Tone-burst auditory brainstem response wave V latencies in normal-hearing and hearing-impaired ears^{a)}

James D. Lewis,^{b)} Judy Kopun, Stephen T. Neely, Kendra K. Schmid,^{c)}
 and Michael P. Gorga

Boys Town National Research Hospital, 555 North 30th Street, Omaha, Nebraska 68131, USA

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The metric used to equate stimulus level [sound pressure level (SPL) or sensation level (SL)] between ears with normal hearing (NH) and ears with hearing loss (HL) in comparisons of auditory function can influence interpretation of results. When stimulus level is equated in dB SL, higher SPLs are presented to ears with HL due to their reduced sensitivity. As a result, it may be difficult to determine if differences between ears with NH and ears with HL are due to cochlear pathology or level-dependent changes in cochlear mechanics. To the extent that level-dependent changes in cochlear mechanics contribute to auditory brainstem response latencies, comparisons between normal and pathologic ears may depend on the stimulus levels at which comparisons are made. To test this hypothesis, wave V latencies were measured in 16 NH ears and 15 ears with mild-to-moderate HL. When stimulus levels were equated in SL, latencies were shorter in HL ears. However, latencies were similar for NH and HL ears when stimulus levels were equated in SPL. These observations demonstrate that the effect of stimulus level on wave V latency is large relative to the effect of HL, at least in cases of mild-to-moderate HL. © 2015 Acoustical Society of America.

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I. INTRODUCTION

Recent work has demonstrated that differences in distortion-product otoacoustic emission (DPOAE) suppression tuning curves (STCs) between ears with normal hearing (NH) and ears with hearing loss (HL) depend on the stimulus level at which comparisons are made (Abdala and Fitzgerald, 2003; Gorga *et al.*, 2003; Gruhlke *et al.*, 2012). When compared at equal stimulus-probe levels (primary levels for f_1 and f_2 , the stimulus frequencies eliciting the DPOAE) relative to threshold (i.e., sensation level, SL), STCs in ears with mild-to-moderate HL were characterized by reduced gain (as estimated by tip-to-tail differences) and broader tuning (based on the quality factor, Q), compared to ears with NH. However, when comparisons were made at equal absolute probe levels (i.e., sound pressure level, SPL), estimates of gain and tuning derived from DPOAE STCs in ears with mild-to-moderate HL were similar to those observed in ears with NH. Due to their elevated thresholds, equating stimulus level in SL results in higher absolute levels being presented to ears with HL compared to ears with NH. As a result, the observed reduced gain and broader tuning may occur as a consequence of normal level effects rather than as a result of abnormal cochlear processing due to HL.

Changes in DPOAE STCs with increasing probe level may be due to broadening of cochlear filters as a by-product of reduced cochlear gain (Gorga *et al.*, 2003). Level-dependent changes in the latencies of physiological measures including otoacoustic emissions (Shera *et al.*, 2002; Sisto and Moleti, 2007; Shera *et al.*, 2010), the compound action potential (Eggermont, 1979; Rutten, 1986; Henry *et al.*, 2011), and wave V of the auditory brainstem response (ABR; Neely *et al.*, 1988; Don *et al.*, 1998; Dau, 2003; Elberling and Don, 2008; Strelcyk *et al.*, 2009; Elberling *et al.*, 2010; Rønne *et al.*, 2012; Rasetshwane *et al.*, 2013; Verhulst *et al.*, 2013) have also been attributed to effects mediated at the level of the cochlea. The present study examined the effect of stimulus level on ABR wave V latencies in NH and HL ears. Given the effects of level on DPOAE STCs in normal and impaired ears, we predicted that there would be significant differences between groups when stimulus level was specified relative to threshold (SL) and that these differences would be reduced when level was specified in absolute terms (SPL).

In humans, wave V is the most robust component of the ABR and can be measured non-invasively using surface electrodes placed on the scalp. Wave V presumably originates from the lateral-lemniscal pathway (Møller *et al.*, 1995) in the brainstem, but depends on peripheral processes at the levels of the auditory nerve and cochlea. For instance, wave V latency decreases with increasing frequency (e.g., Gorga *et al.*, 1988; Dau, 2003; Rasetshwane *et al.*, 2013), reflecting the shorter travel time required by the traveling wave to excite more basal (higher-frequency) regions of the cochlea. Additionally, when evoked by rising-frequency chirps designed to compensate for traveling-wave dispersion,

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^{b)}Present address: Department of Audiology and Speech Pathology, University of Tennessee Health Science Center, Knoxville, TN 37996, USA. Electronic mail: jdllewis@uthsc.edu

^{c)}Also at: Department of Biostatistics, University of Nebraska Medical Center, Omaha, NE 68198, USA.

the amplitude of wave V is larger than it is for both clicks and falling-frequency chirps (Dau *et al.*, 2000; Elberling and Don, 2008; wave I amplitude exhibits similar behavior—Shore and Nuttall, 1985; Chertoff *et al.*, 2010).

The decrease in wave V latency that occurs with increasing stimulus level (Gorga *et al.*, 1988; Neely *et al.*, 1988; Rasetshwane *et al.*, 2013) may also be due, at least in part, to cochlear processing. As level increases for tonal stimulation, the basilar-membrane excitation pattern broadens and the place of maximum excitation shifts toward the cochlear base (Rose *et al.*, 1971; Ruggero *et al.*, 1997; Rhode and Recio, 2000; Ren and Nuttall, 2001; Moore *et al.*, 2002; Ren, 2002; Lopez-Poveda *et al.*, 2007; Rhode, 2007), presumably resulting in shorter response latencies. Similarly, whereas the basilar membrane impulse response measured at a fixed location includes a single, longer-latency peak at low stimulus levels (consistent with maximum excitation at the characteristic-frequency place), additional peaks with shorter latencies emerge as stimulus level increases [consistent with spread of lower-frequency energy to higher-frequency, basal cochlear regions, e.g., Recio *et al.* (1998); Recio and Rhode (2000)]. Moreover, the magnitudes of these shorter latency peaks surpass the magnitude of the long-latency peak as stimulus level increases, consistent with a basal shift in the place of maximum excitation. Based on these changes in the basilar-membrane response, decreases in wave V latency with increasing stimulus level may reflect a basal shift in the population of neurons contributing to the ABR (e.g., Folsom, 1984).

The broadening and basal shift that have been observed in the basilar membrane excitation pattern with increasing stimulus level are presumably due to a decrease in the amplification provided by the outer hair cells (e.g., Ruggero and Rich, 1991; Dallos, 1992; de Boer and Nuttall, 2000). Damage to the outer hair cells also decreases amplification, especially for low-level stimuli, and has been hypothesized to shorten wave V latencies (Don *et al.*, 1993; Don *et al.*, 1998; Strelcyk *et al.*, 2009; Verhulst *et al.*, 2013; also for wave I—Eggermont, 1979; Rutten, 1986; Henry *et al.*, 2011). However, since higher stimulus levels are required to measure a response in ears with HL, concomitant level effects may complicate interpretation of differences in wave V latency between ears with NH and ears with HL.

Previous investigations have examined the effect of HL, and in some cases stimulus level, on wave V latency; however, findings have been inconsistent. For example, using a high-level click, Donaldson and Ruth (1996) found minimal effect of mild-to-moderate HL on wave V latencies, whereas both Don *et al.* (1998) and Strelcyk *et al.* (2009) observed shorter latencies in ears with HL, compared to ears with NH. Moreover, Strelcyk *et al.* (2009) observed that the finding of shorter latencies in ears with HL applied only for the highest click levels. At lower SPLs, latencies in half of the HL ears approximated those in NH ears, whereas latencies for the other half were longer than those in NH ears, perhaps implicating contributions from more apical neural populations (e.g., Coats, 1978; Don and Eggermont, 1978; Attias and Pratt, 1984; Gorga *et al.*, 1985). When compared at equivalent SLs, the latencies from the HL group that were

prolonged at equivalent SPLs approximated latencies for the NH group. In contrast, the latencies from the HL group that approximated NH latencies at equivalent SPLs were shorter than those in NH ears, an observation that is consistent with the level effects observed in DPOAE STCs (Gruhlke *et al.*, 2012).

Using tone-burst stimuli, Henry *et al.* (2011) measured ABR wave I latencies in chinchillas before and after a noise exposure that resulted in a permanent threshold shift of 10–30 dB. Latencies were shorter post-exposure even when compared at equal stimulus SPLs. In contrast to Strelcyk *et al.* (2009), post-exposure latencies were consistently shorter than pre-exposure latencies across a range of stimulus levels. Moreover, the effect was enhanced when latencies were compared at equal relative stimulus levels (i.e., SL). The Henry *et al.* (2011) study and the DPOAE STC studies are both consistent in that the magnitude of differences between responses in NH and HL ears depends on whether responses are compared at equal stimulus SPLs or equal stimulus SLs.

The reasons for differences between the results reported by Strelcyk *et al.* (2009) and Henry *et al.* (2011) are not obvious and suggest that there is need for further work examining the effects of level and HL on ABR latencies in humans. The prolonged latencies in ears with HL that were observed by Strelcyk *et al.* (2009) may have been a result of an increased contribution from neurons apical to the best-frequency place. With a broad-spectrum stimulus like a click, it is possible that in cases of high-frequency HL, low-frequency energy in the click may stimulate more apical cochlear regions which, in turn, result in responses with longer latencies (e.g., Coats, 1978; Don and Eggermont, 1978; Attias and Pratt, 1984; Gorga *et al.*, 1985). Tone-burst stimuli [such as those used by Henry *et al.* (2011)] have narrower spectral bandwidths thereby reducing the likelihood of contributions to the ABR from neural populations apical to the best-frequency place. Accordingly, the present study explored level and threshold effects on tone-burst-evoked ABR wave V latencies in humans with NH and mild-to-moderate HL. It was hypothesized that latencies in ears with HL would be similar to those in NH ears when compared at the same absolute stimulus levels (i.e., SPL) at which responses could be measured in both groups of subjects. However, when compared at the same levels relative to threshold (i.e., SL), it was hypothesized that latencies in ears with HL would be shorter than those in NH ears. These predictions were based on the notion that response latencies are affected similarly by level in both NH and HL ears, and that HL exerts less influence than level, at least in cases of mild-to-moderate HL.

II. METHODS

A. Subjects

Thirty-one adult subjects participated in the present study. Sixteen subjects (mean age = 30.5 yr, standard deviation = 7.3 yr; seven females) had NH (pure-tone audiometric thresholds ≤ 15 dB hearing level between 0.25 and 8 kHz). Fifteen subjects (mean age = 62.4 yr, standard deviation

= 16.6 yr; ten females) had HL with audiometric thresholds between 20 and 65 dB hearing level for frequencies from 2 to 6 kHz. Figure 1 plots the behavioral thresholds for individual subjects in the NH and HL groups at the four frequencies at which ABR measurements were made. Note that thresholds are defined in dB SPL (re 20 μ Pa), not dB hearing level [thresholds in dB hearing level were converted to dB SPL using ANSI S3.6 2004 (ANSI, 2004) reference-equivalent threshold SPLs for insert earphones]. This decision was made to be consistent with the way stimulus levels are specified in the remaining figures, where level is specified in either dB SL or dB SPL, not dB hearing level. Although thresholds tended to increase with frequency, none of the HLs would be characterized as a steeply sloping configuration. All subjects produced normal 226-Hz tympanograms (peak pressure between -100 and +50 daPa, peak-compensated static admittance between 0.3 and 2.5 mmhos) and had normal otoscopic examinations. Subjects were asked to read and sign an informed consent form prior to participation. Subjects received monetary compensation for their participation. The Boys Town National Research Hospital Institutional Review Board approved the experimental protocol.

B. Sound-delivery and data-acquisition

The sound-delivery and data-acquisition techniques have been described in detail elsewhere (Rasetshwane *et al.*, 2013). Briefly, stimuli were routed from a Windows-based (Microsoft Corporation, Redmond, WA) personal computer to an external 24-bit soundcard (Layla3G, Echo Digital Audio Corporation, Santa Barbara, CA) and then to a custom-designed sound-source (TW010F1, Audax, La Chartre-sur-le-Loir, France) assembly, which was provided by Dr. Jonathan Siegel from Northwestern University. Plastic tubing coupled

FIG. 1. (Color online) Hearing thresholds converted to dB SPL for NH (filled circles) and HL (open diamonds) subjects. Before these data were converted to dB SPL, thresholds for the NH group were ≤ 15 dB hearing level, whereas thresholds for the HL group were within the mild-to-moderate range (constrained between 20 and 65 dB hearing level). To facilitate visualization, data points have been shifted slightly along the x axis around the audiometric test frequency.

the source's output to one of the sound ports of an ER10B+ probe assembly (Etymotic Research, Elk Grove Village, IL). Acquisition of the ABR was achieved using electrodes placed at the frontal-midline (Fz) and the left- and right-mastoid processes. The electrode at Fz was non-inverting (active), whereas the ipsilateral and contralateral mastoid electrodes were inverting (reference) and common (ground), respectively. Electrode impedances ≤ 5 k Ω were achieved for all subjects. Electroencephalographic activity was amplified (gain = 100 000) and filtered (0.1–3 kHz passband; Opti-Amp 8001, Intelligent Hearing Systems, Miami, FL) before being directed via a USB Opti-Amp Transmitter (Intelligent Hearing Systems, Miami, FL) to the computer.

C. Stimuli

The ABR was evoked using tone-bursts of frequencies 2, 2.83, 4, and 5.66 kHz presented at a rate of 33/s (the time index of tone-burst onset was not jittered across the multiple presentations). Tone-bursts were windowed using a Blackman function, which has equal rise and fall times with no plateau. For each tone-burst frequency, f_0 (kHz), the duration of the tone-burst, t_0 (ms), was set according to the equation $t_0 = 4/\sqrt{f_0}$. The frequency-dependent duration provides a compromise between rapid onset (necessary to optimize neural synchrony) and spectral definition, in that the total tone-burst duration gradually increased as frequency decreased (1.69 ms at 5.66 kHz, 2 ms at 4 kHz, 2.38 ms at 2.83 kHz, 2.83 ms at 2 kHz). For each tone-burst frequency, it was possible to obtain data from at least ten subjects. Figure 2 plots the time- and frequency-domain representations of the tone-burst stimuli.

Tone-bursts were presented at levels from 90 dB SPL to 20 dB SPL (descending 10-dB steps). For the HL group, 95 dB SPL was also included in order to increase the stimulus-level range over which a response could be measured. Stimulus levels were specified according to the peak-to-peak pressure generated in a 2-cm³ coupler [additional details concerning level calibration are provided in Rasetshwane *et al.* (2013)]. Data collection continued until a response was no longer measurable for two consecutive level decrements. For the NH group, 2048 stimulus repetitions were presented for stimulus levels of 90–70 dB SPL,

FIG. 2. (Color online) Time- (left) and frequency-domain (right) representations of the different-frequency tone-burst stimuli.

4096 repetitions for levels of 60–50 dB SPL, and 8192 repetitions for levels ≤ 40 dB SPL. For the HL group, 8192 stimulus repetitions were presented for all stimulus levels in order to mitigate the influence of HL on our ability to measure ABRs. Data were stored in two collection buffers (odd-numbered presentations in one buffer and even-numbered presentations in a second buffer). Artifact rejection was used to discard individual waveforms contaminated by high-level transient noise. Accepted waveforms were synchronously averaged in each buffer, and the contents were displayed during data collection. Splitting samples into two buffers during data collection provided an ongoing comparison of two waveforms (equivalent to a replication), which was helpful in determining the presence of a response. The contents of the two buffers were summed (resulting in an additional 3-dB improvement in the signal-to-noise ratio) and latencies were then estimated from the summed waveforms.

D. Analysis

Three examiners independently determined wave V latency for each ABR recording. A different set of three examiners determined latencies in the ears with HL as the data were collected later in time than the NH data. Latency was calculated as the delay between the wave V peak and stimulus onset. The latency estimates from the three examiners were averaged to provide a single estimate for each measurement condition (tone-burst frequency and level combination). At stimulus levels near threshold, there were instances where the examiners disagreed as to whether a wave V was present in the recording. When this occurred, an additional examiner with more experience in interpretation of the ABR examined the recording and made the final determination as to the presence/absence of wave V. In these instances, the latency estimates made by the original reviewers who judged wave V as present were averaged to yield the final latency estimate.

To examine how stimulus-level specification (SPL vs SL) influenced interpretation of the effect of HL on ABR latencies, stimulus levels in dB SPL were transformed to dB SL for each subject by subtracting the audiometric threshold (in dB SPL) from the corresponding tone-burst SPL for each measurement frequency. Admittedly, the calculated dB SL is only an approximation as detection thresholds of the short-

duration tone-bursts were not measured. Statistical methods that accounted for the repeated-measures aspect of the experimental design and missing data were applied to investigate the effects of HL on ABR latencies.

III. RESULTS

Figure 3(A) plots ABR wave V latency as a function of absolute stimulus level (dB SPL) for the four tone-burst frequencies in ears with NH and ears with HL. As expected, wave V was measurable at lower stimulus SPLs for the NH subjects. Whereas wave V was consistently measured at levels between 30 and 90 dB SPL in ears with NH, wave V was measured only for stimulus levels exceeding 60 dB SPL in most ears with HL. For both NH and HL subjects, latency decreased as stimulus level increased, consistent with previous studies (e.g., Gorga *et al.*, 1988; Don *et al.*, 1998; Strelcyk *et al.*, 2009; Rasetshwane *et al.*, 2013). Latencies were similar for NH and HL groups for the frequency and level combinations for which data were available for both groups. Figure 3(B) plots wave V latency as a function of relative stimulus level (dB SL). Similar to the data described in Fig. 3(A), latency decreased as stimulus level increased at each frequency. However, the latencies in the HL ears were shorter than those in NH ears, when compared at equal SLs.

The top row of panels in Fig. 4 compares wave V latencies for NH and HL ears as a function of frequency for different absolute stimulus levels (dB SPL). Data are shown only for levels of 70, 80, and 90 dB SPL because both NH and HL subjects had measureable wave Vs at these levels. Mean data for NH subjects are shown as filled circles and thin solid lines on either side of the mean represent ± 2 standard deviations. Individual data from subjects with HL are shown as open diamonds. Latency decreased as frequency increased for both NH and HL groups. For each stimulus level, latencies in ears with HL were within the range for ears with NH with few exceptions. The bottom row of panels in Fig. 4 compares wave V latencies for NH and HL ears as a function of frequency for different relative stimulus levels (dB SL). The number of subjects with HL for whom data were available decreased as SL increased beyond 45 dB SL because their HLs, combined with the highest tone-burst level presented (95 dB SPL), restricted the upper limit of

FIG. 3. (Color online) ABR wave V latency as a function of tone-burst SPL and SL [(A) and (B), respectively] for different tone-burst frequencies. Individual data for NH subjects are indicated by the filled circles, whereas data for HL subjects are indicated by the open diamonds. Recall that 95 dB SPL tone-bursts were presented only to ears with HL.

FIG. 4. (Color online) ABR wave V latency as a function of tone-burst frequency at different tone-burst SPLs and SLs (top and bottom rows of each panel, respectively). Mean data for the NH subjects are indicated by the solid black lines with filled circles. The upper and lower lines around the mean data correspond to ± 2 standard deviations. At 2 kHz, data for the ≤ 25 dB SL condition were only available from a single NH subject and is indicated by the open circle. Individual data for the HL subjects are shown by the open diamonds. To facilitate visualization, HL data points have been shifted slightly along the x axis around the center frequency of the tone-burst.

achievable SLs. For each SL range, latency decreased as frequency increased for both NH and HL groups. However, again with few exceptions, latencies were shorter in ears with HL for all frequencies and for each SL range.

Linear mixed-effect models were applied to the latency data to determine whether statistically significant latency differences were present between NH and HL groups when compared at equivalent stimulus SPLs and SLs, for each tone-burst frequency. For stimulus level expressed in dB SPL, analysis was restricted to stimulus levels between 70 and 90 dB SPL, where most HL subjects had measureable wave V latencies. However, even across this range, there were missing data; therefore, an imputation process was applied. Across subjects with HL, a single data point (latency) was missing at 90 dB SPL, so the missing latency at 90 dB SPL was first imputed using the expectation-maximization (EM) algorithm (Dempster *et al.*, 1977) to arrive at the maximum-likelihood estimate of the missing latency. Next, a monotone pattern of missing data was created for each subject. (A monotone pattern of missing data was selected for the current study as this pattern described the pattern of missing latency values across stimulus levels within each subject. Specifically, when a latency value was missing at a specific stimulus level, all latency values at lower stimulus levels were also missing. Similarly, when a latency value was present at a specific stimulus level, all latency values at higher stimulus levels were also present.) The remaining missing data at 70 and 80 dB SPL were then imputed to create 25 new data sets. The values of the imputed latencies were allowed to vary within a range determined by the variability in the measured data. Linear mixed-effect models with unstructured covariance matrices were fit to the data to produce mean latency estimates and standard errors for the NH and HL groups at each tone-burst frequency (analysis was performed using the PROC MIANALYZE package in SAS, SAS Institute Inc., Cary, NC).

The mean latency difference (for stimulus level in dB SPL) between groups and standard error of the differences were calculated and tested for significance ($\alpha = 0.05$). At 2 kHz, HL latencies were significantly shorter than NH latencies (mean difference = -0.28 ms, standard error = 0.14 , $p = 0.042$) when compared at equivalent SPLs. There were no significant differences between NH and HL latencies at higher frequencies ($p = 0.8$ at 2.83 kHz, $p = 0.28$ at 4 kHz, $p = 0.21$ at 5.66 kHz). For stimulus level expressed in dB SL, analysis was restricted to stimulus levels ≤ 65 dB SL, where most HL subjects had measureable wave V latencies. Furthermore, 5.66 kHz was excluded from analysis due to an excessive amount of missing data in the HL group; for the remaining frequencies, only subjects with at least three latency values were included in the analysis. Stimulus level in dB SL was treated as a continuous covariate due to the non-fixed nature of stimulus levels across subjects. Linear mixed-model analysis was applied to the existing data (imputation was not used) to estimate mean latencies and standard errors for NH and HL groups at each tone-burst frequency. Mean differences and the standard errors of the differences were calculated. At all frequencies for which analyses were performed (2, 2.83, and 4 kHz), latencies in ears with HL were significantly shorter than latencies in ears with NH (all $p < 0.001$). In summary, with the exception of 2 kHz, there were no statistically significant differences in latencies between NH and HL ears when stimulus level was specified in SPL, but latencies were significantly shorter for HL ears at all frequencies when level was specified in SL.

Figure 5 plots wave V latency as a function of hearing threshold (in dB SPL) for stimuli presented at a level of 90 dB SPL. Each panel represents data for a different frequency. Several previous studies have reported shorter latencies at high absolute stimulus levels in ears with HL (Don *et al.*, 1998; Strelcyk *et al.*, 2009). Figure 5 provides a visual description of the effect of threshold on latency for high-level stimuli. For each frequency, latencies were fit by

FIG. 5. (Color online) ABR wave V latency as a function of hearing threshold for the different tone-burst frequencies at a tone-burst level of 90 dB SPL. Open diamonds identify data from subjects with HL, whereas filled circles identify data from subjects with NH. The dashed line in each plot shows the linear fit to the data.

a linear model (1st-degree polynomial) using an ordinary least-squares fitting approach. At 2 kHz, latency decreased with increasing HL (slope = -0.01 ms/dB). This amounts to a change of ~ 0.6 ms over the range of HL shown in the 2-kHz panel (3–58 dB SPL). Still, the relationship between latency and threshold at 2 kHz was significant ($p = 0.01$). For all other frequencies, the relationship between latency and HL was not significant ($p = 0.68$ at 2.83 kHz, $p = 0.16$ at 4 kHz, $p = 0.82$ at 5.66 kHz). Even at 2 kHz, where significant effects were observed, hearing threshold accounted for only 28% of the variance in wave V latency.

IV. DISCUSSION

The present study investigated the effects of mild-to-moderate HL and stimulus level on ABR wave V latencies by comparing latencies for NH and HL ears at equal stimulus SPLs and equal SLs. This study was motivated by recent work demonstrating that the effect of HL on DPOAE STCs is small compared to the effect of stimulus level (Abdala and Fitzgerald 2003; Gorga *et al.*, 2003; Gruhlke *et al.*, 2012). ABR latencies provide another means to evaluate the interactions between HL and stimulus level and it was hypothesized that comparisons between latencies in ears with NH and ears with HL would be consistent with the level effects observed in the DPOAE STC data. Namely, latencies in ears with HL would approximate those in NH ears when compared at equal stimulus SPLs, whereas latencies in ears with HL would be shorter than those in NH ears when compared at equal stimulus SLs. The data shown in Figs. 3–5 are consistent with these predicted level effects.

A. Comparison to previous studies examining the effect of HL on wave V latency

At a high stimulus level (93 dB peSPL), Don *et al.* (1998) and Strelcyk *et al.* (2009) measured shorter

derived-band wave V latencies in ears with mild-moderate HL compared to NH ears. When the present study's latencies were examined at the highest stimulus level tested for both NH and HL groups (90 dB SPL), a significant effect of HL on wave V latency was demonstrated only at 2 kHz and, although significant, the effect was small (a change of ~ 0.6 ms over a 55-dB range of thresholds). It is not clear as to why an effect of HL was evident at lower but not higher frequencies where the degree of HL was more severe. Don *et al.* (1998) also observed HL-induced changes in wave V latency restricted to lower frequencies (≤ 2.8 kHz) and suggested this finding may be because latencies decrease with increasing frequency and any change due to HL is too small to be differentiated from other sources of variability in the measurements. However, both Eggermont (1979) and Strelcyk *et al.* (2009) measured shorter ABR latencies (wave I in Eggermont) up to ~ 10 kHz in at least a subset of ears with HL. In contrast, despite using a high-level stimulus (99 dB peSPL), Donaldson and Ruth (1996) observed no effect of HL on wave V latency at any frequency.

Henry *et al.* (2011) examined ABR wave I latencies in chinchilla in response to tone-bursts. In contrast to the present findings, an effect of HL on latency was observed at all frequencies and stimulus levels. Specifically, post-noise exposure latencies were shorter compared to pre-exposure latencies, when these comparisons were made at equivalent stimulus SPLs. The reason for the conflicting findings between studies is unclear; however, the cochlear trauma induced in Henry *et al.* (2011) likely differed from that experienced by the human listeners with HLs acquired over years that potentially resulted from a variety of etiologies. Despite the shorter latencies post-trauma, Henry *et al.* (2011) did observe that the effect of trauma was enhanced when pre- and post-exposure latencies were compared at equivalent relative levels, a finding that is consistent with the present work.

Whereas Strelcyk *et al.* (2009) reported shorter wave V latencies in HL ears compared to NH ears at high stimulus SPLs, latencies in approximately half of their ears with HL were longer than those in ears with NH when compared at lower stimulus SPLs (see Fig. 4 in Strelcyk *et al.*). This finding was not replicated in the present study despite a subject population with a similar degree of HL as the subjects who participated in the Strelcyk *et al.* (2009) study. Longer latencies in ears with HL could occur if the activated neural population was situated more apically than that in ears with NH. Such a situation may arise when the spectral content of the evoking stimulus (or the bandwidth of the derived band) is sufficiently broad to span a spatial region of the cochlea where the degree of damage is reduced at the apical portion compared to the basal portion. In these cases, the contribution to the ABR from neurons in the basal region would be reduced whereas the contribution from more apical neurons would be increased, resulting in a longer latency (Coats, 1978; Don and Eggermont, 1978; Attias and Pratt, 1984; Gorga *et al.*, 1985). At higher stimulus levels where the magnitude of excitation is large and the spread of excitation is broad, extending primarily toward the cochlear base, the likelihood of observing prolonged latencies in ears with HL

may be reduced. This could explain why [Strelcyk et al. \(2009\)](#) observed prolonged latencies only at lower click levels. In the current study, the use of tone-bursts with narrow spectral bandwidths (see Fig. 2) likely prevented contributions from cochlear regions apical to the frequency of the tone-burst at lower stimulus levels because the first side lobe was about -60 dB relative to the main energy lobe, and continued to decrease at a rate of 6 dB/octave. Under these conditions, direct excitation of apical cochlear regions with a high-frequency tone-burst is unlikely.

Both age and gender contribute to ABR wave V latency and the potential exists that these factors may have influenced the present study's results. Wave V latency has been shown to increase with age; however, the magnitude of the effect is small, ranging from 0.1 to 0.28 ms over an age range of ~ 40 yr (e.g., [Burkard and Sims, 2001](#); [Rupa and Dayal, 1993](#)), and not always significant ([Konrad-Martin et al., 2012](#)). The age difference between NH and HL groups in the present study was ~ 32 yr and it is possible that the latencies in ears with HL were longer than what would have been observed in a younger group of subjects with HL. However, it is unlikely that age exerted an influence on the main effects because latencies were either equal to (dB SPL) or shorter than (dB SL) in ears with HL, compared to data from NH ears. These effects are in the opposite direction of expected effects of age, which are small but toward longer latency with increased age. With regard to gender, [Don et al. \(1993\)](#) measured shorter latencies in females on the order of ~ 0.2 ms at 5.7 kHz, increasing to ~ 0.7 ms at 0.7 kHz. Ten of the 15 subjects with HL were females compared to 7 of the 16 subjects with NH. Thus, there were more females among subjects with HL, but the difference in numbers was small and the effect size would not be expected to influence the main observations in the present study. Taken together, gender and age effects are not likely to confound interpretation of the present study's results concerning the influence of level and HL on latency.

B. The influence of stimulus level on comparisons of wave V latency between NH and HL ears

The main observation from the present study is that NH ears and ears with mild-to-moderate HL produce similar latencies when comparisons are made at equivalent SPL. It is of some interest to speculate on possible underlying factors responsible for this effect, although direct evidence to support the following interpretations is not possible in studies involving humans as subjects.

The cochlear component of wave V latency includes delays associated with propagation of the traveling-wave due to both passive (cochlear transport time) and active (filter build-up time) mechanics (e.g., [Don et al., 1993](#); [Don et al., 1998](#)). Whereas the former may be relatively insensitive to cochlear trauma, the latter is predicted to decrease as cochlear amplifier gain is reduced due to outer hair cell damage. Independent of HL, evidence exists to suggest that cochlear amplifier gain decreases as level increases, even in ears with normal cochleae (e.g., [Ruggero and Rich, 1991](#); [de Boer and Nuttall, 2000](#)). Indirect evidence that this same

effect occurs in humans is provided by DPOAE STC measurements, in which tip-to-tail differences decrease as level increases ([Gorga et al., 2011](#)). As gain is reduced, the cochlear excitation pattern is increasingly shaped by passive mechanics with the effect that the best-frequency place shifts and the peak broadens toward the cochlear base. Consequently, in as much as the ABR reflects synchronous activity across neurons in the vicinity of the peak response, wave V latency is expected to decrease as HL increases ([Don et al., 1998](#); [Strelcyk et al., 2009](#); [Verhulst et al., 2013](#); also for wave I latency—[Eggermont, 1979](#); [Rutten, 1986](#); [Henry et al., 2011](#)) and as level increases. The similarity in latencies between ears with NH and HL when compared at equivalent SPLs suggests that the effects of level are similar for the two groups and that the influence of HL is mainly related to the need for higher levels in order to elicit responses, at least in cases for which mild-to-moderate HL exists.

ABRs with a detectable wave V could only be evoked in the HL group using high stimulus levels (often ≥ 70 dB SPL). At these levels, it may be that in both NH and HL ears the ABR is dominated by passive mechanics and the underlying cochlear filters are equally broad. If this is the case, wave V latency may be insensitive to any reduction in the filter build-up time resulting from HL. Thus, the effect of HL on wave V latency might be expected to be most evident at lower stimulus SPLs where the contribution from filter build-up time is larger in ears with NH due to greater cochlear amplification. Unfortunately, subjects with HL, as a consequence of their elevated thresholds, do not produce responses at low stimulus levels.

[Ren \(2002\)](#) observed that the spatial basilar membrane excitation pattern is indicative of the tuning of basilar membrane vibration at a fixed location. By applying this relationship to wave V latencies in NH ears and ears with mild-to-moderate HL (assuming identical synaptic and neural delays), the similarity in latencies at equivalent SPLs implies similar cochlear tuning. This hypothesis is consistent with the observed similarity of DPOAE STCs in HL and NH ears when level is equated in dB SPL ([Gruhlke et al., 2012](#)). The interpretation of the previous DPOAE STC data and the present latency data may appear to be at odds with work suggestive of broader auditory filters in ears with cochlear damage. Broader tuning has been observed in ears with HL based on basilar membrane isovelocity curves (e.g., [Sellick et al., 1982](#)) and auditory nerve, single-unit frequency-threshold curves (e.g., [Liberman and Dodds, 1984](#)). The comparison between wave V latencies in NH and HL ears at equivalent stimulus levels relative to threshold may explain the apparent contradiction among measures. Specifically, when compared at equal stimulus SLs, latencies in ears with HL were shorter than those in ears with NH, consistent with broader filters. However, this does not appear to be a direct consequence of the HL itself but, rather, from the need to use higher stimulus SPLs in ears with HL. Basilar membrane isovelocity curves and auditory nerve, single-unit frequency-threshold curves are both threshold measures and, therefore, comparisons between healthy and pathologic ears necessitate the use of higher stimulus levels SPLs in damaged ears

(compared to normal ears) due to their reduced sensitivity. Thus, these measures may be equivalent to conditions in which levels relative to threshold were used. Under these conditions, the previous work in lower animals, DPOAE STCs, and the present latency data are not in disagreement.

Level-dependent changes in cochlear tuning are relevant for psychophysical studies in which stimulus level is often specified in relative terms (e.g., Florentine *et al.*, 1980; Moore and Glasberg, 1986; Nelson, 1991; Leek and Summers, 1993; Beveridge and Carlyon, 1996; Desloge *et al.*, 2012). In such studies, a “probe” stimulus is fixed in level relative to behavioral threshold, while masker frequency and level are varied to achieve a threshold response. Under these circumstances, the absolute probe level is higher in ears with HL, compared to probe levels in NH ears. Thus, differences in frequency resolution between NH and HL ears could be due to level effects rather than to changes in underlying cochlear processing resulting from pathology. In an effort to separate changes in tuning due to HL from level-dependent changes, Desloge *et al.* (2012) simulated HL (using masking noise) in a group of NH listeners and then compared behavioral estimates of equivalent rectangular bandwidth (ERB) between the simulated HL group and a group of listeners with HL. The HL simulation elevated detection thresholds of the NH group to approximate those of the HL group such that both groups were listening at similar SPLs and SLs during the tuning measure. In most cases, ERBs measured under simulated-HL conditions were not significantly different from those measured in ears with HL; however, both simulated and real HL ERBs were wider than ERBs measured in NH controls at lower stimulus SPLs but similar SLs. The findings from Desloge *et al.* (2012) corroborate earlier work by Nelson (1991) that showed normal frequency resolution in ears with <40 dB of HL (and in some cases even greater degrees of loss) when forward-masked tuning curves were compared at equivalent masker SPLs at the tip of the psychophysical tuning curve. These findings are consistent with the current work, suggesting only a small effect of HL after the effects of level are taken into account, at least for high stimulus levels and in cases of mild-to-moderate HL.

C. Potential confounding factors

The possible effect of HL on the synaptic delay component of wave V latency has the potential to disassociate latency from HL-induced changes in cochlear propagation delays. Specifically, there is evidence that the synaptic delay depends on the magnitude of the electro-chemical excitation of type I auditory neurons. For instance, Abbas and Brown (1991) reported an increase in wave V latency of the electrically evoked ABR as stimulating current level decreased. Furthermore, Heil and Neubauer (2001, 2003) have argued that the first-spike timing of single auditory neurons depends on temporal integration of the evoking stimuli’s sound-pressure envelope. Last, Burkard and Hecox (1983) demonstrated that wave V latency for a fixed stimulus SPL increases when the ABR is evoked in backgrounds of noise, possibly as a result of reduced in-phase excitation

(synchrony) across the neural population that contributes to the ABR in the absence of noise [although suppression may also contribute, Costalupes *et al.* (1984)]. If HL reduces the drive to auditory neurons (e.g., Neubauer and Heil, 2004), as might occur if the magnitude of BM excitation is reduced (Fridberger *et al.*, 2002), an increase in wave V latency could ensue. Consequently, in ears with HL, any decrease in wave V latency resulting from broader tuning may be offset by an increase in latency due to reduced drive to the auditory neurons.

Comparison of wave V amplitude between ears with NH and HL may provide an indirect means to quantify the drive to auditory neurons and determine whether differences in the synaptic delay between groups should be considered. Specifically, in ears with HL, reduced drive to auditory neurons (and subsequent increased synaptic delay) may result in smaller wave V amplitudes compared to the amplitudes observed in NH ears at equivalent stimulus SPLs. In support of the hypothesized relationship between amplitude, drive to auditory neurons, and synaptic delay, Burkard and Hecox (1983) observed a decrease in wave V amplitude accompanied by an increase in latency when the ABR was evoked in increasing levels of background noise. To address this issue, we measured wave V amplitude¹ (defined as the difference between amplitudes at the peak of wave V and the subsequent trough) as a function of stimulus SPL to determine whether there was evidence of reduced drive to neurons in the ears with HL.

Figure 6 plots wave V amplitude as a function of stimulus SPL in ears with NH and HL for each of the four tone-burst frequencies. For the 2-kHz tone-burst, amplitudes in ears with HL approximated amplitudes in NH ears for most subjects. However, for the higher-frequency tone-bursts, amplitudes at equivalent stimulus SPLs were reduced in ears with HL compared to NH ears, although many were still

FIG. 6. (Color online) ABR wave V amplitude as a function of tone-burst SPL for different tone-burst frequencies. Individual data for NH subjects are indicated by the filled circles, whereas data for HL subjects are indicated by the open diamonds. Recall that 95 dB SPL tone-bursts were presented only to ears with HL.

within the range for NH ears for 2.83 and 4 kHz tone-bursts. For the highest-frequency tone-burst (5.66 kHz), nearly all amplitudes were smaller in the ears with HL. These observations suggest that the drive to auditory neurons in the ears with HL was reduced compared to that in the NH ears (at least for the 2.83, 4, and 5.66 kHz tone-bursts) and, therefore, the synaptic delays in ears with HL may have been prolonged. Only at 2 kHz, where NH and HL wave V amplitudes were similar, was wave V latency significantly shorter in ears with HL. Assuming that wave V amplitude is related to the drive to auditory neurons, it is possible that shorter latencies were not observed at 2.83, 4, and 5.66 kHz because the decrease in latency with HL was offset by prolonged synaptic delays due to lower drive to auditory neurons. Linear regression was performed with latency as the dependent variable and amplitude as the predictor variable at each tone-burst frequency for 90 dB SPL to determine whether any relationship between the two quantities existed. Latency increased with decreasing amplitude (significance level of $\alpha = 0.05$) at 2.83 kHz ($R^2 = 0.16$, $p = 0.039$), 4 kHz ($R^2 = 0.21$, $p = 0.017$), and 5.66 kHz ($R^2 = 0.19$, $p = 0.039$), but not at 2 kHz ($p = 0.11$). These results suggest that a significant effect of HL on wave V latency was not observed at frequencies above 2 kHz (at equal stimulus SPL) due to factors unrelated to those affecting cochlear propagation times, one of which may be prolonged synaptic delays resulting from reduced drive to the auditory neurons.

A final factor that may confound comparison of wave V latency between NH and HL ears and interpretation as it relates to differences in cochlear delays and tuning is the differential effect of HL on tip and tail behavior of single-fiber tuning curves. For instance, in some cases of cochlear damage, threshold at the tip of a frequency-threshold curve will be elevated, but thresholds on the low-frequency tail remain unchanged or may decrease slightly [see Fig. 9 in Liberman and Dodds (1984)]. As a result, cochlear trauma can result in an increase in the sensitivity of high-frequency neurons to lower frequency stimulation. In many ways, this is akin to an “exaggerated” upward spread of excitation. Most of the subjects in the present study had HL that increased with frequency (see Fig. 1) and the shorter 2-kHz latencies may have been due to a greater contribution from basal neurons in which the HL increased their sensitivity to lower frequency excitation.

V. CONCLUSIONS

ABR wave V latencies in ears with NH and ears with HL were compared at equivalent absolute (i.e., dB SPL) and relative stimulus levels (i.e., dB SL). When compared at equivalent absolute levels, latencies in ears with HL approximated those in ears with NH. However, when compared at equivalent relative levels, latencies in ears with HL were significantly shorter than those in ears with NH. The similarity between ABR wave V latencies in ears with NH and ears with HL, when compared at the same SPLs, demonstrates that the effect of mild-moderate HL on latency is small compared to the effect of stimulus level. These findings are consistent with the interactions between HL and stimulus level

that have been observed in DPOAE STCs and certain behavioral measures of tuning.

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¹The individuals who were responsible for scoring the ABR waveforms for the latency analysis (Figs. 3–5) had since graduated and were no longer working in the lab at the time the amplitude analysis (Fig. 6) was performed. Therefore, J.D.L., with past experience judging ABR waveforms, was responsible for picking the peak and trough amplitudes for the wave V amplitude analysis.

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