Effects of age on electrophysiological measures of cochlear synaptopathy in humans

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Introduction

• Studies in rodents indicate that cochlear synaptopathy occurs as a result of aging even in the absence of significant noise exposure [1].

• Cochlear synaptopathy is thought to affect mainly low-spontaneous rate (LSR) fibers resulting in a reduction of wave I of the auditory brainstem response (ABR) at high stimulus levels, and of the frequency following response (FFR) at high levels and low modulation depths [2,3].

Objective

• Determine whether electrophysiological responses in humans show evidence of a reduced contribution of LSR fibers as a result of aging.

Methods

• Ratio measures were used to isolate effects of LSR fibers loss:

- Ratio of ABR wave I response at high and low stimulus levels.

- ABR wave I to wave V ratio at high stimulus levels.

- FFR difference between large and shallow modulation depths.

• Aging is associated with high-frequency hearing loss (HL). At high stimulus levels cochlear regions well above the characteristic frequency contribute to electrophysiological responses [4]. To estimate aging effects independent of HL, highpass (HP) noise was used to mask the contribution of basal cochlear regions.

Participants. ABRs recorded from 82 participants (young=26, F=20, middle aged=32, F=26, N elderly=24, F =18) with audiometric thresholds below 20 dB HL from 0.125 to 2 kHz, and below 40 dB HL at 4 kHz. FFRs recorded from 79 of the same participants.

ABR Stimuli

• 0.35-3 kHz clicks at **80** and **105** dB ppeSPL.

• Clicks presented in **quiet**, or embedded in a 20-ms burst of bandpass-filtered pink **noise** (Fig. 1) to mask the basal response (spectrum levels of 65 and 40 dB SPL at 1 kHz, for the 105 and 80 dB ppeSPL clicks).

• Clicks presented alternately to each ear at rate of 14.1/s. 10,000 presentations per condition.

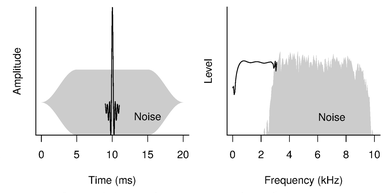

Fig. 1: *Schematic representation of the stimulus used for eliciting the ABR.*

FFR Stimuli

• Simultaneously presented 450-ms AM tones, with a **low (0.6 kHz)**, and a **high (2 kHz)** carrier frequency (CF) (Fig. 2), modulated at a different rate close to 100 Hz.

• Modulated either with **100%**, or **70%** amplitude. 4,000 sweeps, collected in alternating polarity.

• Presented in noise to eliminate the contribution of high-frequency cochlear regions and restrict off-frequency contributions.

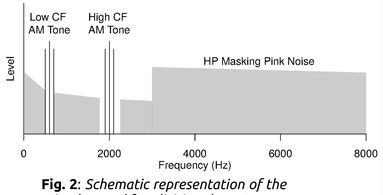

Fig. 2: *Schematic representation of the stimulus used for eliciting the FFR.*

ABR Analyses. Fz-linked earlobes montage. Automatic peak-picking procedure. Wave I measured from peak to trough. Wave V from peak to baseline.

FFR Analyses. Fz-neck montage. Addition and subtraction spectra used to compute the envelope (ENV) and temporal fine structure (TFS) responses respectively. Signal-to-noise ratios (SNRs) computed from the ratio of the signal level at the target frequency and the noise level at adjacent frequencies.

Statistical Analyses

• Bayesian multiple regression models with random subject effects.

• Wave I and V at 80 and 105 dB ppeSPL modeled jointly.

• Average pure tone audiometric thresholds at 4, 8, and 12 kHz ($PTA_{4\text{-}8}$) used as covariate only in the quiet condition to estimate aging effects partialing out the effects of high frequency HL.

• Censored analysis to deal with non-identifiable wave peaks.

• FFR SNRs at both CFs and both modulation depths modeled jointly. $PTA_{1\text{-}2}$ used as covariate to partial out residual audiometric differences at 1 and 2 kHz.

ABR Results

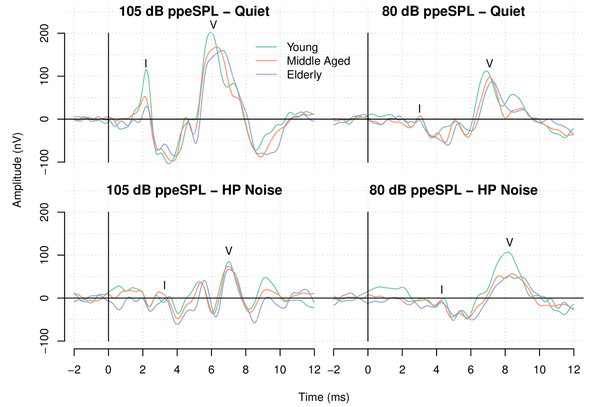

Fig 3 : *Grand-average ABR waveforms for each age group.*

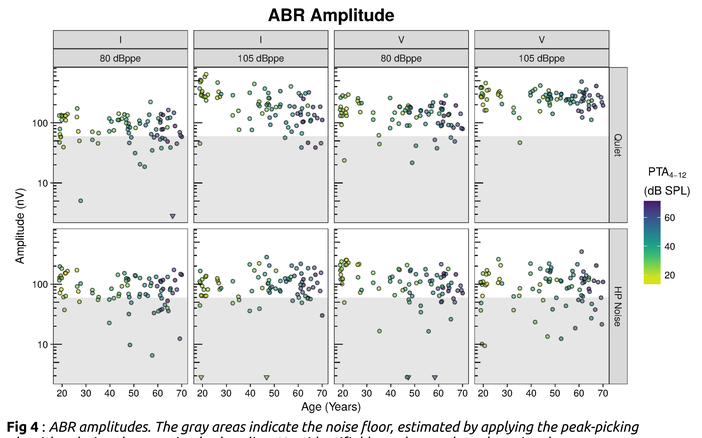

Fig 4 : *ABR amplitudes. The gray areas indicate the noise floor, estimated by applying the peak-picking algorithm during the pre-stimulus baseline. Non-identifiable peaks are plotted as triangles.*

Statistics

• **In quiet:** wave I at high levels and the ratio measures decrease with age independently of HL (Fig. 5A).

• **In HP noise:** no significant age-related decreases of wave I at high levels, or of the ratio measures (Fig. 5C).

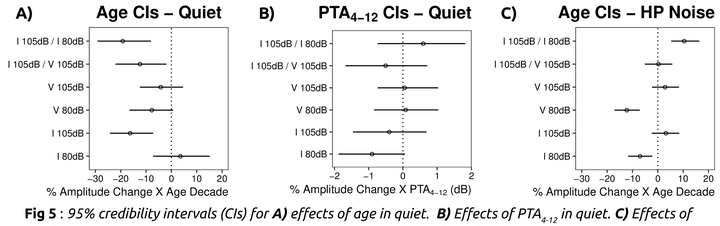

Fig 5 : *95% credibility intervals (CIs) for **A)** effects of age in quiet. **B)** Effects of $PTA_{4\text{-}12}$ in quiet. **C)** Effects of age in the presence of HP noise. The effect of each independent variable is estimated controlling for the effects of other independent variables. Both ratio measures show significant age-related decreases in quiet. In the HP noise condition significant age-related reductions are present only at low levels.*

FFR Results

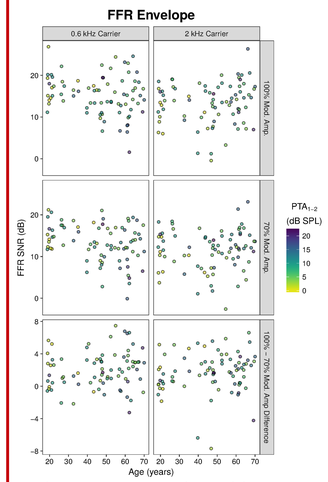

Fig 6 : *FFR SNR at the modulation frequency. The bottom row shows the SNR difference between the large and shallow modulation depths.*

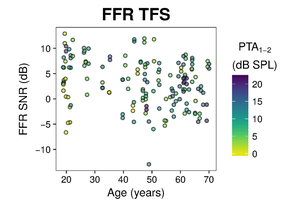

Fig 7 : *FFR SNR at the 0.6 kHz CF.*

Statistics

• ENV responses show age-related decreases only for the 0.6 kHz CF at both modulation depths (Fig. 8).

• No significant age effect on the SNR difference between large and shallow modulation depths (Fig. 8).

• Small $PTA_{1\text{-}2}$ elevations lead to reduced ENV responses at 0.6 kHz (Fig. 9).

• TFS responses at 0.6 kHz show age-related decreases (Fig. 8).

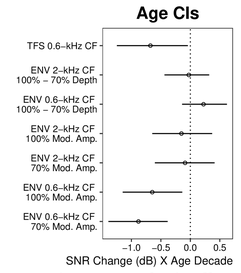

Fig 8 : *95% CIs for the effects of age.*

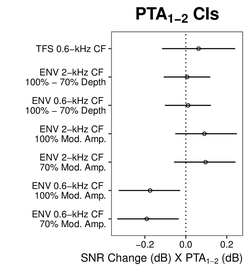

Fig 9 : *95% CIs for the effects of $PTA_{1\text{-}2}$.*

Conclusions

• Absence of age-related decrease in wave I amplitude at high levels in the HP noise condition suggests that in frequency regions where audiometric thresholds are normal the contribution of LSR fibers does not decline with age.

• The presence of age-related decrease in wave I amplitude at high levels (and of the high/low level wave I ratio, and I/V ratio at high levels) in the quiet condition, even with the effects of high-frequency PTA partialed out, suggests that synaptopathy may be occurring in high frequency regions where audiometric losses are present.

• The FFR data show age-related declines (ENV and TFS for 0.6 kHz CF), but do not provide evidence of an age-related FFR difference between large and shallow modulation depths.

References

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