Peripheral Auditory Involvement in Childhood Listening Difficulty

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Abbreviations:

Auditory Processing Disorder (APD); Broad Band Noise (BBN); Central Auditory Nervous System (CANS); Cincinnati Children's Hospital (CCH); decibel Hearing Level (dB HL); decibel Sound Pressure Level (dB SPL); Distortion Product Otoacoustic Emissions (DPOAE); Extended High Frequency (EHF); Hearing Loss (HL); Idiopathic Listening Difficulty (LiD); Inner Hair Cells (IHC); Institutional Review Board (IRB); Middle Ear Muscle Reflex (MEMR); Otitis Media with Effusion (OME); Outer Hair Cells (OHC); Pressure-Equalization (PE); Signal-toNoise Ratio (SNR); Transient Evoked Otoacoustic Emissions (TEOAE); Tympanometric Peak Pressure (TPP); Typically Developing (TD)

Abstract

Objectives: This study tested the hypothesis that undetected peripheral hearing impairment occurs in children with idiopathic listening difficulties (LiD), as reported by caregivers using the Evaluation of Children's Listening and Processing Skills (ECLiPS) validated questionnaire, compared to children with typically developed (TD) listening abilities.

Design: Children with LiD aged 6-14 y.o. (n = 60, mean age = 9.9 yr.) were recruited from audiology clinical records and from IRB-approved advertisements at hospital locations and in the local and regional area. Both groups completed standard and extended high frequency pure tone audiometry, wideband absorbance tympanometry and middle ear muscle reflexes, distortion product and chirp transient evoked otoacoustic emissions. Univariate and multivariate mixed models and multiple regression analysis were used to examine group differences and continuous performance, as well as the influence of demographic factors and pressure equalization (PE) tube history.

Results: There were no significant group differences between the LiD and TD groups for any of the auditory measures tested. However, analyses across all children showed that extended high frequency hearing thresholds, wideband tympanometry, contralateral middle ear muscle reflexes, distortion product and transient evoked otoacoustic emissions were related to a history of PE tube surgery. The physiologic measures were also associated with extended high frequency hearing loss, secondary to PE tube history.

Conclusions: Overall, the results of this study in a sample of children with validated LiD compared to a TD group matched for age and sex showed no significant differences in peripheral function using highly sensitive auditory measures. Histories of PE tube surgery were

significantly related to EHF hearing and to a range of physiologic measures in the combined sample.

Introduction

Otherwise unexplained, idiopathic listening difficulty (LiD) often is termed auditory processing disorder (APD) in children who have symptoms of difficulty hearing and understanding speech, and abnormal results on more complex auditory tests, despite having normal pure-tone hearing sensitivity (Jerger & Musiek, 2000); (Musiek, Shinn, Chermak, & Bamiou, 2017). While there is an assumption that peripheral hearing status is “normal” in children presenting with LiD or APD, peripheral auditory function has rarely been assessed beyond pure tone thresholds and single frequency tympanometry. LiD that impacts communication and academic performance is prevalent in young children, with at least 10% of primary school-aged children reported to have LiD, in association with speech-language and/or reading problems (Sharma, Purdy, & Kelly, 2009). Based on the prevalence of normal hearing thresholds in referrals to audiologists for complaints of listening difficulty, the prevalence of LiD is estimated at 0.5-1% of the general population (Halliday, Tuomainen, & Rosen, 2017; Hind et al., 2011). Thus, LiD is a clinically important childhood disorder, is associated with other common developmental disabilities, and urgently requires improved understanding of the underlying auditory deficits in order to devise appropriate treatment strategies.

Theoretically, ‘hearing’ necessarily involves both ‘bottom-up’ (ear to brain) and ‘topdown’ (cortical to sub-cortical) pathways through simultaneous and sequential processing (Moore & Hunter, 2013). Two general, mechanistic hypotheses for LiD with normal audiometry have been proposed since the 1970’s. Sensory processing difficulties (bottom-up), involving the central auditory nervous system (CANS) were proposed in relation to animal and human lesion studies (Snow, Rintelmann, Miller, & Konkle, 1977). Various proponents of this theory have advocated assessment with low-redundancy speech tests (using added noise, filtering, rapid speech, etc.) to stress the highly redundant central auditory pathways to reveal deficits (Cameron, Dillon, Glyde, Kanthan, & Kania, 2014; Keith, 1995, 2000). Alternatively, LiD was proposed to be a problem of higher-level cognition or attention (top-down), especially in children with language disorders (Moore, Ferguson, Edmondson-Jones, Ratib, & Riley, 2010; Rees, 1973). Individuals could have involvement of one or both mechanisms, and each may suggest different management needs, e.g. remote microphone communication devices versus language and cognitive-behavioral training.

Pure-tone audiometry is, by definition, normal in children with LiD, yet few studies have performed detailed assessments of the peripheral auditory system. There are multiple complex aspects of middle and inner ear function that could affect LiD. Decreased sensitivity in the extended high frequencies (EHF; > 8 kHz), although not currently an exclusion criterion for LiD, could result from pathology in the basal cochlea, as has been reported in association with chronic childhood otitis media with effusion or OME and treated with pressure equalization (PE) tubes (Hunter et al., 1996; Laitila, Karma, Sipila, Manninen, & Rakho, 1997; Margolis, Saly, & Hunter, 2000; Gravel et al., 2006). These studies have found that frequencies above 4 kHz and up to as high as 20 kHz have poorer thresholds that persist after recovery of middle ear function, including tympanometry, high frequency middle ear reflectance and bone conduction. The difference in thresholds increases with greater frequency, suggesting basal cochlear involvement. Because OME is a common childhood condition, poorer EHF hearing could be a basis for poorer speech perception, especially in noise, for children with histories of recurrent or chronic OME. Other possibilities that could selectively affect EHF include cochlear pathology caused by a genetic mutation (Moser, Predoehl, & Starr, 2013; Rance et al., 2012; Wynne et al., 2013), noise trauma (Gopal, Chesky, Beschoner, Nelson, & Stewart, 2013; Sulaiman, Seluakumaran, & Husain, 2013), ototoxicity (Stavroulaki et al., 1999), heavy metal exposure (Shargorodsky, Curhan, Henderson, Eavey, & Curhan, 2011), viral infection (Foulon et al., 2012; Karltorp et al., 2012) or cochlear neuropathy (Bharadwaj, Verhulst, Shaheen, Liberman, & Shinn-Cunningham, 2014). The EHF are usually not included in audiologic testing, so these conditions could be undetected despite complaints of hearing difficulties.

Better hearing thresholds in the region from 6-12.5 kHz (Besser, Festen, Goverts, Kramer, & Pichora-Fuller, 2015; Levy, Freed, Nilsson, Moore, & Puria, 2015) have been associated with better reception of speech in background noise. The converse could also be important in that threshold impairment in higher frequency regions could negatively impact speech perception (Motlagh Zadeh et al., 2019). In a study of frequency selectivity, temporal masking and temporal fine structure, speech recognition was not related to audibility once highfrequency sensitivity differences across subjects (5 to 8 kHz) were removed statistically (Summers, Makashay, Theodoroff, & Leek, 2013). Thus, high-frequency hearing loss appeared to be associated with distortions in lower-frequency processing.

Known sequelae of conductive loss include impaired spatial processing (Cameron et al., 2014) and binaural interaction (Hall, Grose, & Pillsbury, 1995; Hogan, Meyer, & Moore, 1996). Cochlear pathology may affect the endocochlear potential (Li & Steyger, 2009), outer hair cells (Marler, Sitcovsky, Mervis, Kistler, & Wightman, 2010), inner hair cells (Stone, Moore, & Greenish, 2008), and spiral ganglion neurons (Sone, Schachern, & Paparella, 1998), subsequently impairing processing within the central auditory nervous system. Any of these auditory system conditions could underpin symptoms of LiD, for example, impaired temporal processing, increased auditory filter width, or enhanced masking may lead to poor speech perception. In addition, efferent influences that in turn affect outer hair cell (OHC) function may be altered by auditory experience, e.g., pathological midline pontine function (Bajo, Nodal, Moore, & King, 2010; Irving, Moore, Liberman, & Sumner, 2011) or altered forebrain lateralization (Markevych, Asbjornsen, Lind, Plante, & Cone, 2011).

As part of a much broader longitudinal study entitled “sensitive indicators of childhood listening difficulties” (SICLID), we tested the hypothesis that subtle, undetected peripheral hearing impairment occurs in children with LiD. Our approach was to compare highly sensitive peripheral auditory tests in age- and gender-matched groups of children with and without an underlying LiD, based on caregiver-report using the Evaluation of Children's Listening and Processing Skills (ECLiPS) validated questionnaire (Barry, Tomlin, Moore, & Dillon, 2015) independent of a required diagnosis of APD. This design avoids the conundrum that there is no accepted consensus or gold standard diagnosis of APD (Wilson & Arnott, 2013) and fulfills the requirement that the presenting auditory complaints are tightly linked to the condition, while outcome measures are independent of the inclusion criteria. This design further ensures that children with validated LiD comprise the experimental group, but makes no assumptions concerning the etiology of their difficulties, similar to other studies that emphasize clinical presentation of LiD (Cameron & Dillon, 2007a, 2007b, 2008; Dhamani, Leung, Carlile, & Sharma, 2013). Previous research on LiD has been based mainly on either clinical speech-based tests (Musiek, Chermak, Weihing, Zappulla, & Nagle, 2011; Sharma et al., 2009) or a selection of psychoacoustic tests (Moore, 2011). Here, we justified test selection by focusing on defined levels of peripheral processing (middle ear, cochlea, auditory nerve, brainstem, efferent pathways) and proven test sensitivity.

Materials and Methods

Participants

The study was approved by the Cincinnati Children's Hospital (CCH) Institutional Review Board (IRB). The broader SICLID study, encompassing many aspects of LiD, is longitudinal, occurring in "Waves" with repeated assessment every two years for enrolled children. This report concerns Wave 1, in a total of 114 children who completed the full audiologic test battery. The sample was divided into two groups. Children identified with LiD aged 6-14 y.o. at enrollment and typically developing (TD) children. The TD group was aged 614 yr. were age and gender-matched by proportional sampling. The LiD participants were recruited initially from a medical record review study of over 1,100 children assessed for APD at CCH (Moore et al., 2018). We initially attempted to enroll only children who met clinical criteria for APD (2 or more SD below on 2 or more age-appropriate tests used for diagnosing APD). However, few children met these criteria for APD diagnosis, although some had received an audiology diagnosis of "APD weakness", documented in the audiologist's report. While including these children in the study, we defined the score on a standardized and validated parent questionnaire tool, the ECLiPS (see below), to assign children into each group in lieu of an APD diagnosis.

Some children with LiD and all TD children were recruited from flyers that were posted in relevant CCH clinics (Audiology, Pediatrics, Speech-Language Pathology) and emailed to all CCH employees and families interested in research. We maximized efforts to recruit children with APD diagnoses, including sending advertisements to audiology clinics within 300 miles, offering families travel costs for visits. Other IRB-approved social and community listings in the local and regional area were distributed to broaden the sample. Interested caregivers completed eligibility screening for their children, consisting of a detailed medical and educational background questionnaire, and a questionnaire about the child's history of noise exposure. The TD group completed identical clinical and research testing as the LiD group and were required to have no significant listening difficulties, hearing loss or major developmental diagnoses. Children reported to have major neurologic or cognitive dysfunction were excluded on the screening questionnaires. Parental permission and child assent using IRB-approved forms were obtained prior to any assessments. Pure tone hearing sensitivity was required to be normal from .25 to 8 kHz at all frequencies (≤ 20 dB HL) for both groups at the time of the assessments. Of the 60 participants with LiD and normal hearing, 39 had been evaluated with a central auditory processing evaluation by the CCH audiology clinic, but only 16 (27% of the LiD participants) had received a positive diagnosis of APD. The remainder of the LiD group were recruited based on their ECLiPS scores.

To ascertain presence of LiD, validated and normalized caregiver reports of listening skills were completed by parents using the ECLiPS questionnaire, following a referral from the audiology clinic, or by the parent that a child had auditory processing problems (Barry et al., 2015) (Barry et al., 2015; Roebuck & Barry, 2018). The ECLiPS profiles the participant's listening and communication difficulties. The ECLiPS has 38 simple statements (items) describing behaviors commonly observed in children. Caregivers are asked to rate how much they agree with each statement on a five-point Likert scale ranging from strongly disagree to strongly agree. The ratings are averaged to derive scores, scaled by age, on five subscales (speech & auditory processing, environmental & auditory sensitivity, language/ literacy/ laterality, memory & attention, and pragmatic & social skills) each containing 6-9 distinct items. A standardized total composite score can also be calculated; this total score forms the basis of data analysis in this study. In general, total standardized ECLiPS scores of ≥7 defined the TD group, and scores <7 (less than all TD children) defined the LiD group. However, there were 4 children with LiD who had a previous audiologic diagnosis of APD, that scored 7 (x3) or 9 (x1) on the ECLiPS. Because they had a diagnosis of APD, they were assigned to the APD group. The summary ECLiPS scores are shown in Table 1.

All participants' parents completed a comprehensive background questionnaire regarding educational level of both parents, ethnicity, race, child and family history of hearing or listening problems, child histories of otitis media, PE tube surgeries, noise exposures, head injuries, prematurity, vision problems, diagnoses related to auditory, speech, language, psychology, educational and cognitive/development, therapy provided in each of these areas, medications taken presently and in the past. Histories of PE tube surgery, diagnoses and therapy reports were verified by an independent medical record review. The history of PE tubes reported by parents agreed with the medical record in 94.7% of cases.

Several additional tests were completed in the SICLID study, including auditory processing, speech perception, cognition, brainstem and cortical evoked responses, and structural and functional MRI that are beyond the scope of this analysis, and will be reported in subsequent articles.

Table 1 about here

Audiological assessments

Otoscopy was completed and if necessary, cerumen was removed prior to audiometry. All audiometric testing was completed in a double-walled soundproof booth (Industrial Acoustics Company, North Aurora, Illinois) that meets standards for acceptable room noise for audiometric rooms (ANSI/ASA, 1999 (R2018)). Standard and EHF (10-16 kHz) thresholds were measured using the manual Hughson-Westlake method for the range of .25-8 kHz at octave intervals and at four additional frequencies (10, 12.5, 14 and 16 kHz) using the Equinox audiometer (Interacoustics Inc., Middlefart, Denmark) with Sennheiser 300 HDA circumaural earphones (Old Lyme, CT). If any air conduction thresholds were greater than 20 dB HL, bone conduction was tested between 0.5 and 4 kHz using appropriate narrowband masking in the contralateral ear (Radioear Inc. B-71 bone vibrator, New Eagle, PA).

<u>Middle ear measures</u>: Wideband tympanometry (acoustic absorbance and group delay) was measured using click stimuli and analysis from 0.25 to 8 kHz over an ear canal pressure of +200 daPa to -400 daPa using a custom recording system (Keefe, Hunter, Feeney, & Fitzpatrick, 2015) coupled to an AT235 immittance system (Interacoustics Inc., Middlefart, Denmark) to control air pressure. The wideband tympanometry technique is more sensitive and specific than standard clinical testing to many conductive disorders including OME, since it measures the full range of frequencies important for speech perception (Hunter, Prieve, Kei, & Sanford, 2013). This technique has also been used to interpret high frequency hearing thresholds (Margolis et al., 2000) and cochlear measures with respect to possible middle ear effects (Carpenter, Cacace, & Mahoney, 2012).

<u>Middle ear muscle reflexes (MEMR)</u>: To assess the auditory afferent and efferent loop, MEMR were measured using a wideband absorbance technique. The wideband MEMR technique provides lower thresholds due to the more sensitive absorbance measurement across a range of frequencies activated by the middle ear muscle, it incorporates signal averaging to reduce contamination by noise, and it is automated for detection of the reflex based on both change in absorbance and cross correlation of repeated stimuli (Feeney et al., 2017; Hunter, Keefe, Feeney, & Fitzpatrick, 2017). Thus, the subjective bias that may be problematic in visual judgment of typical admittance based MEMR procedures and lack of signal averaging to decrease noise

contamination is improved. Details regarding the measurement and analysis procedures may be found in Keefe, Feeney, Hunter, and Fitzpatrick (2017). Briefly, broad band noise (BBN) and pure tone stimuli (0.5, 1, 2 kHz) were presented both ipsilaterally and contralaterally while absorbance changes were monitored using a click stimulus to measure absorbance changes in the ear with a microphone. Ear canal air pressure was adjusted to the peak tympanometric pressure obtained during wideband tympanometry. To record responses, probe clicks were averaged across 4 stimuli, varying in 5-dB steps from 60 to 120 dB peSPL calibrated in a 2-cc coupler and in the real ear. Contralateral and ipsilateral MEMR testing used response averaging, artifact rejection and signal processing techniques to measure threshold, onset latency and amplitude growth.

<u>Cochlear measures</u>: Activity in the cochlear partition was assessed using two different types of otoacoustic emissions. Distortion Product Otoacoustic Emissions (DPOAE; 1/3 octaves from 210 kHz) were measured with paired tones (f2 and f1) presented at 65- and 55-dB SPL, with an f2/f1 frequency ratio of 1.22 using an Interacoustics Titan system (Interacoustics Inc., Middlefart, Denmark). The DPOAE signal and noise level were measured at DPOAE frequency of 2f1-f2 in descending order at ten f2 frequencies (10, 9.0, 8.2, 7.5, 6.2, 5.1, 3.8, 3.2, 2.6, and 2.1 kHz). The signal-to-noise ratio (SNR) was calculated by subtracting the DPOAE noise level from the DPOAE level at each f2 test frequency.

Chirp transient evoked otoacoustic emissions (TEOAEs) were measured using an experimental system that employed positive swept (low to high frequencies) chirp stimuli, coupled with double-evoked methods to allow broader-frequency recording from 1 kHz up to 14.7 kHz than is possible using commercial TEOAE systems (Keefe et al., 2019). The doubleevoked method removes stimulus artifact, allowing recording at higher frequencies, and the chirp stimuli reduce distortion at higher intensity levels because the stimulus is extended in duration compared to click stimuli. Two chirp stimuli were used; the first covered the standard frequency range (0.5-8 kHz, 78 dB peSPL) and the second covered extended high frequencies (8-14.7 kHz, at 76 and 82 dB peSPL to test a lower and higher intensity), referenced to a click. Both stimuli were delivered at a sweep frequency rate of 188 Hz/ms. The maximum level was limited to 9 dB below the stimulus level that resulted in any system distortion measured in a long, reflection free cylindrical tube (Keefe et al., 2019). TEOAE responses were measured using an Etymotic ER10B+ microphone, a pair of ER2 sound sources and a sound card at 44 kHz sample rate (Card Deluxe), controlled by a custom program written in MATLAB.

Statistical Analysis: Recordings were analyzed during each session for artifacts and noise, and repeated if necessary, during the same session after taking care to obtain the best probe insertion and quietest condition possible. Data were exported for each individual ear and condition, then were analyzed visually for recording errors and artifacts. If the test had been repeated, the cleanest recordings (lowest noise and artifact) were selected for further analysis employing SAS statistical software, version 9.3 (SAS Institute, Cary, N.C.). A two-sided significance level was set at $p < 0.05$.

Results were analyzed first with descriptive statistics to summarize sample demographics and outcome measurements. The interval variables were summarized by central tendency and dispersion, and categorical variables were described by frequencies and percentages. Twosample t-tests, Chi-Square and Fisher Exact tests were performed to compare the demographics between the children with LiD and TD. Boxplots were created to study the distribution of the outcomes. Outcome variables were analyzed first in univariate, then multivariate mixed models that included Group (TD or LiD), age at EHF testing, sex, race, pressure-equalization (PE) tube history, and EHF hearing loss as independent factors. The Pearson correlation coefficient was calculated to explore the relationship among the outcomes. A repeated measure analysis of variance (RMANOVA) using frequency as the repeated measure was conducted to study outcome differences between the LiD and TD group controlling for the above factors. Significant factors from the univariate analysis and between group demographics were included in the final multiple adjusted model, including significant interaction effects. The best variance-covariance structure was chosen by model fitting comparisons. Tukey-Kramer multiple adjustment was applied for pairwise comparisons among the levels of the significant factors. In addition to the group analysis, the entire sample (LiD and TD) was also analyzed using multiple regression including the ECLiPS score as a continuous variable, race, maternal education level, and history of tubes. Covariates that were marginally significant were retained in the final model, while the ECLiPS score was retained in all regression analyses, as it was the primary question of interest.

Results

Demographics: As shown in Table 1, this report includes 114 children with a mean age of 9.9 years (SD = 1.99), ranging from 6.5 to 14.6 years. There were 60 children with LiD and 54 TD children, with equivalent ages for the two groups. Boys comprised the majority in both groups and the sex proportion was not significantly different in the LiD compared to TD group. The majority race was white in both groups, although significantly more so in the TD group, with more African American children in the LiD group. There was no group difference in Hispanic (Latino) ethnicity. There was not a significant group difference in the reported history of ear infections, or in treatment with PE tubes, reported in 28% of the LiD group and 22% of the TD group. In the LiD group, 5 children had 2 or more surgeries for PE tubes, while in the TD group, 3 had two or more PE tube surgeries.

Audiometry: Tone thresholds of individuals across audiometric frequencies were significantly ($p < 0.05$) correlated with each other (r = 0.22-0.76) except for the frequency pairs of 0.25 kHz versus 10 through 16 kHz (r = 0.13, $p = 0.1832$) and 2 kHz versus 8 kHz (r = 0.15, $p = 0.1232$). Generally, the closer the frequencies were, the stronger the intercorrelation coefficient. After controlling for significant factors in the statistical model, the least square means of the audiometric thresholds at EHFs were significantly higher than at lower frequencies. For this reason and due to significant intercorrelation, the four EHFs (10, 12.5, 14 and 16) were averaged for further analysis. No significant proportional difference ($p = 0.6816$) was found between left and right ears in terms of EHF hearing level of >20 dB HL ($X^2 = 0.1683$), thus the right and left ears were averaged for each child for further analysis.

Mean thresholds for standard and EHF audiometry for the TD compared to the LiD group are shown in Fig. 1A, including 95% confidence intervals. No significant difference was found in the overall hearing thresholds for group in the unadjusted or adjusted model (See Table 2). However, the interaction with frequency (group*frequency) was significant ($p = 0.0322$) in the adjusted model, as the average hearing thresholds were not parallel for the two groups (Fig. 1A). The interaction factor showed that the lowest frequencies (.25-1 kHz) were actually a bit better in the LiD group, then reversed to be worse at 8-16 kHz compared to the TD group. There was a highly significant effect of PE tube history as shown in Fig. 1B ($p < .0001$), with poorer hearing thresholds (.5 through 16 kHz) for children with a history of PE tubes (across both groups), and the difference increased with frequency (Fig. 1B). The overall results of multivariate RMANOVA models are provided in Table 2. In addition to the group analysis, a multivariate regression analysis was performed using the ECLiPS score as a continuous variable, along with audiogram test frequency, race, maternal education and history of PE tubes. The ECLiPS score, race and maternal education were not significantly related to EHF hearing thresholds; the regression analysis confirmed that the only significant predictive factor for audiometric thresholds was history of PE tubes (Table 3, $p < 0.0001$).

Wideband acoustic absorbance: Wideband acoustic absorbance (Fig. 2) was analyzed at ambient pressure (equivalent room air pressure, Fig. 2A) and at tympanometric peak pressure (TPP, Fig. 2B) to equilibrate for any pressure differences due to Eustachian tube function. The correlation coefficients indicated significant correlations among most ambient absorbance frequencies, and the closer the frequencies, the stronger the correlation.

In multivariate analyses, there were no significant differences in wideband acoustic absorbance at ambient pressure (p=0.2208), or at TPP (p=0.4211) for the TD compared to the LiD group. There was a significant interaction between group and frequency for ambient wideband absorbance (p=0.0193) due to slightly higher absorbance at 1.5 kHz and slightly lower absorbance at 4 kHz for the LiD group. Age was not significantly associated with ambient absorbance measurements in the adjusted analyses, but there was a significant age by frequency interaction (p <0.0001).

History of PE tubes was not significant for ambient absorbance (p=0.8129) or at TPP (p=0.8912, Fig. 2B) in multivariate analyses, although in univariate analyses there was higher absorbance for the ears with PE tube histories in the 1.5-2 kHz range. There were also no significant effects of age, sex, race, or presence of EHF hearing loss on wideband absorbance at ambient pressure or at TPP in the multivariate models (see Table 2 for p values).

Wideband acoustic group delay: Group delay is a measure of the phase angles of the acoustic absorbance across various frequencies and reveals the influence of middle ear mechanics on transmission of the stimulus through the middle ear. Increased group delay in sound transmission occurs in ears that have more flaccidity, while shorter group delay occurs due to greater stiffness in the middle ear. As shown in Fig. 3A, there was no significant difference between LiD and TD groups for group delay. The main effect of frequency was highly significant ($p < 0.0001$), and the within subject test indicated that the interaction of frequency and group was also highly significant ($p < 0.0001$). This interaction was due to a few frequencies that were higher in the TD group, indicating more stiffness at those frequencies. History of tubes was significantly associated with group delay measurements in both unadjusted and adjusted analysis (Fig. 3B; p=0.0026), as was presence of EHF hearing loss (p = 0.0002). The correlation coefficients indicated significant correlations among the group delay measurements, and the closer the frequencies were, the stronger the correlation. Age was not significantly associated with group delay measurements in the adjusted analysis, but there was an interaction between age and frequency (p=0.001).

Wideband MEMR: There was no significance difference between TD and LiD groups as shown in Fig. 4A for the ipsilateral condition and Fig. 4B for the contralateral condition. The main effect of frequency was significant for both the ipsilateral and contralateral conditions (p <0.0001) among the BBN and pure tone stimuli, but there was no significant interaction of frequency and group.

As shown in Fig. 4B, significantly higher contralateral MEMR thresholds were found for ears with EHF hearing loss for BBN, 1 and 2 kHz stimuli both ipsilaterally (p = 0.0152) and contralaterally (p = .0051). No significant difference was found between LiD and TD groups for wideband MEMR thresholds for BBN, 0.5, 1 or 2 kHz for ipsilateral or contralateral presentation modes. In the regression analysis, the ECLiPS score was not significant predictor of MEMR function (p=0.5109); only history of PE tubes (p=0.015) and test frequency (BBN, 0.5, 1, 2 kHz) remained in the final predictive model (Table 3).

DPOAEs: There was no significant TD-LiD group difference for DPOAE level in the multivariate analyses (p=0.1482), consistent with the lack of audiometric threshold differences (Fig. 5A). However, for both groups combined, children with PE tube histories had significantly lower (poorer) DPOAE levels at most frequencies from 2-10 kHz (p=0.0217), as shown in Fig. 5C. Signal to noise ratio (SNR) was lower for the LiD group (Fig. 5B; p=0.0366) and in ears with PE tube history at most frequencies from 3.8 to 10 kHz (Fig. 5D; p=0.0010;). DPOAE level and SNR were lower at 3-6 kHz in ears with EHF hearing loss (Fig. 5E-F). These effects are generally consistent with the higher-frequency hearing threshold data, and with a cochlear etiology for the EHF hearing loss. In the regression analysis for DPOAE signal level, the ECLiPS score was not a significant predictor (p=0.2831). Only history of PE tubes (p< 0.0001) and DPOAE frequency (f2; p<0.0001) remained in the final predictive model (Table 3).

TEOAEs: TEOAE SNR for LiD compared to TD cases was not significantly different (p=0.1492; Fig. 6). Chirp-evoked TEOAE SNR was significantly lower in ears with PE tube history (p=0.0116; Fig 6A) as well as for cases with EHF hearing loss (p<0.0001; Fig. 6B). Thus, chirp evoked TEOAEs at standard and EHF were consistent with the DPOAE and EHF threshold effects found in ears with a history of PE tubes. In the regression analysis for TEOAE SNR, the ECLiPS score and demographic factors were not significant from 0.7 to 8 kHz (p=0.0858) and from 8-14.2 kHz (p=0.3470). Only history of PE tubes (p<0.0001, 0.0835 for <8 and ≥ 8 kHz, respectively) and TEOAE frequency (p< 0.0001) were significant in the final predictive model (Table 3).

To further examine relationships between OAE results and hearing sensitivity, multivariate canonical correlation analysis was used to test the overall relationships between the two sets of variables. Corresponding variable pairs were chosen at the closest frequencies for DPOAE F_2 frequencies versus audiometric frequencies, and for TEOAE frequencies versus audiometric frequencies. Wilk's lambda indicated that there was significant relationship between TEOAE SNR and hearing thresholds (Wilks' Lambda=0.36, $F(64, 594.8) = 1.78$, $p=0.0003$). TEOAE and hearing thresholds were negatively associated according to the correlations between the hearing thresholds and their canonical variables. The first canonical correlation coefficient was 0.62 (adjusted=0.56) with an eigenvalue of 0.63. The shared variance between TEOAE and hearing thresholds was 38.7%. Wilk's lambda indicated that there was also a significant relationship between DPOAE SNR and hearing thresholds (Wilks' Lambda=0.72, $F(16, 648.3) = 4.60$, $p<0.0001$). DPOAE SNR and hearing thresholds were negatively associated according to the correlations between DPOAE SNR and their canonical variables. The first two canonical correlation coefficients were 0.45 and 0.28 (adjusted=0.54 and 0.08) with eigenvalues of 0.26 and 0.08. The total shared variance between DPOAE SNR and Hearing thresholds was 28.2% (20.5%+7.7%).

Discussion

The main aim of the current study was to determine if evidence for previously undetected peripheral hearing impairment occurs in children with defined LiD, and to explore other factors (PE tube history, sex, race, maternal education) that may relate to their listening difficulties. The literature on peripheral hearing mechanisms in children with LiD is scant, and mostly consists of anecdotal or individual case reports. There is clearly an effect of even mild peripheral hearing loss in early childhood on speech-in-noise hearing and various aspects of cognition (Moore, Zobay, & Ferguson, 2019), including speech and language development (Tomblin et al., 2015), selective attention (Holmes, Kitterick, & Summerfield, 2017), social use of language (MeinzenDerr et al., 2014), and literacy (Harris, Terlektsi, & Kyle, 2017). However, a specific linkage to LiD (aka APD) and peripheral hearing has been difficult to ascertain since, by definition, APD pertains to normal audiologic results. The major finding of this study is that across a range of highly sensitive peripheral auditory tests, there was no difference between TD and LiD groups. It is important to point out that children with mild or greater pure tone hearing thresholds were excluded in both groups, although that condition was infrequent (about 5%) among children referred to the study with APD or listening problems. Because LiD is clearly the hallmark of peripheral hearing loss, only after excluding hearing loss, as routinely excluded in current APD definitions (standard pure tone audiometric thresholds), could we conclude that other subtle peripheral auditory dysfunction does not explain their listening problems.

We identified EHF hearing loss in a subgroup of children in both the LiD and TD groups that was specific to histories of PE tubes. About 32% of the children with listening difficulties and 20% of the TD group had elevated EHF hearing thresholds. However, this was not a significant difference in the proportion with EHF thresholds greater than 20 dB HL As has been shown previously in multiple studies (Gravel et al., 2006; Hunter et al., 1996; Laitila, Karma, Sipila, Manninen, & Rakho, 1997; Margolis et al., 2000), EHF HL is associated with OME and PE tube histories in prospective studies of children. EHF HL in OME is related to the number of PE tubes and the severity of OME (Hunter et al., 1996). Animal studies of experimentallyinduced OME have shown that the mechanism for EHF hearing loss is round window transmission of bacterial endotoxins with basilar cochlear damage (Morizono, Paparella, & Juhn, 1980; Paparella et al., 1984; Schachern et al., 2008). Inner ear morphology shows pathologic changes in the stria vascularis, suggesting it is a target of otitis media-induced damage, which may lead to sensorineural hearing loss (Tsuprun et al., 2008).

Hearing acuity above 8 kHz has been reported to be related to some aspects of challenging speech perception in competing spatial conditions in adults (Besser et al., 2015), but less information has been available regarding speech perception in children with EHF hearing loss. The unique aspect of the current study is the focus on children with LiD, rather than a history of OME, yet our primary finding was that children who had OME severe enough to be treated with PE tubes were the ones with poorer EHF hearing. The EHF hearing loss was also associated with OAE results, i.e., poorer EHF hearing that increased with higher frequencies for cases with PE tube histories, consistent with the previous studies cited above, e.g., outer hair cell effects due to the audiometric threshold configuration in the basal region of the cochlea.

We studied wideband absorbance as a measure of energy transfer into and through the middle ear across a range of frequencies. Increased absorbance corresponds to increased middle ear transmission and occurs in conditions such as ossicular erosion, where impedance is reduced, while decreased absorbance occurs in middle ear disorders such as OME that increase impedance of the middle ear. The LiD group did not have significantly different wideband absorbance compared to the TD group, indicating similar middle ear function across frequencies. However, PE tube history was again implicated, and was associated with increased wideband acoustic absorbance. The frequency region of increased absorbance in the PE tube group was not consistent with EHF hearing loss in ears with PE tube histories, since the frequency region and direction of the effect (increased absorbance with poorer hearing thresholds) was opposite to that expected. These absorbance effects were thus mechanical and restricted to the lower frequency region, in contrast to the EHF and OAE effects that are higher in frequency. Similarly, increased group delay in the lower frequencies was found for ears with a history of PE tubes. Consistent with the effect on wideband absorbance, increased group delay in the low-frequency range indicates increased eardrum flaccidity, a result of PE tube surgery (Hunter, Keefe, Feeney, Brown, et al., 2017). Thus, our interpretation is that increased absorbance and group delay is consistent with previous myringotomy to place PE tubes, resulting in increased flaccidity of the TM.

Otoacoustic emissions, both transient and distortion product, are affected when active OME is present at the time of measurement (Yeo, Park, Park, & Suh, 2002). OAEs are recognized as a highly reliable method of screening and monitoring hearing changes associated with conductive loss due to OME (Ho, Daly, Hunter, & Davey, 2002; Hunter, Keefe, Feeney, Brown, et al., 2017). However, no previous reports were found that linked high-frequency OAE differences to LiD, or to histories of PE tubes and OME. In this study, the LiD group did not have lower DPOAE levels or SNRs compared to the TD group, consistent with their behavioral hearing thresholds and indicating that pure-tone hearing sensitivity was not related to parent complaints of LiD. However, for ears with a history of PE tubes and for those with EHF hearing loss, DPOAE levels and SNR were lower, with a significant relationship between TEOAE levels and hearing thresholds at similar frequencies. Thus, a novel finding in this study is that OAEs appear to be a sensitive measure of the impact upon cochlear function in children with poorer EHF hearing. Thus, inclusion of OAE assessment is warranted to supplement pure tone audiometry due to the brief and non-invasive nature of this test.

Chirp TEOAEs provide information about the reflection component of OAE generation, while DPOAEs are generated by primarily the distortion component, thus we included both emission types. The use of HF TEOAEs (>4kHz), a first in any study for children with LiD, provides a physiological assessment of OHC function in the basal region of the basilar membrane, which is of relevance to the EHF hearing loss found in a subset of children in both groups. Suppression experiments in human ears provide evidence that TEOAEs are mainly generated near the tonotopic region of the stimulus (Keefe, Ellison, Fitzpatrick, & Gorga, 2008; Zettner & Folsom, 2003), making them attractive for detection of OHC damage in the frequency region of both the stimulus and response. Chirp and click TEOAEs have similar properties across stimulus conditions for stimuli with the same energy spectrum, but click stimuli used to measure TEOAEs can generate system distortion at higher levels due to peak clipping by the sound source. The use of chirp stimuli to measure TEOAEs has the advantage of spreading the stimulus energy out over time so as to reduce the peak levels that generate distortion (Neumann, Uppenkamp, & Kollmeier, 1994). In this study, we found significant decreases in chirp TEOAE SNR at frequencies ≥ 8 kHz that were present in cases with PE tube history and with EHF hearing loss, and a significant relationship between TEOAE levels and hearing thresholds at similar frequencies. Interestingly, the effect was specific to EHF regions, strengthening the evidence that these effects were due to cochlear damage, rather than middle ear dysfunction.

MEMR threshold elevation for BBN and pure tone stimuli was found specifically in the contralateral condition in ears that had PE tube histories and with poorer EHF hearing. This finding implicates efferent activation in the children who had a history of OME treated with tubes. This implies a central (brainstem) rather than a peripheral afferent mechanism; otherwise ipsilateral effects would be expected. Ipsilateral MEMR should be at least as sensitive as contralateral measurement since lower thresholds are found with ipsilateral measurement. In other words, the ipsilateral measurement is less affected by stimulus output limitations. These MEMR results are consistent with a previous prospective study showing that frequent OME history in children was associated with elevated MEMR threshold for contralateral acoustic reflexes (Gravel et al., 2006). Thomas, McMurry, and Pillsbury (1985) reported that one-third of children with delays in language, learning disabilities or suspected APD showed abnormal MEMR thresholds in both the ipsilateral and contralateral condition, and there was a slight positive correlation with delayed psychomotor development, but no control group was compared. Allen and Allan (2014) reported no significant difference in MEMR thresholds between a group of children diagnosed with APD compared to a group that passed APD tests, although both groups had absent MEMR reflexes in about 20% of cases. The Allen and Allan study did not include a normal control group, but a later study by the same group (Saxena, Allan, & Allen, 2015) investigated acoustic reflex growth functions in a 'suspected APD' and control group, and found shallower growth of the reflex in children suspected with APD. The present study utilized a more sensitive and reliable wideband absorbance measure to detect MEMR thresholds for both pure-tone and broad-band noise stimuli, as well as a typically developing control group, yet our results did not show differences in children with LiD compared to controls. A bias that can occur in MEMR measures is subjective interpretation of reflex presence. A strength of the technique used in the current study is the automatic detection algorithm that includes correlation and amplitude rules that objectify presence of the acoustic reflex, quantify growth characteristics, and score threshold.

Conclusions

Overall, the results of this study in a carefully controlled sample of children with validated LiD compared to an age- and sex-matched typically developing control group showed no significant differences in peripheral function using highly sensitive measures, including EHF hearing thresholds, DPOAEs, chirp TEOAEs, wideband tympanometry, and wideband MEMR thresholds. In subgroups examining risk factors, EHF hearing thresholds were found to be highly associated with PE tube history. Further, middle ear acoustic absorbance, DPOAE, TEOAE and contralateral MEMR threshold differences were all significantly associated with PE tube histories and with EHF hearing. However, these findings did not appear to explain LiD, since these effects were also present in TD children with tube histories. To further explore factors related to LiD, we carried out additional analysis using the ECLiPS score as a continuous variable across both groups and added maternal education level as a demographic factor along with the factors found to be significant in the group analysis. The regression analysis was consistent with the group analysis, and again showed that PE tube history, not severity of the ECLiPS score, was the primary predictive factor across all the peripheral function tests.

Although we did not uncover peripheral hearing deficits that were specifically associated with LiD, we recommend that peripheral dysfunction be assessed in any child presenting with listening problems to determine whether potentially remediable peripheral hearing problems may be present. The inclusion of pure tone thresholds above 8 kHz, OAE and acoustic reflex measures are quick and inexpensive measures that can ensure that hearing issues are fully investigated in such cases. Recurrent OME and tubes are a frequent occurrence in children, especially those with listening problems. A major result of this study is that these tests are sensitive to those histories. Although peripheral hearing problems may not be the primary cause of LiD, diagnostic audiologists are in the best position to uncover auditory system deficits and to provide appropriate remediation to lessen any additional impact to a child's learning challenges.

Figure Legends

Figure 1. A. Average audiometric thresholds and 95% confidence intervals expressed in hearing level re: ISO 389.5 for the typically developing (TD) and the Listening Difficulty (LiD) groups.

B. Average audiometric thresholds and 95% confidence intervals for both groups combined, subdivided by history of PE tube surgery.

Figure 2. A. Average ambient absorbance ratio and 95% confidence intervals for the typically developing (TD) and the Listening Difficulty (LiD) groups. B. Average ambient absorbance and 95% confidence intervals for both groups combined, subdivided by history of PE tube surgery.

Figure 3. A. Average group delay (in μsec) and 95% confidence intervals for the typically developing (TD) and the Listening Difficulty (LiD) groups. B. Average group delay and 95% confidence intervals for both groups combined, subdivided by history of PE tube surgery.

Figure 4. A. Ipsilateral middle ear muscle reflexes (MEMR) in dB SPL measured in a 2cc coupler for three group contrasts: TD versus LiD, History of PE tubes versus no history, and presence of EHF hearing loss versus normal hearing. Boxplots show median (solid line) within interquartile ranges (colored boxes) and 95% confidence intervals (stems). Outliers are individual dots. B. Contralateral MEMR using the same group contrasts and plot format as in A.

Figure 5. A. Average DPOAE level in dB SPL and 95% confidence intervals expressed in hearing level re: ISO 389.5 for the typically developing (TD) and the Listening Difficulty (LiD) groups. B. Average DPOAE SNR for both groups combined for the typically developing (TD) and the Listening Difficulty (LiD) groups. C. Average DPOAE level and 95% confidence intervals for both groups combined, subdivided by history of PE tube surgery. D. Average DPOAE SNR and 95% confidence intervals for both groups combined, subdivided by history of PE tube surgery. E. Average DPOAE level and 95% confidence intervals for both groups combined, subdivided by presence of EHF hearing loss. E. Average DPOAE SNR and 95% confidence intervals for both groups combined, subdivided by presence of EHF hearing loss.

Figure 6. A. TEOAE SNR in dB SPL measured in a 2-cc coupler for three group contrasts: TD versus LiD, History of PE tubes versus no history, and presence of EHF hearing loss versus normal hearing. Boxplots show median (solid line) within interquartile ranges (colored boxes) and 95% confidence intervals (stems). Outliers are individual dots. B. TEOAE SNR in dB SPL measured in a 2-cc coupler using the same group contrasts and plot format as in A.

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Author Contributions

LLH and DRM designed experiments, co-wrote the paper, and provided interpretive analysis and critical revision to the paper. CMB, LL and HS analyzed data and provided interpretive analysis and critical revision to the paper. NLS and AP oversaw study enrollment, performed experiments, and analyzed data. All authors discussed the results and commented on the manuscript.

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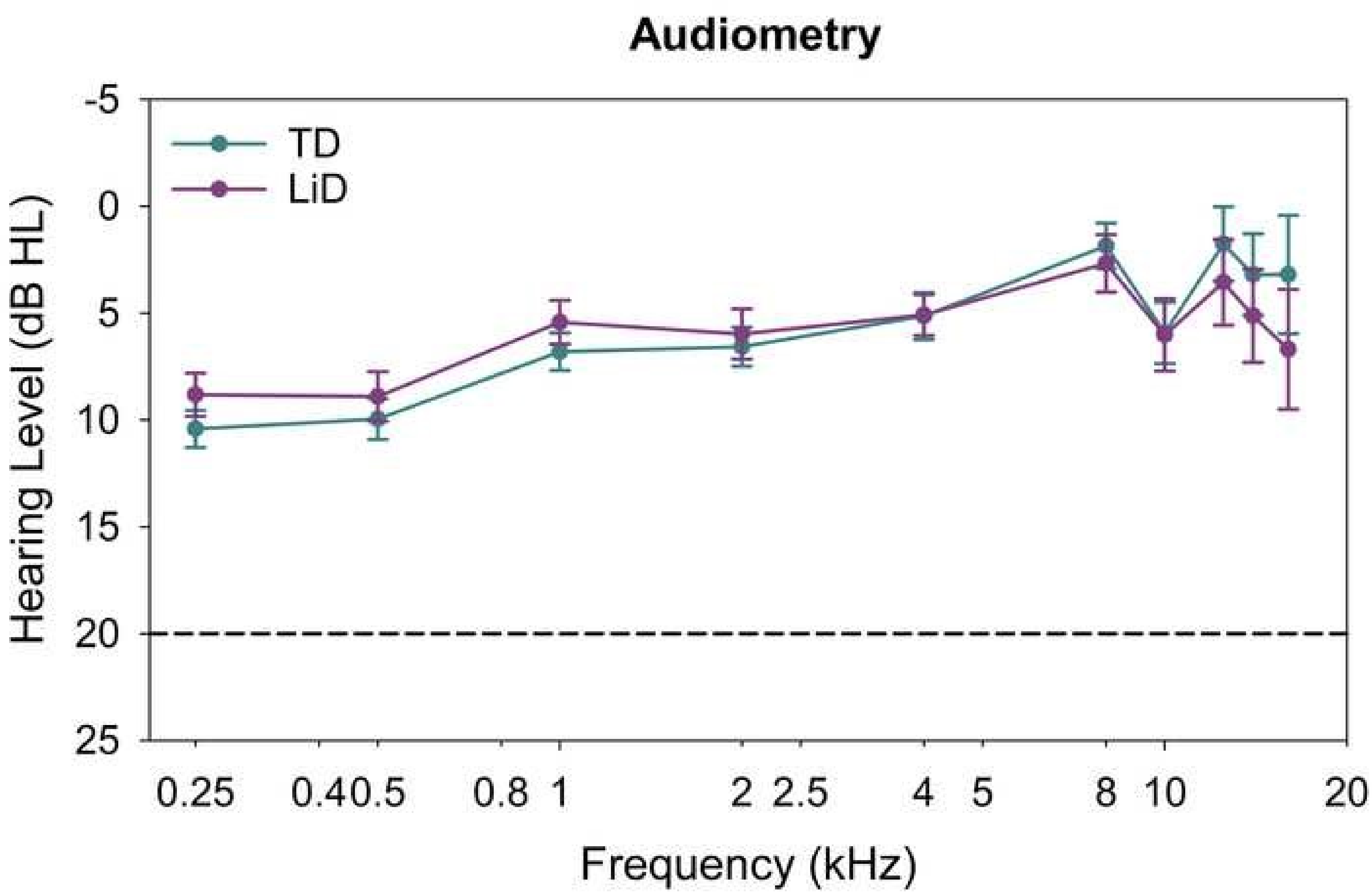
Figure 1A


Audiometry
TD
LiD
Hearing Level (dB HL)
-5
0
5
10
15
20
25
0.25
0.40.5
0.8 1
2 2.5
4 5
8 10
20
Frequency (kHz)

F

Figure 1B

Click here to access/download;Figure;Fig 1B Audiogram Tube Hx.TI

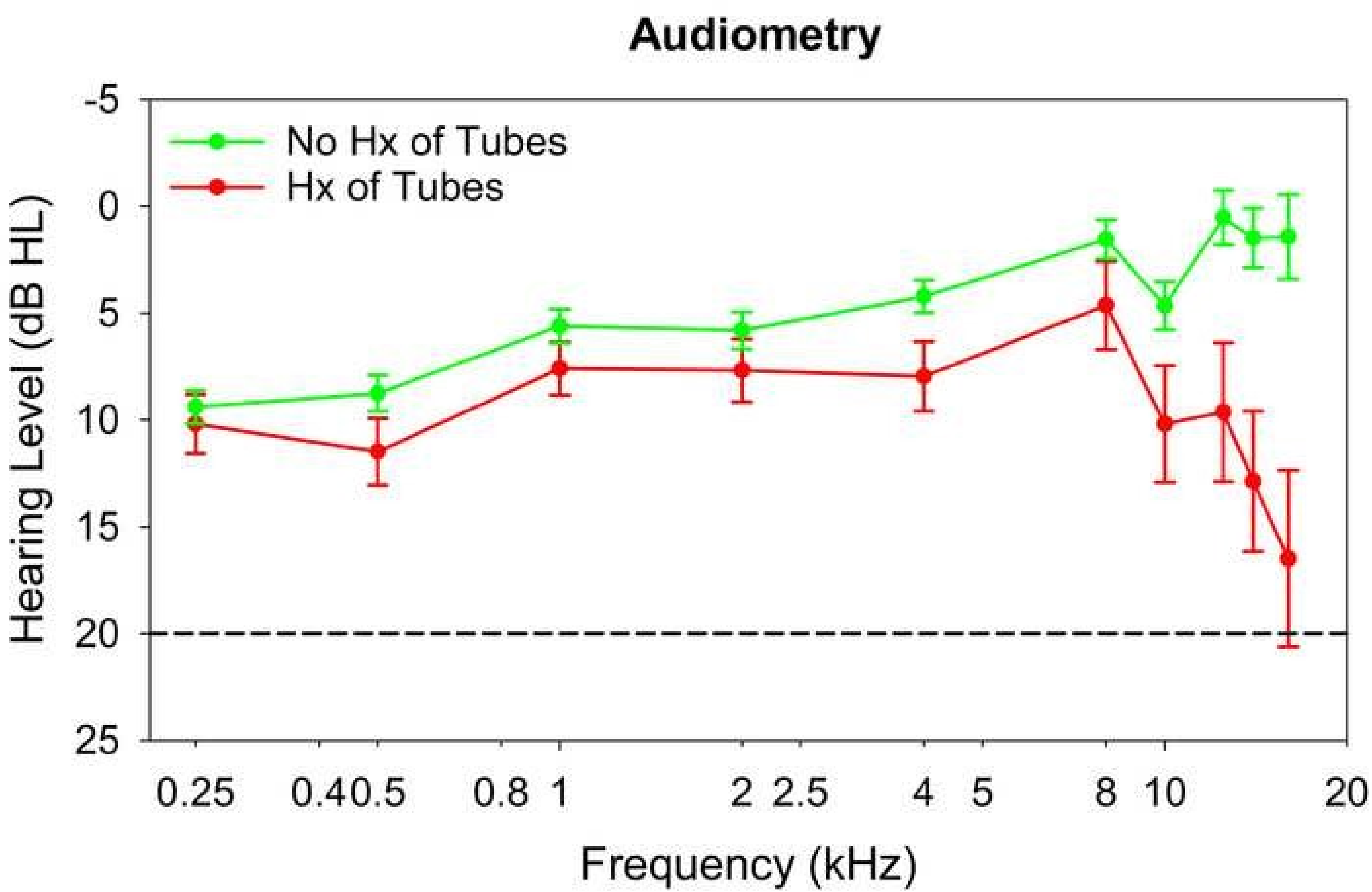

Audiometry
No Hx of Tubes
Hx of Tubes
Hearing Level (dB HL)
-5
0
5
10
15
20
25
0.25
0.40.5
0.8 1
2 2.5
4 5
8 10
20
Frequency (kHz)

Figure 2A

Click here to access/download;Figure;AA-TD vs LiD.TI

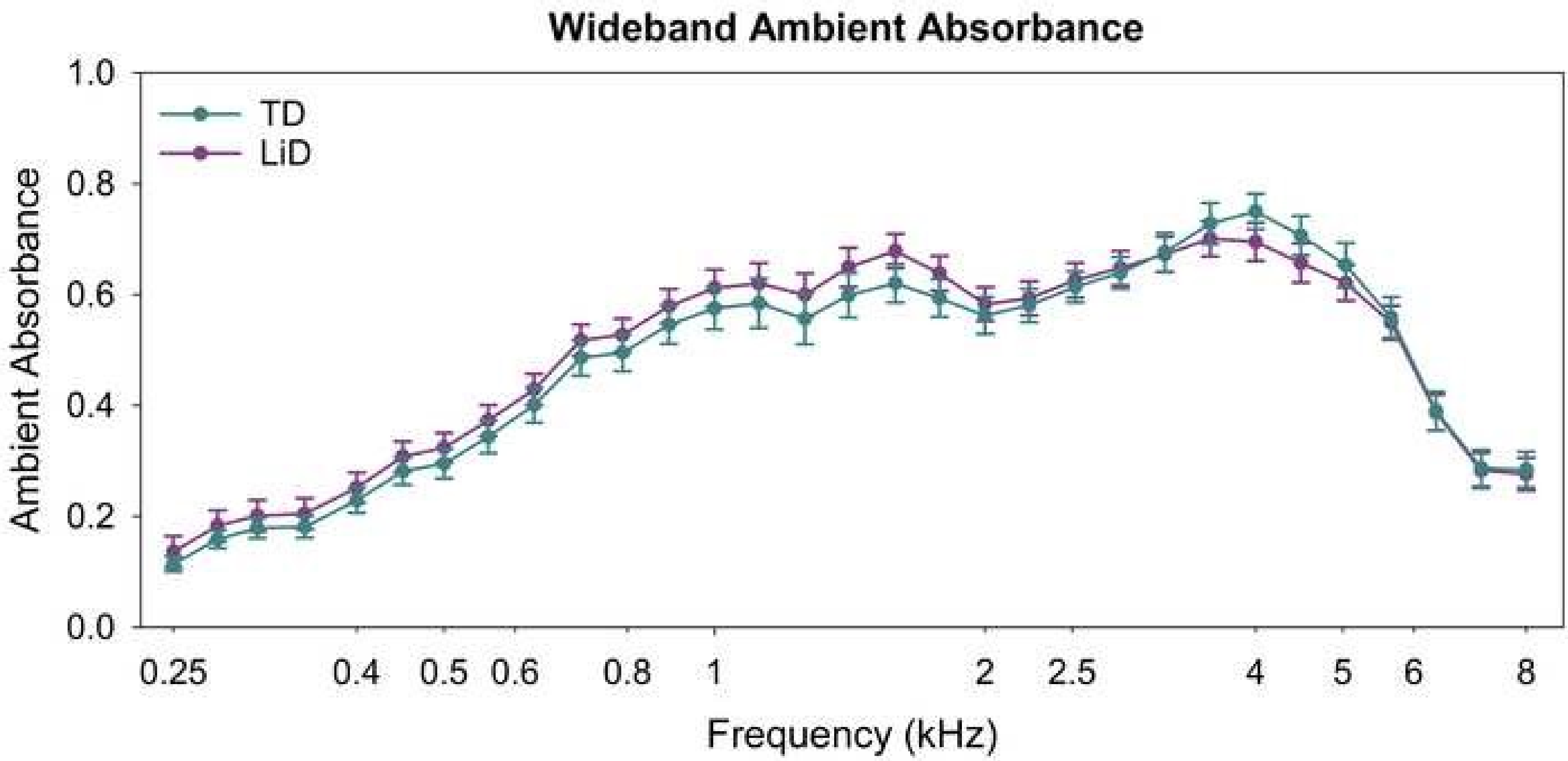
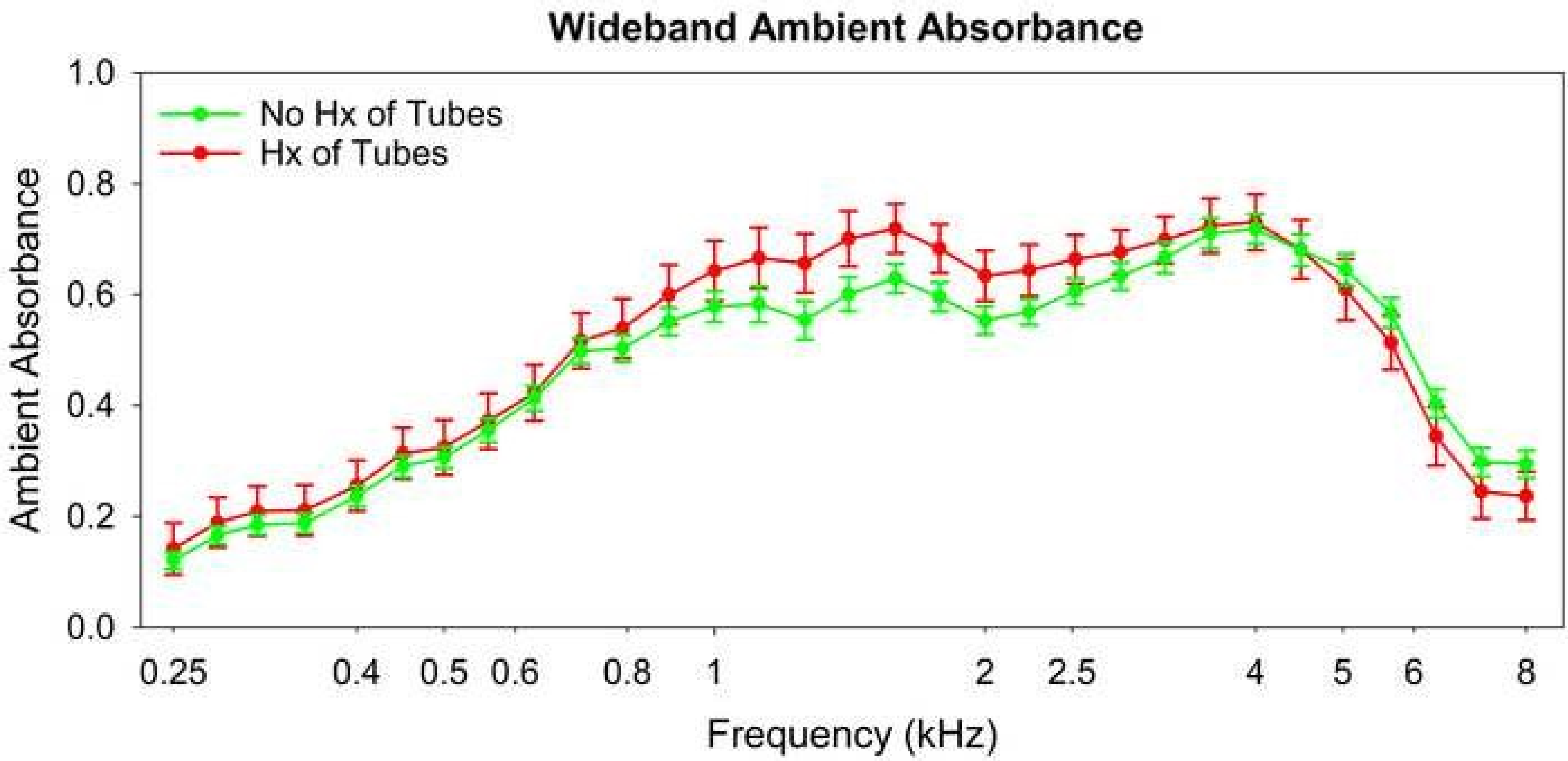
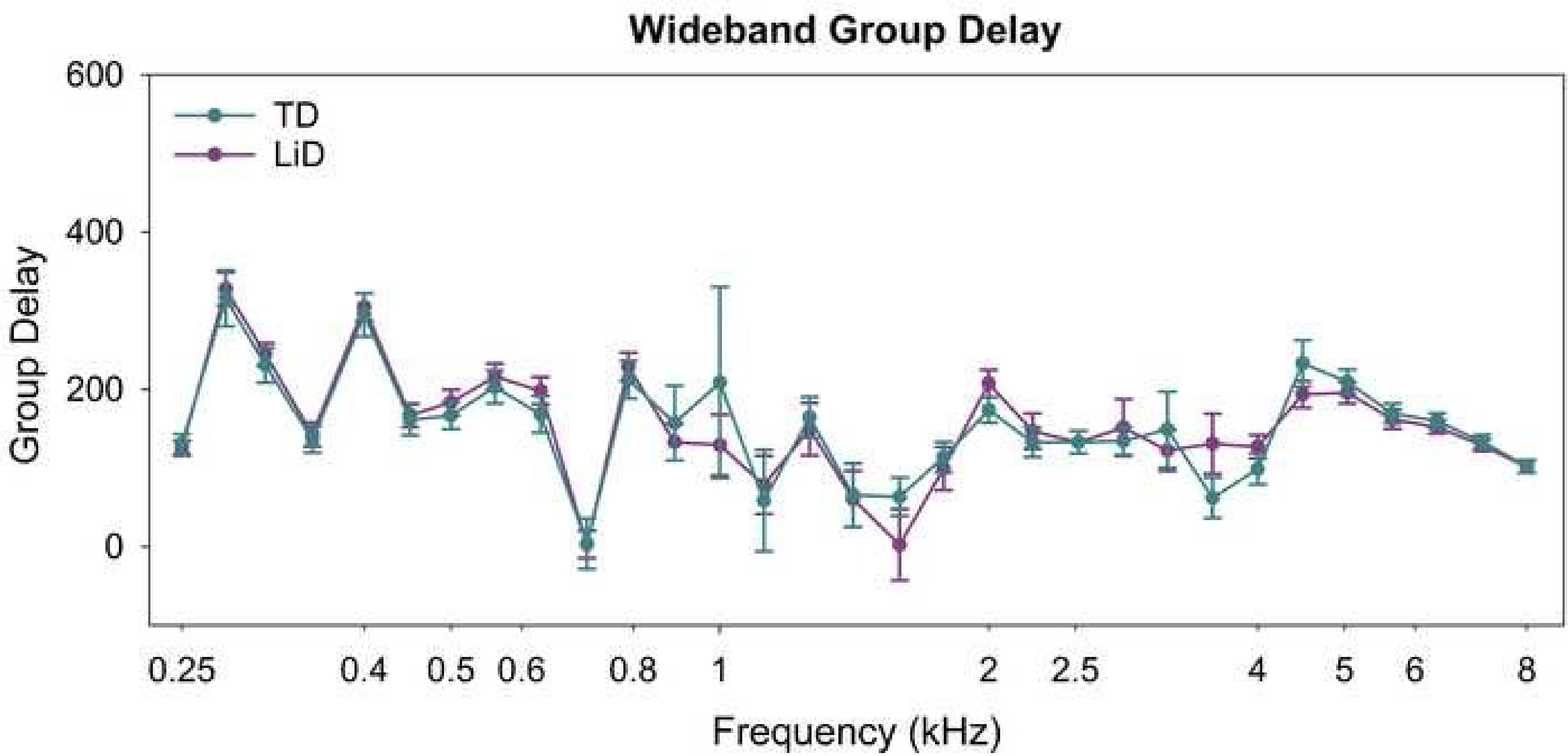


Figure 2B



Wideband Ambient Absorbance
No Hx of Tubes
Hx of Tubes
Ambient Absorbance
1.0
0.8
0.6
0.4
0.2
0.0
0.25
0.4
0.5
0.6
0.8
1
2
2.5
4
5
6
8
Frequency (kHz)

Figure 3A



Wideband Group Delay
TD
LiD
Group Delay
600
400
200
0
0.25
0.4
0.5
0.6
0.8
1
2
2.5
4
5
6
8
Frequency (kHz)

F

Figure 3B

Click here to access/download;Figure;GD-Tube Hx.TI

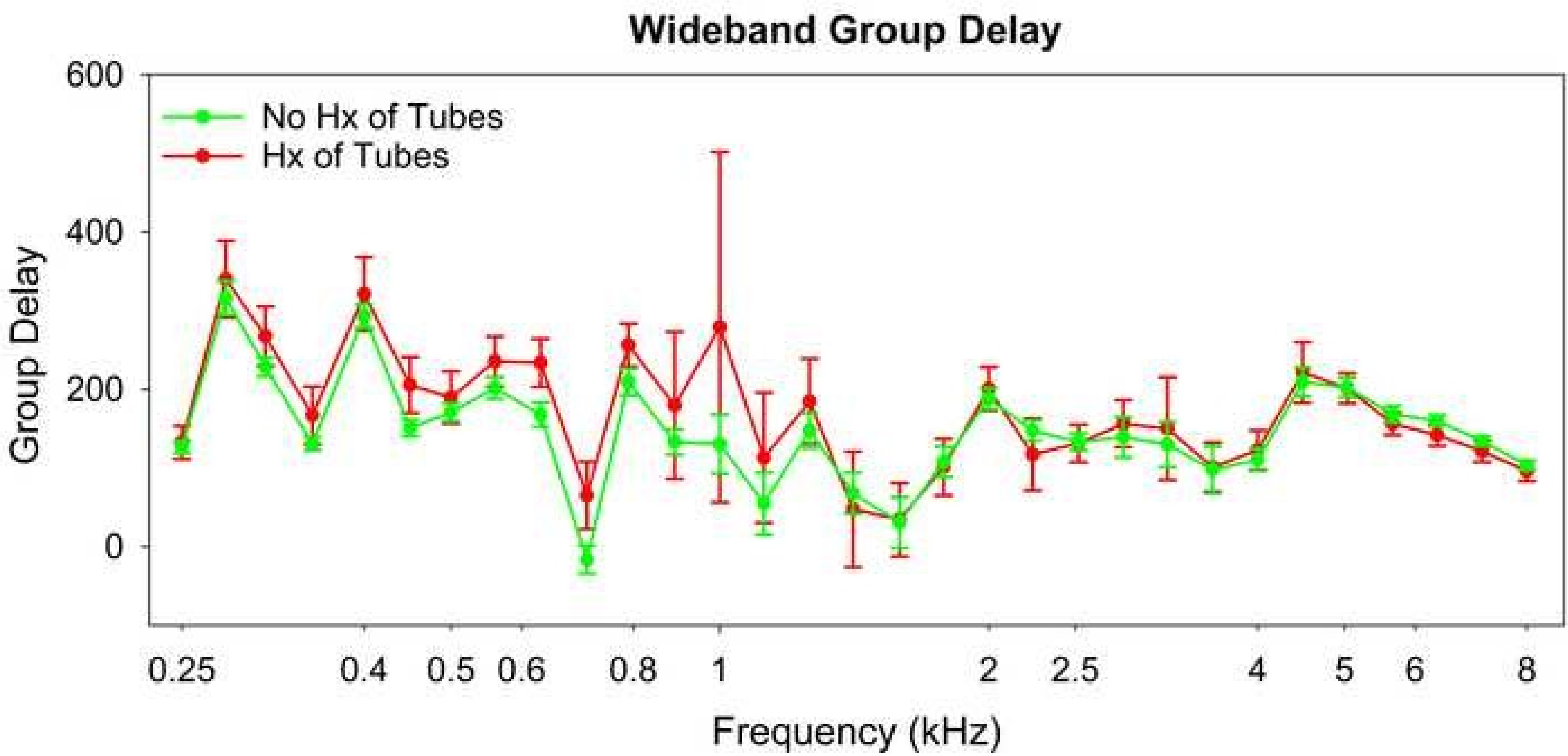
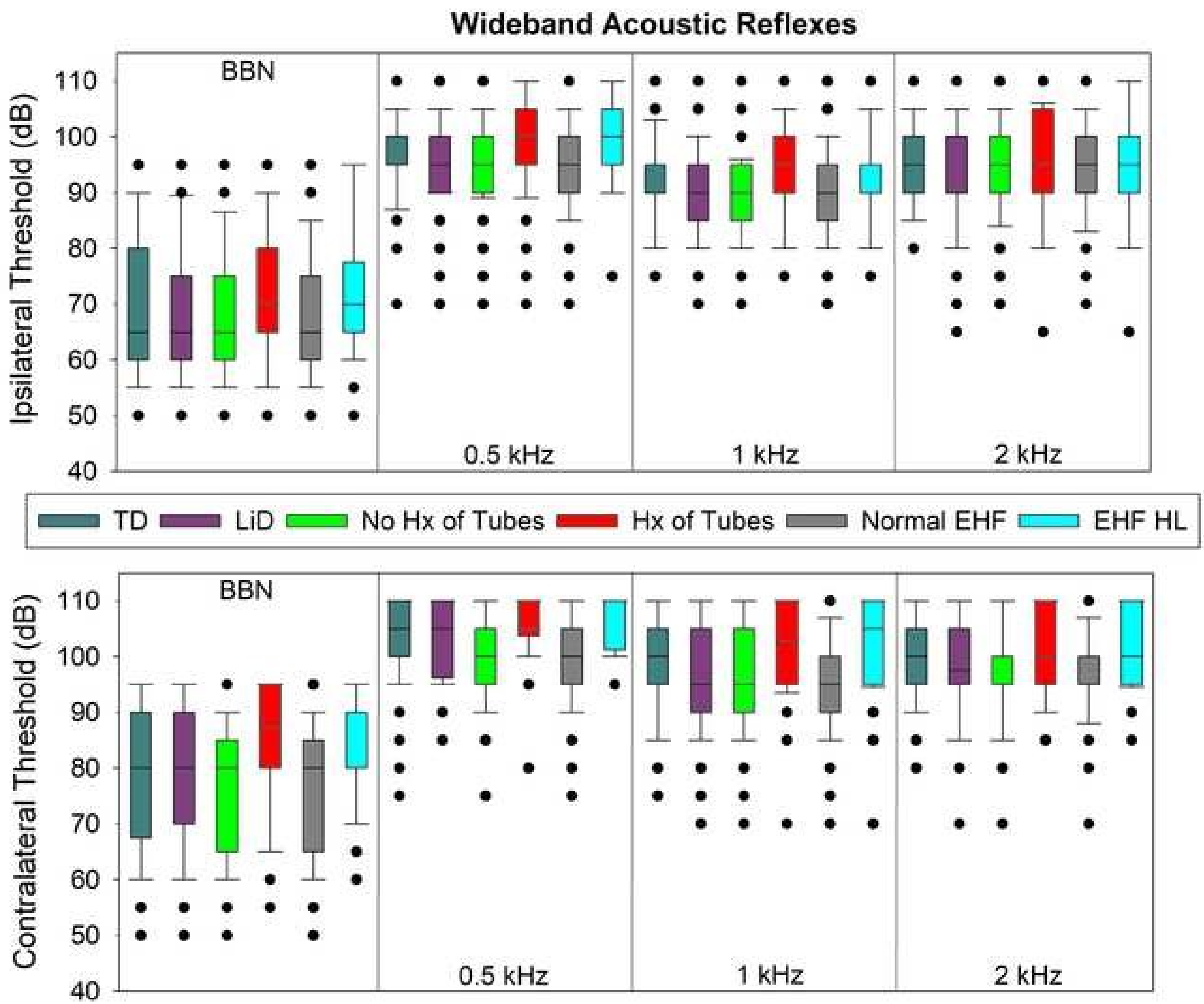


Figure 4

Figure 5



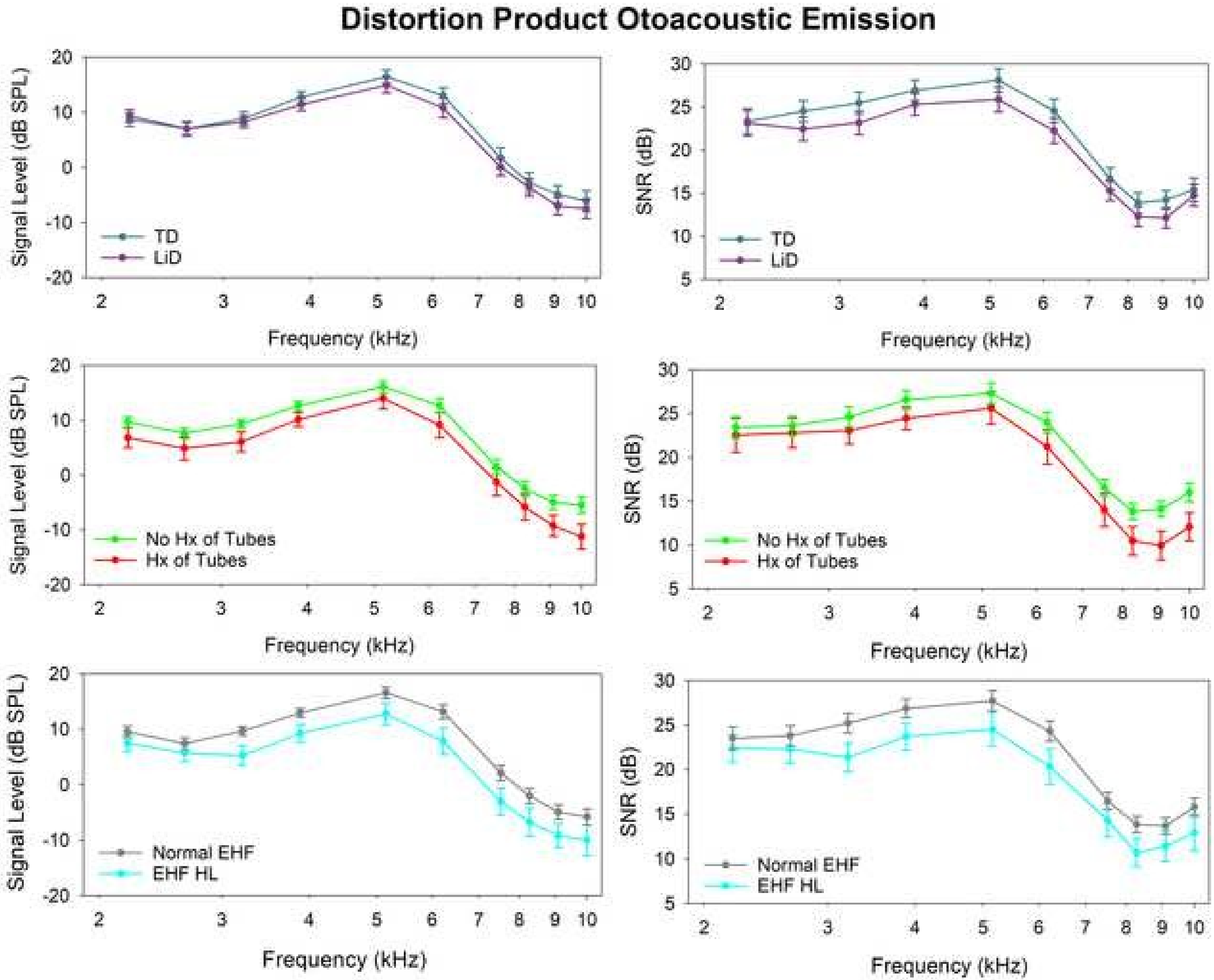
Wideband Acoustic Reflexes
Ipsilateral Threshold (dB)
110
100
90
80
70
60
50
40
BBN
0.5 kHz
1 kHz
2 kHz
TD
LiD
No Hx of Tubes
Hx of Tubes
Normal EHF
EHF HL
Contralateral Threshold (dB)
110
100
90
80
70
60
50
40
BBN
0.5 kHz
1 kHz
2 kHz

Figure 6

Click here to
access/download;Figure;DPOAEs.TI

F

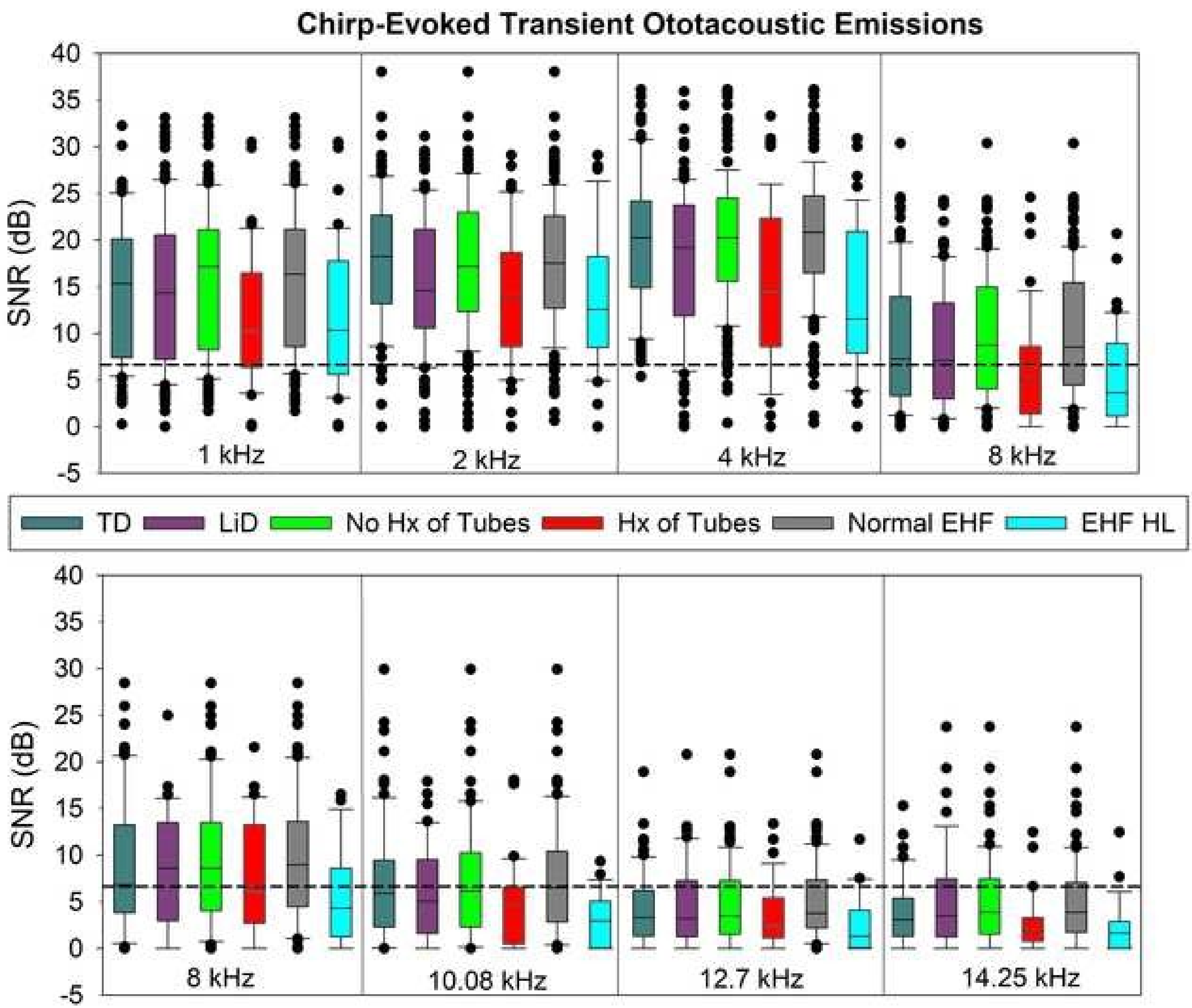
Figure 7



Distortion Product Otoacoustic Emission
Signal Level (dB SPL)
SNR (dB)
Frequency (kHz)
TD
LiD
No Hx of Tubes
Hx of Tubes
Normal EHF
EHF HL
20
10
0
-10
-20
30
25
20
15
10
5
2
3
4
5
6
7
8
9
10

Figure 8

Figure 9



Chirp-Evoked Transient Ototacoustic Emissions
SNR (dB)
40
35
30
25
20
15
10
5
0
-5
1 kHz
2 kHz
4 kHz
8 kHz
TD
LiD
No Hx of Tubes
Hx of Tubes
Normal EHF
EHF HL
8 kHz
10.08 kHz
12.7 kHz
14.25 kHz

Table 1

Table 1. Study sample characteristics for all participants, subdivided for the TD (typically developing) and the LiD (listening difficulties) groups.

	All (N=114)	**TD (n=54)**	**LiD (n=60)**	**p-value**
Age at Test				
mean (SD)	9.94 (1.99)	9.91 (2.06)	9.97 (1.95)	0.8761*
range	6.47-14.55	6.55-14.55	6.47-13.80	
ECLiPS Total mean (SD)	6.57 (4.26)	10.81 (2.56)	3.00 (1.79)	<0.0001*
range	0-14	7-15	0-9	
Sex, n (%)				
Male	68 (59.65%)	30 (55.56%)	38 (63.33%)	0.3980#
Female	46 (40.35%)	24 (44.44%)	22 (36.67%)	
Race, n (%)				
White	93 (81.58%)	50 (92.59%)	43 (71.67%)	0.0067^
Non-White	21 (18.42%)	4 (7.41%)	17 (28.33%)	
Ethnicity, n (%)				
Hispanic or Latino	5 (4.39%)	2 (3.70%)	3 (5.00%)	0.3727#
Not Hispanic or Latino	107 (93.86%)	52 (96.30%)	55 (91.67%)	
Prefer not to Answer	2 (1.75%)	0	2 (3.33%)	

History of Ear Infections				
Never	32 (28.07%)	11 (20.37%)	21 (35.00%)	0.0859#
Occasional	68 (59.65%)	38 (70.37%)	30 (50.00%)	
Often	14 (12.28%)	5 (9.26%)	9 (15.00%)	
History of PE tube, n (%)				
Yes	28 (24.56%)	15 (27.78%)	13 (21.67%)	0.4491#
No	86 (75.44%)	39 (72.22%)	47 (78.33%)	
EHF Hearing Loss, n (%)		43 (79.63%)	41 (68.33%)	

Yes 30 (26.3%) No 84 (73.7%)

11 (20.37%) 19 (31.67%) 0.1714#

Note: EHF = Extended High Frequency; PE = Pressure-Equalization; *Two-sample t-test; # Chi-Square test; ^ Fisher's Exact Test

Table 2

Table 2. Summary of multivariate analyses, with *p*-values and F-test (DF; Degrees of Freedom) from the adjusted repeated measures analysis (N=114). Only the factors that were included in the final models are shown. Note: Sex and race were insignificant for all univariate analyses, so were not included in the multivariate models. Variables not in the final model do not include F.

	Group	**Freq**	**Group* Freq**	**Age at EHF**	**Freq* Age**	**Hx of Tubes**	**EHF HL**
Audiometric Thresholds							
Standard and EHF 0.0322 0.3841 – –		0.9456					*<0.0001* *<0.0001*
F (DF=111)	0.00	22.86	2.40	22.11			
Wideband Tympanometry							
Ambient Pressure	0.2208	*<0.0001*	*0.0193*	0.8998	*<.0001*	0.8129	0.6827
F (DF=97)	1.52	9.36	1.77	0.02	2.94		
Peak Pressure	0.4211	*<0.0001*	0.1557	0.6924	*0.0012*	0.8912	0.4172
F (DF=97)	0.65	11.17	1.32	0.16	2.29		
Group Delay	0.4640	*<0.0001*	*<0.0001*	0.5342	*0.0010*	*0.0026*	*0.0002*
F (DF=96)	0.54	7.79	2.92	0.39	2.33	9.54	2.60
MEMR							
Ipsilateral	0.2497	*<0.0001* 354.45	0.3982	0.3207	–	0.0784	*0.0152*
F (DF=97)	1.34		1.00				6.10
Contralateral	0.5107	*<0.0001*	0.5093	0.7675	–	0.1369	*0.0051*
F (DF=97)	0.16	325.02	1.58			2.25	8.21
DPOAE							

Signal Level	0.1482	*<0.0001*	0.1796	0.9484	–	*0.0217*	*0.0043*
F (DF=107)	2.12	121.35	1.44			5.43	8.51
SNR	*0.0366*	*<0.0001*	0.3616	0.1800	–	*0.0010*	0.1607
F (DF=107)	4.48	67.48	1.11			11.42	2.00
TEOAE							
SNR (1-8 kHz)	0.1492	*<0.0001*	0.1960	–	–	*0.0116*	*<0.0001*
F (DF=95)	2.11	21.49	1.30			6.63	*17.83*
SNR (8-14.25 kHz)	0.8029	<0.0001	0.2362	–	–	0.4107	*0.0128*
F (DF=95)	0.06	11.04	1.40			0.69	6.59

Table 3

Table 3. Results of regression analysis for both groups combined for univariate and multivariate adjusted models.

	Univariate Regression *p*-values	Multivariate Adjusted *p*-values
Dependent Variables	Frequency, ECLiPS scaled score, Race, History of tubes, Maternal Education Level	Frequency, ECLiPS scaled score, History of tubes
Averaged EHF hearing thresholds; 10-16 kHz	N.A, 0.2034, 0.8980, <.0001, 0.8376	N.A., 0.1448, <.0001
Wideband acoustic reflexes, contralateral; BBN, 1, 2, 4 kHz	<.0001, 0.3189, 0.5914, 0.0126, 0.0980	<.0001, 0.5109, 0.015
DPOAE levels; 2-10 kHz	<.0001, 0.2897, 0.5684, 0.0006, 0.6532	<.0001, 0.2831, 0.0005
TEOAE SNR; 0.7-8 kHz	<.0001, 0.0858, 0.7604, <.0001, 0.5750	<.0001, 0.0480, <.0001
TEOAE SNR; 8-14.2 kHz	<.0001, 0.3470, 0.1302, 0.0835, 0.3674	<.0001, 0.8844, 0.1064