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

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## **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  $\leq 20$  dB hearing level (HL) at 0.25 – 6 kHz; and near-normal thresholds were considered as  $\leq 25$  dB HL up to 2 kHz,  $\leq 30$  dB HL at 3 kHz,  $\leq 35$  dB HL at 4 kHz, and  $\leq 40$  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  $\log_{10}\text{Pa}^2\text{h}$ , subjects #S69 to #S74 were recruited with the additional inclusion criteria of having a LNE lower than 3  $\log_{10}\text{Pa}^2\text{h}$  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  $\mu$ s 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 k $\Omega$  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<sup>th</sup> 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  $\pm 90^\circ$  from different-talker target speech at  $0^\circ$  (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 50<sup>th</sup> percentile of the wave I amplitude distribution, i.e. 0.1569  $\mu$ V. 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  $-0.038 \mu\text{V}/\log_{10}\text{Pa}^2\text{h}$ ,  $p$ -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.  $-0.021 \mu\text{V}/\log_{10}\text{Pa}^2\text{h}$ ,  $p$ -value = 0.1051. Similarly, LNE showed a near-significant effect of  $-0.043 \mu\text{V}/\log_{10}\text{Pa}^2\text{h}$  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<sup>th</sup> percentile and those above the 90<sup>th</sup> 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 50<sup>th</sup> percentile, i.e. 0.1569  $\mu$ V. 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 ( $-0.038 \mu\text{V}/\log_{10}\text{Pa}^2\text{h}$ , indicating an  $A_I$  reduction of  $0.133 \mu\text{V}$  (or a 43.66% reduction) across the range of LNE values observed, i.e.  $1.43 - 4.93 \log_{10}\text{Pa}^2\text{h}$ ). 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  $\log_{10}\text{Pa}^2\text{h}$ , only nine were in the low LNE range from 1 to 3  $\log_{10}\text{Pa}^2\text{h}$ . 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  $\log_{10}\text{Pa}^2\text{h}$ ) and the largest wave I amplitude (0.56  $\mu\text{V}$ )], the negative trend between LNE and  $A_i$  [Fz-TIP] becomes non-significant (-0.019  $\mu\text{V}/\log_{10}\text{Pa}^2\text{h}$ ,  $p$ -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  $A_1$  [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  $\log_{10}\text{Pa}^2\text{h}$ , resulting in a spread of 3.5  $\log_{10}\text{Pa}^2\text{h}$ . 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  $\log_{10}(\text{Energy})$ ; 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  $\log_{10}(\text{Energy})$ .

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  $A_1$  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  $A_1$ . This would be expected, not only because  $A_1$  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  $A_1$  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  $A_1$  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  $A_1$  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  $A_1$  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.

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## **Appendix**

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

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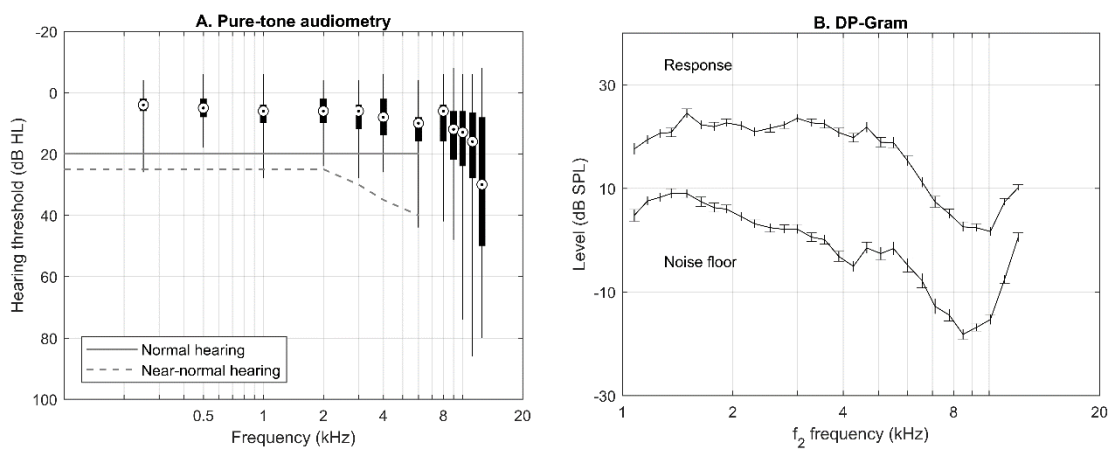
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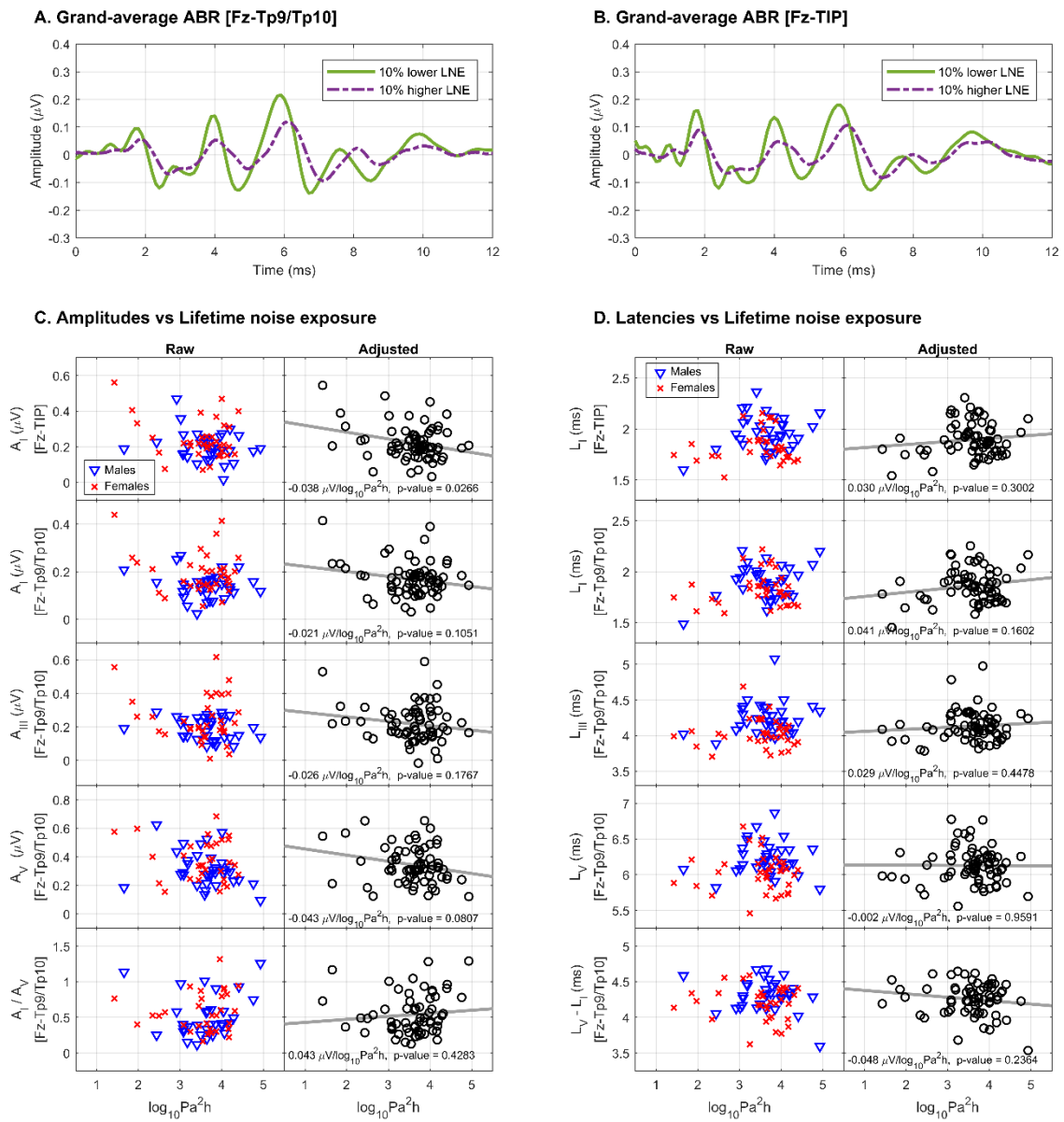
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## Figures

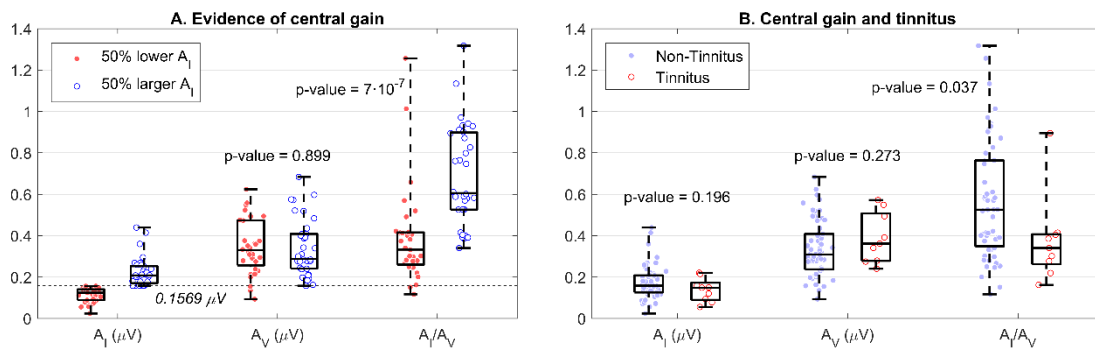
- Figure 1. [A] Pure-tone audiometry threshold distributions in the test ear at the frequencies 0.25, 0.50, 1, 2, 3, 4, 6, 8, 9, 10, 11.25, and 12.5 kHz. Boxplots indicate the minimum value, the 25<sup>th</sup> percentile, the median, the 75<sup>th</sup> percentile, and the maximum value of each distribution. 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.



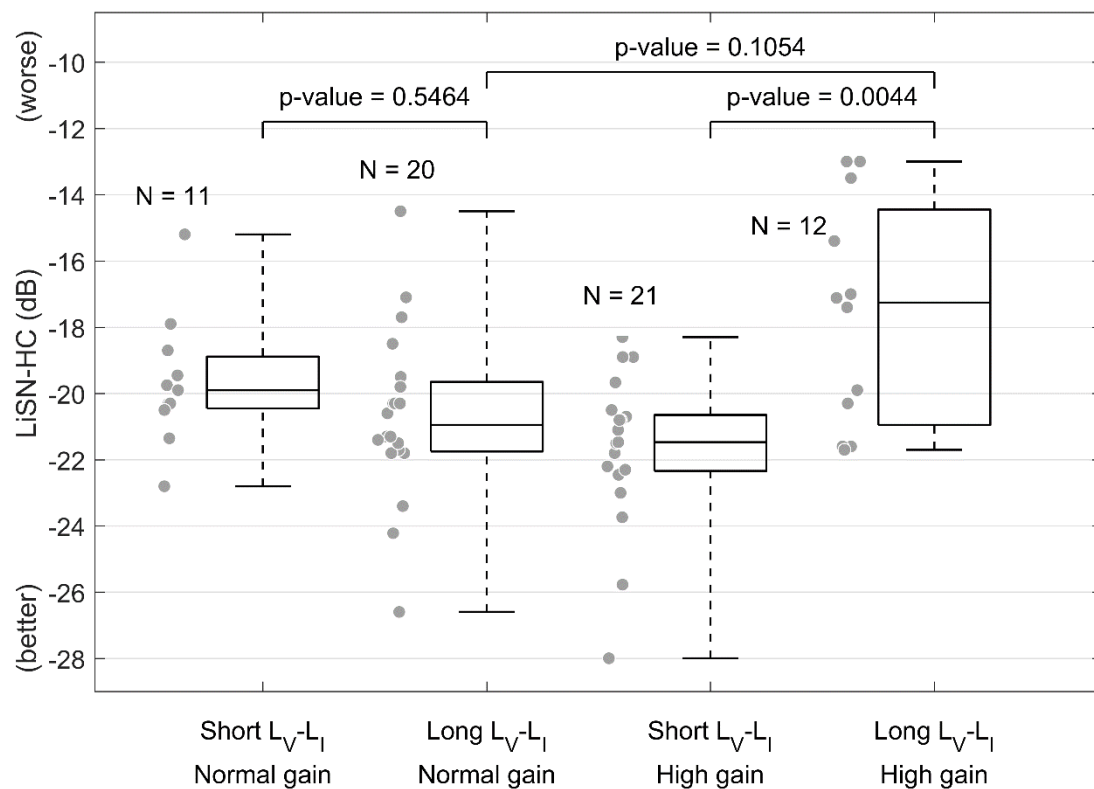
- Figure 2. (Color online) [A,B] Grand-average ABR signals of the group of participants with 10% lower (continuous line) and 10% higher (dashed line) LNE values for the [Fz-Tp9/Tp10] and [Fz-TIP] electrode configurations. [C,D] Raw and adjusted individual data of amplitudes and latencies of the main 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  $\pm$  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) $\mu$ V	0.375 $\pm$ 0.121 $\mu$ V [ $<0.0001$ ]	-0.033 $\pm$ 0.045 $\mu$ V [0.1449]	-0.038 $\pm$ 0.033 $\mu$ V/ $\log_{10}$ Pa <sup>2</sup> h [0.0266]	70	0.0933 $\mu$ V	0.1083	0.0817	0.0215
$A_I$ [Fz-Tp9/Tp10]	0.168 (0.009) $\mu$ V	0.268 $\pm$ 0.093 $\mu$ V [ $<0.0001$ ]	-0.051 $\pm$ 0.035 $\mu$ V [0.0049]	-0.021 $\pm$ 0.026 $\mu$ V/ $\log_{10}$ Pa <sup>2</sup> h [0.1051]	68	0.0714 $\mu$ V	0.1574	0.1314	0.0038
$A_{III}$ [Fz-Tp9/Tp10]	0.218 (0.013) $\mu$ V	0.339 $\pm$ 0.140 $\mu$ V [ $<0.0001$ ]	-0.056 $\pm$ 0.052 $\mu$ V [0.0354]	-0.026 $\pm$ 0.039 $\mu$ V/ $\log_{10}$ Pa <sup>2</sup> h [0.1767]	70	0.1077 $\mu$ V	0.0957	0.0687	0.0344
$A_V$ [Fz-Tp9/Tp10]	0.343 (0.016) $\mu$ V	0.528 $\pm$ 0.177 $\mu$ V [ $<0.0001$ ]	-0.058 $\pm$ 0.063 $\mu$ V [0.0692]	-0.043 $\pm$ 0.048 $\mu$ V/ $\log_{10}$ Pa <sup>2</sup> h [0.0807]	67	0.1284 $\mu$ V	0.0997	0.0716	0.0347
$A_I / A_V$ [Fz-Tp9/Tp10]	0.538 (0.035)	0.421 $\pm$ 0.391 [0.0353]	-0.069 $\pm$ 0.142 [0.3356]	0.043 $\pm$ 0.107 1/ $\log_{10}$ Pa <sup>2</sup> h [0.4283]	64	0.2833	0.0236	-0.0084	0.4820
$L_I$ [Fz-TIP]	1.894 (0.020) ms	1.730 $\pm$ 0.208 ms [ $<0.0001$ ]	0.114 $\pm$ 0.077 ms [0.0044]	0.030 $\pm$ 0.057 ms/ $\log_{10}$ Pa <sup>2</sup> h [0.3002]	70	0.1603 ms	0.1361	0.1103	0.0074
$L_I$ [Fz-Tp9/Tp10]	1.862 (0.020) ms	1.683 $\pm$ 0.210 ms [ $<0.0001$ ]	0.068 $\pm$ 0.079 ms [0.0898]	0.041 $\pm$ 0.058 ms/ $\log_{10}$ Pa <sup>2</sup> h [0.1602]	68	0.1617 ms	0.0776	0.0492	0.0724
$L_{III}$ [Fz-Tp9/Tp10]	4.132 (0.028) ms	3.934 $\pm$ 0.271 ms [ $<0.0001$ ]	0.198 $\pm$ 0.100 ms [0.0002]	0.029 $\pm$ 0.075 ms/ $\log_{10}$ Pa <sup>2</sup> h [0.4478]	70	0.2093 ms	0.2006	0.1767	0.0006
$L_V$ [Fz-Tp9/Tp10]	6.127 (0.031) ms	6.037 $\pm$ 0.319 ms [ $<0.0001$ ]	0.200 $\pm$ 0.117 ms [0.0011]	-0.002 $\pm$ 0.088 ms/ $\log_{10}$ Pa <sup>2</sup> h [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 $\pm$ 0.291 ms [ $<0.0001$ ]	0.115 $\pm$ 0.109 ms [0.0383]	-0.048 $\pm$ 0.080 ms/ $\log_{10}$ Pa <sup>2</sup> h [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  $\pm$  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.

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