate the mean and 90% CI of the model prediction. The mean wave I amplitude for individual subjects was calculated by taking the average across all replicates and frequencies for a 110 dB peSPL tone burst. In contrast, the modeled predictions represent the relationship with the sex and DPOAE-corrected ABR wave I amplitude.

8 Simplifications and assumptions of our deafferentation prediction approach

To help guide the reader, we have listed the simplifications and assumptions we make in fitting the CMAP to the ABR data.

- The human cadaver data from Wu et al. (2019) is representative of the populations the Bramhall et al. (2017, 2018) dataset and Carcagno and Plack (2020, 2021) dataset. As additional human cadaver data becomes available, the priors used in the Bayesian regression model can be updated.
- Human cochleograms, including those with a high degree of synaptopathy, are well approximated by a parabola (Eq. 1, main text). This assumption is based on synapse counts from human temporal bones (Wu et al. 2019; see Supplemental Fig. 5). Alternate equations can easily be accommodated if there is evidence for alternate damage profiles (e.g., focal loss of synapses).
- Low, then medium, then high SR fibers are lost in that order. This is a common assumption based on single-unit recordings of noise-exposed guinea pigs (Furman et al., 2013). However, there is some evidence that high SR fibers are also lost based on a reanalysis of the single-unit data by Marmel et al. (2015). Further, data from envelope following response (EFR) studies also suggest that there may be some loss of high SR fibers (Paul et al., 2017; Encina-Llamas et al., 2019; Bramhall et al., 2021). Alternate approaches to simulating synaptic loss can be tested in future work, particularly for analyses that include EFR data.
- The maximum number of cochlear synapses, regardless of the corresponding cochlear frequency, is most closely associated with potential risk factors and predicted perceptual consequences of cochlear synaptopathy. Since the model can generate alternate metrics such as the predicted number of synapses per inner hair cell at 4 kHz or the percentage of synapses lost across all frequencies, future work can test whether alternate

metrics derived from this model are more predictive of the perceptual consequences of cochlear synaptopathy.

9 Does correcting for cochlear gain improve predictions?

Studies of ABR wave I amplitude typically correct for DPOAE amplitude or audiometric thresholds in their statistical analysis. However, this correction may not be necessary, particularly at high stimulus levels where responses are dominated by passive cochlear mechanics (e.g., Verhulst et al., 2016). To test whether individualizing the CMAP using the participant’s DP-gram (Bramhall et al. dataset) or audiogram (Carcagno & Plack dataset) improves predictions, we repeated our analysis with the cochlear gain stage (i.e., pole function) set to that of a normal hearing person. This gave us a second set of synapse count predictions which we then used to test for relationships with age.

To assess which approach was better, we applied a Bayesian Pareto-smoothed importance leave-one-out cross-validation approach, which enables us to rank models in order of predictive power. This analysis demonstrates that age is more predictive of DP-gram or audiogram adjusted predicted synapse counts than predicted synapse counts that are not DP-gram or audiogram adjusted. However, the difference in predictive ability (0.16 for the DP-gram adjusted Bramhall et al. dataset, 0.19 for the audiogram adjusted Carcagno & Plack dataset) are small relative to the standard error (0.82 for the Bramhall et al. dataset and 0.94 for the Carcagno & Plack dataset). Thus, while adjusting for cochlear gain appears to improve model predictions, the improvement is relatively small.

Metric	Mean	SD	95% CI	
Change in synapse number per decade (Bramhall et al.)	−1.0	0.3	[−1.7	−0.4]
Change in synapse number per decade (Carcagno & Plack)	−0.7	0.1	[−0.9	−0.4]
non-Veteran Controls (NVC; synapses/IHC)	9.4	0.4	[8.6	10.3]
Veteran Low Noise (synapses/IHC)	8.5	0.5	[7.5	9.6]
non-Veteran Firearms (synapses/IHC)	8.1	0.5	[7.2	9.0]
Veteran High Noise (synapses/IHC)	7.4	0.4	[6.6	8.2]
Veteran Low Noise re. non-Veteran controls (%)	90	7	[76	103]
non-Veteran Firearms re. non-Veteran controls (%)	86	6	[73	97]
Veteran High Noise re. non-Veteran controls (%)	78	6	[68	90]
Log-odds of reporting tinnitus (5.7 synapses)	−0.48	0.42	[−1.32	0.33]
Log-odds of reporting tinnitus (16.0 synapses)	−4.29	1.25	[−6.85	−2.19]
Probability of reporting tinnitus (5.7 synapses) (%)	39	10	[21	58]
Probability of reporting tinnitus (16.0 synapses) (%)	2	2	[0	7]
WIN score for 5.7 synapses	4.56	0.24	[4.10	5.04]
WIN score for 16.0 synapses	3.19	0.51	[2.21	4.21]
Change in WIN score (dB SNR/synapse)	−0.13	0.07	[−0.27	−0.01]
DTT score for 5.7 synapses (low noise)	−8.69	0.26	[−9.19	−8.17]
DTT score for 16.0 synapses (low noise)	−10.06	0.38	[−10.78	−9.29]
Change in DTT score (dB SNR/synapse; low noise)	−0.13	0.06	[−0.24	−0.02]
DTT score for 5.7 synapses (high noise)	−8.17	0.26	[−8.67	−7.66]
DTT score for 16.0 synapses (high noise)	−9.14	0.40	[−9.94	−8.39]
Change in DTT score (dB SNR/synapse; high noise)	−0.10	0.06	[−0.21	0.02]

Table 1: 95% credible intervals for the effects reported in the text. Mean and standard deviation (SD) are also shown. See text for 90% credible intervals.

Supplemental Figure 5: A parabola (Eq. 1 in main text) fits known human synapse count data in a sample of 19 subjects ranging 0 to 89 years of age (Wu et al., 2019). Points indicate the actual number of synapses per IHC and the black line is the parabola that best fits the data. Age at death is indicated above each panel. Arrows in each panel show how the parameters of the parabola ($\theta_{i[1]}$ and $\theta_{i[2]}$) can be converted into meaningful values (i.e., the vertex of the parabola, $G(g)$ is the Greenwood equation which transforms fractional distance along the basilar membrane, g , into the corresponding cochlear frequency). The value of $G(\theta_{i[1]})$ and $\exp(\theta_{i[2]})$ are shown for each panel.

References

- Bedrick, E. J., Christensen, R. and Johnson, W. (1996), ‘A New Perspective on Priors for Generalized Linear Models’, *Journal of the American Statistical Association* **91**(436), 1450–1460.
- Bramhall, N. F., Konrad-Martin, D. and McMillan, G. P. (2018), ‘Tinnitus and Auditory Perception After a History of Noise Exposure: Relationship to Auditory Brainstem Response Measures’, *Ear and Hearing* **39**(5), 881–894.
- Bramhall, N. F., Konrad-Martin, D., McMillan, G. P. and Griest, S. E. (2017), ‘Auditory Brainstem Response Altered in Humans With Noise Exposure Despite Normal Outer Hair Cell Function’, *Ear and hearing* **38**(1), e1–e12.
- Bramhall, N. F., McMillan, G. P. and Kampel, S. D. (2021), ‘Envelope following response measurements in young veterans are consistent with noise-induced cochlear synaptopathy’, *Hearing Research* **408**, 108310.
- Bramhall, N., Ong, B., Ko, J. and Parker, M. (2015), ‘Speech Perception Ability in Noise is Correlated with Auditory Brainstem Response Wave I Amplitude’, *Journal of the American Academy of Audiology* **26**(5), 509–517.
- Carcagno, S. and Plack, C. J. (2020), ‘Effects of age on electrophysiological measures of cochlear synaptopathy in humans’, *Hearing Research* **396**, 108068.
- Carcagno, S. and Plack, C. J. (2021), ‘Effects of age on psychophysical measures of auditory temporal processing and speech reception at low and high levels’, *Hearing Research* **400**, 108117.
- Encina-Llamas, G., Harte, J. M., Dau, T., Shinn-Cunningham, B. and Epp, B. (2019), ‘Investigating the Effect of Cochlear Synaptopathy on Envelope Following Responses Using a Model of the Auditory Nerve’, *Journal of the Association for Research in Otolaryngology: JARO* **20**(4), 363–382.
- Folmer, R. L., McMillan, G. P., Austin, D. F. and Henry, J. A. (2011), ‘Audiometric thresholds and prevalence of tinnitus among male veterans in the United States: Data from the National Health and Nutrition Examination Survey, 1999–2006’, *Journal of Rehabilitation Research and Development* **48**(5), 503–516.
- Furman, A. C., Kujawa, S. G. and Liberman, M. C. (2013), ‘Noise-induced cochlear neuropathy is selective for fibers with low spontaneous rates’, *Journal of Neurophysiology* **110**(3), 577–586.
- Greenwood, D. D. (1990), ‘A cochlear frequency-position function for several species—29 years later’, *The Journal of the Acoustical Society of America* **87**(6), 2592–2605.
- Henry, J. A., Griest, S. E., Blankenship, C., Thielman, E. J., Theodoroff, S. M., Hammill, T. and Carlson, K. F. (2019), ‘Impact of Tinnitus on Military Service Members’, *Military Medicine* **184**(Suppl 1), 604–614.
- Konrad-Martin, D., Dille, M. F., McMillan, G., Griest, S., McDermott, D., Fausti, S. A. and Austin, D. F. (2012), ‘Age-related changes in the auditory brainstem response’, *Journal of the American Academy of Audiology* **23**(1), 18–35; quiz 74–75.
- Marmel, F., Rodríguez-Mendoza, M. A. and Lopez-Poveda, E. A. (2015), ‘Stochastic undersampling steepens auditory threshold/duration functions: Implications for understanding auditory deafferentation and aging’, *Frontiers in Aging Neuroscience* **7**, 63.
- Paul, B. T., Bruce, I. C. and Roberts, L. E. (2017), ‘Evidence that hidden hearing loss underlies amplitude modulation encoding deficits in individuals with and without tinnitus’, *Hearing Research* **344**, 170–182.
- Verhulst, S., Jagadeesh, A., Mauermann, M. and Ernst, F. (2016), ‘Individual Differences in Auditory Brainstem Response Wave Characteristics: Relations to Different Aspects of Peripheral Hearing Loss’, *Trends in Hearing* **20**.

Wu, P. Z., Liberman, L. D., Bennett, K., de Gruttola, V., O'Malley, J. T. and Liberman, M. C. (2019), 'Primary Neural Degeneration in the Human Cochlea: Evidence for Hidden Hearing Loss in the Aging Ear', *Neuroscience* **407**, 8–20.

Coefficient	Description	Note
General variables and indices		
i	Index of participant	74 (Bramhall dataset) or 102 (Carcagno dataset) participants
n	Index of ABR wave I amplitude observation	810 observations (Bramhall dataset)
f	Stimulus frequency (either ABR tone pip frequency or DPOAE f_2 frequency)	
l	Stimulus level	
j	Index of randomly generated simulation for neural network	26 simulations
g	Cochlear position as a fractional distance	
k	Index of cochlear frequency	1001 frequencies
a	Age in years	
p	Index of ABR replicate	Two replicates
m	Index of WIN test replicate	Two replicates
r	Index of DTT test replicate	Two tests per participant, one for each masker level
t	Time (in sec)	
L	Low SR fiber	
M	Medium SR fiber	
H	High SR fiber	
S_i	Sex of participant i	1 if female, 0 otherwise
T_i	Tinnitus status of participant i	1 if tinnitus reported, 0 otherwise
VLN_i	Membership of participant i in the Veteran low noise group	1 if a member, 0 otherwise
NVF_i	Membership of participant i in the non-Veteran firearm group	1 if a member, 0 otherwise
VHN_i	Membership of participant i in the Veteran high noise group	1 if a member, 0 otherwise
$\bar{\xi}_i$	Average of DPOAE amplitudes between 3 and 8 kHz	Only available for Bramhall dataset
WI_m	ABR wave I amplitude for observation m	
HN_{ir}	Indicator for high-noise condition in DTT test r from participant i	1 if masker is 80 dB SPL, 0 otherwise
WIN_{im}	WIN score of participant i on replicate m	
D_{ir}	DTT threshold of participant i on test r	
$\bar{o}_i$	Performance of participant i on the reading span task	Only available for Carcagno dataset
Cochlear mechanics (DPOAE simulations)		
α	Double pole of the cochlear admittance (i.e., pole function) for low stimulus levels	
$\mathbf{DP_S}$	Simulated DP-gram for participant with no OHC damage	
$\mathbf{DP_M}$	Hypothetical measured DP-gram for an exemplar participant with no OHC damage	$\mathbf{DP_M}f = \max_{i=1,\dots,74} \xi_{if}$
ξ_i	Measured DP-gram for participant i	
Ξ_i	Simulated DP-gram for participant i (before correcting for overshoot of DPOAE estimate)	
δ_i	Difference between the measured DP-gram for participant i and the hypothetical exemplar measured DP-gram	$\delta_i = \mathbf{DP_M} - \xi_i$
$\mathbf{DP_S} - \delta_i$	Input to trained neural network	
$\hat{\xi}_i$	Predicted DP-gram for participant i (after correcting for overshoot of DPOAE estimate)	$\hat{\xi}_i = \mathbf{DP_M} - (\mathbf{DP_S} - \Xi_i)$

Synaptogram

$N(g)$	Average synapse count per IHC at cochlear position g (i.e., synaptogram)	
$A(g, a)$	Average synapse count per IHC at cochlear position g (i.e., synaptogram) at age a	
$G(g)$	Greenwood equation (maps cochlear position to cochlear frequency)	
$G^{-1}(f)$	Inverse of Greenwood equation (maps cochlear frequency to cochlear position)	
θ_i	Parameters of parabola describing shape of synaptogram for participant i	
Θ	Population mean of parabola describing shape of synaptogram	Priors based on human temporal bone data
Σ	Covariance matrix of Θ	Priors based on human temporal bone data
ν	Parameters of parabola describing shape of synaptogram for participant i when $a = 0$	Priors based on human temporal bone data
Υ	Age-specific coefficients which determine modeled effect of age on the shape of the parabola	Priors based on human temporal bone data
Ψ	Covariance matrix of $\nu + a_i \cdot \Upsilon$	Priors based on human temporal bone data

ABR modeling

$ABR(t, f, l)$	ABR response at time t for ABR tone pip frequency f and level l	
$\exp(c_0)$	Scaling constant for males to reconcile simulated and measured ABR data	
$\exp(c_0 + c_1)$	Scaling constant for females to reconcile simulated and measured ABR data	
N_{ik}^H	Average number of high SR fibers at cochlear frequency k for participant i	
F_k	Average number of fibers at cochlear frequency k in an exemplar cochlea (i.e., a neonate)	
F_k^H	Average number of high SR fibers at cochlear frequency k in an exemplar cochlea (i.e., a neonate)	
$R_{ik}^H(t, f, l)$	Instantaneous firing rate of a high SR fiber at cochlear frequency k for participant i	Calculated using DP-gram adjusted CMAP

Statistical analysis

$\hat{\theta}_i$	Mean of posterior for $\theta_{i[2]}$	
$\text{sd}(\theta_i)$	Standard deviation of posterior for $\theta_{i[2]}$	
ζ_i	Predicted synapse count per IHC for participant i	
Λ_0	Number of synapses per IHC when age is 0	
Λ_1	Change in number of synapses per IHC for each decade of life	
$\exp(\beta_0)$	Number of synapses per IHC in the non-Veteran control group	
$\exp(\beta_1)$	Ratio of the number of synapses per IHC in the Veteran low noise group relative to the non-Veteran control group	
$\exp(\beta_2)$	Ratio of the number of synapses per IHC in the non-Veteran firearm group relative to the non-Veteran control group	
$\exp(\beta_3)$	Ratio of the number of synapses per IHC in the Veteran high noise group relative to the non-Veteran control group	
γ_0	Log-odds of reporting tinnitus when synapse count is 0	
γ_1	Change in log-odds of reporting tinnitus for each additional synapse gained	
η_0	WIN score when synapse count is 0	
η_1	Change in WIN score for each additional synapse gained	

d_0	DTT threshold for 45 dB SPL masker when synapse count is 0
d_1	Change in DTT threshold for 45 dB SPL masker for each additional synapse gained
$d_0 + d_2$	DTT threshold for 80 dB SPL masker when synapse count is 0
$d_1 + d_3$	Change in DTT threshold for 80 dB SPL masker for each additional synapse gained
d_4	Change in DTT threshold for each unit improvement on the cognitive test
ω_{if}	Expected ABR wave I amplitude for participant i at frequency f for a 110 dB peSPL tone burst
λ_i	Change in ABR wave I amplitude with stimulus level
ψ	Effect of sex on ABR wave I amplitude
Π	Effect of DPOAE amplitude (ξ_i) on ABR wave I amplitude
Λ_0^*	Average ABR wave I amplitude when age is 0
Λ_1^*	Change in average ABR wave I amplitude for each decade of life
$\exp(\beta_0^*)$	Average ABR wave I amplitude for the non-Veteran control group in μV
$\exp(\beta_1^*)$	Ratio of the average ABR wave I amplitude in the Veteran low noise group relative to the non-Veteran control group
$\exp(\beta_2^*)$	Ratio of the average ABR wave I amplitude in the non-Veteran firearm group relative to the non-Veteran control group
$\exp(\beta_3^*)$	Ratio of the average ABR wave I amplitude in the Veteran high noise group relative to the non-Veteran control group
γ_0^*	Log-odds of reporting tinnitus when ABR wave I amplitude is 0 μV
γ_1^*	Change in log-odds of reporting tinnitus for each 1 μV increase in ABR wave I amplitude
η_0^*	WIN score when ABR wave I amplitude is 0 μV
η_1^*	Change in WIN score for each 1 μV increase in ABR wave I amplitude