Hearing Research 361 (2018) 80–91

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Research Paper

Evidence of noise-induced subclinical hearing loss using auditory brainstem responses and objective measures of noise exposure in humans

Erika Skoe [a, b, c, *], Jennifer Tufts [a, c]

[a] Department of Speech, Language, and Hearing Sciences, University of Connecticut, Storrs, CT, 06269, USA
[b] Department of Psychological Sciences, Cognitive Sciences Program, University of Connecticut, Storrs, CT, 06269, USA
[c] Connecticut Institute for Brain and Cognitive Sciences, University of Connecticut, Storrs, CT, 06269, USA

ARTICLE INFO

Article history:
Received 20 September 2017
Received in revised form
21 December 2017
Accepted 8 January 2018
Available online 11 January 2018

ABSTRACT

Exposure to loud sound places the auditory system at considerable risk, especially when the exposure is routine. The current study examined the impact of routine auditory overexposure in young human adults with clinically-normal audiometric thresholds by measuring the auditory brainstem response (ABR), an electrophysiological measure of peripheral and central auditory processing. Sound exposure was measured objectively with body-worn noise dosimeters over a week. Participants were divided into low-exposure and high-exposure groups, with the low-exposure group having an average daily noise exposure dose of ~11% of the recommended exposure limit compared to the high-exposure group average of nearly 500%. Compared to the low-exposure group, the high-exposure group had delayed ABRs to suprathreshold click stimuli and this prolongation was evident at ABR waves I and III but strongest for V. When peripheral differences were corrected using the I-V interpeak latency, the high-exposure group showed greater taxation at faster stimulus presentation rates than the low-exposure group, suggestive of neural conduction inefficiencies within central auditory structures. Our findings are consistent with the hypothesis that auditory overexposure affects peripheral and central auditory structures even before changes are evident on standard audiometry. We discuss our findings within the context of the larger debate on the mechanisms and manifestations of subclinical hearing loss.

1. Introduction

For many individuals, exposure to high-intensity sound is a routine part of their occupational and/or leisure activities (Flamme et al., 2012). Chronic and short-term overexposure to sound can stress the auditory system at multiple anatomic levels (Gourevitch et al., 2014) and in ways that are not necessarily evident from conventional audiological assessments. Animal models have brought the auditory brainstem response (ABR) to the forefront as a clinically-viable metric for uncloaking different types of damage caused by exposure to high-intensity sound, including noise-induced synaptopathy and myelinopathy, two classes of pathology that do not necessarily affect hearing thresholds (Kujawa and Liberman, 2009; Wan and Corfas, 2017).

ABRs are evoked neural potentials, recorded from dermal or subdermal electrodes, that emerge as a series of waves with latencies <10 ms. In humans, waves I, III, and V are the most prominent ABR waves, and they reflect the synchronized activity of the auditory nerve (AN) (I), cochlear nucleus (III), lateral lemniscus (V), and inferior colliculus (V) (Melcher and Kiang, 1996). Measurement of ABRs does not require active participation from the listener and their objective nature has enabled widespread use for multiple clinical purposes (Starr and Don, 1988; Sininger, 1993; Starr et al., 1996; Burkard et al., 2007), including universal newborn hearing screenings (Johnson et al., 2005) and neuro-otologic diagnosis (Berlin et al., 2010; Don et al., 2005). For neuro-otologic purposes, the I-V inter-peak interval (IPL) is routinely used as a measure of central conduction time that normalizes for differences in peripheral function (Hall, 2007). There has been growing interest to adopt ABRs for the early detection of noise-induced hearing loss (NIHL) following the seminal publication by Kujawa and Liberman (2009).

* Corresponding author. University of Connecticut, 850 Bolton Rd, U-1085, Storrs, CT, 06129, USA.
E-mail address: erika.skoe@uconn.edu (E. Skoe).

https://doi.org/10.1016/j.heares.2018.01.005
0378-5955/

This study showed that short-term auditory overexposure in mouse could damage the synapses (synaptopathy) between the inner hair cells (IHC) and type I spiral ganglion neurons (SGN), with degeneration of the auditory nerve occurring subsequent to synaptopathy. Kujawa and Liberman (2009) also reported that cochlear synaptopathy can occur even in cases when hearing thresholds recover and hair cells are spared, with later work showing that auditory nerve neuropathy was selective to low-spontaneous, high-threshold fibers (Furman et al., 2013). Important for the current investigation, the number of surviving spiral ganglion cells correlated with ABR wave I amplitude, suggesting that ABR wave I amplitude might serve as a non-invasive proxy for the loss of neural output from the cochlea due to cochlear synaptopathy (Liberman and Kujawa, 2017).

Studies attempting to link noise exposure history and ABR morphology in humans, however, have produced mixed results. Several recent studies provide support for ABR wave I amplitude as a measure of noise-induced cochlear synaptopathy in populations that are occupationally or recreationally exposed to noise but have normal pure tone audiometric thresholds (Bramhall et al., 2017; Grose et al., 2017; Liberman et al., 2016; Pushpalatha and Konadath, 2016). However, other studies have not observed an association between ABR wave I amplitude and noise exposure (Grinn et al., 2017; Guest et al., 2017a; Prendergast et al., 2017). It has also been argued that wave V latency may provide a surrogate metric of the more difficult to measure wave I amplitude (Mehraei et al., 2016); however, the surrogacy of wave V has been called into question by other studies. For example, while Prendergast et al. (2017) found a relation between ABR wave V latency and estimated lifetime noise exposure, this relationship was restricted to one stimulation level (80 dB peSPL but not 100 dB peSPL) and it was rendered not significant once the effects of age were taken into account.

Various explanations have surfaced for why translating findings from animal research to human research has been met with challenges (Grinn et al., 2017; Grose et al., 2017; Hickox et al., 2017; Prendergast et al., 2017). For one, cochlear synaptopathy cannot be directly observed in living humans (Viana et al., 2015); its presence can only be inferred by means of proxy measures such as the ABR. While ABR wave I amplitude has emerged from the animal literature as a candidate measure of cochlear synaptopathy in humans, ABR amplitudes are influenced by a multitude of factors including age, head size, sex, and audiometric thresholds (Gorga et al., 1985; Grose et al., 2017; Mitchell et al., 1989; Strelcyk et al., 2009; Trune et al., 1988; Verhulst et al., 2016). These factors can be more difficult to equate in human versus non-human populations and they may, therefore, confound the interpretation of data from noise-exposed human populations when not adequately controlled (see Stamper and Johnson, 2015a; Stamper and Johnson, 2015b). Other discussions on translational issues have centered on the prevalence of cochlear synaptopathy in human populations. It has been argued that the typical noise exposure patterns of young adults may not be sufficient to produce the type of acute damage to the auditory system that can be revealed through the ABR (Prendergast et al., 2017). A different school of thought is that cochlear synaptopathy is common among human populations (Liberman and Kujawa, 2017) and that synpatopathic damage may, therefore, only be evident in the ABR if comparisons are made to unexposed ears, which may only hypothetically exist, or if the study group includes individuals with much higher noise exposure than is typical of young adults (Liberman et al., 2016).

Another major translational complication is that noise exposures in humans are less well controlled than in experimental animal models. In animal models, exposure levels are precisely calibrated and dosed to animals with similar, and well-documented, genetic profiles, rearing, and noise-exposure histories. With experimental animal models, it is possible to track the physiological changes that arise from the first excitotoxic event and then each subsequent re-exposure to high intensity sound. By contrast, studies involving humans are complicated by more idiosyncratic demographics and noise exposures. For most human populations, the likelihood of being repeatedly exposed to noise is also high, and because hearing damage may accrue overtime, the nature and manifestation of the damage may necessarily be different in humans than has been observed in animals with more controlled noise exposure. The idiosyncratic nature of noise exposure in humans may also increase the likelihood of mixed hearing pathology (i.e., cochlear synaptopathy in combination with other forms of cochlear or central damage) (Eggermont, 2017; Hickox et al., 2017; Liberman and Kujawa, 2017; Verhulst et al., 2016). Thus, cochlear synaptopathy is not expected to be the sole mechanism of subclinical noise-induced hearing loss in human populations (Kopp-Scheinpflug and Tempel, 2015; Salvi et al., 2016), and translational efforts that focus exclusively on ABR wave I amplitudes (e.g., Grinn et al., 2017) may be overlooking other types of noise-induced pathology that can potentially be revealed through the ABR, such as myelinopathy (Tagoe et al., 2014; Wan and Corfas, 2017). Finally, there are also complications with estimating noise exposure from structured interviews or questionnaires (Prendergast et al., 2017; Taylor, 2007), and determining the veracity of the lifetime noise exposure metrics when participants have similar audiograms (Guest et al., 2017a, 2017b). Thus, current methods for measuring/verifying individual differences in noise exposure may be insufficient to map differences in noise exposure to the ABR.

In an effort to address the shortcomings of the previous work, we adopted a novel approach that combined ABRs with objective, multiday measurements of sound exposure in young adults with clinically normal audiograms. The current investigation builds from the assumption that the reliance on subjective, self-report measures of noise exposure is a limiting factor for revealing the electrophysiological signature(s) of the early, subclinical stages of noise-induced hearing loss. Sound exposure was measured continuously over a week using a personal sound level meter, called a dosimeter, attached to the participants' clothing. Participants were subsequently divided into low- and high-exposure groups based on the dosimetry results. Prior to dosimetry, clinical audiometry was performed and suprathreshold ABRs were recorded; these measurements occurred after a 14-hour quiet period to minimize the influence of temporary threshold shifts (TTS), especially for the participants who regularly engage in loud activities. We then related ABRs and dosimetry, treating both as representative snapshots of the individuals' sound exposure routines.

In the current study, ABRs were recorded to suprathreshold clicks at eight stimulation rates, and for each rate, measures of ABR wave amplitude and latency, as well as interpeak latency were obtained. Manipulation of rate provides a window into the temporal dynamics of synaptic function and neural conduction as the auditory system is stressed (Lasky, 1997; Shi et al., 2013). Faster click rates are associated with decreased ABR amplitudes and prolonged ABR absolute and interpeak latencies (Lasky, 1997). If group differences are observed in the ABR rate functions when comparing individuals with low versus high sound exposures, the pattern of the group differentiation could provide insight into the putative mechanism(s) of subclinical NIHL. Two broad categories of group differences could emerge for the ABR rate functions, with each category having a different set of potential explanatory mechanisms, which we outline below. The first category, *preserved differentiation* (Salthouse and Lichty, 1985), predicts that the low- and high-exposure groups have different ABR morphologies but

that the difference is fixed (i.e., equal) across the eight presentation rates, leading to the two groups having separated but parallel ABR rate functions. The second category, *differential preservation,* predicts an interaction between presentation rate and group that would manifest as the high-exposure group having a steeper slope to the ABR rate function than the low-exposure group (i.e., greater rate-dependent changes).

If the high-exposure group is more taxed by fast presentation rates than the low-exposure group, this *differential preservation* pattern would be suggestive of poorer temporal processing in the high-exposure group due to reduced synaptic efficiency (Shi et al., 2013). Synaptic inefficiency could arise from a number of sources, including a selective depopulation of low-spontaneous rate nerve fibers (low-SR), inefficient neurotransmitter release, and/or myelinopathy. Low-SR auditory nerve fibers, which have been found to be more vulnerable to noise-induced damage than high-spontaneous rate fibers (Furman et al., 2013; Liberman and Liberman, 2015), have longer recovery times following adaptation than high-SR fibers (Relkin and Doucet, 1991; Relkin et al., 1995) and their characteristic adaptation properties are evident for human and non-human species in the amplitude of the compound action potential (CAP) (Murnane et al., 1998; Relkin et al., 1995), an analog of ABR wave I. This literature on the CAP sets up the prediction that the selective loss of low-SR nerve fibers that follows cochlear synaptopathy would lead to impaired temporal processing. This impairment is predicted to manifest as decreases in ABR wave I amplitude, but no changes to wave I latency, as the presentation rate increases (Moser and Starr, 2016). (See, however, Bourien et al. (2014) for a different account).

Temporal processing deficits have also been observed in species where noise-induced synaptopathy is repairable (Liu et al., 2012; Shi et al., 2013). IHC-SGN ribbon synapses display fast kinetic properties characterized by the rapid release and recycling of neurotransmitter. Temporal processing deficits, which emerge for time-stress stimuli with short inter-stimulus intervals, have been found to arise during the synaptic repair process that occurs after noise-induced damage (Liu et al., 2012; Shi et al., 2013). Shi et al. (2013) observed increased CAP latency and decreased CAP amplitude for short inter-click intervals one month following a noise exposure event, which they attributed to inefficient neurotransmitter release in the repaired synapses. This line of work predicts decreased ABR wave I amplitude, as well as increased wave I latency, at the fastest presentation rates in the high-exposure group compared to the low-exposure group, due to slow and/or inconsistent neurotransmitter release associated with incomplete synaptic repair following synaptopathy (Liu et al., 2012; Shi et al., 2013, 2015). This prediction, of course, presumes that the human inner ear has the capacity for synaptic repair, an idea that, to date has not been proven nor disproven.

Another possible pathomechanism of delayed ABR latencies and reduced amplitudes at fast stimulation rates is noise-induced myelinopathy. The peripheral and central divisions of Type I SGNs are encased in myelin sheaths that are vulnerable to noise-induced damage (Tagoe et al., 2014). Tagoe et al. (2014), for example, showed that extended exposure to high-intensity sound in rats led to a permanent decrease of the thickness of the myelin sheaths of the auditory nerve. This myelinopathy was associated with decreased ABR wave I amplitude and prolonged ABR wave I latency, resulting from the delayed propagation of the action potential along the auditory nerve. In animals with severe forms of auditory nerve myelinopathy, CAP amplitudes and far-field potentials from the inferior colliculus have also been shown to decline after the initial myelinopathic event but partially rebound over time, although CAP and IC latency nevertheless remained consistently delayed (El-Badry et al., 2007). Myelin loss can also increase the timing jitter of action potentials, which is expected to compound when the presentation rate is speeded, producing a loss of temporal acuity for auditory signals that is predicted to inordinately prolong ABR latencies and reduce ABR amplitudes at fast presentation rates (Kim et al., 2013a). Therefore, noise-induced loss of myelin is predicted to manifest as increased ABR latencies and decreased amplitudes, especially at fast stimulus presentation rates. Applying the same logic, noise-induced disruptions to myelin in brainstem structures is expected to increase the I-V IPL at fast presentation rates (Kim et al., 2013a).

Now turning to the potential pathophysiological mechanism(s) that could underlie the pattern of *preserved differentiation* of group differences. If the high-exposure group differs from the low-exposure group in a rate-independent fashion, this would be suggestive of a neural conduction block for the high-exposure group, with one candidate mechanism being noise-induced damage to IHCs (Burkard et al., 1997; Salvi et al., 2016). Recent work suggests that pure-tone audiometry is relatively insensitive to IHC loss, except in cases of severe loss (Lobarinas et al., 2013). Although mild levels of IHC loss are not expected to manifest on the audiogram, there is reason to predict that IHC loss might be apparent in the ABR. Burkard et al. (1997) studied changes to the inferior colliculus potential (ICP), a homolog of ABR wave V, following the selective neurotoxic loss of IHCs. Selective loss of IHCs produced only a minimal audiometric threshold shift but this reduction of input to the central auditory system was associated with a small, yet consistent, increase in ICP latency and decreased ICP amplitude. The extent of the ICP latency and amplitude change was equivalent for fast and slow presentation rates (i.e., there were no rate-dependent effects), consistent with the IHC potential being rate-invariant (Coats, 1981; Liberman et al., 2016). This literature gives rise to the prediction that noise-induced loss of IHC would manifest as increased ABR wave latencies and decreased ABR amplitudes at all stimulus presentation rates, with the high- and low-exposure groups being separated by a fixed amount as the rate of presentation increases.

Here we tested the hypothesis that routine noise exposure in young adults is associated with changes to the ABR, and that these changes to the ABR are indicators of peripheral and/or central damage in spite of clinically normal audiometric findings. The central finding from this study is that young adult participants with high levels of routine noise exposure have delayed ABRs compared to participants with low levels of noise exposure. For waves I, III and V, the group differences are found to be rate-invariant, and this *preserved differentiation* profile is suggestive of noise-induced damage to IHCs. By contrast, for the I-V IPL, the group differences are rate dependent, and this *differential preservation* profile is potentially suggestive of central auditory system demyelination in participants with greater noise exposure. Our pattern of findings, however, is not suggestive of cochlear synaptopathy or selective damage to low-SR auditory nerve fibers.

2. Methods

2.1. Participants

73 young adults (18–24 years), all students at the University of Connecticut, participated in this study. Recruitment ads were placed in the UConn Student Daily Digest, an email delivered on weekdays to all university students that contains digested notices about events on campus, including opportunities to participate in research. All participants had clinically normal hearing bilaterally (i.e., air conduction audiometric thresholds $\leq$ 25 dB HL for octave frequencies from 0.25 to 8 kHz) and reported a negative neurologic history.

2.2. Experimental protocol overview

All experimental procedures were approved by the Institutional Research Board at the University of Connecticut, and participants provided their written informed consent prior to study enrollment. All testing occurred during the middle of the academic semester when academic, enrichment, and employment activities were ongoing.

Following a mandatory 14-hour quiet period, participants completed audiological threshold testing and electrophysiological assessments (ABRs) in a sound-attenuated audiologic chamber. Noise dosimetry measurements began immediately after this in-lab testing and lasted for 168 continuous hours, spanning eight calendar days. Note that in the present work, "noise" refers to high-volume sounds, without any specific reference to the spectral composition of that sound or the listener's emotional or psychological reaction to that sound.

2.3. Hearing thresholds

Air-conduction thresholds were obtained for the left and right ears at 0.125, 0.25, 0.500, 1, 1.5, 2, 3, 4, 6, and 8 kHz with a clinical audiometer (GSI 61 Audiometer, Grason-Stadler Inc.), using insert earphones. If thresholds at 0.25, 0.5, 1, 2, or 4 kHz were >5 dB HL, leaving room for a potential 15-dB air-bone gap, bone-conduction thresholds were obtained at those frequencies to rule out middle-ear pathology. In these cases, tympanograms were also used to assess middle-ear function. Air-bone gaps $\geq$ 15 dB at two or more adjacent frequencies, or abnormal tympanograms, would have resulted in exclusion from the study due to possible middle-ear pathology. However, it was not necessary to exclude any of the participants on the basis of these criteria.

2.4. Noise dosimetry protocol

Participants were trained to use the noise dosimeter (ER-200DW8 personal noise dosimeter; Etymotic, Inc.) and to record their daily activities into an activity logbook (Tufts and Skoe, 2017). Participants were instructed to wear the dosimeter on their clothing, near the ear, and to leave the microphone inlet uncovered. When sleeping or showering, or during activities when the device might be damaged (e.g., sports), participants were told they could remove the dosimeter but to keep it nearby, if possible. The turnoff button was disabled by the experimenter so that participants could not accidentally shut off the dosimeter. Participants were instructed to contact the research team if any issues relating to the dosimeter arose during the week.

At the end of training, the experimenter turned on the dosimeter and immediately recorded the time of day. Participants were scheduled to return in no less than one week (168 h) to hand in the dosimeter and journal and to receive monetary compensation for their participation in the study. Due to user error or because of issues with the dosimeter batteries dying prematurely, four participants did not complete the full (168-hour) dosimetry protocol. For these participants, their partial recording was used (i.e., 110.25, 120.50, 121.25, 147.31 h).

The dosimeters were configured to an 85-dBA criterion level and 3-dB exchange rate, in conformance with the National Institute for Occupational Safety and Health criteria (NIOSH, 1998), and a 75-dBA threshold. They logged dose data in 3.75-minute increments throughout the entire measurement period. The calibration of all dosimeters was periodically checked to ensure that the instruments were operating properly. This was done by generating a continuous 1000-Hz narrowband signal at a nominal level of 90 dB SPL in an Audioscan Verifit test box, and measuring its level with a calibrated Type 1 sound level meter (Larson-Davis 824) and with each dosimeter in "QuickCheck" mode. For each measurement, the microphone of the device was positioned at the same location in the test box. Measured dosimeter levels fell within 2.5 dB of the mean of three sound level meter measurements.

At the end of the recording period, dosimetry data were downloaded to.txt files, one per participant, using the ER200D Utility Suite software (version 4.04). The data were then processed individually for each participant using an in-house MATLAB routine that separated the data by date, using the dosimeter start time recorded by the investigator. The noise dose for each measurement date was calculated using criteria set by NIOSH. Doses were then averaged across days to derive the average daily noise exposure dose over the course of the measurement week. Individuals routinely exposed to noise in excess of 100% of the recommended daily exposure limit are considered to be at risk for NIHL, but risk cannot be ruled out in cases of routine exposure to lower-level sound, or even single exposures to high-level sound. It should be noted that in the activity logs, participants reported only minimal use of hearing protection devices such as earmuffs or earplugs.

2.5. Low-exposure and high-exposure groups

The participants were divided into "low-exposure" and "high-exposure" groups using the noise dosimetry data. We refer to these two groups as "low-exposure" and "high-exposure", but do so with full recognition of the following limitations: (1) these labels do not capture the wide-ranging exposure levels within the high-exposure group, (2) the assignment of group membership, and the corresponding "high" vs. "low" distinction, is less unequivocal for participants that fall near the group boundaries, (3) the dosimeter microphone is not sensitive to sounds played directly into the ear canal via earbuds or headphones; our noise exposure data may therefore underestimate exposures for some individuals, and (4) the dosimetry measurements can only provide a snapshot of the participants' routine noise exposure.

The low-exposure group was defined as having average daily noise exposure doses $\leq$ 20% (n = 29, 19 females, M = 20.14 years). None of the members of the low-exposure group had any measurement days in excess of 100% dose, and their average daily noise exposure doses ranged from <1% to 20%. The high-exposure group (n = 26, 22 females, M = 19.62 years) was defined as having exposures in excess of 100% dose for two or more measurement days. For this group, the average daily noise exposure doses ranged from 83% to 1114%, with an average of 486% (Fig. 1). This left 18 participants who did not fit the criteria for either group. These moderate-exposure participants had average daily noise exposure doses >20% (range: 22.96–106.62%) but either never exceeded 100% dose on any measurement day (n = 10) or exceeded 100% dose on one day only (n = 8).

The high-exposure group was comprised largely, though not exclusively, of students participating in music ensembles on campus (for a similar demographic makeup, see also Grose et al., 2017 and Liberman et al., 2016). For those 21 participants in music ensembles, the majority of the high-intensity sound exposure occurred during musical rehearsals and performances (Tufts and Skoe, 2017). For the other five participants, the highest levels of noise were associated primarily with their part-time employment in noisy restaurants or music venues, their attendance or participation in sporting/athletic events, listening to music at high volume, or some combination thereof.

Fig. 1 shows the average daily noise dose and audiometric data for the low- and high-exposure groups. Despite having distinctive noise exposure profiles, the low-exposure and high-exposure groups were matched with respect to the 10-frequency pure-tone

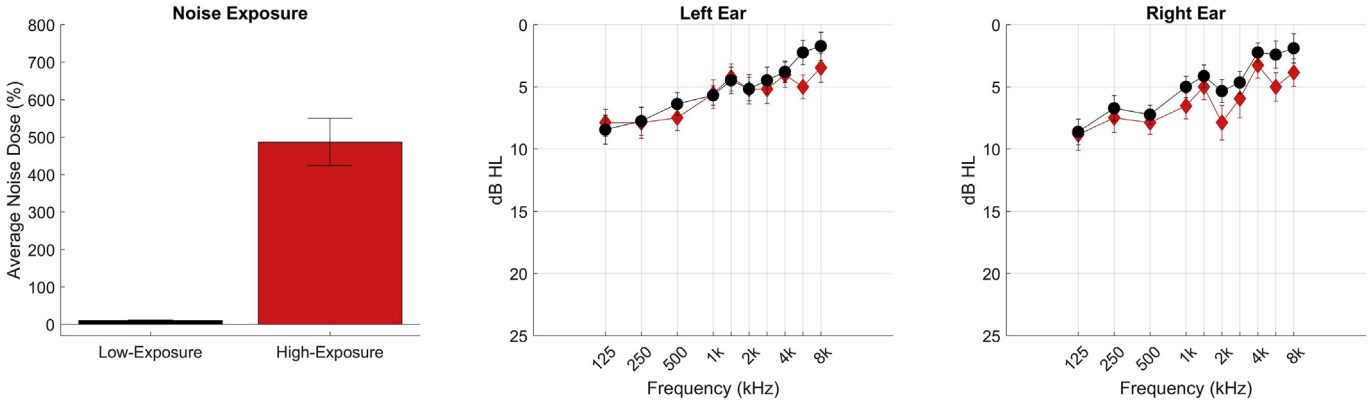

Fig. 1. (A) Average daily noise exposure dose for the low- and high-exposure groups, plotted in black and red, respectively. (B) The low- and high-exposure groups both had clinically-normal audiometric thresholds. Data reflect the mean ± 1 standard error of the mean. Note that in panel A, the error bars for the low-exposure group are so small that they cannot be visualized. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

average (PTA) and both groups had audiometric thresholds within normal clinical limits. For the right ear, the PTA was 4.82 ± 2.7 dB HL for the low-exposure group compared to 6.17 ± 3.64 dB HL in the high-exposure group ($t(53) = -1.52$, $p = .14$). For the left ear, the PTA was 5.02 ± 3.12 dB HL for the low-exposure group, which was very similar to the PTA of 5.60 ± 3.25 in the high-exposure group ($t(53) = 0.67$, $p = .50$). Pairwise comparisons at each test frequency showed that the groups were matched at all test frequencies ($p > .1$) except for 6000 Hz in the left ear where the high-exposure group had slightly elevated thresholds compared to the low-exposure group ($p = .05$) (Fig. 1). Note that ABRs were measured for the right ear only (see below).

2.6. Auditory brainstem responses (ABRs)

ABRs were recorded in Bio-logic AEP (Natus, Inc.), a clinical ABR system, following published procedures (Skoe et al., 2015). The non-inverting electrode was placed on the central vertex of the head (Cz), the inverting electrode was placed on the right earlobe (A2), and the ground electrode was placed on the forehead, following mild cleansing and scrubbing of the skin. Contact impedance of the Ag-AgCl electrodes was ≤5kΩ for all electrodes throughout the recording. ABRs were measured to 100-microsecond rarefaction clicks presented via insert earphone at 75 dB nHL. Using a 2-cc coupler attached to a 2250 Light-G4 B&K sound level meter, this measured as 106.7 peSPL from the output of the ear insert. ABRs were recorded for eight presentation rates (3.4, 6.9, 10.9, 15.4, 31.25, 46.5, 61.5 and 91.24 Hz). To reduce the length of the test session, and because all participants demonstrated symmetric audiometric thresholds, only the right ear was stimulated.

ABRs were recorded initially to the 31.25 Hz rate, a rate for which substantial normative data exists for the Bio-logic AEP system (Skoe et al., 2015). This allowed the experimenter to confirm the quality of the recordings, and then make any necessary modifications, such as re-adjusting the insert earphone or re-instructing the participant, prior to undertaking the full ABR protocol. Following this, the stimulus rates were administered in a fixed order, from slowest to fastest rates.

Responses were digitally sampled at 24 kHz, filtered online from 100to1500 Hz, artifact-rejected using a |23.8| microvolts criterion and averaged online over a 10-ms window that included 0.8 ms prior to the stimulus onset. Two sub-averages of 1000 artifact-free trials were obtained and subsequently combined. Recordings were made in a dimmed double-walled electromagnetically shielded sound booth, while participants sat in a reclined position watching a self-selected, muted video with English captions. The video was projected onto the booth wall, about five feet from the participant's head, using a ceiling-mounted LCD projector placed outside the booth window.

To ensure accuracy in identifying the latency and amplitude of the primary dependent measures (waves I, III, and V), the intervening waves, waves II and IV, were also identified; however, these waves were not incorporated into the analysis, given their limited use in clinical applications (Hall, 2007; Hood, 1998). The ABR waves were initially identified by the experimenter at the time of testing, and their latencies were subsequently confirmed by two additional raters, including the first author, who were blind to the participants' noise exposure data while visually inspecting the ABR waves. Wave latencies and amplitudes were extracted for analysis using custom MATLAB (release 2016a, The Mathworks, Inc.) routines. For each wave, ABR amplitude was analyzed in two ways: (1) from peak to baseline and (2) from peak to trough. The trough was identified using an automated trough-picking procedure implemented in MATLAB that located the first local minimum that followed the peak. The I-V IPL was calculated for each rate by subtracting wave I latency from wave V latency. I-V IPL is considered a measure of central conduction time that through the process of subtracting out wave I latency normalizes for differences in middle ear and inner ear physiology and anatomy (Eggermont and Don, 1986), including those differences associated with biological sex, although this may be a slightly simplified characterization (for a discussion see Hall, 2007). To calculate the effect of stimulus presentation rate, the IPL at the slowest rate (3.4 Hz) was subtracted from the IPL at the fastest rate (91.25 Hz).

ABR latencies increase as the rate of presentation is speeded and for rates >40 Hz the waves begin to lose some of their morphological distinctiveness compared to the slower rates where the morphology is very clear (Lasky, 1997). Fig. 2 shows group average ABRs at three of the eight presentation rates; note that the ABR waves become less distinct as the rate is speeded but that they are still reliably identifiable. However, in a small subset of the participants, wave I was not reliably present at one or more of the fast stimulation rates ≥ 46.5 Hz (3 participants, 4 data points total). These data points were replaced by the series mean in the statistical analyses.

2.7. Experimental design and statistical analysis

We focus our analyses on the low-exposure and high-exposure groups, with the rationale that this extreme-groups approach

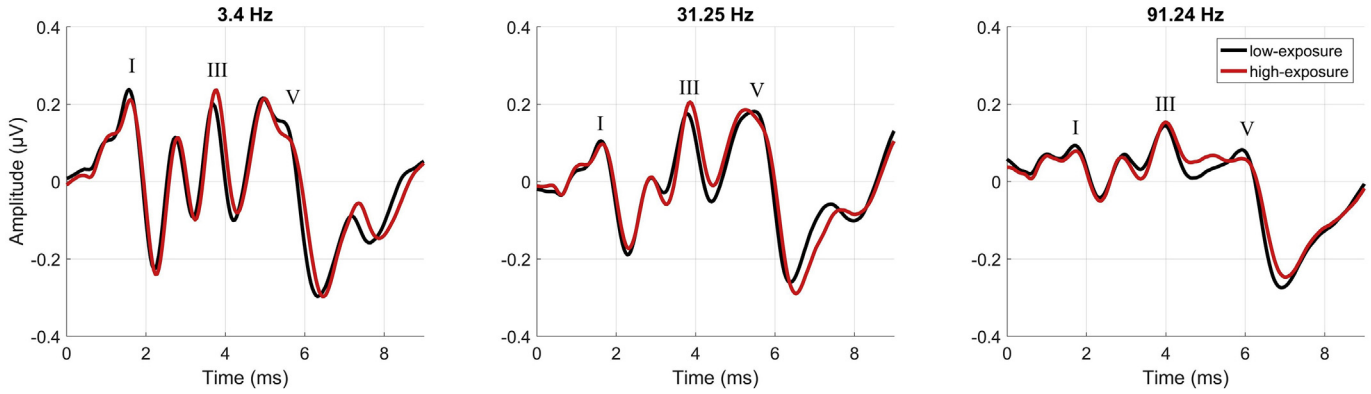

Fig. 2. ABR waveforms for the 3.4 Hz, 31.25 Hz, and 91.24 Hz stimulus presentation rates comparing the low- and high-exposure groups, plotted in black and red, respectively. The peak amplitudes are reduced and the peak latencies are prolonged as the stimulus presentation rate increases, but the characteristic features of the ABR are still present even in the fastest, most taxing presentation rate. Across the slow and fast presentation rates, the groups have comparable amplitudes (see also Fig. 3). The ABR delays that are evident for the high-exposure group in Fig. 4 appear here as a slight phase shift between the two waveforms. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

maximizes the likelihood of observing an association between routine noise exposure and ABR characteristics, should one exist. For the ABR data, mixed-model repeated measures ANOVAs (RMANOVA) were used to compare the group effects and group-level interactions. This analysis included ABR wave (3 levels) and stimulus presentation rate (8 levels) as within subject factors and group as a between subject factor. Greenhouse-Geisser corrections were applied in cases where the assumption of sphericity was violated. Although the low- and high-exposure groups were sex-matched ($\chi^2(1) = 2.38$, $p = .12$), there were proportionally more females in the dataset than males. Given the well-described effects of sex on ABR amplitudes and latencies (Don et al., 1993; Jerger and Hall, 1980; Trune et al., 1988), sex was added as a covariate to the analysis and the results with and without the covariate are presented.

The ABR variables that emerged as significant in the group analysis were further explored using bivariate correlations and regression models that treated the entire dataset, including the 18 moderate-exposure participants that did not meet the criteria for either the low or high exposure groups. The correlation analysis first examined whether a relationship between noise exposure (assessed by the average daily noise exposure dose metric) and the ABR measure is evident within the entire dataset, and then, second, whether noise exposure is a predictor of the ABR measure, even after accounting for the influences of audiometric thresholds and sex. Although the low- and high-exposure groups are audiometrically matched at all test frequencies for the ear that was stimulated for the ABR measurements (right ear) and all participants had audiometric thresholds in the clinically-normal range, as can be seen in Fig. 1, the high-exposure group has, on average, slightly higher thresholds than the low-exposure group at the higher test frequencies within the standard audiometric range (>=1 kHz), prompting us to more directly consider the influence of pure tone averages on the specific ABR variables that emerged as significant in the group analyses. For the regression analyses, we used the average pure tone detection threshold from 1-8 kHz ($PTA_{1\text{-}8kHz}$).

3. Results

3.1. ABR wave amplitudes

We measured suprathreshold click-evoked ABRs across eight presentation rates and compared the results between young adults with different amounts of routine noise exposure. Fig. 3 shows the peak-to-baseline ABR amplitudes for Waves I, III, and V for the high- and low-exposure groups. Although there is an overall effect of rate on the ABR peak amplitudes ($F(7,371) = 18.53$, $p < .001$, $\eta^2 = 0.26$), no clear trends emerge that distinguish one group from the other. A significant group effect is not found for either the peak-to-baseline measure ($F(1,53) = 0.12$, $p = .73$, $\eta^2 = 0.002$) or the peak-to-trough measure ($F(1,53) = 0.02$, $p = .88$, $\eta^2 = 0.00$) and none of the two-way interactions involving the group term are significant nor is the three-way interaction (all $p > .5$) (Fig. 3).

Even with sex added as a covariate, no significant differences emerge for ABR amplitude between the high- and low-exposure groups for the peak-to-baseline measure ($F(1,52) = 0.23$, $p = .64$, $\eta^2 = 0.004$) or the peak-to-trough measure ($F(1,52) = 0.31$, $p = .58$, $\eta^2 = 0.01$). However, there is an overall trend for females to have higher amplitudes than males for the peak-to-trough measure ($F(1,52) = 3.70$, $p = .06$, $\eta^2 = 0.07$) but for not the peak-to-baseline measure ($F(1,52) = 0.44$, $p = .51$, $\eta^2 = 0.01$).

3.2. ABR wave latencies

Fig. 4 shows the average latencies for waves I, III, and V for the high- and low-exposure groups for the eight stimulation rates. Across the three waves, there is a rate-dependent effect on latency, with the latencies increasing as the rate of presentation speeds ($F(7, 371) = 17877.87$, $p < .001$, $\eta^2 = 0.99$). However, the graph shows the high-exposure group as having generally longer latencies than the low-exposure groups for all three waves. Consistent with this, a significant main effect of group is evident ($F(1,53) = 4.15$, $p = .05$, $\eta^2 = 0.07$), while neither of the two-way group interaction terms are significant (Group x Rate: $F(7,371) = 0.57$, $p = .63$, $\eta^2 = 0.01$; Group x Wave: $F(2,106) = 1.09$, $p = .34$, $\eta^2 = 0.02$). However, the three-way interaction is significant ($F(14,742) = 2.21$, $p = .03$, $\eta^2 = 0.04$), suggesting that the strength of the group effect varies as a function of both wave and rate.

To unpack this three-way interaction, separate repeated-measures ANOVAs were run for waves I, III, and V. This analysis revealed that the group differences emerge more strongly for wave V than the earlier waves (Wave I: $F(1,53) = 2.97$, $p = .09$, $\eta^2 = 0.05$; Wave III: $F(1,53) = 1.78$, $p = .18$, $\eta^2 = 0.03$; Wave V: $F(1,53) = 4.33$, $p = .04$, $\eta^2 = 0.08$), confirming the trends that are visually apparent in Fig. 4. For waves III and V, the low- and high-exposure groups have nearly parallel rate functions, with the rate functions being separated by a small, yet constant increase in latency (Fig. 4). In contrast, for wave I, the rate-latency functions diverge for the two

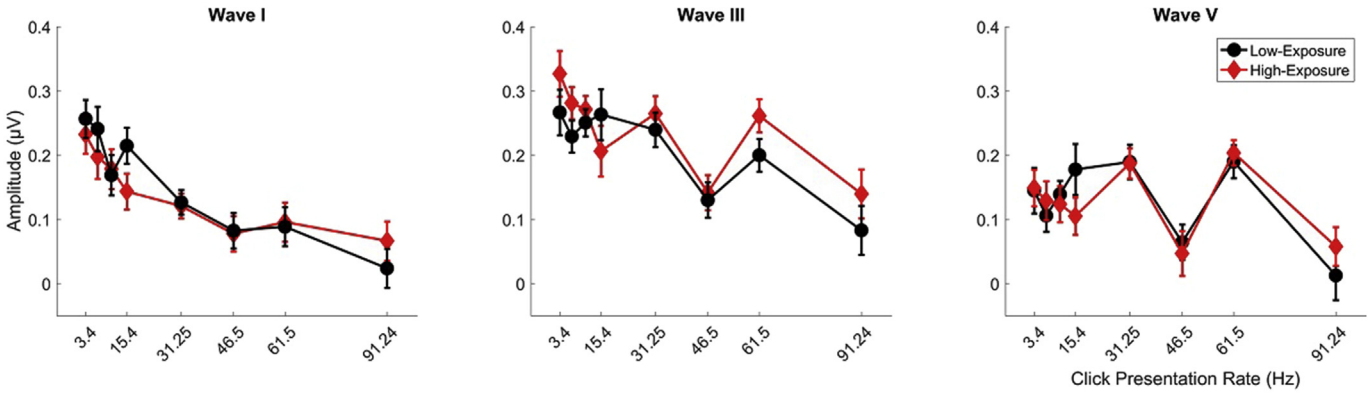

Fig. 3. The low- and high-exposure groups do not differ significantly with respect to ABR amplitudes. Rate-amplitude functions for the peak-to-baseline metric are plotted for Waves I, III, and V for the low-exposure (black) and high-exposure (red) groups. Data represent the mean ± 1 standard error of the mean. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

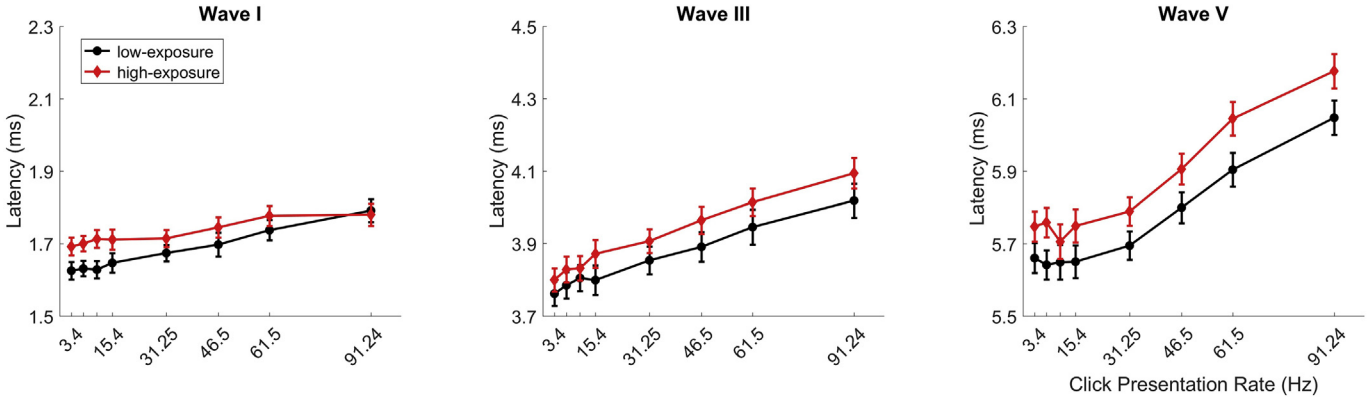

Fig. 4. The high-exposure group (red) has delayed ABR peak latencies compared to the low-exposure group (black). ABR rate-latency functions are plotted for waves I, III, and V for the low-exposure (black) and high-exposure (red) groups. Data represent the mean ± 1 standard error of the mean. The three subpanels are plotted on the same scale to facilitate visual comparison. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

groups at the slowest presentation rates and converge at the fastest rates. Consistent with these visual patterns, there is a significant group by rate interaction at wave I but not the other two waves (Wave I: $F(7,371) = 2.59$, $p = .04$, $\eta^2 = 0.05$; Wave III: $F(7,371) = 1.03$, $p = .37$, $\eta^2 = 0.02$; Wave V: $F(7,371) = 1.12$, $p = .35$, $\eta^2 = 0.02$). However, once the influence of sex is taken into account, the interaction between group and presentation rate does not persist for wave I latency ($F(7,364) = 1.42$, $p = .23$, $\eta^2 = 0.03$), while there is still a trend for the high-exposure group to have overall longer wave I latencies than the low-exposure group ($F(1,52) = 2.62$, $p = .11$, $\eta^2 = 0.05$). For wave V, the group differences hold, even after co-varying for sex-related effects on wave V latency (Wave V: $F(1,52) = 4.81$, $p = .03$, $\eta^2 = 0.08$).

3.3. ABR I-V interpeak latency

To probe the degree to which group differences observed at wave V reflect central conduction delays, the I-V IPL measure was analyzed. Fig. 5 shows the I-V IPL for the high- and low-exposure groups across the eight stimulation rates. The groups align at the lowest presentation rates but diverge as the stimulus presentation rate is increased (i.e., the rate functions have different slopes). Consistent with the rate-latency trajectories plotted in Fig. 5, the group-level effect is not significant for I-V IPL ($F(1,53) = 1.30$, $p = .26$, $\eta^2 = 0.02$) but a significant group by rate interaction emerged ($F(7,371) = 3.00$, $p = .02$, $\eta^2 = 0.05$), and this interaction effect holds when co-varying for sex-effects ($F(7,364) = 2.47$, $p = .04$, $\eta^2 = 0.05$).

3.4. Correlation and regression analyses

The group comparisons revealed that the high-exposure group had delayed absolute latencies compared to the low-exposure group, with the rate-independent delays being greater for wave V compared to the preceding waves. This finding prompted us to ask whether wave V latency (averaged across presentation rates) correlates with average daily noise exposure dose. Across the full dataset, there is a weak trend for higher noise dose to be associated with prolonged wave V latency ($r = 0.21$, $p = .07$). When average daily noise expsosure dose, sex, and $PTA_{1\text{-}8kHz}$ are then entered into a regression model as predictors of wave V latency, neither sex nor audiometric thresholds are significant predictors of wave V latency, although noise dose continues to weakly predict wave V latency (Average daily noise exposure dose, Standardized Coefficients Beta = 0.21, $p = .08$; $PTA_{1\text{-}8kHz}$, Standardized Coefficients Beta = 0.16, $p = .18$; Sex, Standardized Coefficients Beta = −0.13, $p = .26$).

A second finding emerging from the group comparisons was that the high-exposure group had longer I-V IPLs as the stimulus presentation rate increased, compared to the low-exposure group. Across the entire dataset, we find that higher average daily noise exposure doses are associated with greater rate effects for I-V

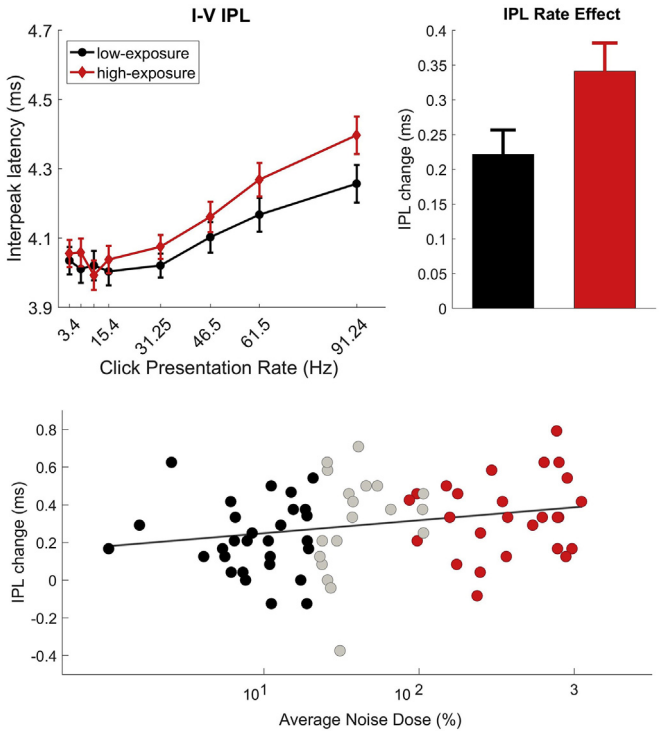

Fig. 5. I-to-V interpeak latency (IPL), a measure of central auditory system conduction time, for the low-exposure (black) and high-exposure (red) groups. Top left: Rate-latency function is plotted for the I-V IPL. Top right: Change in IPL between the slowest and fastest stimulus presentation rates (IPL rate effect). Bottom: Correlation between average daily noise exposure dose (plotted on log scale) and the IPL rate effect ($r = 0.26$, $p = .03$). Data for the 18 participants with moderate-exposure are plotted as gray circles. In the few cases where the IPL rate effect was <0 ms, this was the consequence of the rate-dependent delays being greater for wave I than wave V for the 91.24 Hz presentation rate. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

IPL($r = 0.26$, $p = .03$), as measured by the change in I-V IPL between the slowest and fastest presentation rates. A regression model that includes average daily noise exposure dose, $PTA_{1\text{-}8kHz}$, and sex as predictors shows that neither $PTA_{1\text{-}8kHz}$, or sex are significant predictors of the IPL rate effects. However, their inclusion into the model weakens the association between noise dose and the IPL rate effect (Average daily noise exposure dose, Standardized Coefficients Beta = 0.21, $p = .08$; $PTA_{1\text{-}8kHz}$, Standardized Coefficients Beta = 0.15, $p = .21$; Sex, Standardized Coefficients Beta = 0.10, $p = .37$).

3.5. Comparisons to clinical norms

In this study, noise-exposed college students, spanning a narrow age range, were compared to their peers who engage in less-noisy activities. This comparison, however, does not get to the question of whether routine noise exposure is associated with clinically significant ABR latency delays. To begin to address the question of whether the observed delays rise to the level of clinical significance, the current data were compared against a large, published normative dataset that exists for the 31.25 Hz rate (but not the other rates) (Skoe et al., 2015). Using these normative data, only one member of the high-exposure group and two of the moderate-exposure participants were found to have wave V delays exceeding two standard deviations of the mean for their age group, a commonly used clinical cutoff. However, a caveat is that the normative dataset itself likely contains participants with normal audiograms yet excessive routine noise exposure. Thus, current clinical norms for the ABR may be ill suited for identifying noise-induced subclinical auditory damage.

4. Discussion

This study used a weeklong noise dosimetry protocol to gain unprecedented access into the "noise lives" of young adults beyond what can be achieved via questionnaire or interview. Objectively measuring sound exposure rather than relying on self-report brings the field closer to bridging the gap between human and non-human investigations of the early biological warning signs of NIHL. With this protocol, we found that young, normal-hearing adults with sound exposure repeatedly exceeding NIOSH's safety recommendations have delayed ABR latencies, yet comparable ABR amplitudes, relative to their audiometrically-matched peers whose noise exposure was routinely low. This delay is evident at all ABR waves but strongest for wave V. In addition, the I-V IPL was found to be delayed at the fastest, more taxing stimulus presentation rates.

The pathophysiology of subclinical hearing loss in humans is undoubtedly complex, and our findings, together with other recent work, suggest that multiple, potentially interacting, types of noise-induced changes to the auditory system can occur without significant compromises to hearing thresholds (Verhulst et al., 2016). As we discussed below, our pattern of findings are suggestive of two types of noise-induced damage: (1) noise-induced loss of IHCs and (2) decreased temporal precision within the central auditory system due to noise-induced demyelination. However, while our findings could potentially be explained by noise-induced damage to the peripheral and central auditory system, our findings are not consistent with the purported neuro-electric signature of cochlear synaptopathy, according to the hypothesis that synaptic loss disrupts ABR amplitudes but not ABR latencies (Kujawa and Liberman, 2009; Moser and Starr, 2016). That said, ABR amplitudes are known to be less reliable than ABR latencies (Dzulkarnain et al., 2014; Hall, 2007), potentially making them less sensitive measures of subtle disease processes than ABR latencies. Thus, we cannot completely rule out cochlear synaptopathy as a contributing mechanism to our findings without a post-mortem examination of the temporal bone (Viana et al., 2015) and we must leave open the possibility that some degree of synaptopathy may be present in all participants. Another explanation for the lack of group differences for ABR amplitudes is compensatory plasticity, including increased central gain or afferent rescaling, in the high-exposure group following cochlear damage that leads to a normalization of group differences for ABR amplitudes (Chambers et al., 2016; Eggermont, 2017; Salvi et al., 2016; Sheppard et al., 2017).

4.1. Rate-independent latency shifts as evidence of noise-induced inner hair cell loss

In this study, suprathreshold ABRs were recorded at eight stimulation rates. In addition to providing converging evidence of delayed ABR latencies in noise-exposed individuals, the ABR rate functions yield greater insight into the potential pathophysiology of subclinical NIHL than could have been achieved if only a single presentation rate had been tested. In the current study, delays are observed at ABR waves I, III, and V for the high-exposure group compared to the low-exposure group at all presentation rates, with the group differences being greater for wave V compared to the preceding waves. There is also a weak trend for wave V latency to correlate with the average daily noise exposure dose. As seen in Fig. 4, the rate-latency functions for waves III and V for the low- and high-exposure groups showed parallel lines that are separated by a fixed delay across the set of eight rates. For wave I, the rate-latency

functions for the two groups followed parallel trajectories except at the two fastest rates where they converge. The visual convergence seen in Fig. 4, however, is likely an artifact of the female participants having shallower rate-latency functions than the male participants; when sex is added as a covariate to the analysis, the interaction between rate and latency for wave I is non-significant (i.e., the rate-latency functions for the two groups are more nearly parallel).

As outlined in the introduction, this pattern of *preserved group differentiation* is suggestive of IHC damage that reduces the input to the central auditory system, leading to rate-independent ABR delays across the three waves (Burkard et al., 1997). Consistent with this interpretation, delays that emerge from peripheral damage are expected to manifest not only at ABR wave I but to also be inherited by waves III and V. The increased delay at wave V could simply be a byproduct of wave V being easier to detect than the preceding waves (Mehraei et al., 2016), or there may be an exaggeration of the delay due to the compounding of peripheral and central damage (Salvi et al., 2016). To support our hypothesis that rate-independent delays are the consequence of noise-induced damage to IHCs, we draw on the work reviewed in the introduction, which predicts that IHC damage would manifest as rate-independent ABR delays without significantly compromising audiometric thresholds (Burkard et al., 1997; Lobarinas et al., 2013). We also point to data on the summating potential (SP) of the electrocochleogram (ECochG), a component that is generated primarily from IHCs (Durrant et al., 1998) and that is sensitive to noise exposure (Gans, 1983; Kim et al., 2005; Liberman et al., 2016; Sheppard et al., 2017). The SP, unlike the action potential (AP) component of the ECochG, is stable in morphology, even as the rate of stimulus presentation increases (Coats, 1981; Liberman et al., 2016). Based on this non-adapting characteristic of the SP, a loss of IHCs is predicted to produce a constant, rate-independent, change in the SP, similar to the pattern of parallel lines observed in Fig. 4. However, because our ABR recording paradigm was not optimized for separating the SP from the cochlear microphonic, we are not able to compare the SP functions between the high- and low-exposure groups, and, therefore, future studies examining the SP are needed to strengthen our hypothesis of noise-induced subclinical damage to IHCs.

4.2. Rate-dependent changes to I-V interval as evidence of noise-induced demyelination

In addition to greater delays at waves I, III, and V, we find longer central conduction times (as indexed by the I-V IPL) for the high-exposure group compared to the low-exposure group at the fastest, most taxing stimulation rates (Fig. 5). A weak, but statistically significant, correlation between average daily noise exposure dose and rate-dependent changes to the I-V IPL is also observed. This pattern of *differential preservation* for the I-V interval is potentially indicative of greater conduction inefficiencies when the central auditory system (CAS) is taxed, with our working hypothesis being that noise-induced damage to CAS myelin is a source of this inefficiency. While auditory nerve myelinopathy has been recently proposed as a mechanism of subclinical hearing loss (Wan and Corfas, 2017) and noise-induced auditory nerve myelinopathy (Tagoe et al., 2014) and CAS demyelination (Chang et al., 2004; Lin et al., 2008) have been shown to accompany permanent audiometric threshold shifts, to the best of our knowledge, we are the first to theorize that noise exposure might impair CAS myelin but spare audiometric thresholds. Several lines of evidence lend initial credence to this novel, working hypothesis. First, loss of myelin within the CAS has been linked to increased CAS conduction times as well as less reliable neurotransmission for fast stimulation rates in animal models (Kim et al., 2013b). Second, in newborn humans, lower white-matter integrity in IC, as assessed by diffusion tensor imaging (DTI), has been found to correlate with prolonged I-V IPLs (Reiman et al., 2009). To gain a more complete picture of how the CAS is affected by noise-exposure (Eggermont, 2017), and to test our working hypothesis, future investigations of noise-induced subclinical hearing loss in humans might consider including DTI or other structural and functional measures of the CAS.

4.3. ABRs: a measure of recent or lifetime noise exposure?

For the current investigation, testing occurred during the middle of the academic semester, with the goal of capturing a week that was generally representative of the participants' "noise lives" (Tufts and Skoe, 2017). Our recruitment also targeted college students who regularly engage in activities that place them at risk for noise-induced hearing loss (e.g., participation in music ensembles). While this study design was intended to capture routine noise exposure when academic, recreational, and employment activities were underway, we recognize that college students, like other populations, experience week-by-week variations in noise exposure that cannot be captured in a single dosimetry session, even if that session spans multiple days, as it did in the current study. However, we operate under the assumption that the noise dosimetry was reflective of the participants' typical noise exposure patterns and that if the dosimetry were repeated in the same participants, the specific noise doses would vary, but the participants' category (i.e., high-vs. low-exposure) is unlikely to change.

In the current investigation, audiological and electrophysiological measurements were completed prior to the noise dosimetry. This test order (i.e., dosimetry last) — together with the implementation of a 14-hour quiet period immediately preceding hearing threshold and ABR measurements — allowed us to minimize potential contamination from a TTS, which would be a concern for participants who regularly engage in loud activities. However, because the dosimetry occurred after the audiometry and ABR measurements, the group differences observed in the ABR rate functions cannot be interpreted as the result of the noise exposures measured as part of the study. The weak nature of the relationship between noise exposure dose and the ABR measurements could also suggest that the noise dosimetry measurements are not perfectly representative of the noise exposures that pre-date study enrollment. Furthermore, as discussed by Grinn et al. (2017), it remains to be seen whether the relationship between noise exposure and noise-induced damage is indeed linear, or whether damage only emerges after some critical level of exposure is reached. Other complications to interpreting the correlations with noise exposure include that there are individual differences in the degree of vulnerability to noise-induced hearing loss (Maison and Liberman, 2000) and that noise conditioning can protect the auditory system from subsequent noise trauma (Canlon et al., 1988). Thus, the high-exposure group might be tempered from hearing damage by virtue of their previous noise exposures.

Our study design also cannot answer whether the ABR differences that were observed between the low- and high-exposure group are indicative of temporary or permanent changes to the auditory system or whether recent or lifetime noise exposure make a greater contribution to ABR latency. However, the recent study by Grinn et al. (2017) is relevant to answering these questions. Grinn et al. (2017) related ABR wave I amplitude to noise exposures over two time scales: noise exposure history over the past year and acute noise exposure while attending a loud event. With a smartphone app, the instantaneous sound level (dBA) was measured at 10 time points during the loud event, from which the estimated noise dose was calculated. (This approach contrasts with the current investigation where we obtained more than 2500 individual

sound level measurements over the course of a week). Grinn et al. (2017) did not find any statistically significant relationships between noise exposure history and ABR wave I amplitude, nor did they find that noise dose was predictive of ABR wave I amplitude measured one day or even one week after the acute noise exposure. Thus, ABR wave I amplitude does not appear to vary in a linear fashion with respect to recent or more long-term noise exposure. However, the study by Grinn et al. (2017) did not examine ABR wave latencies or IPLs, limiting generalizations to the current study. The prospective ABR monitoring paradigm adopted by Grinn et al. (2017), nevertheless, serves as a template for examining the relationships between noise exposure and ABR latencies in future work.

Lastly, it should be noted that the body-worn dosimeters used in our study, and the smartphone application used in the Grinn et al. (2017) study, both measure environmental sound levels but neither measure spectral information (Grinn et al., 2017; Grose et al., 2017). This is an important consideration given that the amount of damage may not be the same for different types of sound, even when the sound exposures have equivalent long-term energies (Strasser et al., 2003). Future work should consider adopting other sound recording techniques, such as the data logging features of hearing aids, to obtain more spectrotemporally detailed measures of noise exposure patterns (Franklin et al., 2014) to enable a better delineation of the relation between noise exposure and ABRs.

4.4. Clinical applications

Our findings add to the growing body of evidence that noise damages the auditory system in ways that are invisible to the common screening and diagnostic measures of NIHL. Our study illustrates that tests that are already part of the audiological toolkit (e.g., ABRs) can potentially identify the early stages of NIHL. Yet because noise-induced damage to the auditory system may have multiple contributing mechanisms that manifest differently at various stages and because it likely affects individuals differently (Barrenas and Hellstrom, 1996), this underscores the need for a comprehensive test battery that combines ABR metrics with envelope-following responses (Bharadwaj et al., 2015), otoacoustic emissions, standard and high-frequency audiometry (>8 kHz) (Le Prell et al., 2013; Liberman et al., 2016), and that also includes objective and subjective measures of noise exposure, functional measures of hearing in noise, noise tolerance, and indices of cochlear and central gain (Bidelman et al., 2017; Chambers et al., 2016; Grose et al., 2017). However, although it may be feasible to implement this type of comprehensive test battery in laboratory settings, it would be outside the scope of what is practical for a clinical assessment of subclinical hearing loss. As the field develops a better understanding of each of these candidate measures of subclinical hearing loss, a more time-efficient clinical battery is likely to evolve. While the field is still striving towards optimizing and standardizing clinical procedures for identifying the early stages of hearing loss and elucidating the degree to which damage is reversible, our findings nevertheless emphasize the importance of providing hearing conservation services to populations that routinely engage in risky auditory behaviors.

5. Conclusions

Our use of ABRs in combination with objective dosimetric measurements of noise exposure is an important methodological advance in the study of the early stages of NIHL. Our findings are consistent with the hypothesis that routine exposure to high-intensity sound affects both peripheral and central auditory structures even before changes are evident on standard audiometric measures, and the outcomes of this study serve to inform future research into the potential mechanisms and manifestations of subclinical hearing loss in humans. The pattern of ABR results observed in this study is suggestive of IHC loss and central auditory system demyelination but not cochlear synaptopathy, in young, noise-exposed adults with normal audiometric thresholds. With more data, including wider-scale adoption of objective noise measurements, longitudinal assessments, and expanded test batteries, a more complete understanding of the complex pathogenesis of noise-induced hearing loss in humans at both pre-clinical and clinical stages of damage is expected to emerge.

Conflict of interest

None.

Acknowledgements

This work was supported by a grant from the American Hearing Research Foundation awarded to ES and JT. We acknowledge Christine Njuki for her input on the experimental protocol, Ryan Masi and Sarah Camera for their assistance with data collection and coding, Meghan Brady for her assistance with participant scheduling and data processing, and Maggie Small, Meghan Robitaille, Michaela Caporaso, Olivia DeWald, Elizabeth Gernert, and Kristine Aikens for their assistance with data entry and coding. We would also like to thank Travis White-Schwoch for his feedback on an earlier version of the manuscript.

References

Barrenas, M.L., Hellstrom, P.A., 1996. The effect of low level acoustic stimulation on susceptibility to noise in blue- and brown-eyed young human subjects. Ear Hear. 17, 63–68.

Berlin, C.I., Hood, L.J., Morlet, T., Wilensky, D., Li, L., Mattingly, K.R., Taylor-Jeanfreau, J., Keats, B.J., John, P.S., Montgomery, E., 2010. Multi-site diagnosis and management of 260 patients with auditory neuropathy/dys-synchrony (auditory neuropathy spectrum disorder*). Int. J. Audiol. 49, 30–43.

Bharadwaj, H.M., Masud, S., Mehraei, G., Verhulst, S., Shinn-Cunningham, B.G., 2015. Individual differences reveal correlates of hidden hearing deficits. J. Neurosci. 35, 2161–2172.

Bidelman, G.M., Schneider, A.D., Heitzmann, V.R., Bhagat, S.P., 2017. Musicianship enhances ipsilateral and contralateral efferent gain control to the cochlea. Hear. Res. 344, 275–283.

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.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.

Burkard, R.F., Eggermont, J.J., Don, M., 2007. Auditory Evoked Potentials: Basic Principles and Clinical Application. Lippincott Williams and Wilkins, Philadelphia.

Burkard, R., Trautwein, P., Salvi, R., 1997. The effects of click level, click rate, and level of background masking noise on the inferior colliculus potential (ICP) in the normal and carboplatin-treated chinchilla. J. Acoust. Soc. Am. 102, 3620–3627.

Canlon, B., Borg, E., Flock, Å., 1988. Protection against noise trauma by pre-exposure to a low level acoustic stimulus. Hear. Res. 34, 197–200.

Chambers, A.R., Resnik, J., Yuan, Y., Whitton, J.P., Edge, A.S., Liberman, M.C., Polley, D.B., 2016. Central gain restores auditory processing following near-complete cochlear denervation. Neuron 89, 867–879.

Chang, Y., Lee, S.-H., Lee, Y.-J., Hwang, M.-J., Bae, S.-J., Kim, M.-N., Lee, J., Woo, S., Lee, H., Kang, D.-S., 2004. Auditory neural pathway evaluation on sensorineural hearing loss using diffusion tensor imaging. Neuroreport 15, 1699–1703.

Coats, A.C., 1981. The summating potential and Meniere's disease: I. Summating potential amplitude in Meniere and non-Meniere ears. Arch. Otolaryngol. 107, 199–208.

Don, M., Ponton, C.W., Eggermont, J.J., Masuda, A., 1993. Gender differences in cochlear response time: an explanation for gender amplitude differences in the unmasked auditory brain-stem response. J. Acoust. Soc. Am. 94, 2135–2148.

Don, M., Kwong, B., Tanaka, C., Brackmann, D., Nelson, R., 2005. The stacked ABR: a sensitive and specific screening tool for detecting small acoustic tumors. Audiol. Neurootol. 10, 274–290.

Durrant, J.D., Wang, J., Ding, D., Salvi, R.J., 1998. Are inner or outer hair cells the source of summating potentials recorded from the round window? J. Acoust. Soc. Am. 104, 370–377.
Dzulkarnain, A.A.A., Buyong, A.S., Sulaiman, N.H., 2014. Intra-subject variability in the auditory brainstem response using a vertical montage recording. Speech Lang. Hear. 17, 160–167.
Eggermont, J.J., 2017. Effects of long-term non-traumatic noise exposure on the adult central auditory system. Hearing problems without hearing loss. Hear. Res. 352, 12–22.
Eggermont, J.J., Don, M., 1986. Mechanisms of central conduction time prolongation in brain-stem auditory evoked potentials. Arch. Neurol. 43, 116–120.
El-Badry, M.M., Ding, D.l., McFadden, S.L., Eddins, A.C., 2007. Physiological effects of auditory nerve myelinopathy in chinchillas. Eur. J. Neurosci. 25, 1437–1446.
Flamme, G.A., Stephenson, M.R., Deiters, K., Tatro, A., van Gessel, D., Geda, K., Wyllys, K., McGregor, K., 2012. Typical noise exposure in daily life. Int. J. Audiol. 51 (Suppl. 1), S3–S11.
Franklin, C.A., White, L.J., Franklin, T.C., Smith-Olinde, L., 2014. The relationship between the acceptance of noise and acoustic environments in young adults with normal hearing: a pilot study. J. Am. Acad. Audiol. 25, 584–591.
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.
Gans, D.P., 1983. Effects of acoustic trauma on the cochlear potentials. J. Acoust. Soc. Am. 74, 1742–1746.
Gorga, M.P., Worthington, D.W., Reiland, J.K., Beauchaine, K.A., Goldgar, D.E., 1985. Some comparisons between auditory brain stem response thresholds, latencies, and the pure-tone audiogram. Ear Hear. 6, 105–112.
Gourevitch, B., Edeline, J.-M., Occelli, F., Eggermont, J.J., 2014. Is the din really harmless? Long-term effects of non-traumatic noise on the adult auditory system. Nat. Rev. Neurosci. 15, 483–491.
Grinn, S.K., Wiseman, K.B., Baker, J.A., Le Prell, C.G., 2017. Hidden hearing Loss? No effect of common recreational noise exposure on cochlear nerve response amplitude in humans. Front. Neurosci. 11, 465.
Grose, J.H., Buss, E., Hall 3rd, J.W., 2017. Loud music exposure and cochlear synaptopathy in young adults: isolated auditory brainstem response effects but No perceptual consequences. Trends Hear. 21, 2331216517737417.
Guest, H., Munro, K.J., Plack, C.J., 2017a. Tinnitus with a normal audiogram: role of high-frequency sensitivity and reanalysis of brainstem-response measures to avoid audiometric over-matching. Hear. Res. 356, 116.
Guest, H., Munro, K.J., Prendergast, G., Howe, S., Plack, C.J., 2017b. Tinnitus with a normal audiogram: relation to noise exposure but no evidence for cochlear synaptopathy. Hear. Res. 344, 265–274.
Hall, J.W., 2007. New Handbook of Auditory Evoked Responses. Allyn and Bacon, Boston.
Hickox, A.E., Larsen, E., Heinz, M.G., Shinobu, L., Whitton, J.P., 2017. Translational issues in cochlear synaptopathy. Hear. Res. 349, 164–171.
Hood, L.J., 1998. Clinical Applications of the Auditory Brainstem Response. Singular Pub. Group, San Diego.
Jerger, J., Hall, J., 1980. Effects of age and sex on auditory brainstem response. Arch. Otolaryngol. 106, 387–391.
Johnson, J.L., White, K.R., Widen, J.E., Gravel, J.S., James, M., Kennalley, T., Maxon, A.B., Spivak, L., Sullivan-Mahoney, M., Vohr, B.R., 2005. A multicenter evaluation of how many infants with permanent hearing loss pass a two-stage otoacoustic emissions/automated auditory brainstem response newborn hearing screening protocol. Pediatrics 116, 663–672.
Kim, J.H., Renden, R., von Gersdorff, H., 2013a. Dysmyelination of auditory afferent axons increases the jitter of action potential timing during high-frequency firing. J. Neurosci. 33, 9402–9407.
Kim, J.S., Nam, E.-C., Park, S.I., 2005. Electrocochleography is more sensitive than distortion-product otoacoustic emission test for detecting noise-induced temporary threshold shift. Otolaryngol. Head Neck Surg. 133, 619–624.
Kim, S.E., Turkington, K., Kushmerick, C., Kim, J.H., 2013b. Central dysmyelination reduces the temporal fidelity of synaptic transmission and the reliability of postsynaptic firing during high-frequency stimulation. J. Neurophysiol. 110, 1621–1630.
Kopp-Scheinpflug, C., Tempel, B.L., 2015. Decreased temporal precision of neuronal signaling as a candidate mechanism of auditory processing disorder. Hear. Res. 330, 213–220.
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.
Lasky, R.E., 1997. Rate and adaptation effects on the auditory evoked brainstem response in human newborns and adults. Hear. Res. 111, 165–176.
Le Prell, C.G., Spankovich, C., Lobariñas, E., Griffiths, S.K., 2013. Extended high-frequency thresholds in college students: effects of music player use and other recreational noise. J. Acad. Audiol. 24, 725–739.
Liberman, L.D., Liberman, M.C., 2015. Dynamics of cochlear synaptopathy after acoustic overexposure. J. Assoc. Res. Otolaryngol. 16, 205–219.
Liberman, M.C., Kujawa, S.G., 2017. Cochlear synaptopathy in acquired sensorineural hearing loss: manifestations and mechanisms. Hear. Res. 349, 138–147.
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.
Lin, Y., Wang, J., Wu, C., Wai, Y., Yu, J., Ng, S., 2008. Diffusion tensor imaging of the auditory pathway in sensorineural hearing loss: changes in radial diffusivity and diffusion anisotropy. J. Magn. Reson. Imag. 28, 598–603.
Liu, L., Wang, H., Shi, L., Almuklass, A., He, T., Aiken, S., Bance, M., Yin, S., Wang, J., 2012. Silent damage of noise on cochlear afferent innervation in guinea pigs and the impact on temporal processing. PLoS One 7, e49550.
Lobarinas, E., Salvi, R., Ding, D., 2013. Insensitivity of the audiogram to carboplatin induced inner hair cell loss in chinchillas. Hear. Res. 302, 113–120.
Maison, S.F., Liberman, M.C., 2000. Predicting vulnerability to acoustic injury with a noninvasive assay of olivocochlear reflex strength. J. Neurosci. 20, 4701–4707.
Mehraei, G., Hickox, A.E., Bharadwaj, H.M., Goldberg, H., Verhulst, S., Liberman, M.C., Shinn-Cunningham, B.G., 2016. Auditory brainstem response latency in noise as a marker of cochlear synaptopathy. J. Neurosci. 36, 3755–3764.
Melcher, J.R., Kiang, N.Y.S., 1996. Generators of the brainstem auditory evoked potential in cat III: identified cell populations. Hear. Res. 93, 52–71.
Mitchell, C., Phillips, D.S., Trune, D.R., 1989. Variables affecting the auditory brainstem response: audiogram, age, gender and head size. Hear. Res. 40, 75–85.
Moser, T., Starr, A., 2016. Auditory neuropathy – neural and synaptic mechanisms. Nat. Rev. Neurol. 12, 135–149.
Murnane, O.D., Prieve, B.A., Relkin, E.M., 1998. Recovery of the human compound action potential following prior stimulation1This investigation has been performed in accordance with the principles of the Declaration of Helsinki. Hear. Res. 124, 182–189.
NIOSH, 1998. Criteria for a Recommended Standard: Occupational Noise Exposure (Revised Criteria 1998). No. 98–126.
Prendergast, G., Guest, H., Munro, K.J., Kluk, K., Leger, A., Hall, D.A., Heinz, M.G., Plack, C.J., 2017. Effects of noise exposure on young adults with normal audiograms I: Electrophysiology. Hear. Res. 344, 68–81.
Pushpalatha, Z.V., Konadath, S., 2016. Auditory brainstem responses for click and CE-chirp stimuli in individuals with and without occupational noise exposure. Noise Health 18, 260–265.
Reiman, M., Parkkola, R., Johansson, R., Jaaskelainen, S.K., Kujari, H., Lehtonen, L., Haataja, L., Lapinleimu, H., Group, P.S., 2009. Diffusion tensor imaging of the inferior colliculus and brainstem auditory-evoked potentials in preterm infants. Pediatr. Radiol. 39, 804–809.
Relkin, E.M., Doucet, J.R., 1991. Recovery from prior stimulation. I: relationship to spontaneous firing rates of primary auditory neurons. Hear. Res. 55, 215–222.
Relkin, E.M., Doucet, J.R., Sterns, A., 1995. Recovery of the compound action potential following prior stimulation: evidence for a slow component that reflects recovery of low spontaneous-rate auditory neurons. Hear. Res. 83, 183–189.
Salthouse, T.A., Lichty, W., 1985. Tests of the neural noise hypothesis of age-related cognitive change. J. Gerontol. 40, 443–450.
Salvi, R., Sun, W., Ding, D., Chen, G.D., Lobarinas, E., Wang, J., Radziwon, K., Auerbach, B.D., 2016. Inner hair cell loss disrupts hearing and cochlear function leading to sensory deprivation and enhanced central auditory gain. Front. Neurosci. 10, 621.
Sheppard, A.M., Chen, G.-D., Manohar, S., Ding, D., Hu, B.-H., Sun, W., Zhao, J., Salvi, R., 2017. Prolonged low-level noise-induced plasticity in the peripheral and central auditory system of rats. Neuroscience 359, 159–171.
Shi, L., Liu, L., He, T., Guo, X., Yu, Z., Yin, S., Wang, J., 2013. Ribbon synapse plasticity in the cochleae of Guinea pigs after noise-induced silent damage. PLoS One 8, e81566.
Shi, L., Guo, X., Shen, P., Liu, L., Tao, S., Li, X., Song, Q., Yu, Z., Yin, S., Wang, J., 2015. Noise-induced damage to ribbon synapses without permanent threshold shifts in neonatal mice. Neuroscience 304, 368–377.
Sininger, Y.S., 1993. Auditory brain stem response for objective measures of hearing. Ear Hear 14, 23–30.
Skoe, E., Krizman, J., Anderson, S., Kraus, N., 2015. Stability and plasticity of auditory brainstem function across the lifespan. Cereb Cortex 25, 1415–1426.
Stamper, G.C., Johnson, T.A., 2015a. Letter to the Editor: examination of potential sex influences in Stamper, GC & Johnson, TA (2015). Auditory function in normal-hearing, noise-exposed human ears. Ear Hear. 36, 172–184. Ear Hear 36, 738.
Stamper, G.C., Johnson, T.A., 2015b. Auditory function in normal-hearing, noise-exposed human ears. Ear Hear. 36, 172–184.
Starr, A., Don, M., 1988. Brain potentials evoked by acoustic stimuli. In: Picton, T.W. (Ed.), Handbook of electroencephalography and clinical neurophysiology (revised volume 3), Human event-related potentials. Elsevier, Amsterdam.
Starr, A., Picton, T.W., Sininger, Y., Hood, L.J., Berlin, C.I., 1996. Auditory neuropathy. Brain 119 (Pt 3), 741–753.
Strasser, H., Irle, H., Legler, R., 2003. Temporary hearing threshold shifts and restitution after energy-equivalent exposures to industrial noise and classical music. Noise Health 5, 75–84.
Strelcyk, O., Christoforidis, D., Dau, T., 2009. Relation between derived-band auditory brainstem response latencies and behavioral frequency selectivity. J. Acoust. Soc. Am. 126, 1878–1888.
Tagoe, T., Barker, M., Jones, A., Allcock, N., Hamann, M., 2014. Auditory nerve perinodal dysmyelination in noise-induced hearing loss. J. Neurosci. 34, 2684–2688.
Taylor, J.S., 2007. Subjective versus Objective Measures of Daily Listening Environments. Independent Studies and Capstones. Paper 492. Program in Audiology and Communication Sciences. Washington University School of Medicine. https://digitalcommons.wustl.edu/pacs_capstones/492.
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.
Tufts, J.B., Skoe, E., 2017. Examining the noisy life of the college musician: weeklong noise dosimetry of music and non-music activities. Int. J. Audiol. 1–8.
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.
Wan, G., Corfas, G., 2017. Transient auditory nerve demyelination as a new mechanism for hidden hearing loss. Nat. Commun. 8, 14487.