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Influence of tinnitus, lifetime noise exposure, and firearm use on hearing thresholds, distortion product otoacoustic emissions, and their relative metric

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ABSTRACT:
Distortion product otoacoustic emissions (DPOAEs) and hearing thresholds (HTs) are widely used to evaluate auditory physiology. DPOAEs are sensitive to cochlear amplification processes, while HTs are additionally dependent upon inner hair cells, synaptic junctions, and the auditory nervous system. These distinctions between DPOAEs and HTs might help differentially diagnose auditory dysfunctions. This study aims to differentially diagnose auditory dysfunctions underlying tinnitus, firearm use, and high lifetime noise exposure (LNE) using HTs, DPOAEs, and a derived metric comparing HTs and DPOAEs, in a sample containing overlapping subgroups of 133 normal-hearing young adults (56 with chronic tinnitus). A structured interview was used to evaluate LNE and firearm use. Linear regression was used to model the relationship between HTs and DPOAEs, and their regression residuals were used to quantify their relative agreement. Participants with chronic tinnitus showed significantly elevated HTs, yet DPOAEs remained comparable to those without tinnitus. In contrast, firearm users revealed elevated HTs and significantly lower DPOAEs than predicted from HTs. High LNE was associated with elevated HTs and a proportional decline in DPOAEs, as predicted from HTs. We present a theoretical model to interpret the findings, which suggest neural (or synaptic) dysfunction underlying tinnitus and disproportional mechanical dysfunction underlying firearm use. https://doi.org/10.1121/10.0019880
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NOMENCLATURE

HT	hearing threshold
DPOAE	distortion product otoacoustic emission
LNE	lifetime noise exposure
OHC	outer hair cell
IHC	inner hair cell
THF	Tinnitus Functional Index
THI	Tinnitus Handicap Inventory
ΔDPOAE	the difference between predicted and observed distortion product otoacoustic emission (regression residuals)

INTRODUCTION

Puretone hearing thresholds (HTs) and distortion product otoacoustic emissions (DPOAEs) are widely used for assessing auditory physiology in audiology clinics and research laboratories. Behavioral HTs are the current "gold standard" for quantifying hearing sensitivity. DPOAEs, which have screening purposes and diagnostic value, are correlated with HTs (e.g., Gorga *et al.*, 1997). An important distinction between the two measures is that DPOAEs are strong indicators of cochlear outer hair cell (OHC) function and the process of cochlear amplification, while HTs are additionally dependent on inner hair cells (IHCs), afferent synapses on IHCs, and function of the auditory nervous system. These distinctions may enable the relationship between DPOAEs and HTs to be a useful tool to help identify individuals with greater OHC/mechanical cochlear dysfunction and individuals with greater synaptic/neural dysfunction. In this study, we examined the relationship between HTs, DPOAEs, and a metric that evaluated the relative agreement between HTs and DPOAEs in a sample of normal-hearing young adults. The study sample included overlapping subgroups of individuals with tinnitus and noise exposure (non-impulse and impulse), which may be associated with greater synaptic/neural damage or OHC/mechanical damage, respectively.

Tinnitus is the phantom perception of sound in the absence of any external sound source. It can be associated with damage to afferent neural synapses on IHCs (Schaette and McAlpine, 2011). In a meta-analysis of human studies, Chen *et al.* (2021) showed that people with tinnitus and normal hearing sensitivity can have reduced amplitudes of auditory brainstem response (ABR) wave I, which is known to originate from the synchronous excitation of numerous auditory nerve fibers (Goldstein and Kiang, 1958; Earl and Chertoff, 2010). Therefore, reductions in ABR wave I amplitudes could, in part, originate from the damage to afferent neural synapses on IHCs. In response to reduced cochlear

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neural output, the central auditory system may compensate by abnormal increases in spontaneous neural firing rates, neural synchronicity, and tonotopic reorganization of the auditory cortex. Tinnitus could be triggered in part by a decrease in cochlear output and subsequent maladaptive compensation in the central auditory nervous system (e.g., Wu *et al.*, 2016; Wang *et al.*, 2011; Salvi *et al.*, 2021; Eggermont, 2006).

Tinnitus is often accompanied by a wide range of comorbidities (e.g., Basso *et al.*, 2021; Blazer, 2020; Lee *et al.*, 2018) that may confound the relationship between DPOAEs and HTs. The investigation of tinnitus in otherwise healthy young adults might help to limit the influence of age-related and other confounders. Tinnitus is a prevalent hearing health concern in young adults (e.g., Bhatt, 2018; Degeest *et al.*, 2017; Guichard *et al.*, 2016; Park *et al.*, 2014). In the United States, approximately 4.7% of youth aged 12–19 years report bothersome chronic tinnitus (Mahboubi *et al.*, 2013) and about 8.4% of college-aged young adults experience chronic tinnitus (Bhatt, 2018). Systemic diseases and medical conditions do not always show a significant association with chronic tinnitus in youth (Bhatt, 2018; Mahboubi *et al.*, 2013), though some young adults with chronic tinnitus may experience anxiety, frustration, and sleep disturbances (Bhatt *et al.*, 2017). These observations suggest that the population of young adults reporting tinnitus, but who are otherwise healthy, should facilitate identifying the influence of tinnitus on HTs and DPOAEs.

Although there are clear links between traumatic noise exposure and OHC/mechanical damage, and between tinnitus and synaptic/neural damage, the separation between these types of damage is not always cleanly delineated with currently available clinical diagnostic tests. Animal models have shown that impulse noise can disrupt mechanical motions by disrupting the reticular lamina, Hensen's and Deiter's cells, and hair cell stereocilia bundles (Gratias *et al.*, 2021; Hamernik *et al.*, 1984), and acoustic trauma can damage afferent synapses on IHCs and microcirculation in stria vascularis (e.g., Kujawa and Liberman, 2009; Shin *et al.*, 2019). Noise exposure is a known risk factor for tinnitus in young adults (e.g., Bhatt, 2018; Mahboubi *et al.*, 2013; Shargorodsky *et al.*, 2010; Rawool and Colligon-Wayne, 2008). It is thus believed that the co-occurrence of tinnitus and lifetime noise exposure (LNE) may conflate the relationship between noise exposure, tinnitus, DPOAEs, and HTs. To make matters worse, additional confounds in young adults include a history of reoccurring ear infections (e.g., Bhatt, 2018; Mahboubi *et al.*, 2013) that could influence the mechanical transfer of outer and middle ears and thus, HT and DPOAEs measurements (e.g., Sanfins *et al.*, 2020). Therefore, the effects of impulse and non-impulse noise exposure and reoccurring ear infections should be controlled while investigating the influence of tinnitus on DPOAEs and HTs and their relationship.

The present study evaluated the relationship between DPOAEs and HTs in young adults with clinically normal hearing (i.e., $\leq$ 25 dB HL from 250 to 8000 Hz) in a sample containing overlapping subgroups of participants reporting tinnitus, firearm use, and high LNE. It is worth noting that although the participants in this study had clinically normal hearing, this criterion still allowed for a 35 dB range of HTs to be considered (–10 to 25 dB HL). We used ΔDPOAEs [the difference between predicted and observed DPOAEs (regression residuals)] as a derived metric to evaluate the relative agreement between DPOAEs and HTs in subgroups with tinnitus and noise exposure compared to the relationship observed for the entire group of participants considered together. To account for potential confounds and repeated measures, we used a linear mixed model with the following predictors: tinnitus, LNE, firearm use, reoccurring ear infections, sex, ethnicity, and repeated measures: ear and frequency. Our overarching hypothesis was that participants with tinnitus and noise exposure would exhibit elevated HTs and reduced DPOAEs, indicating cochlear deafferentation.

METHODS

Initial screening questionnaire

The Institutional Review Board approved the protocol for the present study, and informed consent was obtained from each participant. An initial screening questionnaire was distributed to potential participants via mass email, in-class survey administration, recruitment flyers, and word of mouth. The questionnaire inquired about demographic details (e.g., age, sex, ethnicity), tinnitus, history of ear infection, and general health. Tinnitus questions were adopted from the National Health and Nutrition Examination Survey (NHANES) and were used in past epidemiological studies (e.g., Bhatt *et al.*, 2016; Mahboubi *et al.*, 2013; Shargorodsky *et al.*, 2010) (see supplementary material for details on the tinnitus screening questionnaire and individual responses).[1] We obtained responses from 3173 individuals. About 8% (273 out of 3173) of the participants reported bothersome chronic tinnitus (e.g., tinnitus for $>$ 1 year), and about 40% (1293 out of 3173) of the participants reported no tinnitus. From this cohort, individuals 18–35 years of age, who reported good health and had either bothersome chronic tinnitus or no tinnitus, were invited to participate in the present study. A detailed tinnitus evaluation (see Tinnitus evaluation section) was subsequently performed to identify individuals with chronic tinnitus and no tinnitus.

Study questionnaire

The participants filled out a questionnaire inquiring about demographic details (e.g., age, sex, ethnicity, occupation), a history of reoccurring middle ear infection, a history of health conditions, active health conditions, use of medications, and hearing loss. Individuals reporting active health conditions (including systemic diseases, medical conditions, and audiological conditions) were excluded from the study.

Tinnitus evaluation

Participants filled out a questionnaire inquiring about tinnitus. Participants reporting no tinnitus were instructed to

skip the section. Tinnitus questions were adapted from NHANES 2015-2016. The questionnaire inquired about duration, laterality (e.g., right ear, left ear, both ears, head), type of tinnitus perception (e.g., continuous, intermittent), potential triggering factors (e.g., noise, music, head injury), and perceived tinnitus distress. Tinnitus-related distress was evaluated with two standardized questionnaires–Tinnitus Handicap Inventory (THI) and Tinnitus Functional Index (TFI) (Newman *et al.*, 1996; Meikle *et al.*, 2012). Responses to tinnitus questions were verified by examiners, who were trained and supervised by a certified clinical audiologist with >10 years of experience in tinnitus evaluation and management. To verify the accuracy of the responses, the examiner engaged the invited participants in conversation by reading the text of the questions and inquiring why they chose the selected answers. The examiner offered clarification on the question texts, asked follow-up questions to verify their understanding, and rephrased questions to ascertain the reliability of the responses. Following the questionnaire response, the invited participants were asked to sit on a recliner sofa for 5 min in a double-walled, sound-treated booth that met American National Standards Institute standards for maximum permissible ambient noise. Participants were instructed to avoid using electronic devices and other distractors. After 5 min inside the sound-treated booth, they were asked, "Did you experience ringing, roaring, buzzing, or perception of any other types of sound in your ears or head in the last 5 min?" If participants answered "yes," the follow-up questions inquired about laterality, type of tinnitus perception, and perceived tinnitus-related distress in the sound-treated booth. The participants were requested to rate the loudness and pitch of their tinnitus on a 0–100 scale. Participants reporting chronic tinnitus and tinnitus perception in a sound-treated booth and participants reporting no tinnitus and no tinnitus perception in a sound-treated booth were included in the study. The present study included 56 participants with bothersome chronic tinnitus experiencing tinnitus perception in a sound-treated booth and 77 participants with no tinnitus experiencing no tinnitus in a sound-treated booth (see supplementary material for further details about the characteristics of tinnitus for the study sample).[1]

Lifetime noise exposure (LNE)

A structured interview was conducted using a list of noisy occupational and recreational activities described in Jokitulppo *et al.* (2006). These noisy activities included playing in a band or orchestra, practicing a musical instrument, listening to music via loudspeakers, listening to music via headphones, watching television or electronic devices, playing loud computer games, watching movies or theatre, going to nightclubs or pubs, attending concerts and festivals or musical events, exposure to fireworks, shooting firearms for recreational or occupational purposes, attending or participating in motorsports events, using noisy tools indoors, using noisy tools outdoors, attending or participating in sports events, exercising to music, and any other noisy activities not listed above that were reported by participants. Participants were instructed to indicate duration, loudness, and use of hearing protection for each activity. Exposure duration was reported in hours/week, or hours/month, or hours/year, or hours in a lifetime—as preferred by the participants for each activity.

The original questionnaire by Jokitulppo *et al.* (2006) did not account for changing exposure habits over time (Guest *et al.*, 2018). To address this concern, participants were instructed to report exposure duration in a weighted grand average. An examiner facilitated the calculation of the weighted grand average by inquiring about average exposure duration separately for each period during which the exposure habits remained relatively stable. Participants indicated the number of years they were exposed to each loud/noisy activity. Lifetime exposure duration ($T_{Lifetime}$) for each activity was calculated by multiplying duration (in hours/years) by a total number of years. If participants expressed duration in hours/week, the duration figure was multiplied by 52 (# of weeks in a year) to derive hours/year. If the duration was expressed in hours/month, it was multiplied by 12 (# of months in a year) to derive hours/year. Participants were instructed to rate the loudness of each noisy activity on a 1 (quiet) to 5 (very loud) scale (Paul *et al.*, 2017; Jokitulppo *et al.*, 2006). The scale used vocal effort to estimate sound level [1—sound level of normal conversation, 2—sound levels of loud conversation, 3—sound levels at which you must shout over a distance of 1 m (over a table) to be heard, 4—refers to the normal sound level of disco music that makes you shout to be heard to a person standing close to you, and 5—loud disco music that makes communication almost impossible]. The five-point rating scale was converted to 60, 70, 80, 90, and 100 dBA L_{Aeq}, following the scoring procedures used by the past studies (Paul *et al.*, 2017; Jokitulppo *et al.*, 2006).

The original questionnaire by Jokitulppo *et al.* (2006) also did not account for the use of hearing protection (Guest *et al.*, 2018). To address this concern, we asked participants to indicate the frequency (and type) of hearing protection use in percentage (P_{HP}), and to rate the loudness of the noisy activity with ($L_{AeqwithHP}$) and without ($L_{AeqwithoutHP}$) hearing protection. The cumulative lifetime noise exposure for each activity was calculated using the following equation:

$$E_{cum} = \left[4\,(T_{Lifetime})\left(1 - \frac{P_{HP}}{100}\right)10^{0.1\left(L_{Aeq_{withoutHP}} - 100\right)}\right] + \left[4\,(T_{Lifetime})\left(\frac{P_{HP}}{100}\right)10^{0.1\left(L_{Aeq_{withHP}} - 100\right)}\right].$$

E_{cum} represents calculated noisy activity-specific lifetime noise exposure measured in $kPa^2\,h$ (Paul *et al.*, 2017). E_{cum} was summed for all activities (except firearm exposure) to calculate LNE. We identified 50% of the participants with the highest LNE scores [mean = 1.09, standard deviation (SD) = 0.94, range: 0.24–4.05 $kPa^2\,h$], and 50% of the participants with the lowest LNE scores (mean = 0.08, SD = 0.06, range: 0.0005–0.24 $kPa^2\,h$) (Fig. 1). Nineteen participants

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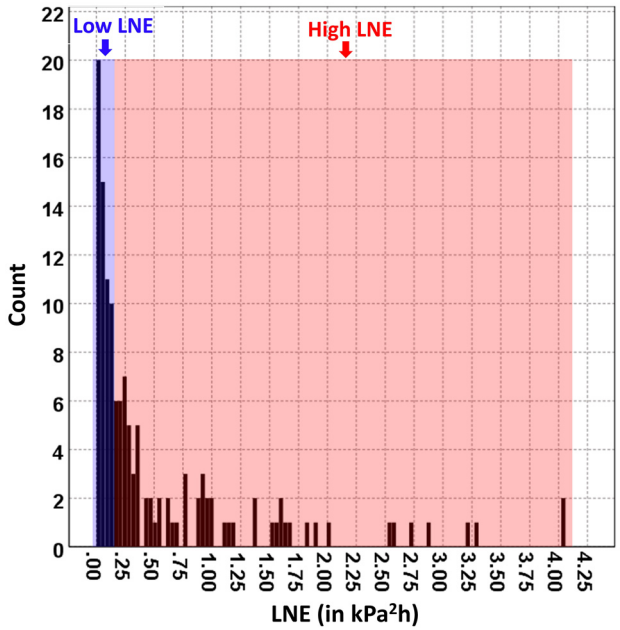

FIG. 1. (Color online) Histogram showing the distribution of lifetime noise exposure (LNE).

reported they used firearms for occupational or recreational purposes with large inter-subject variability in exposure duration, type of firearm used, and type and frequency of hearing protection use (E_{cum} mean = 0.07, SD = 0.13, range = 0.001–0.495 kPa^2 h). Among 19 participants reporting firearm use, 13 participants reported using rifles. Fifteen participants (out of 19) reported hearing protection use. Firearm use was recoded as a binary variable. Nine participants reporting firearm use were in the low LNE group, and 10 were in the high LNE group.

Audiometric tests

An otoscopic examination was conducted on each participant. Individuals with normal otoscopic findings were included for further testing. Immittance audiometry was performed with Titan IMP440 (Interacoustics, Middelfart, Denmark). Participants with a "type A" tympanogram (e.g., static compliance: 0.3–1.75, middle ear pressure: +50 to −100 deca-Pascal) were then tested with puretone audiometry. Audiometric procedures were performed in a double-walled, sound-treated room that met ANSI standards. HTs were obtained with the modified Hughson–Westlake procedure using the Stealth Clinical Audiometer (MedRx Inc., Largo, FL) connected to IP30 insert receivers (RadioEar, Middelfart, Denmark) from both ears. Conventional HTs were tested at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz. We performed extended–high frequency audiometry with circumaural headset DD450 (RadioEar, Middelfart, Denmark) at 9000, 10000, 11 200, 12 0500, 14 0000, and 16 000 Hz. All participants in the present study showed HTs ≤ 25 dB HL from 250 to 8000 Hz.

DPOAE measurement

DPOAEs were measured using a Mimosa HearID system (Mimosa Acoustics, Champaign, IL) connected to an ER-10 °C probe-microphone system (Etymotic Research. Inc, Elk Grove Village, IL). The HearID system was calibrated following the manufacturer's guidelines. The calibration was verified weekly during the data collection period with the HearID DPOAE coupler test performed using a 2 ml syringe. An output linearity check was performed at the beginning, middle, and end of the data collection to ensure that DPOAE measurements were not influenced by the nonlinear distortion of the system. Participants were instructed to sit comfortably on a recliner sofa and avoid biological noises (e.g., coughing, heavy breathing, yawning) during the testing procedure. The probe was fitted with an ER10C-14A foam tip and carefully placed in the ear canal. The deepest possible probe insertion was obtained following the manufacturer's guidelines. The in-ear dB sound pressure level (SPL) calibration was performed before obtaining DPOAE measurements. DPOAEs at 2f1–f2 were measured for f2 values at 1000, 2000, 3000, 4000, 6000, 8000, 9000, 10 000, 11 200, 12 500, 14 000, and 16 000 Hz. F2 values were selected to match HTs obtained at audiometric frequencies from 1000 to 16000 Hz. DPOAEs from both ears were measured. A stimulus frequency ratio of 1.22 and a stimulus level combination of 65/55 dB SPL was used. The stimuli were presented at each F2 frequency until one of the stopping conditions was reached: a signal-to-noise ratio (SNR) >12 dB, a noise floor of ≤ 20 dB SPL, or a maximum signal duration >10 s. The noise rejection threshold was set at 10 dB SPL. DPOAEs and noise floor levels were obtained. While DPOAEs can be influenced by interactions between reflection and distortion components, it was nevertheless reasoned that high and low DPOAE values provide an objective measure of the overall strength of cochlear amplification (Shera and Guinan, 1999; Zweig and Shera, 1995).

Statistical analysis

The statistical analyses were performed using the IBM SPSS version 25 statistics package (Chicago, IL). The relationships between the experimental variables were evaluated using Pearson's correlation coefficients and independent-sample t-tests. A chi-square analysis was performed to identify the factors associated with chronic tinnitus.

ΔDPOAEs: DPOAE and HT comparison metrics

DPOAEs and HTs cannot be directly compared, as they evaluate the phenomenological reality of the auditory system in different ways and are measured on different scales. We used linear regression to model DPOAEs as a function of HTs to compare these measures. The linear regression model was used to obtain regression residuals, referred to as ΔDPOAE, to quantify the distance between the predicted and observed DPOAEs, given HTs. Since ΔDPOAEs can be derived from clinically available data (DPOAEs and HTs) without needing additional data collection, it may serve as a clinically useful tool for interpreting HT and DPOAE measurements. *This comparison metric that quantifies the relative agreement*

between DPOAEs and *HTs could potentially differentially diagnose underlying cochlear pathologies*.

We constructed a regression model for predicting DPOAEs from HTs at each frequency with the least squares fitting (see supplementary material for details on scatter plots between hearing thresholds and distortion product otoacoustic emissions).[1] The following equation was used to define the linear regression model:

$$\textit{Predicted DPOAE amplitude} = \mathrm{a} + (\mathrm{b} \times \mathrm{HT}).$$

Here, a is the intercept and b is the slope of the regression line obtained with the least squares fitting, and HT is the hearing threshold value at the respective frequency for each ear. We created 24 linear regression models for calculating the predicted DPOAEs (12 frequencies × 2 ears). Next, we used the regression models to predict the DPOAE from HT for each participant and calculated the difference between the predicted and observed DPOAE to obtain regression residuals:

$$\Delta\mathrm{DPOAE} = \textit{Observed DPOAE amplitude} - \textit{Predicted DPOAE amplitude}.$$

ΔDPOAE is the regression residual that quantifies the difference between the actual and predicted DPOAEs. Positive values of ΔDPOAEs indicate the observed DPOAEs were higher than the predicted DPOAEs based on HTs, and vice versa. ΔDPOAEs were calculated for each test frequency.

Investigating the relationship among tinnitus, LNE, and firearm use and HT, DPOAE, and ΔDPOAE

A linear mixed model regression (LMM) was used to evaluate the effects of tinnitus, LNE, and firearm noise exposure on HTs, DPOAEs, and ΔDPOAEs. LMM allows for investigating the effects of tinnitus, high LNE, and firearm exposure while controlling for demographic factors (sex and ethnicity), a potential confounding factor of reoccurring ear infections, and repeated measures (ear and frequency). The LLM modeling was performed using the following equation:

$$y = X\beta + Z\mu + \varepsilon.$$

Here, y is an outcome measure, X is a matrix of the predictor variables (tinnitus, LNE, firearm use, sex, ethnicity, reoccurring ear infection), β is a vector of the fixed effect regression coefficients, Z is a design matrix for random effects and groups. Ear (right/left), and frequency (12 values from 1000 to 16 000 Hz) were used as random effects. Three linear mixed models were constructed to study the relationship between the predictors and the outcome measures: (1) HT, (2) DPOAE, and (3) ΔDPOAE. Further details about the LMM can be found elsewhere (e.g., Fox, 2015; Bolker, 2015).

RESULTS

Demographic details

Table I provides descriptive statistics for the demographic and hearing health-related factors. Among the study sample of 133 individuals, 56 individuals (42.1%) reported bothersome chronic tinnitus. The study sample included 85 females (63.9%) and 48 males (36.1%). Within the study sample, 95 (71.4%) reported European ethnic backgrounds. The rest of the participants included those reporting Hispanic/Latino, Asian, Alaskan Native, African, and multiethnic backgrounds. Ethnicity was recoded into a binary variable (Europeans and others). Thirty-four (31.2%) participants reported having three or more episodes of reoccurring ear infections. Chi-square analysis showed that ethnicity, LNE, and ear infection were significantly associated with tinnitus (Table I). Table II shows a crosstab showing participant counts for the overlapping subgroups of tinnitus, LNE, and firearm exposure.

The sample included 56 (42.1%) participants with bothersome chronic tinnitus. Among those reporting chronic tinnitus, 52 (92.9%) reported they perceive tinnitus in both ears (or head). Forty-five participants (80.4%) reported they could perceive continuous tinnitus when they were in quiet conditions and actively paying attention to tinnitus. Forty-four participants with chronic tinnitus were unsure about factors that triggered tinnitus perception, while 16 participants suggested music, noise, or head injury as potential triggers (Table III). Thirty-four participants with chronic

TABLE I. Descriptive statistics (counts and sub-table percentage).

		Tinnitus		
		No	Yes	X^2 (N = 133)
Biological sex	Male	27 (20.3%)	21 (15.8%)	0.83 ($p = 0.77$)
	Female	50 (37.6%)	35 (26.3%)	
Ethnicity	European American	50 (37.6%)	45 (33.8%)	3.77 ($p = 0.05$)
	Others + Multiracial	27 (20.3%)	11 (8.3%)	
Ear infection	Yes	12 (9.0%)	22 (16.5%)	9.57 ($p = 0.002$)
	No	65 (48.9%)	34 (25.6%)	
LNE	Low	45 (33.8%)	21 (15.8%)	5.68 ($p = 0.01$)
	High	32 (24.1%)	35 (26.3%)	
Firearm exposure	Yes	10 (7.1%)	9 (18.4%)	0.25 ($p = 0.61$)
	No	67 (54.6%)	47 (19.9%)	

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TABLE II. A crosstab showing participant counts for the overlapping subgroups of tinnitus, LNE, and firearm exposure for the study sample (N = 133).

		LNE		Firearm		Tinnitus	
		Low	High	No	Yes	No	Yes
LNE	Low	66	0	57	9	45	21
	High	0	67	57	10	32	35
Firearm	No	57	57	114	0	67	47
	Yes	9	10	0	19	10	9
Tinnitus	No	45	32	67	10	77	0
	Yes	21	35	47	9	0	56

tinnitus reported they consider tinnitus as "a small problem." Five participants reported they were bothered by tinnitus only after listening to loud music or noise. All participants with chronic tinnitus included in this study reported tinnitus perception in a sound-treated booth. Fifty-one participants reported tinnitus perception in both ears (or head) while being in a sound-treated booth (Table III). TFI and THI scores indicated that participants reporting bothersome chronic tinnitus were suffering from no to minimum tinnitus-related distress in daily living, which is consistent with our past study (Bhatt, 2018).

TABLE III. Characteristics of tinnitus among the study sample.

Characteristics of tinnitus		Frequency (%)
Duration	1–4 years	26 (46.4%)
	5–9 years	13 (23.2%)
	10 years or more	17 (30.4%)
Laterality	Both ears/head	52 (92.9%)
	Right	3 (5.4%)
	Left	1 (1.8%)
Type of tinnitus perception	Continuous	45 (80.4%)
	Intermittent	11 (29.6%)
Triggering factor(s)	Not sure	44 (78.6%)
	After noise exposure	4 (7.1%)
	After music exposure	4 (7.1%)
	After head injury	3 (5.4%)
	After ear infection	1 (1.8%)
Tinnitus problem	No problem	9 (16.1%)
	A small problem	34 (60.7%)
	A moderate problem	10 (17.9%)
	A big problem	3 (5.4%)
Bothered by tinnitus only after listening to loud music/noise	Yes	5 (8.9%)
	No	51 (91.1%)
Tinnitus in a sound-treated booth—laterality	Both ears/head	51 (91.0%)
	Right	3 (5.3%)
	Left	2 (1.7%)
Tinnitus in sound-treated booth—type of perception	Continuous	54 (96.4%)
	Intermittent	2 (3.6%)
Loudness (Scale: 0–100)	Mean (±SD)	32.4 (20.0)
THI score (Scale: 0–100)	Mean (±SD)	18.1 (13.8)
TFI score (Scale: 0–100)	Mean (±SD)	19.0 (15.0)

DPOAE data handling

Table IV provides the descriptive statistics for DPOAEs. We observed that about 5% of the data points showed SNR < 0 dB, and these were coded as missing values (see supplementary material for missing value analysis).[1] About 50% of participants had at least one missing value. About 5% of the total DPOAE data points (total data points = 3192; 133 participants × 12 frequencies × 2 ears) revealed SNR < 0 dB. Chi-square analysis revealed that participants with firearm exposure were 4.5 times more likely to exhibit at least one missing value than their counterparts (Odds ratio = 4.5, $p < 0.05$; 15 out of 19 participants with firearm exposure). No other factors revealed a significant association with the missing data. We performed a missing value pattern analysis and found that missing values were more common for f2 > 8000 Hz, but otherwise did not follow a consistent pattern. For the statistical analysis, it was essential to include participants with missing values, as these participants might be more likely to exhibit cochlear pathology related to tinnitus and noise exposure. We substituted the noise floor level for missing DPOAEs as the noise floor was acceptably lower (<10th percentile of corresponding DPOAEs across the subjects). This method is conservative as it overestimates true DPOAEs (Lapsley Miller *et al.*, 2006).

Relationship between tinnitus, HT, DPOAE, and ΔDPOAE

Table V presents the results of the LMM analysis. Individuals with chronic tinnitus had significantly elevated HTs relative to those with no tinnitus [mean difference (MD) = 1.12 dB, $p < 0.001$]. Chronic tinnitus did not significantly correlate with DPOAE ($p > 0.05$). Individuals with chronic tinnitus showed significantly higher ΔDPOAEs (MD = 1.05 dB, $p < 10^{-8}$) than those without tinnitus. Figure 2 shows HT, DPOAE, and ΔDPOAE across the audiometric frequency range between the tinnitus groups. DPOAE noise floor values were not significantly different between the groups ($p > 0.05$) [Fig. 2(B)]. Positive values of ΔDPOAE indicate that participants with chronic tinnitus showed an average of 1.05 dB higher DPOAE than predicted from their HTs [Fig. 2(C)].

Relationship between firearm noise exposure, HT, DPOAE, and ΔDPOAE

The results of the LMM showed that participants reporting firearm noise exposure had significantly elevated HTs (MD = 2.6 dB, $p < 10^{-8}$) and reduced DPOAEs (MD = –1.73 dB, $p < 0.001$) compared to those reporting no history of firearm noise exposure. Individuals with firearm noise exposure showed significantly lower ΔDPOAEs (MD = –1.1 dB, $p < 0.001$). Figure 3 shows that participants reporting firearm use exhibited significantly elevated HTs and reduced DPOAEs compared to their counterparts. Independent-sample t-tests showed no significant differences in noise floor values between the firearm use groups

TABLE IV. Descriptive statistics for the DPOAE measures (N = 133). The mean and standard error (in parenthesis) are presented. The data were reported before substituting the noise levels for DPOAEs with SNR < 0 dB.

					Right ear						
F2	1000	2000	3000	4000	6000	8000	9000	10500	11200	12500	14000	16000
Amplitude	5.46 (0.61)	7.83 (0.59)	6.18 (0.51)	6.86 (0.60)	9.93 (0.67)	−1.96 (0.87)	−3.31 (0.69)	−2.05 (0.83)	6.00 (0.97)	7.33 (1.02)	4.69 (0.92)	−5.69 (0.99)
Noise	−11.90 (0.38)	−15.69 (0.37)	−19.91 (0.30)	−21.01 (0.29)	−13.59 (0.28)	−13.82 (0.35)	−13.79 (0.34)	−11.41 (0.37)	−7.88 (0.39)	−7.61 (0.38)	−13.65 (0.37)	−16.95 (0.39)
SNR	17.36 (0.59)	23.53 (0.61)	26.09 (0.59)	27.87 (0.60)	23.52 (0.69)	11.85 (0.61)	9.40 (0.52)	9.35 (0.57)	13.14 (0.68)	14.94 (0.73)	17.60 (0.71)	11.25 (0.69)
#SNR > 6 dB	128	132	133	133	132	105	94	92	114	115	122	95
#SNR 0–6 dB	2	1	0	0	1	17	26	26	13	12	7	18
#SNR < 0 dB	3	0	0	0	0	11	13	15	6	6	4	20
					Left ear							
F2	1000	2000	3000	4000	6000	8000	9000	10500	11200	12500	14000	16000
Amplitude	4.16 (0.62)	7.77 (0.54)	5.05 (0.53)	6.33 (0.60)	8.65 (0.71)	−1.70 (0.84)	−5.44 (0.82)	−3.24 (0.82)	4.03 (0.95)	6.38 (0.97)	2.59 (1.08)	−5.92 (1.01)
Noise	−11.31 (0.42)	−14.34 (0.38)	−18.76 (0.36)	−20.44 (0.33)	−13.67 (0.29)	−14.20 (0.36)	−13.64 (0.39)	−11.12 (0.35)	−7.66 (0.37)	−7.44 (0.41)	−13.80 (0.40)	−17.14 (0.42)
SNR	15.47 (0.53)	22.11 (0.59)	23.81 (0.60)	26.73 (0.60)	21.53 (0.74)	10.37 (0.61)	8.19 (0.54)	7.87 (0.58)	11.70 (0.67)	13.82 (0.67)	16.38 (0.82)	11.20 (0.69)
#SNR > 6 dB	125	132	132	132	129	93	80	78	100	115	116	96
#SNR 0–6 dB	5	0	1	0	0	21	35	26	19	10	10	20
#SNR < 0 dB	3	1	0	1	4	19	18	29	14	8	7	17

TABLE V. Results of the linear mixed model regression analyses. The adjusted mean differences (MD) and *p*-values are presented. Superscripts indicate the reference category for calculating the adjusted MD. Frequency was used as a categorical repeated measure for all models ($p < 10^{-8}$ for models 1–2, and $p > 0.05$ for model 3).

Factors		Model 1: HT MD (in dB)	Model 2: DPOAE MD (in dB)	Model 3: ΔDPOAE MD (in dB)
Tinnitus	Yes	1.12[b]	0.6	1.05[b]
	No[Ref]	0	0	0
Firearm	Yes	2.6[c]	−1.73[b]	−1.10[a]
	No[Ref]	0	0	0
LNE	High	1.36[b]	−0.76[b]	−0.37
	Low[Ref]	0	0	0
Ear infection	Yes	0.81[a]	−0.90[a]	−0.56
	No[Ref]	0	0	0
Sex	Male	2.23[c]	−1.31[b]	−0.46
	Female[Ref]	0	0	0
Ethnicity	European	−0.09	−1.19[b]	−1.06[b]
	Others[Ref]	0	0	0
Ear	Right	−0.12	0.99[b]	0.00
	Left[Ref]	0	0	0

[a] $p < 0.05$.
[b] $p < 0.001$.
[c] $p < 10^{-8}$.

($p > 0.05$). Figure 3(C) shows ΔDPOAEs across the frequency range. Negative ΔDPOAE values indicated that participants reporting firearm use exhibited an average of 1.1 dB lower DPOAEs than predicted by their HT values [Fig. 3(C)].

Relationship between LNE on HT, DPOAE, and ΔDPOAE

The results of the LMM analysis revealed that participants with high LNE had elevated HTs (MD = 1.44 dB, $p < 0.001$) and reduced DPOAEs (MD = –0.76 dB, $p < 0.001$) relative to participants with low LNE. ΔDPOAE was not significantly different between the LNE groups (MD = –0.37, $p < 0.05$). Consistent with these findings, Fig. 4 shows that individuals with high LNE exhibited significantly elevated HTs [Fig. 4(A)] and reduced DPOAEs [Fig. 4(B)] at the extended–high frequency range compared to their counterparts. ΔDPOAE values indicated that the reduction in DPOAE was consistent with (or proportional to) the elevation in HTs [Fig. 4(C)].

Effects of the confounding factors on HT, DPOAE, and ΔDPOAE

The LMM regression analysis revealed that individuals with a positive history of ear infection exhibited elevated HTs, reduced DPOAEs, and reduced ΔDPOAEs, compared to those with no history of ear infection. These results suggest that participants with a history of reoccurring ear infections exhibit a greater reduction in DPOAE than predicted by HTs compared to those with no history of reoccurring ear

https://doi.org/10.1121/10.0019880

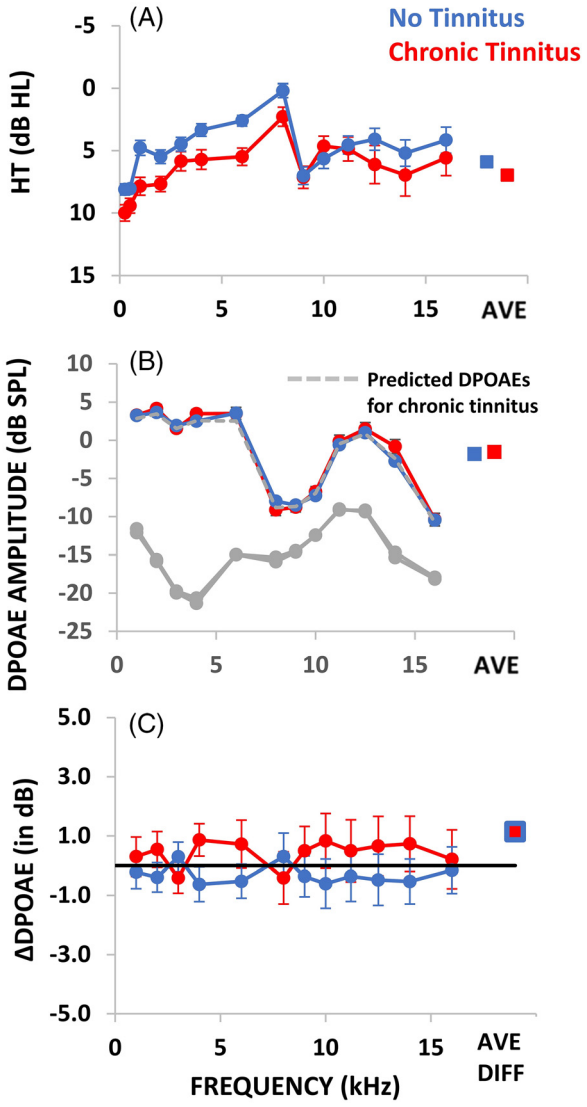

FIG. 2. (Color online) (A) Average HTs across the frequency range for participants with and without tinnitus. AVE on the far right of the *x* axis presents adjusted average HTs between the groups, with covariates accounted for by the LMM. (B) Average DPOAE (red and blue lines) and noise floor (gray line) as a function of f2 between the tinnitus groups. The dashed gray line presents predicted DPOAEs for chronic tinnitus. AVE presents adjusted average DPOAE between the groups. (C) Average ΔDPOAE across the frequency range for participants with chronic tinnitus and no tinnitus. AVE DIFF presents the adjusted group difference. The error bars indicate ±1 standard error.

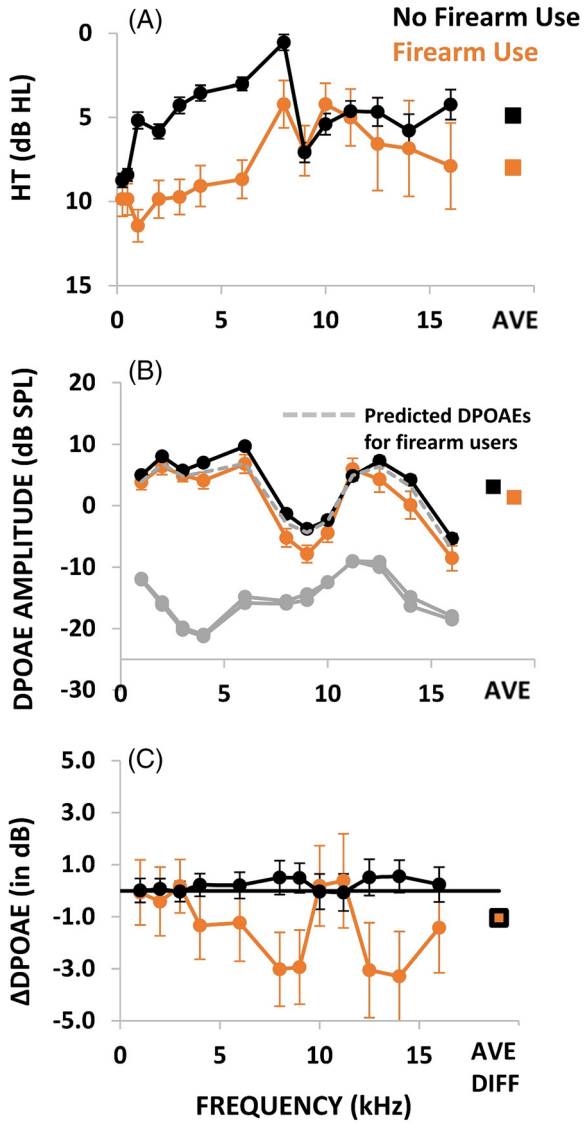

FIG. 3. (Color online) (A) Average HTs across the frequency range for participants with and without firearm use. AVE on the far right of the *x* axis presents adjusted average HTs between the groups, with covariates accounted for by the LMM. (B) Average DPOAE and noise floor as a function of f2 between the firearm use groups. The dashed gray line presents predicted DPOAE for participants reporting firearm use. AVE presents adjusted average DPOAE between the groups. (C) Average ΔDPOAE across the frequency range between the firearm use groups. AVE DIFF presents the adjusted group difference. The error bars indicate ±1 standard error.

infections. Other predictors also showed significant associations with the outcome measures (Table V).

DISCUSSION

The present study evaluated the effects of tinnitus, firearm noise exposure, and LNE on HTs and DPOAEs and their comparative metric (ΔDPOAE) in young adults. The major findings of the study were as follows: (1) Participants with chronic tinnitus revealed elevated HTs, no significant reduction in DPOAE, and significantly higher ΔDPOAE than those without tinnitus. These results suggest that participants with chronic tinnitus had larger (better) DPOAEs than predicted from their HTs (using a regression model based on all subjects grouped together). (2) Participants reporting firearm use revealed significantly elevated HTs, reduced DPOAEs, and lower ΔDPOAEs than those with no firearm use. Considering the combined results of three LLM models (Table V), we observed that participants with firearm use revealed an average reduction of 1.73 dB in their *observed DPOAE* compared to their counterparts. This *observed* reduction in average DPOAE was 1.1 dB (i.e., the magnitude of mean difference in ΔDPOAEs for firearm use) more than their *predicted* DPOAE based on their HTs compared to their counterparts. (3) Participants with high LNE

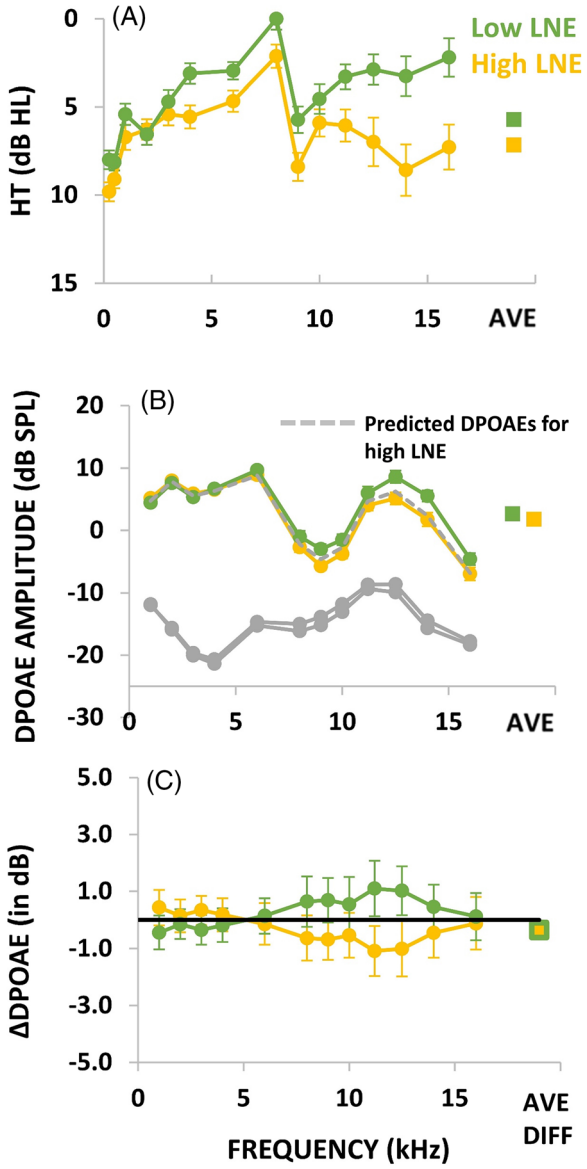

FIG. 4. (Color online) (A) Average HTs across the frequency range between the LNE groups. AVE on the far right of the x axis presents adjusted average HTs between the groups, with covariates accounted for by the LMM. (B) Average DPOAE and noise floor as a function of F2 between the LNE groups. The dashed gray line presents predicted DPOAE for participants reporting high LNE. AVE presents adjusted average DPOAE between the groups. (C) Average ΔDPOAE across the frequency range between the LNE groups. AVE DIFF presents the adjusted group difference. The error bars indicate ±1 standard error.

revealed elevated HTs, reduced DPOAEs, and reduced ΔDPOAEs compared to those with lower LNE. These results suggest that participants with high LNE had smaller (worse) DPOAEs than predicted from their HTs. (4) Our study documented the effects of sex, ethnicity, ear, and a history of an ear infection on DPOAEs and HTs, which are consistent with some prior reports (e.g., Lee *et al.*, 2012; Keefe *et al.*, 2008; Dreisbach *et al.*, 2007; Sininger and Cone-Wesson, 2004, 2006).

Previous studies suggested that DPOAEs and HTs might be differentially influenced by pathologies affecting *mechanical* (e.g., hair cell lesions), *metabolic* (e.g., dysfunction in stria vascularis), and *neural* mechanisms in the cochlea (e.g., Gates *et al.*, 2002; Rubsamen *et al.*, 1995; Mills *et al.*, 1993). These studies utilized the classical hypotheses on the origins of presbycusis. While we did not study presbycusis here, and some of the classical hypotheses have been expanded and even called into question (e.g., Wu *et al.*, 2020; Wu *et al.*, 2021; Wu and Liberman, 2022), we believe the information learned from studies on presbycusis can offer some help with interpreting the results of our current study. Here, we consider a theoretical model to interpret our results and review the relevant literature while considering how comparative analysis of DPOAEs and HTs (i.e., ΔDPOAEs) may help differentially diagnose auditory dysfunction by understanding the underlying mechanisms.

Figure 5 presents a model showing a linear relationship between DPOAEs and HTs. The negative slope of a regression line suggests an inverse relationship between DPOAEs and HTs, meaning that DPOAEs decrease as HTs elevate. The green dot near the top left represents a *hypothesized* control group showing DPOAEs and HTs within a normal range. The black dot near the bottom right represents a substantially elevated HT compared to the control group and a corresponding "proportional" decline in DPOAE, as predicted by the linear model. The "proportional" reduction in DPOAE indicates the dysfunction of a shared mechanism(s) underlying the linear predictive relationship between DPOAEs and HTs.

The blue dot in Fig. 5 represents an elevated HT compared to the control group and a greater decline in DPOAE than predicted by the control group linear model. A larger-than-predicted decline in DPOAE is hypothesized to be consistent with a mechanical dysfunction that is "disproportional"

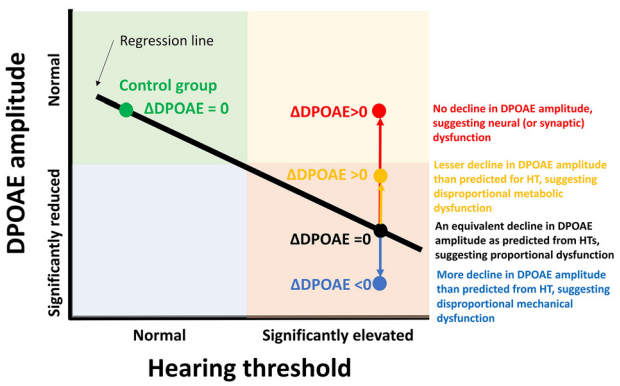

FIG. 5. (Color online) Schematic diagram showing the effects of mechanical, metabolic, and neural pathologies on DPOAEs and HTs. The regression line shows an inverse relationship between DPOAEs and HTs. The green dot on the regression line depicts a relationship between DPOAE and HT in "normal" individuals (control group). The black dot shows reduced DPOAE and elevated HT as predicted by the linear model (i.e., "proportional" decline in DPOAE). The blue dot presents more decline in DPOAE than predicted by the linear model, indicating predominant mechanical damage to the cochlea. The yellow dot shows less decline in DPOAE than predicted by the linear model, which suggests disproportional metabolic damage to the cochlea. The red dot presents elevated HT and no decline in DPOAE, suggesting a disproportional neural origin of the cochlear damage. The blue, yellow, and red lines show the error in prediction (ΔDPOAE).

to what is predicted by the linear model. We used regression residuals (ΔDPOAEs) to quantify the degree of disproportionality. Others have interpreted their data as suggesting that mechanical dysfunction might cause DPOAEs to decline to a greater extent than HT elevations at corresponding frequencies (e.g., Marshall *et al.*, 2009; Hamernik *et al.*, 1996; Engdahl and Kemp, 1996). A loss of up to 30% of OHCs at a specific location on the basilar membrane could remain undetected by HTs (Clark and Bohne, 1986). As a by-product of the process of cochlear amplification, mediated in part by electromotile OHCs, DPOAEs might be more sensitive than HTs for detecting OHC dysfunction (Liberman *et al.*, 2002; Emmerich *et al.*, 2000; Atchariyasathian *et al.*, 2008; Lapsley Miller *et al.*, 2006; Attias *et al.*, 2001; Marshall *et al.*, 2001; Engdahl and Kemp, 1996). DPOAEs could likely be influenced by functional changes in OHC physiology that are not reflected in gross histology, like cochleocytograms. For example, a stereocilin knock-out mouse model shows that disruption of the horizontal connectors of OHC stereocilia that could be challenging to visualize in cochleocytograms without optimized histological procedures can result in normal hearing sensitivity but no recordable DPOAEs (Verpy *et al.*, 2008). Taken together, a reduction in DPOAEs that is larger than predicted by the theoretical model might indicate "disproportional" mechanical dysfunction. *Our results associated "disproportional" mechanical dysfunction with firearm use*.

The red dot in Fig. 5 hypothesizes an elevation of HT without associated reduction in DPOAE. This pattern is characterized by positive ΔDPOAE and is consistent with *neural pathologies*. For example, pathologies that selectively affect neural excitation without affecting the OHC function are often referred to as auditory neuropathy (e.g., Starr *et al.*, 1996; De Siati *et al.*, 2020). *Our study associated neural dysfunction with chronic tinnitus*.

The yellow dot in Fig. 5 shows a hypothesized elevation in HTs and a relatively lesser decline in DPOAEs than predicted by the model. Elevated HTs with a lesser decline in DPOAEs have been thought to result from metabolic dysfunction (e.g., Gates *et al.*, 2002; Mills *et al.*, 1993). It is reasoned that metabolic dysfunction that reduces the endolymphatic potential could reduce the input to the IHCs in two ways—first, by diminishing the OHC-drive of IHCs excitation; and second, by reducing the resting membrane potential across the IHC's transduction channels (Mills *et al.*, 1990). OHC-mediated DPOAEs would be affected only by reduced resting membrane potential, whereas a decline of the resting membrane potential and drive from OHC function would affect IHC-mediated HTs more than DPOAEs (Mills, 2001). Indeed, a decrease in the endolymphatic potential from furosemide administration causes a greater decline in neural thresholds compared to DPOAEs (e.g., Rubsamen *et al.*, 1995). DPOAEs might remain relatively less affected due to a recalibration of the operating properties of the mechanoelectrical channels of OHCs (e.g., Wang *et al.*, 2019). A comparative analysis associated a greater decline in HTs than DPOAEs with aging, which is believed to be consistent with the metabolic dysfunction that may be associated with presbycusis (Gates *et al.*, 2002; Schuknecht *et al.*, 1974). *It appears that we did not have ears with substantial hearing loss from metabolic dysfunction in our study*. Future studies with elderly female participants may be an opportunity to study metabolic dysfunction (Grant *et al.*, 2022).

Indication of neural dysfunction associated with tinnitus

Tinnitus was associated with elevated HTs, but DPOAEs remained comparable to the no-tinnitus group. The elevation in HTs without a reduction in the DPOAE is typically associated with auditory neuropathy (e.g., Abdala *et al.*, 2000; Starr *et al.*, 1996). This pattern could also arise from selective damage to IHCs. For example, carboplatin-induced selective loss of IHCs causes a significant elevation in auditory nerve compound action potential thresholds without reducing DPOAEs in animal models (Ding *et al.*, 1999; Wang *et al.*, 1997), although human studies have reported dose and frequency-dependent changes in DPOAEs (e.g., Dreisbach *et al.*, 2017). Participants in the present study were healthy and reported no exposure to ototoxins that could cause selective damage to IHCs. Therefore, selective damage to IHCs could be ruled out as a putative mechanism underlying the elevation in HTs without a reduction in the DPOAEs.

A slight elevation in HTs with no reduction in DPOAEs might result from IHC synaptic loss. HTs could remain within normal limits while losing up to 50% of afferent synapses on IHCs (Kujawa and Liberman, 2015). Initial studies indicated that cochlear synaptopathy disproportionally affects auditory nerve fibers with high thresholds that remain "hidden" from conventional audiometric assessment, as they are not involved with coding threshold-level sounds (e.g., Liberman and Kujawa, 2017; Furman *et al.*, 2013). However, recent evidence suggests that cochlear synaptopathy could uniformly impact all types of auditory nerve fibers, including those with low thresholds that contribute to HTs (Suthakar and Liberman, 2021; Fernandez *et al.*, 2020). This evidence suggests that cochlear synaptopathy might have a modest influence on HTs. We used LMM to control for the potential confounders (sex, ethnicity, reoccurring ear infection) and repeated measures (ear and frequency), which could help identify modest elevation in HTs (e.g., Krueger and Tian, 2004). We found that the marginal means of HTs for tinnitus and control groups were within normal limits (<10 dB HL), with a mean difference of 1.12 dB ($p < 0.001$) (Table V). A minor elevation in HTs with marginal means within normal limits might indicate early-stage dysfunction in the IHC synaptic junctions. Suprathreshold auditory measures are relatively more sensitive to identifying synaptic dysfunction than HTs and DPOAEs (e.g., Kohrman *et al.*, 2020; Liberman *et al.*, 2016). Recent studies showing a relationship between tinnitus and suprathreshold proxy measures of cochlear synaptopathy in individuals with clinically normal hearing thresholds further support our interpretation

(e.g., Jafari *et al.*, 2022; Chen *et al.*, 2021; Valderrama *et al.*, 2018; Bramhall *et al.*, 2018; Wojtczak *et al.*, 2017; Gu *et al.*, 2012; Schaette and McAlpine, 2011). It is noteworthy that some studies investigating proxy measures of cochlear synaptopathy did not observe a significant association with tinnitus (e.g., Guest *et al.*, 2017). Further research is necessary to replicate these findings and identify the physiological substrates for tinnitus in young adults.

Disproportional mechanical dysfunction associated with firearm noise exposure

Individuals with firearm noise exposure showed significantly elevated HTs and reduced DPOAEs. A significant reduction in ΔDPOAEs in individuals reporting firearm use shows that the decline in DPOAEs was larger than predicted from the model (cf. Figs. 3 and 5). According to the model, these results are consistent with mechanical dysfunction. Past studies showed that DPOAEs could be more sensitive than HTs for detecting incipient inner-ear damage due to impulse noise exposure (Sonstrom Malowski *et al.*, 2022). ΔDPOAEs might help identify mechanical dysfunction in firearm users.

Figures 3(A) and 3(B) show DPOAEs and HTs in participants with and without firearm use. The effect of firearm noise exposure is observable across the conventional frequency range from 1 to 8 kHz and at the extended high frequency of 14–16 kHz, with a general agreement between HTs and DPOAEs. Animal studies showed that impulse noise exposure–induced HTs and DPOAE shifts could be observed around 3–8 kHz (e.g., Dancer *et al.*, 1991; Konopka *et al.*, 2001). Some studies observed a reduction in otoacoustic emissions and elevation in HTs at lower frequencies, around 0.5–4 kHz, following impulse noise exposure (Rezaee *et al.*, 2012). Recent evidence suggests that the degeneration of IHC's synaptic junctions following noise exposure can be observed at the lower frequency regions than in the center frequency of noise (e.g., Fernandez *et al.*, 2020; Hickman *et al.*, 2018). A complex pattern of sensory and neural (or synaptopathic) dysfunction following impulse noise exposure could be present in participants with firearm noise exposure.

Proportional cochlear dysfunction associated with high LNE

Individuals with high LNE revealed significantly elevated HTs and reduced DPOAEs. The group difference in ΔDPOAEs did not achieve statistical significance (MD = –0.37 dB, $p > 0.05$). These findings suggest proportional cochlear dysfunction associated with high LNE (Fig. 5). The group difference in ΔDPOAEs was higher for firearm groups (MD = –1.73 dB, $p < 0.001$) than for LNE groups [Figs. 3(C) and 4(C), Table V]. The simplest interpretation of these results would be that acoustic trauma from firearm noise exposure produces a greater decline in DPOAEs than long-term exposure to non-impulsive noise with a lower crest factor. If true, these results suggest impulse noise exposure could produce disproportional mechanical dysfunction than steady-state noise. Exposure to impulse noise could cause instant mechanical trauma by tearing OHCs, IHCs, and supporting cells from the basilar membrane (Hamernik *et al.*, 1984). Impulse noise could induce greater permanent threshold shifts than long-term non-impulsive noise (e.g., Suvorov *et al.*, 2001; Mäntysalo and Vuori, 1984). Exposure to noise with highly impulsive components could be more traumatic than noise with non-impulsive components (Goley *et al.*, 2011; Zhao *et al.*, 2010). Our results suggest that participants reporting high LNE (non-impulse noise) might exhibit proportional mechanical dysfunction, and those with firearm exposure exhibit disproportionally more mechanical dysfunction than their counterparts.

Figures 4(A) and 4(B) show the effect of high LNE on HTs and DPOAEs across the frequency range. Participants with high LNE revealed the highest group difference in HTs and DPOAEs at the extended–high frequency range. These results are consistent with past studies investigating proxy measures of cochlear synaptopathy in young adults with clinically normal hearing thresholds (e.g., Liberman *et al.*, 2016). Cochlear synaptopathy is typically present at the mid-to-high frequency region in the cochlear partition when OHC loss is found at the far-basal end (Kujawa and Liberman, 2015). These observations suggest that participants with high LNE might exhibit cochlear synaptopathy at the mid-to-high frequency region, but it might remain "hidden" from HTs as they are relatively less sensitive to detecting synaptic damage (Suthakar and Liberman, 2021). Including proxy measures of cochlear synaptopathy in the comparative analysis might help differentiate disproportional synaptic damage.

Effects of sex, ethnicity, and ear on DPOAEs and HTs

Females, participants reporting non-European ethnicity and right ears revealed significantly lower (better) HTs and higher DPOAEs than their counterparts (Table V). These results are consistent with some past studies (e.g., Lee *et al.*, 2012; Dreisbach *et al.*, 2007; Keogh *et al.*, 2001). The individual variability in outer ears could influence the relationship between cochlear measures and demographic factors. The SPL calibration technique used in most clinical studies, including the present study, might not effectively account for individual variation in external ears (Souza *et al.*, 2014). Using forward pressure level calibration to account for some morphological variations, Boothalingam *et al.* (2018) challenged the notion of a "right ear advantage" in DPOAEs and HTs. They showed that the effect of sex on DPOAEs and HTs was limited to participants of European ethnic backgrounds, with white females exhibiting better DPOAEs and HTs than white males. Future studies should employ forward pressure level calibration methods to help control for individual differences in ear canals and middle ears.

Clinical utility of the model-based comparison between HTs and DPOAEs

In clinics, DPOAEs are frequently utilized for hearing screening and differential diagnostic purposes. A traditional

approach for evaluating DPOAEs is to compare the measured amplitudes and SNRs between patients and normal-hearing healthy controls. A reduction in DPOAEs and SNRs compared to the normative range is considered to be an indication of cochlear dysfunction. DPOAEs present a wealth of information on cochlear mechanics; some might be complementary to HTs, while others might be unique. Therefore, comparing HTs and DPOAEs in clinical situations might elucidate a dimension of auditory physiology that could remain "hidden" by individually evaluating both measures. Here, we utilized a model-based comparison between HTs and DPOAEs, quantifying the relative agreement between DPOAEs and HTs. The derived metric, ΔDPOAE, might be helpful for differential diagnostic purposes (Fig. 5). The calculations of ΔDPOAEs do not require additional data collection from clinicians, and they could be employed within DPOAE reporting software.

Methods for calculating ΔDPOAEs could be improved by creating baseline predictive models from large cohorts of healthy young adults (without tinnitus, high LNE, firearm use, reoccurring infections, etc.). Baseline predictive models created with small and non-representative databases could result in biased estimations of ΔDPOAEs. The present study did not have access to a large database for designing such baseline predictive models. Therefore, we created predictive models by fitting HTs and DPOAE data from the entire sample. This approach prevents biased estimations of ΔDPOAEs as the predicted DPOAEs were derived from the same sample; however, the predictive models could produce overly conservative estimates of ΔDPOAEs in certain subgroups. The predictive accuracy of the models could be affected by subsamples with pathologies that influence the relationship between HTs and DPOAEs (e.g., tinnitus, firearm use). For example, DPOAEs for firearm users were significantly lower (Table V). Including firearm users in the baseline predictive model could reduce the slope of the regression line, producing a conservative estimate of ΔDPOAEs for the firearm users (see supplementary material for baseline predictive model).[1] Therefore, in future work, there is a need to construct unbiased and efficient predictive models for quantifying ΔDPOAEs using large cohorts of healthy young adults with an optimal representation of demographic factors (e.g., age, sex, ethnicity). Future studies could employ machine learning approaches for quantifying ΔDPOAEs and investigating their clinical utility.

Experimental caveats

The present study was limited by its non-invasive nature. We obtained regression residuals (ΔDPOAEs) at each frequency using a linear regression model which assumes a linear relationship between HTs and DPOAEs at each frequency (see supplementary material for regression residuals).[1] The comparative analysis did not include suprathreshold proxy measures of cochlear synaptopathy, which could help differentiate synaptic dysfunction. The present study utilized a commercially available DPOAEs system with the ER-10 °C probe assembly and in-ear dBSPL calibration. In-ear and in-coupler calibration errors could contribute to observing the notch at around 8000–10 500 Hz and a steep rise at the extended–high frequencies in DPgram [Fig. 2(A)]. While the notch and other calibration-related issues were unlikely to influence the major findings of the study, we recognize the need for recording DPOAEs with methods that could more efficiently compensate for the acoustical properties of the external ear canal (see the supplementary material for linear mixed model analysis after removing data from 8000 to 10 500 Hz).[1] Caution should be applied by readers when interpreting the configuration of DPgrams and audiograms (see the supplementary material for DPgrams and audiograms).[1] Last, participation bias cannot be ruled out, which might affect the sampling process by internally motivating participants (potentially those with chronic tinnitus) to participate. Future research should focus on creating baseline predictive models for HTs and DPOAEs from a large cohort of healthy young adults and to investigate their efficacy in quantifying ΔDPOAE.

CONCLUSIONS

This study investigated the relationship between HTs and DPOAEs between overlapping subgroups of tinnitus, firearm use, and LNE. Participants with tinnitus showed elevated HTs, no reduction in DPOAEs, and significantly better DPOAEs than predicted from their HTs (ΔDPOAEs) compared to their counterparts, after controlling for the effects of other predictors and repeated measures. In contrast, participants with firearm use showed elevated HTs, reduction in DPOAEs, and significantly poorer DPOAEs than predicted from their HTs compared to those with no firearm use, after controlling for the effects of other predictors and repeated measures. The results were interpreted using a theoretical model (Fig. 5), wherein the relative agreement between HTs and DPOAEs were compared for different putative mechanisms underlying cochlear pathology. Our findings associated tinnitus with neural (or synaptic) dysfunction, and firearm noise exposure with disproportional mechanical dysfunction. Further research is needed to critically evaluate the theoretical model using invasive investigations in modeled organisms and complementary clinical studies.

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[1]See supplementary material at https://doi.org/10.1121/10.0019880 for details on the tinnitus screening questionnaire and individual responses; details on scatter plots between hearing thresholds and distortion product otoacoustic emissions; missing value analysis; and the linear mixed model analysis after removing data from 8000 to 10 500 Hz.

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