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Development and validation of an efficient and safe loud music exposure paradigm

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Development and validation of an efficient and safe loud music exposure paradigm

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Abstract

Purpose: To develop a time-efficient music exposure and testing paradigm, that safely creates temporary cochlear dysfunction that could be used in future temporary threshold shift (TTS) studies.

Method: A 30-min audio compilation of pop-rock music tracks was created. Adult volunteers with normal hearing were then exposed to this music material monaurally through headphones for 30 min at 97 dB A or 15 min at 100 dB A. Levels were measured from the ear of a manikin and are considered to provide an equivalent daily noise dose based on a 3-dB exchange. We assessed the changes in their hearing, by means of distortion product otoacoustic emission (DPOAE) testing, and standard and extended high-frequency pure-tone audiometry before and after exposure. There were 17 volunteers in total. In a first trial, eight volunteers [four females; median age = 31 years (IQR = 4.25)] were included. Although TTS was observed in all eight participants for at least one frequency, a large variation in affected frequencies was observed. To address this issue, the audio material was further remastered to adjust levels across the different frequency bands. Fourteen adults [nine newly recruited and five from the first trial; seven females; median age = 31 years (IQR = 5)] were exposed to the new material.

Results: All but 2 out of 17 participants presented clinically significant TTS or decrease in DPOAE amplitude in at least one frequency. Statistically significant average TTS of 7.43 dB was observed at 6 kHz. There were statistically significant average DPOAE amplitude shifts of -2.55 dB at 4 kHz, -4.97 dB at 6 kHz, and -3.14 dB at 8 kHz. No participant presented permanent threshold shift.

Conclusions: A monaural music paradigm was developed and shown to induce statistically significant TTS and DPOAE amplitude shifts, without evidence of permanent loss. This realistic and time-efficient paradigm may be considered a viable option for experimental studies of temporary music-induced hearing loss.

1 Introduction

Temporary threshold shift (TTS) has long been investigated as a proxy of noise- and music-induced hearing loss (NIHL and MIHL). Previously, paradigms of noise or music exposure with sound levels up to 100 dBA and lasting up to 4 hours caused detectable TTS without causing any permanent hearing disorder to the participating subjects (Kramer et al., 2006; Le Prell et al., 2012, 2016). Being able to create safely and reliably detectable TTSs under controlled laboratory conditions, using stimuli that are pleasant to participants, may facilitate future studies on TTS and its relation to participants' characteristics, hearing loss biomarkers, or effect of otoprotective agents. The aim of this study is the development and validation of: (i) a new music exposure paradigm, briefer than previous examples and with real-world validity, in order to achieve temporary cochlear dysfunction without participants being at risk of permanent hearing loss or other hearing disorder; and (ii) a test battery which is brief yet capable of reliably detecting temporary changes in cochlear function as measured by TTS and DPOAE shifts. Such a paradigm could safely and efficiently be used by researchers in future interventional TTS studies.

Concerning the selected audio material used in experimental settings, it should be pleasant and at levels easily acceptable to the average listener. Researchers should also be able to document in detail the dynamic range and exposure levels of each participant's exposure. In our case, we selected pop-rock music regarded as pleasant by participants, to mimic regular music exposure and to eliminate drop out risk. Music was delivered monaurally through headphones at levels compatible with the Greek legislation ("Protection of Public Health from Music Sounds in Entertainment and other venues" (Y.A. Y2/Οικ. 15438/2001 (ΦΕΚ 1346/Β` 17.10.2001)) and the in-ear exposure levels did not exceed the recommended daily exposure limits of the National Institute for Occupational Safety and Health (NIOSH) standards, which allow up to 15 min at 100 dB and up to 30 min at 97 dBA for U.S. workplace exposures (National Institute for Occupational Safety and Health. Division of Biomedical and

Behavioral Science, 1998). Taking into account that NIOSH standards and permitted daily noise “dose” are based on the hazard associated with repeated noise exposure during five workdays for 40 work years, and not on one single exposure as in our experiment, we considered that our paradigm was safe for our participants. Moreover, NIOSH standards concern free-field levels of sound. In our study, music was delivered via headphones, hence levels were lower than free-field. Since assessing the efficacy of our paradigm in creating TTS does not require exposure and thus insult of both ears, only monaural exposure was considered. Monaural delivery of noise/music was chosen in multiple previous studies (Attias et al., 2004; Bhagat & Davis, 2008; Keppler et al., 2010; Quaranta et al., 2003, 2004).

Concerning the optimal test battery, this had to be quick yet efficient. In our case, we selected hearing tests that have previously been proven to detect temporary changes in cochlear function reliably (Kikidis et al., 2019; Kil et al., 2017; Le Prell et al., 2011, 2012). We thus decided to use a previously tested modified pure tone audiometry method, the 6 dB down, 2 dB up method, instead of the 10 dB down, 5 dB up method, to be able to detect TTS less than 5 dB (Kil et al., 2017; Le Prell et al., 2016). We chose to test 1, 3, 4, 6, 8, 10, and 12.5 kHz of the exposed ear to focus on frequencies that are more prone to be affected quickly, to avoid missing short-term TTS, and to be comparable to previous literature (Kil et al., 2017; Le Prell et al., 2012). DPOAE amplitude measurement (1-8 kHz) with unequal primaries was also selected, since the measurement is quick and sensitive to detection of temporary cochlear dysfunction (Le Prell et al., 2012).

2 Methods

2.1 Audio material

A 30-min compilation of 2-3 min excerpts from pop-rock music tracks was created. Short-term audio levels (such as the sound pressure level which would yield the same energy to the instantaneous sound signal, within a duration of 1s, namely $L_{eq,1s}$) in pop-rock music may fluctuate considerably across tracks, and along the time-course of any single song (e.g., between different chorus, verse, or bridge parts of a song, albeit much less than in other musical genres). Additionally, dynamic ranges across frequencies (especially for frequencies <200 Hz and >3-4 kHz) also show significant variability, as observed by measurements of the long-term average spectrum (LTAS) of different music tracks (Hill et al., 2021; Le Prell et al., 2011). Level variation between consecutive parts (whose durations may be of the order of several seconds, mostly following the musical structure of the track, e.g., intro, verse, chorus, etc.) of music tracks is about 5 dB. The average level (i.e., over the whole duration of a track) between different music tracks may differ by 15 dB. The dynamic range of within bands of the LTAS of a track is also typically around 15 dB.

To achieve a relatively low variability of exposure time (e.g., "constant" level; Le Prell et al, 2011) under such variations of level, we followed a low-moderate nonuniform compression scheme of the audio material which would avoid over-compressing (Réveillac, 2017). The nonuniform compression scheme comprised of a 3:1 compression of peak levels ($L_{eq,1s} > -6\ \mathrm{dB_{max}}$) and a 2:1 compression over the rest (the lowest parts) of the dynamic range, for each music track, with appropriate makeup gain value (again, applied individually on each track). Thus, we achieved a roughly constant average level between tracks, and at the same time, we avoided severe distortions due to clipping. Finally, the mastering level of the whole audio material was adjusted to obtain an average level of 100 dBA, measured on a BK4128 HATS with TDH-39 headphones, played from a laptop. The same headphones and laptop were also used for each subject during the exposure. The BK4128 HATS microphones' calibrations were conducted using a BK4228 pistonphone calibrator. The BK4128 output was continuously sampled at 44.1 kHz using a National Instruments USB-6251 and LabView 2010 software, and voltage values were converted to SPL using the HATS microphone sensitivity values obtained from the calibration. Subsequently, the whole length of the sampled audio material was analysed by computing the Leq SPL at 1 s consecutive intervals, from which all audio material statistics were calculated. The dynamic level change around the average SPL varied between -4 dB SPL and +2.5 dB SPL (5%-95% range of cumulative distribution of 1s SPL values). During a small informal pilot study, conducted with five naive normal-hearing listeners prior to the main investigation, the audio material was delivered in lower intensity, and the above compression scheme achieved high acceptability of the processed audio without any complaints regarding sound quality compared to the original material. An exact copy of the mastered audio material with a gain of -3 dB yielded an SPL of 97dBA. Whenever the 100 dB A exposure level was selected by the participant, the initial 15-min of the 100 dB A audio material was played, while in two cases where 97 dB A exposure was chosen the full 30-min length of the audio material was used. Figure 1 shows the evolution of instantaneous SPL of the 15-min long audio material, and Figure 2 shows the distribution of SPLs .Table 1 shows the main statistics of the SPL distribution. Figure 3 shows the 95th, 50th and 5th percentiles of the 1/3-octave LTAS of the audio material.

2.2 Participants

Participants were recruited by the 1st Otorhinolaryngology Department of the National and Kapodistrian University of Athens and underwent medical and hearing loss history, otomicroscopy, tympanometry, and pure tone audiometry. Screening pure tone audiometry (PTA) was performed according to the British Society of Audiology (2018) guidelines. The inclusion criteria included no self-reported current or previous history of hearing loss, no loss of speech perception, tinnitus or other hearing disorder, no abnormality in otoscopy or tympanometry, pure tone thresholds within normal limits in both ears (≤ 25 dB HL for 0.5 – 8 kHz) and symmetric across ears (no more than 15 dB difference between the ears at any frequency). Candidates with middle ear pathology (abnormal otomicroscopy or tympanometry), with previous or current inner ear pathology, asymmetry in pure tone audiometric thresholds >15 dB at any of the tested frequencies, radiotherapy or ingestion of ototoxic substances during the last 12 months, or exposure to hazardous noise during the last 72 h were excluded. Tympanometry was considered normal when middle ear pressure values ranged from −140 to +40 daPa, peak compensated static acoustic admittance from 0.3 to 1.8 ml and acoustic equivalent volume (Vea) from 0.8 to 2.1 cm (Le Prell et al., 2012). Candidates fulfilling criteria received oral and written explanations of the study purpose and procedures and were asked to sign the relevant consent form.

2.3 Participants' assessment

Included participants underwent:

(1) Medical and hearing loss history: Lifetime noise exposure was evaluated using a recently developed instrument that attempts to estimate lifetime recreational, occupational and fire-arm noise exposure based on self-report, the Noise Exposure Structured Interview (NESI; (Guest et al., 2018).The full interview lasted 10 min on average, while the collected data concerned participants' age, sex, and NESI units.

(2) Hearing testing:

   a. PTA and extended high frequency PTA using Interacoustics Affinity audiometer (EN 60645-1, ANSI S3.6), and TDH39 and HDA 300 headphones (for >8 kHz). Findings of previous studies show that more pronounced TTS may be found at 1-8 kHz (Kil et al., 2017; Le Prell et al., 2012, 2016), while extended high frequency PTA has been associated with the early diagnosis of NIHL (Mehrparvar et al., 2014; Schmuziger et al., 2007). Hence, tested frequencies in our study were 1, 3, 6, 8, 10, and 12.5 kHz [with the addition of 4 kHz after the further manipulation of our audio material (see below)]. The signal level was varied in a 6 dB down, 2 dB up manner (Kil et al., 2017; Le Prell et al., 2016). The whole procedure lasted approximately 5 min. Collected data included pure tone audiometry thresholds before and after music exposure per frequency.

b. DPOAEs using Interacoustics Titan. The frequency ratio of primary tones, f1:f2, was 1.22, and their levels were 65 and 55 dB SPL, respectively. Maximum residual noise was set to 30 dB SPL. The geometric mean of the pair was swept from 8 to 1 kHz. Data collection was terminated after three such sweeps, lasting 1 min. The DPOAE-related endpoints were the DPOAE amplitude before and after music exposure per frequency.

2.4 Procedure

All participants were advised not to expose themselves to further loud noise or music 72 h prior and during study procedures. At the day of the experiment, participants had to confirm their adherence to this advice, otherwise their participation would be postponed to another day. A medical history was taken and baseline pure tone audiometry and DPOAE testing occurred just before music exposure. Participants were subsequently exposed to the audio material at 100 dBA or 97 dBA (exposures that both provide an equivalent daily noise dose based on the 3-dB exchange rate), according to their preference for 15 min or 30 min respectively. The audio material was provided by means of headphones to the left ear connected to the same laptop, always under the same conditions, in an audiological booth. The contralateral (right) ear was sealed. Caution was taken not to exceed the overall acoustic energy that would result in PTS, according to previous studies' findings and national and European legislation. Immediately after music exposure, participants were asked to rate their comfort level during the experimentation and the degree of aural fullness, on scales from 1 to 10. For safety reasons, they were also asked if they experienced any tinnitus or other symptoms. Two minutes after the end of the music, they underwent DPOAE testing. At 3 – 4 min after the end of music exposure, pure tone audiometry was performed. Pure tone audiometry and DPOAEs were repeated later, within 24h, to ensure that pure tone audiometry and DPOAEs returned to baseline. All post-exposure pure tone audiometry and DPOAEs testing was conducted unilaterally (left ear). In our study, the return of threshold to within 4 dB of baseline was used as a conservative cut-off point for clinically significant pure tone audiometry threshold change in healthy adults. The same cut-off point has been used in previous studies using the same PTA methods (Kil et al., 2017). However, this was not used as a criterion for categorical data analysis, but only for purposes of safety characterization (i.e., PTS identification).

2.5 Statistical analysis

A three-level linear mixed effect model was used to reflect the multilevel structure of data (repeated measurements of pure tone audiometry thresholds and DPOAE levels at different frequencies, before and after exposure, within the same participant) of cochlear regions corresponding to tested frequencies nested into participants. Age, Sex, NESI units, and the interaction between Exposure and Frequency were modelled as fixed factors. Random effects were modelled by a random intercept of Frequency within Participant to account for individual differences in thresholds for each frequency for each participant, before exposure. A random slope of Exposure within Participant was also fitted to account for differences in the magnitude of the effect of music exposure for each individual.

Statistics were computed using R statistical language. The linear mixed models were created using the lme4 package and fitted by the restricted maximum likelihood method and t-tests using Satterthwaite's method (Bates et al., 2015). Model selection was based on backward stepwise regression. Deviation from homoscedasticity or normality was verified by visual inspection of both residual and random effect plots, and the Kolmogorov-Smirnov test. Analysis of variance tables (using the Kenward–Rogers method for estimating degrees of freedom), marginal means and significance testing of their differences (using Tukey's HSD method to adjust p-values for multiple comparisons) were calculated via the lmerTest package.

The structural equation of the final model selected was:

$[\text{Pure tone audiometry threshold or DPOAE level}]_{tij} = \beta_0 + \beta_1[\text{Exposure}]_{tij} + \beta_2[\text{Frequency}]_{tij} + \beta_3[\text{Exposure}] \text{ x Frequency}]_{tij} + u_{0j} + u_{0i|j} + u_{1i} \times [\text{Exposure}]_t + \varepsilon_{tij}$

where, u_{0j} is the random intercept for Participant (capturing individual differences in threshold for each participant, before exposure), u_{1i} is the random slope of [Exposure] for each Participant (capturing differences in the magnitude of the effect of music exposure for each individual irrespective of frequency), $u_{0i|j}$ is the random intercept of Frequency nested within Participant (capturing individual differences in threshold for each frequency for each participant, before exposure), and ε_{tij} is the residual (unexplained) error for each participant.

3 Results

3.1 Population

Seventeen volunteers with normal hearing participated to the study. Initially, audio material was tested in eight volunteers that fulfilled the inclusion criteria [four females; median age = 31 years (IQR = 4.25); $PTA_{1\text{-}8kHz}$ = 4 dB HL and $PTA_{1\text{-}12.5kHz}$ = 2.63 dB HL]. DPOAE average amplitudes for these eight volunteers were 7.14 dB SPL (1 kHz), 13.16 dB SPL (1.5 kHz), 10.11 dB SPL (2 kHz), 5.82 dB SPL (3 kHz), 7.74 dB SPL (4 kHz), 1.28 dB SPL (6 kHz), and -7.83 dB SPL (8 kHz). The range of lifetime noise exposures was 1.46 to 66.93 NESI units (median = 13.48, IQR = 8.3). One NESI unit is equivalent to one working year (2080 hrs) of exposure to 90 dBA. Two participants were exposed to 97 dBA for 30 min and six participants were exposed to 100 dBA for 15 min, according to their preference. Although TTS larger than 4 dB was observed in six out of eight participants for at least one frequency, a large variation in affected frequencies was observed (Supplementary Material 1).

Music material was then further manipulated digitally to adjust levels across the different frequency bands. Fourteen adults (nine newly recruited and five that were also exposed to the initial audio material; seven females; median age = 31 years; IQR = 5 years) met the inclusion criteria. Their PTA average before exposure was 3.87 dB for 1-8 kHz and 4.44 dB for 1-12.5 kHz. DPOAE average amplitudes for these fourteen volunteers were 3.34 dB SPL (1 kHz), 8.35 dB SPL (1.5 kHz), 6.95 dB SPL (2 kHz), 4.33 dB SPL (3 kHz), 5.16 dB SPL (4 kHz), 3,10 dB SPL (6 kHz), and -6.19 dB SPL (8 kHz). NESI units ranged from 1.46 to 219.90 (median = 12.40, IQR = 29.92). All 14 participants were exposed to 100 dBA for 15 min, according to their preference (Supplementary Material 1). Their data were included in our analyses.

3.2 TTS in standard and extended high frequency pure tone audiometry

TTS larger than 4 dB was observed in at least one frequency in six out of eight participants in the first trial, and in twelve out of fourteen participants in the second one (Supplementary Material 1). Time of baseline measurements ranged between 08.00 and 18.30, so four participants had to return the following day to repeat the hearing test and assess recovery. Estimated marginal means of pure tone audiometry threshold for each frequency before and after exposure for the 14 participants of trial 2 are presented Figure 4A and Table 2. There is a statistically significant pure tone audiometry threshold shift of 7.43 dB at 6000 Hz [($t_{(114.9)}$ = -4.31, 95% CI: (4.06, 10.80), *p* <.001)]. For the pure tone audiometry analysis, the Akaike information criterion (AIC) for the null and the selected model were 2006 and 1980 respectively ($x^2_{(20)}$ = 66.53, *p* < .001). The adjusted and conditional intraclass correlations (ICCs) for the selected model were 0.829 and 0.718, respectively. For particular participants, for some frequencies a reduction of threshold was observed following music exposure (up to 14 dB for standard audiometry and up to 16 dB for extended high frequency audiometry). These data were included in the analysis. Within 24h, all participants' pure tone thresholds recovered at all tested frequencies (within 4 dB from baseline, see Supplementary Material 2 and 3). . There was statistically significant decrease of pure tone thresholds when compared to the baseline ones at 8000 Hz [4.57, $t_{(99.5)} = 2.58$, 95% CI: (1.02, 8.11), $p = .03$)], 10000 Hz [5.57, $t_{(99.5)} = 3.15$, 95% CI: (2.03, 9,11), $p = .006$)], and 12500 Hz [5.43, $t_{(99.5)} = 3.06$, 95% CI: (1.89, 8.97), $p = .006$). After Bonferroni correction for multiple comparisons only the 10000 Hz statistical significance survived.

3.3 DPOAE amplitude shift

DPOAE amplitude shift was reliably observed in all 17 participants in at least one frequency. DPOAE amplitude shifts for the 14 participants of trial 2 per frequency are presented in Figure 4B. The difference between the estimated marginal means of DPOAE levels for each frequency before and after exposure are reported in Table 2. For the DPOAE analysis, the AICs for the null model and the selected model were 1060 and 1017 respectively ($x^2_{(6)} = 54.54$, $p < .0001$). Adjusted and conditional ICCs for the selected model were 0.90 and 0.64 respectively. A deviation from normality was noted in both tails of the residual distribution, but not of the random effects, in the DPOAE data. Linear mixed models are considered robust regarding distribution assumptions, but the estimates, although unbiased, may be imprecise (Schielzeth et al., 2020).

There was a statistically significant DPOAE amplitude shift of -2.55 dB at 4 kHz [($t_{(92)} = 2.68$, 95% CI: (-4.45, -0.65), $p = .0087$)], -4.97 dB at 6 kHz [($t_{(92)} = 5.23$, 95% CI: (-6.87, -3.07), $p < .0001$)], and -3.14 dB at 8 kHz [($t_{(92)} = 3.30$, 95% CI: (-5.04, -1.24), $p = .0014$)]. Although no formal DPOAE test-retest reliability analysis was performed, the 90% CIs of the Standard Error of Measurement (Demorest & Walden, 1984) between the pre-exposure and recovery DPOAE amplitudes for all frequencies were calculated. These were narrower than those reported by a recent meta-analysis on DPOAE test-retest variability (Reavis et al., 2015). We are hence confident that no permanent DPOAE amplitude shift occurred. For more details, please see Supplementary Material 4.

4 Discussion

TTS has long been used as an early audiometric marker of traumatic noise exposure, since it may be indicative of sound energy high enough to create cochlear insult, and at the same time it can safely be tested in both experimental and observational studies (Lindgren & Axelsson, 1983; Ryan et al., 2016). Nevertheless, its use as outcome measure has been limited by its high variability. Human studies have shown that similar exposures may lead to different degrees of TTS, and recovery threshold shifts, or affect different frequencies (Kil et al., 2017; Kramer et al., 2006; Le Prell et al., 2011, 2016; Lee et al., 1985; Lindgren & Axelsson, 1983). This variability may be linked with differences in the methods used, or participants' individual vulnerability to noise. Use of one single standardized and validated exposure and hearing assessment paradigm could eliminate part of this variability. In this technical report, we present the development and validation of an experimental model that safely creates a measurable temporary cochlear dysfunction as evidenced by TTS. In our study, although the degree of recovery showed variability per individual participant and per frequency (Figure 5.), the average recovery threshold shifts showed uniform directionality (elevation in comparison to the baseline, see Supplementary material 5.2 and 5.3). There was statistically significant decrease of pure tone audiometry thresholds at 8000, 10000 και 12500 Hz, but after correction only the 10000 Hz statistical significance survived. This phenomenon may be explained by a learning effect that may occurred after the first two audiograms. It could also be a result of the fact that participants were aware that their hearing was being tested to confirm full recovery, and this knowledge may have increased their attention and alertness during the procedure.

Our paradigm had a shorter duration than previous ones that were effective in demonstrating TTS. Le Prell et al. (2012; 2016) exposed participants to music for 4 h at coupler levels of 97-100 dBA and Kramer et al. (2006) for 2h at 92.5 to 102.8 dBA (free field, mean exposure levels = 98.1 dBA). Other short paradigms did not create any clinically or statistically significant TTS: Krishnamurti and Grandjean (2003) exposed participants to music of 90 dB SPL (estimated in-ear levels) for 20 min and detected TTS of 1-6 dB, but no change in participants' DPOAE amplitudes. Reduction of exposure time may lead to higher recruitment and lower drop-out rates and save resources.

Our paradigm was efficient in creating temporary cochlear dysfunction that was evident in pure tone audiometry and DPOAE amplitude shift in all participants. We calculated mean TTS value and mean DPOAE amplitude shift per frequency, and we analyzed our results by a mixed-effects linear model to take into account the hierarchical structure of data and the repeated measurement of the outcome variables at each level. The frequency region with higher TTSs was 3-6 kHz, while the maximum TTS obtained in our experiment was 24 dB (at 6 kHz). The same frequencies were also those most affected by noise and music in previous studies (Kramer et al., 2006; Krishnamurti & Grandjean, n.d.; Le Prell et al., 2012; Ryan et al., 2016). Although our exposure lasted only 15 min and included lower levels of music than other studies, our maximum TTS was slightly higher than those from other studies assessing music-induced TTS. Exposure to music at 100 dBA coupler level for 4h was reported to cause immediate TTS up to 13 dB (Le Prell et al., 2012; Ryan et al., 2016), while in another paradigm of 2h of music exposure at a nightclub (93-103 dBA) maximum TTS of 14 dB was found at 4 kHz (Kramer et al., 2006). Mean TTS and DPOAE amplitude shifts in our study were compatible to those reported in previous studies. No TTS was detected in extended high frequency pure tone audiometry. This finding is in agreement with previous studies (Le Prell et al., 2012).

Apart from efficient, our paradigm is also safe. Our exposure "dose" was lower than the upper Leq 15-min sound levels limit during a music event according to WHO guidelines (World Health Organization, 2022). The free field equivalent level (FFE) transformation, used to adjust for individual ear canal amplification, was conservatively assumed equal to 5 dB, although individual measurements are often greater than that (Shaw, 2005). This practically means that participants would be exposed for 15 or 30 min to free-field equivalent music of 95 dBA or 92 dBA (less than 1/3 of the maximum permissible dose) respectively . Moreover, we asked them to avoid exposure to loud noise three days before, and 7 days after the music exposure, so that their weekly exposure dose would remain lower than the weekly permissible dose, which according to the recent WHO guidelines equals 18.75 min per week at 101 dBA or 37.5 min per week at 98 dBA (World Health Organization & International Telecommunication Union, 2019). Previous rodent (mice) studies using cochlear functional assays and confocal imaging have shown that noise exposures capable of inducing temporary pure tone threshold elevations of ~40–50 dB may lead to (permanent) rapid synaptic deficits and decreased evoked potential amplitude (Kujawa & Liberman, 2009, 2015). Researchers hypothesize that in humans a similar neurodegenerative noise-induced phenomenon would add to difficulties in hearing in noisy environments, tinnitus, hyperacusis, and other perceptual anomalies commonly associated with inner ear damage (Kujawa & Liberman, 2009). Although, many studies have attempted to identify signs of cochlear synaptopathy in human, methods and findings across studies present high heterogeneity (Bramhall et al., 2019). It is also proven that much higher levels are required to produce cochlear synaptopathy to primates than in rodents (Valero et al., 2017). Furthermore, in all previous study paradigms, levels of exposures were higher and/or longer than ours (Bramhall et al., 2019; Wang et al., 2021). In a recent commentary about justification of modification of current regulation of occupational noise exposure based on research findings on noise-induced cochlear neuropathy in rodents, authors conclude that these findings cannot be directly translated in humans, and that humans seem to be less susceptible to TTS and probably cochlear synaptopathy (Dobie & Humes, 2017). Levels and duration of exposure chosen in our paradigm, based on methodological aspects, ethical considerations, and audiometric results of previous studies, were considered tolerable by all participants. Most participants characterized the listening experience as comfortable, answering 6 or higher to the question "How comfortable was listening to this music in this setting for you?". Moreover, although all participants presented measurable and reliable temporary changes of their auditory function, no PTS or other permanent hearing disorder (i.e., tinnitus) was observed in any of them. This study hence provides some assurance for the future reproduction of the same paradigm in larger samples. Nevertheless, if, in the future, a clinical test is proven sensitive to cochlear synaptopathy and neurodegeneration in humans, this should be included as part of the pre- and post-exposure assessments to ensure synaptic and neural integrity.

One of the limitations of our study is the fact that no formal test-retest reliability analysis for DPOAEs was conducted. However, the 90% CIs of the Standard Error of Measurement between the pre-exposure and recovery DPOAE amplitudes for all frequencies were calculated and were found to be narrower than the test-retest variability reported by the meta-analysis of Reavis et al (2015). Although measurements were performed in a sound-treated room, in compliance with the ANSI/ASA S3.1-1999 (R2018) standard for environmental noise, no real-time noise monitoring was employed during the measurements. Thus, we cannot exclude the possibility of variability, especially at lower frequencies [as can also be indirectly seen by the fact that the DP noise floors were higher and more varying at lower frequencies (e.g., 1 kHz)]. This may possibly also explain the larger PTA shifts that were observed in some of our participants compared to the expected test-retest reliability limits of +/- 5 dB, as commonly assumed in PTA measurements (Le Prell et al., 2012; Ryan et al., 2021; Schlauch & Carney, 2007) However, observations of larger test-retest differences may be observed by chance, as shown by Schlauch and Carney (2007). The authors estimated that, when thresholds of six frequencies are measured, 14% of the people tested would be expected to have at least one threshold differing by 15 dB or more. To conclude, there are some extreme values in our data. However, as the analysis has to take into account the above factors in calculating the F statistic, we chose not to exclude these extrema. Additionally, the use of mixed effect models also takes into account intrasubject variability for the estimation of expected mean values.

5 Conclusion and implications

A brief, safe, and pleasant music exposure and testing paradigm, showing consistent and reliable effects on pure tone audiometry thresholds and DPOAE amplitudes for adults with normal hearing, was created. In the future, our paradigm may be used to further assess TTS degree and time of recovery function. It could also be useful in studies that correlate TTS with participants' characteristics and habits, with progressive and permanent types of hearing loss, or with subjective impressions such as listening comfort and post-exposure aural fulness or tinnitus. Finally, it may be a useful instrument for measuring objectively the effect of otoprotective agents or ear protection devices.

6 Author Contributions

EI: Conceptualization, Data curation, Formal analysis; Investigation; Methodology; Project administration; Writing - original draft; Writing - review & editing. CJP: Formal analysis, Writing - review & editing, Supervision, KP: Audio material development, Writing - review & editing. DD: Audio material development, Writing. AB: Conceptualization, Funding acquisition, Formal analysis, Project administration, Writing-review & editing, Supervision.

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9 Data Availability Statement

The data and code that support the findings of this study are available in

https://osf.io/8g6jw/?view_only=3d597866bb9e4f8cb5c0b2c44c26919f

10 Ethical approval

Study protocol was approved by the Institutional Scientific Board of Hippokrateion General Hospital (Ε.Σ.62/10-9-2021).

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Supplementary Material

Supplementary Material 1. TTS per frequency for the 17 participants.

Supplementary Material 2. Ultimate PTA threshold shift per frequency for the first part of the experimental study (trial 1). PTA thresholds have returned within 4 dB from baseline for all participants.

Supplementary Material 3. Ultimate PTA threshold shift per frequency for the second part of the experimental study (trial 2). PTA thresholds have returned within 4 dB from baseline for all participants.

Supplementary Material 4. Distortion product otoacoustic emission data for trial 1 and 2.

Figure Captions

Figure 1. Sound pressure levels (dB A) of 15 min of the audio material, measured on a BK4128 HATS with TDH-39 headphones. The levels reported here are HATS measured levels. The free field equivalent level (FFE) transformation, used to adjust for individual ear canal amplification, is conservatively assumed to be 5 dB, although individual measurements are often greater than 5 dB. If the 100 dB A exposure level was chosen, then the initial 15min of the 100 dB A audio material was played, while in the 97 dB A exposure the full 30min length of the audio material was used.

Figure 2. Histogram of SPL (dB A) of the 15-min audio material.

Figure 3. 1/3-octave LTAS of the 15-min audio material.

Figure 4. Participants' mean pure tone audiometry thresholds (A) and DPOAE amplitudes and noise floor levels (solid and dashed lines respectively) (B) before and immediately after music exposure per frequency. Error bars show 1 standard error and the shaded area the 95% confidence intervals.

Figure 5. Pure tone audiometry (PTA) threshold change, per frequency, per subject.

Table 1: Leq,1s SPL (dBA) statistics of the 15-min audio material.

Mean	Median	SD	IQR
99.68	99.73	2.29	3.38 (98.12-101.5)

Table 2. Estimated marginal means of pure tone audiometry threshold and DPOAE temporary amplitude shifts for each frequency.

Frequency (Hz)	Estimated marginal means of pure tone audiometry temporary thresholds shifts (dB HL) (95% CI)	p-value	Estimated marginal means of DPOAEs temporary amplitude shifts (dB SPL) (95% CI)	p-value
1000	0.143 (-3.26, 3.54)	0.99	1.66 (-0.22, 3.56)	0.0795
2000	-	-	-1.54 (-3.44, 0.362)	0.1223
3000	-3.00 (-6.4, 0.4)	0.19	-1.66 (-3.56, 0.24)	0.0833
4000	-2.71 (-6.11, 0.686)	0.26	**-2.55 (-4.452 -0.65)**	**0.0087***
6000	**7.43 (4.06, 10.80)**	**= 0.0001 *****	**-4.97 (-6.87, -3.07)**	**<0.0001 *****
8000	-0.29 (-3.69, 3.11)	0.98	**-3.14 (-5.04, -1.24)**	**0.0014 ****
10000	- 0.71 (-2.69, 3.59)	0.91	-	-
12500	-2.86 (-0.54, -6.26)	0.26	-	-

Figure 1

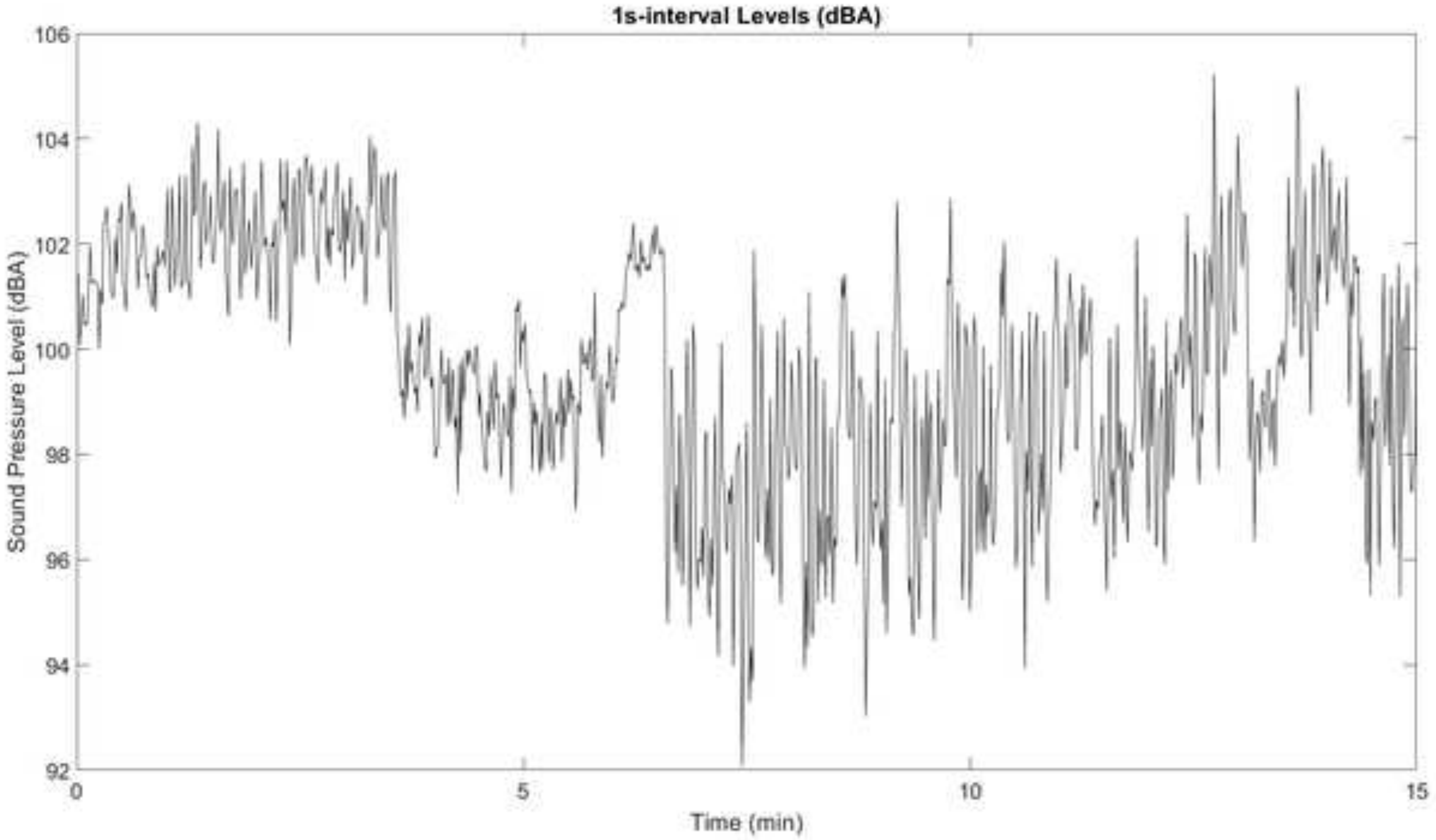

1s-interval Levels (dBA)
Sound Pressure Level (dBA)
106
104
102
100
98
96
94
92
0
5
10
15
Time (min)

Figure 2

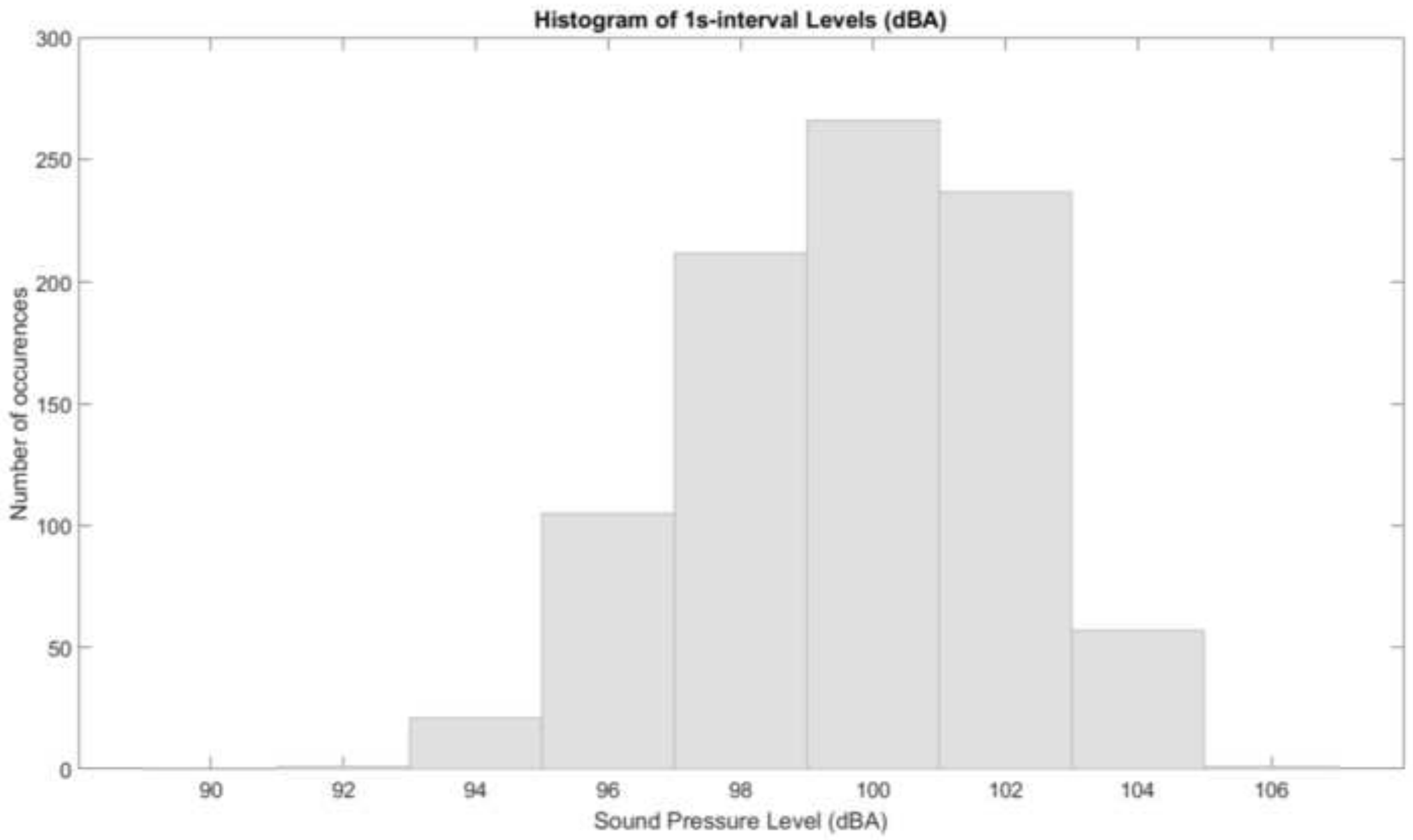

Histogram of 1s-interval Levels (dBA)
Number of occurences
0
50
100
150
200
250
300
90
92
94
96
98
100
102
104
106
Sound Pressure Level (dBA)

Figure 3

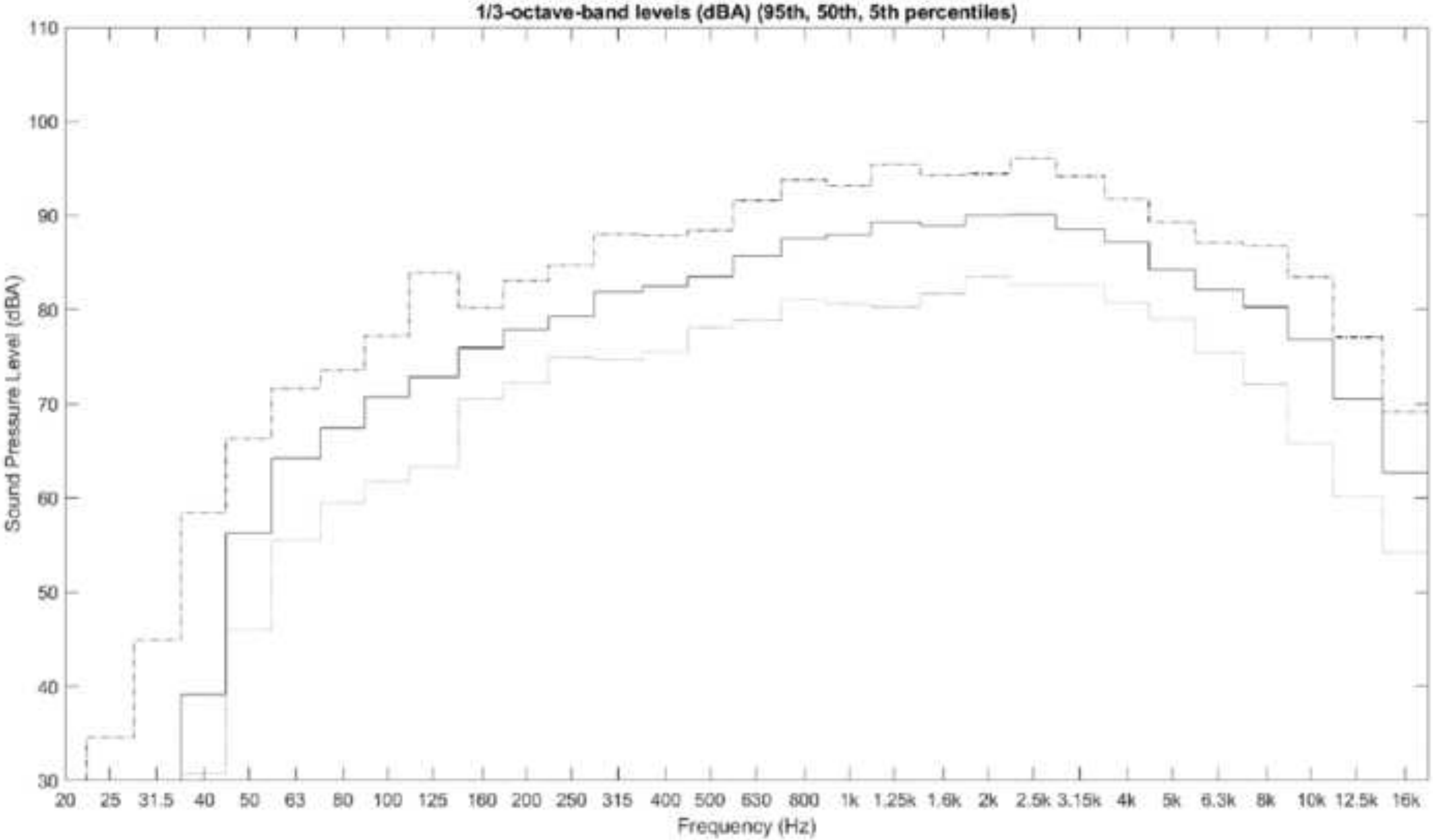

1/3-octave-band levels (dBA) (95th, 50th, 5th percentiles)
Sound Pressure Level (dBA)
110
100
90
80
70
60
50
40
30
20
25
31.5
40
50
63
80
100
125
160
200
250
315
400
500
630
800
1k
1.25k
1.6k
2k
2.5k
3.15k
4k
5k
6.3k
8k
10k
12.5k
16k
Frequency (Hz)

Figure 4a

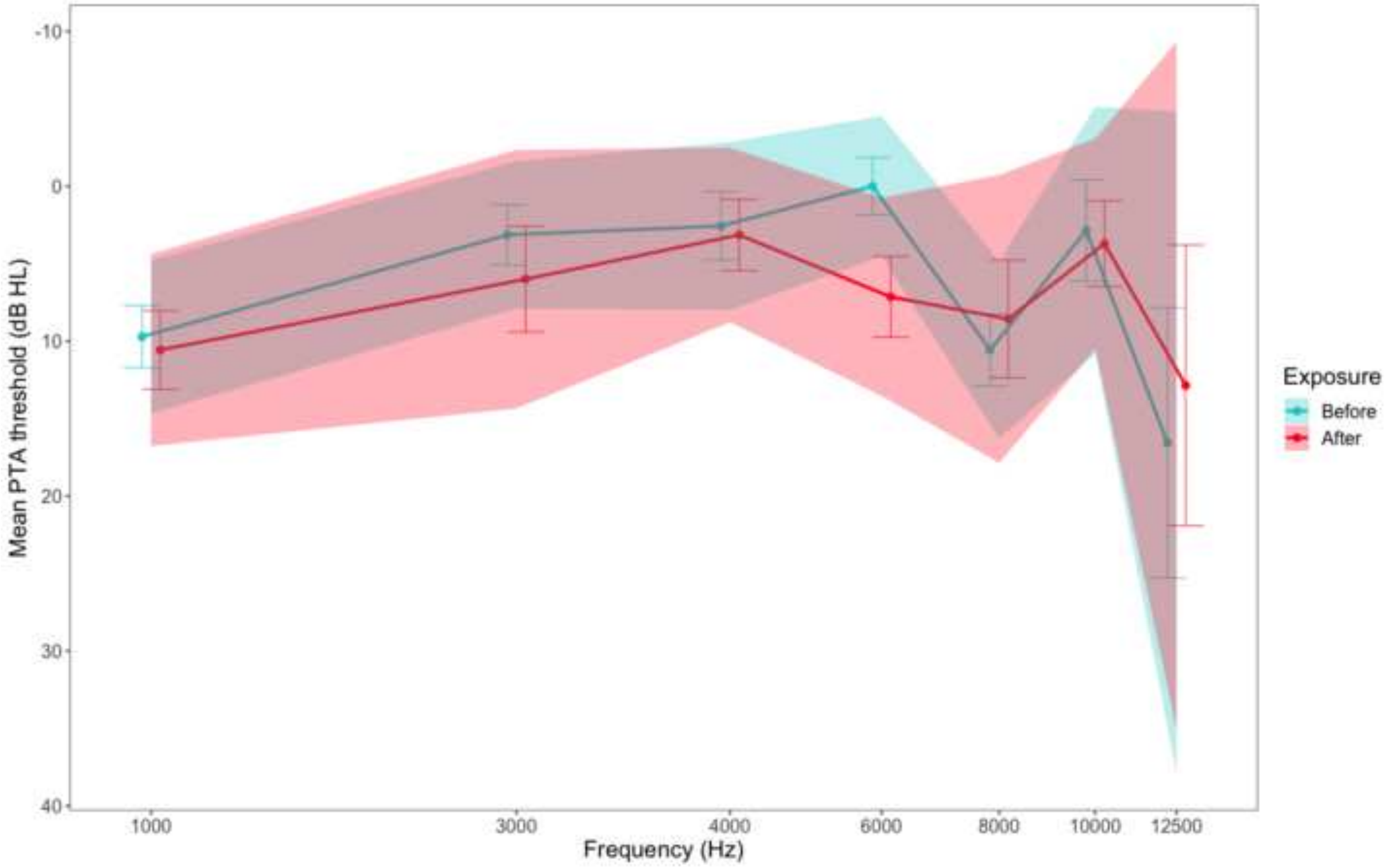

Mean PTA threshold (dB HL)
-10
0
10
20
30
40
1000
3000
4000
6000
8000
10000
12500
Frequency (Hz)
Exposure
Before
After

Figure 4b

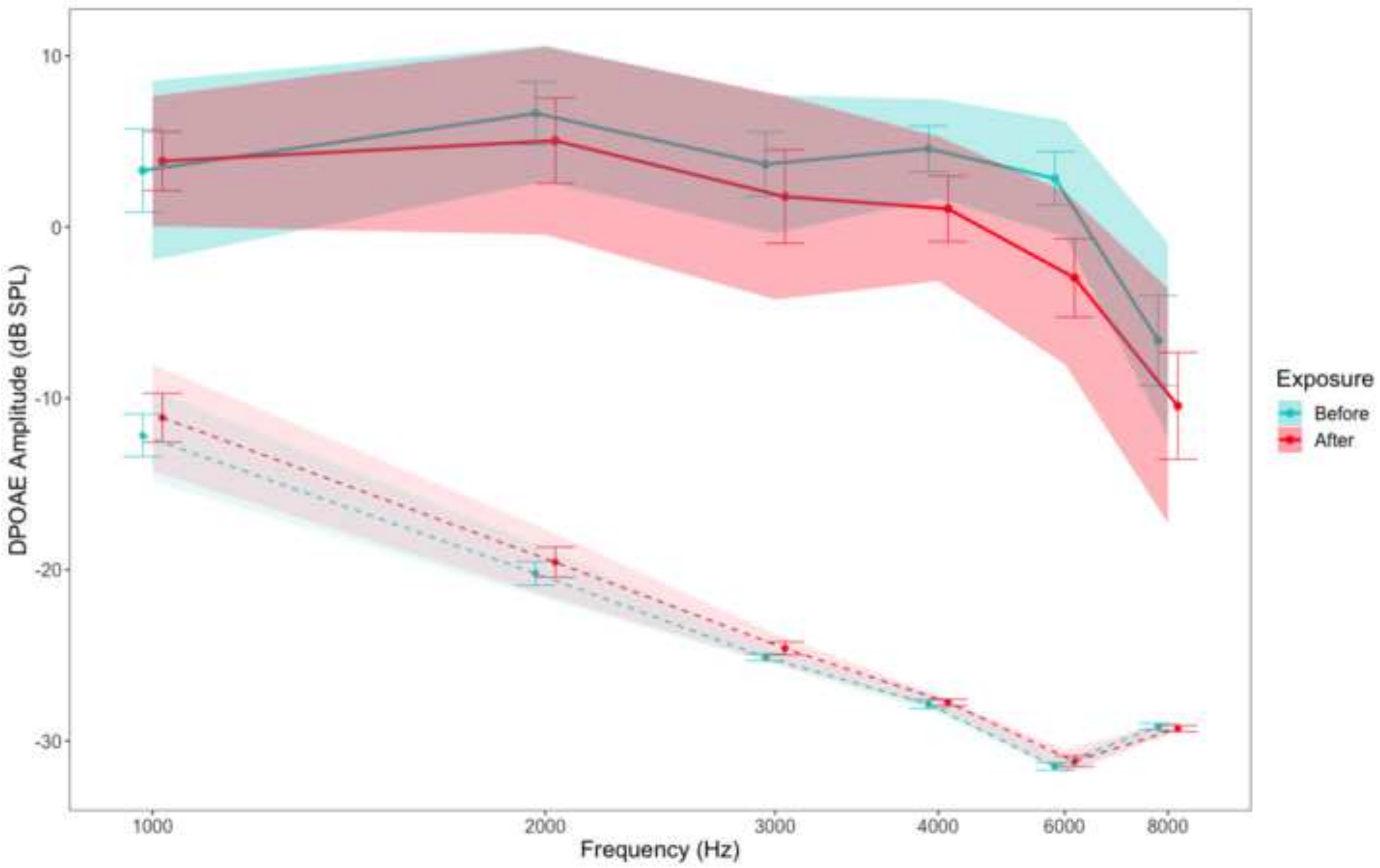
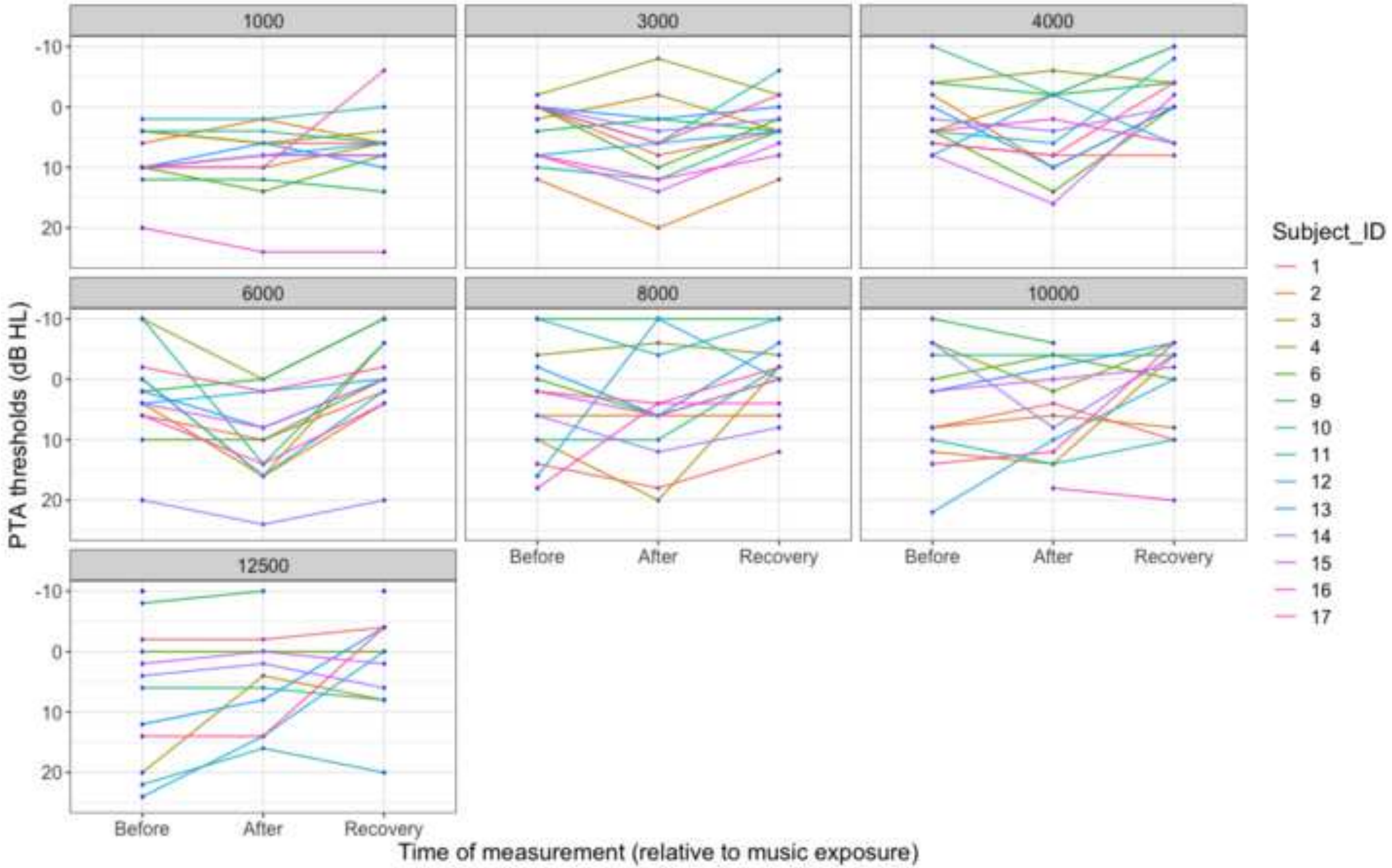

DPOAE Amplitude (dB SPL)
10
0
-10
-20
-30
Frequency (Hz)
1000
2000
3000
4000
6000
8000
Exposure
Before
After

Figure 5


1000
3000
4000
6000
8000
10000
12500
-10
0
10
20
PTA thresholds (dB HL)
Before
After
Recovery
Time of measurement (relative to music exposure)
Subject_ID
1
2
3
4
6
9
10
11
12
13
14
15
16
17