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Age-Related Changes in the Auditory Brainstem Response

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Abstract

Purpose—This cross-sectional study had two goals: (1) Identify and quantify the effects of aging on the auditory brainstem response (ABR); (2) Describe how click rate and hearing impairment modify effects of aging.

Research Design and Analysis—ABR measures were obtained from 131 predominately male Veteran participants aged 26 to 71 yr. Metrics analyzed include amplitude and latency for waves I, III, and V, and the I–V interpeak latency interval (IPI) at three repetition rates (11, 51, and 71 clicks/sec) using both polarities. In order to avoid confounding from missing data due to hearing impairment, participants had hearing thresholds <40 dB HL at 2 kHz and 70 dB HL at 4 kHz in at least one ear. Additionally, the median 2, 3, and 4 kHz pure tone threshold average (PTA_{2,3,4}) for the sample, ~17 dB HL, was used to delineate subgroups of better and worse hearing ears, and only the better hearing sample was modeled statistically. We modeled ABR responses using age, repetition rate, and PTA_{2,3,4} as covariates. Random effects were used to model correlation between the two ears of a subject and across repetition rates. Inferences regarding effects of aging on ABR measures at each rate were derived from the fitted model. Results were compared to data from subjects with poorer hearing.

Results—Aging substantially diminished amplitudes of all of the principal ABR peaks, largely independent of any threshold differences within the group. For waves I and III, age-related amplitude decrements were greatest at a low (11/sec) click rate. At the 11/sec rate, the model-based mean wave III amplitude was significantly smaller in older compared with younger subjects even after adjusting for wave I amplitude. Aging also increased ABR peak latencies, with significant shifts limited to early waves. The I–V IPI did not change with age. For both younger and older subjects, increasing click presentation rate significantly decreased amplitudes of early peaks and prolonged latencies of later peaks, resulting in increased IPIs. Advanced age did not enhance effects of rate. Instead, the rate effect on wave I and III amplitudes was attenuated for the older subjects due to reduced peak amplitudes at lower click rates. Compared with model

predictions from the sample of better hearing subjects, mean ABR amplitudes were diminished in the group with poorer hearing, and wave V latencies were prolonged.

Conclusions—In a sample of veterans, aging substantially reduced amplitudes of all principal ABR peaks, with significant latency shifts limited to waves I and III. Aging did not influence the I–V IPI even at high click rates, suggesting that the observed absolute latency changes associated with aging can be attributed to changes in auditory nerve input. In contrast, ABR amplitude changes with age are not adequately explained by changes in wave I. Results suggest that aging reduces the numbers and/or synchrony of contributing auditory nerve units. Results also support the concept that aging reduces the numbers, though perhaps not the synchrony, of central ABR generators.

Keywords

Aging; auditory brainstem response; auditory nerve; hearing loss; veterans

Identifying and quantifying effects of aging along the auditory pathway is a clinical challenge. Not only is it difficult to distinguish effects of aging from damaging environmental exposures or disease, it is tricky to parse age-related changes in central auditory processing from declines of peripheral hearing ability or cognition. The auditory brainstem response (ABR) has been used to study the aging auditory system because it is not subject to declines in memory or attention and can be evaluated using stimulus paradigms that might identify breakdowns in temporal processing among the elderly (Schneider et al, 2002). Results from human research using the ABR can also be compared with the animal literature on aging where the ABR is often used and environmental and genetic factors are controlled.

The ABR is a far field electrophysiological response primarily to a sound's onset. It consists of up to seven waveform peaks occurring within a 10 msec window following sound stimulation. In humans, wave V arises from the termination of the lateral lemniscal tract within the inferior colliculus and is affected by alterations of neural generators located primarily in the rostral pons up to this midbrain point (Moller, 1999). Waves I and II arise respectively from the distal and proximal auditory nerve while wave III is generated from within the cochlear nucleus.

Age-related changes for the standard click evoked ABR have been extensively studied. Decreases in ABR amplitude with advanced age are frequently reported, with slight changes also found for latency and interpeak intervals (IPIs) though not always in a consistent pattern (Rowe, 1978; Jerger and Hall, 1980; Maurizi et al, 1982; Allison et al, 1983; Debruyne, 1986; Costa et al, 1990). When results for early peaks are reported, the amplitude of wave I or the auditory nerve compound action potential (CAP) is typically more affected by age compared to wave V (Psatta and Matei, 1988; Costa et al, 1990; Sand, 1991; Burkard and Sims, 2001).

A number of confounds may affect comparisons of ABRs from younger and older subjects. Chief among them is the association between aging and hearing loss. This association is often found even among subjects with clinically normal hearing. Subjects' gender may

complicate interpretation of age-related changes in the ABR also, since it is associated with both head size (length of fiber tracts and proximity of electrodes to neural generators) and environmental exposure to noise (Frisina, 2009). Diseases common to the elderly such as microvascular disease and diabetes can be a further complication since they may impact hearing, brain function, or both (Bainbridge et al, 2008; Austin et al, 2009; Friedland et al, 2009; Knopman et al, 2009; Konrad-Martin et al, 2010).

An approach in humans for avoiding some of these confounds has been to develop statistical models of the ABR based on multiple linear regressions with age and other influential factors. Wave V latency shows slight, but significant, age-related delays using this approach to account for effects of gender, hearing loss (Lightfoot, 1993; Rupa and Dayal, 1993), and also head size (Mitchell et al, 1989). Model-based results for I–V IPI changes with age are inconsistent, however.

Elberling and Parbo (1987) modeled ABR I–V IPIs as a function of age and hearing loss in separate groups of 235 female and 249 male clinic patients with similar ages from about 20 to 80 yr. ABRs were elicited to rarefaction clicks presented at a rate between 20 and 30 per second at stimulus levels of 115, 105, and 95 dB peak equivalent (pe) SPL. They found substantial IPI changes with age with larger changes in males than females, using the mean pure-tone threshold average of 4 and 8 kHz as an index for hearing loss. Over a 40 yr age range, I–V IPIs increased 0.22 msec in males.

Mitchell and colleagues (1989) separately modeled ABR amplitudes, latencies, and IPIs as a function of head diameter, age, and hearing for 96 females and 81 males ranging in age from 13 to 80 yr. Models were fitted to the entire sample as well as subgroups of normally hearing or impaired subjects, females and males. Each audiometric test frequency was included in these models. ABRs for this study were obtained using 80 dB nHL rarefaction clicks. For the entire sample, head diameter, hearing at 4 and 8 kHz, and age were the major factors affecting the modeled I–V IPI. A more pronounced age-related I–V IPI increase was obtained for the subjects with normal hearing through 8 kHz (0.44 msec over a 40 yr span) as compared with that described by Elberling and Parbo (1987). In contrast, age was not a significant determinant of the I–V IPI among the male subjects. Instead, head diameter and hearing determined the wave I–V IPI. Hearing loss at 8 kHz shortened the I–V interval by prolonging primarily wave I. Hearing loss at 4 kHz lengthened the interval, which they speculate was due to the greater influence on wave V latency than wave I.

Numerous investigators have suggested that ABRs evoked using experimental paradigms designed to desynchronize neural activity may more readily reveal deficits in the older auditory system. For example, high rates of stimulation prolong ABR IPIs, a change that indicates neural synchrony has been reduced at a central level (Willott et al, 2008). With respect to the influence of age on rate-induced shifts in waveform peaks or IPIs, results again are mixed.

Harkins (1981) investigated the effects of age, rate, and their interaction on ABR peak latency and IPIs. The 16 female subjects were divided into younger (19–32 yr) and older (63–79 yr) groups. Both groups had similar click thresholds though the young group

averaged 0 dB HL pure tone thresholds across 1–4 kHz while the older group averaged 13 dB across the same frequency range with 4 kHz hearing loss extending up to 26 dB HL. Clicks varied in rate from 10–100 Hz and were presented at 70 dB nHL. They found no effects of age on latency or IPIs that could not be explained by differences in hearing between the two groups. Consistent with other studies, amplitudes were significantly lower in the older group than in the younger group.

Debruyne (1986) investigated effects of age on rate-induced changes in the ABR using 100 dB SPL clicks presented at rates from 9 to 63 Hz in 77 subjects with normal hearing through 4 kHz. Greater rate-related shifts were observed for wave V peak latencies compared with wave III (where no age effect was observed), with the greatest shifts observed among subjects older than age 55. Effects of hearing loss were evaluated separately using 62 subjects with varying degrees of sensorineural hearing impairment. Age distributions were the same as the normally hearing subjects. In this circumstance, rate-induced latency shifts were associated with hearing loss, not age.

Burkard and Sims (2001) used a standard ABR rate paradigm to evaluate effects of rate changes from 11 to 75 Hz, and also a maximum length sequence that allowed stimulus rates of 100–500 Hz to be tested, using stimuli presented at a level of 115 dB peak sound pressure level (pSPL). A tympanic membrane recording electrode was used to enhance wave I (or equivalently, CAP) recordings, and responses were obtained in 11 young adults aged 20–27 yr and 11 older adults aged 62–78 yr with normal or near-normal hearing. Increasing the click rate reduced wave I and V amplitudes to an extent that was greater in younger than older subjects. In contrast it prolonged wave I and V latencies and I–V IPIs to a similar extent for both age groups. Older adults were further divided into better and worse ears since few had normal hearing defined as 20 dB HL or better across the entire 0.25–8 kHz range. Wave V latencies and I–V IPIs were generally longer in the older better hearing ears compared with the older worse hearing ears.

It is clear that previous studies provide little consensus on the pattern of ABR latency and IPI changes with age, and reveal a complex poorly understood relationship between age, hearing loss, stimulus rate, and ABR measures. A significant difficulty encountered using the ABR to investigate effects of aging, stimulus rate, or hearing loss is that these factors often cause smaller amplitude waves (I, III) to be lost. When this occurs, peripheral effects cannot be easily controlled as one cannot assume that delays in the ABR are occurring in the central nervous system without an accurate assessment of wave I. Moreover, reported IPI changes may represent a skewed sample of ears, those with better hearing and/or auditory nerve function.

There were two main goals of this study: (1) identify and quantify the effects of advancing age on the ABR; (2) describe how click rate and hearing impairment modify effects of aging. Our approach was to use multivariate regression to jointly model features of the ABR obtained in veterans without substantial hearing loss as a function of age, click repetition rate, and pure tone threshold. Other studies did not model these effects contemporaneously. Like some previous modeling approaches, ours was designed to adjust for threshold differences across subjects. We also adjusted for correlations among ABR measures arising

from the same subjects and missing data—conditions that represent potential confounds of most prior reports. Inferences regarding the effects of aging on different ABR measures at each rate are derived from the fitted model. We reasoned that if significant effects of aging were found for the later ABR peaks after adjusting for response levels of earlier peaks, that result would suggest aging affects the auditory brainstem. The alternative result would suggest that aging affects brainstem responses primarily through changes in the auditory periphery, and/or that the click-evoked ABR is not sensitive to central age changes even at high stimulus rates.

MATERIALS AND METHODS

Subjects

From a large cross-sectional study of veterans (predominately male) with and without diabetes, we assessed the ABR among participants *without* diabetes. A detailed description of the methods used can be found elsewhere (Austin et al, 2009). Subjects up to age 70 and receiving treatment through the Portland VA Medical Center (PVAMC) were eligible for the parent study, and a random sample of such subjects with and without diabetes was invited to participate.¹ Exclusions included those wearing a hearing aid; those undergoing treatment for cancer, multiple sclerosis, or other neurologic diseases; and those with dementia or communication difficulties. Since ABR wave I is frequently absent in subjects with substantial cochlear hearing loss (Lightfoot, 1992), we further excluded subjects with a hearing loss in both ears exceeding 40 dB HL at 2 kHz or 70 dB HL at 4 kHz. We also excluded those with a clinically significant conductive loss (air-bone gap >10 dB) or evidence of active otitis externa. Of initially identified eligible subjects, nearly 85% either declined (about 83%) or were excluded upon examination (2%), so the remaining 15% were a self-selected group meeting study criteria. Of 137 eligible subjects who had demographic questionnaire data, and who did not have diabetes as confirmed by clinical diagnosis and HbA1c (glycated hemoglobin) measures obtained as part of the study, six were missing ABR data on both ears. This left 131 subjects with data available for analysis. Of the 131, six subjects contributed data for one ear only (three right only, three left only), so that a total of 256 ears were available for analysis (128 for each ear).

Despite exclusions based on hearing loss, examination of ABR data available for analyses revealed the existence of missing data considered nonignorable from a statistical standpoint. Of concern was a lack of data particularly for the early waves in young subjects with hearing loss, because the absence of these data could prevent model-based statistical approaches from separating effects of aging and hearing (for more details see Table 1 and related description in the “Results” section). To mitigate this potential problem, the median 2, 3, and 4 kHz pure tone threshold average (PTA_{2,3,4}) for the sample, 17.5 dB HL, was used to delineate subgroups of better and poorer hearing ears, and only the better hearing sample was modeled statistically. Two subjects in the better hearing sample proved to have highly influential ABR measures and were eliminated from the analysis. One subject was a 37-yr-old male with a wave III amplitude (in μ V) of 0.95, more than three times the mean of 0.31

¹One subject, recruited at age 70, had a birthday prior to testing and was allowed to participate at age 71.

observed for that age group (Table 2). The other was a 56-yr-old male with a wave V amplitude of 1.7, more than five times the mean of 0.34 observed in that age group (Table 2). Inferences regarding the effects of aging and click rate on different ABR measures were derived from the model fitted to the “better hearing” half of the sample, comprised of 125 ears with $PTA_{2,3,4} < 17.5$ dB HL from 80 subjects. Potential modifying effects of hearing loss on age-related ABR changes were explored qualitatively by graphically comparing model-based results to raw data from the “poorer hearing” half of the sample, comprised of 127 ears with $PTA_{2,3,4} \geq 17.5$ dB HL from 83 subjects.

All subjects were consented to participate in the study following the guidelines of the Portland VA Medical Center Institutional Review Board (IRB), signed an IRB-approved consent form, and were compensated for their time.

Data Collection

Subjects completed initial questionnaires on demographic, medical, and noise exposure history. A complete audiometric test of both ears was conducted including pure tone air conduction thresholds and ABR. Several measures were used to rule out retrocochlear disorder including speech audiometry, acoustic reflex testing, and hearing asymmetries not attributable to noise exposure. No subject was suspected of having retrocochlear abnormalities based on results of these tests, and no subject was found to have substantial asymmetries in their ABR results. Data collection for the parent study included additional tests and required 5–7 hr per subject, including breaks. During testing, subjects were seated in a comfortable chair within a double-walled sound-attenuated booth.

Pure Tone Threshold Testing—Pure tone thresholds were obtained for pulsed tones using a modified Hughson-Westlake procedure (Carhart and Jerger, 1959). Stimuli were presented by a Grason-Stadler GSI Clinical Audiometer through Etymotic Research (ER3A) insert earphones. Frequencies tested were octave frequencies from 0.25 to 8 kHz, and the interoctave frequencies 1.5, 3, and 6 kHz.

ABR Measurement—Auditory brainstem response testing was performed using the SmartEP Version 3.95 (Intelligent Hearing Systems, Miami, FL). The stimuli were 100 μ sec broadband clicks, presented at 110 dB peak-to-peak equivalent SPL through Etymotic Research ER-3A insert earphones. This presentation level is approximately 75 dB nHL using the international standard reference level for clicks (ISO 389-6, 2007). Calibration was done using a Bruel and Kjaer (B&K) Modular Precision Sound Level Meter (Type 2231) with the earphone seated in an occluded ear simulator (B&K Type 4157) that meets IEC 711 specifications. Since the duration of a click stimulus is too short to register on a sound level meter, its electrical output was displayed on an oscilloscope. This representation of the acoustic waveform then was adjusted to be superimposed on a 3 kHz continuous sine wave at 110 dB SPL in the coupler.

The clicks were presented at two polarities (rarefaction, condensation) and three rates (11, 51, and 71 clicks/sec) in each ear monaurally. The ABR was recorded differentially using a silver/silver chloride surface electrode secured to the ipsilateral mastoid for the active (inverting) channel. A surface electrode attached to the high forehead (Fz) served as the

reference (noninverting) electrode, and a surface electrode attached to the brow (Fpz) served as the ground. A fixed artifact rejection threshold of 31 μ V was used. The recorded signal was amplified (100,000), filtered (0.3–3.0 kHz), and digitized in a 10 msec time window. Waveforms collected in two interleaved buffers of 512 runs were stored as the average of 1024 waveforms. Replication across at least two samples of 1024 runs was used to determine that a waveform was reliable. Two samples of 1024 runs were then averaged to form a grand average of 2048 runs and used to obtain ABR metrics for analysis.

Two research audiologists, each with more than 10 yr experience routinely collecting and scoring ABRs, separately identified positive peak latencies for waves I, III, and V (see Figure 1 for examples) and peak to trough amplitudes using visual overlay cursors on a computer screen. Any interscorer disagreements were resolved by reviewing the data together. Audiologists were blinded to subject information at the time grand average traces were labeled but had the benefit of viewing all traces from a given subject when labeling waveforms. This was helpful for identifying small amplitude peaks. It is conceivable that some small amplitude peaks could have been spurious measures of the background EEG since we did not adopt criterion amplitude or latency fences for particular waves. However, there is no reason to believe that any spurious artifact would systematically bias the results.

Data Management

The Statistical Package for the Social Sciences (SPSS v. 13) was used for initial data cleaning, variable conversions, data reduction, and preliminary analyses. Definitive analyses were performed using SAS (Statistical Analysis Software) software version 9.2.

Statistical Methods

Development of Statistical Model of ABR Amplitudes and Latencies—A statistical model was developed using data from the “better hearing” half of the sample in order to investigate effects of age and click rate on ABR component peaks, with which data from the “poorer hearing” ears could be compared. We jointly modeled the set of wave I, III, and V amplitudes and latencies obtained for each ear at each click rate and stimulus polarity. Each set of responses was used to define a vector of mean wave I, III, and V amplitudes and latencies that was indexed by age and rate, and also behavioral PTA_{2,3,4} in an effort to account for the slight differences in hearing across ears.

A set of ABR amplitude and latency responses obtained for the same ear are correlated, as are responses obtained for the two ears of the same subject. Because of this, we developed a multivariate response regression model (Hastie et al, 2009) of the mean vector as a function of age, click rate, and PTA_{2,3,4} as continuous covariates. This approach is a natural extension of standard repeated measures MANOVA (multivariate analysis of variance) models to include continuous predictors while accounting for the correlation among ABR components. Furthermore, this approach allowed us to model (and adjust for) the correlation among repeated measurements on each subject across ears, stimulus polarities, and click rates using random effects. This approach provided the distinct advantage of allowing us to include all available data on each subject, even if some waveform peaks were missing. This resulted in

six distinct linear models, one per ABR component, with correlated residuals across the ABR components.

A linear model with age, click rate, and mean $PTA_{2,3,4}$ as continuous predictors was fit to the data, along with two- and three-way interactions in each ABR component. We did not specifically adjust for gender to simplify the model and because there were very few women in the final sample. However, the subject-specific random intercepts at each ABR component allowed for variability among individuals in their mean ABR traces. This adjusted for overall larger or smaller amplitudes/shorter or longer latencies as may be associated with an individual's gender. No effort was made to adjust for stimulus polarity, in order to further simplify the model and because polarity was associated with only minor, nonsystematic effects in our earlier study (Konrad-Martin et al, 2010). Model fit was assessed by examining conditional and marginal residual plots and by comparing the fitted models to the observed data for specific age by $PTA_{2,3,4}$ subgroups. These evaluations did not support more complex, nonlinear models for either age, $PTA_{2,3,4}$, or click rate effects. The full model, with all interactions, was reduced by backward elimination to find the most parsimonious model that reasonably characterized the ABR data observed in this sample. Tests of specific effects, such as the age by rate interaction for wave V latency, were conducted using the F-statistic with denominator degrees of freedom approximated using the Satterthwaite method.

RESULTS

Sample Characteristics

One-hundred thirty-one subjects provided data from 256 ears for this analysis. Characteristics of the study participants are given in Table 3 for better and poorer hearing groups. Note that Table 3 uses each subject as the unit of analysis, and each subject may contribute ears to either category of hearing impairment or to both. For this reason the subject counts do not total 131. Age ranges were identical in both hearing groups (range = 26–71, but a greater proportion of subjects in the better hearing group (50%) were below age 50 yr compared to poorer hearing subjects (25%). Male subjects made up 79 and 92% of the better and poorer hearing groups, respectively. Education was similarly distributed among the two groups. Education was not expected to affect the ABR response measures. It was a metric obtained as a part of the larger parent study. A total of 8,502 wave I, III, and V amplitudes and latencies were measured across click rates of 11, 51, and 71 Hz and at condensation and rarefaction click polarities. Of these measures, 4,266 came from the better hearing ears and 4,236 came from the poorer hearing ears.

Table 1 shows ear-level nonresponse rates for each ABR wave by click rate and hearing group. The highest nonresponse rate was observed for a click rate of 71 Hz. Across click rates, the nonresponse rates decreased with later ABR waves (from wave I to wave V). For subjects with better hearing, wave I was generally present at all ages for slower rates but was missing more frequently with increasing age and click rate. This trend was accentuated for subjects with poorer hearing.

Pure Tone Thresholds

Figure 2 shows right and left ear audiograms for participants in the better and poorer hearing groups. As reflected in the spaghetti plots, subjects' hearing differed somewhat between ears, as is common for individuals exposed to noise, but mean thresholds for the sample are similar between ears. For the better hearing group, pure tone thresholds at 2, 3, and 4 kHz fell within the normal hearing to mild hearing loss range, whereas thresholds for these frequencies range from mild to severely impaired for the poorer hearing group. Threshold variability differed considerably among test frequencies, particularly near the highest frequencies. Primary analyses concerned data from ears with mean PTA_{2,3,4} of 17.5 or less (i.e., the better hearing ears).

ABR Amplitudes and Latencies

Unadjusted ABR Measures—Figure 1 shows example ABRs obtained using rarefaction polarity at each click rate used in this study. Responses were from one younger adult (<50 yr) and one older adult (>50 yr) in the better hearing group, and one younger adult and one older adult in the poorer hearing group. Generally, wave I, III, and V amplitudes decreased and latencies increased with increasing click rate.

Table 2 provides unadjusted ABR responses obtained using a click rate of 11/sec. Data are stratified by groups based on age (in decades) and hearing (better and poorer hearing groups). Also included in Table 2 are PTA_{2,3,4} values by decade for each of the hearing groups. This breakdown is intended to assist with comparisons to earlier studies as described later. Some decades contain data from very few ears. Those means should be interpreted with caution.

Table 2 offers some indication of the pattern in ABR with respect to age. Consistent with the literature, there was a trend for amplitudes to decrease and latencies to increase with advancing age, primarily for the ears with better hearing. Interestingly, this trend did not hold for those with poorer hearing where the greatest change in amplitude and latency for all waves occurred between the <40 yr group and the 40–59 yr group. Because statistical tests need to take into account the repeated testing design of the study and missing data, we conducted statistical analyses on the modeled data. Age and hearing were continuously scaled in all of the statistical analyses of results provided below.

Model Results—The model-based correlation matrix among ABR measures taken on the same ear is shown in Table 4 for a click rate of 11/sec. Matrix elements in Table 4 show the correlation between amplitude and latency components of all waves. Not surprisingly, latency was positively correlated between ABR waves, as was amplitude. Correlations among the latency measures were larger than correlations among the amplitude measures. Also not surprisingly, amplitude and latency were negatively correlated across all waves, meaning that a high amplitude measure is associated with a short latency

Table 5 shows the final, reduced model selected by backward elimination. Coefficients estimate the effect size of each predictor on mean amplitudes in μV and mean latencies in msec. There were significant main effects of age on the amplitudes of all principal ABR

peaks. Aging also increased ABR peak latencies slightly, with significant shifts limited to the early waves. These age-related changes were largely independent of any threshold differences within the group. (The main effect of $PTA_{2,3,4}$ was significant for wave I amplitude only, and there were no interactions involving $PTA_{2,3,4}$ for this sample of better hearing ears.) There was, however, a significant Rate $\times$ Age interaction for ABR wave III amplitude, and the same interaction approached significance for wave I amplitude. The Rate $\times$ Age interaction for ABR wave V amplitude was not significant. This result illustrates that the mean amplitudes of the early waves depended jointly on the age of the subject and the presentation rate of the click. The Rate $\times$ Age interaction was not significant for wave I, III, or V latencies.

All fitted mean ABR amplitudes and latencies, amplitude differences, and IPIs were computed from the final, reduced models shown in Table 5. Effect sizes are also shown in Table 5. For any particular ABR component,

$$Mean(ABR) = b_0 + b_1 \times PTA_{2,3,4} + b_2 \times Rate + b_3 \times Age + b_4 \cdot Rate \times Age, \quad (1)$$

where b_0 , b_1 , b_2 , b_3 , and b_4 correspond to the intercept, $PTA_{2,3,4}$, Rate, Age, and Age by Rate. For example, mean wave I amplitude at a click rate of 11/sec for 45-yr-olds with $PTA_{2,3,4}$ of 13 dB HL is $0.39448 - 0.00395 \times 13 - 0.00255 \times 11 - 0.00269 \times 45 - 0.00003 \times 11 \times 45 = 0.209 \mu V$. ($PTA_{2,3,4} = 13$ is used since it corresponded to the median average among better hearing ears.) Curves relating mean amplitude and latency to age, click rate, and hearing were thus computed, as were mean IPIs from differences in the mean latencies derived from Equation 1. P-values and confidence intervals were computed from the covariances among the fitted parameters according to the methods described in Neter et al, 1996. These procedures were the basis of most analyses in the remainder of this paper.

Analysis of Modeled Means: Age Effects—Since degradation of the ABR was expected (and found) with increases in the age of the subject, threshold loss for an ear, and click presentation rate, we examined the relationship between ABR measures and age using model-based means (equation [1]) for PTA set to 13 dB HL and click rate set to 11/sec. Figure 3A shows mean ABR amplitudes for wave I (circles), wave III (squares), and wave V (triangles) plotted against age. P values obtained using these model parameters are provided for the age effect on each wave, and coefficients estimate the amplitude change per year (i.e., the slope of the function). Over a 40 yr span from age 30 to 70 yr, adjusted mean amplitudes decreased $0.09 \mu V$ (38%), $0.13 \mu V$ (43%), and $0.15 \mu V$ (34%) for waves I, III, and V, respectively. Thus the amplitude decrements attributable to aging were substantial and differed slightly across waves, with the largest absolute age-related changes found for wave V and the largest relative changes found for wave III.

Figure 3B shows the mean ABR peak latencies using the same format as Figure 3A. Adjusted mean wave I and III latencies increased by 0.25 msec (16%) and 0.29 msec (8%), respectively, from age 30 to 70 yr. Wave V latencies changed about the same amount in absolute terms, 0.21 msec (<4%), but these changes did not reach statistical significance.

The vertical distance between the lines for waves I, III, and V can be used to visualize I–III, III–V, and I–V IPIs for a click rate of 11/sec. The lines are nearly parallel, suggesting IPIs were constant with age, and age and rate did not interact. Figure 4 shows wave I–V IPIs by age for each of the click rates tested. Slopes differed somewhat across click rates, but the age effect on the I–V IPI never approached significance. These results indicate that after controlling for hearing loss, aging does not prolong central conduction times as measured by the ABR.

Analysis of Modeled Means: Variation in the Age Effects with Rate—Using the fitted model, we computed mean amplitudes and latencies for a 45-yr-old, a 55-yr-old, and a 65-yr-old subject for each ABR component and click rate with PTA set to 13 dB HL (equation [1]). The resulting means are presented in Figure 5 with values for each point identified by the numbers on each line. Variations in age effects with rate can be assessed by comparing the vertical distances between lines in each panel for different positions along the x (click rate) axis. Variations in rate effects with age can be appreciated by comparing the slopes of the lines in each panel. (Note that the vertical axis scale is different in each panel).

Effects of age were most prominent for a low click rate. At a click rate of 71 Hz, amplitudes of waves I and III are similar for each age. Increasing the click rate substantially reduced wave I and III amplitudes for the average 45- and 55-yr-old, but the influence of rate change on the amplitude of the early waves was less for older subjects, as illustrated by the apparent shallower slope of the lines for the 65-yr-old. The effect of rate on wave V amplitude did not vary with age (i.e., the slopes of the lines in Figure 5C are similar for the three ages examined). That is, even at a rate of 71 Hz, wave V amplitude was not substantially impacted by age.

Data in the right column of Figure 5 (D–F) show that mean wave I, III, and V latencies increase with increasing click rate. Slopes of the latency by rate curves were similar for the modeled 45-, 55-, and 65-yr-old subjects. The rate-related latency increase was considerably greater for wave V (as well as for wave III) compared with wave I, which resulted in the rate-related increase in I–V IPI shown in Figure 4.

As expected for a forehead electrode recording site, wave V amplitudes were generally greater than amplitudes of waves I or III obtained under identical stimulus conditions. Additionally, the nonresponse rates for wave V were nearly zero under all conditions, but the nonresponse rates for the generally lower-amplitude early peaks increased with click rate (Table 1). Therefore, we considered the possibility that the age by rate interactions found for wave I and III amplitudes were caused by a floor effect at the high rates. Specifically, slope differences in Figure 5A and B could be indicative of an age-related increase in nonresponses at the highest click rates, rather than a slope change in the data obtained from individual older subjects. Higher non-response rates among older subjects with already lower average ABR amplitude could have resulted in overrepresentation of the older subjects with the highest amplitudes at the higher click rates. Theoretically, this could result in smaller differences among age groups at the higher click rates. This is unlikely for several reasons. First, the differential effects of click rate were based on a linear model with subject-specific random intercepts (see “Methods”) to allow for variability in overall mean ABR

amplitude. Second, we investigated whether scorable early waves at high rates were obtained mostly from ears of older subjects with larger overall ABRs. Inspection of the data did not support this hypothesis. Third, fitted mean latencies shown in Figure 5D and E for wave I and III did not suggest the presence of a floor effect. Rather, wave I and III latencies increased with increasing click rate, and the rate of latency increase was similar for the modeled 45-, 55-, and 65-yr-old subjects.

Further analysis of ABR amplitudes was done to determine whether aging impacted central ABR generators independent of changes in the periphery. Specifically, estimates of the effects of age on wave III amplitude after adjusting for wave I amplitude were derived from the parameters of the fitted model shown in Table 5 (see Appendix A). For example, the wave I-adjusted mean wave III amplitude decrement due to age was a -0.0029 per-annum decrease, compared to the marginal effect (not adjusted for wave I) of -0.0032 per annum. Thus, after adjusting for wave I amplitude, there was about 8.4% smaller degradation in wave III amplitude with increasing age. A test of the statistical significance of the wave I-adjusted effects of age on wave III amplitude was based on the bootstrap (see Appendix A). Results indicated that there was a persistent, wave I-adjusted effect of age on wave III amplitude at a click presentation rate of 11/sec (Bootstrap median age effect = -0.0029 ; 95% CI = -0.0049 to -0.0011) but not at rates of 51/sec (Bootstrap median age effect = -0.00097 ; 95% CI = -0.0024 to 0.0003) or 71/sec (Bootstrap median age effect = -0.00004 ; 95% CI = -0.00136 to 0.00133).

Comparison of Modeled Means with Results Obtained in Subjects with Poorer Hearing—Figure 6 is a scatterplot showing raw ABR measures across age for the group of ears with poorer hearing. The solid line in each plot is a cubic spline smooth of the mean for poorer hearing ears with data from individual subjects represented by open circles. For comparison, model-based means for the group of better hearing ears are replotted in Figure 6 (dashed lines and filled circles). Poorer hearing ears were excluded from our statistical analysis. However this comparison might illustrate, at least qualitatively, how substantial hearing loss in a sample might impact results. Compared with the model based on better hearing ears, mean amplitudes were diminished in the group with poorer hearing, and wave V latencies were slightly prolonged. We evaluated mean I–V IPIs for those individuals with both a recordable wave I and V (not shown) and found that mean I–V IPIs were prolonged slightly (~ 0.15 msec) in the older subjects with poorer hearing compared to their better hearing counterparts. Subjects under about age 50 with poorer hearing had similar or shorter I–V IPIs on average when compared to subjects with better hearing. In general, however, the I–V IPIs among the poorer hearing ears were within the boundaries set by the better hearing group.

DISCUSSION

This report investigated effects of advancing age and click presentation rate on the ABR, controlling for confounding effects of hearing, missing and correlated data, and modeling all of the ABR components jointly to avoid inflated rates of type I error. In a cross-sectional sample of veterans without diabetes and with no more than a mild hearing loss through 4 kHz, our results confirmed that aging increased peak latencies slightly, with significant

changes limited to early waves. Results further showed that for click rates as high as 71 Hz, aging did not prolong IPI-based estimates of neural transmission time within the auditory brainstem. Instead there was a very slight, nonsignificant I–V IPI decrease with age at a click rate of 11.1 Hz. These results suggest that the ABR latency changes associated with aging can be attributed to changes in auditory nerve input. An important effect of aging confirmed in this report is that it substantially reduces amplitudes of all principal ABR peaks. We found that wave III amplitude decrements persisted even after controlling for cochlear and auditory nerve changes reflected in wave I amplitude. Thus, the ABR amplitude changes provide evidence that aging alters neural elements within the central auditory system as well as the auditory nerve.

Comparison to Earlier Findings

The above results are consistent with some of the published literature and may help explain discrepancies across other earlier studies. First, our model-based latency data are largely consistent with published norms developed using data from young male subjects comparing wave I latency, wave V latency, and I–V IPI (Rosenhall et al, 1985). The small age-related ABR latency changes in the present report (Fig. 3B) are also consistent with earlier research studies within the precision of the measurement. Mean latency differences between older and younger subjects for wave I and wave V was ~0.1 msec in Burkard and Sims (2001). Differences reported in the Harkins study were similar (latencies were 0.14 and 0.13 msec for waves I and V, respectively). Using a multiple linear regression modeling approach, Mitchell et al (1989) found a 0.116 msec wave V latency increase over 40 yr for male subjects in a clinical population. Our model-based results show wave V latency increased 0.214 msec over a span of 40 yr, in closer agreement with Rupa and Dayal (1993), who estimated a change over 40 yr of 0.28 msec for males. However, unlike these reports and others that also used multiple regression approaches to investigate effects of aging on wave V latencies (Lightfoot, 1993), we found the effect was not significant.

Second, effects of aging on the I–V IPI were also negligible in the present report (Fig. 5) and failed to reach statistical significance at any of the click rates tested ($p < 0.05$). These results are in agreement with Mitchell et al. (1989) for males, but not for a model fitted to a sample that included both males and females. However, Mitchell et al (1989) did not model all ABR metrics jointly or adjust for correlations among multiple metrics (ABR wave I, III, and V amplitudes and latencies) and multiple measures from each subject (taken from two ears). Mitchell et al's results could therefore have been influenced by type I error. Our results are also incompatible with Elberling and Parbo (1987), who found I–V IPIs increased 0.22 msec in males over 40 yr. The I–V IPI evaluations were done on subjects in whom both waves I and V could be observed potentially skewing the sample, particularly for older subjects, toward those with the best hearing and/or auditory nerve function, which could explain differences in results across studies.

Third, our study showed that high click presentation rates diminish amplitudes of early peaks and prolong latencies of later peaks and I–V IPIs, as expected. Lightfoot (1992) used multiple regression to examine effects of aging, hearing, and stimulus rate jointly on IPIs and rate-related wave V shifts. Lightfoot did not adjust for correlations in the data, which

differs from the present report. However, he found no significant association between the I–V IPI and aging. He also found that shifts in wave V produced by increasing stimulus rates from 11/sec to 44/sec were not associated with age, but when stimulus rates were increased from 11/sec to 88/sec, older subjects had slightly larger shifts. However, the authors note that the r^2 value of 0.002 suggested an effect of little real clinical significance. Our model-based results did not reveal a significant Rate by Age interaction on I–V IPIs, consistent with results of Lightfoot's statistical modeling approach (1992), *t*-tests of group differences in Harkins (1981), and qualitative comparisons of Burkard and Sims (2001). Thus, it appears that rate-related neural dys-synchrony affects ABR latencies and IPIs in a similar manner for younger and older adults.

Finally, our model-based amplitude results (Fig. 3A) show good quantitative agreement with previously published ABR studies of aging, especially considering that age-related amplitude changes tend to increase with even small hearing threshold losses among the older participants (Boettcher et al, 1993). Many previous human and animal studies report up to 50% amplitude reductions for the early ABR peaks in older compared with younger subjects (for a review of both animal and human studies see Boettcher, 2002). For example, using a click presented at a rate of ~11/sec, Burkard and Sims (2001) and Harkins (1981) observed mean amplitude differences between older and younger subjects of roughly 45% for wave I.

Some investigators have found that threshold at 8 kHz, in addition to frequencies around 4 kHz, was an important predictor of ABR latencies and/or I–V IPI (e.g., Mitchell et al 1989). In light of this, we refit the model adding 8 kHz threshold. With this additional adjustment for hearing, the age effects on amplitudes were still significant ($p < 0.01$). Moreover, the age effects on the wave V latency and I–V IPI remained nonsignificant.

Clinical Implications

Our final model, reduced by backward elimination, had no main effects of age or PTA_{2,3,4} for wave V latency or I–V IPIs and no interactions involving age or PTA_{2,3,4}. One clinical indication is that among patients who meet the criterion of no more than a mild hearing loss in their PTA_{2,3,4}, measurements of wave V or I–V IPIs can be compared to normative data without adjusting for age or hearing loss. This is consistent with prior work indicating that for clinical purposes, wave V latency adjustments for age are unnecessary and adjustments for hearing are necessary only for losses at 4 kHz in excess of about 50 dB HL (Selters and Brackmann, 1977; Hyde and Blair, 1981). These results also suggest that either ABR latencies are not sensitive to timing changes in the brainstem associated with aging or these changes are slight in older individuals with reasonably good hearing. Comparing changes in the ABR related to aging and rate manipulations may provide some insight into this question. As click presentation rate is increased, the click is less able to trigger synchronous neural firing leading to fewer contributing neural units, resulting in smaller ABR amplitudes and prolonged wave V latencies and I–V IPIs. None of the changes associated with aging in the better hearing sample impacted central conduction times as measured by the ABR. Thus age-related changes are either more subtle or are different as compared with the observed synchrony-related changes produced by increasing the click rate. Even so, reduced ABR

amplitudes among older subjects could be an indication of pathological processes that might impact temporal processing as described below.

Implications of Results for Temporal Processing by the Elderly

Reduced wave I amplitudes and increased wave I latencies could be an indication of abnormal temporal responses at the individual auditory nerve fiber level. Old rats with long-standing hearing loss show increased adaptation as indicated by abnormal recovery from brief auditory stimulation (Shepherd et al, 2004). However, we are not aware of single unit data indicating this occurs in nonnoise exposed ears.

It has also been hypothesized that because neurons in the cochlear nucleus receive multiple auditory nerve inputs, having fewer inputs from the auditory nerve could reduce temporal precision at the central neuron level. One argument is that this could occur because the firing of neural action potentials is a stochastic process influenced by the refractory period (as described by Dries et al, 2004). Another argument is that less robust or desynchronized afferent neural transmission would render the receiving (central) neuron less able to code small stimulus level changes or gaps in the stimulus because such changes would make a silent gap in an ongoing sound more difficult to pick out of background spontaneous activity (Zeng et al, 2005).

The chinchilla model has recently been used to test the hypothesis that reduced input from the periphery changes temporal responses of neurons in the inferior colliculus (Cowper-Smith et al, 2010). In the chinchilla, experimental treatment with carboplatin produces inner hair cell loss accompanied by loss of auditory nerve fibers and reduced spike rates of surviving fibers (Wake et al, 1994). Cowper-Smith and colleagues (2010) showed that temporal responses of individual auditory nerve fibers and inferior colliculus neurons are similar in chinchilla before and after carboplatin treatment, suggesting that reduced afferent neural transmission is insufficient to desynchronize neural activity in the inferior colliculus, at least over the short term.

Over the long term, reductions in the overall level of excitation produced by the auditory nerve may destabilize the tight regulation of excitatory/inhibitory neuro-transmission needed for temporal processing. A recent study in rats reared in quiet found that behavioral gap detection and temporal responses of neurons within the inferior colliculus are abnormal in aged rats (Casparly et al, 1995). These abnormalities coincided with plastic changes associated with the down regulation of inhibitory neurotransmission apparently in response to decreased auditory nerve (excitatory) input (Casparly et al, 2008). Unfortunately, these researchers did not report the ABR central conduction time, so we do not know whether such changes were sufficient to increase inter-peak intervals or not. Even so, their data suggest that behavioral measures of temporal processing may depend in part on the preservation of peripheral auditory function over time. Diminished ABR wave I amplitudes observed in the present study even after adjusting for effects of hearing loss are an indication that auditory nerve function is not preserved over time in older human subjects.

Implications of Prior Noise Exposure

We evaluated whether a history of noise exposure explains the age effects observed in this study. A noise index was created from questionnaire data collecting the history of noise exposure and use of hearing protection in a variety of military, occupational, and recreational settings and past sudden intense noise exposures. Index values from the four queried sources of noise were combined into a total noise exposure scale ranging from 8 (no noise exposure) to 40 (frequent noise exposure without hearing protection) in all exposure categories. Even though our noise index was an unvalidated measure, we refit the reduced model and included the total noise exposure index, along with all interactions. Age remained a statistically significant predictor of ABR amplitudes and latencies (Likelihood ratio statistic = 72.1; $df = 24$; $p < 0.001$) after adjusting for our noise exposure index.

Limitations

A limitation of this of this study is that most of the veterans tested were male. Thus, we were unable to evaluate effects of gender on aging, which is an important area of inquiry (e.g., Jerger and Hall, 1980). We also did not include gender or head diameter in our regression model but did include a subject specific random intercept to adjust for overall larger or smaller amplitudes/longer or shorter latencies as might be related to gender.

Another potential limitation was that our veteran subjects may have had more noise exposure than the general population. The individuals sampled all reported exposures to noise without consistent use of hearing protection, though all of our age groups had similar noise histories. As with most other human studies, it was therefore not possible to separate normal effects of aging from any enhanced effects related to prior noise exposure. However, our inferences about age and rate effects are based primarily on analyses of participants with good hearing (as defined by $PTA_{2,3,4} < 17.5$ dB HL) and pre-sumably less noise damage. Furthermore, ABR results in the present study are consistent with the literature for a similar range of ages with hearing stringently controlled (see comparison with prior studies above).

We were interested in determining whether the age-related change remained relatively stable until a certain decade of life then changed rapidly or whether it was a gradual change with increasing years. Previous research had not addressed this issue. For this sample of ears with good hearing, the ABR measures were well fit by a model that was linear for age. Residual analysis showed no systematic deviation of the fitted model from the data, indicating that when hearing is stringently controlled, there is no sudden change in the rate of neural decline with age. However, more precise evaluation of nonlinear effects of age on ABR using, for example, generalized additive models (Hastie and Tibshirani, 1990) may be possible with larger samples that include greater representation of subjects in the youngest and oldest age categories.

An important consideration of any aging study, including this study, is that older subjects are those who have survived longest and, therefore, tend to be the healthiest at any age, i.e., the healthy cohort effect. Therefore, they are not truly representative examples of an “aging” that might have been observed if all subjects from the younger group had survived to old

age. Longitudinal studies may be better suited to address the effects of aging though they are prone to the healthy cohort effect as well.

CONCLUSIONS

Aging substantially reduced amplitudes of all principal ABR peaks, with significant latency shifts limited to waves I and III. There were central changes induced by increasing the click presentation rate in young and older subjects. In contrast, aging did not increase the I–V IPI at any click rate tested. Aging was associated with amplitude decrements in wave III that persisted after controlling for cochlear and auditory nerve changes reflected in wave I amplitude. Results were interpreted as evidence that aging reduces the numbers and/or synchrony of contributing units in the auditory nerve and cochlear nucleus. Based on aging/click rate comparisons, it is also tempting to speculate that the major impact of aging is a reduction in the numbers, rather than the synchrony, of ABR generators. Our results were obtained in a predominantly male, veteran population without diabetes or substantial hearing loss. Results may differ for females or persons with more substantial hearing loss and/or less noise exposure in their history.

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Abbreviations

ABR	auditory brainstem response
CAP	compound action potential of the auditory nerve
dB nHL	decibels hearing level re:locally developed normative data
IPI	ABR interpeak interval
PTA_{2,3,4}	2, 3, and 4 kHz pure tone threshold average

References

- Allison T, Wood CC, Goff WR. Brain stem auditory, pattern-reversal visual, and short-latency somatosensory evoked potentials: latencies in relation to age, sex, and brain and body size. *Electroencephalogr Clin Neurophysiol.* 1983; 55(6):619–636. [PubMed: 6189692]
- Austin DF, Konrad-Martin D, Griest S, McMillan GP, McDermott D, Fausti S. Diabetes-related changes in hearing. *Laryngoscope.* 2009; 119(9):1788–1796. [PubMed: 19593813]
- Bainbridge KE, Hoffman HJ, Cowie CC. Diabetes and hearing impairment in the United States: audiometric evidence from the National Health and Nutrition Examination Survey, 1999 to 2004. *Ann Intern Med.* 2008; 149(1):1–10. [PubMed: 18559825]
- Boettcher FA. Presbycusis and the auditory brainstem response. *J Speech Lang Hear Res.* 2002; 45(6):1249–1261. [PubMed: 12546491]

- Boettcher FA, Mills JH, Norton BL, Schmiedt RA. Age-related changes in auditory evoked potentials of gerbils. II. Response latencies. *Hear Res.* 1993; 71(1–2):146–156. [PubMed: 8113133]
- Burkard RF, Sims D. The human auditory brainstem response to high click rates: aging effects. *Am J Audiol.* 2001; 10(2):53–61. [PubMed: 11808720]
- Carhart R, Jerger JF. Preferred method for clinical determination of pure-tone thresholds. *J Speech Hear Disord.* 1959; 24:330–345.
- Caspary D, Ling L, Turner J, Hughes L. Inhibitory neuro-transmission, plasticity, and aging in the mammalian central auditory system. *J Exp Biol.* 2008; 211:1781–1791. [PubMed: 18490394]
- Caspary DM, Milbrandt JC, Helfert RH. Central auditory aging: GABA changes in the inferior colliculus. *Exp Gerontol.* 1995; 30(3–4):349–360. [PubMed: 7556513]
- Costa P, Benna P, Bianco C, Ferrero P, Bergamasco B. Aging effects on brainstem auditory evoked potentials. *Electromyogr Clin Neurophysiol.* 1990; 30(8):495–500. [PubMed: 2286175]
- Cowper-Smith CD, Dingle RN, Guo Y, Burkard R, Phillips DP. Synchronous auditory nerve activity in the carboplatin-chinchilla model of auditory neuropathy. *J Acoust Soc Am.* 2010; 128(1):EL56–EL62. [PubMed: 20649190]
- Debruyne F. Influence of age and hearing loss on the latency shifts of the auditory brainstem response as a result of increased stimulus rate. *Audiology.* 1986; 25(2):101–106. [PubMed: 3707434]
- Dries H, Louage G, van der Heijden M, Joris PX. Temporal properties of responses to broadband noise in the auditory nerve. *J Neurophysiol.* 2004; 91:2051–2065. [PubMed: 15069097]
- Elfron, B., Tibshirani, R. *An Introduction to the Bootstrap.* New York: Chapman and Hall; 1993.
- El-Badry MM, McFadden SL. Electrophysiological correlates of progressive sensorineural pathology in carboplatin-treated chinchillas. *Brain Res.* 2007; 1134(1):122–130. [PubMed: 17198689]
- Elberling C, Parbo J. Reference data for ABRs in retrocochlear diagnosis. *Scand Audiol.* 1987; 16(1):49–55. [PubMed: 3589481]
- Friedland DR, Cederberg C, Tarima S. Audiometric pattern as a predictor of cardiovascular status: development of a model for assessment of risk. *Laryngoscope.* 2009; 119(3):473–486. [PubMed: 19235737]
- Frisina RD. Age-related hearing loss. *Ann N Y Acad Sci.* 2009; 1170:708–717. [PubMed: 19686217]
- Harkins SW. Effects of age and interstimulus interval on the brainstem auditory evoked potential. *Int J Neurosci.* 1981; 15:107–118. [PubMed: 7287325]
- Hastie, T., Tibshirani, R. *Generalized Additive Models.* Boca Raton: Chapman and Hall; 1990.
- Hastie, T., Tibshirani, R., Friedman, J. *The Elements of Statistical Learning.* 2. New York: Springer; 2009.
- Hyde ML, Blair RL. The auditory brainstem response in neuro-otology: perspectives and problems. *J Otolaryngol.* 1981; 10(2):117–125. [PubMed: 7241628]
- Jerger J, Hall J. Effects of age and sex on auditory brainstem response. *Arch Otolaryngol.* 1980; 106(7):387–391. [PubMed: 7387524]
- Knopman DS, Mosley TH, Catellier DJ, Coker LH. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. *Alzheimers Dement.* 2009; 5(3):207–214. [PubMed: 19362884]
- Konrad-Martin D, Austin DF, Griest S, McMillan GP, McDermott D, Fausti S. Diabetes-related changes in auditory brainstem responses. *Laryngoscope.* 2010; 120(1):150–158. [PubMed: 19904812]
- Lightfoot GR. ABR screening for acoustic neuromata: the role of rate-induced latency shift measurements. *Br J Audiol.* 1992; 26(4):217–227. [PubMed: 1446185]
- Lightfoot GR. Correcting for factors affecting ABR wave V latency. *Br J Audiol.* 1993; 27(3):211–220. [PubMed: 8241970]
- Maurizi M, Altissimi G, Ottaviani F, Paludetti G, Bambini M. Auditory brainstem responses (ABR) in the aged. *Scand Audiol.* 1982; 11(4):213–221. [PubMed: 7163763]
- Mitchell C, Phillips DS, Trune DR. Variables affecting the auditory brainstem response: audiogram, age, gender and head size. *Hear Res.* 1989; 40(1–2):75–85. [PubMed: 2768085]
- Moller AR. Review of the roles of temporal and place coding of frequency in speech discrimination. *Acta Otolaryngol.* 1999; 119(4):424–430. [PubMed: 10445056]

- Neter, J., Kutner, M., Nachtsheim, C., Wasserman, W. Applied Linear Statistical Models. Homewood, IL: McGraw-Hill/Ricard Irwin; 1996.
- Psatta DM, Matei M. Age-dependent amplitude variation of brain-stem auditory evoked potentials. *Electroencephalogr Clin Neurophysiol.* 1988; 71(1):27–32. [PubMed: 2446843]
- Rosenthal U, Björkman G, Pedersen K, Kall A. Brain-stem auditory evoked potentials in different age groups. *Electroencephalogr Clin Neurophysiol.* 1985; 62(6):426–430. [PubMed: 2415338]
- Rowe MJ 3rd. Normal variability of the brain-stem auditory evoked response in young and old adult subjects. *Electroencephalogr Clin Neurophysiol.* 1978; 44(4):459–470. [PubMed: 76554]
- Rupa V, Dayal AK. Wave V latency shifts with age and sex in normals and patients with cochlear hearing loss: development of a predictive model. *Br J Audiol.* 1993; 27(4):273–279. [PubMed: 8312850]
- Sand T. BAEP amplitudes and amplitude ratios: relation to click polarity, rate, age and sex. *Electroencephalogr Clin Neurophysiol.* 1991; 78(4):291–296. [PubMed: 1706250]
- Schneider BA, Daneman M, Pichora-Fuller MK. Listening in aging adults: from discourse comprehension to psychoacoustics. *Can J Exp Psychol.* 2002; 56(3):139–152. [PubMed: 12271745]
- Selters WA, Brackmann DE. Acoustic tumor detection with brain stem electric response audiometry. *Arch Otolaryngol.* 1977; 103(4):181–187. [PubMed: 849194]
- Shepherd RK, Roberts LA, Paolini AG. Long-term sensor-ineural hearing loss induces functional changes in the rat auditory nerve. *Eur J Neurosci.* 2004; 20(11):3131–3140. [PubMed: 15579167]
- Wake M, Takeno S, Ibrahim D, Harrison R. Selective inner hair cell ototoxicity induced by carboplatin. *Laryngoscope.* 1994; 104(4):488–493. [PubMed: 8164491]
- Willott JF, Vanden-Bosche J, Shimizu T, Ding DL, Salvi R. Effects of exposing C57BL/6J mice to high- and low-frequency augmented acoustic environments: auditory brainstem response thresholds, cytochrome c oxidase, anterior cochlear nucleus morphology and the role of gonadal hormones. *Hear Res.* 2008; 235:60–71. [PubMed: 18077117]
- Zeng FG, Kong YY, Michalewski HJ, Starr A. Perceptual consequences of disrupted auditory nerve activity. *J Neurophysiol.* 2005; 93(6):3050–3063. [PubMed: 15615831]

Appendix A. Derivation of the Relationship between the Conditional Mean Amplitude at Each Peak on the Amplitude at Wave I

The estimated regression coefficients in Table 5 indicate an important effect of age on the marginal mean wave III amplitude. We also sought to determine if the effect of aging on wave III amplitude persists after adjusting for the magnitude of wave I amplitude. This entailed defining the conditional expectation of wave III amplitude given wave I amplitude, which was directly obtained from properties of multivariate normal distributions.

Let

W_i = the amplitude at wave i , $i = 1, 3$;

β_1^i = age main effect for wave i (from Table 5);

β_2^i = age-rate interaction for wave i (from Table 5);

$\mathbf{X}$ = covariates other than age and age-rate (i.e. $PTA_{2,3,4}$ and click repetition rate in this analysis. See Table 5);

β^i = regression coefficients for effects other than age and age-rate (Table 5);

σ_i = model-based standard deviation of the amplitude at the i^{th} wave;

ρ_{ij} = correlation between amplitudes at i^{th} and j^{th} wave (See Table 4); and

μ_i = mean amplitude at i^{th} wave.

The wave I and III amplitude vector has a bivariate normal distribution with mean μ_1 , and μ_3 . Thus,

$$E[W_i|\mathbf{X}, \beta_i, \beta_1^i, \beta_2^i, \text{Age}, \text{Age} \times \text{Rate}] = \mu_i = \mathbf{X}^T \beta^i + \text{Age} \cdot (\beta_1^i + \text{Rate} \cdot \beta_2^i). \quad (1)$$

This is a simple linear model of mean amplitude with the age effect, dependent on Rate, contained in the right-hand portion of the sum.

By definition of multivariate random variables (Neter et al, 1996), the conditional mean of W_3 given W_1 is

$$E[W_3|\mathbf{X}, \beta_3, \beta_1^3, \beta_2^3, \text{Age}, \text{Age} \cdot \text{Rate}, W_1=W_1] = \mu_3 + (\sigma_3/\sigma_1)\rho_{31} \cdot (w_1 - \mu_1).$$

Substituting (1) for each μ_i gives

$$E[W_3|\mathbf{X}, \beta_3, \beta_1^3, \beta_2^3, \text{Age}, \text{Age} \cdot \text{Rate}, W_1=w_1] = \mathbf{X}^T \beta^3 + \text{Age} \cdot (\beta_1^3 + \text{Rate} \cdot \beta_2^3) + (\sigma_3/\sigma_1)\rho_{31} \cdot \left(w_1 - \left(\mathbf{X}^T \beta^1 + \text{Age} \cdot (\beta_1^1 + \text{Rate} \cdot \beta_2^1) \right) \right)$$

so that the age effect on the conditional mean of W_3 given W_1 reduces to

$$\text{Age} \cdot ((\beta_1^3 + \text{Rate} \cdot \beta_2^3) + (\sigma_3/\sigma_1) \cdot \rho_{31} \cdot (\beta_1^1 + \text{Rate} \cdot \beta_2^1)). \quad (2)$$

The function in parentheses is the wave I-adjusted slope relating age to wave III amplitude. The adjustment subtracts the age effect on wave I from the age effect on wave III. The size of the adjustment depends on the ratio of the standard deviations of the amplitudes, the correlation between wave I and wave III amplitude, and the regression coefficients relating the marginal mean of wave I amplitude and age.

A confidence interval for the modified slope in equation (2) was estimated using the bootstrap (Efron and Tibshirani, 1993). We constructed 1,000 bootstrap samples by sampling 80 subjects with replacement from the original sample and refitting the full model described in the paper to each bootstrap sample. Equation (2) was computed from the estimated parameters fit at each bootstrap iteration, and a 95% confidence interval was defined as the 2.5 and 97.5% of the resulting distribution. Intervals that do not cover zero indicate statistically significant wave I-adjusted age effects on wave III amplitude.

Figure 1.

ABR traces for each click rate and rarefaction polarity shown for one young adult participant (*top left*) and one older adult participant (*bottom left*) in the better hearing group. ABRs are also shown for one young adult participant (*top right*) and one older adult participant (*bottom right*) in the poorer hearing group. Peaks are labeled to indicate how ABR metrics were obtained.

Figure 2. Audiograms for participants in the better (*top row*) and poorer (*bottom row*) hearing groups. Thresholds are provided in dB HL as a function of pure tone frequency. Right and left ear data are provided separately for individual ears (in gray).

Figure 3.

Model-based mean amplitudes in μV (A) and latencies in msec (B) as a function of age with $\text{PTA}_{2,3,4}$ set to 13 dB HL and click rate set to 11/sec (equation [1]). Results are shown for wave I (circles), wave III (squares), and wave V (triangles) as a function of age in years. P values obtained using the model parameters are also given for the age effect on each wave; slopes estimate the amplitude or latency change per year.

Figure 4.

Model-based mean IPIs in msec as a function of age in years with $PTA_{2,3,4}$ set to 13 dB HL (equation [1]). The parameter is click rate shown for 11/sec (circles), 51/sec (squares), and 71/sec (triangles).

Figure 5. Model-based mean amplitudes and latencies for average 45-yr-olds, 55-yr-olds, and 65-yr-olds as a function of click rate with PTA set to 13 dB HL. Values for each point are identified by the numbers on each line.

Figure 6.

Scatterplots showing raw ABR amplitudes and latencies as a function of age for the group of ears with poorer hearing for an 11/sec click rate. The black curve in each panel is the loess smooth of the scatterplot data. For comparison, model-based mean data are provided from the group of better hearing ears (gray lines and circles). The 95% confidence interval of the fitted mean is shown in gray to show precision of the estimated mean function and to contrast with the loess curve.

Table 1

Ear-Level Missing Data Rates by Click Rate and ABR Wave

		Click Rate											
		11				51				71			
		Mean PTA _{2,3,4}				Mean PTA _{2,3,4}				Mean PTA _{2,3,4}			
		<17.5				<17.5				<17.5			
Wave	Age	N	% Missing	N	% Missing	N	% Missing	N	% Missing	N	% Missing	N	% Missing
I	<40	33	9%	2	0%	32	6%	2	0%	33	18%	2	0%
	40-49	96	10%	45	27%	95	22%	43	30%	90	28%	43	42%
	50-59	98	9%	146	21%	99	26%	140	26%	95	25%	141	32%
	60-69	11	18%	42	19%	12	25%	42	26%	11	55%	40	28%
	70+	2	0%	6	67%	2	0%	6	33%	2	50%	6	50%
III	<40	33	0%	2	0%	32	3%	2	0%	33	0%	2	0%
	40-49	96	8%	45	16%	95	13%	43	21%	90	19%	43	30%
	50-59	98	7%	146	13%	99	13%	140	19%	95	23%	141	27%
	60-69	11	0%	42	7%	12	0%	42	5%	11	45%	40	18%
	70+	2	0%	6	33%	2	0%	6	50%	2	0%	6	33%
V	<40	33	0%	2	0%	32	0%	2	0%	33	0%	2	0%
	40-49	96	1%	45	2%	95	1%	43	0%	90	4%	43	5%
	50-59	98	4%	146	2%	99	3%	140	4%	95	0%	141	1%
	60-69	11	0%	42	2%	12	0%	42	0%	11	0%	40	5%
	70+	2	0%	6	0%	2	0%	6	0%	2	50%	6	17%

Note: Data are provided separately for the better hearing and worse hearing groups.

Table 2

Unadjusted Mean and SD ABR Response Measures

Mean PTA < 17.5 dB HL													
Age													
		<40		40–49		50–59		60–69		70+			
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	SD
Wave I Latency	30	1.59	0.2	86	1.67	0.2	89	1.76	0.2	9	1.79	0.2	1.94
Wave III Latency	33	3.78	0.2	88	3.83	0.2	91	3.93	0.3	11	4.08	0.2	4.00
Wave V Latency	33	5.74	0.2	95	5.72	0.3	94	5.79	0.4	11	5.75	0.3	6.53
Wave I Amplitude	30	0.27	0.2	86	0.21	0.1	89	0.19	0.1	9	0.16	0.1	0.06
Wave III Amplitude	33	0.31	0.1	88	0.26	0.1	91	0.23	0.1	11	0.15	0.1	0.26
Wave V Amplitude	33	0.45	0.1	95	0.37	0.2	94	0.34	0.2	11	0.34	0.1	0.35
I–V IPI	30	4.13	0.2	85	4.04	0.3	86	4.00	0.3	9	3.95	0.3	4.59
I–III IPI	30	2.18	0.1	81	2.16	0.2	83	2.14	0.2	9	2.28	0.2	2.06
III–V IPI	33	1.95	0.1	88	1.90	0.3	88	1.87	0.3	11	1.67	0.2	2.53

Mean PTA 17.5 dB HL													
Age													
		<40		40–49		50–59		60–69		70+			
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	SD
Wave I Latency	2	1.68	—	33	1.79	0.3	116	1.72	0.2	34	1.79	0.3	1.88
Wave III Latency	2	3.95	—	38	3.96	0.2	127	3.94	0.3	39	4.06	0.4	4.11
Wave V Latency	2	5.66	—	44	5.94	0.3	143	5.94	0.3	41	6.06	0.3	6.81
Wave I Amplitude	2	0.20	—	33	0.15	0.1	116	0.16	0.1	34	0.15	0.1	0.12
Wave III Amplitude	2	0.19	—	38	0.19	0.1	127	0.19	0.1	39	0.18	0.1	0.14
Wave V Amplitude	2	0.36	—	44	0.30	0.1	143	0.29	0.1	41	0.30	0.1	0.41
I–V IPI	2	3.99	—	32	4.11	0.3	113	4.17	0.3	34	4.25	0.3	3.74
I–III IPI	2	2.28	—	31	2.19	0.3	109	2.22	0.2	32	2.23	0.2	2.24
III–V IPI	2	1.71	—	37	1.93	0.2	124	1.97	0.2	38	2.02	0.2	1.70

Note: For ease in comparing to previous results, data stratified by age. Only data presented at 11/sec are provided as an example. Amplitude is in μV , and latency is in msec.

Table 3

Characteristics of Study Participants

		Mean PTA _{2,3,4}											
		<17.5						17.5					
		Age						Age					
		<40	40-49	50-59	60-69	70+	All	<40	40-49	50-59	60-69	70+	All
Total N	N	9	30	35	5	1	80	2	18	48	13	2	83
Gender													
Male	N	6	24	28	5	.	63	1	16	45	13	1	76
Female	%	67	80	80	100	.	79	50	89	94	100	50	92
	N	3	6	7	.	1	17	1	2	3	.	1	7
	%	33	20	20	.	100	21	50	11	6	.	50	8
PTA _{2,3,4}	Mean	9.4	12.1	13.1	13.3	15.0	12.4	19.2	27.2	29.6	35.5	20.8	29.5
	Min	3.3	5.0	5.0	8.3	15.0	3.3	18.3	18.3	18.3	20.0	18.3	18.3
	Max	16.7	16.7	16.7	16.7	15.0	16.7	20.0	48.3	56.7	56.7	23.3	56.7
Education													
Some HS or less	N	.	1	3	.	.	4	.	2	.	1	1	4
	%	.	3	9	.	.	5	.	11	.	8	50	5
Completed HS	N	.	7	4	.	1	12	1	3	9	3	1	17
	%	.	23	11	.	100	15	50	17	19	23	50	20
Post-HS	N	6	13	14	1	.	34	.	8	23	3	.	34
	%	67	43	40	20	.	43	.	44	48	23	.	41
Completed college	N	3	9	14	4	.	30	1	5	16	6	.	28
	%	33	30	40	80	.	38	50	28	33	46	.	34

Note: The number of study participants is given for the better hearing (PTA_{2,3,4} < 17.5 dB HL) and worse hearing (PTA_{2,3,4} 17.5 dB HL) groups along with participant characteristics. Data are stratified by decade.

Table 4
Model-Based Estimate of the Correlation Matrix for the Better Hearing Group and Click Rate of 11/sec

	Amplitude					Latency				
	wave I	wave III	wave V	wave I	wave III	wave I	wave III	wave V	wave I	wave V
Amplitude										
I	1.00	0.17	0.13	-0.15	0.00	-0.15	0.00	-0.16		
III		1.00	0.00	-0.07	-0.15	-0.07	-0.15	-0.08		
V			1.00	0.03	-0.01	0.03	-0.01	-0.29		
Latency										
I				1.00	0.30	1.00	0.30	0.08		
III					1.00		1.00	0.31		
V								1.00		

Table 5

Regression Coefficients for the Reduced Model of Mean ABR Components

ABR Component	Predictor	Effect Size	Standard Error	p-value
Wave I Amplitude	Intercept	0.39448	0.04931	<.01
	PTA _{2,3,4}	−0.00395	0.00146	<.01
	Rate	−0.00255	0.00081	<.01
	Age	−0.00269	0.00099	<.01
	Rate*Age	0.00003	0.00002	0.07
Wave I Latency	Intercept	1.36565	0.13112	<.01
	PTA _{2,3,4}	0.00282	0.00382	0.46
	Rate	0.00164	0.00166	0.32
	Age	0.00602	0.00261	0.02
	Rate*Age	0.00001	0.00003	0.81
Wave III Amplitude	Intercept	0.47860	0.04930	<.01
	PTA _{2,3,4}	−0.00241	0.00149	0.11
	Rate	−0.00400	0.00073	<.01
	Age	−0.00387	0.00099	<.01
	Rate*Age	0.00005	0.00001	<.01
Wave III Latency	Intercept	3.41075	0.14038	<.01
	PTA _{2,3,4}	0.00573	0.00362	0.11
	Rate	0.00451	0.00139	<.01
	Age	0.00748	0.00279	<.01
	Rate*Age	−0.00001	0.00003	0.77
Wave V Amplitude	Intercept	0.55322	0.06987	<.01
	PTA _{2,3,4}	0.00003	0.00206	0.99
	Rate	−0.00087	0.00092	0.35
	Age	−0.00354	0.00139	0.01
	Rate*Age	−0.00001	0.00002	0.75
Wave V Latency	Intercept	5.38328	0.16556	<.01
	PTA _{2,3,4}	0.00607	0.00438	0.17
	Rate	0.00506	0.00172	<.01
	Age	0.00480	0.00329	0.15
	Rate*Age	0.00005	0.00003	0.19

Note: Results are for the better hearing group.