Original Article

Trends in Hearing
Volume 22: 1–13

DOI: 10.1177/2331216518797848
journals.sagepub.com/home/tia
SAGE

Transient-Evoked Otoacoustic Emissions Reflect Audiometric Patterns of Age-Related Hearing Loss

Kenneth I. Vaden Jr[1], Lois J. Matthews[1], and Judy R. Dubno[1]

Abstract

Distinct forms of age-related hearing loss are hypothesized based on evidence from animal models of aging, which are identifiable in human audiograms. The Sensory phenotype results from damage (e.g., excessive noise or ototoxic drugs) to outer hair cells and sometimes inner hair cells, producing large threshold increases predominately at high frequencies. The Metabolic phenotype results from a decline in endocochlear potential that can reduce outer hair cell motility throughout the cochlea, producing gradually sloping thresholds from lower to higher frequencies. Finally, the combined Metabolic + Sensory phenotype results in low-frequency losses similar to the Metabolic phenotype and high-frequency losses similar to the Sensory phenotype. Because outer hair cell function appears to be affected differently in each phenotype, this study used audiograms from 618 adults aged 50 to 93 years ($n = 1{,}208$ ears) to classify phenotypes and characterize differences in transient-evoked otoacoustic emission (TEOAE) data. Significant phenotype differences were observed in frequency-band TEOAEs and configuration (intercept and slope), including large and broadly distributed TEOAE reductions for Metabolic and Metabolic + Sensory ears and more focused high-frequency TEOAE reductions for Sensory ears. These findings are consistent with metabolic declines that reduce cochlear amplification across a broad range of frequencies and more basally situated, high-frequency declines in sensory hearing loss. The results provide further validation for the classification of age-related hearing loss phenotypes based on audiograms and show human TEOAE declines that are highly consistent with animal models.

Keywords

presbyacusis, transient-evoked otoacoustic emissions, auditory threshold, outer hair cells, phenotypes of age-related hearing loss

Date received: 2 May 2018; revised: 3 August 2018; accepted: 7 August 2018

Introduction

Hearing loss is common among older adults and can result from a combination of genetic and environmental factors. Techniques to determine distinct pathologies with audiometric data (Dubno, Eckert, Lee, Matthews, & Schmiedt, 2013; Vaden, Matthews, Eckert, & Dubno, 2017) could lead to targeted approaches for prevention and treatment. Although audiograms from older adults reflect a unique mixture of exposures and risks over the lifespan (Schmiedt, 2010), audiometric configurations established in better controlled animal models are evident in human audiograms (Dubno et al., 2013; Schmiedt, Lang, Okamura, & Schulte, 2002). Cochlear amplification refers to active processes that increase sensitivity to sounds, which depend on the function of electromotile outer hair cells. Age-related hearing loss is hypothesized to result from metabolic declines that broadly reduce cochlear amplification, sensory damage to inner and outer hair cells that more focally reduce cochlear amplification, or a combination of both (D. M. Mills, 2006; J. H. Mills, Schmiedt, Schulte, & Dubno, 2006; Schmiedt, 2010; Schmiedt et al., 2002). This study tested the hypothesis that differential declines occur in transient-evoked otoacoustic emissions

[1]Hearing Research Program, Department of Otolaryngology—Head and Neck Surgery, Medical University of South Carolina, Charleston, SC, USA

Corresponding author:
Kenneth I. Vaden Jr, Hearing Research Program, Department of Otolaryngology—Head and Neck Surgery, Medical University of South Carolina, 135 Rutledge Avenue, MSC 550, Charleston, SC 29425-5500, USA.
Email: vaden@musc.edu

(TEOAEs) that reflect audiometric configurations for phenotypes of age-related hearing loss.

Hearing sensitivity to low-level sounds is highly dependent on cochlear amplification by healthy outer hair cells and their power source. Outer hair cells react to sound energy and sharpen the peak of traveling waves on the basilar membrane, which enhances both frequency tuning and sensitivity to sounds (Davis, 1983; Kemp, 2002). Through rapid electromotile responses, outer hair cells provide additional oscillatory energy to the basilar membrane. Outer hair cell damage or losses can dramatically reduce sensitivity to sounds at specific frequencies or regions in the cochlea. Because outer hair cell motion is powered by the positive charge of the endolymph, decreases in the endocochlear potential reduce electromotility without any obvious damage to outer hair cells (J. H. Mills et al., 2006; Schmiedt & Adams, 1981). When outer hair cell function is reduced or eliminated, pure-tone thresholds increase and otoacoustic emissions are weakened. The relationship between elevated pure-tone thresholds and weaker otoacoustic emissions is well established (e.g., Gorga et al., 1993; Harris & Probst, 1991; Kemp, Bray, Alexander, & Brown, 1986; Lonsbury-Martin & Martin, 1990; Prieve et al., 1993).

TEOAEs are used to estimate the energy added to the traveling wave on the basilar membrane by cochlear amplification (Kemp, 1978, 2002). Echo emissions such as the TEOAE result from coherent linear reflections of sound energy that are scattered by changes in impedance along the cochlear partition, especially near the peak of the traveling wave (Shera & Guinan, 1999). The peak occurs where amplification is strongest and tuning is sharpest and back-scatters energy such that wavelets originating near the peak sum coherently in the emission (Shera & Guinan, 2008). Thus, reflection emissions originating near the peak of the traveling wave can be sensitive to aspects of cochlear amplification. Linear reflectance emissions are more susceptible to declines in cochlear amplification (Martin, Lonsbury-Martin, Probst, & Coats, 1988) compared with nonlinear distortion emissions (i.e., distortion-product otoacoustic emissions; DPOAEs; Shera & Guinan, 1999).

One of the most common clinical applications of OAE measurements is to screen infants for hearing impairments (Prieve, 2002) as well as other patient populations who cannot provide reliable responses with standard audiometric tests. Although infants with normal audiometric thresholds generally have robust TEOAEs, it is not uncommon for adult TEOAEs to become smaller with increasing age (Dorn, Piskorski, Keefe, Neely, & Gorga, 1998; Engdahl, 2002; Uchida et al., 2008), although these emissions can covary with even small differences in hearing sensitivity. Consistent with distinct generation mechanisms (Shera & Guinan, 1999), reflection OAEs, such as the TEOAE, decline more slowly with increasing age compared with the distortion component of DPOAEs measured from the same older adults (Abdala & Dhar, 2012). Because both linear and nonlinear emission components may be sensitive to different etiologies, measurement of both TEOAEs and DPOAEs could potentially provide a more detailed characterization of age- or hearing-related declines (Abdala & Kalluri, 2017). Because of the resistance of reflection OAEs to age-related and hearing-related declines in older adults, as compared with DPOAEs, this study examined variation in TEOAEs in relation to audiometric phenotypes. We predicted that TEOAEs and their configuration across frequency-bands would differ among phenotypes because pure-tone thresholds used to classify phenotypes are known to vary with TEOAE measures. Confirming this prediction could demonstrate the potential value of emissions data for classifying phenotypes of age-related hearing loss.

Sensory contributions to hearing loss in older adults primarily reflect damage to outer hair cells that can reduce or eliminate cochlear amplification, particularly at high frequencies, that is, basal regions that are more vulnerable to damage (e.g., Sha, Taylor, Forge, & Schacht, 2001). Damage to outer hair cells can eliminate cochlear amplification of low-level sounds and dramatically reduce sensitivity at higher frequencies (50–70 dB SPL; Dallos & Harris, 1978) even while sparing sensitivity at lower frequencies. Although human temporal bone studies have shown basal outer hair cell loss that aligns with high-frequency hearing loss (e.g., Bredberg, 1968; Johnsson & Hawkins, 1972), evidence of limited outer hair cell loss in quiet-aged gerbil models indicates that such damage likely accumulates over time rather than resulting from an age-related process, *per se* (Schmiedt, 2010). For example, exposure to noise and ototoxic drugs can lead to outer hair cell damage and hearing loss for younger and older ears. High-frequency hearing loss appears to increase longitudinally for Sensory ears (Vaden et al., 2017), which may reflect continued exposure and susceptibility over time.

In contrast to sensory contributions, metabolic declines that affect cochlear amplification in age-related hearing loss have been clearly shown in aging gerbil models with carefully controlled exposure to environmental factors (D. M. Mills & Schmiedt, 2004; J. H. Mills, Schmiedt, & Kulish, 1990; Schmiedt, 1996). Furosemide applications to the cochlea in younger gerbils confirmed that a lower endocochlear potential increases hearing thresholds (Lang et al., 2010; Schmiedt et al., 2002). Together, these studies with laboratory animals demonstrate that the stria vascularis in the cochlear lateral wall undergoes an age-related deterioration that reduces cochlear amplification and hearing sensitivity, even in the absence of sensory inner hair cell damage due to exposure to ototoxic drugs and

noise. This change occurs because declines in the stria vascularis lower the endocochlear potential, thereby reducing outer hair cell motility and cochlear amplification of low-level sounds. Strial atrophy is common in postmortem histopathological studies of older adult temporal bones, further evidence of metabolic declines in age-related hearing loss (Schuknecht & Gacek, 1993).

Cochlear amplification is more extensive in basal than apical regions, based on *in vivo* measurements of mechanical responses to single-tone and dual-tone stimuli in chinchillas and guinea pigs (Cooper & Rhode, 1997; Hemmert, Zenner, & Gummer, 2000). Sensitivity to low-level sounds is amplified more extensively in basal regions than apical regions (~60 and 20 dB SPL, respectively; Cooper & Rhode, 1997; Robles & Ruggero, 2001; Ruggero & Rich, 1991; Schmiedt et al., 2002), which likely accounts for the pattern of sensitivity losses at high and low frequencies with reduced endocochlear potentials (Schmiedt, 2010). For example, thresholds for compound action potentials in quiet-aged gerbils and gerbils chronically exposed to furosemide each show similar, relatively larger sensitivity losses for high-frequency sounds compared with low-frequency sounds as endocochlear potentials decreased (Lang et al., 2010; Schmiedt et al., 2002 for additional details). Similar frequency-dependent effects of furosemide exposure on endocochlear potentials and compound action potentials have also been observed in cats (Sewell, 1984).

Based on the evidence for distinct pathologies involved with age-related hearing loss, four phenotypes of age-related hearing loss were proposed: (a) Older-Normal, (b) Metabolic, (c) Sensory, and (d) Metabolic + Sensory (Dubno et al., 2013; Schmiedt, 2010). Older-Normal ears were defined by pure-tone thresholds <20 dB HL and slightly elevated high-frequency thresholds. Metabolic ears were characterized by low-frequency thresholds ⩾20 dB HL and gradually sloping higher frequency thresholds (J. H. Mills et al., 2006; Schmiedt et al., 2002). Sensory ears exhibited steeply sloping thresholds at high frequencies. Finally, the combined Metabolic + Sensory ears were defined by lower frequency thresholds ⩾20 dB HL similar to Metabolic ears and steeply sloping thresholds at higher frequencies similar to Sensory ears. Audiograms from older adults can be reliably classified into these four common phenotype configurations based on machine-learning algorithms (Dubno et al., 2013; Vaden et al., 2017).

Different changes in outer hair cell function are predicted for each phenotype, based on endocochlear potential declines (i.e., Metabolic) and outer hair cell losses (i.e., Sensory). Metabolic declines in quiet-reared, aging gerbil models with lower endocochlear potentials exhibit weaker cochlear amplification (higher DPOAE thresholds and lower emission amplitudes) in addition to gradually sloping hearing thresholds (Lang et al., 2010; D. M. Mills & Schmiedt, 2004; J. H. Mills et al., 1990; Schmiedt et al., 2002). D. M. Mills (2006) showed increased DPOAE thresholds and lower emission amplitudes in gerbil models of age-related hearing loss compared with controls, with weaker DPOAEs at higher frequencies for sensory hearing loss and weaker DPOAEs across frequencies for metabolic hearing loss. These distinctions may be difficult to obtain in small, heterogeneous human OAE data sets with a mixture of metabolic and sensory losses (Ueberfuhr, Fehlberg, Goodman, & Withnell, 2016). In a larger sample with 432 older adults, Gates, Mills, Nam, Agostino, and Rubel (2002) reported a relatively stronger association between age and hearing sensitivity versus age and growth function metrics (DPOAE input/output), which suggested that outer hair cell damage did not account for age-related hearing loss.

This study used TEOAE data collected from 618 middle-aged and older adults to confirm the assumption of differential OAE declines among hearing loss phenotypes. Because increased pure-tone thresholds are strongly associated with lower OAEs, the audiometric configurations that typify each phenotype were predicted to be reflected in the shape of frequency-band TEOAE measurements. We tested the predictions that (a) Metabolic ears and Metabolic + Sensory ears have shallow-sloping losses in frequency-band TEOAEs and (b) Sensory ears have steeper-sloping losses in frequency-band TEOAEs. The goal of this study was to link differential patterns of OAE decline to age-related hearing loss phenotypes, based on endocochlear potential declines in metabolic hearing loss and outer hair cell damage in sensory hearing loss.

Materials and Methods

Participants, Hearing Loss, and Otoacoustic Emissions

The Hearing Research Program at the Medical University of South Carolina has collected audiograms and other hearing-related data from more than 1,500 participants enrolled in a longitudinal study of age-related hearing loss from 1987 to the present. This research was conducted according to the World Medical Association Declaration of Helsinki. Informed consent was obtained in compliance with the approvals for the study (HRE-607 and HRE-607R), provided by the Medical University of South Carolina Institutional Review Board for Human Research. Participants were excluded if evidence of conductive hearing loss or otologic or neurologic disease were present. Pure-tone thresholds were measured at conventional audiometric frequencies (0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz) using either a Madsen OB822, OB922, or Astera^2 clinical audiometer calibrated according to American National Standards Institute standards (1969, 1989, 1996, 2004, and 2010) with TDH-39 headphones in MX-41/AR

cushions and a protocol recommended by the American Speech-Language-Hearing Association (2005).

Phenotype classification was based on averaged audiogram data that were collected over multiple visits, which reduces measurement variability and its potential impact on classification accuracy (Dubno et al., 2013; Vaden et al., 2017). Each participant in this study completed a *cluster* of three to six visits, with approximately one month between visits. Because an audiogram was collected during each visit, cluster-averaged audiograms were calculated based on three or more audiograms from a single year. Left and right ears were analyzed separately for each participant, given that each ear can exhibit a different audiometric profile and phenotype of age-related hearing loss (Dubno et al., 2013).

Analyses that related pure-tone thresholds to frequency-band TEOAEs only used pure-tone thresholds collected during the same visit as the TEOAE. Because the frequency-band TEOAE measures included 1.5 kHz, a pure-tone threshold for 1.5 kHz was calculated for each ear by averaging the 1 and 2 kHz pure-tone thresholds. To ensure consistency, the 1.5 kHz pure-tone thresholds were computed for each ear regardless of whether that threshold was measured or not. Tympanometry measurements to assess middle ear (ME) integrity were collected using either a Grason-Stadler 33 or Grason-Stadler TympStar^2 ME analyzer. Ear canal volume (ml), ME compliance (ml), and pressure (daPa) measurements were used as regressors of no interest when available for TEOAE analyses.

TEOAE Measurement

The TEOAE data were collected using either an Otodynamics ILO88 or Otodynamics Echoport 292 system operated in the default, nonlinear mode to present clicks at 80 dB SPL peak level. Each participant was presented with transient stimuli and recorded response waveforms were used to calculate frequency-band measures of the TEOAE signal-to-noise ratio (TEOAE-SNR) and confidence (TEOAE-CNF; i.e., reproducibility). The TEOAE-SNR is based on $\overline{A}$ and $\overline{B}$ response waveforms that each average 260 response waveforms, which increases sensitivity to subtle but consistent features across responses. The *signal* is computed in dB as the average of the $\overline{A}$ and $\overline{B}$ waveforms, and *noise* is computed as the power of the $\overline{A} - \overline{B}$ difference. Because both measures are on the decibel scale, the TEOAE-SNR is calculated by subtracting the noise from the signal.[1] Frequency-band specific TEOAE-SNRs are each calculated by applying half-octave band-pass filters centered at 1, 1.5, 2, 3, and 4 kHz to the response waveforms, then calculating TEOAE-SNR for the filtered responses.

The TEOAE-CNF also measures consistency across TEOAE waveforms, computed as the average correlation between $\overline{A}$ and $\overline{B}$ average waveforms after every 20 presentations. The TEOAE-CNF never exceeds zero or one, because R^2 is bounded [0, 1]. Frequency-band TEOAE-CNF is calculated after filtering the responses, as with TEOAE-SNR. Because both TEOAE measures are sensitive to signal magnitude and variability based on the same response waveforms, a strong nonlinear relationship exists between these measures. For example, a subject with a relatively small and "noisy" TEOAE response would also likely demonstrate a low SNR with lower correlations between $\overline{A}$ and $\overline{B}$ averaged waveforms. Both TEOAE measures were separately analyzed under the expectation that each is sensitive to phenotype differences, and common findings are presented in the results.

Summary of Analyses

Because multiple analyses are detailed later, an overview of the analyses is presented here and summarized in Table 1. First, we empirically justified the use of minimal data acceptance criteria, which specified the number of measurements per ear needed to perform statistical tests but did not limit the range of measurements. This involved testing the repeatability of frequency-band TEOAE measures for participants who had TEOAE data from two visits. Furthermore, well-established associations were tested between pure-tone thresholds and TEOAE measurements in the main data set selected using minimal criteria. The second analysis used a machine-learning algorithm to classify ears into audiometric phenotypes. The third analysis used general linear model (GLM) regression tests to characterize phenotype differences in frequency-band TEOAE measurements. The fourth, shape-based analysis, tested for phenotype differences in TEOAE configuration across frequency-bands (i.e., intercept and slope), based on generalized linear mixed model (GLMM) regression tests. Together,

Table 1. Summary of Analyses.

1. Data acceptance criteria and repeatability analyses: justify minimal data acceptance criteria based on reliability of TEOAE measurements (SNR, CNF), associations between TEOAE measurements and hearing thresholds.
2. Classifying audiometric phenotypes: audiogram-based classification of individual ears into Older-Normal, Metabolic, Sensory, and Metabolic + Sensory phenotypes.
3. Frequency-band TEOAE analyses: phenotype-related differences in frequency-band TEOAE measurements.
4. TEOAE shape analyses: phenotype-related differences in the configuration of TEOAE measurements across frequency-bands.

Note. TEOAE = transient-evoked otoacoustic emission; SNR = signal-to-noise ratio; CNF = confidence.

the results of these analyses support the hypothesis that metabolic and sensory pathologies have different consequences for cochlear amplification and TEOAEs.

Data Acceptance Criteria and Repeatability Analyses

The data acceptance criteria for this study did not limit the range of acceptable pure-tone threshold, TEOAE-SNR, or TEOAE-CNF measurements under the rationale that narrow criteria could distort phenotype differences by truncating the distribution of data. Instead, the main criterion was that a sufficient number of measurements were collected from each ear to perform all of the TEOAE-SNR or TEOAE-CNF analyses. The regression models required ears to have at least three measurements for either the TEOAE-SNR or TEOAE-CNF (1, 1.5, 2, 3, and 4 kHz). Data were excluded from analysis for the following reasons: data were from participants less than 50 years of age, TEOAE data were collected more than 12 months before or after the visits that produced an average audiogram for phenotype classification, or the averaged audiograms had missing thresholds. The selected audiograms and TEOAE data included 618 participants (378 females and 240 males; age = 68.5 ± 8.5 years; mean ± standard deviation [*SD*]). The following measures were available for a large proportion of the 1,208 selected ears: 92.9% TEOAE-SNR, 88.9% TEOAE-CNF, 97.4% pure-tone thresholds (1–4 kHz) from the TEOAE-visit, and 94.4% tympanometry.

Repeatability analyses were performed to empirically justify the acceptance criteria for this study by demonstrating the reliability of longitudinal TEOAE data. We predicted there would be a high degree of consistency in TEOAEs collected years apart, to the extent that TEOAE values across the entire measurement range were meaningful. We examined a subset of data from 188 participants (123 females; average age = 70.1 ± 6.8 years; 355 ears) who had audiogram and TEOAE data collected over two visits within four years (1.6 to 4 years; average = 2.9 ± 0.5 years). Two measures of repeatability described in Helleman and Dreschler (2012) were calculated for the frequency-band TEOAE-SNR and TEOAE-CNF data: reliability and standard error of the measurement (SEM). The reliability of each measure across two time points was computed using the Pearson's correlation coefficient (r). The measurement error was computed as $\mathrm{SEM} = \mathrm{SD}_{\mathrm{pooled}} \times \sqrt{1 - \mathrm{r}}$, where the SD_{pooled} was the average within-participant *SD*.

We also confirmed that well-established associations between TEOAE-SNR, TEOAE-CNF, and pure-tone thresholds were preserved when minimal data acceptance criteria were used for the analyses. We expected that elevated pure-tone thresholds relate to lower TEOAE-SNR and TEOAE-CNF values across the measurement range, consistent with the literature (e.g., Gorga et al., 1993; Harris & Probst, 1991; Kemp et al., 1986; Lonsbury-Martin & Martin, 1990; Prieve et al., 1993). Regression analyses were performed to test the prediction that weaker TEOAEs were associated with higher pure-tone thresholds at the nearest frequency. Regression analyses were also used to test the strength of the association between frequency-band TEOAE-SNR and TEOAE-CNF measurements. Because TEOAE-CNF values are distributed in the [0, 1] range, those regression models specified a beta distribution for the dependent variable (R package: betareg v3.0.1). Each regression entered the following demographic and tympanometric information as nuisance regressors: participant age, participant sex, ear canal volume, ME compliance, and pressure. Model testing was performed to remove control variables that did not significantly improve model fit.

Classifying Audiometric Phenotypes

Average audiograms were classified into phenotype categories of age-related hearing loss using a quadratic discriminant analysis (QDA) model (R-Project package MASS, 7.3-29). The QDA model was trained on data from 897 baseline average audiograms that were manually labeled by two expert raters as one of the four phenotypes (Dubno et al., 2013). Five shape parameters (e.g., slope and intercept) were used as multivariate predictors for the QDA model, derived by fitting a five-parameter orthogonal polynomial curve to each audiogram (R-Project package nlme version 3.1-113). We previously used cross-validation tests to demonstrate that fitted curve parameters and a large, variable audiogram training data set produced the highest accuracy, based on classification agreement with expert labels (Vaden et al., 2017). After training the QDA model, posterior probabilities were calculated for each of the audiograms with TEOAE data to quantify how well it matched the distribution of training examples for each phenotype. Each audiogram was classified by QDA based on the phenotype with the highest posterior probability.

Frequency-Band TEOAE Analyses

GLM regression analyses were performed to identify significant phenotype differences in frequency-band TEOAE-SNR and TEOAE-CNF measures. Separate tests were performed to identify significant phenotype differences in TEOAEs within each frequency-band. Consistent with the other GLM analyses, a beta distribution was specified for testing TEOAE-CNF, and model testing was used to remove nonpredictive control variables. Significance was Bonferroni corrected for six phenotype comparisons within each frequency-band. Because pure-tone thresholds were used to classify phenotypes, those thresholds were excluded from the regression tests of phenotype differences to avoid circular statistical tests.

TEOAE Shape Analyses

GLMM regression analyses were performed to test for significant phenotype differences in TEOAE configurations across frequency-bands. We predicted that ears classified with a Metabolic or Metabolic + Sensory phenotype would exhibit lower TEOAEs across frequency-bands (i.e., lower intercept). In contrast, ears with a Sensory phenotype were predicted to exhibit steeper TEOAE declines with increasing frequency-bands (i.e., more negative slope). GLMM regression analyses were performed to test the extent to which intercept and slope parameters interacted with audiometric phenotypes in predicting frequency-band TEOAE-SNR or TEOAE-CNF (e.g., Kuchinsky et al., 2013; Mirman, Dixon, & Magnuson, 2008). A Gaussian distribution was specified for TEOAE-SNR tests (R package: lme4 v1.1.12), and a beta distribution was specified for TEOAE-CNF tests (R package: glmmTMB v0.1.4). The GLMM regression analyses included the demographic and tympanometric nuisance regressors described earlier, which were removed if they did not significantly improve model fit. The significant results were Bonferroni corrected for the six unique comparisons between the four phenotypes.

Results

Repeatability Analyses

Results from the two-visit data sample ($N = 188$ participants; 355 ears) showed that TEOAEs appear stable over 1.6 to 4 years (Figure 1). The mean absolute repeated-measure difference in frequency-band TEOAE-SNR $= 3.6 \pm 0.8$ dB and TEOAE-CNF $= 13.3 \pm 1.5\%$. Significant, moderate-to-strong correlations were observed for TEOAEs across the two visits (TEOAE-SNR: $r = .66$ to $.84$; TEOAE-CNF: $r = .61$ to $.82$; all $p < .001$). The SEM was less than 2 dB for TEOAE-SNR and less than 7.1% for TEOAE-CNF. The high reliability and low error both indicate that rank order was preserved across 1.6 - to 4-year intervals. The TEOAE-SNR had a similar range for the two-visit sample [−26.7, 29.0] and the main sample [−35.2, 29.0], and the TEOAE-CNF range for the two-visit sample [0.2, 99.8] was nearly identical to the main sample [0.1, 99.9]. Together with evidence of strong associations between TEOAE-SNR, TEOAE-CNF, and pure-tone thresholds presented later, these findings provide an empirical justification for using minimal data acceptance criteria.

Pure-Tone Thresholds and Frequency-Band TEOAE Measurements

The results of the GLM regression analyses indicated that higher pure-tone thresholds were significantly associated with lower TEOAEs in the corresponding frequency-band (TEOAE-SNR: all $Z \leqslant -16.91$, $p < .001$; TEOAE-CNF: all $Z \leqslant -14.95$, $p < .001$). For each of the frequency-bands, ears with higher TEOAE-SNR also had significantly higher TEOAE-CNF (all $Z \geqslant 70.22$, $p < .001$). Examples of these relationships are illustrated in Figure 2 and Supplementary Figure 1. All of the GLMs included participant age, participant sex, and at least one tympanometry control variable

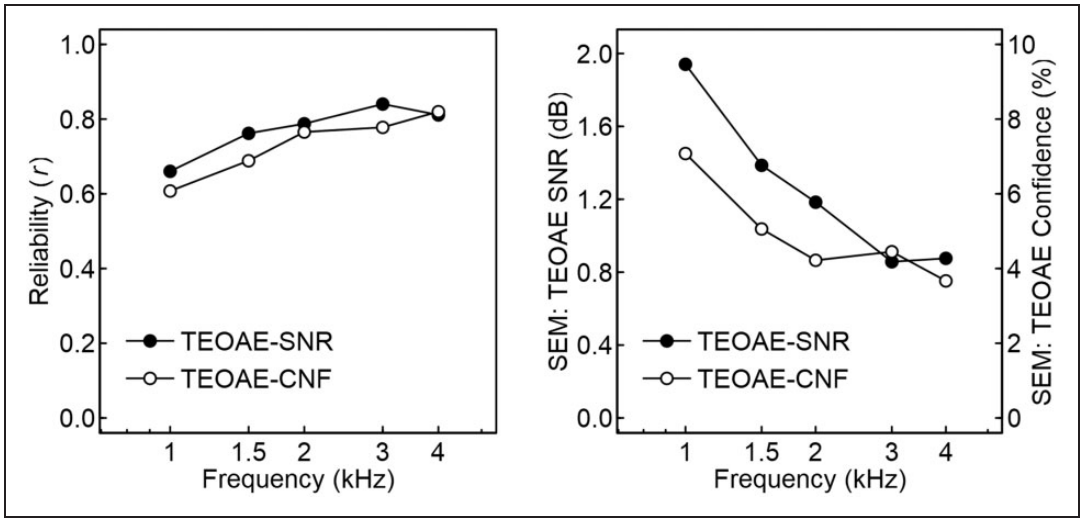

Figure 1. Repeatability for TEOAE-SNR and TEOAE-CNF for 188 participants with two measurements collected over 1.6 to 4 years. Left: Significant, moderate-to-strong correlations were observed across visits. Right: The measurement error (SEM) also indicated minimal within-subject variance across both measurements. In the right panel, the SNR scale is shown on the left *y*-axis and the CNF scale is shown on the right *y*-axis. TEOAE = transient-evoked otoacoustic emission; SNR = signal-to-noise ratio; CNF = confidence.

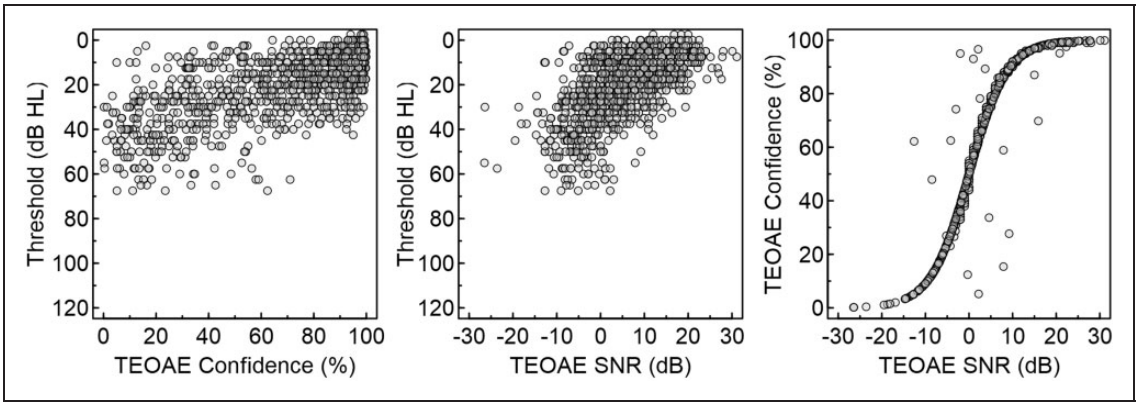

Figure 2. Increased pure-tone thresholds were associated with decreased frequency-band TEOAE-CNFs (left) and TEOAE-SNRs (middle), illustrated here with representative 1.5 kHz data. A strong nonlinear association exists between 1.5 kHz frequency-band TEOAE-SNR and TEOAE-CNF (right). This relationship is due to consistent waveforms having a higher $\overline{A}$ and $\overline{B}$ average and lower $\overline{A} - \overline{B}$ difference (i.e., higher SNR), as well as higher correlations in serially computed average $\overline{A}$ and $\overline{B}$ waveforms (CNF). Conversely, noisier and less consistent response waveforms are also more poorly correlated. The sigmoid function reflects the mapping between the logarithmic scale for TEOAE-SNR and the TEOAE-CNF correlation scale, which is bounded at [0, 1]. Because pure-tone thresholds at 1.5 kHz were interpolated, they are not spaced apart in 5 dB HL intervals and more clearly show the same relationships between TEOAEs and pure-tone thresholds observed at other frequencies. Supplementary Figure 1 includes each of these scatterplots for each frequency-band: 1, 1.5, 2, 3, and 4 kHz. TEOAE = transient-evoked otoacoustic emission; CNF = confidence; SNR = signal-to-noise ratio.

(ear canal volume, ME compliance, or pressure) based on significant improvements in model fit ($p < .05$). These findings replicate previous observations in the literature (e.g., Gorga et al., 1993; Harris & Probst, 1991; Kemp et al., 1986; Lonsbury-Martin & Martin, 1990; Prieve et al., 1993).

QDA Classifications

Based on the QDA classifications, the sample included 245 Older-Normal ears, 145 Metabolic ears, 510 Sensory ears, and 308 Metabolic + Sensory ears. Demographic information for each of the phenotypes is presented in Table 2. Results from a one-way analysis of variance showed that the ages of classified ears were significantly different between phenotypes, $F(3,1204) = 92.2$, $p < .001$. Follow-up comparisons indicated that Older-Normal ears were significantly younger than the other phenotypes (Tukey $p < .001$), Metabolic ears were significantly older than Sensory ears (Tukey $p = .02$) and Metabolic + Sensory ears were older than the other phenotypes (Tukey $p < .05$). Significant phenotype differences were observed in participant sex ($\chi^2 = 66.8$, $p < .001$), with male ears most likely to be classified as Sensory and female ears most likely to be classified as Older-Normal or Metabolic.

Unlike our previous studies of audiometric phenotypes, which included more male Sensory ears than female Sensory ears (Dubno et al., 2013; Vaden et al., 2017), the sample for the current TEOAE study included nearly equal proportions of female and male Sensory ears (Table 2). Further examination of the data set revealed that male Sensory ears were more likely to be excluded due to an insufficient number of frequency-band TEOAE measures than female Sensory ears. This suggests that the data inclusion criteria could slightly reduce apparent differences between Sensory ears and the other phenotypes. The current sample also included a slightly higher proportion of female Metabolic + Sensory ears, which reflected the original TEOAE data set before applying the data acceptance criteria. Otherwise, the distribution of females and males among phenotypes, as well as participant ages, was similar to our previous studies (Dubno et al., 2013; Vaden et al., 2017).

Table 2. Demographic Information for the Audiometric Phenotypes.

Phenotype	Age (Years)	Sex
Older-Normal	62.1 ± 6.6	80% F (196 F, 49 M)
Metabolic	70.5 ± 8.6	71% F (103 F, 42 M)
Sensory	68.4 ± 7.4	51% F (258 F, 252 M)
Metabolic + Sensory	72.8 ± 8.3	60% F (185 F, 123 M)
Average	68.5 ± 8.4	61% F (742 F, 466 M)

Note. F = female; M = male.

Distinct patterns of age-related hearing loss and TEOAE declines were demonstrated for each phenotype (Figure 3). Relatively isolated decreases in TEOAEs at the highest and lowest frequency-band were observed for

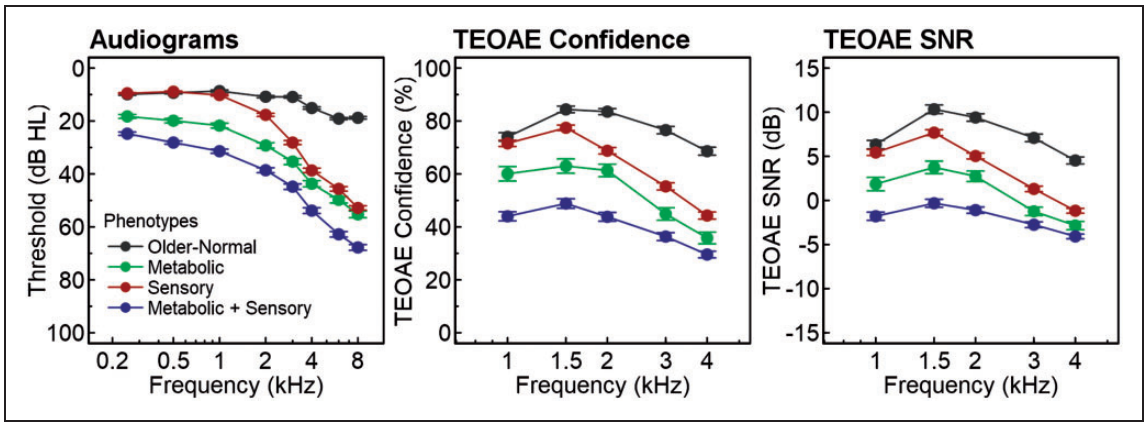

Figure 3. Average audiometric profiles (left) and frequency-band TEOAEs (middle and right) show consistent configurations for each of the presbyacusis phenotypes. Averages are plotted with error bars that display the standard error of the mean. TEOAE = transient-evoked otoacoustic emission; SNR = signal-to-noise ratio.

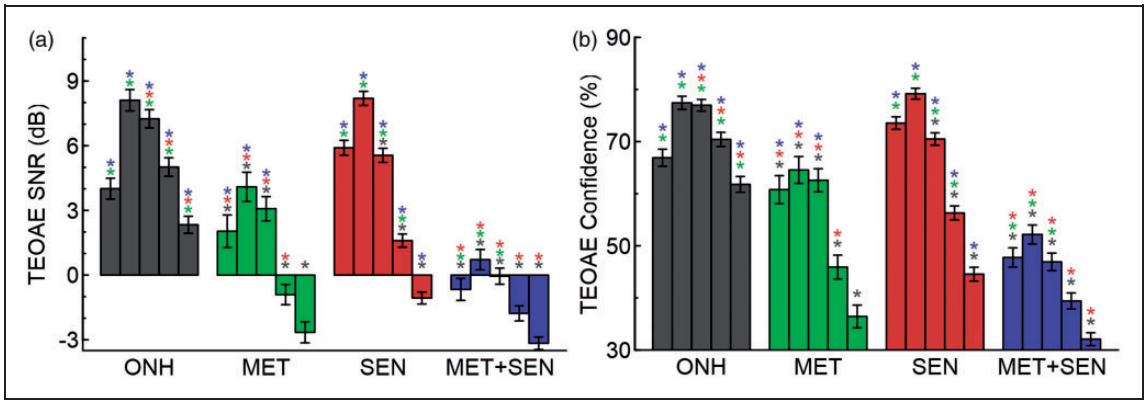

Figure 4. Each frequency-band demonstrated significantly lower TEOAEs for Metabolic and Metabolic + Sensory ears, with well-preserved TEOAEs in the 1 and 1.5 kHz bands for Sensory ears compared with Older-Normal ears. Bar plots show the average frequency-band TEOAE-SNR (a) and TEOAE Confidence (b) plotted with standard error of the mean bars for each phenotype, after residualizing variance related to ME compliance, participant age, and participant sex. Each set of bars is grouped by phenotype and shows the TEOAEs measured at 1, 1.5, 2, 3, and 4 kHz frequency-bands in ascending order. Asterisks indicate significant within-band phenotype differences in the GLMM regression analyses (Bonferroni-corrected $\alpha = .05 \div 6$), with colors indicating the significantly different phenotypes: gray-Older-Normal (ONH), green-Metabolic (MET), red-Sensory (SEN), blue-Metabolic + Sensory (MET+SEN). TEOAE = transient-evoked otoacoustic emission; SNR = signal-to-noise ratio; ME = middle ear.

Older-Normal ears, despite normal or slightly elevated pure-tone thresholds. We speculate this may correspond to minor apical and basal outer hair cell losses (Tarnowski, Schmiedt, Hellstrom, Lee, & Adams, 1991). The Metabolic and Metabolic + Sensory ears showed the highest pure-tone thresholds and lowest TEOAEs. A steep decline affecting the high frequencies was also seen in thresholds and frequency-band TEOAEs for the Sensory ears.

Phenotypes and Frequency-Band TEOAEs

Significant differences in frequency-band TEOAEs were observed between phenotypes for both TEOAE-CNF and TEOAE-SNR (Supplementary Table 1; Figure 4). The Metabolic, Sensory, and Metabolic + Sensory ears had significantly lower TEOAEs compared with the Older-Normal ears (26/30 tests; $p_{BONF} \leqslant .05$). Comparing each phenotype to Metabolic or Sensory also identified significant TEOAE differences for 24 of the 30 tests each ($p_{BONF} \leqslant .05$). These results are consistent with the relationships between pure-tone thresholds and TEOAEs (Figure 3) and the distinct audiometric patterns that define each phenotype. The Metabolic or Metabolic + Sensory ears consistently had the lowest TEOAEs in each of the frequency-bands. The Older-Normal ears had significantly higher TEOAEs compared with the other phenotypes, except for the 1 and 1.5 kHz

frequency-bands, which were not significantly different from the Sensory ears.

Phenotypes and TEOAE Configurations

The pattern of TEOAE declines differed significantly between audiometric phenotypes for both TEOAE-CNF and TEOAE-SNR (Figure 5; Supplementary Table 2). After correcting for participant age, participant sex, ear canal volume, and ME compliance, the results indicated that TEOAE intercepts were significantly lower for the Metabolic and Metabolic + Sensory ears compared with the other phenotypes. Sensory ears showed a significantly more negative TEOAE slope compared with the Older-Normal and Metabolic + Sensory ears. These phenotype differences in TEOAE shape reflect pure-tone threshold differences and confirm our predictions that the Metabolic and Metabolic + Sensory phenotypes reflect broader OAE declines across frequencies, while the Sensory phenotype involves more focal, steeper declines at higher frequencies.

Discussion

The results from this study demonstrate that distinct audiometric phenotypes are reflected in the configuration of TEOAE declines, consistent with predictions from metabolic and sensory forms of age-related hearing loss. Ears classified as different phenotypes demonstrated significantly different frequency-band TEOAE measurements and configurations, with the lowest intercepts for the Metabolic and Metabolic + Sensory phenotypes and the steepest slopes for the Sensory phenotype. These findings reinforce the proposal that distinct changes in cochlear amplification contribute to phenotypes of age-related hearing loss, whether they result from lower endocochlear potentials affecting sensitivity to a broad range of frequencies or more focal outer hair cell damage that primarily affects high frequencies. Sensitivity to phenotype differences was enhanced due to our large data set, wide range of TEOAEs and pure-tone thresholds, as well as demographic and tympanometric control variables.

We demonstrated that TEOAE-SNR and TEOAE-CNF data selected with minimal acceptance criteria had low measurement error, high reliability, and replicated established TEOAE associations with pure-tone thresholds. Consistency in the results from each measure has been noted previously in the literature, and there were almost no discrepancies in the significant results based on TEOAE-SNR and TEOAE-CNF (Supplementary Tables 1 and 2). This appears to result from the highly regular, nonlinear relationship between TEOAE-SNR and TEOAE-CNF (Figure 2; Supplementary Figure 1).

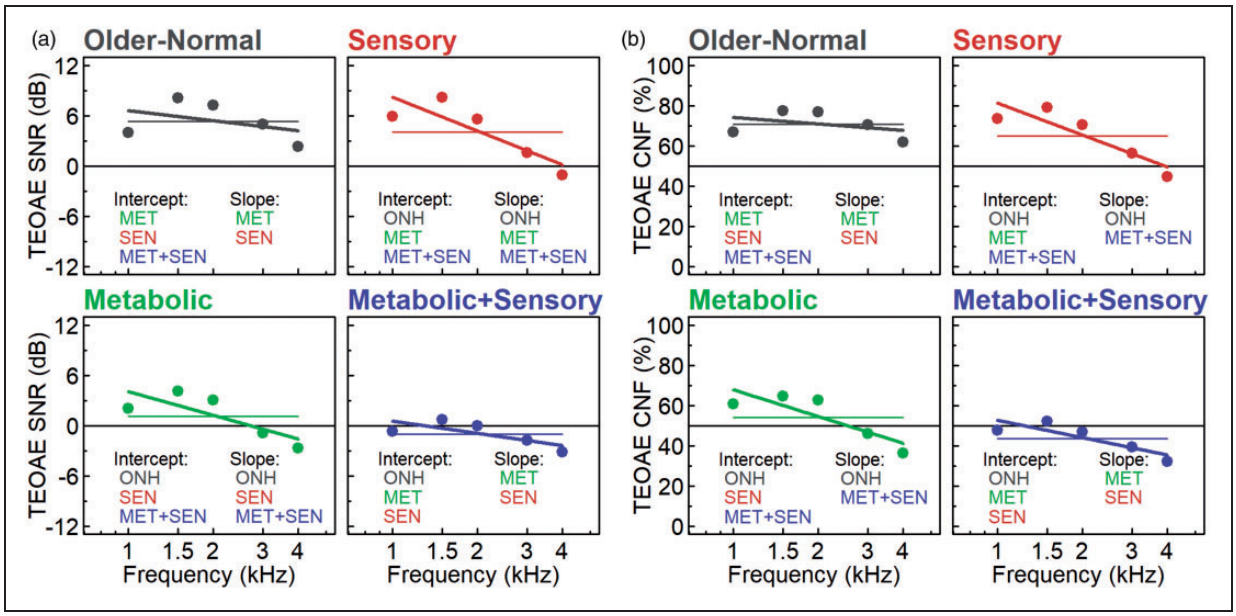

Figure 5. Average TEOAE profiles for each presbyacusis phenotype, after removing variance related to participant age, participant sex, ear canal volume, and ME compliance. Fitted intercepts and slopes are shown and significant differences are listed within each plot. Significantly lower intercepts were observed for Metabolic (MET) and Metabolic + Sensory (MET+SEN) ears compared with the other phenotypes (a and b). Sensory ears (SEN) had significantly more negative TEOAE-SNR slopes compared with all the other phenotypes (a), and significantly more negative TEOAE-CNF slopes than Older-Normal (ONH) and Metabolic + Sensory ears (b). TEOAE = transient-evoked otoacoustic emission; SNR = signal-to-noise ratio; CNF = confidence.

As described earlier, the Metabolic phenotype reflects strial declines that reduce the endocochlear potential and affect outer hair cell function across the cochlea. Findings from animal models suggest that cochlear amplification is more extensive for high-frequency sounds, providing an explanation for why strial declines result in a characteristic gradually sloping pattern of pure-tone thresholds (Schmiedt et al., 2002). Consistent with those broad declines, the Metabolic and Metabolic + Sensory ears showed significantly lower TEOAEs across frequency-bands. Furthermore, the audiometric configuration for Metabolic and Metabolic + Sensory ears was reflected in lower intercepts fitted to frequency-band TEOAEs.

The Sensory phenotype is typically reflected in normal pure-tone thresholds at lower frequencies that increase steeply at higher frequencies. This could reflect both more extensive cochlear amplification for high frequencies than low frequencies (Cooper & Rhode, 1997) and greater susceptibility to outer hair cell damage in basal cochlear regions compared with apical regions (Sha et al., 2001). Consistent with their audiometric profile, the 1 and 1.5 kHz TEOAEs were not different for Sensory and Older-Normal ears, although Sensory ears had the most negative slope across frequency-bands in the configuration analysis. The TEOAE intercept was lower for Sensory compared with Older-Normal ears, which appeared to be driven by the significant TEOAE declines at the 2 kHz frequency-band and above.

Because this study focused on patterns of TEOAE declines in age-related hearing loss, we performed analyses to empirically justify our data inclusion criteria. Our results confirmed that the entire range of TEOAE measurements was reliable across a 1.6 - to 4-year interval. This result was consistent with the previous observations that TEOAEs are reliable over a period of days or weeks ($r > .85$) for ears with a narrower range of pure-tone thresholds (Chan & McPherson, 1998; Franklin, McCoy, Martin, & Lonsbury-Martin, 1992). Sufficient variance has been observed in longitudinal data to advise against serial TEOAE monitoring for individual patients (Helleman & Dreschler, 2012). We also observed well-known associations between pure-tone thresholds, TEOAE-SNR, and TEOAE-CNF. Together, these observations provided an empirical justification to analyze the entire range of TEOAE measures at least for this study.

We note some limitations in this study. First, the TEOAE data were collected with a standard clinical implementation rather than the specialized measures often developed by researchers. Although using nonspecialized TEOAE measures could decrease statistical sensitivity, the data set included a large and well-characterized sample of middle-aged and older adults with a range of hearing losses. Related to the commercial instrumentation used, the default nonlinear mode of recording could potentially eliminate linear elements of the TEOAE. Although the nonlinear mode is recommended for clinical applications for its reduction of stimulus-related artifact in recordings, it is less than ideal for the measurement of a linear reflection emission in the context of testing hypotheses on age-related hearing loss. Second, we report strong associations between pure-tone thresholds and TEOAEs that are well-known (e.g., Lonsbury-Martin & Martin, 1990) and could contribute to phenotype difference in TEOAEs. To avoid circularity in our statistic tests, we did not perform tests with pure-tone thresholds as those defined each ear's phenotype. Because TEOAE data were not used to classify phenotypes, the TEOAE measures were collinear with pure-tone thresholds but not dependent on audiometric phenotypes. Future studies could potentially examine linear coherent reflectance and nonlinear distortion components in the same set of classified ears to determine their relative sensitivity to metabolic and sensory changes in age-related hearing loss.

According to the current view of OAEs and their emission-generation taxonomy (Abdala & Kalluri, 2017; Shera & Guinan, 1999, 2008), DPOAEs are considered more sensitive to nonlinear distortion and TEOAEs more sensitive to coherent linear reflections. In particular, the nonlinear distortion component of DPOAEs appears to decline more quickly with increasing age for older adults compared with their linear reflectance component (Abdala & Dhar, 2012). Thus, we predict that DPOAEs may demonstrate weaker responses and similar phenotype configurations to those currently shown for TEOAEs: lower intercepts for Metabolic and Metabolic + Sensory ears and steeper high-frequency declines for Sensory ears. Future studies will also examine phenotype differences in DPOAE growth functions based on the rationale that these are more sensitive to outer hair cell function in specific frequency regions (Gates et al., 2002).

Conclusion

Future individualized treatments for hearing loss that can target specific subtypes of cochlear dysfunction will require the reliable identification of distinct pathologies (e.g., outer hair cell damage or strial dysfunction). In that context, our observations suggest that OAE measurements could potentially enhance phenotype classification or substitute pure-tone thresholds for this purpose, if needed. This study provides TEOAE evidence for metabolic and sensory declines in cochlear amplification that reflect audiometric phenotypes. Configuration-based analyses of frequency-band TEOAEs indicated that the Metabolic and Metabolic + Sensory phenotypes are associated with broadly distributed OAE declines, whereas the Sensory phenotype relates to negative sloping, high-frequency OAE declines. These differences are

consistent with audiometric profiles for each phenotype and predictions for broadly distributed endocochlear potential declines versus more focal, apical outer hair cell damage. These results link audiometric patterns to differences in a measure of outer hair cell function predicted by animal models of sensory and metabolic pathologies. Our findings suggest that detailed configuration analyses of OAEs can facilitate the characterization of distinct subtypes of age-related hearing loss in older adult populations.

Acknowledgments

The authors are grateful for Rick Schmiedt's comments on this manuscript and his contributions to the audiometric phenotypes model used for this article. The authors also thank the study participants.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Institutes of Health/National Institute on Deafness and Other Communication Disorders (P50 DC 000422) and the South Carolina Clinical and Translational Research (SCTR) Institute, NIH/NCRR grant number UL1 RR029882. This investigation was conducted in a facility constructed with support from Research Facilities Improvement Program, NIH/NCRR grant number C06 RR014516.

Note

1. The TEOAE-SNR corrects the TEOAE response level for the variability in the $\overline{A}$ and $\overline{B}$ waveforms, often referred to as the "noise floor." This computation is analogous to the standard deviation term used as the denominator for Z-scores, because it corrects the average measurement for variability in the measurement.

ORCID iD

Kenneth I. Vaden Jr http://orcid.org/0000-0002-3621-2043

Supplemental Material

Supplemental material for this article is available online.

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