Using thresholds in noise to identify hidden hearing loss in humans

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INTRODUCTION

Recent animal studies suggest that noise-induced synaptopathy may underlie hidden hearing loss (HHL; Kujawa and Liberman, 2009; Lin et al., 2011; Furman et al., 2013; Mehraei et al., 2016). Noise exposure preferentially damages low spontaneous rate (SR) auditory-nerve fibers, which are involved in the processing of moderate-to-high level sounds and are more resistant to masking by background noise. Therefore, the effect of synaptopathy may be more evident in suprathreshold measures of auditory function, especially in the presence of background noise. Thresholds in noise may be sensitive to loss of low-SR fibers. Lobarinas et al. (2016) showed that selective carboplatin-induced IHC loss in chinchillas leads to elevated thresholds in noise, while thresholds in quiet remained unchanged. Currently, functional tests of IHC loss in humans do not exist. However, the amplitude of ABR Wave I may be sensitive to IHC deafferentation (Kujawa and Liberman, 2009; Wynne et al., 2013). The purpose of this study was to develop a statistical model for estimating HHL in humans using thresholds in noise as the outcome variable and several experimental measures, including ABR, that reflect the integrity of sites along the auditory pathway as predictor variables. Our working definition of HHL is that it is the portion of the variability in the thresholds in noise measure that is not dependent on thresholds in quiet, but is evident in other measures of suprathreshold function.

METHODS

Participants

Study participants included 13 adults with normal hearing (≤15 dB HL) and 20 adults with sensorineural hearing loss (>15 dB HL) at 4 kHz. All participants had thresholds within normal limits at 1 kHz.

Outcome measures

Thresholds in noise were measured using the TEN (HL) test (Moore et al., 2004). Measurements were performed monaurally on all participants at 1 and 4 kHz using a 2-dB step size. The SNR, i.e. level of tone at threshold of detection minus the level of the TEN masker (which was fixed at 70 dB HL) was calculated and used as the primary outcome measure in the statistical analysis.

Noise Exposure Questionnaire (NEQ) assesses the frequency and duration of exposure to 9 noisy occupational and recreational activities over the last 12 months (Stamper and Johnson, 2015). The activities include use of power tools, heavy equipment and machinery, commercial sporting and entertainment events, motorized vehicles, small/private aircraft, musical instrument playing, music listening via personal earphones, and music listening via audio speakers. Annual noise exposure was quantified using $L_{Aeq8760h}$.

Experimental measures

- Distortion-product otoacoustic emissions
- Auditory brainstem response (ABR)
- Electrocochleographic (ECochG) action potential (AP) and summating potential (SP)
- Categorical loudness scaling (CLS)

All measurements were made at two frequencies (1 and 4 kHz). ABR and ECochG measurements were made at 80 and 100 dB SPL, while wider ranges of levels were tested during DPOAE and CLS measurements.

ECochG and ABR were measured simultaneously in response to tone bursts (27/s), using an ear-canal electrode (tiptrode) and surface electrodes at the vertex (Cz, noninverting active) and on the high forehead (Fpz, ground).

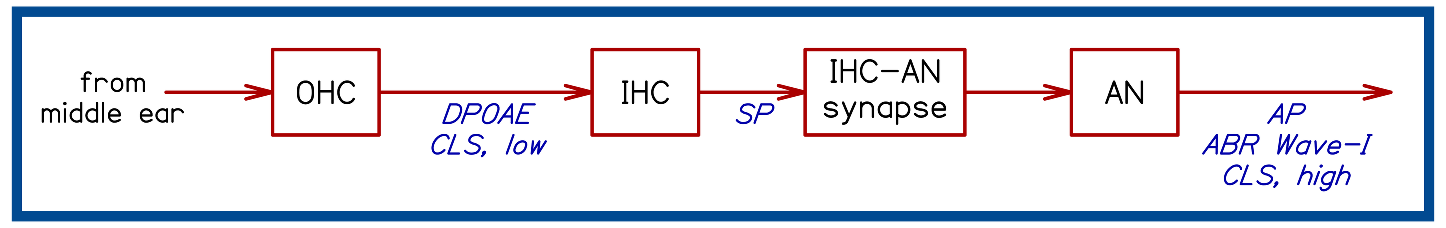

FIGURE 1. Sites along the auditory pathway and the experimental measures (in italic font) that indicate their integrity. Outer hair cell (OHC) integrity is reflected in DPOAE and the lower segment of CLS. The SP reflects the integrity of both OHCs and inner hair cells (IHC). Auditory nerve (AN) integrity is reflected in ABR Wave I (AP) and the upper segment of CLS. Wave V reflects the health of the entire auditory system and is related to audiometric thresholds.

Model of hidden hearing loss

The residual of the correlation of thresholds in noise with thresholds in quiet was calculated using correlational analysis and served as our estimate of HHL.

Multiple linear regression (MLR) was used to characterize the relationships between our estimate of HHL and predictor variables derived from experimental measures. The model was of the form:

$$HHL \sim \alpha \cdot AP + \beta \cdot SP + \gamma \cdot SP/AP + \cdots + \omega \cdot L_{40\,CU} + Intercept$$

where α, β, γ, ..., ω are the model coefficients relating the experimental predictor variables to the estimate of HHL.

Sex, age and $L_{Aeq8760h}$ were included as predictor variables.

Three models were created

1. Prediction of HHL at 1 kHz.
2. Prediction of HHL at 4 kHz.
3. Differential analysis utilizing the ratio of the data at 4 kHz to the data at 1 kHz.

For (1) and (2), data at both 1 and 4 kHz served as predictor variables.

Principal component analysis (PCA), utilizing an alternating least squares algorithm (ALSA), was used to reduce the dimensionality of the data from 37 to 7 prior to MLR analysis. The ALSA was required due to missing values in our dataset. However, because the ALSA starts with random initial values, 1000 simulations were completed and the predicted HHL was the mean of these simulations.

Table 1. Experimental measures and their predictor variables.

Measure	ABR	ECochG	DPOAE	CLS
Variables	- Wave-I amplitude - Wave-V amplitude - Wave I amplitude difference* - Wave V/Wave I ratio	- SP - AP - AP amplitude difference - SP/AP ratio	- DPOAE at L_2 = 55 dB SPL	- SPL required for 10 CU ($L_{10\,CU}$) - SPL required for 40 CU ($L_{40\,CU}$)

* The difference between the amplitude at 100 dB peSPL and the amplitude at 80 dB peSPL.

RESULTS

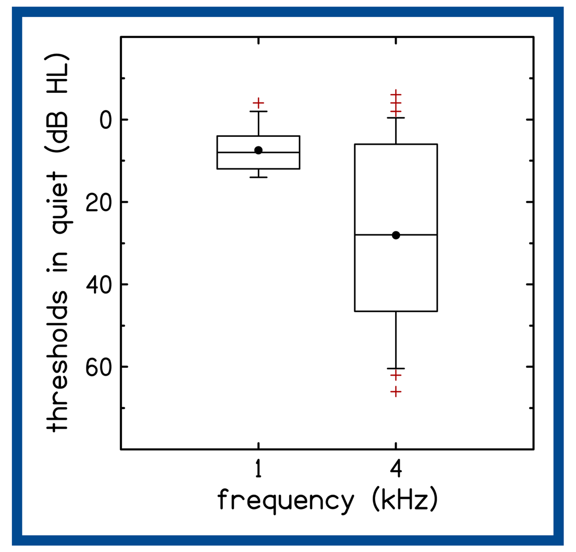

FIGURE 2. Audiometric thresholds at 1 kHz and 4 kHz. The lower and upper margins of the boxes represent the 25th and 75th percentiles, respectively. The lower and upper whiskers represent the 10th and 90th percentiles, respectively. The line within the box represents the median, the filled circles represent the mean, and the plus signs indicate outliers, i.e., points that lie outside the 10th-to-90th percentile range. Recall that all participants had thresholds within the normal limit at 1 kHz, which explains the smaller distribution at this frequency.

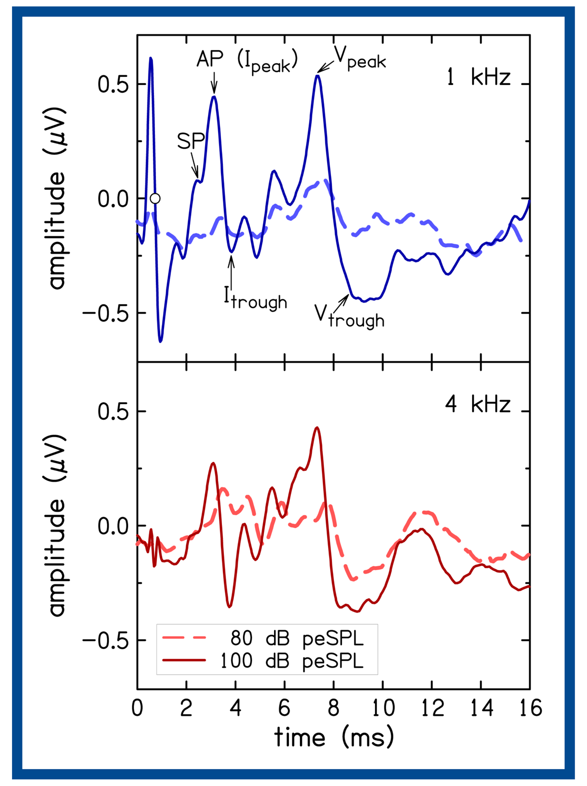

FIGURE 3. ABR and ECochG waveforms for a representative participant. The top and bottom panels show waveforms for 1 and 4 kHz, respectively. In each panel, waveforms are shown for 100 dB peSPL (solid line) and 80 dB peSPL (dashed line). The AP, SP and the baseline (circle symbol at 0.7 ms), as well as the peaks and troughs of ABR Waves I and V, are identified in the top panel. The peak at 0.6 ms is stimulus artifact. Baseline was selected as the midpoint of the alternating current signal resulting from either stimulus artifact or cochlear microphonic. If stimulus artifact was not present in the recording, the baseline was selected as the trough before or after the AP, whichever was clearer. Our electrode configuration enhanced Wave I (AP) and SP, while still providing a robust Wave V.

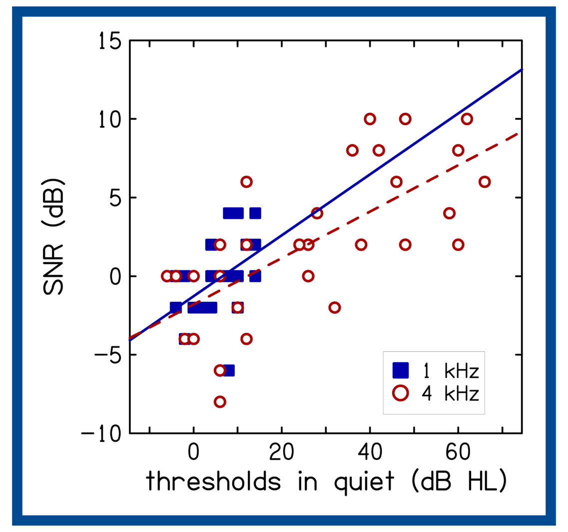

FIGURE 4. SNR for TEN (HL) test as function of audiometric thresholds in quiet. There was a correlation between thresholds in quiet and SNR at both 1 kHz and 4 kHz. That is, a portion of the variability in thresholds in noise is due to hearing thresholds. Removing this component of the total variance provides the basis for our definition of HHL.

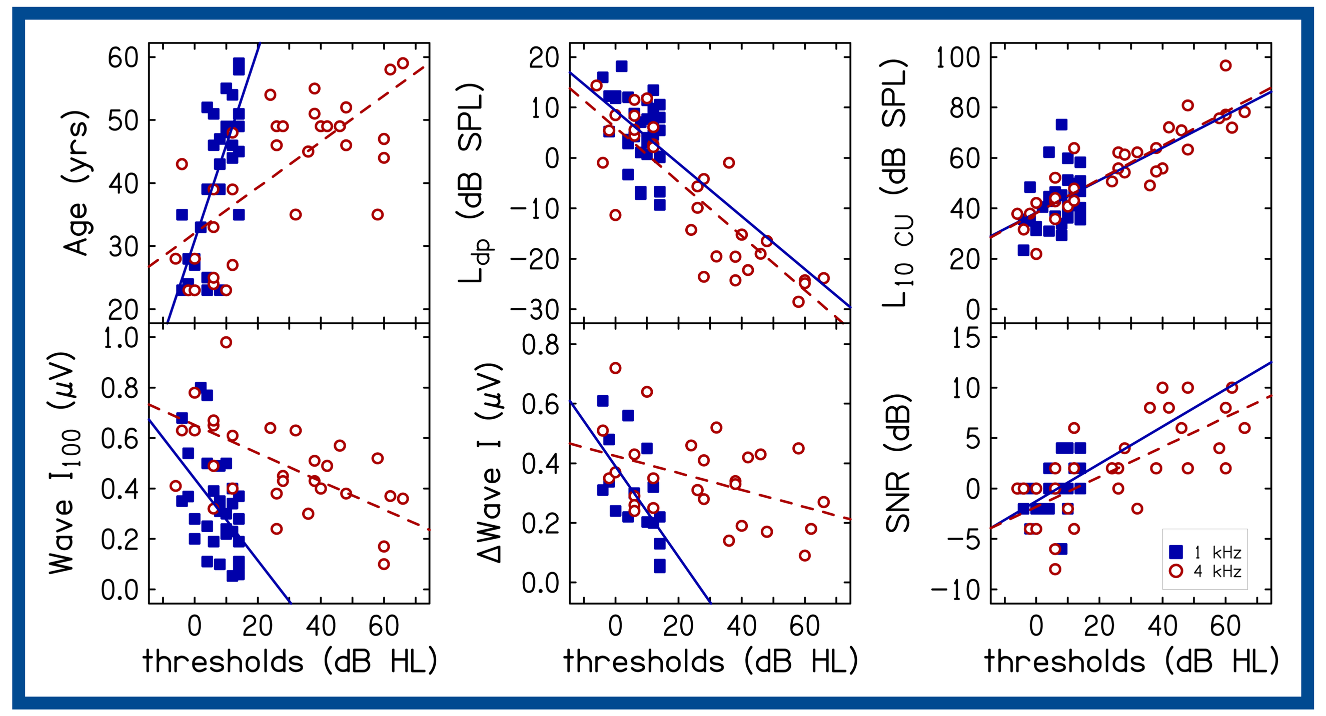

FIGURE 5. Relationship of audiometric thresholds in quiet with *measured* variables at 1 kHz (closed squares) and 4 kHz (open circles) with correlations having p<0.05 at both frequencies. Correlations with p<0.05 were observed for age, L_{dp}, $L_{10\,CU}$, Wave I amplitude at 100 dB peSPL (bottom left panel), Wave I amplitude difference (ΔWave I; bottom middle panel) and SNR for the TEN test (bottom right panel). Correlations between thresholds in quiet and DPOAE level and the lower portion of the CLS function ($L_{10\,CU}$) were expected because these measures reflect OHC function which is affected by audiometric thresholds. Correlation between thresholds in quiet and age is consistent with previous studies (e.g. Lee et al., 2005).

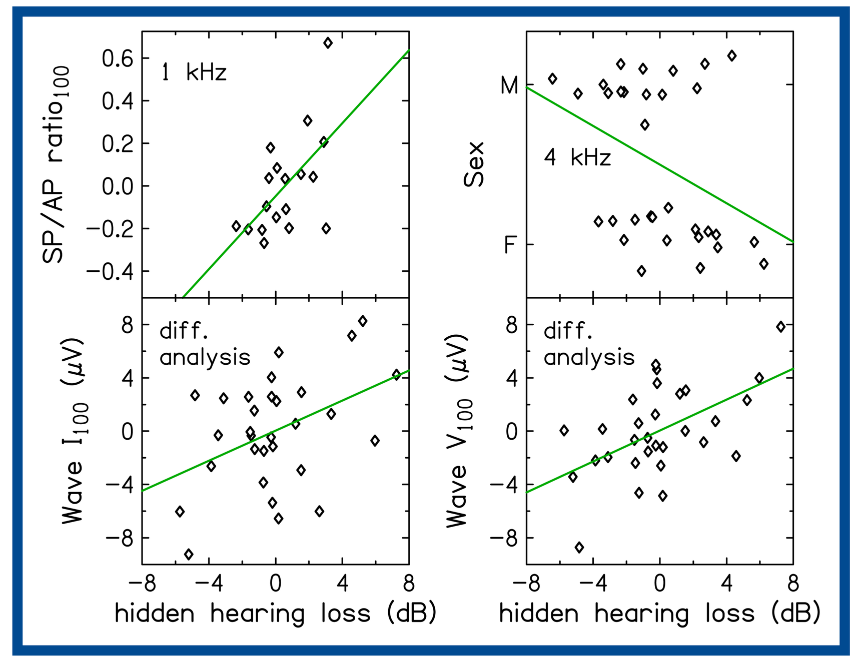

FIGURE 6. Relationship of HHL with *residuals* having correlations of p<0.05. Correlations with p<0.05 were observed for SP/AP ratio at 1 kHz and 100 dB peSPL and sex at 4 kHz. For the differential analysis, correlations of p<0.05 were observed for Wave I amplitude (bottom left panel) and Wave V amplitude, both at 100 dB peSPL. The correlation of HHL with SP/AP ratio is consistent with results of Liberman et al. (2016). The greater HHL in females compared to males was not expected because males are more likely to have higher noise exposure than females. This result is also in contrast with amount of noise exposure, as assessed using the NEQ, where males claimed higher amounts of noise exposure than females. Correlation of HHL with Wave I amplitude was expected since this variable reflects ANF integrity. The lack of a correlation of HHL with AP was unexpected and may be a reflection of the way in which the AP was quantified. While the peaks for the AP and ABR Wave I were identical, the amplitude of the AP was calculated with reference to a baseline and the amplitude of Wave I was calculated with reference to the following trough.

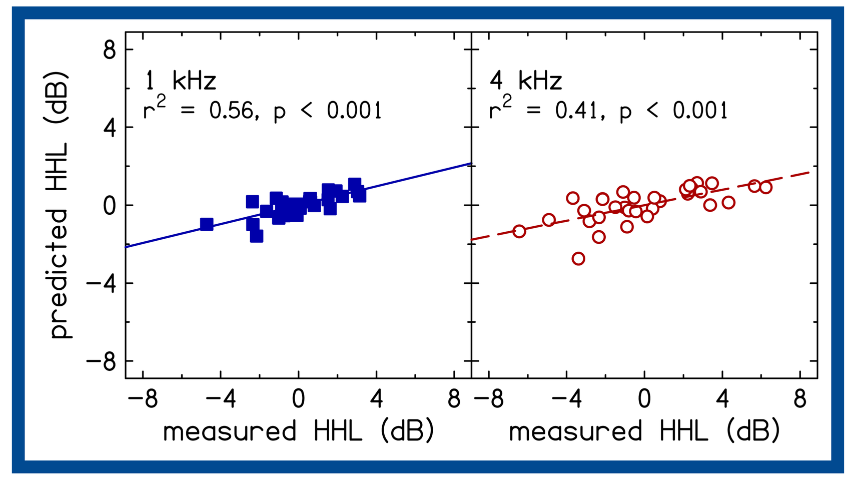

FIGURE 7. Prediction of HHL using PCA and MLR. Predictions for 1 and 4 kHz are shown in the left and right panels, respectively. Over the 1000 simulations, the 7 PCA components used in the model accounted for an average of 81.54% and 80.73% of the variance in the input variables at 1 and 4 kHz, respectively. Our model of HHL can predict HHL to some extent. The model, however, is limited by the accuracy of all measures, including estimates of noise exposure (derived from the NEQ), lack of a gold standard for HHL, the generally smaller "variance due to HHL" compared to "variance due to unhidden hearing loss," and the relatively small sample size (especially in relation to the number of variables).

DISCUSSION

- Before removal of the "variance due to thresholds in quiet," "thresholds in noise" were correlated with measures that reflect OHC function.
- After removal of the "variance due to thresholds in quiet" from "thresholds in noise," our estimate of HHL was correlated with measures that reflect IHC and ANF integrity
- "Noise exposure history" was not correlated with AP, ABR Wave I, SP/AP ratio, or HHL at either 1 or 4 kHz, contrary to our predictions.
- The lack of correlation between "noise exposure history" and "ABR Wave I" disagrees with Stamper and Johnson (2015) who observed a weak but statistically significant correlation.
- The "upper segment of the CLS function" ($L_{40\,CU}$) was not correlated with variables that reflect IHC and ANF integrity (AP, SP, Wave I), contrary to our predictions. However, it was correlated with "ABR Wave V amplitude" and the "Wave V/Wave I amplitude ratio" at 4 kHz.
- Future efforts to model HHL will include (1) a larger sample size, (2) focus on populations with a history of noise exposure, and (3) measures that may be more predictive of HHL such as middle-ear muscle reflex, medial olivocochlear reflex and frequency-following response.

CONCLUSIONS

- SP/AP ratio, ABR Wave I, and ABR Wave V were the most significant indicators of HHL.
- The significant correlation of our model predictions with TEN residuals supports our approach as being predictive of HHL.
- The results of our correlational analyses are consistent with suggestions that IHC and AN pathology may underlie suprathreshold auditory performance.

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