Relations between auditory brainstem response and threshold metrics in normal and hearing-impaired listeners

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Auditory brainstem responses (ABRs) offer a potential tool to diagnose auditory-nerve deficits in listeners with normal hearing thresholds as abnormalities in the amplitude of this population response may result from a loss in the number of auditory-nerve fibers contributing to this response. However, little is known about how cochlear gain loss interacts with auditory-nerve deficits to impact ABRs. We measured level-dependent changes in click-ABR wave-I and V in listeners with normal and elevated thresholds to study which measures are dominated by cochlear gain loss. ABR wave-V latency-vs-intensity functions correlated well to the distortion-product otoacoustic emission threshold and this relation was also observed for the slope of supra-threshold ABR wave-I level growth in listeners with thresholds above 20 dB SPL. ABR wave-I and wave-V growth were not related to each other, demanding caution when using ABR wave-V growth or level as a direct measure for auditory-nerve deficits.

INTRODUCTION

Auditory brainstem responses (ABRs) have regained popularity in the diagnostics of subcomponents of peripheral hearing loss. As the ABR is easily recorded in humans and its wave peaks result from population responses at different ascending processing stages along the auditory pathway, it can be used to isolate auditory-nerve (AN) deficits (i.e., cochlear neuropathy) due to noise exposure or ageing. Particularly, in subjects with normal auditory thresholds, the ABR wave-I level is reduced when the number of auditory nerve (AN) fibers synapsing onto the inner-hair cell is reduced (Kujawa and Liberman, 2009; Sergeyenko *et al.*, 2013; Furman *et al.*, 2013). The ABR wave-I contains information about many AN fibers firing synchronously to transient stimuli and its level reduction can thus occur while correlates of outer-hair-cell health such as otoacoustic emissions are normal.

While in animal physiology the ABR wave-I is strong, humans have a weak wave-I compared to the wave-V that is thought to be generated by medial-superior-olive (MSO) primary cells projecting on to the lateralis lemniscus and inferior colliculus (Melcher and Kiang, 1993). It is currently unclear whether auditory-nerve deficits impact wave-V in similar ways as wave-I since it has been suggested that homeostatic

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mechanisms can undo effects of the ABR wave-I reduction in tinnitus patients (Schaette and McAlpine, 2011) and that greater wave-V/I level ratios have been associated with hyperacusis and tinnitus (Hickox and Liberman, 2014; Gu *et al.*, 2012). Although hearing diagnostics have mostly focused on wave-V in humans, it may not directly reflect auditory-nerve deficits that occur at more peripheral processing stages. Another confounding factor in using ABRs is that they are an output measure that is influenced by both auditory-nerve *and* hair-cell deficits. While cochlear neuropathy studies have so far focused on listeners with normal thresholds, it is not clear how outer-hair-cell-loss-related cochlear gain loss impacts the ABR wave-I and wave-V. Because in clinical practice, one would ideally use one measure that can differentially diagnose subcomponents of hearing loss in listeners with mixtures of pathologies, it is important to study how different hearing deficits interact and impact the ABR.

The present study addresses this topic by reporting click-ABR wave-I and wave-V levels and latencies in listeners with normal and elevated hearing thresholds. The ABR measures were correlated to distortion-product otoacoustic emission (DPOAE) thresholds as an objective correlate of hearing threshold to test whether cochlear gain mechanisms are the dominant factor accounting for the ABR results. Lastly, it was tested whether one measure for cochlear neuropathy – ABR wave-I growth (Furman *et al.*, 2013) – follows the same trend in listeners with normal and elevated hearing thresholds.

METHODS

Audiograms, ABRs, and DPOAEs were measured in 37 subjects who were divided into two groups. The *normal-threshold* group consisted of 23 participants (mean age = 26.8 years) who were ensured to have hearing thresholds below 15 dB HL in the octave frequencies between 250 and 4000 Hz (mean threshold at 4 kHz = 3.4 dB). The *elevated-threshold* group consisted of 14 participants (mean age=64.4 years) who had a minimum of 20 dB of hearing loss at and above 4 kHz in the better ear (mean threshold at 4 kHz = 26.4 dB). The subjects had mild to moderate hearing losses and measureable DPOAEs. All study participants signed an informed consent according to the ethical review board of the University of Oldenburg.

Instrumentation: Sounds were presented using ER-2 insert earphones attached to a TDT-HB7 headphone driver and a Fireface UCX sound card. All stimuli were generated in Matlab and calibrated using a B&K type 4157 ear simulator and sound level meter. OAEs were recorded using the OLAMP software and an ER10B+ microphone. ABRs were recorded using a 32-channel Biosemi EEG amplifier and a custom built triggerbox, and analysed using the ANLFFR and Matlab software.

Click-ABR: 100-µs condensation clicks (0-1-0) were presented monaurally to the better ear at a rate of 33.3 Hz with a 10% jitter on the recording window duration. 7000 clicks were presented at peak-equivalent sound pressure levels (peSPL) of 70, 80, 90, and 100 dB. For each stimulus level, the raw EEG from the Cz channel was referenced to the mean of the reference electrodes placed on the earlobes, and filtered

from 70 Hz to 2000 Hz. ABR waveforms were epoched from −10 ms to 20 ms, baseline corrected, and averaged. ABR peak latency and the peak-to-peak amplitudes were determined for wave-I and V. ABR latency was reported to the start of the stimulus and no compensation for the (fixed) recording delay of the sound delivery system was applied. The ABR peaks were hand picked by two independent observers. If the peak-to-peak levels were less than 2 dB apart results were averaged, else the data-point was discarded. Similarly, for ABR latency measurement points were discarded when readings were more than 0.3 ms apart. Slopes of ABR level and latency across the 30-dB stimulus level range were calculated using a linear fit across the data points corresponding to the four stimulus levels. Group statistics on the intensity curves of ABR latency and level were calculated using a *t*-test and correlation statistics were obtained using linear regression.

DPOAEs: DPOAEs were measured for a fixed f_2/f_1 ratio of 1.2 and primary levels were either chosen according to the Neely-level paradigm (half of the participants) or the Scissors paradigm (other half; Kummer *et al.*, 1998). Because the two level paradigms yield similar growth functions at low stimulus levels (Neely *et al.*, 2005), this methodological difference is not expected to influence the derived DPOAE thresholds substantially. The primary frequencies were exponentially swept up (2s/octave) over a 1/3 octave range around the geometric mean of 4 kHz at a constant frequency using a sweep method (Long *et al.*, 2008). Using a sufficiently sharp least squared fit filter (here ca. 2.2 Hz), the distortion component was extracted from the DPOAE recording. This distortion component is generated around the characteristic site of f_2 and thus predominantly provides information about the f_2 site without being influenced by DPOAE fine structure (Mauermann and Kollmeier, 2004). Growth functions were computed as the average over 34 distortion-source DPOAE functions across the measured frequency range and a matched cubic function:

$$L_{DP} = a + \left(\frac{1}{q} (L_2 - b) \right)^3$$

with parameters a, b, and q fitted to the data points. DPOAE thresholds were determined as the level of L_2 at which the extrapolated fitting curve reached a level of −25 dB SPL (~0 Pa).

RESULTS

Figure 1 shows ABR intensity functions of ABR wave-V latency (A) and ABR wave-V and I level (B and C) for the normal-threshold and elevated-threshold group.

Whereas the wave-V latencies of the two groups are not significantly different at 100 dB peSPL (p=0.23), the latency difference between groups becomes significantly greater as stimulus level is reduced (p<0.01). Specifically, the listeners with elevated hearing thresholds exhibit steeper latency-vs-level slopes (p<0.001), due to overall increased wave-V latencies at the lower stimulus levels. Even though increased ABR wave-V latencies for listeners with elevated hearing thresholds are somewhat at odds with linear filter theory that predicts shorter local basilar-membrane impulse responses for wider auditory filters, another study has similarly reported increased

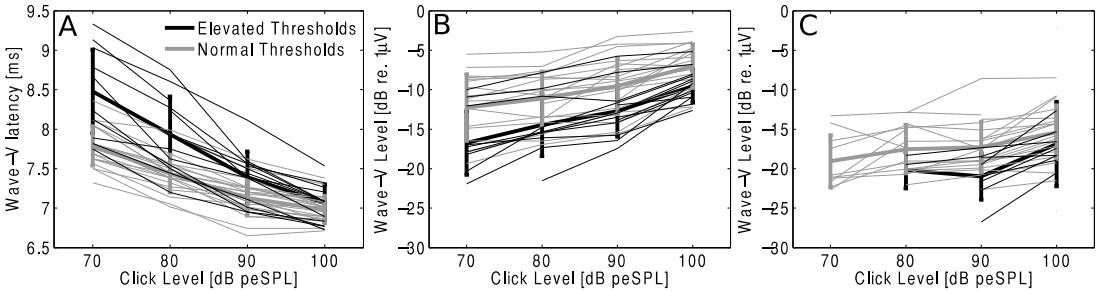

Fig. 1: ABR wave-V latency (A), level (B), and ABR wave-I level (C) for the normal (gray) and elevated-hearing threshold (black) group. Both the mean results +/- 1 standard deviation (thick lines) and individual (thin lines) results are shown.

wave-V latencies for 2-kHz derived band ABRs at moderate intensities (60-70 dB peSPL) in listeners with sloping hearing losses (Strelcyk *et al.*, 2009). A study with few participants also reported steeper click ABR wave-V latency slopes for those listeners with sloping audiograms (Gorga *et al.*, 1985).

Overall, ABR wave-V levels (panel B) were higher for the normal-threshold group ($p<0.05$), and the growth of ABR wave-V levels across all 4 intensities was steeper for the elevated threshold group ($p<0.05$). However, when only considering the highest two stimulus levels (90 and 100 dB peSPL), ABR wave-V was not significantly steeper for the elevated threshold group than for the normal-threshold group ($p=0.15$). A similar trend was observed for the ABR wave-I level growth functions (panel C), which did not show significant level growth differences across groups (90-100 dB peSPL; $p=0.13$).

Whereas cochlear neuropathy studies report shallower ABR wave-I growth in normal-threshold subjects with auditory nerve-deficits (Furman *et al.*, 2013), the results for the ABR wave-V seem to indicate that cochlear gain loss might in stead steepen the ABR growth function (across 4 intensities). Because it is not clear whether this relation also holds true for the measured ABR wave-I, Fig. 2 studies the relation between cochlear gain loss and the ABR slope metrics in more detail.

Figure 2 demonstrates that DPOAE thresholds at 4 kHz did not significantly correlate to ABR wave-V (panel B; $p=0.08$) and wave-I level growth (panel C; $p=0.5$) when only considering the highest two stimulation levels (90-100 dB peSPL). Differently, for participants with DPOAE thresholds above 20 dB SPL, Fig. 2C shows significantly steeper ABR wave-I growth functions, whereas this relation is missing for listeners with thresholds below 20 dB. With respect to the neuropathy hypothesis that predicts shallower ABR wave-I growth functions for normal-threshold listeners with auditory-nerve deficits, it could be that the absence of a relation between the DPOAE threshold and ABR wave-I growth in the normal-threshold group can be explained by cochlear neuropathy (or other) effects. However, the steeper wave-I growth functions found for elevated-threshold listeners are in clear contrast to the

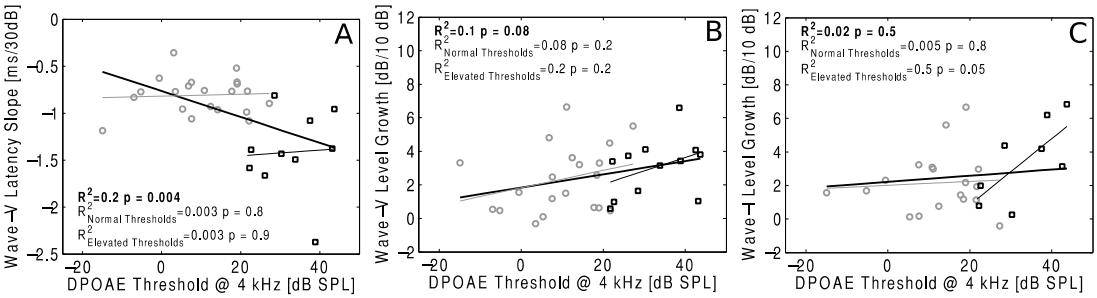

Fig. 2: Relation between the DPOAE threshold at 4 kHz and the ABR wave-V latency slope (A), wave-V level slope (B), and wave-I level slope (C) for the normal (gray) and elevated (black) hearing threshold group. The latency slope was calculated for levels between 70 and 100 dB peSPL, and the wave-I and V level slopes were calculated between the 90 and 100 dB peSPL levels.

neuropathy hypothesis and demonstrate that cochlear gain losses can steepen the ABR growth function even though it can be assumed that cochlear neuropathy occurs before thresholds are elevated (Sergeyenko *et al.*, 2013). Even though more compelling (and physiological) evidence is required, the steep wave-I level growth functions could result from cochlear gain loss being the dominant effect in determining ABR wave-I level growth when both gain and auditory-nerve deficits are present. Lastly, ABR wave-I and wave-V level growth did not correlate in individual listeners (p=0.7) demanding caution when using wave-V level or growth metrics to diagnose auditory-nerve deficits as level-dependent properties of processing centers between the auditory nerve and inferior colliculus might contribute to the ABR wave-V level.

Lastly, Fig. 2A shows a significant relation between the ABR wave-V latency slope and the DPOAE threshold at 4 kHz (p<0.01) yielding steeper slopes for listeners with elevated thresholds. Because the ABR latency slope is a relative metric within a specific listener, and not related to the amplitude of the ABR that can be reduced because of cochlear neuropathy (Sergeyenko *et al.*, 2013; Furman *et al.*, 2013), it might potentially be a differential diagnostic tool of cochlear gain loss. Further, the observed correlation between wave-I and wave-V latency-vs-intensity slopes in individual listeners (p<0.05) supports the view that the cochlear gain loss influence on cochlear excitation that steepens the wave-I latency-vs-intensity slope is still present at the level of the ABR wave-V. However, to prove that ABR wave-V or wave-I latency-vs-intensity curves are fully independent from cochlear neuropathy, it needs to be demonstrated that the onset latency characteristics of the different AN fiber types (low vs high-spontaneous rate) do not significantly influence ABR wave-V latency-vs-intensity curves. There is currently no explicit proof. However, a physiological study that shows a relatively small contribution of low-spontaneous rate AN fibers to the onset peak of the supra-threshold population compound action potential in gerbils (Bourien *et al.*, 2014) does support the limited role of low-spontaneous rate AN fibers to the population onset response.

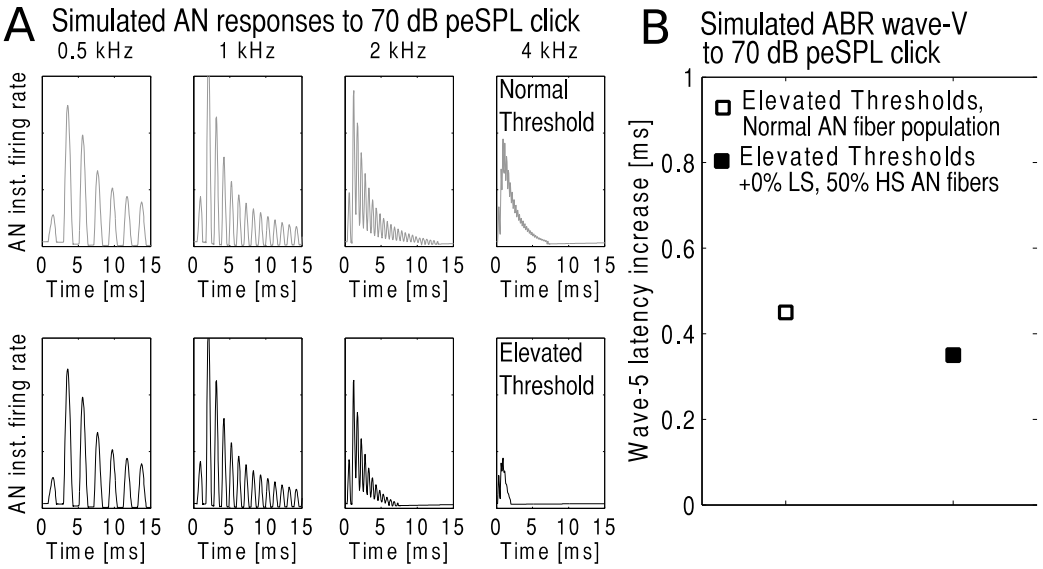

Fig. 3: A: Simulated single-unit auditory-nerve responses to a 70 dB peSPL click at 4 CFs for a normal-hearing model (top) and model with a sloping hearing loss (bottom). Note the reduced contribution of the 2 and 4 kHz channels in the model with elevated thresholds. B: ABR wave-V latency change in the elevated threshold model compared to the normal-hearing model in response to a 70 dB-peSPL click.

DISCUSSION

In this section, the relationship between the ABR wave-V latency slope and cochlear gain loss is further investigated by studying how cochlear filter changes at local basilar-membrane locations can yield population responses with increased ABR wave latencies for listeners with elevated DPOAE thresholds. For this purpose, the functional ABR model by Verhulst *et al.* (2015) was adopted in which cochlear gain loss and auditory-nerve fiber loss can be manipulated on a frequency-dependent basis. ABR wave-V latency was evaluated for a 70 dB peSPL click in three models: (i) a normal-hearing model with normal cochlear filter tuning characteristics (Shera *et al.*, 2010) and a normal auditory-nerve fiber population (70% high, 15% medium and low spontaneous-rate fibers), (ii) a model with a normal AN fiber population, but with a sloping cochlear gain loss (0 dB until 1kHz; 30 dB at 8 kHz), and (iii) a model with a sloping cochlear gain loss and a reduced AN fiber population (loss of 100% medium/low and 50% high spontaneous-rate fibers).

Figure 3A shows that local AN firing responses (summed across all available AN fibers and types for each CF) for the elevated-threshold model (bottom) have reduced in amplitude and exhibit earlier peak latencies at those frequency where a cochlear gain loss was introduced (2 and 4 kHz). This observation stems from the shorter duration and lower amplitude basilar-membrane impulse responses as cochlear gain is reduced and local cochlear filters widen. However, when summing up all energy in

individual CF channels to yield the population response wave-V, Fig. 3B demonstrates that even though local BM impulse responses had shorter peak-latencies, the overall wave-V latency is increased by 0.4 ms. The increased latency of the wave-V response can be explained by the higher dominance of the longer-latency low-frequency channels to the population response when a sloping high-frequency cochlear gain loss is introduced.

In support, the slope of the audiometric hearing loss also has also experimentally been shown to influence to the latency-vs-intensity characteristics of the ABR (Gorga *et al.*, 1985). Additional simulations confirm this relation to the audiogram shape, as a flat hearing loss configuration yields an overall ABR wave-V latency decrease because shorter basilar-membrane impulse response peak-latencies occur in all frequency channels contributing to the population response (Verhulst *et al.*, 2013).

Figure 3B further demonstrates that the impact of cochlear gain loss on the ABR wave-V latency outweighs that of the loss of medium and low spontaneous-rate fibers. Low-spontaneous rate AN fibers generally fire with delayed onset peaks (Bourien et al., 2014) and seem to have a small effect on the population response latency in the present simulations. An explanation for their small contribution to population responses has been empirically explained by the large jitter in first-spike-latency for low- compared to high-spontaneous rate AN fibers (Bourien et al., 2014).

CONCLUSION

Overall, the ABR wave-V latency slopes showed a good correlation to the DPOAE threshold in listeners with normal and elevated hearing thresholds. Taken together with the simulations that show that cochlear neuropathy only has a small effect on click-ABR latency, this metric may form an auditory brainstem correlate of cochlear gain loss. Additionally, it was found that supra-threshold ABR wave-I growth was related to the DPOAE threshold in listeners with elevated thresholds, demanding caution when using this metric as an indicator for cochlear neuropathy in listeners with mixed pathologies. However, it remains possible that the wave-I growth function to narrow-band tone-pip stimuli (Furman *et al.*, 2013) – as opposed to the clicks adopted here – are more sensitive to neuropathy in listeners with elevated thresholds. Lastly, click-ABR wave-V and wave-I growth characteristics were different in individual listeners, complicating a direct and straightforward interpretation of wave-V levels in terms of auditory-nerve deficits.

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