Research Article

Age-Related Changes in the Relationship Between Auditory Brainstem Responses and Envelope-Following Responses

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Received: 16 December 2013; Accepted: 24 April 2014; Online publication: 21 May 2014

ABSTRACT

Hearing thresholds and wave amplitudes measured using auditory brainstem responses (ABRs) to brief sounds are the predominantly used clinical measures to objectively assess auditory function. However, frequency-following responses (FFRs) to tonal carriers and to the modulation envelope (envelope-following responses or EFRs) to longer and spectro-temporally modulated stimuli are rapidly gaining prominence as a measure of complex sound processing in the brainstem and midbrain. In spite of numerous studies reporting changes in hearing thresholds, ABR wave amplitudes, and the FFRs and EFRs under neurodegenerative conditions, including aging, the relationships between these metrics are not clearly understood. In this study, the relationships between ABR thresholds, ABR wave amplitudes, and EFRs are explored in a rodent model of aging. ABRs to broadband click stimuli and EFRs to sinusoidally amplitude-modulated noise carriers were measured in young (3–6 months) and aged (22–25 months) Fischer-344 rats. ABR thresholds and amplitudes of the different waves as well as phase-locking amplitudes of EFRs were calculated. Age-related differences were observed in all these measures, primarily as increases in ABR thresholds and decreases in ABR wave amplitudes and EFR phase-locking capacity. There were no observed correlations

between the ABR thresholds and the ABR wave amplitudes. Significant correlations between the EFR amplitudes and ABR wave amplitudes were observed across a range of modulation frequencies in the young. However, no such significant correlations were found in the aged. The aged click ABR amplitudes were found to be lower than would be predicted using a linear regression model of the young, suggesting altered gain mechanisms in the relationship between ABRs and FFRs with age. These results suggest that ABR thresholds, ABR wave amplitudes, and EFRs measure complementary aspects of overlapping neurophysiological processes and the relationships between these measurements changes asymmetrically with age. Hence, measuring all three metrics provides a more complete assessment of auditory function, especially under pathological conditions like aging.

Keywords: frequency-following response, colliculus, aging, brainstem, auditory, ASSR, AMFR, inhibition, central gain, synaptopathy, neuropathy, evoked potential

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INTRODUCTION

Auditory evoked potentials provide a noninvasive neurophysiological metric to measure peripheral and central changes in auditory processing (Picton et al. 1974; Picton et al. 1981; Rowe 1981), depending on the stimulus used and the window of analysis. Auditory brainstem responses (ABRs) are the predominant clinical measure of objec-

tively determining hearing thresholds (Hood 1990; Starr et al. 1996; Thompson et al. 2001). Wave amplitudes measured from ABRs also provide insight into the representation of phasic information to short stimuli, based on clearly defined peaks that have been mapped onto specific generators in the auditory brainstem and midbrain (Lev and Sohmer 1972; Rowe 1981; Chen and Chen 1991). Frequency-following responses (FFRs) to tonal carriers or to the modulation envelope (envelope-following responses or EFRs), though still not widely used in the clinic, are rapidly gaining prominence as a means of assessing processing of complex sounds from the auditory pathway (Cunningham et al. 2001; Aiken and Picton 2008; Swaminathan et al. 2008; Basu et al. 2010; Clinard et al. 2010; Krishnan et al. 2010; Parbery-Clark et al. 2011; Anderson et al. 2012). FFRs and EFRs are evoked in response to longer, often more spectro-temporally complex stimuli (Krishnan 1999, 2002; Krishnan et al. 2004; Swaminathan et al. 2008), and are strongly influenced by rostral brainstem and midbrain generators (Kiren et al. 1994; Kuwada et al. 2002; Akhoun et al. 2010; Chandrasekaran and Kraus 2010; Parthasarathy and Bartlett 2012). They have been used to show differences in processing of complex stimuli under various pathological conditions, such as age-related hearing loss, dyslexia, and autism (McAnally and Stein 1997; Chandrasekaran et al. 2009; Russo et al. 2009; Anderson et al. 2012; Clinard and Tremblay 2013).

Age-related changes in auditory processing occur as a combination of peripheral hearing loss as well as central processing deficits in neuronal coding of temporally complex sounds in the auditory pathway (Hansen and Reskenie 1965; Frisina and Frisina 1997; Gates and Mills 2005). Elderly listeners with normal hearing thresholds still have deficits in complex temporal processing tasks (Dubno et al. 1984; Schneider et al. 1994; Snell and Frisina 2000; Mazelova et al. 2002; Ruggles et al. 2011). Among listeners with matched thresholds, the actual amplitudes of the ABR waves are significantly lower with age (Boettcher et al. 1993; Konrad-Martin et al. 2012). Human studies using FFRs have found changes in neural timing and precision with age (Tremblay et al. 2002, 2003; Clinard et al. 2010; Anderson et al. 2012; Clinard and Tremblay 2013). Changes with age have also been observed at the level of single neurons in terms of decreased temporal coding and changes in rate coding in the dorsal cochlear nuclei (Schatteman et al. 2008), inferior colliculus (IC) (Walton et al. 1998; Palombi et al. 2001; Walton et al. 2002; Walton 2010; Rabang et al. 2012), and auditory cortex (Mendelson and Ricketts 2001) and at a population level using EFRs in rodent aging models (Parthasarathy et al. 2010; Parthasarathy and Bartlett 2011; Parthasarathy and Bartlett 2012).

Various physiological mechanisms have been proposed to explain peripheral and central aspects of age-related hearing loss. In the periphery there is an

observed decrease in the number and function of the hair cells in the cochlea leading to increased hearing thresholds (CHABA 1988) and widened auditory filters (CHABA 1988; Buckiova et al. 2007; Chen et al. 2009; Syka 2010) as well as a reduction in the endocochlear potential of the scala media (Mills et al. 2006) and cochlear synaptic loss (Sergeyenko et al. 2013). These changes are characterized by increases in ABR thresholds and decreases in ABR wave amplitudes at supra-threshold sound levels. Central factors implicated in the age-related loss of temporal processing may be attributed in part to mechanisms that alter the excitability of central auditory neurons in response to reduced peripheral input, as has been shown in cases of conductive hearing loss (Kotak et al. 2003; Miko and Sanes 2009; Sanes and Bao 2009). This may result in changes such as a decrease in GABAergic function seen with age (Caspary et al. 1990). Reduction in GABA would disrupt the balance between excitation and inhibition, which is thought to be essential in maintaining the precise temporal coding properties of neurons (LeBeau et al. 1996; Wang et al. 2000; LeBeau et al. 2001; Caspary et al. 2002; McAlpine and Palmer 2002; Wang et al. 2002; Zhang and Kelly 2003), upsetting the normal relationships between auditory nerve activity and subsequent nuclei in the ascending auditory pathway. FFRs and EFRs which are obtained to complex stimuli and emphasize more central generators (Herdman et al. 2002; Kuwada et al. 2002; Picton et al. 2003; Parthasarathy and Bartlett, 2012) would thus be ideally suited to measure these changes in central auditory processing.

This study focuses on the age-related changes in the relationships between ABR thresholds, ABR wave amplitudes, and EFR amplitudes. Since ABRs and EFRs engage overlapping and distinct neurophysiological processes (e.g., phasic vs. tonic) and measure global changes in auditory processing from the auditory pathway, any differences in ABRs and EFRs observed with age are likely to reflect a subset or a combination of physiological changes. If the processes eliciting ABRs and EFRs are similar, or change symmetrically with age, then any relationships observed in the young would be preserved in the aged, suggesting a general decrease in auditory processing reflected similarly by both ABRs and EFRs. However, if these processes are different, or change asymmetrically with age, then the relationships between these metrics would change as well. This can help provide a better insight into the aberrant auditory processing with age as well as the relationships between ABRs and EFRs.

METHODS

Subjects

Eighteen young (3–6 months, weighing ~275 g) and 21 aged (22–24 months, weighing ~425 g) male

Fischer-344 rats obtained from Taconic were used in this study. The animals were housed in the animal care facility for the period of the study in relatively quiet, standard conditions. All protocols are approved by the Purdue Animal Care and Use Committee (PACUC-1111000167). A subset of these animals (12 young and 10 aged) have been used in a previous study looking at changes in ABRs and EFRs due to different recording montages (Parthasarathy and Bartlett 2012), and these data are included in the analyses performed in this study.

Experimental procedures

The experimental procedures used to obtain the ABRs and EFRs were identical to those described in detail in Parthasarathy and Bartlett (2012). The experiments were conducted in a double-walled sound chamber lined with anechoic foam. The animals were initially anesthetized using isoflurane (4 % induction, 1.5–2 % maintenance) for the placement of subdermal needle electrodes in a two-channel configuration. Then the animals were removed from anesthesia, and an intramuscular injection of dexmedetomidine (Dexdomitor, 0.1–0.2 mg/kg) was administered. Dexmedetomidine is an α -adrenergic agonist that acts as an analgesic and a sedative and is known to not affect auditory responses in the midbrain (Ter-Mikaelian et al. 2007). This maintains the animals in an unanesthetized condition, where they still respond to pain stimuli, like a foot pinch, but are otherwise immobile and amenable for 2 to 3-h recording sessions. The animals were monitored through a video camera, and the recording sessions were discontinued if the animal moved, changed its head position substantially, or showed any signs of discomfort. The positive electrode for channel 1 was placed along the midline of the head, sagittally, in the Fz to Cz position. The second positive electrode for channel 2 was placed horizontally, along the interaural line, above the location of the inferior colliculus. The negative or inverting electrode was placed under the mastoid of the ipsilateral ear facing the speaker, and the ground electrode was placed in the nape of the neck.

The stimulus was presented free-field to the right ear of the animal, at a distance of 115 cm from speaker to ear which resulted in a travel time of 3.35 ms from speaker to ear. Impedances from the electrodes were always less than 1 k Ω as tested using the head-stage (RA4LI, Tucker-Davis Technologies or TDT). Sounds were generated by SigGenRP (TDT). Signal presentation and acquisition was done by BioSig software (TDT). Waveforms were converted to sounds and delivered via a multichannel processor (RX6, TDT) through a Bowers and Wilkins DM601 speaker. The output from the speaker was calibrated free-field, using a Brüel & Kjaer microphone with a

0.25-in. condenser, pointed at frontal incidence to the speaker, from the same location as the animal's stimulated ear, and SigCal (TDT), and was found to be within ± 6 dB for the frequency range tested. Digitized waveforms were recorded with a multichannel recording and stimulation system (RZ-5, TDT) and analyzed with BioSig or custom written programs in MATLAB (MathWorks).

EFRs were recorded in response to sinusoidally amplitude-modulated (sAM) noise carriers at 100 % modulation depth and 200 ms in duration. The acquisition window was 300 ms long, and each response was an average of 200 repetitions. The noise carrier consisted of broadband noise in the 40-Hz to 40-kHz frequency region. The modulation frequency of the stimulus was varied from 16 to 1,024 Hz in half octave steps. The stimuli were presented at peak response level, which was determined as the lowest sound level that produced the maximum EFR for each animal assessed using the amplitude at modulation frequency following a fast-Fourier transform (FFT) of the time-domain response. This typically corresponded to 70–75 dB sound pressure level (SPL) for the young and 80–85 dB SPL for the aged. The FFT amplitudes at various modulation frequencies were used as a measure of phase-locking to assess group differences.

ABRs were recorded using brief broadband click stimuli of 0.1-ms duration or tone stimuli of 2 ms duration varying in sound levels from 95 to 5 dB SPL in 10 dB steps. The frequencies of the tones were varied from 1 to 32 kHz in one-octave steps, and 12 kHz was added to improve the resolution. The stimuli were presented in alternating polarity at 26.6 clicks per second. The acquisition window was 20 ms, and each ABR was an average of 1,500 repetitions. The ABR threshold was calculated for each frequency as the minimum sound level that produced a distinct ABR and reviewed by an independent observer blind to the age of the animals. The click ABR wave amplitudes of waves I and III from channel 1 and I (referred to as I'), IV, and V from channel 2 were calculated as the amplitude of the wave from the baseline, in BioSig, as this was found to be more consistent across recording sessions in this setup, compared to the peak-to-peak amplitudes.

The efficacy of obtaining ABRs and EFRs simultaneously using two different electrode configurations has been previously demonstrated (Parthasarathy and Bartlett 2012). This two-channel configuration allows the measurement of the various ABR waves and the EFRs over a wide range of modulation frequencies with a greater degree of accuracy and sensitivity. Figure 1 (top row) shows the grand averaged ABRs from channel 1 and channel 2 from the young (red) and aged (blue) animals, elicited to broadband click stimuli. The middle and bottom rows show grand averaged EFRs from channel 1 and channel 2 obtained to a sinusoidally

FIG. 1. Grand averaged ABRs and EFRs channel 1 (left column) and channel 2 (right column) for young (red) and aged (blue) animals exhibit complementary waveforms and sensitivities to modulation frequencies. ABR waveforms from animals presented with broadband clicks at peak EFR level, from channel 1 (top, left) and channel 2 (top, right), showing prominent waves I and III in channel 1 and waves I' (labeled I' in subsequent figures), IV, and V from channel 2. EFR waveforms at peak EFR level from animals presented with sAM noise stimuli modulated at 45 Hz AM (middle row) and 256 Hz AM (bottom row) indicated preferential sensitivity to slower modulation frequencies in channel 2 (middle, right) and to faster modulation frequencies in channel 1 (bottom, left). The Y-axis represents amplitudes in microvolts, and the X-axis represents time in milliseconds (includes travel time to the ear).

amplitude-modulated noise carrier at two representative modulation frequencies, presented at peak response level to the young (red) and aged (blue) animals. Channel 1 emphasizes waves I and III of the ABR, and modulation frequencies between 100 and 500 Hz in the EFR, while channel 2 emphasizes waves I', IV, and V of the ABR, as well as amplitude modulation frequencies below 100 Hz in the EFR. The aged animals also show reduced response amplitudes for both ABRs and EFRs.

Statistical analyses

Group differences

Statistically significant group differences were reported for the means of the ABR thresholds, ABR wave amplitudes, and the FFT amplitudes of the EFR, using Wilcoxon's rank-sum test with 5 % significance level for differences between the young and aged animals.

Correlation matrices

In order to study the degree of linear relationship between EFR and ABR variables, the cross-correlation matrices between thresholds, click ABR amplitudes,

and the EFR amplitudes for both the channels were calculated. The entries of the cross-correlation matrices are Pearson's product-moment correlation coefficients between the FFT amplitudes of the EFRs and the ABR amplitudes or the ABR thresholds and the ABR amplitudes. The corresponding two-tailed *P* values were used to test if the cross-correlations are significantly different from zero. The MATLAB[®] in-built function "corr" was used to calculate the correlation matrices for the two channels.

Canonical correlation

Multivariate analyses were performed to look at the relationship between the click ABR wave amplitudes and the EFR FFT amplitudes using the canonical correlation analysis (CCA). CCA measures the strength of the linear relationship between two sets of multidimensional random variables by finding linear combinations of the variables in each set such that the standard Pearson correlation coefficient between them is maximized. These linear combinations are called canonical variates (or linear composites), and the canonical correlation is defined as the maximum bivariate correlation coefficient between the canonical covariates for the two sets of variables. CCA thus provides a way to combine a large number

of cross-correlations into a univariate measure of dependence. It also helps to identify subsets of variables with the maximum linear relationship. The SAS procedure PROC CANNCORR was used to implement CCA using SAS 9.3 between FFT amplitudes of the EFRs and the ABR wave amplitudes.

Regression models

Once the optimum dimensionality of the variable sets was identified, the young and aged animals were compared in terms of the degree of the linear relationship between the corresponding click ABR and EFR variables. The strength of dependence was explored by comparing the predicted values of a linear model fit to the data. A linear model was fit to the young animals' data, with each individual ABR variable as the response variable and a subset of the EFR variables as the explanatory variable using PROC REG in SAS[®] 9.3. The estimated coefficients for the linear model for the young animals were used to predict the ABR variables for the aged animals using the EFR variables as covariates. The prediction of ABR variables using the estimates from the young linear model was done using PROC SCORE in SAS[®] 9.3.

RESULTS

Hearing thresholds assessed using ABRs

The hearing thresholds were assessed using ABRs for broadband clicks as well as tone pips of various frequencies from 1 to 32 kHz. The thresholds were within 5 dB SPL between the two channels. Figure 2 shows the auditory thresholds for young (red) and aged (blue) animals from channel 1. The ABR thresholds significantly increased with age for all the stimuli tested ($p < 0.05$,

FIG. 2. ABR thresholds for broadband clicks and pure tones of various frequencies indicate a significant increase in thresholds with age. The Y-axis represents ABR thresholds in decibels SPL; the X-axis represents type and frequency (in kHz) of stimuli presented for young (red) and aged (blue) animals. Error bars indicate standard error, and asterisks indicate statistically significant differences ($p < 0.05$, rank-sum test).

Wilcoxon's rank-sum test). For the broadband click stimuli, there was a loss of ~15 dB with age. For the lower frequency tones, of 1 and 2 kHz, the aged animals exhibited a loss of ~25 dB. At 8 kHz, the most sensitive region of the rat's hearing, the hearing loss was closer to 10 dB. In the higher frequencies of 16 and 32 kHz, the aged animals exhibited a typical high frequency hearing loss, with increases in thresholds up to 40 dB.

Click ABR wave amplitudes

Figure 3 shows the amplitudes of the various ABR waves obtained to broadband click stimuli. Waves I and III were measured from channel 1, and waves I (hence denoted as I'), IV, and V were measured from channel 2. There was a significant decrease in the ABR amplitudes for all the waves with age ($p < 0.05$, Wilcoxon's rank-sum test), compared to the young, at peak EFR response level, where the sound level of presentation was typically 10–15 dB higher for the aged animals (Fig. 3A) and when measured 30 dB above click threshold for each animal (Fig. 3B). Panels C–G of Figure 3 show the growth of the various click ABR wave amplitudes with increasing sound level. The young animals exhibited significantly higher wave amplitudes for all waves measured, for all sound levels above threshold, compared to the aged animals ($p < 0.05$, Wilcoxon's rank-sum test).

Temporal modulation transfer function assessed using EFRs

Figure 4 shows the temporal modulation transfer function, with the amplitude modulation frequency in the X-axis and the FFT amplitude at modulation frequency along the Y-axis. Modulation frequencies below 100 Hz AM were selected from channel 2 and above 100 Hz from channel 1, to maximize the response amplitudes for the various frequencies, as seen in Parthasarathy and Bartlett (2012). Significant decreases in phase-locking as measured by the FFT amplitudes were observed with age, primarily for modulation frequencies above 100 Hz AM ($p < 0.05$, Wilcoxon's rank-sum test). The overall shape of the temporal modulation transfer function (tMTF) was unchanged with age, exhibiting a low-pass behavior with amplitudes decreasing with increasing AM frequencies.

Correlation between ABR thresholds and wave amplitudes

The correlations between the click ABR thresholds and the ABR wave amplitudes and age-related changes in them were measured. Thresholds were calculated at 5-dB steps. In the young, the thresholds within the group exhibited very little variability with most

FIG. 3. Click ABR wave amplitudes reveal a significant decrease with age. Aged animals (blue bars) showed a significant decrease in click ABR wave amplitudes measured at peak EFR level (A) and at 30 dB above individual click thresholds (B) compared to the young (red bars). The Y-axis indicates wave amplitudes in microvolts, and the X-axis indicates ABR waves. C–G show growth of ABR amplitudes with sound level for the various waves and significant

decreases in the amplitudes in the aged (blue) compared to the young (red) at all sound levels above threshold. The Y-axis shows wave amplitudes in microvolts, and the X-axis indicates the sound level of the click stimuli in decibels SPL. Error bars indicate standard error, and asterisks indicate statistically significant differences ($p < 0.05$, rank-sum test).

young animals exhibiting a threshold of 35 dB SPL for click stimuli. The thresholds for the aged animals

were more variable, ranging from 45 to 75 dB SPL, with the majority of the animals exhibiting a threshold of 55 dB SPL (Fig. 2). The amplitudes of the ABR waves exhibited much more variability than the thresholds within the young and the aged animals (compare to Fig. 3). Figure 5 shows the heatmap of the cross-correlation matrix, with significant correlations in color and the nonsignificant correlations in gray scale. As can be seen from the figure, there were no significant correlations between the click ABR thresholds and the ABR amplitudes of any of the waves for the young or the aged animals.

Correlation between the ABR wave amplitudes and EFR amplitudes

Correlation matrices

Figure 6 shows the heatmap of the correlation matrix between the amplitudes of the dominant waves of the click ABRs in each channel and the FFT amplitudes at modulation frequency from the EFRs for young and aged animals. Similar to Figure 5, the significant R values are shown in color, while the insignificant R values are shown in gray scale. In the young animals, the amplitude

FIG. 4. Temporal modulation transfer functions show decreases in phase-locking primarily for faster modulation frequencies. FFT amplitudes of the envelope-following responses at modulation frequencies for young (red) and aged (blue) animals presented with sinusoidally amplitude-modulated noise carriers presented at peak response level. The Y-axis indicates FFT amplitudes in millivolts, and the X-axis indicates modulation frequency in hertz on a log scale. Error bars indicate standard error, and asterisks indicate statistically significant differences ($p < 0.05$, rank-sum test).

FIG. 5. No significant correlations were observed between click ABR thresholds and wave amplitudes in young and aged animals. The *plot* shows the heatmap of cross-correlation matrices between click ABR thresholds (Y-axis) and wave amplitudes (X-axis) for young

(top) and aged (bottom) animals. Significant correlations ($p < 0.05$) are shown in color (none were present in this case), and nonsignificant correlations are shown in grayscale.

of wave I, generated from the auditory nerve, is significantly correlated with the EFR amplitudes ranging over a wide variety of AM frequencies in both channels 1 and 2 (Fig. 6A, C). The amplitude of wave III, thought to be generated from the cochlear nucleus, is significantly correlated with a range of frequencies only in the 100–500-Hz region, the sensitive region of EFRs in channel 1 (Fig. 6A). Wave IV and V amplitudes, whose generators are thought to be the superior olivary complex and the midbrain, are significantly correlated with EFR amplitudes to AM frequencies primarily below 100 Hz, the sensitive region of EFRs in channel 2 (Fig. 6C).

In the aged animals, there were no significant correlations between the ABR amplitudes of waves I or III and the EFR amplitudes at any modulation frequency (Fig. 6B). A significant correlation was observed between the ABR amplitudes of wave IV in the aged for modulation frequencies ≤ 64 Hz in the aged. These, however, generally exhibited smaller correlation values (Fig. 6D).

Canonical correlation

In order to look more quantitatively at the multivariate relationships between the EFR amplitudes and

the click ABR wave amplitudes, and to reduce the occurrence of type I errors, canonical correlations were analyzed between the wave amplitudes of the ABRs and the EFR amplitudes in each channel (Rao 1973; Mardia et al. 1979). CCA is advantageous over more traditional methods of correcting for type I errors such as the more stringent Bonferroni correction, which does not take into account the correlation structure between the different test statistics, i.e., different modulation frequencies or ABR values. The CCA takes into account the correlation structure and automatically adjusts for the multiplicity through degrees of freedom in the numerator and denominator of the F statistics.

A CCA was performed between the click ABR amplitudes and the EFR amplitudes from the sensitive regions of the tMTF for each channel (ABR waves I', IV, and V and modulation frequencies between 16 and 90 Hz AM for channel 2, waves I and III, and modulation frequencies between 128 and 1,024 Hz AM for channel 1). Canonical correlation analysis revealed significant correlations in the young for both channel 1 and channel 2 between ABR and EFR amplitudes. However, in the aged, similar to the correlation matrix, no significant correlations were

FIG. 6. Young animals showed greater correlations between the click ABR amplitudes and EFR amplitudes compared to the aged. The *plot* shows the heatmap of cross-correlation matrices between click ABR amplitudes and the EFR amplitudes for channel 1 (A, B) and channel 2 (C, D), for young (A, C) and aged (B, D) animals. The Y-axis represents ABR waves, and the X-axis represents EFRs for various modulation frequencies. Significant correlations ($p < 0.05$) are shown in color, and nonsignificant correlations are shown in grayscale.

TABLE 1

Canonical correlations between the ABR amplitudes and EFR amplitudes, as well as their corresponding F and p values for young and aged animals from the two channels

Test case	Canonical correlation	Standard error	F value	Num DF	Den DF	$Pr > F$ (p)
Young ch 1	0.8721	0.0877	3.06	14	18	0.014
Young ch 2	0.8859	0.0538	3.07	18	23.11	0.0062
Aged ch 1	0.8381	0.0795	1.08	14	12	0.45
Aged ch 2	0.9095	0.0462	1.57	10	17.46	0.17

found between the ABRs and the EFRs in any case. The correlation values for the best models in young and aged animals are given in Table 1. Similar results were obtained when CCA was performed using the prominent ABR waves and all the modulation frequencies from each channel (data not shown).

Each F value in Table 1 corresponds to the test that all the canonical correlations for that channel are zero. A higher F value (or a lower p value) indicates departure from the null hypothesis that all the canonical correlations equal zero and a lower F value (or a higher p value) indicates failure to reject the null hypothesis. From the table above, it can be seen that for young channel 1 and channel 2, the F values are relatively larger, implying the presence of at least one significant canonical correlation, with the p values being 0.014 and 0.0062. However, for both the aged channels, the F values are lower and the p values are 0.45 and 0.17, respectively—i.e., we fail to reject the null hypothesis and conclude that all the canonical correlations for the aged channels are zero. It should be noted that a higher value of the raw canonical correlation coefficient does not alone guarantee significance, as the final F value depends on the standard errors as well. For example, the channel 2 data from the aged animals do not show any significance, in spite of having a higher canonical correlation value than the others, because of its lower standard error.

Model prediction for aged ABR amplitudes

A linear regression model was created modeling the click ABR wave amplitudes based on the EFR amplitudes in the young. Using the coefficients of the model from the young animals, the aged EFR amplitudes were used to predict the aged ABR amplitudes that would be present if the aged animals followed a similar relationship between the ABRs and the EFRs as in the young.

Waves I and III from channel 1 and waves I', IV and V from channel 2 were used, along with their respective EFR amplitudes. Figure 7 shows the observed values for the click ABR amplitudes in young (red) and aged (blue) animals, as well as the

predicted ABR values from the linear regression model for the aged (green). The predicted ABR amplitudes were significantly higher than the observed ABR amplitudes for the aged, for waves I, I', III, and IV ($p < 0.01$, Wilcoxon's signed-rank test). Comparing the young ABR amplitudes with the predicted ABR amplitudes for the aged, there was no significant difference between the two for wave I amplitudes in either channel ($p > 0.05$, Wilcoxon's rank-sum test). However, the predicted amplitudes of waves III, IV, and V in the aged were significantly lower than the observed young amplitudes ($p < 0.05$, Wilcoxon's rank-sum test).

DISCUSSION

Consistent with previous studies (Jerger and Hall 1980; Hunter and Willott 1987; Boettcher et al. 1993;

FIG. 7. Predicted values for aged ABR amplitudes are significantly higher than the observed values for the aged. Bar graph showing observed click ABR amplitudes for the various waves in young (red) and aged (blue) animals as well as predicted aged ABR amplitudes (green) using coefficients of a linear regression model constructed using the young ABRs and EFRs. The Y-axis shows ABR wave amplitudes in microvolts, and the X-axis shows the various ABR waves from both channels. Error bars indicate standard error, and asterisks indicate statistically significant differences ($p < 0.05$, rank-sum test).

Boettcher 2002), in this study, the ABR thresholds increased with age, with a sloping high frequency hearing loss of up to 40 dB in the higher frequencies (Fig. 2). This audiogram is typically found in studies where animals are raised in standard laboratory conditions and have not experienced significant noise exposure (Mills et al. 1990; Suta et al. 2011). Auditory steady state responses (ASSRs) have been used to estimate thresholds instead of ABRs in human clinical populations (Herdman and Stapells 1999; Firszt et al. 2003; Johnson and Brown 2005; Scherf et al. 2006; Lin et al. 2009) and in some studies have been observed to correlate better to behavioral hearing thresholds (Rance et al. 2005). The EFR thresholds observed in this study were typically higher than the ABR thresholds (data not shown), similar to observations made in humans (Cone-Wesson et al. 2002). A uniform decrease in the click ABR wave amplitudes was observed with age, when the stimuli were presented both at peak EFR response level (Fig. 3A) and at 30 dB above click threshold (sensation level) for each animal (Fig. 3B) suggesting a decrease in the number or ability of the neurons representing these brief phasic stimuli. A decrease in the phase-locking amplitude of the EFRs at higher modulation frequencies with age, observed in earlier studies (Parthasarathy et al. 2010; Parthasarathy and Bartlett 2012), was present in this study as well (Fig. 4), along with a slightly greater deficit in phase-locking to modulation frequencies 32 Hz and below, compared to previous studies.

There were no correlations observed between the hearing thresholds and any of the wave amplitudes in either the young or the aged animals (Fig. 5). This suggests that ABR thresholds are largely independent of wave amplitudes and reflect only the minimum response rather than predicting the maximum capacity to respond. A recent study has also shown the reduction in ABR wave amplitudes with age, corresponding to the loss of synaptic strength in the auditory nerve and the number of spiral ganglion cells, much prior to changes seen in hearing thresholds (Sergeyenko et al. 2013). Hence, the thresholds, which measure the lowest detectable level of activity, seem to be indicative of the sensitivity of level coding and detection of sound, while the ABR wave amplitudes, especially at peak response level, seem to be indicative of the number and synchronicity of the neurons in effectively representing these phasic stimuli at their highest capacity.

The wave amplitudes of ABRs elicited to click stimuli were highly correlated with the EFR amplitudes for various AM frequencies in young rats (Fig. 6). The amplitude of wave I was correlated with various AM frequencies from 22 to 512 Hz AM. Wave III was correlated strongly with AM frequencies in the 100–500-Hz region, while wave IV and V were correlated with

AM frequencies below 100 Hz (Fig. 6), consistent with declining maximal synchronization frequencies as one ascends the auditory pathway (reviewed in Joris et al. 2004) and with increasingly more central generators of later ABR waves (Lev and Sohmer 1972; Buchwald and Huang 1975; Hashimoto et al. 1981). Multivariate analysis using canonical correlations showed a strong correlation between the click ABR waves and the sensitive AM frequency regions of each channel in the young (Table 1). In the aged, even though both the ABR amplitudes and the EFR amplitudes showed a significant decrease, the changes in ABR and EFR amplitudes were not correlated with each other (Fig. 6). Multivariate analysis also showed no significant correlations between the click ABR wave amplitudes and the EFRs in the aged (Table 1). These results suggest that unlike the young brain, in the aged, the neural synchrony required in representing phasic stimuli and temporally complex, sustained stimuli becomes decoupled.

To estimate the direction of decoupling in aged animals, the coefficients of the linear regression model that best fit young ABR and EFR amplitudes were used to predict the ABR values from EFR responses in aged animals. Predicted ABR values were then compared with the measured values. Interestingly, the predicted ABR amplitudes for waves I and I' in the aged were significantly higher than observed values but were not significantly different from the young ABR amplitudes. The predicted values for waves III and IV were also significantly higher than the measured responses in the aged (Fig. 7) although they were significantly lower than the observed values in the young. One potential reason for this decoupling could be changes in the relative number of neurons representing each kind of stimulus at different levels of the auditory pathway. Previous studies have reported a decrease in the relative number of IC neurons that respond to sAM stimuli in a temporally sustained manner in aged animals, and an increase in the number of onset-only IC neurons, resulting in altered coding of envelope periodicities, with minimal change in transient onset rates (Palombi and Caspary 1996; Walton et al. 2002; Rabang et al. 2012). Hence, using the IC as an example generator, if many of the neurons contribute to the click ABR, and a subset of these also contribute to the temporally sustained EFR, then these two metrics would be correlated in the young. The size of the subset will be dictated by mechanisms such as inhibition that shape the modulation frequency selectivity of IC neurons. Thus, although there may be a decrease in the proportion of neurons responding in a sustained manner with age, potentially a loss of selectivity can explain how predicted ABR values are much larger than measured ABR values in aged animals given their EFR responses. The

loss of selectivity would permit a much greater number of neurons to respond to the NAM stimulus, similar to what has been observed in aged gerbils (Khouri et al. 2011), and therefore restore the amplitude of the EFR even with diminished ascending input and reduction of sustained activity.

Impaired selectivity in aged IC neurons could result from altered gain control mechanisms in the central auditory pathway. The balance between excitation and inhibition is maintained by homeostatic mechanisms in many areas of the brain (Poo 2001; Turrigiano 2008; Turrigiano 2012) including the central auditory pathway (Kotak and Sanes 2003; Miko and Sanes 2009; Sanes and Bao 2009). When the proper balance is disrupted by perturbations such as age or conductive hearing loss, there are multiple potential mechanisms that may contribute to compensate these responses. In many cases, GABAergic inhibition is known to decrease (Kotak et al. 2003; Caspary et al. 2008). In addition, there may be nonsynaptic mechanisms by which the balance can be altered, such as changes in chloride, calcium, and potassium channels that have been implicated in sensorineural hearing loss (Kharkovets et al. 2000; Vale et al. 2003; Liu and Kaczmarek 2005; Cui et al. 2007; Miko and Sanes 2009). However, these compensatory mechanisms may not work efficiently, especially under complex listening conditions like rapid modulation frequency, reduced modulation depth, or the presence of background noise where the signal to noise ratio is already reduced. Such age-related changes have been observed previously using EFRs (Parthasarathy et al. 2010; Parthasarathy and Bartlett 2011).

Certain experimental factors need to be considered while interpreting the results from this study. Given the comparative nature of the study, and that the young and aged animals were maintained at similar experimental conditions, any effects due to the free-field presentation of the stimulus, the use of dexmedetomidine, and electrode positions are expected to be minimal. The specific stimulus properties including spectral content, sound level, and repetition rates have a substantial impact on the ABR and EFR amplitudes. In this study, for young and aged animals, the ABR and EFR were compared at the same sound level. At the repetition rate of 26.6 Hz, there are no differential age-related decrements in ABR amplitudes (Burkard and Sims 2001). The 0.1-ms click duration was chosen to be consistent with other animal and human studies (Rowe 1978; Sand 1991; Backoff and Caspary 1994; Popelar et al. 2006; Parthasarathy et al. 2010). Though the exact spectral content of the 0.1-ms clicks and sAM noise are different, both are broadband stimuli, and the correlations observed likely measure the relationship between the phasic synchrony of the ABRs and the

sustained temporal processing of the EFRs. The difference in the weights of the animals, between the young and the aged, is primarily due to changes in body mass, with minimal change in the skull growth (Wright et al. 1966; Hughes et al. 1978) or the organ weight of the brain (Marino 2012). Hence, this should also have a minimal effect on changes in ABR and EFR amplitudes seen with age. All the animals used in the current study were male. Since sex effects have been observed across species both in ABRs as well as EFRs (Jerger and Hall 1980; Eggermont and Don 1982; Krizman et al. 2012; Gall et al. 2013), the presence of such effects with these stimuli and any changes with age remain a valid avenue of investigation. The canonical correlations used in this study are sensitive only to the presence of a linear relationship amongst the variables. Hence, from this study, it can be interpreted that there exists a highly significant linear relationship between the click ABR wave amplitudes and the EFR amplitudes for sAM noise stimuli in the young and this linear relationship is not significant in the aged (Table 1). The existence of a nonlinear relationship between these variables and its changes with age remain to be explored. Figure 7 demonstrates how the aged neurons deviate from the linear model in the young, with EFR amplitudes that significantly overestimate ABR amplitudes.

This study further provides evidence of the complementary sensitivity of our two channel recordings (Parthasarathy and Bartlett 2012). Despite the larger amplitudes from wave I' and the steeper slope of the growth function compared to wave I, thresholds were similar between wave I and I' (Fig. 3). Channel 1 also had a prominent wave III while channel 2 had prominent waves IV and V. Channel 1 ABRs and EFRs are correlated tightly with each other in the young, primarily in its most sensitive region of 100–500 Hz, while channel 2 ABRs and EFRs are correlated tightly in the most sensitive region of that channel, less than 100 Hz. These also provide further insight into the relative contribution of the different generators for the EFR response, with the generator of wave I, the auditory nerve, contributing to the EFRs across a wide range of modulation frequencies and subsequent ascending generators contributing to decreasing AM frequency ranges in the young.

Overall, the ABR thresholds, the ABR wave amplitudes, and the EFRs seem to represent differing aspects of ongoing neurophysiological processes. The ABR thresholds are an indicator of sound sensitivity, outer hair cell function, and the presence of a minimal number of functional auditory nerve synapses (Boettcher 2002; Kujawa and Liberman 2009; Konrad-Martin et al. 2012). The ABR wave amplitudes are an indicator of overall auditory neuronal number and short-term synchrony of each generator and are a better

predictor of peripheral synaptic function than ABR thresholds (Kujawa and Liberman 2009; Sergeyenko et al. 2013). The FFRs and EFRs are an indicator of sustained temporal processing, emphasizing the functions of more central generators (Kuwada et al. 2002; Parthasarathy and Bartlett 2012), given a normal or altered number of hair cells and ribbon synapses, and have been observed to be better predictors of speech perception in quiet and in noise (Anderson et al. 2013). Measuring all three metrics would provide a better understanding of an individual's auditory capacity, enabling the design of effective interventional strategies based on the kind of deficits seen for that particular pathology. Moreover, these results suggest that the central auditory system boosts impoverished auditory nerve responses to attain a regulated final level of excitation, potentially at the expense of response precision, but the mechanisms by which they accomplish this longer-term gain adjustment are not known.

ACKNOWLEDGMENTS

This study was supported by grants from the National Institutes of Health (NIDCD R01DC011580) and the American Federation for Aging Research (AFAR).

Conflict of Interest

The authors declare that they have no conflict of interest.

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