Effects of lifetime noise exposure on the middle-age human auditory brainstem response, tinnitus and speech-in-noise intelligibility

Joaquin T. Valderrama [a,b,c,*] Elizabeth Francis Beach [a,c], Ingrid Yeend [a,b,c], Mridula Sharma [b,c], Bram Van Dun [a,c], Harvey Dillon [a,c].

[a] *National Acoustic Laboratories, Australian Hearing Hub, 16 University Avenue, Macquarie University, New South Wales, 2109, Sydney, Australia.*

[b] *Department of Linguistics, Australian Hearing Hub, 16 University Avenue, Macquarie University, New South Wales, 2109, Sydney, Australia.*

[c] *The HEARing CRC, 550 Swanston Street, Audiology, Hearing and Speech Sciences, University of Melbourne, Victoria, 3010, Melbourne, Australia.*

* Corresponding author

Joaquin T. Valderrama
National Acoustic Laboratories
Australian Hearing Hub
Level 5, 16 University Avenue
Macquarie University NSW 2109
Sydney, Australia
Email address: joaquin.valderrama@nal.gov.au, joaquin.valderrama@mq.edu.au.

Abstract

Recent animal studies have shown that the synapses between inner hair cells and the dendrites of the spiral ganglion cells they innervate are the elements in the cochlea most vulnerable to excessive noise exposure. Particularly in rodents, several studies have concluded that exposure to high level octave-band noise for 2 hours leads to an irreversible loss of around 50% of synaptic ribbons, leaving audiometric hearing thresholds unaltered. Cochlear synaptopathy following noise exposure is hypothesized to degrade the neural encoding of sounds at the subcortical level, which would help explain certain listening-in-noise difficulties reported by some subjects with otherwise 'normal' hearing. In response to this peripheral damage, increased gain of central stages of the auditory system has been observed across several species of mammals, particularly in association with tinnitus. The auditory brainstem response (ABR) wave I amplitude and waves I-V amplitude ratio have been suggested as non-invasive indicators of cochlear synaptopathy and central gain activation respectively, but the evidence for these hearing disorders in humans is inconclusive. In this study, we evaluated the influence of lifetime noise exposure (LNE) on the human ABR and on speech-in-noise intelligibility performance in a large cohort of adults aged 29 to 55. Despite large inter-subject variability, results showed a moderate, but statistically significant, negative correlation between the ABR wave I amplitude and LNE, consistent with cochlear synaptopathy. The results also showed (a) that central gain mechanisms observed in animal studies might also occur in humans, in which higher stages of the auditory pathway appear to compensate for reduced input from the cochlea; (b) that tinnitus was associated with activation of central gain mechanisms; (c) that relevant cognitive and subcortical factors influence speech-in-noise intelligibility, in particular, longer ABR waves I-V interpeak latencies were associated with poorer performance in understanding speech in noise when central gain mechanisms were active; and (d) absence of a significant relationship between LNE and tinnitus, central gain activation or speech-in-noise performance. Although this study supports the possible existence of cochlear synaptopathy in humans, the great degree of variability, the lack

of uniformity in central gain activation and the significant involvement of attention in speech-in-noise performance suggests that noise-induced cochlear synaptopathy is, at most, one of several factors that play a role in humans' speech-in-noise performance.

Keywords

Noise-induced hearing loss; cochlear synaptopathy; hidden hearing loss; central gain; speech-in-noise; cocktail party; tinnitus.

List of abbreviations

ABR: auditory brainstem response. A_I, A_{III}, A_V: amplitude of waves I, III, and V. A_I/A_V: waves I/V amplitude ratio. ANF: auditory nerve fiber. CAP: compound action potential. DPOAEs: distortion product otoacoustic emissions. EEG: electroencephalogram. HHL: hidden hearing loss. HL: hearing level. HL-LF: hearing loss in low frequencies. HL-HF: hearing loss in high frequencies. HL-EHF: hearing loss in extended-high frequencies. IHC: inner hair cell. LNE: lifetime noise exposure. LSR: low spontaneous rate. L_I, L_{III}, L_V: latency of waves I, III, and V. L_V-L_I: waves I-V interpeak latency. OHC: outer hair cell. RMSE: root-mean-square error. SD: standard deviation. SPL: sound-pressure level. TE: test ear. TEA: test of everyday attention. TIP: TIPtrode placed in the ipsilateral ear canal.

Highlights

- ABR wave I amplitude negatively correlates with lifetime noise exposure.
- Subjects with tinnitus presented active central gain mechanisms.
- No systematic effect of noise exposure on human auditory evoked activity.
- No clear evidence for noise exposure influencing speech-in-noise performance.
- Central gain and brainstem conduction speed are relevant factors in speech-in-noise.

1. Introduction

The effect of noise exposure on animal and human auditory structures has been a topic of research for decades. Initial studies established that cochlear outer hair cells were the primary element affected by excessive noise, and that auditory nerve fibers (ANFs) degenerated only after their target hair cell was damaged (Hu and Henderson, 1997; Bohne and Harding, 2000; Emmerich et al., 2000; Wang et al., 2002). However, recent animal studies suggest that inner hair cell (IHC) synapses are the most vulnerable element in the cochlea (for a review, Hickox et al., 2017; Liberman and Kujawa, 2017). Kujawa and Liberman (2009) found in mice that a 2-hour exposure to octave-band noise (8-16 kHz) at 100 dB sound-pressure level (SPL) [also known as synaptopathic noise] led to an irreversible loss of around 50% of IHC synaptic ribbons. As a consequence, a reduced wave I amplitude of the auditory brainstem response (ABR) was recorded at suprathreshold levels in the 32 kHz frequency band, despite a complete recovery in hearing thresholds. Additional animal studies have further clarified the nature of this cochlear synaptopathy: fibers with low-spontaneous rate (LSR), (i.e. those which activate at high sound levels) are more vulnerable to noise exposure (Furman et al., 2013), and the degenerative effects of aging are accelerated by noise exposure (Fernandez et al., 2015). Simulations (but no empirical data) have shown that the loss of LSR fibers is likely to degrade the neural representation of temporal features and fine details of the stimulus (Lopez-Poveda and Barrios, 2013; Lopez-Poveda, 2014). These results underpin the theoretical concept known as 'hidden hearing loss' (HHL, Schaette and McAlpine, 2011), in which cochlear synaptopathy in humans is hypothesized to explain speech intelligibility deficits (especially in difficult listening environments) hidden behind normal-threshold audiograms.

To date, evidence of cochlear synaptopathy derived from noise exposure in humans has been inconclusive, and it remains unclear whether occupational and recreational noise exposures typically found in humans are sufficient to cause cochlear synaptopathy (Dobie and Humes, 2017). Prendergast et al. (2017) found no evidence in either ABR or frequency-following

response measures in 126 normal-hearing young adults (aged between 18 and 36 years) with varying degrees of lifetime noise exposure (LNE). Consistent with these results, Grinn et al. (2017) found that self-reported exposure to occupational and recreational noise over a 1-year period was not associated with an expected decrease in the amplitude of the compound action potential (CAP). This study included 32 young adults (13 males), aged 21-27. Moreover, Fulbright et al. (2017) also found no statistically significant relationship between the ABR wave I amplitude and noise exposure evaluated over a 1-year period in a group of 60 normal-hearing young adults (34 females, 18-30 years). Grose et al. (2017) compared a group of young adults who regularly attended loud music venues (n=31, 21 males, 18-35 years) with an age-matched control group (n=30, 11 males), and despite finding a reduced amplitude ratio of waves I/V in the experimental group, they found no differences in (a) any absolute measure of ABR amplitudes or latencies, (b) the amplitude of envelope-following responses, (c) the amplitude of the acoustic change complex, or (d) performance in any psychoacoustic test, which included temporal and spectral modulation detection, and sensitivity to inter-phase differences. In contrast, Stamper and Johnson (2015a,b) did find a statistically significant negative correlation between self-reported occupational and leisure noise exposure over a 1-year period, and the ABR wave I amplitude recorded at suprathreshold levels, but only in the female subset of 30 normal-hearing young adults (20 females, 19-28 years). Bramhall et al. (2017) also found reduced wave I amplitudes, this time in a group of veterans with high levels of noise exposure (n=11) and non-veterans with a history of firearm use (n=4), compared to veterans with low noise exposure (n=7) and non-veterans without a history of firearm use (n=12). The age range in this study was 19-35 years, and the noise exposure history was estimated over the lifetime. Despite finding wave I amplitude differences, the authors did not find a difference in the amplitude of waves III and V between the exposed and the non-exposed groups, which the authors speculated may indicate the activation of “central gain” mechanisms.

The "central gain" model has been posited to explain the increase in the spontaneous and sound-evoked neural activity of central auditory structures, such as the auditory cortex, medial geniculate body, and inferior colliculus, as a compensatory response to reduced input from the cochlea arising from noise exposure or the use of ototoxic drugs (Salvi et al., 2000; Sun et al., 2012; Chen et al., 2013; Niu et al., 2013; Auerbach et al., 2014). This maladaptation of the central auditory system to cochlear damage has been suggested to underlie tinnitus, loudness intolerance, and hyperacusis (Hébert et al., 2013; Auerbach et al., 2014; Hickox and Liberman, 2014; Diehl and Schaette, 2015; Salvi et al., 2017). In humans, central gain activation has been measured by evaluating the wave I/V amplitude ratio, with a lower ratio being a marker of central gain activation (Schaette and McAlpine, 2011; Gu et al., 2012; Bramhall et al., 2018). These three studies reported that subjects with tinnitus presented lower wave I amplitudes, but similar (Schaette and McAlpine, 2011; Bramhall et al., 2018) or enhanced wave V amplitudes (Gu et al., 2012), resulting in lower waves I/V ratios in the tinnitus population.

The primary objective of this research was to use ABR signals to investigate noise-induced cochlear synaptopathy in a large cohort of middle-age adults, in which their history of noise exposure was evaluated over the lifetime. We hypothesized that participants with higher levels of LNE would show degraded ABRs, particularly in the more peripheral components.

We also hypothesized that, consistent with animal studies, cochlear synaptopathy (if present) would trigger the activation of central gain mechanisms, and we aimed to investigate the existence of these mechanisms in our human cohort, particularly in subjects reporting tinnitus.

A final aim of the study was to consider speech-in-noise perception holistically to determine the relative influence of LNE, ABR amplitude, ABR latency, central gain, and other factors already identified in previous research as having an effect on speech-in-noise, including age (Glyde et al., 2013; Moore et al., 2014), audiometric thresholds from low to extended-high frequencies (Glyde et al., 2013), and attention (Schvartz et al., 2008; Mattys et al., 2012; Wild et al., 2012). We anticipated that greater noise exposure, increasing age, and poorer hearing thresholds

would be associated with worse speech-in-noise intelligibility performance, while better attention skills were expected to have a positive effect on speech-in-noise performance.

2. Methods

2.1. Ethics

All protocols followed in this study were in accordance with the National Statements on Ethical Conduct in Human Research and were approved by the Macquarie University and the Australian Hearing Human Research Ethics Committees (Refs 5201400862; AHHREC2014-5).

2.2. Participants

Seventy-four participants (aged 29-55, mean = 43.36 years, SD = 6.94 years, 37 females) with self-reported normal hearing were recruited from the general community. The participants presented with different levels of leisure- and work-related noise exposure, musical training, and self-reported listening-in-noise difficulties. The inclusion criteria required that participants had English as a first language, did not speak a tonal language, and had normal or near-normal pure-tone hearing thresholds in both ears in the range of frequencies typically evaluated in current clinical protocols (Dillon, 2012; Katz, 2014). Normal hearing was defined as a hearing loss ≤ 20 dB hearing level (HL) at 0.25 – 6 kHz; and near-normal thresholds were considered as ≤ 25 dB HL up to 2 kHz, ≤ 30 dB HL at 3 kHz, ≤ 35 dB HL at 4 kHz, and ≤ 40 dB HL at 6 kHz (Moore et al., 2012). Subjects #S01 to #68 were a subset from a larger study of 122 participants (63 female), who undertook a number of behavioural tests (Yeend et al., 2017). Since most of these subjects presented LNE values between 3 and 4.5 $\log_{10}Pa^2h$, subjects #S69 to #S74 were recruited with the additional inclusion criteria of having a LNE lower than 3 $\log_{10}Pa^2h$ in order to have the lower LNE range better represented. All participants gave written consent to participate, were paid $40 for their participation, and received a report that detailed their hearing thresholds and other test results.

2.3. Electrophysiology

The stimuli consisted of 12,500 rarefaction clicks of 113 µs duration (five positive samples using a sampling rate of 44.1 kHz), presented with a rate of 39.1 stim/sec at 108.5 dB peak-to-peak equivalent SPL, corresponding to 75 dB HL. The duration of the stimulation sequence was about 320 seconds. This sequence was presented monaurally to the test ear (TE) through ER-3A insert earphones (Etymotic Research, Inc., Elk Grove Village, IL), placed in the ear canal after otoscopic inspection. The right ear was assigned as the TE, in all but three participants who showed slightly better hearing thresholds in the left ear (participants #S20, #S30, and #S67). The insert earphones were connected to a Fireface UCX audio soundcard (RME Audio, Haimhausen, Germany). Stimulus level was calibrated in a type HA2 artificial ear 2-cc acoustic coupler connected to a type 4144 pressure microphone, which was connected to a type 2636 measuring amplifier through a type 2639 preamplifier cable (Brüel & Kjær Sound & Vibration Measurement A/S, Nærum, Denmark).

The electrophysiology sessions took place in an electromagnetically shielded booth at the National Acoustic Laboratories (Sydney, Australia). The recording of the neural response was carried out by three gold-plated surface electrodes placed on the high forehead (Fz, active), middle forehead (FPz, ground), and ipsilateral mastoid (Tp9 or Tp10, i.e. Tp9/Tp10, reference 1), and by a disposable gold TIPtrode (Natus Neurology Inc., Middleton, WI) placed in the ipsilateral ear canal (TIP, reference 2). Two electroencephalograms (EEGs) were recorded in each subject with an electrode setup [Fz-Tp9/Tp10] and [Fz-TIP]. The impedance of the electrodes with the scalp was kept below 3 kΩ in all recordings. The system used to record auditory evoked potentials was the SmartEP with Continuous Acquisition Module (SmartEP-CAM, Intelligent Hearing Systems, Miami, FL). The recording sampling rate was 10 kHz, the gain of the preamplifier was 50K, and the cut-off frequencies for the bandpass analogue filters were [50-3000] Hz. During the recording session, participants were lying down on a comfortable couch, with their eyes closed and neck and shoulder muscles relaxed.

EEG processing was carried out by custom scripts developed in Matlab (The Mathworks Inc., Natick, MA), using functions from the 'Signal Processing' toolbox. Two ABR signals ([Fz-Tp9/Tp10] and [Fz-TIP]) were obtained in each subject by averaging the EEG segments corresponding to the first 12 ms from each stimulus onset in each of the EEG channels. Digital filtering consisted of a 50 Hz notch filter and a zero-phase 4^{th} order Butterworth [200-2000] Hz bandpass filter. In order to maintain a constant number of averaged sweeps across participants, the upper 20% of EEG segments with the highest root-mean-square (RMS) values were not included in the average, thus each ABR signal was obtained by averaging 10,000 sweeps. The time-delay introduced by the plastic tube of the insert earphones was estimated at 0.81 ms by dividing the length of the tube (0.278 m) by the speed of sound in air (343 m/s). Since the sampling rate was 10 kHz, the ABRs were shifted 8 samples to compensate for this time-delay.

Latencies were measured in waves I, III, and V as the time difference in milliseconds between the stimulus onset and the top of the peak. The amplitudes of these waves were measured in microvolts as the voltage difference between the peak of each wave and the minimum trough occurring within the 2 ms following each peak. The analysis of the latency and amplitude in waves I, III, and V, as well as the waves I-V interpeak latency and ratio of amplitudes, was performed conventionally using the [Fz-Tp9/Tp10] ABR signal. However, since the TIPtrode provides an improved performance in wave I analysis (Bauch and Olsen, 1990), the analysis of wave I latency and amplitude was also conducted using the [Fz-TIP] ABR signal.

2.4. Audiometry

Hearing thresholds were measured using the Interacoustics AC40 audiometer (Interacoustics A/S, Middelfart, Denmark) following a 2 dB step staircase method with pure tones presented at 0.25, 0.50, 1, 2, 3, 4, 6, 8, 9, 10, 11.25, and 12.5 kHz. An average threshold was estimated in the test ear for frequencies 0.25 to 2 kHz (hearing loss in low frequencies, HL-LF), for 3 to 6 kHz (hearing loss in high frequencies, HL-HF), and for 8 to 12.5 kHz (hearing loss in extended-high frequencies, HL-EHF).

2.5. Distortion product otoacoustic emissions

Distortion product otoacoustic emissions (DPOAEs) were recorded using a Mimosa Acoustics HearID Auditory Diagnostics System (Mimosa Acoustics Inc., Champaign, IL), connected to an Etymotic ER10C probe coupled to the ear canal with a disposable foam eartip. An f_2/f_1 ratio equal to 1.25 was used at levels of f_1 = 65 dB SPL and f_2 = 55 dB SPL (Dhar and Hall, 2012). A DP-Gram was obtained in each participant by representing the cubic difference tone ($2 \cdot f_1 - f_2$) amplitude response (DPOAE response) at 29 different f_2 frequencies distributed logarithmically between 1 and 12 kHz.

2.6. Lifetime noise exposure and tinnitus

LNE was estimated for each participant considering both leisure and work-related activities through a questionnaire adapted from an online survey previously developed by the research group (Beach et al., 2013; Yeend et al., 2017). This online survey is provided as supplementary material in appendix A. In this survey, respondents were asked to list all jobs in which they had been exposed to noise, the duration of their employment, the average hours per week spent in noise, and the use of hearing protection. Using these estimates and a nominal noise value of 90 dB L_{Aeq} total workplace noise exposure was calculated in $\log_{10}Pa^2h$. In addition, the survey asked respondents to quantify their lifetime participation in 12 known high-noise leisure activities, and use of hearing protection. Using these data, together with average noise levels (L_{Aeq}) and typical durations from the NOISE database (Beach et al., 2013), total exposure for each leisure activity was also calculated in $\log_{10}Pa^2h$. Workplace and leisure exposure figures were then added to arrive at a total lifetime noise exposure estimate after adjusting for hearing protection use.

In this survey, participants were also asked to indicate how often they experienced tinnitus, defined as a buzzing, ringing, whistling, hissing or pulsing sound. The closed set of possible responses included ‘never or almost never’, ‘occasionally’, ‘sometimes’, ‘frequently’, and

'always or almost always'. Participants were categorized as 'non-tinnitus' if their response was one of the first three options, and as 'tinnitus' otherwise.

2.7. Attention

Attention was evaluated with three auditory subtests from the Test of Everyday Attention (TEA; Robertson et al., 1996). A shortened version of subtest 2 'elevator counting', which evaluates sustained attention, was used to help participants familiarize with the test protocol. Subtest 3 'elevator counting with distraction' was used to assess selective attention. In this subtest, listeners were asked to count the repetitions of a mid-pitch tone (500 Hz) while ignoring a higher pitch tone (600 Hz). Attention switching was evaluated by subtest 5 'elevator counting with reversal', which required listeners to count the repetitions of a mid-pitch tone (500 Hz) considering other tones of higher pitch (600 Hz) and lower pitch (400 Hz) as cues to reverse-count in order to determine the floor at which an elevator had arrived. An overall attention score was obtained by averaging the results obtained in subtests 3 and 5.

2.8. Speech-in-noise performance

Participant's speech-in-noise performance was evaluated using the high-cue (HC) condition of the Australian version (2.202) of the LiSN-S test, in which two-talker masker noise was spatially separated ±90° from different-talker target speech at 0° (Cameron and Dillon, 2008). The LiSN-HC condition was selected because it is considered the most realistic speech-in-noise scenario (Glyde et al., 2013). The initial unamplified target sentence was presented at 68 dB SPL and the masker at 61 dB SPL. Audibility was improved in each participant by modifying the signal according to the NAL-RP prescription (Byrne et al., 1990). The NAL-RP correction was applied to minimize a possible confound effect of varying audibility between the subjects. The sentences were presented binaurally through Sennheiser HD215 circumaural headphones (Sennheiser electronic GmbH & Co. KG, Wedemark, Germany).

2.9. Data analysis

Three statistical analyses were carried out in Matlab, using functions from the 'Statistics and Machine Learning' toolbox. The level for statistical significance (*p*-value) was set at 0.05.

The first analysis aimed to evaluate the influence of LNE on the neural encoding of sounds at the level of the cochlea and the brainstem. Analysis of ABR components in the electrode configuration [Fz-Tp9/Tp10] was carried out through eight linear regression models [i.e., wave I amplitude (A_I), wave III amplitude (A_{III}), wave V amplitude (A_V), the ratio between waves I and V amplitudes (A_I/A_V), wave I latency (L_I), wave III latency (L_{III}), wave V latency (L_V), and the interpeak latency between waves I and V (L_V-L_I)], considering LNE and gender as predictor variables. In addition, A_I and L_I were also analysed in the electrode configuration [Fz-TIP]. Gender was included as a predictor variable in these models to account for ABR components of greater amplitudes and shorter latencies normally exhibited in females (Jerger and Hall, 1980; Trune et al., 1988; Mitchell et al., 1989; Dehan and Jerger, 1990).

The second analysis aimed to evaluate the existence of central gain mechanisms in our human cohort. To test the hypothesis that those with low wave I amplitudes would not show reduced wave V amplitudes, we evaluated whether the wave V amplitude distribution in those with low wave I amplitudes was different from the wave V amplitude distribution in the remaining subjects. In addition, L_I, L_V, and L_V-L_I were also compared between the two groups. This analysis was carried out on the [Fz-Tp9/Tp10] ABR signals. The two groups were formed by splitting the sample at the 50th percentile of the wave I amplitude distribution, i.e. 0.1569 μV. In addition, we compared the waves I and V amplitude and latency distributions between the 'tinnitus' and 'non-tinnitus' groups in order to evaluate if subjects reporting tinnitus had active central gain mechanisms. The group comparisons were tested using the two-sample *t*-test in cases where data were normally distributed according to the Lilliefors normality test, and by the non-parametric two-sample Wilcoxon sum rank test otherwise.

The purpose of the third analysis was to determine the influence of eight factors on the performance of understanding speech in noise. This was assessed by fitting a linear regression model with the LiSN-HC score as the dependent variable; and age, LNE, HL-LF, HL-HF, HL-EHF, attention measured through the TEA, L_V-L_I [Fz-Tp9/Tp10], A_I/A_V [Fz-Tp9/Tp10], and the interaction between L_V-L_I and A_I/A_V. Considering that L_V-L_I and A_I/A_V could have similar or interconnected underlying neural mechanisms, this interaction was included to investigate the influence of one on the other.

3. Results

The raw data of all analyses are available as supplementary material in appendix B and in comma-separated values format.

3.1. Hearing thresholds and DPOAEs

(Figure 1, double column)

Eighty-four percent of participants had clinically normal audiometric thresholds, and 12% had near-normal hearing. The remaining 4% (participants #S09, #S64, and #S66) had only one or two thresholds slightly outside the inclusion criteria, and a decision was made to include them in the study. All participants showed symmetrical hearing, with no more than a 10 dB difference between the two ears, and we found no statistical difference in audiometric thresholds between males and females. Figure 1A shows the pure-tone audiometric threshold distributions at the test frequencies. The DP-Gram in figure 1B represent the mean and standard-error of the DPOAE amplitude and noise floor as a function of f_2 frequency. All participants had DPOAEs present at the test frequencies, thus indicating normal-functioning outer hair cells (OHC).

3.2. Effects of lifetime noise exposure on the ABR morphology

(Table 1, double column)

(Figure 2, double column)

The main components of ABR signals obtained with the electrode configurations [Fz-Tp9/Tp10] and [Fz-TIP] were evaluated in terms of LNE through a number of linear regression models, considering gender as a predictor variable. Table 1 shows the results of these models, most of which were statistically significant, except for L_I [Fz-Tp9/Tp10] and for the relative measures A_I/A_V [Fz-Tp9/Tp10] and L_V-L_I [Fz-Tp9/Tp10]. In these models, absence of statistical significance indicates that the variability of the dependent variable was not explained by the predictor variables, thus no firm conclusions can be reached for these models. It is noteworthy that LNE was not a statistically significant predictor of A_I/A_V [Fz-Tp9/Tp10].

The only dependent variable in which the effect of LNE was statistically significant was A_I [Fz-TIP], with an effect size of -0.038 $\mu V/\log_{10}Pa^2h$, *p*-value = 0.0266. In this model, the adjusted R^2 indicates that only the 8.17% of the variability of A_I [Fz-TIP] was accounted for by the effects of LNE and gender. The effect of LNE on A_I [Fz-Tp9/Tp10] showed a trend consistent with A_I [Fz-TIP], but with a lower effect size that was not significant, i.e. -0.021 $\mu V/\log_{10}Pa^2h$, *p*-value = 0.1051. Similarly, LNE showed a near-significant effect of -0.043 $\mu V/\log_{10}Pa^2h$ on the A_V [Fz-Tp9/Tp10], *p*-value = 0.0807.

When we examined the grand-average ABR signals of participants with the lowest and highest levels of LNE (those below the 10^{th} percentile and those above the 90^{th} percentile respectively), one can see that those with lower LNE levels showed greater amplitudes in all ABR components than those with higher LNE levels (see figures 2A and 2B).

Figures 2C and 2D show the raw and adjusted values (i.e., after compensating for the predicted effect of gender) of the amplitudes and latencies of the main ABR components against LNE. The slopes of the trends fitted to the adjusted values correspond to the effect sizes estimated in the linear regression models presented in table 1. The statistically significant correlation between A_I [Fz-TIP] and LNE is shown in the top panel of figure 2C.

Table 1 also shows that overall (a) males presented ABR components of smaller amplitude and greater latency; and (b) L_I had similar mean values in the [Fz-TIP] and [Fz-Tp9/Tp10] electrode setups, but the mean A_I in [Fz-TIP] was larger than in [Fz-Tp9/Tp10].

3.3. Evidence of central gain mechanisms and its relation with tinnitus

(Figure 3, double column)

Figure 3A shows the A_I, A_V and A_I/A_V distributions for the groups of subjects with a wave I amplitude lower (filled circles), and greater (empty circles), than the 50th percentile, i.e. 0.1569 μV. By design, all A_I values were lower in the first group than in the second group, and yet we found no statistically significant differences between the A_V distributions of the two groups, *p*-value = 0.899. As a consequence, the A_I/A_V values were significantly lower in the low-A_I group, indicating the activation of central gain. The latency analysis showed that subjects with lower wave I amplitudes presented delayed L_I (mean latency 1.91 vs 1.81 ms, *p*-value = 0.019), but similar latencies for L_V (*p*-value = 0.524), and L_V-L_I (*p*-value = 0.587).

Figure 3B shows the A_I, A_V and A_I/A_V distributions for the 'non-tinnitus' (filled circles) and 'tinnitus' (empty circles) groups. This figure shows that the 'tinnitus' group presented a statistically significant lower A_I/A_V values than the 'non-tinnitus' group. The A_I and A_V distributions were similar between the two groups. In addition, there were no statistically significant differences between the two groups for (1) L_I (*p*-value=0.616), L_V (*p*-value=0.768), or L_V-L_I (*p*-value=0.957); and (2) for LNE (*p*-value=0.354), i.e. both the 'tinnitus' and 'non-tinnitus' groups presented similar LNE values.

3.4. Factors influencing speech intelligibility in background noise

(Table 2, single column)

(Figure 4, single column)

Table 2 presents the linear regression model for LiSN-HC test performance, with predictor variables: A_I/A_V, L_V-L_I, age, gender, LNE, HL-LF, HL-HF, HL-EHF, TEA, and an interaction between A_I/A_V and L_V-L_I. The model was statistically significant (p-value < 0.0001), indicating that approximately 40% of the variability of the LiSN-HC score (adjusted R^2 = 41.80%) could be explained by the predictor variables. Of the predictors, four had no significant effect on the LiSN-HC score: age, LNE and mean audiometric thresholds at high and extended-high frequencies. In contrast, mean low-frequency thresholds were significant. For every 1 dB of HL-LF, performance on the LiSN-HC decreased by 0.231 dB. Attention was also a significant predictor of LiSN-HC, with better performance by those with higher scores on the TEA subtests. In addition, A_I/A_V and L_V-L_I each had a statistically significant effect on the LiSN-HC performance; and the significant interaction between A_I/A_V and L_V-L_I suggests that the effect of the interpeak latency on the LiSN-HC performance depends on the ratio of amplitudes, and vice versa.

Figure 4 shows the combined effect of A_I/A_V and L_V-L_I on the LiSN-HC score. The LiSN-HC scores of four groups of subjects were categorized according to: (a) 'short L_V-L_I' or 'long L_V-L_I' relative to the median (i.e., 4.29 ms); and (b) 'high gain' or 'normal gain' relative to 0.43, which corresponds to the mean of the A_I/A_V median values for the 'non-tinnitus' group (median = 0.53) and 'tinnitus' group (median = 0.34) groups, where lower A_I/A_V values are an indicator of central gain activation or 'high gain'. This threshold was selected as an appropriate central-gain boundary between subjects with and without tinnitus. Since the LiSN-HC score distributions in the four groups of subjects were not normally distributed, they were compared using the non-parametric Kruskal-Wallis analysis of variance test, with the Tukey-Kramer correction for multiple comparisons. The results showed that when gain was 'normal', the effect of L_V-L_I on the LiSN-HC score was not significant. However, when the gain was 'high' (i.e., central gain mechanisms were active) the interpeak latency played a significant role in LiSN-HC performance. That is, those who performed worst on LiSN-HC test were those with both long interpeak latencies and high gain.

4. Discussion

4.1. Evidence of noise-induced cochlear synaptopathy in humans

This study showed a statistically significant negative correlation between self-reported levels of lifetime noise exposure and the amplitude of wave I of ABR signals evoked at a suprathreshold level using a TIPtrode in the ear canal as the reference electrode, after compensating for the predicted effect of gender. This result is consistent with the main hypothesis of the study, and also accords with the well-established animal model in which noise exposure damages the synaptic connections between IHCs and ANFs (Kujawa and Liberman, 2009; Liberman and Kujawa, 2017), particularly those with LSR (Furman et al., 2013), thus providing some evidence of cochlear synaptopathy in humans.

Despite the large degree of variation in A_I across the sample (figure 2C), we observed that the statistically significant effect of LNE on A_I was moderate (-0.038 $\mu V/\log_{10}Pa^2h$, indicating an A_I reduction of 0.133 μV (or a 43.66% reduction) across the range of LNE values observed, i.e. 1.43 – 4.93 $\log_{10}Pa^2h$). This moderate effect might be explained by a combination of several factors. First, the highly variable levels, durations and energy distributions of humans' typical noise exposures are very different to the highly controlled, narrow-band insults typically used in animal studies (Hickox et al., 2017). Second, the auditory structures in humans are possibly more robust to noise exposure than in rodents. Variation in inter-species susceptibility has been demonstrated by Valero et al. (2017), who found that the sound pressure levels of the noise needed to be 10-fold (20 dB) higher to produce a similar degree of cochlear synaptopathy in primates when compared to rodents. Another possibility is that not all subjects are equally susceptible to noise exposure, and therefore noise exposure would induce cochlear synaptopathy only in certain individuals. It could also be possible that noise exposure induces cochlear synaptopathy only in selected portions of the cochlea (Kujawa and Liberman, 2009; Furman et al., 2013; Kujawa and Liberman, 2015), and therefore, the effect of cochlear synaptopathy is obscured when ABRs are evoked by short-duration clicks, which present energy

in a broad range of frequency components. It is also plausible that synapses disrupted by noise exposure partially repair, thus leading to partially-recovered wave I amplitudes, as has been reported in guinea pigs (Shi et al., 2016a,b; Song et al., 2016). Moreover, it could be the case that the LSR ANFs selectively targeted by noise exposure (Furman et al., 2013; Yin et al., 2014; Liberman et al., 2015) contribute little to the A_I, as has been suggested by Bourien et al. (2014). In this study, Mongolian gerbils and guinea pigs were infused with different doses of ouabain, to which LSR ANFs are most vulnerable, and they found that LSR ANFs do not contribute to either CAP threshold or amplitude, probably because of their lack of synchronization with the stimulus and long first spike latency.

Although the negative effect of LNE on A_I provides some evidence of cochlear synaptopathy in humans, there are two factors, which should be considered when interpreting this result. The first factor refers to the degree of uncertainty in our data at the low LNE region. Although we did attempt to recruit participants across a broad range of noise exposures, the actual spread of LNE values across the range was not uniform. In particular, while 65 subjects presented LNE values between 3 and 5 $\log_{10}Pa^2h$, only nine were in the low LNE range from 1 to 3 $\log_{10}Pa^2h$. This lack of uniformity may have introduced a higher level of uncertainty in the low LNE region. For example, if we exclude subject #S36 (50 yr, female) from the data analysis [#S36 is the subject with the lowest level of LNE (1.43 $\log_{10}Pa^2h$) and the largest wave I amplitude (0.56 μV)], the negative trend between LNE and A_I [Fz-TIP] becomes non-significant (-0.019 μV/$\log_{10}Pa^2h$, *p*-value=0.278). The second factor refers to the possibility that OHC or IHC dysfunction may have contributed to the observed trend (Dallos and Harris, 1978; Stebbins et al., 1979; Ohlms et al., 1991; Qiu et al., 2000; Salvi et al., 2017). It is highly unlikely that OHC function played a major role in the observed trend because we confirmed that mean audiometric thresholds and averaged DPOAE levels at low-, high-, and extended-high frequencies did not have a significant effect on A_I [Fz-TIP] (data not shown). However, the possibility that IHC dysfunction played a role in the observed trend cannot be excluded because without histology, there is no way we

can be certain that those with lower A_I [Fz-TIP] have synaptopathy, IHC dysfunction, or a combination of both. The results presented here contribute to the growing body of conflicting evidence with regard to this phenomenon (supporting: Stamper and Johnson, 2015a,b; Bramhall et al., 2017; and non-supporting: Fulbright et al., 2017; Grinn et al., 2017; Grose et al., 2017; Prendergast et al., 2017). The different results obtained by the various groups might be accounted for by several methodological factors. Firstly, the age of the participants varies between studies. In previous studies the age range of the participants was 19-28 years (Stamper and Johnson, 2015a,b), 19-35 years (Bramhall et al., 2017), 18-36 years (Prendergast et al., 2017), 18-30 years (Fulbright et al., 2017), 18-35 years (Grose et al., 2017), and 21-27 years (Grinn et al., 2017). In contrast, the age range in the present study was 29-55 years – representing the first attempt to evaluate the impact of LNE on ABR morphology in older adults. This age range was the result of a deliberate decision that took into account previous findings suggesting that noise exposure may accelerate the degenerative effects of aging, possibly as a result of several micro-lesions accumulated over the years (Kujawa and Liberman, 2006, 2015; Fernandez et al., 2015). Thus, the effects of noise exposure on the human ABR morphology may become more evident in participant groups of older age as seen here.

Another factor relates to the manner in which noise exposure was estimated in the various studies. To date, the most efficient procedure used to evaluate human noise exposure is through questionnaires, which are subject to individual bias and recall errors. The lack of standardization in these questionnaires and the different timeframes they cover makes it difficult to compare the results from different studies. For example, the retrospective noise survey used by Stamper and Johnson (2015a,b) and Grinn et al. (2017) was the Noise Exposure Questionnaire, developed by Megerson (2010), which estimates the amount of noise exposure in the previous year. However, Bramhall et al. (2017), Prendergast et al. (2017) and the present study evaluated the amount of noise exposure across the lifetime. Considering the effects of noise exposure being cumulative, the longer the period in which noise exposure is evaluated, the more accurate the

estimate should be, thus a better estimate is likely when noise exposure is evaluated across the lifetime.

The inclusion of participants with a broad range of noise exposures is another critical factor. The LNE range in this study was 1.43 to 4.93 $\log_{10}Pa^2h$, resulting in a spread of 3.5 $\log_{10}Pa^2h$. This means that the participant with the highest LNE had more than 3000 times the noise exposure of the participant with the lowest LNE. A significant effort was made in this study to recruit participants with particularly low and high levels of noise exposures in order to obtain a wide range of LNE. The LNE range in the present study was around 10-fold larger than in Prendergast et al. (2017), where the reported noise exposures ranged from 0 to 2.5 $\log_{10}$(Energy); but significantly lower than in Bramhall et al. (2017), in which control subjects and young military veterans with firearm use reported noise exposures ranging from 3 to 18 $\log_{10}$(Energy).

We also observed that using a TIPtrode in the ear canal as a reference enhanced the amplitude of the ABR wave I, which seemed to improve the sensitivity of A_I to LNE since the slope between these two variables was steeper, and the correlation larger, when the TIPtrode was used as reference compared to the mastoid electrode. This could be a consequence of the larger wave I amplitudes obtained by the TIPtrode. This result is consistent with Stamper and Johnson (2015a), who also found a steeper slope in the correlation between wave I amplitude and noise-exposure background with the reference electrode placed in the tympanic membrane; and with Fulbright et al. (2017), who found a reduced wave I amplitude in ABRs evoked by 4 kHz tone burst in a subgroup of "high-risk" subjects reporting "sometimes", "often", or "always" having auditory symptoms after exposure to noise, but only when the reference electrode was a TIPtrode placed in the ear canal.

In addition, we used a large number of averaged sweeps in our stimulus sequence (10,000 after artifact rejection) to ensure ABR signals of high quality. Taking into account that the signal-to-noise ratio of AEPs increases by 3 dB for every doubling of averaged sweeps (Thornton, 2007), the quality of the ABR signals in this study was approximately 4 dB greater than in Grose et al.

(2017) [4056 sweeps] and Stamper and Johnson (2015a,b) [4000 sweeps]; 7 dB greater than in Fulbright et al. (2017) [2000 sweeps]; 10 dB greater than in Bramhall et al. (2017) [1000 sweeps]; and 13 dB greater than in Grinn et al. (2017) [500 sweeps]. Thus, the reduced levels of electrophysiological noise in our ABR signals might have increased the precision of the latency and amplitude estimates of the ABR components. In order to corroborate this point, we carried out an analysis of the recorded electrophysiology noise, measured in terms of (1) RMS value in the ABR signals and their pre-response baseline; and (2) Fsp, an objective indicator of neural response detection (Elberling and Don, 1984) [data shown in supporting material, appendix C]. This analysis showed that because of the high Fsp and the low RMS values obtained in the pre-response baseline, the amplitude and latency estimates were obtained from neural evoked responses with low levels of electrophysiology noise.

The large number of stimuli used in our stimulus sequence could be presented within a reasonable recording time by using a presentation rate of 39.1 stim/sec. This stimulus rate was higher than in other studies (Bramhall et al., 2017: 11.1 stim/sec; Fulbright et al., 2017: 21.1 stim/sec; Grinn et al., 2017: 11.7 stim/sec; Grose et al., 2017: 7.7 stim/sec; Prendergast et al., 2017: 11 stim/sec; Stamper and Johnson, 2015a,b: 11.3 stim/sec). However, it is plausible that this higher stimulus rate might have led to a lower effect size of LNE on A_I. This would be expected, not only because A_I values are typically larger using a presentation rate closer to 10 stim/sec (Lasky, 1997; Burkard and Sims, 2001; Liberman et al., 2016); but also because (a) LSR fibers have a longer recovery time to prior stimulation than that of high-SR (HSR) fibers (>100 ms; Relkin and Doucet, 1991) and (b) a selective loss of LSR fibers yields a faster recovery of the compound action potential (Schmiedt et al., 1996), thus hypothetically leading to an overall lower contribution of LSR fibers to A_I at higher presentation rates.

Taken together, the results of this paper along with those reported by similar studies point out that while a trend correlating noise exposure and A_I might be useful to understand the influence of noise exposure on the integrity of the human auditory system at the level of the cochlea in a

specific population of subjects, the large inter-subject variability in the A_I measure, the potential role of human bias on the amount of noise exposure estimated through questionnaires, the lack of a significant link between LNE and speech-in-noise performance, and the possibility of different individual susceptibility to noise exposure indicate that neither the estimate of noise exposure or A_I are meaningful indicators for diagnosing cochlear synaptopathy at an individual level. It is likely that we will need a new research approach, which aims to determine the particular profile of those at risk of noise-induced synaptopathy, rather than employing the large-scale group-based methods which have been used in the studies published to date.

4.2. Are tinnitus and central gain activation a consequence of cochlear synaptopathy?

We investigated whether the activation of central gain mechanisms observed in animal studies as a consequence of peripheral damage (Salvi et al., 2000; Sun et al., 2012; Chen et al., 2013; Niu et al., 2013; Auerbach et al., 2014) were also present in humans. We observed that subjects with low A_I had similar A_V to the rest of the cohort. Assuming that A_I serves as a reliable proxy for cochlear synaptopathy, this result is consistent with the hypothesis of the central gain model, in which central stages of the auditory system compensate for a loss of sensory input from the cochlea (Auerbach et al., 2014; Chambers et al., 2016; Salvi et al., 2017).

An alternative explanation for this result is that the neural activity in the midbrain is independent of activity in the auditory nerve, and therefore, no central gain mechanisms are involved. Although possible, the fact that the midbrain is a neural station of the ascending auditory pathway and the strong evidence of central gain mechanisms across several species of mammals (Saunders et al. 1972; Lonsbury-Martin and Martin, 1981; Gerken et al., 1984; Popelar et al., 1987; Salvi et al., 1990) suggest that this alternative explanation is highly unlikely.

This study also showed that subjects reporting tinnitus ‘frequently’ or ‘always or almost always’ presented statistically significant lower waves I-V amplitude ratios, thus supporting the notion of tinnitus being associated with increased neural gain at the level of the brainstem. This result is consistent with Schaette and McAlpine (2011), Gu et al. (2012), and Bramhall et al. (2018),

who also found a significant difference in the waves I-V amplitude ratio in those subjects reporting tinnitus. However, in contrast to these studies, we found no differences in the wave I amplitude between the 'tinnitus' and 'non-tinnitus' groups nor a statistically significant association between tinnitus and LNE, which impedes our ability to draw conclusions about possible lines of causality between tinnitus and LNE or cochlear synaptopathy.

Additionally, in contrast to our initial hypothesis, no relationship was found between LNE and activation of central gain mechanisms, measured in terms of A_I/A_V. These results concur with previous studies in which A_I/A_V was also shown to be unrelated to LNE in young adults with varying noise exposures (Prendergast et al., 2017) and those with and without tinnitus (Guest et al., 2017), but they are in contrast to the underlying theory of central gain and tinnitus being triggered by excessive noise exposure (Sun et al., 2012; Niu et al., 2013; Auerbach et al., 2014; Hesse et al., 2016; Bramhall et al., 2017,2018; Moore et al., 2017).

Although this study provides some evidence that the central gain mechanisms observed in animal studies might also be present in humans, and that the activation of these central gain mechanisms might induce tinnitus, the question of whether tinnitus and central gain mechanisms in humans are activated by accumulated noise exposure and cochlear synaptopathy remains unanswered. It might be the case that noise exposure reduces wave I amplitude, and reduced wave I amplitude activates a central gain, but the variation in the manifestation of noise exposure effects in individuals prevents a relationship between noise exposure and central gain or tinnitus being observed.

4.3. Peripheral and central factors influencing speech intelligibility

This study revealed no significant correlation between LNE and scores on the LiSN-HC test. Although this result was counter to the initial hypothesis of the study, it was not totally unexpected considering that about 92% of the participants also participated in the larger-study that also showed no clear link between participants' LNE and performance on a range of speech-in-noise and other auditory tasks (Yeend et al., 2017). This lack of association between LNE and

speech-in-noise performance also concurs with Grose et al. (2017), who reported no behavioural effects of noise exposure despite finding differences in the auditory brainstem responses of a group of young adults who regularly attended loud music venues vs an age-matched control group without such a history. It may be that LNE induces a relatively mild cochlear synaptopathy in humans that is compensated for in latter stages of the auditory pathway either by central gain or other neural reorganization (Auerbach et al., 2014; Chambers et al., 2016). Another possibility is that the effect of LNE in understanding speech in noise is not as important relative to cognitive processes which are also involved in this complex task, such as attention (*p*-value = 0.0098) and other factors not considered here, such as language proficiency, working memory, motivation, noise suppression, etc. (Mayo et al., 1997; Fraser et al., 2010; Rönnberg et al., 2010; Yeend et al., 2017).

Clearly further research is required to clarify the relative impact of LNE on an individual's speech-in-noise performance. Taking into account that a moderate effect of LNE on A_I was observed in the present study, possibly as a result of mild cochlear synaptopathy, it is reasonable to suppose that more pronounced effects of LNE on human hearing and speech understanding might be expected in (a) populations of more advanced age (greater than 55) as a consequence of accumulated effects across years; and (b) target groups who are frequently exposed to lengthy and very high doses of noise exposure, such as lifelong factory workers or veterans with a significant history of firearm use.

This analysis also showed that low-frequency hearing thresholds (i.e., [0.25-2] kHz) play an important role in understanding speech in noise. This result is consistent with Glyde et al. (2013), who carried out a study with 80 participants (aged 7-89 years) with a broad range of audiometric thresholds, and found a strong relationship between the four-frequency average hearing loss (calculated as the average hearing threshold at 250, 500, 1000, 2000, 4000 and 8000 Hz) and performance on the high-cue condition of the LiSN-S test (*p*-value < 0.001, $R^2 = 0.82$).

The results of this analysis also suggest that selective attention and attention switching are crucial factors in speech-in-noise perception. On average, subjects with a better score on the test of everyday attention achieved a better performance on the LiSN-HC test. This result is consistent with Yeend et al. (2017), and with numerous studies that have reported attention as a key cognitive factor influencing speech-in-noise performance (Schvartz et al., 2008; Mattys et al., 2012; Wild et al., 2012).

Our analysis showed that age was not a significant factor in speech-in-noise performance. This is not surprising since Moore et al. (2014) found in a large scale study that speech reception thresholds increased (performance worsened) exponentially with age, but only from around 50 years. In line with this, Glyde et al. (2013) found that LiSN-HC performance improved from 8 to 30 years, was relatively stable between 30 and 60 years, and progressively declined from 60 years onwards. Since the age range in our study (29-55 years) is in the plateau section of the aforementioned trends, age differences do not contribute to the variability observed in LiSN-HC performance.

Finally, this study showed that central gain and the speed of brainstem neural conduction – measured in terms of waves I and V interpeak latency (Jonquieres et al., 2014; Stange-Marten et al., 2017), are important predictors of the ability to perceive speech in noise. In particular, we found that longer L_V-L_I was associated with poorer LiSN-HC scores, especially when central gain was active, i.e. A_I/A_V was low. Consistent with this result, Anderson et al. (2013) also found that the offset latency of complex-ABRs negatively correlated with the Speech, Spatial, and Qualities of Hearing Scale (Gatehouse and Noble, 2004), i.e. longer offset latencies were associated with poorer self-reported speech-in-noise performance.

One possible reason for these results could be different levels of hypomyelination of spiral ganglion nerves and medial olivocochlear efferents (Eggermont and Don, 1986; Moore and Linthicum, 2001), driven by either Schwann cell loss, damage, or incomplete repair (Kuwabara and Yuki, 2013; Kremer et al., 2016). Indeed, it has been shown that auditory nerve

demyelination could cause effects similar to those expected from noise-induced cochlear synaptopathy (Wan and Corfas, 2017). In this study, Schwann and satellite cells of the spiral ganglion nerve fibers of mice were selectively ablated, leaving ANFs practically unmyelinated. Four months after the injury, Schwann cells completely regenerated, leading to fibres with normal axon calibre and myelin thickness. However, suprathreshold ABR waves I showed a permanent decrease in the amplitude (around 25% reduction) and increase in the latency (around 1 ms delay), while ABR- and DPOAE-thresholds were not affected. The authors concluded that noise-induced cochlear synaptopathy and demyelination are different processes that could coexist, and result in similar outcomes. The increased latency derived from an incomplete repair of Schwann cell ablation could compromise the temporal precision needed to detect microsecond-order differences in the arrival of low frequency sounds at the two ears (interaural time differences) in the medial superior olive (Brand et al., 2002; Grothe et al., 2010; Golding and Oertel, 2012; Ford et al., 2015; Stange-Marten et al., 2017). This process underpins the ability to localize sound sources and is important in spatial hearing when separating a target source from noise distractors (Grothe, 2003; Hawley et al., 2004; Swaminathan et al., 2016).

At the same time, a central gain mechanism may also be active, in which an increase in the neural activity of central stages of the auditory pathway, like the midbrain and the auditory cortex, compensates for a reduced input from the cochlea (Auerbach et al., 2014; Salvi et al., 2017). Chambers et al. (2016) found that activation of these mechanisms helps restore, and even enhance, the encoding of rudimentary sound features of the stimulus, like sound level and frequency; but not features associated with precise spike timing, like speech or modulated noise. In the present study, we showed that central gain modulates the influence of delayed brainstem conduction (i.e., longer latencies) on speech-in-noise intelligibility. When central gain mechanisms were active, subjects with faster brainstem conduction benefit from this enhanced neural activity, however, for those with long brainstem conduction delays, central gain activation increased the negative effect on speech-in-noise performance. To the best of our

knowledge, this study shows for the first time the interactive roles of central gain and brainstem neural conduction speed in speech-in-noise intelligibility performance.

4.4. Conclusion

This paper aimed to evaluate, in a large cohort of middle-age adults, the influence of LNE on (a) ABRs evoked at a suprathreshold level and (b) speech intelligibility performance in background noise. Our results showed (a) a statistically significant, negative association between LNE and the A_I measured on the [Fz-TIP] channel; (b) that central gain mechanisms observed in animal studies might also occur in humans; (c) an association between tinnitus and central gain; and (d) an interactive effect of central gain and brainstem neural conduction speed on speech-in-noise performance. Although this paper does provide some evidence that noise-induced cochlear synaptopathy, as reported in animal studies, is also present in humans, the overriding conclusion to be drawn from this work is that the effect of noise exposure on the neural structures of the auditory system and speech-in-noise performance is neither systematic nor predictable. It is not the case that all subjects with higher doses of noise exposure will have low wave I amplitudes, central gain activation, or poor speech-in-noise performance. Rather, our data reveal large inter-subject variability in both susceptibility to noise and its manifestations. Our results also imply that wherever possible, cochlear synaptopathy and associated central gain activation should be considered in a holistic context that takes into account other important factors that play a role in speech-in-noise understanding, such as attention. When considered more broadly, it may well be that the relative effects of cochlear synaptopathy on human hearing turn out to be not quite as pronounced as first thought.

Acknowledgements

The authors gratefully acknowledge Mr Mark Seeto (NAL: National Acoustic Laboratories, Sydney, Australia) for his help with the statistical analysis; Mr Greg Stewart (NAL) for his help with the calibration of the stimuli; and Prof David McAlpine (Macquarie University, Sydney, Australia) for his invaluable comments in previous drafts of this manuscript. This research was

supported by the Australian Government Department of Health, grants from the National Health and Medical Research Council (grant ID 1063905), and the Hearing Industry Research Consortium. This work was also supported by the HEARing CRC, established and supported under the Cooperative Research Centres Program – Business Australia.

Appendix

Supplementary material related to this article can be found at [URL].

References

Anderson, S., Parbery-Clark, A., White-Schwoch, T., Kraus, N. (2013). Auditory brainstem response to complex sounds predicts self-reported speech-in-noise performance. Journal of Speech, Language, and Hearing Research 56, 31-43. https://doi.org/10.1044/1092-4388(2012/12-0043).

Auerbach, B.D., Rodrigues, P.V., Salvi, R.J. (2014). Central gain control in tinnitus and hyperacusis. Frontiers in Neurology 5, article 206, 21p. https://doi.org/10.3389/fneur.2014.00206.

Bauch, C.D., Olsen, W.O. (1990). Comparison of ABR amplitudes with TIPtrode™ and mastoid electrodes. Ear and Hearing 11, 463-467. https://journals.lww.com/ear-hearing/pages/articleviewer.aspx?year=1990&issue=12000&article=00010&type=abstract.

Beach, E., Gilliver, M., William, W. (2013). The NOISE (Non-Occupational Incidents, Situations and Events) database: a new research tool. Annals of Leisure Research 16, 149-159. https://dx.doi.org/10.1080/11745398.2013.793157.

Bohne, B.A., Harding, G.W. (2000). Degeneration in the cochlea after noise damage: Primary versus secondary events. American Journal of Otology 21, 505-509. https://ovidsp.tx.ovid.com/sp-3.26.1a/ovidweb.cgi?&S=EFILFPJEOGDDBCAKNCGKEBGCGOFDAA00&Link+Set=jb.search.56%7c1%7csl_10.

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. Journal of Neurophysiology 112, 1025-1039. https://dx.doi.org/10.1152/jn.00738.2013.

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 and Hearing 38, e1-e12. https://dx.doi.org/10.1097/AUD.0000000000000370.

Bramhall, N.F., Konrad-Martin, D., McMillan, G.P. (2018). Tinnitus and auditory perception after a history of noise exposure: Relationship to auditory brainstem response measures. Ear and Hearing, *publish ahead of print*. https://doi.org/10.1097/AUD.0000000000000544.

Brand, A., Behrend, O., Marquart, T., McAlpine, D., Grothe B. (2002). Precise inhibition is essential for microsecond interaural time difference coding. Nature 417, 543-547. https://doi.org/10.1038/417543a.

Burkard, R.F., Sims, D. (2001). The human auditory brainstem response to high click rates: aging effects. American Journal of Audiology 10, 53-61. https://doi.org/10.1044/1059-0889(2001/008).

Byrne, D., Parkinson, A., Newall, P. (1990). Hearing aid gain and frequency response requirements for the severely/profoundly hearing impaired. Ear and Hearing 11, 40-49. https://journals.lww.com/ear-hearing/Abstract/1990/02000/Hearing_Aid_Gain_and_Frequency_Response.9.aspx.

Cameron, S., Dillon, H. (2008). The listening in spatialized noise-sentences test (LiSN-S): Comparison to the prototype LISN and results from children with either a suspected (central) auditory processing disorder or a confirmed language disorder. Journal of the American Academy of Audiology 19, 377-391. https://doi.org/10.3766/jaaa.19.5.2.

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. https://doi.org/10.1016/j.neuron.2015.12.041.

Chen, G.-D., Stolzberg, D., Lobarinas, E., Sun, W., Ding, D., Salvi, R. (2013). Salicylate-induced cochlear impairments, cortical hyperactivity and re-tuning, and tinnitus. Hearing Research 295, 100-113. https://doi.org/10.1016/j.heares.2012.11.016.

Dallos, P., Harris, D. (1978). Properties of auditory nerve responses in absence of outer hair cells. Journal of Neurophysiology 41, 365-383. https://doi.org/10.1152/jn.1978.41.2.365.

Dehan, C.P., Jerger, J. (1990). Analysis of gender differences in the auditory brainstem response. Laryngoscope 100, 18-24. https://doi.org/10.1288/00005537-199001000-00005.

Dhar, S., Hall III, J.W. (2012). Otoacoustic emissions: Principles, procedures and protocols. San Diego, CA: Plural Publishing. https://www.pluralpublishing.com/publication_oe.htm.

Diehl, P.U., Schaette, R. (2015). Abnormal auditory gain in hyperacousis: investigation with a computational model. Frontiers in Neurology 6, article 157, 14p. https://doi.org/10.3389/fneur.2015.00157.

Dillon, H. (2012). Hearing Aids (Thieme Publishers, New York), 608 p. https://www.thieme.com/books-main/audiology/product/1888-hearing-aids.

Dobie, R.A., Humes, L.E. (2017). Commentary on the regulatory implications of noise-induced cochlear neuropathy. International Journal of Audiology 56, 74-78. https://dx.doi.org/10.1080/14992027.2016.1255359.

Eggermont, J.J., Don, M. (1986). Mechanisms of central conduction time prolongation in brainstem auditory evoked potentials. Archives of Neurology 43, 116-120. https://doi.org/10.1001/archneur.1986.00520020010007.

Elberling, C., Don, M. (1984). Quality estimation of averaged auditory brainstem response. Scandinavian Audiology 13, 187-197. https://doi.org/10.3109/01050398409043059.

Emmerich, E., Richter, F., Reinhold, U., Linss, V., Linss, W. (2000). Effects of industrial noise exposure on distortion product otoacoustic emissions (DPOAEs) and hair cell loss of

the cochlea – long term experiments in awake guinea pigs. Hearing Research 148, 9-17. https://doi.org/10.1016/S0378-5955(00)00101-5.

Fernandez, K.A., Jeffers, P.W.C., Lall, K., Liberman, M.C., Kujawa, S.G. (2015). Aging after noise exposure: Acceleration of cochlear synaptopathy in "recovered" ears. Journal of Neuroscience 35, 7509-7520. https://doi.org/10.1523/JNEUROSCI.5138-14.2015.

Ford, M.C., Alexandrova, O., Cossell, L., Stange-Marten, A., Sinclair, J., Kopp-Scheinpflug, C., Pecka, M., Attwell, D., Grothe, B. (2015). Tuning of Ranvier node and internode properties in myelinated axons to adjust action potential timing. Nature Communications 6, 8073. https://doi.org/10.1038/ncomms9073.

Fraser, S., Gagné, J.-P., Alepins, M., Dubois, P. (2010). Evaluating the effort expended to understand speech in noise using a dual task paradigm: The effects of providing visual speech cues. Journal of Speech, Language, and Hearing Research 53, 18-33. https://doi.org/10.1044/1092-4388(2009/08-0140).

Fulbright, A.N.C., Le Prell, C.G., Griffiths, S.K., Lobarinas, E. (2017). Effects of recreational noise on threshold and suprathreshold measures of auditory function. Seminars in Hearing 38, 298-318. https://doi.org/10.1055/s-0037-1606325.

Furman, A.C., Kujawa, S.G., Liberman, M.C. (2013). Noise-induced cochlear synaptopathy is selective for fibers with low spontaneous rate. Journal of Neurophysiology 110, 577-586. https://doi.org/10.1152/jn.00164.2013.

Gatehouse, S., Noble, W. (2004). The Speech, Spatial and Qualities of Hearing Scale (SSQ). International Journal of Audiology 43, 85-99. https://doi.org/10.1080/14992020400050014.

Gerken, G.M., Saunders, S.S., Paul, R.E. (1984). Hypersensibility to electrical stimulation of auditory nuclei follows hearing loss in cats. Hearing Research 13, 249-259. https://doi.org/10.1016/0378-5955(84)90078-9.

Glyde, H., Cameron, S., Dillon, H., Hickson, L., Seeto, M. (2013). The effects of hearing impairment and aging on spatial processing. Ear and Hearing 34, 15-28. https://doi.org/10.1097/AUD.0b013e3182617f94.

Golding, N.L., Oertel, D. (2012). Synaptic integration in dendrites: Exceptional need for speed. The Journal of Physiology 590, 5563-5569. https://doi.org/10.1113/jphysiol.2012.229328.

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. Frontiers in Neuroscience 11, article 465, 24 p. https://doi.org/10.3389/fnins.2017.00465.

Grose, J.H., Buss, E., Hall III, J.W. (2017). Loud music exposure and cochlear synaptopathy in young adults: Isolated auditory brainstem response effects but no perceptual consequences. Trends in Hearing 21, 1-8. https://doi.org/10.1177/2331216517737417.

Grothe, B., Pecka, M., McAlpine, D. (2010). Mechanisms of sound localization in mammals. Physiolocial Reviews 90, 983-1012. https://doi.org/10.1152/physrev.00026.2009.

Grothe, B. (2003). New roles for synaptic inhibition in sound localization. Nature Reviews Neuroscience 4, 540-550. https://doi.org/10.1038/nrn1136.

Gu, J.W., Herrmann, B.S., Levine, R.A., Melcher, J.R. (2012). Brainstem auditory evoked potentials suggest a role for the ventral cochlear nucleus in tinnitus. JARO - Journal of the Association for Research in Otolaryngology 13, 819-833. https://doi.org/10.1007/s10162-012-0344-1.

Guest, H., Munro, K.J., Prendergast, G., Howe, S., Plack, C.J. (2017). Tinnitus with a normal audiogram: Relation to noise exposure but no evidence for cochlear synaptopathy. Hearing Research 344, 265-274. https://doi.org/10.1016/j.heares.2016.12.002.

Hawley, M.L., Litovsky, R.Y., Culling, J.F. (2004). The benefit of binaural hearing in a cocktail party: Effect of location and type of interferer. Journal of the Acoustical Society of America 115, 833-843. https://doi.org/10.1121/1.1639908.

Hébert, S., Fournier, P., Noreña, A. (2013). The auditory sensitivity is increased in tinnitus ears. Journal of Neuroscience 33, 2356-2364. https://doi.org/10.1523/JNEUROSCI.3461-12.2013.

Hesse, L.L., Bakay, W., Ong, H.C., Anderson, L., Ashmore, J., McAlpine, D., Linden, J., Schaette, R. (2016). Non-monotonic relation between noise exposure severity and neuronal hyperactivity in the auditory midbrain. Frontiers in Neurology 7, 133, 13 p. https://doi.org/10.3389/fneur.2016.00133.

Hickox, A.E., Larsen, E., Heinz, M.G., Shinobu, L., Whitton, J.P. (2017). Translational issues in cochlear synaptopathy. Hearing Research 349, 164-171. https://doi.org/10.1016/j.heares.2016.12.010.

Hickox, A.E., Liberman, M.C. (2014). Is noise-induced cochlear neuropathy key to the generation of hyperacusis or tinnitus? Journal of Neurophysiology 111, 552-564. https://doi.org/10.1152/jn.00184.2013.

Hu, B.H., Henderson, D. (1997). Changes in F-actin labeling in the outer hair cell and the Deiters cell in the chinchilla cochlea following noise exposure. Hearing Research 110, 209-218. https://doi.org/10.1016/S0378-5955(97)00075-0.

Jerger, J., Hall, J. (1980). Effects of age and sex on auditory brainstem response. Archives of Otolaryngology 106, 387-391. https://doi.org/10.1001/archotol.1980.00790310011003.

Jonquieres, G., Froud, K.E., Klugmann, C.B., Wong, A.C.Y., Housley, G.D., Klugmann, M. (2014). Loss of central auditory processing in a mouse model of Canavan Disease. PLOS One 9, e97374, 8p. https://doi.org/10.1371/journal.pone.0097374.

Katz, J. (2014). Handbook of clinical audiology, edited by Marshall Chasin, Kristina English, Linda J. Hood, and Kim L. Tillery (Wolters Kluwer Health, Philadelphia), 927 p. https://shop.lww.com/Handbook-of-Clinical-Audiology/p/9781451191639.

Kremer, D., Göttle, P., Hartung, H.P., Küry, P. (2016). Pushing forward: remyelination as the new frontier in the CNS diseases. Trends in Neuroscience 39, 246-263. https://doi.org/10.1016/j.tins.2016.02.004.

Kujawa, S.G., Liberman, M.C. (2006). Acceleration of age-related hearing loss by early noise exposure: Evidence of a misspent youth. Journal of Neuroscience 26, 2115-2123. https://doi.org/10.1523/JNEUROSCI.4985-05.2006.

Kujawa, S.G., Liberman, M.C. (2009). Adding insult to injury: Cochlear nerve degeneration after “temporary” noise-induced hearing loss. The Journal of Neuroscience 29, 14077-14085. https://doi.org/10.1523/JNEUROSCI.2845-09.2009.

Kujawa, S.G., Liberman, M.C. (2015). Synaptopathy in the noise-exposed and aging cochlea: Primary neural degeneration in acquired sensorineural hearing loss. Hearing Research 330, 191-199. https://doi.org/10.1016/j.heares.2015.02.009.

Kuwabara, S., Yuki, N. (2013). Axonal Guillain-Barre syndrome: Concepts and controversies. The Lancet Neurology 12, 1180-1188. https://doi.org/10.1016/S1474-4422(13)70215-1.

Lasky, R.E. (1997). Rate and adaptation effects on the auditory evoked brainstem response in human newborns and adults. Hearing Research 111, 165-176. https://doi.org/10.1016/S0378-5955(97)00106-8.

Liberman, L.D., Suzuki, J., Liberman, M.C. (2015). Dynamics of cochlear synaptopathy after acoustic overexposure. Journal of the Association for Research in Otolaryngology 16, 205-219. Erratum in: Journal of the Association for Research in Otolaryngology 2015 16, 221. https://dx.doi.org/10.1007/s10162-015-0510-3.

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, 15 p. https://doi.org/10.1371/journal.pone.0162726.

Liberman, M.C., Kujawa, S.G. (2017). Cochlear synaptopathy in acquired sensorineural hearing loss: Manifestations and mechanisms. Hearing Research 349, 138-147. https://doi.org/10.1016/j.heares.2017.01.003.

Lonsbury-Martin, B.L., Martin, G.K. (1981). Effects of moderately intense sound on auditory sensitivity in rhesus monkeys: behavioural and neural observations. Journal of Neurophysiology 46, 563-586. https://doi.org/10.1152/jn.1981.46.3.563.

Lopez-Poveda, E.A., Barrios, P. (2013). Perception of stochastically undersampled sound waveforms: A model of auditory deafferentation. Frontiers in Neuroscience 7, 124, 13p. https://doi.org/10.3389/fnins.2013.00124.

Lopez-Poveda, E.A. (2014). Why do I hear but not understand? Stochastic undersampling as a model of degraded neural encoding of speech. Frontiers in Neuroscience 8, 348, 7p. https://doi.org/10.3389/fnins.2014.00348.

Mattys, S.L., Davis, M.H., Bradlow, A.R. (2012). Speech recognition in adverse conditions: A review. Language and Cognitive Processes 27, 953-978. http://dx.doi.org/10.1080/01690965.2012.705006.

Mayo, L.H., Florentine, M., Buus, S. (1997). Age of second-language acquisition and perception of speech in noise. Journal of Speech, Language, and Hearing Research 40, 686-693. https://doi.org/10.1044/jslhr.4003.686.

Megerson, S.C. (2010). Development of a screening tool for identifying young people at risk for noise-induced hearing loss. PhD Dissertation, University of Kansas. Ann Arbor: ProQuest, 126p. http://hdl.handle.net/1808/6931.

Mitchell, C. Phillips, D.S., Trune, D.R. (1989). Variables affecting the auditory brainstem response: Audiogram, age, gender and head size. Hearing Research 40, 75-85. https://doi.org/10.1016/0378-5955(89)90101-9.

Moore, B.C.J., Creeke, S., Glasberg, B.R., Stone, M.A., Sek, A. (2012). A version of the TEN Test for use with ER-3A insert earphones. Ear and Hearing 33, 554-557. https://doi.org/10.1097/AUD.0b013e31824b9e43.

Moore, D.R., Edmondson-Jones, M., Dawes, P., Fortnum, H., McCormack, A., Pierzycki, R.H., Munro, K.J. (2014). Relation between speech-in-noise threshold, hearing loss and cognition from 40-69 years of age. PLOS One 9, e107720, 10p. https://doi.org/10.1371/journal.pone.0107720.

Moore, D.R., Zobay, O., Mackinnon, R.C., Whitmer, W.M. Akeroyd, M.A. (2017). Lifetime leisure music exposure associated with increased frequency of tinnitus. Hearing Research 347, 18-27. https://doi.org/10.1016/j.heares.2016.10.030.

Moore, J.K., Linthicum, F.H.Jr. (2001). Myelination of the human auditory nerve: different time courses for Schwann cell and glial myelin. Annals of Otology, Rhinology, and Laryngology 110, 655-661. https://doi.org/10.1177/000348940111000711.

Niu, Y., Kumaraguru, A., Wang, R., Sun, W. (2013). Hyperexcitability of inferior colliculus neurons caused by acute noise exposure. Journal of Neuroscience Research 91, 292-299. https://doi.org/10.1002/jnr.23152.

Ohlms, L.A., Lonsbury-Martin, B.L., Martin, G.K. (1991). Acoustic-distortion products: separation of sensory from neural dysfunction in sensorineural hearing loss in human beings and rabbits. Otolaryngology – Head and Neck Surgery 104, 159-174.https://doi.org/10.1177/019459989110400203.

Popelar, J., Syka, J., Berndt, H. (1987). Effect of noise on auditory evoked responses in awake guina pigs. Hearing Research 26, 239-247. https://doi.org/10.1016/0378-5955(87)90060-8.

Prendergast, G., Guest, H., Munro, K.J., Kluk, K., Léger, A., Hall, D.A., Heinz, M.G., Plack, C.J. (2017). Effects of noise exposure on young adults with normal audiograms I: Electrophysiology. Hearing Research 344, 68-81. https://doi.org/10.1016/j.heares.2016.10.028.

Qiu, C., Salvi, R., Ding, D., Burkard, R. (2000). Inner hair cell loss leads to enhanced response amplitudes in auditory cortex of unanesthetized chinchillas: evidence for increased system gain. Hearing Research 139, 153-171. https://doi.org/10.1016/S0378-5955(99)00171-9.

Relkin, E.M., Doucet, J.R. (1991). Recovery from prior stimulation. I: Relationship to spontaneous firing rates of primary auditory neurons. Hearing Research 55, 215-222. https://doi.org/10.1016/0378-5955(91)90106-J.

Robertson, I.H., Ward, T., Ridgeway, V., Nimmo-Smith, I. (1996). The structure of normal human attention: The Test of Everyday Attention. Journal of the International Neuropsychological Society 2, 525-534. https://doi.org/10.1017/S1355617700001697.

Rönnberg, J., Rudner, M., Lunner, T., Zekveld, A.A. (2010). When cognition kicks in: Working memory and speech understanding in noise. Noise and Health 12, 263-269. https://doi.org/10.4103/1463-1741.70505.

Salvi, R.J., Saunders, S.S., Gratton, M.A., Arehole, S., Powers, N. (1990). Enhanced evoked response amplitudes in the inferior colliculus of the chinchilla following acoustic trauma. Hearing Research 50, 245-257. https://doi.org/10.1016/0378-5955(90)90049-U.

Salvi, R.J., Sun, W., Ding, D., Chen, G.-D., Lobarinas, E., Wang, J., Radziwon, K., Auerbach, B.D. (2017). Inner hair cell loss disrupts hearing and cochlear function leading to sensory deprivation and enhanced central auditory gain. Frontiers in Neuroscience 10, article 621, 14p. https://doi.org/10.3389/fnins.2016.00621.

Salvi, R.J., Wang, J, Ding, D. (2000). Auditory plasticity and hyperactivity following cochlear damage. Hearing Research 147, 261-274. https://doi.org/10.1016/S0378-5955(00)00136-2.

Saunders, J.C., Bock, G.R., James, R., Chen, C.S. (1972). Effects of priming for audiogenic seizure on auditory evoked responses in the cochlear nucleus and inferior colliculus of BALB/c mice. Experimental Neurology 37, 388-394. https://doi.org/10.1016/0014-4886(72)90082-9.

Schaette, R., McAlpine, D. (2011). Tinnitus with a normal audiogram: Physiological evidence for hidden hearing loss and computational model. Journal of Neuroscience 31, 13452-13457. https://doi.org/10.1523/JNEUROSCI.2156-11.2011.

Schmiedt, R.A., Mills, J.H., Boettcher, F.A. (1996). Age-related loss of activity of auditory-nerve fibers. Journal of Neurophysiology 76, 2799-2803. https://doi.org/10.1152/jn.1996.76.4.2799.

Schvartz, K.C., Chatterjee, M., Gordon-Salant, S. (2008). Recognition of spectrally degraded phonemes by younger, middle-aged, and older normal-hearing listeners. Journal of the Acoustical Society of America 124, 3972-3988. https://doi.org/10.1121/1.2997434.

Shi, L., Chang, Y., Li, X., Aiken, S., Liu, L., Wang, J. (2016a). Coding deficits in noise-induced hidden hearing loss may stem from incomplete repair of ribbon synapses in the cochlea. Frontiers in Neuroscience 10, 231, 6p. https://doi.org/10.3389/fnins.2016.00231.

Shi, L., Chang, Y., Li, X., Aiken, S., Liu, L., Wang, J. (2016b). Cochlear synaptopathy and noise-induced hearing loss. Neural Plasticity 2016, 6143164, 9p. http://dx.doi.org/10.1155/2016/6143164.

Song, Q., Shen, P., Li, X., Shi, L., Liu, L., Wang, J., Yu, Z., Stephen, K., Aiken, S., Yin, S, Wang, J. (2016). Coding deficits in hidden hearing loss induced by noise: the nature and impacts. Nature Scientific Reports 6, 25200, 13p. https://doi.org/10.1038/srep25200.

Stamper, G.C., Johnson, T.A. (2015a). Auditory function in normal-hearing, noise-exposed human ears. Ear and Hearing 36, 172-184. https://doi.org/10.1097/AUD.0000000000000107.

Stamper, G.C., Johnson, T.A. (2015b). Letter to the editor: Examination of potential sex influences in Stamper, G.C. & Johnson, T.A. (2015). Auditory function in normal-hearing, noise-exposed human ears, Ear and Hearing 36, 172-184. Ear and Hearing 36, 738-740. https://doi.org/10.1097/AUD.0000000000000228.

Stange-Marten, A., Nabel, A.L., Sinclair, J.L., Fischl, M., Alexandrova, O., Wohlfrom, H., Kopp-Scheinpflug, C., Pecka, M., Grothe, B. (2017). Input timing for spatial processing is precisely tuned via constant delays and myelination patterns in the auditory brainstem. Proceedings of the National Academy of Sciences (PNAS) of the United States of America 114, E4851–E4858. https://doi.org/10.1073/pnas.1702290114.

Stebbins, W.C., Hawkins Jr., J.E., Johnson, L.G., Moody, D.B. (1979). Hearing thresholds with outer and inner hair cell loss. American Journal of Otolaryngology – Head and Neck Medicine and Surgery 1, 15-27. https://doi.org/10.1016/S0196-0709(79)80004-6.

Sun, W., Deng, A., Jayaram, A., Gibson, B. (2012). Noise exposure enhances auditory cortex responses related to hyperacusis behavior. Brain Research 1485, 108-116. https://doi.org/10.1016/j.brainres.2012.02.008.

Swaminathan, J., Mason, C.R., Streeter, T.M., Best, V., Roverud, E., Kidd Jr, G. (2016). Role of binaural temporal fine structure and envelope cues in cocktail-party listening. The Journal of Neuroscience 36, 8250-8257. https://doi.org/10.1523/JNEUROSCI.4421-15.2016.

Thornton, A.R.D. (2007). Instrumentation and recording parameters. In: Burkard, R., Don, M., Eggermont, J. (Eds.), Auditory Evoked Potentials: Basic Principles and Clinical Application. Lippincott William & Wilkins, Baltimore, MD, pp. 73-101. https://www.scopus.com/record/display.uri?eid=2-s2.0-68949202642&origin=inward&txGid=e4c0afec9f08fe36b807042e05db52d8.

Trune, D.R., Mitchell, C., Phillips, D.S. (1988). The relative importance of head size, gender and age on the auditory brainstem response. Hearing Research 32, 165-174. https://doi.org/10.1016/0378-5955(88)90088-3.

Valero, M.D., Burton, J.A., Hauser, S.N., Hackett, T.A., Ramachandran, R., Liberman, M.C. (2017). Noise-induced cochlear synaptopathy in rhesus monkeys (Macaca mulatta). Hearing Research 353, 213-223. https://doi.org/10.1016/j.heares.2017.07.003.

Wan, G., Corfas, G. (2017). Transient auditory nerve demyelination as a new mechanism for hidden hearing loss. Nature Communications 8, 14487, 13p. https://doi.org/10.1038/ncomms14487.

Wang, Y., Hirose, K., Liberman, M.C. (2002). Dynamics of noise-induced cellular injury and repair in the mouse cochlea. JARO - Journal of the Association for Research in Otolaryngology 3, 248-268. https://doi.org/10.1007/s101620020028.

Wild, C.J., Yusuf, A., Wilson, D.E., Peelle, J.E., Davis, M.H., Johnsrude, I.S. (2012). Effortful Listening: The Processing of Degraded Speech Depends Critically on Attention. Journal of Neuroscience 32, 14010-14021. https://doi.org/10.1523/JNEUROSCI.1528-12.2012.

Yeend, I., Beach, E.F., Sharma, M., Dillon, H. (2017). The effects of noise exposure and musical training on suprathreshold auditory processing and speech perception in noise. Hearing Research 353, 224-236. http://dx.doi.org/10.1016/j.heares.2017.07.006.

Yin, Y., Liberman, M.D., Maison, S.F., Liberman, M.C. (2014). Olivocochlear innertaion maintains the normal modiolar-pillar and habenular-cuticular gradients in cochear synaptic morphology. JARO - Journal of the Association for Research in Otolaryngology 15, 571-583. https://doi.org/10.1007/s10162-014-0462-z.

Figure legends

- Figure 1. [A] Pure-tone audiometry threshold distributions in the test ear at the frequencies 0.25, 0.50, 1, 2, 3, 4, 6, 8, 9, 10, 11.25, and 12.5 kHz. Boxplots indicate the minimum value, the 25th percentile, the median, the 75th percentile, and the maximum value of each distribution. The limits for normal hearing and near-normal hearing are also plotted in the figure. [B] Mean (standard error in errorbars) of the DPOAE response and noise floor at different f_2 frequencies.
- Figure 2. (Color online) [A,B] Grand-average ABR signals of the group of participants with 10% lower (continuous line) and 10% higher (dashed line) LNE values for the [Fz-Tp9/Tp10] and [Fz-TIP] electrode configurations. [C,D] Raw and adjusted individual data of amplitudes and latencies of the main ABR components versus LNE. Adjusted values show the raw data after compensating for the predicted effect of gender. The slopes of the regression lines and *p*-values fitted to the adjusted data correspond, respectively, to the estimated effect size and *p*-value in the linear regression models shown in table 1.
- Figure 3. (Color online) [A] Evidence of central gain: The 50% of participants with lower A_I (filled circles) presented a similar A_V distribution compared to the 50% of participants with larger A_I (empty circles). [B] Subjects reporting tinnitus had active central gain mechanisms: the 'tinnitus' group (empty circles) had lower A_I/A_V values than the 'non-tinnitus' group (filled circles), but similar A_I and A_V values.
- Figure 4. Combined effect of A_I/A_V and L_V-L_I on the LiSN-HC score. This figure shows the LiSN-HC distributions for subjects categorized according to their waves I-V interpeak latency (shorter or longer than the median value of the distribution, i.e. 4.29 ms) and amplitude ratio ('low gain' for those with $A_I/A_V < 0.43$, i.e. the mean of the A_I/A_V median values for the 'non-tinnitus' and 'tinnitus' groups; 'high gain' otherwise). Subjects presenting longer interpeak latencies and active central gain mechanisms performed worst on the LiSN-HC test.

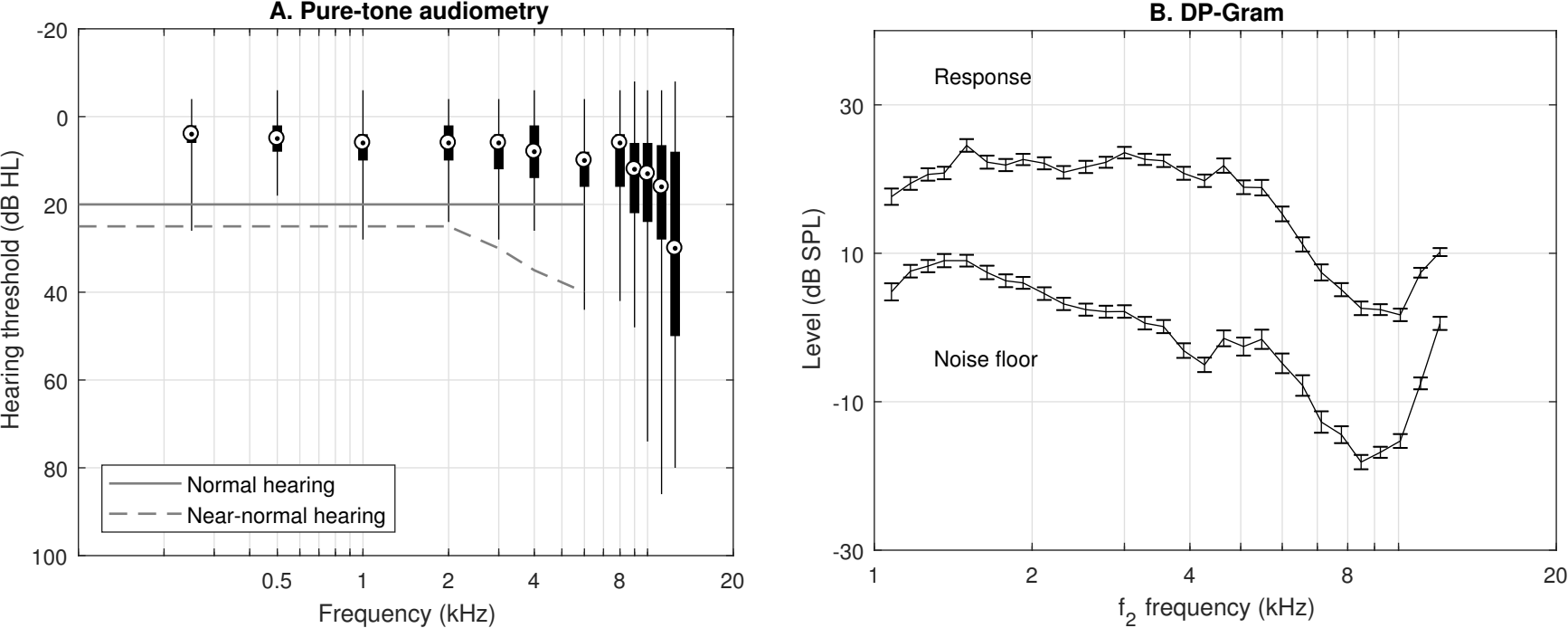
Tables

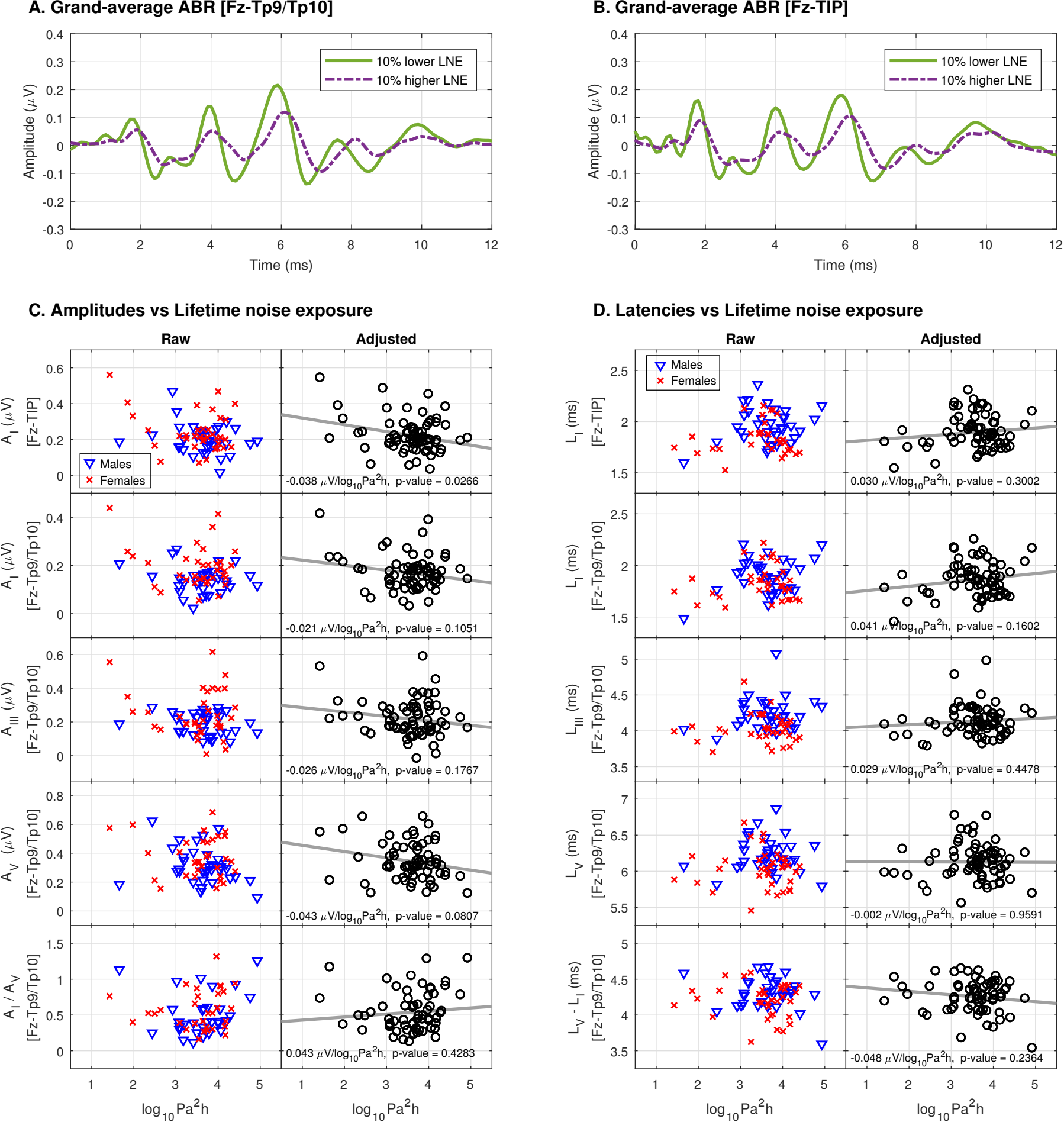
Table 1. Linear regression models for the amplitude of wave I (A_I), amplitude of wave III (A_{III}), amplitude of wave V (A_V), the amplitude ratio of waves I and V (A_I/A_V), the latency of wave I (L_I), the latency of wave III (L_{III}), the latency of wave V (L_V), and the waves I-V interpeak latency (L_V-L_I). The models show: (column 2) the mean and standard deviation (SD) in parentheses; (columns 3-5) the effect size ± 95% confidence interval [*p*-value] for the intercept and the predictor variables gender and lifetime noise exposure (LNE); (columns 6-10) the number of observations (N), the root mean squared error (RMSE), the coefficient of determination (R^2), the adjusted R^2, and the *p*-value of the model.

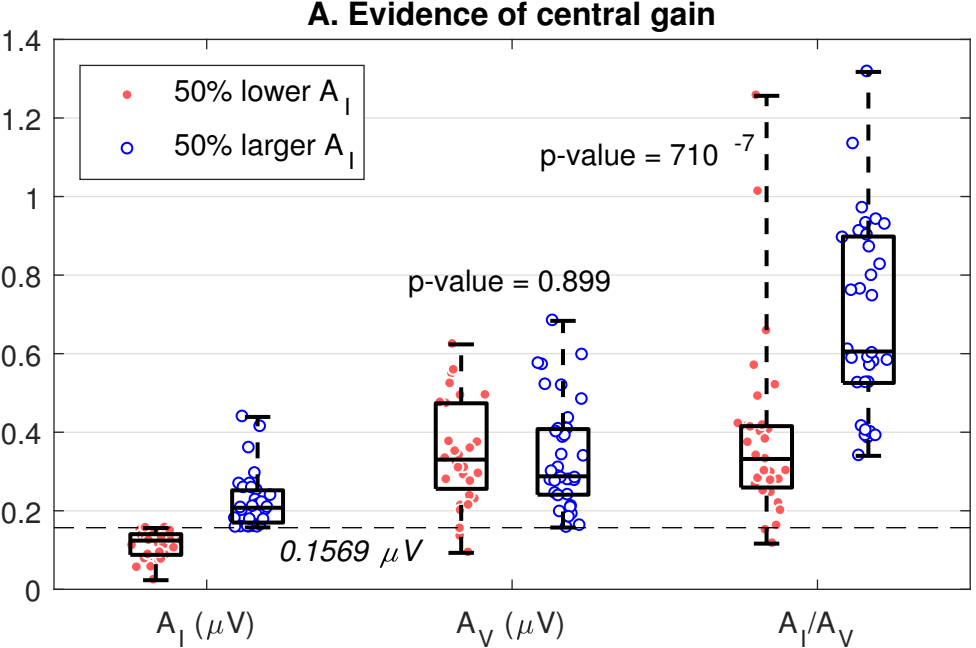
	Mean (SD)	(Intercept)	Males	LNE	N	RMSE	R^2	Adjusted R^2	*p*-value
A_I [Fz-TIP]	0.222 (0.012) µV	0.375 ± 0.121 µV [<0.0001]	-0.033 ± 0.045 µV [0.1449]	-0.038 ± 0.033 µV/$log_{10}Pa^2h$ [0.0266]	70	0.0933 µV	0.1083	0.0817	0.0215
A_I [Fz-Tp9/Tp10]	0.168 (0.009) µV	0.268 ± 0.093 µV [<0.0001]	-0.051 ± 0.035 µV [0.0049]	-0.021 ± 0.026 µV/$log_{10}Pa^2h$ [0.1051]	68	0.0714 µV	0.1574	0.1314	0.0038
A_{III} [Fz-Tp9/Tp10]	0.218 (0.013) µV	0.339 ± 0.140 µV [<0.0001]	-0.056 ± 0.052 µV [0.0354]	-0.026 ± 0.039 µV/$log_{10}Pa^2h$ [0.1767]	70	0.1077 µV	0.0957	0.0687	0.0344
A_V [Fz-Tp9/Tp10]	0.343 (0.016) µV	0.528 ± 0.177 µV [<0.0001]	-0.058 ± 0.063 µV [0.0692]	-0.043 ± 0.048 µV/$log_{10}Pa^2h$ [0.0807]	67	0.1284 µV	0.0997	0.0716	0.0347
A_I / A_V [Fz-Tp9/Tp10]	0.538 (0.035)	0.421 ± 0.391 [0.0353]	-0.069 ± 0.142 [0.3356]	0.043 ± 0.107 1/$log_{10}Pa^2h$ [0.4283]	64	0.2833	0.0236	-0.0084	0.4820
L_I [Fz-TIP]	1.894 (0.020) ms	1.730 ± 0.208 ms [<0.0001]	0.114 ± 0.077 ms [0.0044]	0.030 ± 0.057 ms/$log_{10}Pa^2h$ [0.3002]	70	0.1603 ms	0.1361	0.1103	0.0074
L_I [Fz-Tp9/Tp10]	1.862 (0.020) ms	1.683 ± 0.210 ms [<0.0001]	0.068 ± 0.079 ms [0.0898]	0.041 ± 0.058 ms/$log_{10}Pa^2h$ [0.1602]	68	0.1617 ms	0.0776	0.0492	0.0724
L_{III} [Fz-Tp9/Tp10]	4.132 (0.028) ms	3.934 ± 0.271 ms [<0.0001]	0.198 ± 0.100 ms [0.0002]	0.029 ± 0.075 ms/$log_{10}Pa^2h$ [0.4478]	70	0.2093 ms	0.2006	0.1767	0.0006
L_V [Fz-Tp9/Tp10]	6.127 (0.031) ms	6.037 ± 0.319 ms [<0.0001]	0.200 ± 0.117 ms [0.0011]	-0.002 ± 0.088 ms/$log_{10}Pa^2h$ [0.9591]	71	0.2464 ms	0.1469	0.1218	0.0045
$L_V - L_I$ [Fz-Tp9/Tp10]	4.255 (0.028) ms	4.369 ± 0.291 ms [<0.0001]	0.115 ± 0.109 ms [0.0383]	-0.048 ± 0.080 ms/$log_{10}Pa^2h$ [0.2364]	68	0.2239 ms	0.0778	0.0495	0.0718

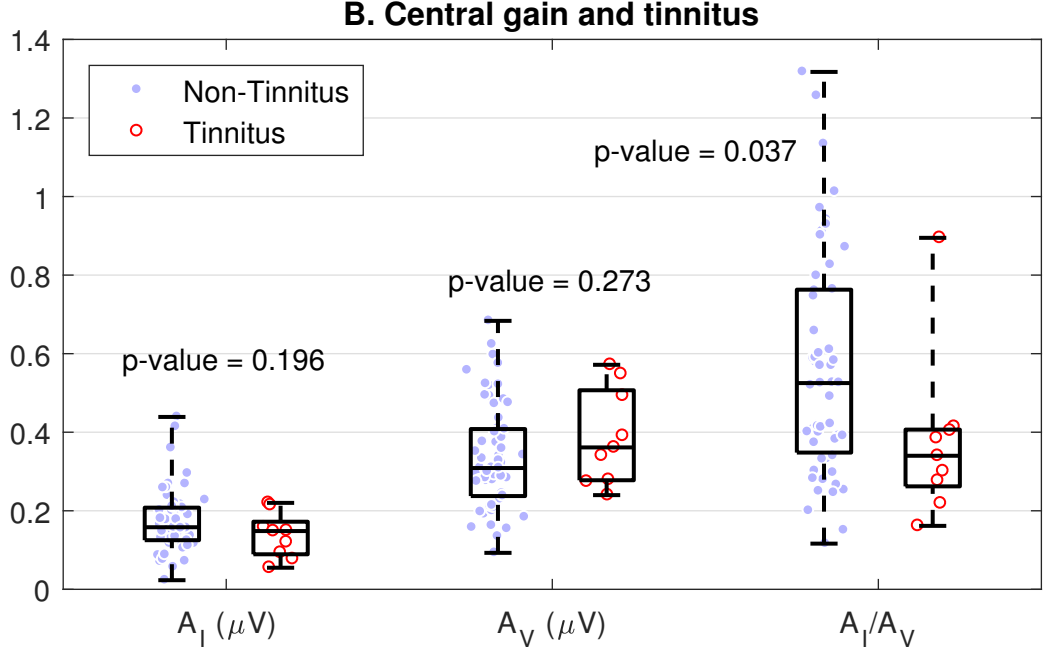
Table 2. Linear regression model for LiSN-HC test performance (in dB). The table shows (rows 2-11) the effect size ± 95% confidence interval [*p*-value] for the intercept and the predictor variables: A_I/A_V, L_V-L_I, age, lifetime noise exposure (LNE), hearing loss in low frequencies (HL-LF), in high frequencies (HL-HF), and in extended-high frequencies (HL-EHF), the score on the test of everyday attention (TEA), and the interaction between A_I/A_V and L_V-L_I (A_I/A_V:L_V-L_I); (rows 12-16) the number of observations (N), the root mean squared error (RMSE), the coefficient of determination (R^2), the adjusted R^2, and the *p*-value of the model.

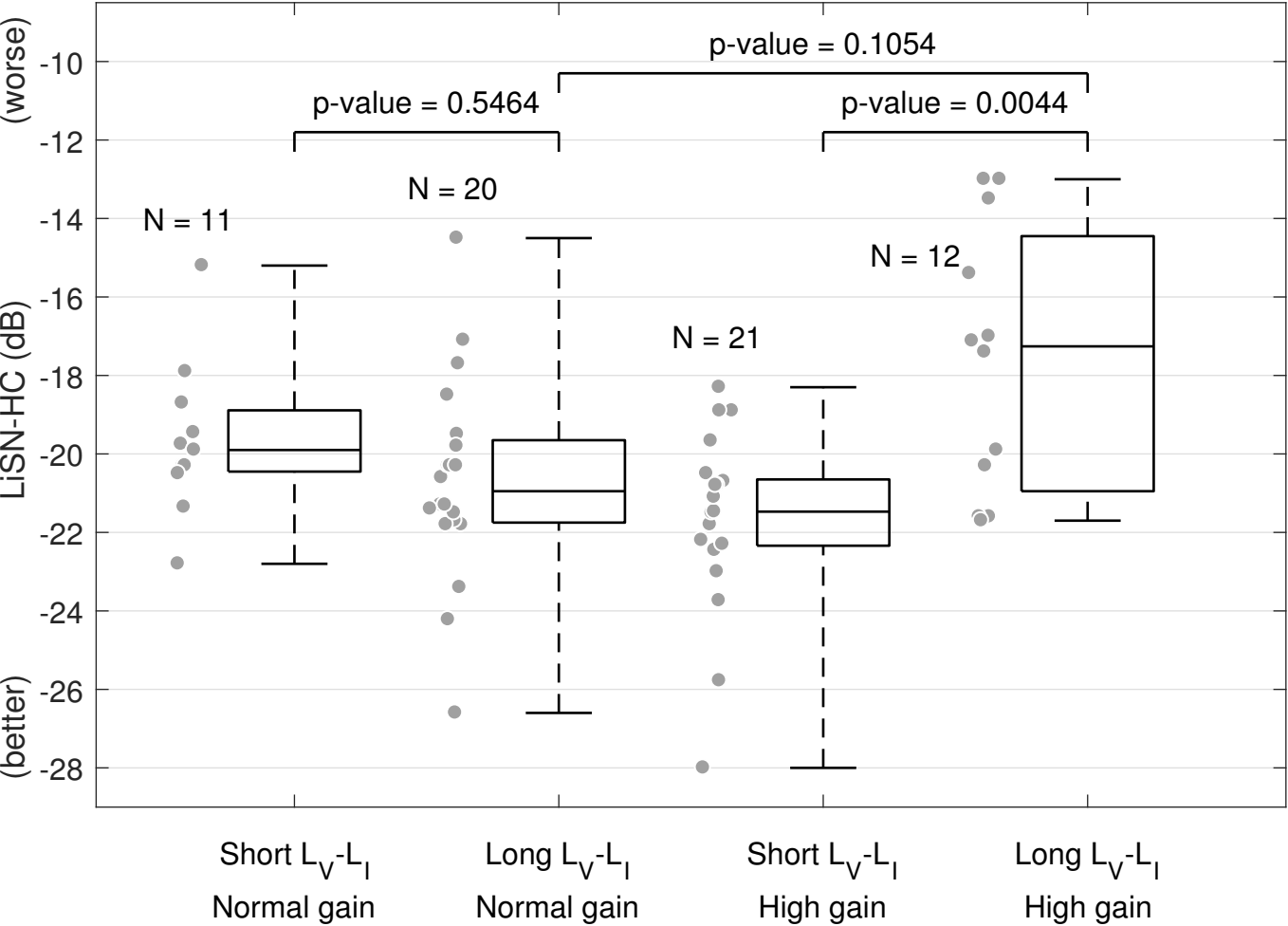
	LiSN-HC
(Intercept)	-54.701 ± 21.149 dB [<0.0001]
A_I/A_V	39.213 ± 30.992 dB [0.0141]
L_V-L_I	8.630 ± 5.192 dB/ms [0.0016]
Age	-0.010 ± 0.096 dB/year [0.8418]
LNE	-0.370 ± 0.906 dB/$\log_{10}Pa^2h$[0.4159]
HL-LF	0.231 ± 0.147 dB/dB HL [0.0027]
HL-HF	0.041 ± 0.105 dB/dB HL [0.4403]
HL-EHF	0.029 ± 0.040 dB/dB HL [0.1557]
TEA	-0.380 ± 0.284 dB [0.0098]
A_I/A_V : L_V-L_I	-9.174 ± 7.259 dB/ms [0.0142]
N	64
RMSE	2.2019
R^2	0.5011
Adjusted R^2	0.4180
***p*-value**	<0.0001


A. Pure-tone audiometry
Hearing threshold (dB HL)
-20
0
20
40
60
80
100
0.5
1
2
4
8
20
Frequency (kHz)
Normal hearing
Near-normal hearing
B. DP-Gram
Level (dB SPL)
30
10
-10
-30
Response
Noise floor
1
2
4
8
20
f2 frequency (kHz)


A. Grand-average ABR [Fz-Tp9/Tp10]
B. Grand-average ABR [Fz-TIP]
10% lower LNE
10% higher LNE
Amplitude (μV)
Time (ms)
C. Amplitudes vs Lifetime noise exposure
D. Latencies vs Lifetime noise exposure
Raw
Adjusted
Males
Females
A_I (μV) [Fz-TIP]
A_I (μV) [Fz-Tp9/Tp10]
A_III (μV) [Fz-Tp9/Tp10]
A_V (μV) [Fz-Tp9/Tp10]
A_I / A_V [Fz-Tp9/Tp10]
L_I (ms) [Fz-TIP]
L_I (ms) [Fz-Tp9/Tp10]
L_III (ms) [Fz-Tp9/Tp10]
L_V (ms) [Fz-Tp9/Tp10]
L_V - L_I (ms) [Fz-Tp9/Tp10]
-0.038 μV/log10Pa2h, p-value = 0.0266
-0.021 μV/log10Pa2h, p-value = 0.1051
-0.026 μV/log10Pa2h, p-value = 0.1767
-0.043 μV/log10Pa2h, p-value = 0.0807
0.043 μV/log10Pa2h, p-value = 0.4283
0.030 μV/log10Pa2h, p-value = 0.3002
0.041 μV/log10Pa2h, p-value = 0.1602
0.029 μV/log10Pa2h, p-value = 0.4478
-0.002 μV/log10Pa2h, p-value = 0.9591
-0.048 μV/log10Pa2h, p-value = 0.2364
log10Pa2h


A. Evidence of central gain
50% lower A_I
50% larger A_I
p-value = 710^-7
p-value = 0.899
0.1569 μV
A_I (μV)
A_V (μV)
A_I/A_V


B. Central gain and tinnitus
Non-Tinnitus
Tinnitus
p-value = 0.037
p-value = 0.273
p-value = 0.196
A_I (μV)
A_V (μV)
A_I/A_V


p-value = 0.1054
p-value = 0.5464
p-value = 0.0044
N = 11
N = 20
N = 21
N = 12
(worse)
-10
-12
-14
-16
-18
-20
-22
-24
-26
-28
(better)
LiSN-HC (dB)
Short L_V-L_I Normal gain
Long L_V-L_I Normal gain
Short L_V-L_I High gain
Long L_V-L_I High gain

[Supporting information] Effects of lifetime noise exposure on the human auditory brainstem response and speech intelligibility

Joaquin T. Valderrama[a,b,c,*], Elizabeth F. Beach[a,c], Ingrid Yeend[a,b,c], Mridula Sharma[b,c]
Bram Van Dun[a,c], Harvey Dillon[a,c]

[a] *The National Acoustic Laboratories, Australian Hearing, Sydney, Australia.*
[b] *Department of Linguistics, Macquarie University, Sydney, Australia.*
[c] *The HEARing CRC, Melbourne, Australia.*
[*] joaquin.valderrama@nal.gov.au, joaquin.valderrama@mq.edu.au

Contents

A Online survey

Below is the online survey that participants completed prior attending the laboratory test session. This survey covers questions about demographics, hearing health, lifetime noise exposure, listening ability, and musical training.

Online Early Indicators of Noise Injury Survey

Welcome to the NAL Survey on Hearing, Noise, and Music. This survey is in five parts and will take you around 20-30 minutes to complete:

1. About You
2. Your Hearing
3. Listening and Hearing
4. Your Noise Exposure
5. You and Music

Please complete all questions as accurately as you can. In the **Your Noise Exposure** section, you will be asked to estimate your participation in various activities throughout your lifetime. We understand that no-one has a perfect memory but please give your best estimate.

Be assured that your personal information and any data collected as part of the research project will be treated as strictly confidential. Any data released or referred to in scientific reports or publications will be de-identified and contain no personal information. NAL will not release your personal information either verbally or in writing to any individual or outside agency without your written consent.

ABOUT YOU

Are you
( ) Female ( ) Male ( ) Indeterminate/intersex/unspecified

How old are you?

Do you speak a language other than English?
( ) No, English only
( ) Yes, Italian
( ) Yes, Greek
( ) Yes, Cantonese
( ) Yes, Arabic
( ) Yes, Vietnamese
( ) Yes, Mandarin
( ) Yes, other (please specify):

What is the postcode of the suburb you live in?

What is the highest level of education that you have completed?
( ) Primary school
( ) Secondary school up to Year 10 (or equivalent)
( ) Secondary school up to Year 12 (or equivalent)
( ) Trade or technical qualification
( ) Undergraduate university degree
( ) Postgraduate university degree

Select the option that best describes your current job
( ) Community/personal worker
( ) Clerical/administrative worker
( ) Labourer
( ) Machinery operator/driver
( ) Manager
( ) Professional
( ) Sales worker
( ) Technician/trade worker

( ) Student
( ) Full time home duties
( ) Retired
( ) Currently not working

If you are studying and/or working, please select as many options as appropriate to describe your current arrangements. If not, please select 'Not applicable'.
( ) Working full-time
( ) Working part-time
( ) Studying full-time
( ) Studying part-time
( ) Not applicable - I am not working or studying right now

In your current or past jobs, have you been in contact with chemicals such as solvents, paints, degreasers, jet fuels, gasoline, or cleaning fluids?
( ) No
( ) I don't know
( ) Yes, please describe:

In general, would you say your health is
( ) Excellent
( ) Very good
( ) Good
( ) Fair
( ) Poor

Please indicate which of the following best describes your usual level of leisure activity in the past 12 months:
( ) Reading, watching television, or engaging in sedentary activities
( ) At least 4 hours a week walking, bicycling, or engaging in other types of physical activity
( ) At least 4 hours a week exercising to keep fit and participating in recreational athletics
( ) Regular, vigorous training or participating in competitive sports several times a week

When you have free time, do you:
( ) almost always prefer to do something with others
( ) usually prefer to do something with others
( ) sometimes like to be with others but also enjoy spending time by yourself
( ) usually prefer to spend time alone
( ) almost always prefer to spend time alone

When you were at school did you have any difficulties with reading or literacy?
( ) Yes, please describe:
( ) No

Have you participated in any research studies or other activities that involved auditory, psychoacoustic or hearing tasks?
( ) Yes, please describe:
( ) No

Is there any history of hearing loss amongst your siblings, parents or grandparents?
( ) No
( ) I don't know
( ) Yes, please describe:

Which hand do you use for writing and other hand-related activities?

( ) Left hand
( ) Right hand
( ) Both hands

YOUR HEARING

Do you, or other people, notice any problems with your hearing?
( ) Yes, please describe:
( ) No
( ) I don't know

Have you had a hearing test/s in the past and if so, what was the most recent result?
( ) Yes, normal hearing in both ears
( ) Yes, hearing loss in one ear
( ) Yes, hearing loss in both ears
( ) Yes, but I don't know the result
( ) No, I have not had a hearing test

Would you say that you are particularly sensitive to loud sounds?
( ) Yes, please describe:
( ) No

Have you ever noticed that your hearing was dull or impaired after exposure to loud sound?
( ) Yes, please describe:
( ) No

Have you ever been exposed to any sudden, very loud sound, e.g., an explosion or gunshot?
( ) Yes, please describe:
( ) No

Tinnitus is defined as any sound that a person can hear internally that is not present externally. It may be heard as a buzzing, ringing, whistling, hissing or pulsing sound. Have you ever experienced tinnitus?
( ) Never or almost never
( ) Occasionally
( ) Sometimes
( ) Frequently
( ) Always or almost always
( ) Unsure

[Note: The next three questions were displayed only if respondent reported at least occasional tinnitus in the previous question]

Where do you hear the tinnitus?
( ) Left ear only
( ) Right ear only
( ) Both ears
( ) In my head

Below are some statements relating to your tinnitus. Please read each statement and indicate whether you agree or disagree with it by selecting the appropriate option on the scale *[Note: this was shown in a table format with the six statements below]*.

---

strongly disagree /	disagree /	neither agree nor disagree /	agree /	strongly agree
1	2	3	4	5

My tinnitus makes it uncomfortable to be in a quiet room.
I can easily ignore my tinnitus when it is present.
My tinnitus makes it difficult to concentrate.
My tinnitus rarely interferes with sleep.
My tinnitus is more noticeable than usual after I've been in a noisy environment.
My tinnitus interferes with my overall enjoyment of life.

LISTENING and HEARING

[Note: These questions were taken from the SSQ12 (Gatehouse and Noble 2004)]

Now we are going to ask 12 questions about aspects of your ability and experience hearing and listening in different situations.

For each question, the scale runs from 0 through to 10. Selecting 10 means that you would be perfectly able to do or experience what is described in the question. Selecting 0 means that you would be quite unable to do or experience what is described***. [Note: the scale was 0-10 in 0.5 steps for all 12 questions]***

For example, the first question asks about having a conversation with someone while the TV is on at the same time. If you are well able to do this then select a button toward the right-hand end of the scale. If you could follow about half the conversation in this situation select a button around the mid-point, and so on.

We expect that all the questions are relevant to your everyday experience, but if a question describes a situation that does not apply to you select the "Not applicable" button. Please also explain why it does not apply in your case in the comments box.

[Note: The scale below was used for the 10 questions listed below].

Not at all Perfectly
( ) 0_____ ( ) 10 ( ) N/A
Comments:

You are talking with one other person and there is a TV on in the same room. Without turning the TV down, can you follow what the person you're talking to says?
You are listening to someone talking to you, while at the same time trying to follow the news on TV. Can you follow what both people are saying?
You are in conversation with one person in a room where there are many other people talking. Can you follow what the person you are talking to is saying?
You are in a group of about five people in a busy restaurant. You can see everyone else in the group. Can you follow the conversation?
You are with a group and the conversation switches from one person to another. Can you easily follow the conversation without missing the start of what each new speaker is saying?
You are outside. A dog barks loudly. Can you tell immediately where it is, without having to look?
Can you tell how far away a bus or a truck is, from the sound?
Can you tell from the sound whether a bus or truck is coming towards you or going away?
When you listen to music, can you make out which instruments are playing?

Do every day sounds that you can hear easily seem clear to you (not blurred)?

[Note: The scale below was used for the question listed after it].

Jumbled Not Jumbled
( ) 0_____ ( ) 10 ( ) N/A
Comments:

When you hear more than one sound at a time, do you have the impression that it seems like a single jumbled sound?

[Note: The scale below was used for the question listed after it].

Concentrate hard No need to concentrate
( ) 0_____ ( ) 10 ( ) N/A
Comments:

Do you have to concentrate very much when listening to someone or something?

YOUR NOISE EXPOSURE: LEISURE

Now we would like to find out how much noise you have been exposed to over your lifetime. We've divided this into two sections - leisure activities and workplace noise.

Leisure Activities: Each leisure activity is presented in a table with a separate row for each decade of your life. Complete all the tables by estimating how often you participated in the activity in each decade. Remember to answer for each decade of your life for all activities.

[Note: A Table, as shown below, was displayed with appropriate decades according to respondent's age, for each of the twelve questions listed after it.]

	Never	**About once or twice a year**	**About once every 2-3 months**	**About once a month**	**About once a fortnight**	**About once a week**	**More than once a week**
in your teens	( )	( )	( )	( )	( )	( )	( )
in your 20's	( )	( )	( )	( )	( )	( )	( )
in your 30's	( )	( )	( )	( )	( )	( )	( )
Etc…							

How often did you attend nightclubs or dance clubs?
How often did you attend amplified music events such as pop/rock concerts, live gigs or outdoor music festivals?
How often did you attend parties, dances or discos with amplified music?
How often did you perform in or rehearse with a band that played amplified music?
How often did you perform in or rehearse with an orchestra or concert band?
How often did you play solo (e.g., in practice or lesson) one of the following instrument types: saxophone, clarinet, flute, piccolo, drums, any brass instrument, or any amplified instrument?
How often did you listen to a personal audio device through headphones or earbuds at 80% of the full volume or higher?
How often did you attend a live professional sporting event?
How often did you attend a live motor sports event?
How often did you drive a motorcycle, motorised scooter or a noisy recreational vehicle?
How often did you go shooting?
How often did you use garden power tools, other power tools or a chainsaw?

YOUR NOISE EXPOSURE: LEISURE (HEARING PROTECTION)

Hearing Protection in Leisure Activities: Now we would like you to tell us whether you wore hearing protection (e.g., earplugs or earmuffs) and how often you wore it during the leisure activities.

Depending on your previous answers, you will see a series of tables showing all the leisure activities you have participated in with a separate row for each decade in which you participated. Complete all the tables by indicating how often you wore hearing protection for each activity/decade.

If you have **never** worn hearing protection during any leisure activities in any decade of your life, please tick the box below. Otherwise, click on the 'Next' button to start completing the tables.
[ ] I have never worn hearing protection during any leisure activities

[Note: A table, as shown below, was presented, containing appropriate decades according to respondent's age, and only for those activities/events (see list below) that the respondent had previously indicated that they had participated in].

	Select the appropriate option
in your teens	( ) No ( ) Yes, < 10% of the time ( ) Yes, <50% of the time ( ) Yes, about 50% of the time ( ) Yes, > 50% of the time ( ) Yes, > 90% of the time
in your 20's	Etc…
in your 30's	Etc…

Did you wear hearing protection at nightclubs or dance clubs?
Did you wear hearing protection at amplified music events such as pop/rock concerts, live gigs or outdoor music festivals?
Did you wear hearing protection at parties, dances or discos with amplified music?
Did you wear hearing protection when you performed in or rehearsed with a band that played amplified music?
Did you wear hearing protection when you performed in or rehearsed with an orchestra or concert band?
Did you wear hearing protection when you played solo on saxophone, clarinet, flute, piccolo, drums, any brass instrument, or any amplified instrument?
Did you wear hearing protection at a live professional sporting event?
Did you wear hearing protection at a live motor sports event?
Did you wear hearing protection when you drove a motorcycle, motorised scooter or a noisy recreational vehicle?
Did you wear hearing protection when you went shooting?
Did you wear hearing protection when you used garden power tools, other power tools or a chainsaw?

YOUR NOISE EXPOSURE: WORK

Workplace noise: Now we'd like to find out more about any noisy environments that you work in or have previously worked in where the noise level was loud enough that you had to raise your voice to be heard.

When thinking about the noisy work environments you have been in, it's important to consider the level of noise you worked in rather than the type or place of work. For example, if you worked in a noisy pub for three years and your job changed from glass collector to bar tender but the noise level remained the same, make this a single work environment.

For each work environment there are five short questions to answer. When you have completed all questions for your first work environment, click on the button labelled "Add next work environment" to answer the questions again for your next work environment (if you have one).

[Note: The respondent was able to enter details for as many work environments as needed].

If you have never worked in a noisy work environment, please tick the box below. Otherwise, click on the 'Next' button to start entering your first noisy work environment.
[ ] I have never worked in a noisy environment

Please answer the 5 questions below for **each work environment** in which you were exposed to loud noise. Remember: loud noise = **noise loud enough that you had to raise your voice to be heard**.

Click on "Add next work environment" to answer the questions again for your next work environment (if you have one).

Describe the work environment: _____

Estimate how many hours you work / worked in this environment each week
( ) 1 hour – 50+ hours [*Note: a full set of options was provided but is not listed here]*

What proportion of time is / was the noise level so loud that you had to raise your voice to be heard?
( ) about 10% of the time
( ) about 20% of the time
( ) about 30% of the time
( ) about 40% of the time

( ) about 50% of the time
( ) about 60% of the time
( ) about 70% of the time
( ) about 80% of the time
( ) about 90% of the time
( ) 100% of the time

How many years have you spent / did you spend in that work environment? *[Note: a full set of options was provided but is not listed here]*.
( ) < 1 year - 50 years

Do / did you wear hearing protection in this work environment?
( ) No
( ) Yes, < 10% of the time
( ) Yes, < 50% of the time
( ) Yes, around 50% of the time
( ) Yes, > 50% of the time
( ) Yes, > 90% of the time

YOU and MUSIC
[*Note: These questions were taken from the Music Use Questionnaire (MUSE) (Chin and Rickard, 2012)]*

We will now ask you to tell us about your experiences with music. Read each question carefully and select the option that describes you best.

On average, how often do you listen to music in a week?
( ) Less than once a week
( ) 1 - 2 times a week
( ) 3 - 4 times a week
( ) 5 - 6 times a week
( ) More than 6 times a week

On average, how many hours a day do you purposely listen to music (as opposed to music in the environment that you have no control over e.g., music in cafes, stores)
( ) Less than 1 hour per day
( ) 1 - 2 hours per day
( ) 3 - 4 hours per day
( ) 5 - 6 hours per day
( ) More than 6 hours per day

Have you played / do you play a musical instrument (includes singing, practice and performance)?
( ) No ( ) Yes

How many years have you played a musical instrument for? *[Note: a full set of options was provided but is not listed here]*.
( ) < 1 year – 60 years

At the peak of your interest, how many hours per day did you play/practise the musical instrument (includes singing)? *[Note: a full set of options was provided but is not listed here]*.
( ) 0.5 hours – 18 hours

How long since you last regularly played a musical instrument (includes singing, practice and performance)?

( ) Less than a week ago
( ) Less than a month ago
( ) Less than 1 year ago
( ) Between 1 and 5 years ago
( ) Between 5 and 10 years ago
( ) More than 10 years ago

What is the highest level of formal music training you have received?
( ) None
( ) Primary (Elementary) school music classes
( ) Secondary (High) school music lessons
( ) Tertiary (University) undergraduate training, Conservatory of music or master classes
( ) Postgraduate training, or advanced overseas training

What other type of music training did you receive?
( ) None
( ) Self-taught (no formal training)
( ) Private (individual) music classes/tuition
( ) Group music classes/tuition

Have you completed AMEB (or equivalent such as ABRSM) music examinations?
( ) No
( ) Yes, the highest grade (Theory or Performance/Practical) I have completed is Grade 1
( ) Yes, the highest grade (Theory or Performance/Practical) I have completed is Grade 2
( ) Yes, the highest grade (Theory or Performance/Practical) I have completed is Grade 3
( ) Yes, the highest grade (Theory or Performance/Practical) I have completed is Grade 4
( ) Yes, the highest grade (Theory or Performance/Practical) I have completed is Grade 5
( ) Yes, the highest grade (Theory or Performance/Practical) I have completed is Grade 6
( ) Yes, the highest grade (Theory or Performance/Practical) I have completed is Grade 7
( ) Yes, the highest grade (Theory or Performance/Practical) I have completed is Grade 8
( ) Yes, the highest level I have completed is Associate and/or Licentiate Diploma in Music

Participation with music activities

[Note: The scale shown below was displayed, for each of the 24 statements listed below. A "Not Applicable" option was also available to respondents].

strongly disagree / 1	disagree / 2	neither agree nor disagree / 3	agree / 4	strongly agree 5

Music is often a source of inspiration for me
I often play challenging pieces
There is a greater connection with my friends when we like the same music
Music provides me with a good pace for exercising
Music often takes away tension at the end of the day
Performing music is emotionally rewarding for me
I often listen to new compositions
I often look forward to attending music practices with my friends
Certain types of music help me think
Mastering a piece of music gives me greater recognition as a performer
Having a similar taste in music often helps me relate better to my peers
Dance is an expression of my feelings

I often listen to music when I am feeling down
I often get recognition from my friends for playing in a group
I am able to make more friends when we like the same type of music
Listening to music whilst exercising often helps me exercise for longer
Specific types of music make me feel better
Being able to improvise whilst playing music gives me a great sense of satisfaction
Dancing keeps me fit
I feel good when my performance is applauded
Practice helps me improve my music playing skills
I use a particular type of music to get me through tough times
Music performance demonstrates my knowledge of music theory
Music improves my physical endurance level

Thank You

Congratulations! You have reached the end of our survey. We appreciate the time you have taken to complete the questions and we will now review your responses. If necessary we will seek clarification and/or additional information when you attend your appointment at our research laboratory.

Appointment questions *(Note: the questions below were administered verbally by the audiologist at the beginning of the laboratory session; the participant was given a laminated copy to follow)*

Do you have or have you a history of:

- ☐ Vertigo or balance problems?
- ☐ Otalgia (ear pain)?
- ☐ Ear surgery?
- ☐ Ear infections?

Have you had an ear infection/s in the past 3 months?

- ☐ Yes
- ☐ No

To the best of your knowledge have you ever taken the following medications?

- ☐ Aspirin in high doses
- ☐ Non-steroidal anti-inflammatory drugs eg., ibuprofen
- ☐ Antibiotics – especially aminoglycosides eg., gentamicin
- ☐ Loop diuretics
- ☐ Anti-cancer drugs eg., cyclophosphamide, cisplatin
- ☐ None of the above
- ☐ None of the above but I have taken other medication that affected my hearing
- ☐ I don't know

Have you been diagnosed with diabetes (*females not gestational)?*

- ☐ Yes
- ☐ No

Do you currently smoke tobacco on a daily basis, less than daily or not at all?

- ☐ Yes, daily
- ☐ Yes, less than daily
- ☐ No, not at all

In the past have you smoked tobacco on a daily basis, less than daily or not at all?

- ☐ Yes, daily
- ☐ Yes, less than daily
- ☐ No, not at all

Have you been exposed to loud noise in past 48 hours?

- ☐ Yes
- ☐ No

Note details:

B Raw data

Table 1 shows the raw data collected in the set of 74 participants. This table shows the amplitudes (μV) and latencies (ms) of waves I and V, and the waves I-V interpeak latency and ratio of amplitudes. These parameters have been estimated on the [Fz-Tp9/Tp10] ABR signals. The amplitude and latency of wave I has also been estimated on the Fz-TIP ABR signal (indicated as TIP on the table). This table also shows the age (years) and gender of each participant, as well as the lifetime noise-exposure (LNE, $\log_{10} Pa^2h$), the hearing loss (dB HL) in high frequencies (HL-HF) and in extended-high frequencies (HL-EHF), the score in the test of everyday attention (TEA) and in the LiSN-HC test (dB SNR), and the presence of tinnitus. Table 2 shows the rationale for missing data in electrophysiology measures.

ID	A_I (TIP)	A_I	A_{III}	A_V	A_I/A_V	L_I (TIP)	L_I	L_{III}	L_V	$L_V - L_I$	AGE	GENDER	LNE	HL-LF	HL-HF	HL-EHF	TEA	LiSN-HC	Tinnitus
#S01	0.47	0.25	0.26	0.44	0.58	1.95	1.93	4.08	6.06	4.13	39	Male	2.92	4.50	10.67	16.50	8.0	-19.75	No
#S02	0.13	0.07	0.08	0.21	0.33	1.90	1.89	4.16	6.21	4.32	36	Male	3.64	11.50	7.33	9.33	10.0	-21.60	No
#S03	0.19	0.12	0.14	0.09	1.26	2.16	2.20	4.34	5.79	3.59	52	Male	4.93	10.50	12.00	47.50	7.0	-18.70	No
#S04	0.19	0.17	0.22	0.28	0.61	1.78	1.70	4.00	6.04	4.34	48	Male	3.75	4.50	10.67	31.50	9.5	-20.60	No
#S05	0.36	0.27	0.22	0.28	0.97	1.90	1.95	4.14	6.08	4.14	37	Male	3.02	1.50	8.00	-0.50	9.5	-21.35	No
#S06	0.22	0.13	0.09	0.32	0.41	1.87	1.79	3.97	5.91	4.11	51	Male	3.85	4.00	16.00	26.00	6.5	-18.90	No
#S07	0.31	0.15	0.04	0.36	0.41	1.73	1.67	4.14	5.86	4.19	36	Female	4.18	4.50	6.00	15.50	10.0	-22.20	Yes
#S08	0.20	0.12	0.48	0.55	0.22	1.73	1.86	3.78	5.73	3.87	38	Female	4.17	3.00	1.33	5.00	10.0	-28.00	Yes
#S09	0.39	0.29	0.12	0.34	0.87	1.90	1.86	4.23	6.03	4.17	36	Female	3.50	16.00	5.33	25.00	6.0	-15.20	No
#S10	0.19	-	-	-	-	2.12	-	-	-	-	51	Male	3.82	2.00	6.00	29.00	10.0	-21.00	Yes
#S11	0.22	0.12	0.23	0.49	0.25	2.03	1.98	4.43	6.17	4.19	37	Male	3.50	7.00	6.00	-0.50	9.5	-21.80	No
#S12	0.14	0.06	0.14	0.37	0.15	2.21	2.03	4.19	6.50	4.47	50	Male	3.18	7.00	8.67	43.00	6.5	-17.40	No
#S13	0.23	0.15	0.40	0.49	0.30	2.08	2.05	4.20	6.24	4.19	44	Female	3.87	1.50	10.67	23.50	10.0	-22.20	No
#S14	0.27	0.22	0.26	0.57	0.39	2.05	2.06	4.34	6.34	4.28	47	Male	4.01	7.00	19.33	55.00	6.0	-21.10	Yes
#S15	0.26	-	-	-	-	1.94	-	-	-	-	52	Male	3.97	2.50	8.67	26.50	10.0	-17.70	No
#S16	0.25	0.16	0.17	0.28	0.57	1.70	1.72	4.00	6.11	4.39	50	Male	3.63	13.00	18.67	8.50	8.0	-17.10	No
#S17	0.16	0.12	0.15	0.29	0.40	2.21	2.21	4.38	6.38	4.17	52	Male	3.07	2.00	10.00	19.00	3.0	-22.45	No
#S18	0.09	0.12	0.01	0.38	0.33	2.11	2.08	4.40	6.07	3.99	43	Female	3.72	10.00	8.67	23.50	9.0	-25.78	No
#S19	0.21	0.14	0.14	-	-	1.99	1.91	4.04	6.22	4.30	52	Female	3.58	8.00	4.67	23.50	4.0	-16.60	No
#S20	0.15	-	-	-	-	1.79	-	-	-	-	46	Female	3.93	0.00	23.33	48.50	8.5	-18.60	Yes
#S21	0.25	0.14	0.26	0.13	1.01	1.84	1.88	4.40	6.47	4.59	51	Male	3.59	7.50	20.00	39.50	5.0	-14.50	No
#S22	0.27	0.16	0.25	0.41	0.39	1.98	1.97	4.04	6.10	4.14	51	Male	3.41	1.00	15.33	22.00	7.0	-18.90	No
#S23	0.16	0.20	0.22	0.34	0.59	1.68	1.68	3.87	5.99	4.31	44	Female	4.31	4.00	12.00	5.00	9.5	-21.30	No
#S24	0.15	0.16	0.08	0.19	0.83	1.72	1.67	4.07	6.08	4.41	38	Female	4.13	6.00	0.00	0.50	5.5	-21.80	No
#S25	0.20	0.15	0.31	0.56	0.27	1.88	1.83	4.02	5.95	4.12	33	Female	3.66	7.00	-0.67	4.50	9.0	-21.50	No
#S26	0.11	0.11	0.08	0.23	0.49	1.84	1.76	4.04	6.17	4.41	45	Male	4.28	4.50	5.33	21.50	5.5	-20.30	No
#S27	0.20	0.14	0.19	0.47	0.30	1.77	1.83	3.95	5.46	3.62	44	Female	3.25	6.50	6.00	16.50	1.0	-19.67	No
#S28	0.22	0.16	0.19	0.24	0.66	1.89	1.86	4.23	6.15	4.30	43	Female	3.45	-2.00	1.33	7.50	9.5	-26.60	No
#S29	0.33	0.24	0.26	0.60	0.40	1.69	1.61	3.85	5.84	4.23	44	Female	1.97	5.00	5.33	9.50	7.0	-20.70	No
#S30	0.25	0.20	0.27	0.39	0.53	2.11	2.11	3.98	6.12	4.01	29	Female	3.77	1.50	2.67	48.00	9.5	-17.90	No
#S31	0.18	0.14	0.27	0.33	0.42	1.79	1.78	4.02	6.14	4.35	40	Male	4.20	4.00	4.67	-4.00	10.0	-19.90	No
#S32	0.09	0.09	0.14	0.31	0.28	2.11	1.94	4.50	6.54	4.60	52	Male	4.07	12.50	10.67	23.00	6.0	-13.50	No
#S33	0.07	0.06	0.18	0.34	0.16	2.16	2.22	4.23	6.52	4.30	50	Female	3.55	14.50	24.67	28.00	7.0	-17.12	Yes
#S34	0.02	0.17	0.23	0.28	0.58	2.04	1.76	4.21	6.10	4.34	46	Male	4.04	11.50	8.67	22.50	9.0	-21.70	No
#S35	0.19	0.20	0.21	0.48	0.41	1.88	1.81	4.04	5.97	4.16	45	Female	3.64	5.00	7.33	21.50	5.5	-21.47	No
#S36	0.56	0.44	0.56	0.57	0.76	1.74	1.75	3.99	5.88	4.13	50	Female	1.43	2.00	0.00	18.00	10.0	-20.30	No
#S37	0.18	0.07	0.20	-	-	1.83	1.94	3.76	5.71	3.77	33	Female	4.01	0.50	0.00	-2.50	8.0	-20.50	No
#S38	0.16	0.13	0.20	0.33	0.38	1.88	1.76	3.92	5.94	4.18	52	Female	3.45	3.50	13.33	27.00	10.0	-20.50	No
#S39	0.21	0.13	0.20	0.35	0.37	2.10	2.10	4.50	6.54	4.45	52	Male	3.19	9.00	9.33	26.00	9.0	-21.60	No
#S40	0.16	0.16	0.23	0.39	0.40	1.76	1.72	4.15	5.98	4.26	33	Male	3.74	7.00	12.00	22.67	8.5	-20.80	Yes
#S41	0.21	0.13	0.38	0.47	0.28	1.73	1.61	3.72	5.82	4.21	41	Female	3.74	5.50	6.00	6.50	8.5	-23.74	No
#S42	0.22	0.16	0.23	0.41	0.39	2.13	2.13	4.69	6.68	4.54	51	Female	3.09	12.00	19.33	55.50	10.0	-17.00	No
#S43	0.12	0.08	0.26	0.28	0.28	1.99	1.85	4.21	6.38	4.54	37	Male	3.72	13.50	14.67	8.00	6.0	-13.00	Yes
#S44	0.11	0.02	0.13	0.20	0.12	2.36	2.01	4.24	6.67	4.67	48	Male	3.41	10.50	5.33	48.00	9.0	-13.00	No
#S45	0.18	0.15	0.29	0.36	0.41	1.93	1.91	4.19	6.17	4.26	37	Male	4.00	7.00	8.67	-1.33	10.0	-21.10	No

ID	A_I (TIP)	A_I	A_{III}	A_V	A_I/A_V	L_I (TIP)	L_I	L_{III}	L_V	$L_V - L_I$	AGE	GENDER	LNE	HL-LF	HL-HF	HL-EHF	TEA	LiSN-HC	Tinnitus
#S46	0.30	0.12	0.13	0.29	0.42	1.96	2.04	4.11	6.35	4.31	47	Male	4.20	6.00	10.00	49.00	8.5	-21.70	No
#S47	0.24	0.16	0.15	0.28	0.59	1.73	1.62	4.29	6.29	4.68	49	Male	3.66	-2.50	3.33	7.50	7.0	-21.80	No
#S48	-	-	-	0.16	-	-	-	-	6.19	-	45	Male	3.61	0.00	6.00	19.00	8.0	-22.60	No
#S49	-	-	0.14	0.31	-	-	-	3.93	6.04	-	55	Female	3.61	9.00	24.67	47.00	7.0	-15.20	No
#S50	-	-	0.12	0.29	-	-	-	5.08	6.87	-	46	Male	3.85	5.00	12.00	19.50	9.5	-15.20	No
#S51	0.47	0.41	0.39	0.52	0.80	1.82	1.80	3.98	6.05	4.25	42	Female	4.00	2.50	0.00	1.50	6.0	-20.30	No
#S52	0.25	0.22	0.09	0.28	0.76	2.07	2.08	4.24	6.42	4.35	45	Female	3.52	5.50	7.33	5.50	9.5	-21.40	No
#S53	0.26	0.27	0.40	-	-	1.77	1.77	3.80	5.71	3.94	48	Female	3.64	11.00	15.33	5.50	10.0	-24.10	No
#S54	0.40	0.26	0.29	0.27	0.94	1.70	1.66	3.90	6.07	4.41	49	Female	4.40	7.50	7.33	5.50	9.0	-19.50	No
#S55	0.18	0.16	0.20	0.21	0.75	2.02	2.07	4.41	6.36	4.29	40	Male	4.76	4.50	11.33	9.50	9.0	-19.90	No
#S56	0.27	0.15	0.24	0.49	0.30	1.85	1.83	4.30	6.14	4.30	37	Male	3.08	5.00	-1.33	22.67	8.0	-15.40	Yes
#S57	0.17	0.08	0.11	0.31	0.25	1.91	1.87	4.28	6.32	4.44	52	Male	3.79	1.50	12.67	27.50	7.0	-20.30	No
#S58	0.32	0.19	0.17	0.21	0.91	1.79	1.76	4.10	6.18	4.42	47	Female	4.05	5.50	5.33	71.50	9.0	-20.30	No
#S59	0.20	0.10	0.27	0.52	0.20	2.18	2.13	4.40	6.26	4.12	41	Male	3.64	4.50	15.33	14.00	8.0	-22.30	No
#S60	0.22	0.23	0.19	0.24	0.93	1.88	1.89	4.24	6.48	4.59	43	Female	3.24	2.50	4.00	24.00	9.0	-24.22	No
#S61	0.16	0.09	0.14	0.27	0.34	2.06	2.02	4.41	6.30	4.27	54	Male	3.09	10.50	8.67	40.00	7.0	-18.30	Yes
#S62	-	0.18	0.40	0.52	0.34	-	1.77	3.94	5.74	3.97	42	Female	4.16	5.00	1.33	6.50	9.0	-20.80	No
#S63	0.21	0.21	0.18	0.16	1.32	1.80	1.80	4.09	6.17	4.37	52	Female	3.96	3.50	14.67	23.00	10.0	-20.30	No
#S64	0.21	0.21	0.18	0.24	0.89	1.69	1.77	4.03	6.12	4.36	35	Female	4.05	9.00	28.67	52.00	9.5	-18.50	Yes
#S65	0.26	0.22	0.15	0.24	0.93	1.91	1.97	4.20	5.99	4.02	38	Male	4.41	7.50	23.33	33.33	9.5	-20.50	No
#S66	0.15	0.18	0.24	0.30	0.60	1.64	1.65	4.14	6.05	4.40	45	Female	3.98	19.00	18.67	32.00	6.5	-17.70	No
#S67	0.37	0.36	0.62	0.68	0.53	1.82	1.87	3.97	5.66	3.79	40	Female	3.87	8.00	16.67	22.00	10.0	-19.45	No
#S68	0.17	0.18	0.09	0.20	0.90	1.77	1.73	4.13	6.21	4.48	34	Male	3.86	13.50	6.00	-0.67	8.5	-21.50	No
#S69	0.22	0.16	0.29	0.62	0.25	1.80	1.77	3.89	5.82	4.05	32	Male	2.44	4.50	10.67	10.00	7.5	-23.00	No
#S70	0.19	0.21	0.19	0.18	1.13	1.60	1.49	4.02	6.07	4.58	39	Male	1.66	5.50	2.00	1.50	10.0	-21.30	No
#S71	0.08	0.09	0.16	0.15	0.56	1.53	1.59	3.98	6.14	4.55	34	Female	2.64	4.00	8.67	10.00	9.0	-23.40	No
#S72	0.17	0.11	0.17	0.21	0.52	1.73	1.69	4.02	6.03	4.34	32	Female	2.50	1.00	3.33	3.50	2.5	-19.80	No
#S73	0.25	0.21	0.26	0.40	0.53	1.74	1.73	3.70	5.71	4.97	30	Female	2.34	-1.50	0.67	5.00	4.5	-22.80	No
#S74	0.41	0.26	0.35	-	-	1.85	1.87	4.06	6.21	4.34	30	Female	1.85	1.50	5.33	13.50	10.0	-22.20	No

Table 1: Raw data.

ID	Missing data
#S10	All components in Fz-MAS ABR signal contaminated by post-auricular muscle (PAM) artifact.
#S15	All components in Fz-MAS ABR signal contaminated by PAM.
#S19	Wave V amplitude in Fz-MAS contaminated by PAM.
#S20	No clear components in Fz-MAS.
#S37	Wave V amplitude in Fz-MAS contaminated by PAM.
#S48	Waves I and III not clear in any channel.
#S49	Wave I not clear in any channel.
#S50	Wave I not clear in any channel.
#S53	Wave V amplitude in Fz-MAS contaminated by PAM.
#S62	Fz-TIP channel could not be recorded due to a technical problem.
#S74	Wave V amplitude in Fz-MAS contaminated by PAM.

Table 2: Missing data rationale in electrophysiology measures.

C Noise-level in ABR signals

This section presents an analysis of the electrophysiology noise of the ABR signals obtained in this study in order to control for the amount of uncertainty in the ABR measures. This analysis consists of (1) a comparison of the root-mean-square (RMS) values between the ABRs and their pre-response baseline; and (2) an analysis of automatic response detection based on Fsp.

Methods. The time ranges for the ABR signal and for the pre-response baseline were determined considering the grand-average ABR response across all participants, which is shown in figure 1. The ABR signal range was considered between [1 , 8] ms, and the pre-response baseline range between [-5 , -2] ms to avoid any contribution from the stimulus artifact. The Fsp value was calculated for each ABR signal as specified in Elberling and Don [2007] considering the variance of the averaged ABR in the specified time range, i.e. [1 , 8] ms, and the variance of a single point (corresponding to the sample at 4 ms) across all accepted sweeps. Since all distributions were not normally distributed (according to the Lilliefors test), they were compared using the non-parametric, paired, two-sided Wilcoxon rank sum test.

Analysis. Figure 2.A shows the RMS-value distributions of the ABR and pre-response baseline corresponding to the [Fz-Tp9/Tp10] and [Fz-TIP] ABR responses. Boxplots indicate the quartiles of the distributions. This figure shows that (1) the RMS level in the pre-response baseline is within a normal range [Elberling and Don, 1996]; (2) the RMS level in the pre-response baseline is significantly lower than in the ABR section both in [Fz-Tp9/Tp10] and [Fz-TIP] channels; and (3) the [Fz-TIP] channel present statistically significant lower RMS values than the [Fz-Tp9/Tp10] channel. The Fsp distributions are shown in figure 2.B. Considering that a Fsp-value equal to 3.1 determines the presence of neural response with a 99% confidence level [Elberling and Don, 1984], the Fsp distributions shown in figure 2.B indicate that it is highly probable that the ABR signals evaluated in this study are actual neural responses and not noise. All subjects had Fsp-values above the 3.1 threshold in the [Fz-TIP] channel, and only three subjects had Fsp values below that threshold in the [Fz-Tp9/Tp10] channel. These subjects were #S03 (Fsp=2.73), #S34 (Fsp=1.68), and #S48 (Fsp=1.41).

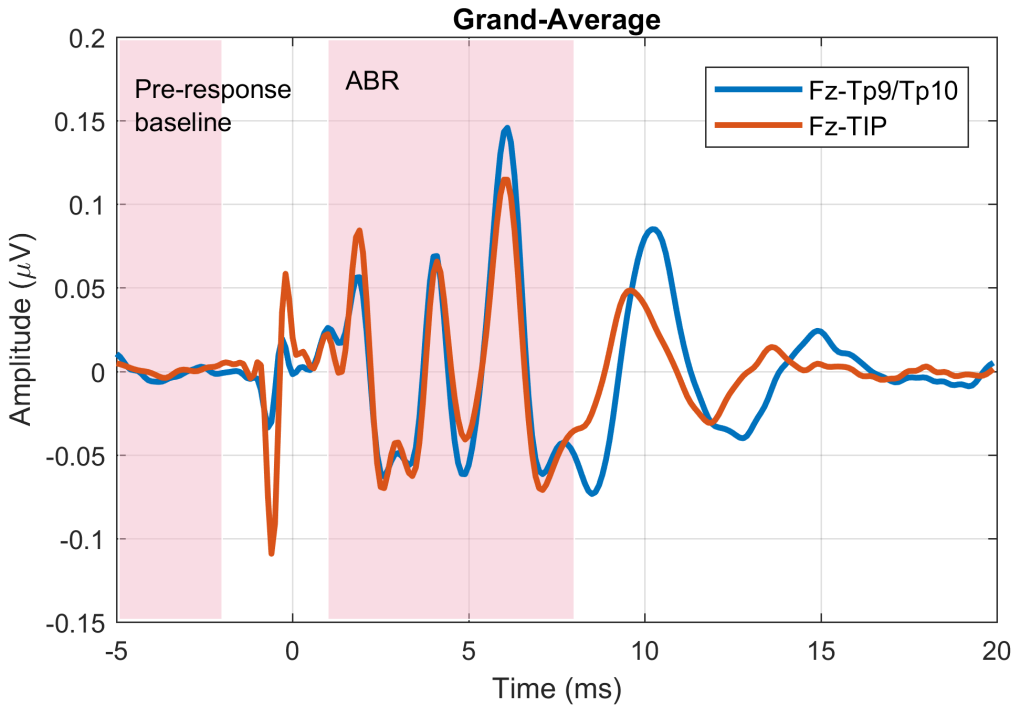


Figure 1: Time ranges considered in the analysis of the RMS value.

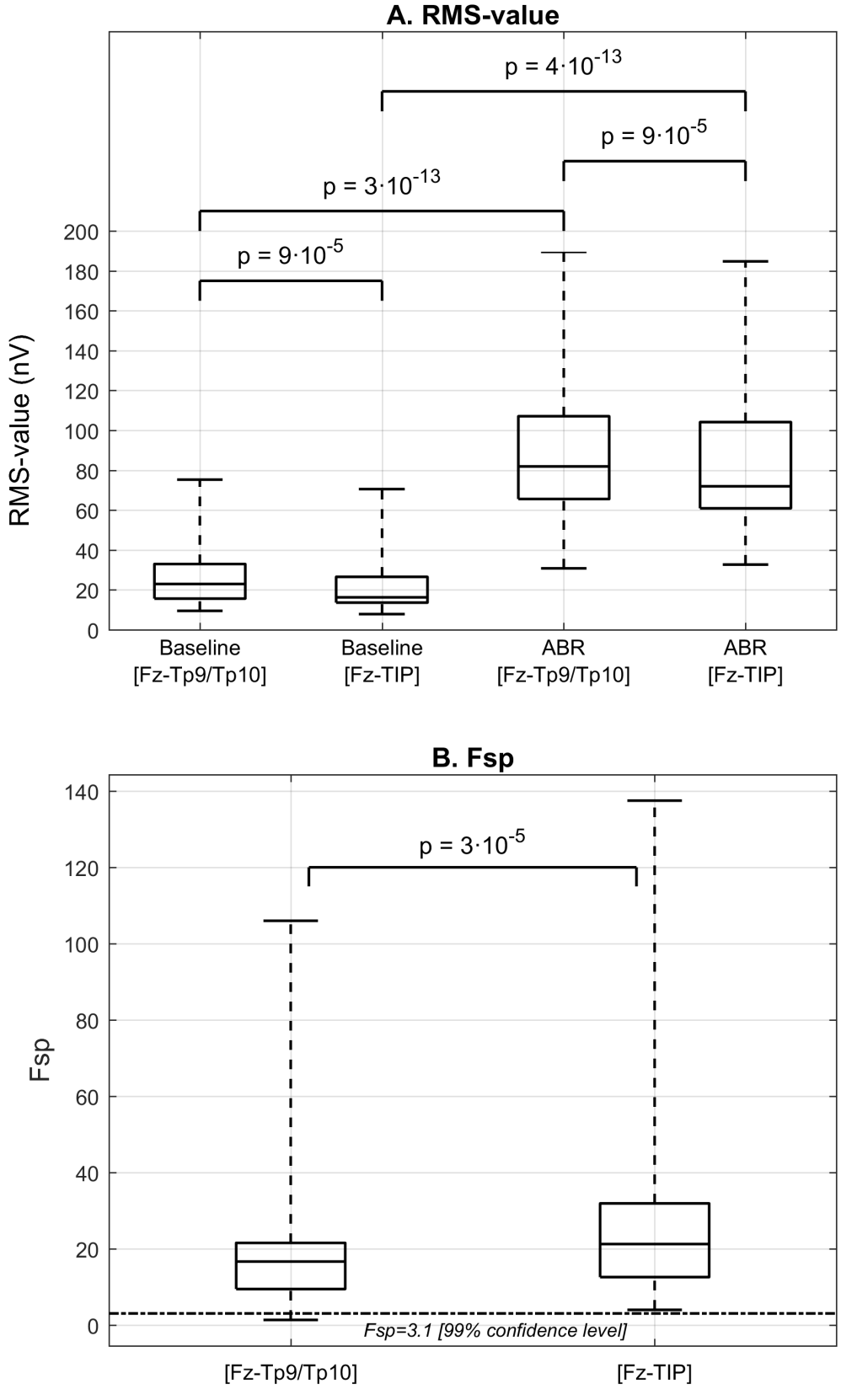


Figure 2: [A] RMS-value analysis. [B] Fsp analysis.

References

Elberling C, Don M (2007). Detecting and assessing synchronous neural activity in the temporal domain (SNR, response detection), in Auditory Evoked Potentials. Basic Principles and Clinical Application, Lippincott Williams & Wilkins, Baltimore, MD, (Chapter 5).

Elberling C, Don M (1984). Quality estimation of averaged auditory brainstem responses. Scand Audiol **13**, 187-197.

Elberling C, Don M (1996). Use of quantitative measures of auditory brain-stem response peak amplitude and residual background noise in the decision to stop averaging. J Acoust Soc Am **99**, 491-499.