Characterizing Patterns of Early Aging in Cochlear and Auditory Brainstem Function

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Introduction

Advancing the prevention and treatment of hearing loss hinges on early and accurate diagnosis of auditory decline. However, ***current clinical tools like the audiogram are inadequate for detecting subtle changes at specific anatomical locations in the auditory system.***

This early, differential diagnosis is particularly important for age-related hearing loss. Also known as presbycusis, auditory aging can occur decades before it is detected by the clinical audiogram (Glavin et al. 2021) and can arise from multiple pathologies. While *sensory* presbycusis arises from the dysfunction of outer and/or inner hair cells (OHC and IHC, respectively), *neural* presbycusis is due to the dysfunction of cochlear nerve fibers, and *metabolic* presbycusis from the degeneration of the stria vascularis. As untreated hearing loss is a significant risk factor for cognitive decline in older adults, ***it is important to work towards a method of clinically differentiating these types of presbycusis at their onset.***

Two potentially powerful tools to fill this significant clinical gap are distortion product otoacoustic emissions (DPOAEs) and auditory brainstem responses (ABRs). DPOAEs provide a metric of OHC function and have been shown to be sensitive to subtle age-related changes in the auditory system, particularly at higher stimulus intensities (Glavin et al., 2021). Wave I of the ABR provides a metric of early neural function, as it represents synchronized electrical activity between cochlear IHCs and spiral ganglion cells. Research in animal models has demonstrated cochlear neural degeneration due to aging selectively targets low spontaneous rate nerve fibers (Sergeyenko et al., 2013). Thus, subtle changes in neural function due to early aging (in humans) may also be most clearly observed at higher intensities.

Here, we examine the effects of early aging on auditory function across a wide dynamic range using DPOAE and ABR measures in tandem. Our goals were to 1) characterize early signs of age-related auditory decline and 2) work towards the differential diagnosis of presbycusis by pinpointing the site(s) of age-related auditory decline. We hypothesized that the growth functions of DPOAEs and ABRs would decline with age, reflecting subclinical auditory aging.

Methods and Participant Demographics

Participants had clinically normal audiometric thresholds (≤ 25 dB HL) from 0.25-8 kHz as well as unremarkable otoscopy and tympanometry. 33 individuals across two age groups participated; 15 participants in the 18–29-year-old age group (mean age = 23.9; 3 males) and 18 participants in the 30–49-year-old age group (mean age = 36.7; 8 males). Test ear was randomized across participants.

DPOAEs were measured using an ER-10X probe. Stimuli were generated using custom MATLAB software. DPOAE growth functions were measured at three f_2 frequencies: 2, 4, and 8 kHz. Their f_2/f_1 *ratio* varied by frequency. The stimulus, L_1, was fixed at 70 dB forward pressure level (FPL) while L_2 swept from 0-70 dB FPL. DPOAEs were estimated using a weighted least-squares fitting (LSF) procedure.

ABRs were recorded on the Intelligent Hearing Systems SmartEP Duet platform using an ear canal (-) to Fz (+) electrode montage. Responses were evoked using 2 and 4 kHz iChirp stimuli presented at 27.1/s between 80 and 30 dB nHL in 10-dB increments. For each stimulus and intensity, two repeatable responses of 2048 sweeps each were collected and summed to obtain a grand average response (4096 total sweeps). Wave I peak and trough were marked in SmartEP and reviewed by the first three authors.

Study procedures were approved by the Northwestern University Institutional Review Board (STU00217879).

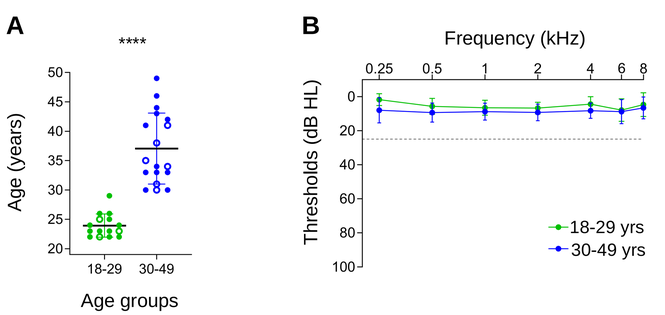

Figure 1. Participant Demographic Data. (A) Age and gender distributions of participants. Open circles represent male participants. Thick horizontal bar represents mean age, bracketed by ±1 standard deviation. **(B)** Audiometric thresholds for both age groups from 0.25 to 8 kHz (averaged across ears). Error bars at each frequency represent ±1 standard deviation. **** = $p < 0.0001$.

DPOAE Level Growth Functions

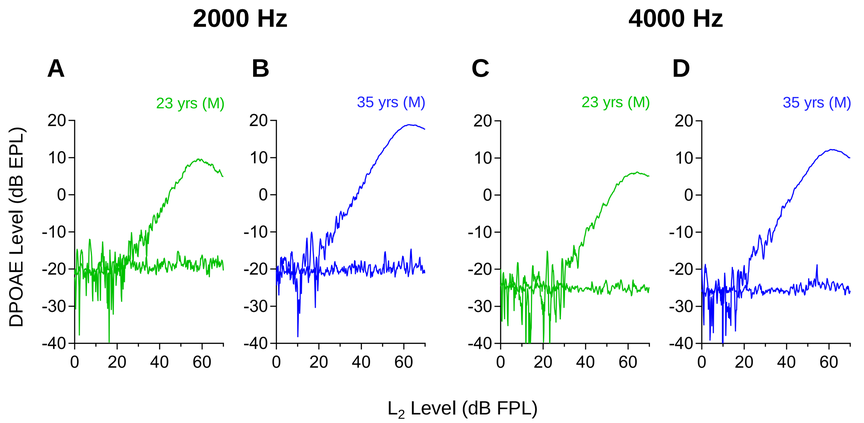

Figure 2. Exemplar DPOAE Level Growth Functions
Representative DPOAEs from a 23-year-old male participant (green) and a 35-year-old male participant (blue) as a function of stimulus frequency and intensity. **(A-B)** DPOAEs in response to a 2 kHz stimulus presented from 0 to 70 dB FPL in 10-dB increments. **(C-D)** DPOAEs in response to a 4 kHz stimulus from 0 to 70 dB FPL in 10-dB increments. In all panels, noise floor is represented by the lines between -20 and -30 dB EPL.

ABR Wave I Level Growth Functions

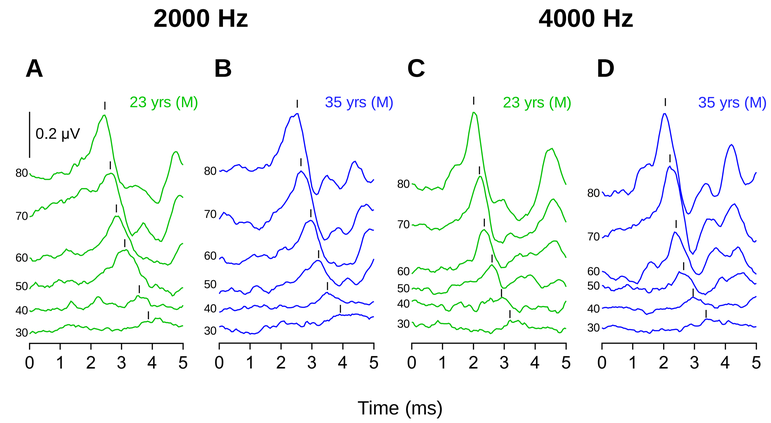

Figure 3. Exemplar ABR Wave I Level Growth Functions
Representative ABR traces from a 23-year-old male participant (green) and a 35-year-old male participant (blue) as a function of stimulus frequency and intensity. The participant data shown here are the same participants in Figure 2. Panels show ABRs to **(A-B)** a 2 kHz iChirp and **(C-D)** a 4 kHz iChirp from 80 to 30 dB nHL in 10-dB increments. In all panels, stimulus intensity is labeled to the left of the corresponding ABR trace. Time window is narrowed to first 5 ms of the response to highlight Wave I; peaks are indicated with "I".

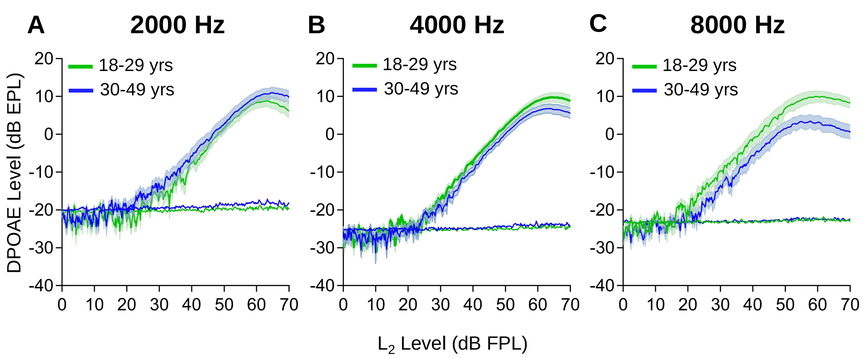

Figure 4. Mean DPOAE Level Growth Functions
Average DPOAE levels for the 18–29-year-old age group (green line) and the 30–49-year-old age group (blue line) for a (A) 2 kHz, **(B)** 4 kHz, and **(C)** 8 kHz stimulus. The shaded regions represent the standard error of the mean. Noise floor is represented by the lines between -20 and -30 dB EPL.

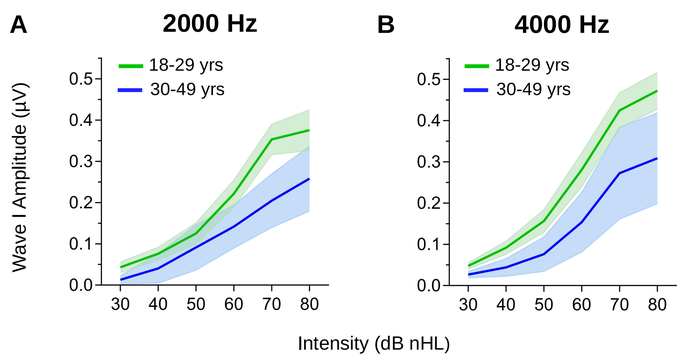

Figure 5. Mean ABR Wave I Level Growth Functions
Average wave I peak-to-trough amplitudes for the 18–29-year-old age group (green line) and the 30–49-year-old age group (blue line) for a **(A)** 2 kHz narrowband iChirp and **(B)** 4 kHz narrowband iChirp. The shaded regions represent the standard error of the mean.

Results

On average, the data shows a decline in both DPOAE and ABR level growth functions of the 30–49-year-old age group relative to the 18-29-year-old age group. However, the patterns of decline manifest differently across our two primary outcome measures:

- **DPOAE**: Average DPOAE growth is similar between age groups at 2 and 4 kHz. Interestingly, differences between groups appear to emerge at 8 kHz. At this frequency, the 30-49-year-old age group showed reduced DPOAE growth compared to the 18-29-year-old age group, particularly at the highest measured intensities.
- **ABR**: Average Wave I peak to trough amplitudes are lower at 2 and 4 kHz in the 30-49-year-old age group relative to the 18-29-year-old age group, particularly at moderate to high stimulus intensity levels. There is a flatter slope of growth for the 30-49-year-old age group compared to the 18-29-year-old age group.

Conclusions

Overall, our results suggest the presence of frequency-dependent, subclinical age-related decline in early-aged ears. This is notable because all individuals had clinically normal hearing and were relatively young (mean age = 36.7 years).

- While both ABR and DPOAEs declined in the older ears, the patterns of decline were distinct. **ABR growth was shallower in older ears at 2 and 4 kHz, where DPOAE growth was relatively similar between groups. This suggests the presence of age-related IHC and/or spiral ganglion decline at lower frequencies.**
- **In contrast, DPOAEs declined with age at 8 kHz. This suggests the presence of age-related OHC dysfunction in early-aged ears at higher test frequencies.**

Together, these results highlight that auditory aging is a multifaceted and complex condition.

Future Directions

- Recruit additional participants in the 40-49-year-old age range.
- Recruit younger participants (i.e., < 18 years old) to serve as a "baseline".
- Measure ABR growth functions at 8 kHz
- Understand individual differences in DPOAE and ABR level growth patterns, as only average data were explored here.
- Examine the functional consequences of this subclinical auditory decline (i.e., speech-in-noise testing).

References: Glavin, C. C., Siegel, J., & Dhar, S. (2021). Distortion Product Otoacoustic Emission (DPOAE) Growth in Aging Ears with Clinically Normal Behavioral Thresholds. *Journal of the Association for Research in Otolaryngology: JARO*, *22*(6), 659–680. https://doi.org/10.1007/s10162-021-00805-3.

Sergeyenko, Y., Lall, K., Liberman, M. C., & Kujawa, S. G. (2013). Age-related cochlear synaptopathy: an early-onset contributor to auditory functional decline. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *33*(34), 13686–13694. https://doi.org/10.1523/JNEUROSCI.1783-13.2013

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