Published in final edited form as:
Hear Res. 2010 June 1; 264(1-2): 48–55. doi:10.1016/j.heares.2009.11.010.

Aging alters the perception and physiological representation of frequency: Evidence from human FFR recordings*

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Abstract

Older adults, even with clinically normal hearing sensitivity, have auditory perceptual deficits relative to their younger counterparts. This difficulty may in part, be related to a decline in the neural representation of frequency. The purpose of this study was to examine the effect of age on behavioral and physiological measures of frequency representation. Thirty two adults (ages 22 – 77), with hearing thresholds ≤ 25 dB HL at octave frequencies 0.25 – 8.0 kHz, participated in this experiment. Frequency discrimination difference limens (FDLs) were obtained at 500 and 1000 Hz using a two-interval, two-alternative forced choice procedure. Linear regression analyses showed significant declines in FDLs at both frequencies as age increased. Frequency-following responses (FFRs) were elicited by 500 and 1000 Hz tonebursts, as well as at frequencies within and outside those FDLs. Linear regression of FFR phase coherence and FFR amplitude at frequencies at and slightly below 1000 Hz showed significant decreases as age increased. Therefore, pitch discrimination, as measured by FDLs, and neural representation of frequency, as reflected by FFR, declined as age increased. Although perception and neural representation concurrently declined, one was not predictive of the other.

Keywords

aging; frequency discrimination; frequency-following response; FFR; auditory evoked potentials; auditory brainstem

1. Introduction

Many older adults have difficulty understanding speech, especially in the presence of background noise (Dubno et al., 1984; Pichora-Fuller et al., 1995;Frisina and Frisina, 1997). Older adults frequently report, “I can hear you but I can’t understand you.” Because speech is

*Portions of these data were presented at the 2009 International Evoked Response Audiometry Study Group Meeting in Rio de Janiero, Brazil and at the 2009 Aging and Speech Communication: An International and Interdisciplinary Research Conference in Bloomington, IN, USA.

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a complex signal, composed of multiple time-varying acoustic cues, one explanation for impaired speech understanding is that aging adversely affects the ability to process temporal cues (Frisina and Frisina, 1997).

Age-related declines in temporal resolution have been documented, in humans, with perceptual studies using: gap-detection thresholds (Schneider and Hamstra, 1999), voice onset time (VOT) discrimination (Tremblay et al., 2003), duration discrimination (Gordon-Salant et al., 1999), temporal modulation transfer functions (He et al., 2008), interaural timing differences (Strouse et al., 1998; Ross et al., 2007), and masking level differences (Strouse et al., 1998). Human physiological studies have also documented age-related changes in temporal resolution in response to silent gaps in noise (Poth et al., 2001), VOT (Tremblay et al., 2002; Tremblay et al., 2003), sound duration (Ostroff et al., 2003) amplitude-modulated (AM) tones (Leigh-Paffenroth and Fowler, 2006), AM noise (Purcell et al., 2004), as well as interaural timing cues (Ross et al., 2007). Animal models of auditory aging have suggested several physiologic mechanisms which may be related to at least some of these declines in temporal resolution. They include: 1) decreased neural inhibition (e.g. Caspary et al., 2005), 2) temporal jitter, or greater variance, affecting neural firing and synchrony (Pichora-Fuller and Schneider, 1992; Frisina and Frisina, 1997; Pichora-Fuller et al., 2007) and 3) longer neural recovery time (Walton et al., 1998). It should also be noted that decreased numbers of neurons in auditory nuclei also occur with increasing age (Frisina and Walton, 2006).

Although many studies have documented age-related declines in temporal resolution, fewer studies have examined spectral processing. Spectral information is important because it conveys suprasegmental information, such as prosody that helps to indicate the emotional state of the speaker or whether a sentence is a question or statement. Spectral information also conveys acoustic/phonetic information, such as formant transitions, used to differentiate vowels as well as consonant-vowel syllables. A decline in the ability to process acoustic properties (e.g. periodicity and temporal fine structure) could therefore contribute to impaired speech perception (Rosen, 1992; Leek and Summers, 2001; Elhilali et al., 2004; Drennan et al., 2007; Hopkins et al., 2008).

Much of what is known about the effect of age on spectral processing, in humans, has been documented using perceptual tasks. For example, frequency discrimination and frequency modulation detection studies have consistently reported age-related deficits that are more prevalent at lower frequencies, such as 500 and 1000 Hz, than at higher frequencies, such as 2000 and 4000 Hz (Konig, 1957; Abel et al., 1990; Moore and Peters, 1992; Humes, 1996; He et al., 1998; Espinoza-Varas and Jang, 2006; He et al., 2007). One interpretation of this frequency effect is that age-related declines in neural synchrony contribute to poor perception since frequency coding, at about 1000 Hz and below, is thought to be robustly represented by phase locking (Palmer and Russell, 1986).

Age-related declines in neural synchrony in the human auditory system have also been inferred through the use of auditory evoked potentials (AEPs). One frequently used auditory cortical evoked response is the P1-N1-P2 complex, and age-related differences affecting its latency and amplitude have been reported (Pfefferbaum et al., 1980; Tremblay et al., 2002; Ostroff et al., 2003; Tremblay et al., 2003; Tremblay et al., 2004; Harkrider et al., 2005; Harris et al., 2007; Ross et al., 2007; Harris et al., 2008; Ross and Tremblay, 2009). A recent study by Harris et al. (2008) used cortical P1-N1-P2 AEPs evoked by changes in frequency, and reported that the P1-N1-P2 change responses of the older group were less sensitive to frequency changes than those of the younger group. Moreover, the absence and/or presence of the physiological change response related well to frequency modulation detection perceptual thresholds. Although the presence of an AEP change response indicates that a stimulus change was physiologically discriminated, its presence neither quantifies the quality of stimulus encoding

nor indicates if subcortical age-related changes, such as reduced neural synchrony, contribute to elevated cortical thresholds in older adults.

Subcortical age-related biological changes have been documented using the auditory brainstem response (ABR) (for a review see Tremblay and Burkard, 2007). In animals and in humans, decreased neural synchrony, sometimes referred to as temporal jitter, is believed to contribute to some of the perceptual problems and abnormal ABR patterns seen in older populations (e.g. Pichora-Fuller et al., 2007). The click-evoked ABR, however, is a gross measure of time-locked neural activity in response to stimulus onset. It does not reflect how well sustained features of a stimulus are encoded. In contrast, the frequency-following response (FFR) is a steady-state AEP that is sensitive to sustained features within a stimulus and is dependent on the integrity of phase-locked neural activity in the auditory brainstem (Worden and Marsh, 1968). The FFR reflects the fine structure and/or the temporal envelope of the stimulus. It is also highly sensitive to the spectral characteristics of a stimulus.

In humans, the FFR has been used to study subcortical representations of sinusoids (Moushegian et al., 1973; Davis and Hirsh, 1976; Sohmer et al., 1977), tonal sweeps (Krishnan and Parkinson, 2000), two-tone approximations of vowels (Krishnan, 1999), synthetic steady-state vowels (Krishnan, 2002), synthetic consonant-vowel stimuli (Plyler and Ananthanarayan, 2001; Russo et al., 2004; Krishnan et al., 2005), pitch encoding of lexical tones (Krishnan et al., 2004; Wong et al., 2007), naturally-produced vowels (Aiken & Picton, 2008), as well as static and dynamic spectral-ripple stimuli (Swaminathan et al., 2008). Although many people with impaired communication abilities are older, there has been no published report of how, or if, the FFR is affected by biological aging, even when elicited by simple stimuli such as sinusoids. Moreover, it is unknown what the brain-behavior relationship is when behavioral (frequency discrimination) and physiologic (FFR) procedures use the same stimuli.

For these reasons, the purpose of this study was to characterize the effect of age on the perception and neural representation of simple stimuli such as tones. The aims were: 1) to characterize the effect of age on the perception of frequency, as reflected by frequency discrimination difference limens (FDLs) at 500 and 1000 Hz, 2) to characterize the effect of age on the neural representation of frequency, as reflected by FFR phase coherence (PC) and amplitude, and 3) to identify any relationship between the perceptual and physiologic measures. It was expected that FDLs would become poorer at both frequencies as age increased and that FFR phase coherence (PC) and amplitude would decrease at all frequencies as age increased. Moreover, it was hypothesized that subjects with poor FFR PC would be the same subjects with poor FDLs and that FFRs evoked by stimuli that are easily discriminated would appear more distinct from each other than when evoked by stimuli that were indiscriminable.

2. Materials and Methods

2.1. Subjects

Thirty two subjects (ages 22 – 77; 4 male, 28 female) participated in the 1000-Hz range conditions; 28 of these subjects (ages 22 – 77; 4 male, 24 female) also participated in the 500-Hz range conditions. All subjects had clinically normal hearing sensitivity, defined as thresholds ≤ 25 dB HL at octave frequencies from 250 – 8000 Hz. There were approximately five subjects per age decade. All subjects were native, monolingual English speakers, had normal tympanometric measures, had no history of otological or neurological disorders, and were not taking interfering prescription medications. All procedures in this study were approved by the institutional review board at the University of Washington.

2.2. Stimuli

Stimuli for the behavioral and physiological conditions were tonebursts of 500-ms duration, including 15-ms rise/fall time with a hanning window. Onset polarity was positive. Tones were generated with a sampling frequency of 44.1 kHz. A magnetically shielded ER3-A insert earphone delivered stimuli to the right ear at 80 dB SPL for both the behavioral and physiological conditions. Calibration was performed with a Bruel and Kjaer type 2250 sound level meter, a type 4192 half-inch microphone, and a 2 cc coupler.

2.3. Behavioral Procedure

Frequency discrimination methods were based on those of Olsho et al. (1988). Frequency discrimination was tested separately at 500 Hz and 1000 Hz using an adaptive two-interval, two-alternative forced choice procedure with a two-down, one-up adaptive rule (Levitt, 1971). A custom Matlab (version 7.5; MathWorks, Natick, MA) program was developed for this procedure. For each trial, a warning light with 500-ms duration preceded each pair of tones. One of the tones was always the test frequency (e.g. 1000 Hz); the other tone was always lower than the test frequency by a given amount, Δf. The order of the tones for each trial was randomized. Inter-stimulus interval was 500 ms. Subjects were instructed to mouse-click on a button on a computer monitor corresponding to the tone that had the higher pitch. Following the subject's selection, the button that corresponded to the interval that had the higher pitch would briefly light up to indicate the correct interval. The first trial had a large Delta;*f* of 5 %, corresponding to 25 and 50 Hz for 500 and 1000 Hz, respectively, and was discriminated by all subjects. If the subject answered two consecutive trials correctly, Delta;*f* decreased by half the previous value; conversely, Delta;*f* doubled following each incorrect answer. The procedure continued until there were ten reversals. The mean of the last eight reversals was taken as the frequency discrimination threshold. FDLs were obtained by calculating Delta;*f*/*f*. FDLs for 500 Hz were obtained on a separate session from the 1000-Hz FDLs. All testing was performed in a double-walled, sound-attenuating booth.

2.4. Physiology Procedure

FFRs were collected using a single-channel recording (Aiken and Picton, 2008; Krishnan, 1999; Krishnan and Parkinson, 2000; Krishnan et al., 2005; Swaminathan et al., 2008) with a Neuroscan Synamps2 acquisition system. FFRs were recorded from Cz (vertex) to the nape-of-the-neck, and the ground electrode was located on the left mastoid. Inter-stimulus interval (ISI) was 513 ms, similar to the ISI of the frequency discrimination task. Online EEG filters were 100 – 3000 Hz. Analysis time window was 0 – 520 ms. Analog-to-digital sampling rate was 20 kHz. One thousand individual artifact-free responses, or sweeps, were collected to each stimulus. Artifact rejection was performed online, rejecting any sweeps with voltage exceeding ± 30 μV. Electrode impedances were below 1 kΩ. During testing, subjects were in a double-wall, sound-attenuated booth, comfortably seated in a reclining chair and were instructed to relax quietly. A five-minute break followed each physiology condition. FFRs were collected separately to each of six frequencies: 463, 499, 500, 925, 998, and 1000 Hz.

FFR data was analyzed offline in two traditional ways: amplitude and PC (Batra et al., 1986; Dobie and Wilson, 1989; John et al., 1998; Levi et al., 1995). Amplitude indicates the averaged magnitude of the neural response. PC indicates the degree of phase locking to the stimulus frequency and is independent of response amplitude. Both analyses were performed on the output of a fast Fourier transform (FFT) and were used as statistical detection algorithms to verify response presence. Custom Matlab programs were developed for these calculations. Consecutive pairs of sweeps were concatenated to obtain FFT resolution of 0.96 Hz (John et al., 1998). Amplitude was calculated by averaging the concatenated sweeps (500 double-sweeps) and submitting the average to an FFT. Each stimulus frequency was precisely specified using coherent sampling, which limits the FFR to one bin, or point, in the FFT output; each

stimulus frequency had an integer number of cycles in the analysis window. FFR amplitude was obtained from the FFT bin where the averaged response was located, if present; for an example of amplitude, see figure 1.

Background noise was estimated as the mean of five FFT bins above and below the response FFT bin, corresponding to ± 5 Hz. Using these amplitude and noise measures, the resulting signal-to-noise ratio was used as an F-ratio with 2, 20 degrees of freedom (Zurek, 1992; Dobie and Wilson, 1996). A p-value <0.05 determined if the FFR amplitude was significantly greater than the surrounding background noise and would indicate that a response was present or absent. PC was calculated using the non-averaged, concatenated sweeps. The sweeps were submitted to an FFT analysis and phase data from the stimulus frequency's FFT bin was compared across sweeps to statistically determine the degree of phase locking to the stimulus frequency (Dobie and Wilson, 1989). PC values range from 0 to 1, where a value of 0 would indicate random phase across sweeps, or no phase locking, and a value of 1 would indicate perfect phase locking. The Rayleigh test (Fisher, 1993) was used to assess circular uniformity and response presence was indicated by a p-value < 0.05.

3. Results

3.1. Frequency Discrimination

Simple linear regression analyses were used to examine the effect of age on FDLs, where the FDL at either 500 or 1000 Hz was the dependent variable and age was the independent variable. Prior to regression analyses, FDLs were log-transformed to normalize their frequency distribution. Age was significantly predictive of the 500-Hz FDL, $t(26) = 3.35$, $p = .002$, $R^2 = .30$, as well as the 1000-Hz FDL $t(30) = 2.59$, $p = .015$, $R^2 = .18$. At both 500 and 1000 Hz, FDLs became significantly poorer as age increased (Figure 2).

3.2. Frequency-Following Response

The effect of age on the neural representation of frequency was assessed using simple linear regression analyses with PC or amplitude as the dependent variable and age as the independent variable. Figure 3 shows PC and amplitude data for 463, 498, and 500-Hz FFR conditions. PC analyses indicated that age was not significantly predictive of FFR PC at these frequencies [463 Hz, $t(26) = -.63$, $p = .535$, 498 Hz, $t(26) = -0.36$, $p = .722$, or 500 Hz, $t(26) = -1.66$, $p = .110$]. There was no significant effect of increasing age according to FFR amplitude values [463 Hz, $t(26) = -1.10$, $p = .283$, 498 Hz, $t(26) = -.78$, $p = .443$, or.500 Hz, $t(26) = -1.42$, $p = .168$].

Figure 4 shows PC and amplitude data for the 925, 998, and 1000-Hz conditions. Age was significantly predictive of FFR PC at 925 Hz, $t(30) = -2.84$, $p = .008$, $R^2 = .21$, and 1000 Hz, $t(30) = -2.27$, $p = .030$, $R^2 = .15$,, and less so at 998 Hz, $t(30) = -1.92$, $p = .065$, $R^2 = .11$. This effect was also seen when amplitude of the FFR was considered. Amplitude analyses indicated that age was significantly predictive of FFR amplitude at 925 Hz, $t(30) = -2.94$, $p = .006$, $R^2 = .22$, but less so at 998 Hz, $t(30) = -2.01$, $p = .053$, $R^2 = .12$, and 1000 Hz, $t(30) = -1.88$, $p = .070$, $R^2 = .11$.

3.3. Perceptual-physiologic relationship

To assess the relationship between the perceptual and physiologic measures, simple linear regression analyses were performed with the log-transformed 500 or 1000-Hz FDL as the dependent variable and corresponding FFR PC and amplitude data as the independent variable (Figure 5). Although there were concurrent declines in the perception and neural representation of frequency, FFR PC or amplitude did not predict FDLs (500-Hz PC × 500-Hz FDL, $t(26) = -0.317$, $p = .754$; 500-Hz amplitude × 500-Hz FDL, $t(26) = 0.360$, $p = .721$; 1000-Hz PC ×

1000-Hz FDL, $t(30) = -1.115$, $p = .274$; 1000-Hz amplitude × 1000-Hz FDL, $t(30) = -0.883$, $p = .384$).

To further examine this perception-physiology relationship, simple linear regression analyses were used to evaluate the relationship between two ratios of FFR PC or amplitude and the corresponding FDL. First, the ratio of 998:1000 Hz PC was related to the FDL at 1000 Hz, reflecting two frequencies that were difficult to discriminate. Second, the 925:1000 Hz PC ratio was related to the 1000-Hz FDL, reflecting two frequencies that were relatively easy to discriminate by all subjects. Ratios of 463:500 and 498:500 Hz were related to the 500-Hz FDL. These ratios were not significantly predictive of FDL (all p-values > .05).

4. Discussion

The present study examined the effect of advancing age on the perception and neural representation of tones of different frequency. Consistent with previous studies, the ability to discriminate different frequencies, as measured by FDLs, became poorer as age increased (Konig, 1957; Abel et al., 1990; Moore and Peters, 1992; Humes, 1996; He et al., 1998; Espinoza-Varas and Jang, 2006; He et al., 2007). The neural representation of frequency, as measured by the FFR, also declined with advancing age but these age effects were frequency dependent. Based on PC and amplitude values of the FFR, frequencies near 1000 Hz were represented less robustly in the brainstem of older adults when compared to 500 Hz.

Reduced FFR PC and amplitude results are consistent with the interpretation of an age-related decline in phase-locking ability involving the brainstem. However, reduced neural synchrony could also result from peripheral and/or central auditory changes with age. For example, disrupted neural synchrony may be related to age-related changes in physiology such as metabolic activity in the cochlea (Mills et al., 2006), levels of inhibitory neurotransmitters (Caspary et al., 2005), or decreased cell counts in auditory nuclei (Frisina and Walton, 2006). Age-related related changes to the capacitance and input resistance of inner hair cells (IHCs) or changes in synapses between IHCs and auditory nerve fibers could also influence the upper frequency limit of phase locking (for review see Moser et al., 2006) and in turn explain the frequency effects observed here. It might be that temporal jitter may be more detrimental for the 1000-Hz than the 500-Hz response for reasons related to 1000 Hz having a shorter period than 500 Hz, resulting in a reduced upper frequency limit of phase locking for older adults.

Although the present study reported significant age-related declines in perception that coincided with abnormal physiologic measures, the neural representation of frequency (FFR) was not predictive of FDLs. The lack of a predictive relationship between the neural representation of frequency and FDLs could be related to the cues participants used during the psychophysical task. Participants may have used place-based cues instead of, or in addition to, a temporal, phase-locked representation of frequency. Previous studies have demonstrated that rate-place codes in the auditory nerve are sufficient to represent frequency in quiet (e.g. Sachs and Young, 1979). However, rate-place models do not explain how FDLs change over frequency and stimulus level (Heinz et al., 2001). In addition, the FFR reflects one representation of frequency, but it does not reflect all of the neural pathways and activity associated with frequency discrimination. Therefore, all of the age-related changes in neural activity that are relevant to frequency discrimination might not have been observed in the FFR, contributing to the lack of a predictive brain-behavior relationship.

Another point to consider is that phase locking does not accurately represent all frequencies in the CANS. Above the upper frequency limit of phase locking, frequency is thought to be represented by the average firing rate of neurons along the tonotopic basilar membrane (rate-place coding) (for review, see Winter, 2005). Further, as the CANS ascends, the maximum

frequency represented by phase locking decreases. Therefore, there is a rate-to-place transformation that must occur when transitioning from phase locking to rate-place coding. For example, the upper frequency limit of phase locking is approximately 5000 Hz in the auditory nerve and approximately 250 Hz in the auditory cortex (for review, see Winter, 2005). It is plausible to speculate that this transformation may also be affected by the aging process. If there are age-related changes in how phase-locked frequency information from the brainstem is transformed and transmitted to the auditory cortex, then there would be additional aging effects that may not be seen in FFR measures. Thus, the FFR measures would not necessarily reflect age-related changes along the entire auditory pathway from cochlea to cortex, whereas the frequency discrimination task involves the entire afferent and perhaps efferent pathways in addition to nonsensory factors such as attention and memory.

Another factor that may contribute to the poor predictive relationship between perception and physiology involves stimulus context. During the frequency discrimination task, tones were presented in pairs – a necessary paradigm if one wishes to test discrimination. One tone was always 1000 Hz, while the other varied in frequency but was always less than 1000 Hz. In contrast, repeated presentations of a single tone were used to record the FFR. This difference in stimulus context requires different sensory processing for each of the two procedures, and this too might have obscured the brain-behavior relationship. .

It is also important to acknowledge that factors other than aging might have contributed to the perceptual and physiology data, since *R*-squared values suggest that age does not explain the majority of variance. We therefore question if non-sensory processes such as attention, memory, and motivation contributed to the perceptual scores, but not the FFR measures, and in turn created a disconnect between brain and behavioral measures. Along the same lines, brain-behavior relationships might have been influenced by the amount of musical training that each individual had. Musical training has been reported to improve frequency discrimination (e.g. Micheyl et al., 2006) and also affects the FFR evoked by some, but not all, pitch contours (Wong et al., 2007). The combined effect of musical training and aging was not a research question in this experiment; however, when probed afterwards, not surprisingly, older adults had more years of musical experience than their younger counterparts. This issue is an interesting one and worthy of further exploration when musical training, as a variable, can be controlled and quantified.

4.4 Conclusions

Pitch discrimination, as measured by FDLs, becomes significantly poorer as age increases. Neural representation of frequency, as reflected by the FFR, also becomes weaker as age increases. Although there are concurrent declines in the perception and neural representation, one was not predictive of the other.

Acknowledgments

This work was supported by the National Institutes of Health R01-DC007705 (KT), T32-DC00033 (CC), P30-DC04661, and R01 DC008549 (ARK). Funding for KT from the UW Virginia Merrill Bloedel Scholar Program is also acknowledged. Thanks to Sasha John, Terry Picton, and G. Christopher Stecker for their programming assistance, as well as Jordan Cannon for his assistance with data collection.

Abbreviations

ABR	auditory brainstem response
AEP	auditory evoked potentials
AM	amplitude modulated

CANS	central auditory nervous system
EFR	envelope following response
FDL	frequency discrimination difference limen
FFR	frequency-following response
FFT	fast Fourier transform
IHC	inner hair cell
IPD	interaural phase difference
PC	phase coherence
VOT	voice onset time

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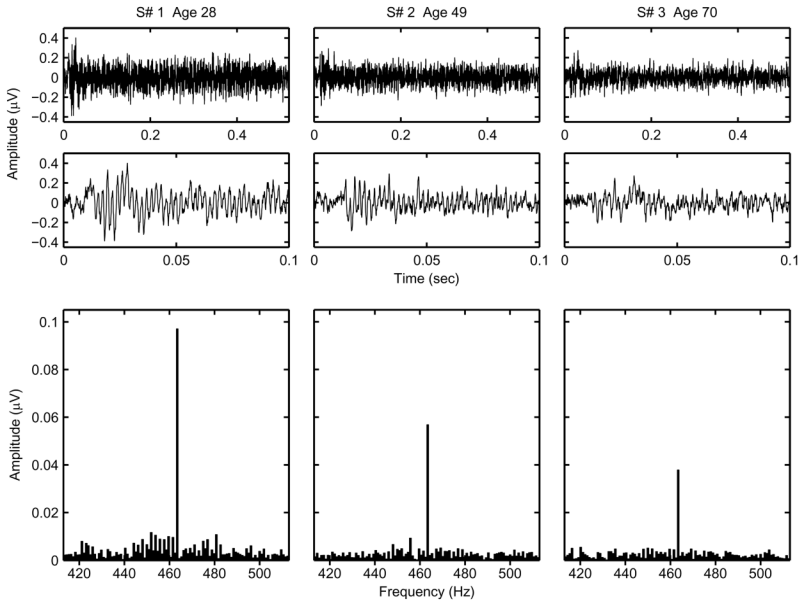

Figure 1.

FFR data from the 463-Hz condition. Individual data is shown from three separate subjects of different ages in three columns. The first row shows FFR data over the entire 520 ms time window. The second row shows FFR data over the first 100 ms, to illustrate the periodicity of the FFR. The third row shows output of FFT analyses to illustrate amplitude of the FFR and that the FFR is limited to one FFT bin. Subject number and age is located at the top of each column.

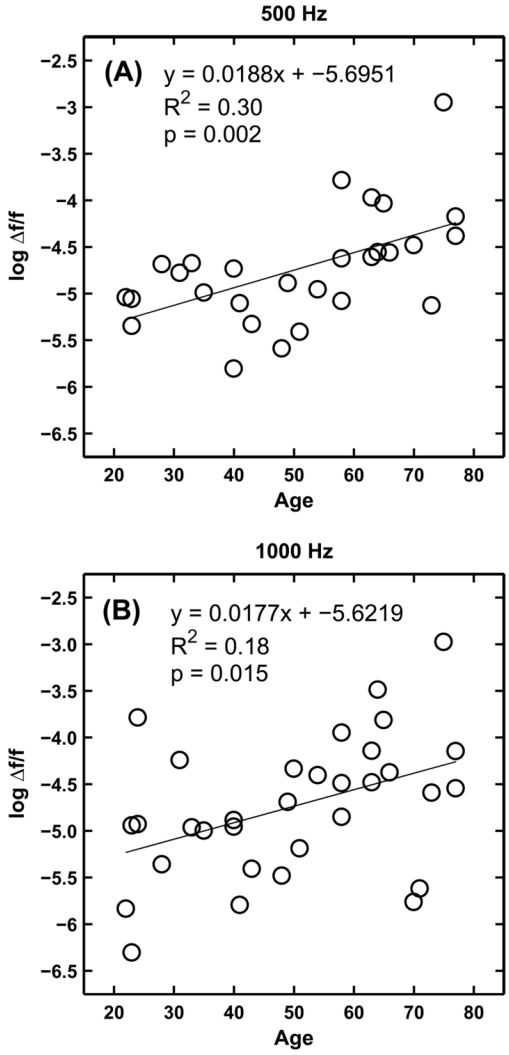

Figure 2.

Log-transformed FDLs as a function of age for 500 Hz (A) and 1000 Hz (B). The linear fit, regression formula, and p-value are shown in each panel. FDLs became significantly poorer as age increased.

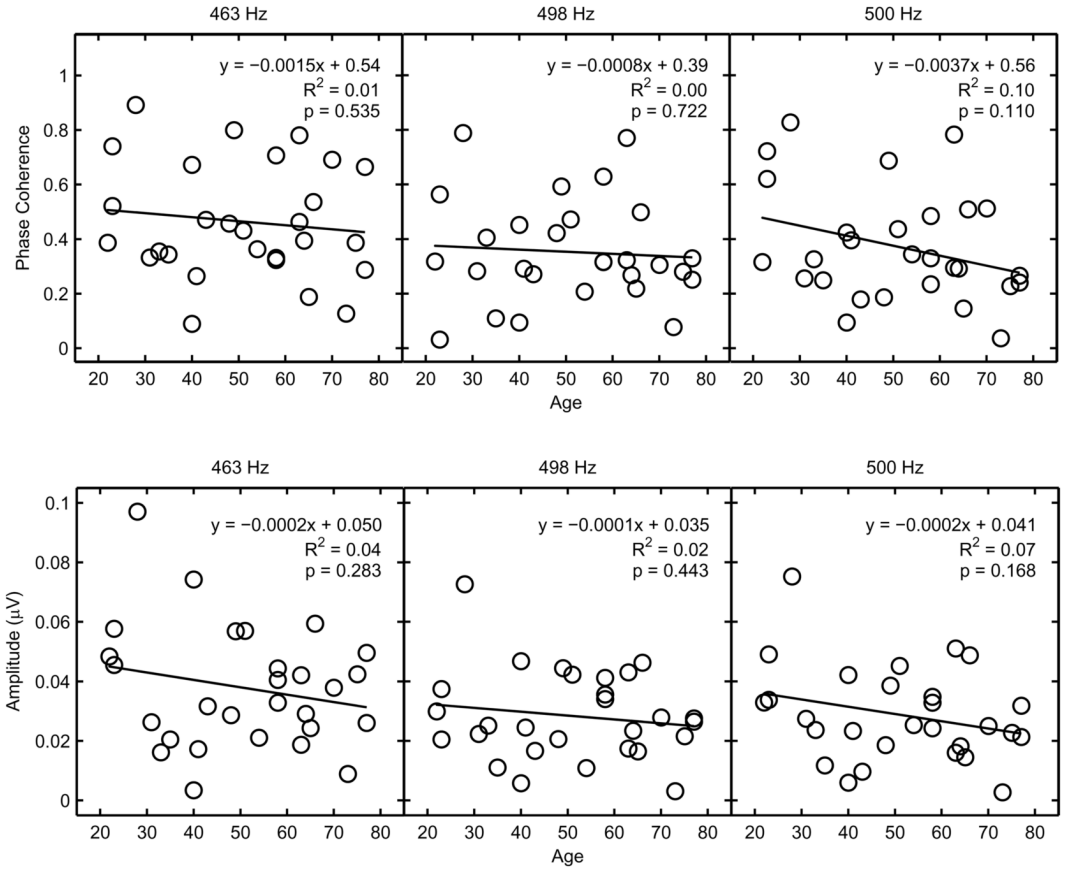

Figure 3.

FFR data from 463, 498, and 500-Hz conditions. PC (top row) and amplitude (bottom row) are plotted as a function of age. The linear fit, regression formula, and p-value are shown in each panel.

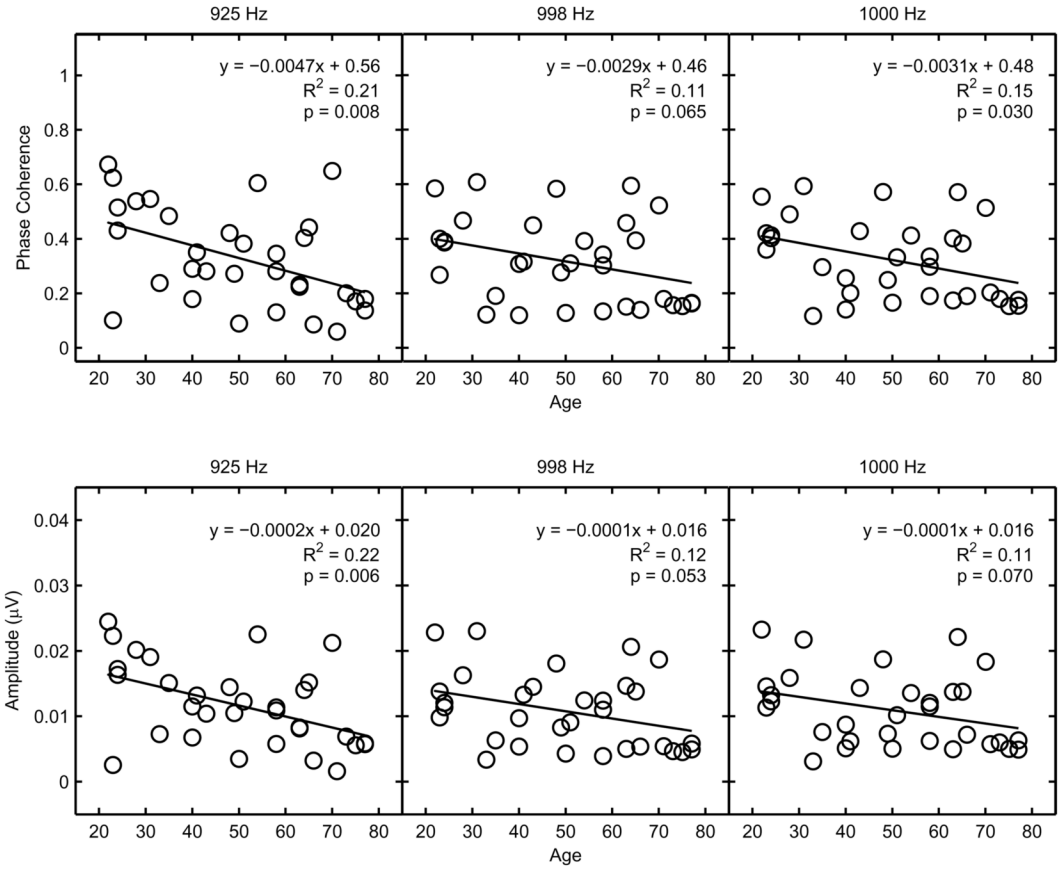

Figure 4.

FFR data from 925, 998, and 1000-Hz conditions. PC (top row) and amplitude (bottom row) are plotted as a function of age. The linear fit, regression formula, and p-value are shown in each panel. FFR measures significantly decreased as age increased.

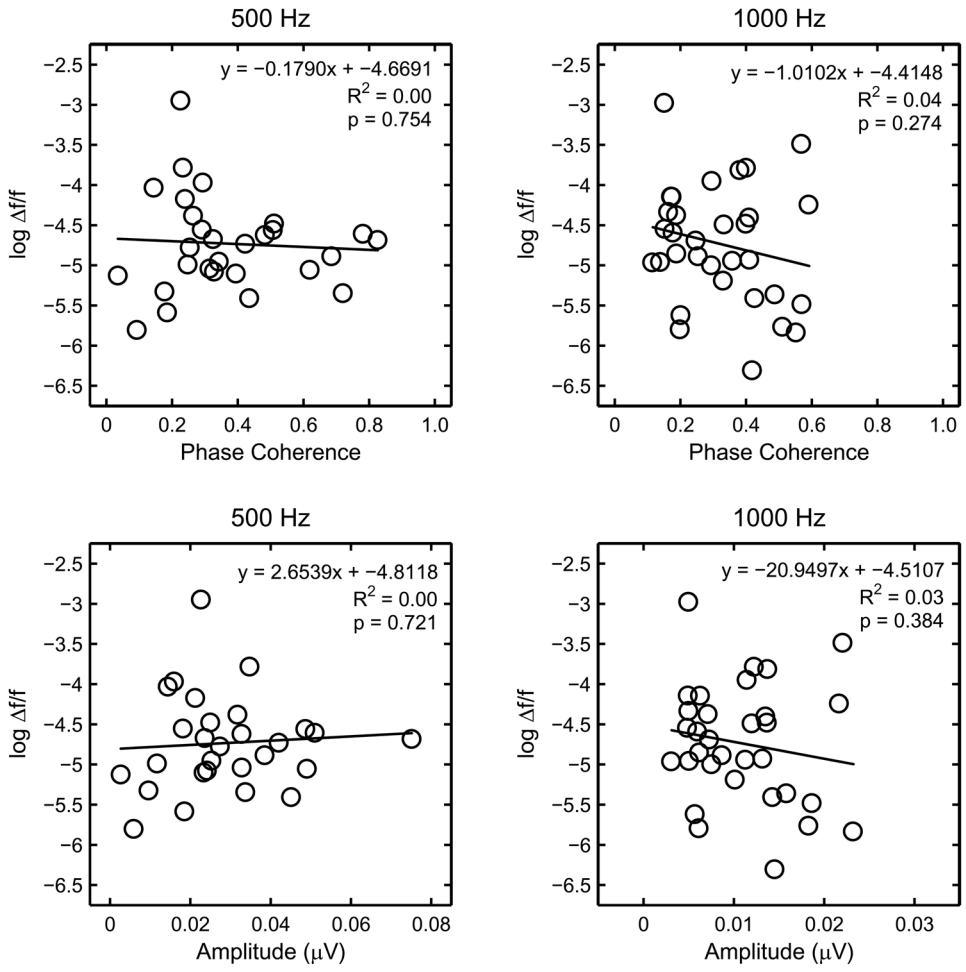

Figure 5.
Bivariate plots of FFR PC or amplitude and log-transformed FDLs. FFR data was not significantly predictive of FDLs.