Spring 2015

Examining monaural and binaural measures of phase-locking as a function of age

Larissa M. Heckler
James Madison University

Recommended Citation

Heckler, Larissa M., "Examining monaural and binaural measures of phase-locking as a function of age" (2015). *Dissertations*. 12.
https://commons.lib.jmu.edu/diss201019/12

Examining Monaural and Binaural Measures of Phase-Locking as a Function of Age

Larissa M Heckler

A dissertation submitted to the Graduate Faculty of

JAMES MADISON UNIVERSITY

In

Partial Fulfillment of the Requirements

for the degree of

Doctor of Audiology

Communication Sciences and Disorders

May 2015

Acknowledgments

I would like to acknowledge everyone who has assisted me throughout my doctoral studies over the years. I would first like to acknowledge my committee chairman, Dr. Christopher Clinard, for agreeing to serve as my adviser and for his patience and feedback during the many courses I took with him and as I completed my dissertation. Additionally, I would like to thank Dr. Brenda Ryals and Dr. Lincoln Gray for agreeing to serve on my dissertation committee. I truly appreciate all of their time and assistance as I navigated this process.

I also want to thank the Roger Ruth Memorial Grant and a JMU College of Integrated Science and Technology Research Grant for the support they provided. Their funding made it possible to recruit subjects for the extensive amount of time needed to collect out data.

Lastly, a very special thanks is due to my friends and future colleagues here at JMU along with my wonderful family. I am forever grateful for their patience, assistance, support, and faith in me. I could not have completed my dissertation without the support of all these wonderful people.

Table of Contents

List of Figures

Abstract

Understanding speech in the presence of background noise is a common complaint of middle-aged and older listeners with clinically normal audiograms. There is great interest in understanding how age-related changes in auditory physiology make it harder for older adults to understand speech in difficult listening situations, compared to young listeners. It was recently reported that middle-aged and older normal-hearing listeners showed frequency-dependent, age-related declines in the behavioral and physiological detection of interaural phase differences (Grose & Mamo, 2010; Ross et al, 2007). There is also evidence of an age-related, frequency-dependent decline in the frequency-following response (FFR) (Clinard et al., 2010), an auditory evoked potential dependent on phase-locked neural activity (Worden & Marsh, 1968). Age-related declines in binaural processing may be related to age-related declines in phase locking.

This study used the frequency-following response (FFR) to examine monaural and binaural phase locking in subjects of two groups; younger and middle-aged. Responses were obtained from 300 ms toneburst stimuli at four frequencies (500, 750, 1000, and 1125 Hz) at an intensity of 80 dB SPL. FFRs were analyzed for response amplitude, binaural amplitude differences, and stimulus-to-response cross-correlations.

Results showed FFR amplitude decreased as frequency increases and, at 500 Hz, the summed left and right monaural FFR amplitudes were smaller than the binaural FFR amplitude, which is in contrast to previous literature (Clinard, 2010; Fowler, 2004; Krishnan & McDaniel, 1998). Results further indicated that the stimulus-to-response correlation coefficient is greatest for 500 Hz and declines as frequency increases.

There was no significant difference between the age groups but perhaps a broader age range including older adults would show the hypothesized amplitude differences between groups. Further, results may be different than expected due to minimal difference between summed monaural and binaural processing at 750, 1000, and 1125 Hz. When looking at the data there is a larger difference between groups at 1125 Hz and, while it is not significantly different, it may be that a broader frequency range (e.g., 1250 Hz or above) and age range (e.g. 0 to 100), may be more effective at revealing a group x frequency interaction.

Chapter I

Review of the Literature

Introduction

There is increasing interest about the effect of aging on the auditory system. Aging affects the auditory system in numerous ways even in the absence of peripheral hearing loss. As we age, there are diverse anatomical, physiological, and perceptual changes related to the auditory system. Difficulty understanding speech in challenging listening environments is one of the main complaints of older listeners. It is unknown if this difficulty is due to decreasing peripheral function, a diminished ability in central processing, or changes in cognition and attention.

Several studies have compared the temporal processing of younger and older listeners with normal hearing sensitivity. These studies have typically focused on temporal processing related to the envelope of sound (e.g., gap detection thresholds) in monaural tasks. A relatively small number of studies have examined effects of aging on temporal resolution using binaural tasks, which may be more closely related to the listening-related complaints of aging humans. Earlier studies examining aging effects on binaural processing include a study by Strouse, Ashmead, Ohde and Grantham (1998) that used gap detection thresholds, interaural time difference thresholds, masking level difference tasks, and syllable discrimination tasks to compare the performance of young and older normal-hearing listeners. They found that the older group performed worse than the younger group on these measures of temporal resolution and speech perception

(Strouse, Ashmead, Ohde & Grantham; 1998). However, the majority of their stimuli were broadband in nature. More recent studies have used tonal or narrow band stimuli to better understand if age-related deficits in binaural processing are frequency dependent.

In a study by King, Hopkins and Plack (2014), researchers used a 20 Hz amplitude-modulated tone with carrier frequencies of 250 and 500 Hz with interaural phase differences (IPD) either in the stimulus envelope or in the temporal fine structure. Researchers measured IPD thresholds to assess the effects of age on temporal processing. They found that age was positively correlated with the envelope-IPD thresholds at both frequencies and temporal fine structure-IPD at 500Hz suggesting that age negatively affects the binaural processing of envelope and temporal fine structure at some frequencies (King, Hopkins & Plack, 2014).

Recently, effects of aging on interaural phase differences, using pure tones, have revealed concurrent declines in behavioral and physiological measures. Investigation into the binaural processing of temporal fine structure as we age has revealed a decline in the perceptual and auditory evoked cortical responses to interaural phase differences (Grose & Mamo, 2010; Ross et al., 2007). In addition, it has been shown that this physiological sensitivity to interaural phase differences, at least at the level of the auditory cortex, starts to decline in adults as young as middle-aged (Ross et al, 2007). It is currently unknown if these recently-reported age-related declines in the perception of interaural phase differences have corresponding physiological declines at those same frequencies at levels below the auditory cortex.

Binaural Processing

Humans are designed to listen with two ears. Optimal hearing is achieved when the brain can integrate a signal from both ears, as this provides many benefits. The ability to analyze the differences between the signals arriving at the two ears is called binaural processing. The benefits from binaural processing include better understanding of speech in the presence of noise, selective listening, and release from masking, which means your brain can focus on the targeted signal and ignore the background noise when the signal and noise are in different locations (Gelfand, 2010). Normal-hearing listeners also benefit from binaural loudness summation, or redundancy. This is when sounds presented to two ears are perceived as 6-10 dB louder than when presented to one ear (Gelfand, 2010). Further benefit from binaural signal processing is sound localization, which means that you can tell from which direction someone is speaking to you by comparing the differences in the signal's intensity and phase at the two ears (Gelfand, 2010).

Two basic cues are most important for binaural hearing. First is the interaural intensity difference (IID). This is the change in the intensity of a signal at each ear as sound varies in azimuth and is affected in a frequency-dependent manner by head shadow. Comparing intensity levels at each ear provides localization cues primarily for higher frequencies, above approximately 1500 Hz (for a review, see McAlpine & Grothe, 2003). This second is interaural time/phase difference (ITD/IPD). This is when the timing or phase of a sound is compared at both ears; this comparison provides horizontal localization cues, primarily for lower frequencies, below 1500 Hz (Gelfand, 2010). Interaural time differences (ITDs) correspond to interaural phase differences (IPDs) if the signal is a pure tone. This dissertation will focus on interaural time, or phase, differences.

The phase of a signal is coded by the systematic firing of auditory nerve fibers. When auditory neurons fire action potentials, they sometimes prefer to fire during one particular phase of the waveform during a phenomenon called phase locking. This phenomenon is one way the brain represents frequency, however, it is primarily a low-frequency phenomenon due to the declining ability of the VIIIth nerve to phase lock to frequencies above approximately1500 Hz (e.g., Palmer & Russell, 1986). Phase locking is related to binaural processing because the brain integrates information about the differences in phase from the signals arriving at each ear to determine the lateralization or internal direction of a sound from headphones (for a review, see Pickles, 2008) . Most of what we have learned about single-unit phase locking in the central auditory nervous system has come from various animal models; less is known about phase locking in humans, as we are typically limited to scalp recordings.

The Jeffress Model of spatial hearing (Jeffress, 1948) is a popular model explaining how humans extract interaural phase differences for sound localization. This model suggests that neurons, presumably in the medial superior olive, are tuned to specific interaural time differences. Due to differences in axonal conduction delay from the two ears, these coincidence-detecting neurons are tuned to respond maximally when phase-locked inputs from the two ears arrive at the neuron in coincidence (Jeffress, 1948, Joris, P & Smith, P, 1998; McAlpine & Grothe, 2003.

Phase Locked Neural Activity Can Be Recorded From Humans

Physiological measures of phase locking can be obtained via the frequency-following response (FFR). The FFR reflects sustained neural activity in the rostal brainstem that is phase-locked to the stimulus waveform, and is sometimes described as a neurophonic response. It has similar characteristics to the cochlear microphonic generated in the cochlea, however the FFR is distinguishable by a number of properties, such as its longer latency for rostal brainstem generators and its frequency-dependent changes. During scalp recordings, the FFR waveform is primarily generated by the inferior colliculus (Smith et al., 1975).

The neurons in a typical, young adult's auditory system can only lock onto the phase of low-frequency tones, less than approximately 1500 Hz, due to the physiological limits of the neuron. This is referred to as the upper frequency limit. Unlike the cochlear microphonic, which can accurately mimic stimuli up to approximately 40 kHz, the FFR has an upper frequency limit of about 1.5 to 2 kHz when measuring from the inferior colliculus (Krishnan, 2007).

In a study by Clinard et al (2010), it was found that the FFR becomes weaker with increasing age. In addition, researchers noticed these age effects were frequency dependent. FFR amplitudes for 1000 Hz were less robust than 500 Hz in older adults. Grose and Mamo (2010) found a similar trend with no age effects for 500 Hz FFRs. However, this age-related reduction in FFRs at higher frequencies (e.g., 1000 Hz) has not been systematically examined. One model of auditory aging hypothesizes that temporal jitter, or greater variance in neural firing, contributes to poorer listening in older adults. The frequency-dependent decline reported by Clinard et al. (2010) is consistent with a model of temporal jitter; greater variance in the timing of neural firing would have a more severe negative impact on phase locking as the stimulus frequency increased.

Therefore, the purpose of this study was to examine phase locked neural activity to monaural and binaural stimuli to determine if age-related changes in FFRs across frequency have concurrent declines to those reported in interaural phase difference literature. Using the FFR and binaural interaction component in young and middle-aged listeners we hope to examine age-related declines in binaural processing.

Age-related Declines in Binaural Processing

There are many physiological changes that occur as we age. Growing evidence indicates a decline in the auditory performance of aging listeners, and that this decline begins as early as middle age (Clinard et al., 2010; Gordon-Salant & Fitzgibbons, 1999; Grose & Mamo, 2010; Ross et al, 2007; Strouse et al; 1998). Behavioral evidence show aging adults to have binaural deficits in a number of behavioral tasks including interaural phase detection, localization, masking level differences, and minimum audible angle detection (Strouse et al; 1998; Grose & Mamo, 2010). Recent papers examining effects of age on the processing of interaural phase differences indicate that middle-aged and older adults have a reduced frequency range over which they can detect interaural phase differences (Ross et al, 2007; Grose & Mamo, 2010; Hopkins & Moore, 2011; Moore, Vickers, & Mehta, 2012; Neher et al, 2011)

In a study by Ross et al (2007), researchers compared auditory evoked cortical P1-N1-P2 change responses to interaural phase differences in young, middle-aged and older adults. The auditory evoked cortical responses to changes in interaural phase differences showed that as we age, there is a decline in the physiological ability to detect those changes at higher frequencies. Responses occurred for frequencies up to 1225 Hz in young subjects, but only up to 940 Hz in the middle-aged subjects, and older adults only showed responses up to 760 Hz. Ross et al. also investigated behavioral performance on detecting interaural phase differences and found that behavioral IPD thresholds decreased with increasing age, but unlike the physiological results which illustrated the decline in frequency with age, the behavioral results much more variable in the middle-age and older groups.

Grose and Mamo (2010) were inspired by previous study and investigated whether using IPD stimuli that changed during the presentation would reduce the interobserver variability seen in the behavioral results found by Ross et al (2007). They found that the highest frequency that the difference in phase could be detected was significantly lower in middle-aged and older listeners than when compared to young listeners. These experiments suggest that there is a decline in the binaural processing of temporal fine structure that emerges in middle age.

One explanation for this age-by-frequency interaction, where age differences become larger as carrier frequency increases, is that phase locking at higher frequencies declines with age. This is consistent with the temporal jitter hypothesis (Anderson 1973; Pichora-Fuller et al, 1992); higher amounts of temporal jitter in neural firing, thought of as variance in the timing of phase-locked neural activity, are more detrimental to frequencies with smaller periods – the higher frequencies. At lower frequencies, increased temporal jitter can have minimal-to-absent effects, and this trend has been seen in human FFR data (Clinard et al., 2010; Grose and Mamo, 2010).

Looking at the literature, the cortical P1-N1-P2 change responses reported by Ross et al (2007) are consistent with a lower upper frequency limit of phase locking, however those cortical data do not reflect phase locking; they reflect cortical activity that detects an acoustic change within an ongoing stimulus. Physiological measures of phase locking in aging humans may help to identify deficits underlying declines in listening performance over the adult lifespan.

Of particular interest to aging and binaural processing, it is known that with increased age, there is a reduction of inhibitory activity in the auditory brainstem (for a review, see Caspary, et al, 2008). Inhibitory activity plays an important role in the processing of interaural time differences, as well as phase locking.

The medial superior olivary complex receives bilateral input that allows for the localization of sound by virtue of spatially sensitive neurons maximally responding to the interaural time differences between the inputs from each ear. Strong evidence suggests that neural inhibition narrows the neural tuning of interaural phase difference for more precise processing. Evidence from single-neuron recordings from the MSO of the gerbil shows that when inhibition is blocked, the neuron discharges at increasing rates and shows a degraded tuning to its peak ITD (McAlpine & Grothe, 2003). Further, blocking the inhibitory inputs to the auditory midbrain in bats showed similar changes in detecting stimulus periodicities from binaural cues (Koch & Grothe, 2000).

There is evidence of age-related declines in inhibitory neurotransmission throughout the auditory central nervous system. As we age there is a loss of inhibitory neurotransmitters and other changes in the synaptic receptors. The loss of inhibition in the auditory midbrain results in increased spontaneous neural activity and increased neural noise that may reduce the accuracy of binaural cues that rely on phase locked timing cues. Behavioral studies in humans and animals suggest loss of this time-locked inhibition may reflect age-related loss of binaural temporal processing and poorer localization (for a review, see Caspary et al, 2008).

Binaural Interaction Component

One way that physiological binaural processing has been measured in humans, using auditory evoked potentials, is the binaural interaction component (BIC). The BIC reflects the difference between monaural and binaural processing. It is calculated by finding the difference between the sum of the monaural waveforms (i.e., left and right) and the waveform elicited with binaural stimulation. The BIC has previously been calculated from auditory brainstem responses, FFRs, middle latency responses, and long-latency potentials (for a review, see Fowler, 2004).

The BIC was first used to understand binaural interaction by comparing monaurally and binaurally recorded auditory brainstem responses (ABR) in humans. The ABR is a transient response reflecting the neural synchrony to the onset of a sound stimulus by neurons originating from the cochlea, lower auditory brainstem, and sequential and parallel activity from the superior olivary complex (SOC), the initial site of binaural encoding (McPherson & Starr, 1995). The ABR-BIC has been studied more frequently than the middle latency responses, and long-latency potentials, and typically, the ABR-BIC results from a smaller binaural response when compared to the sum of the monaural responses. Studies show that this response correlates with psychophysical measures of binaural processing such as the masking level differences and localization/lateralization (for a review, see Fowler, 2004).

The binaural interaction component has also been used to compare binaural processing of older adults to those of young, normal-hearing adults. Previous studies using the BIC to address effects of aging have used the ABR and middle-latency responses with varying results (Fowler & Beach, 2000; Kelly-Ballweber & Dobie, 1984; Woods & Clayworth, 1986). Using older and younger men, Kelly-Ballweber and Dobie (1984) found that the ABR-BIC was similar between the age groups with noted prolonged latencies in the monaural waveforms of the older group. While there was no effect of age in the ABR-BIC, a negative effect of age was found in the middle-latency response (Kelly-Ballweber & Dobie, 1984). In contrast, Woods and Clayworth (1986) found that the BIC in the middle-latency response was the same in young and older participants while Fowler and Beach (2000) reported an age-related decline in amplitude in both the ABR and middle-latency response.

The few FFR studies that have reported findings from the binaural interaction component have only used young, normal-hearing individuals. Because binaural processing is believed to rely, at least in part, on synchronous phase-locked neural activity, comparing monaural and binaural processing, using FFRs, has potential to reflect age-related differences in binaural processing that have not been addressed in the literature.

FFR Studies Using The Binaural Interaction Component

The FFR has been used to examine the binaural interaction component; FFR-BIC represents the difference in FFR amplitude between summed monaural FFRs from the left and right ears and binaural FFR (BIC wave = summed monaural waves – binaural wave). Previous studies using the FFR-BIC have examined interaural time and intensity differences (Ballachanda & Moushegian, 2000; Krishnan & McDaniel, 1998), and stimulus presentation rate (Parthasarathy & Moushegian, 1993). Although the FFR has been used to examine the binaural interaction component, few studies have utilized this approach and none have related the FFR-BIC to either perception or aging.

The FFR-BIC has been found to be more than the sum of two monaural responses and is presumed to be a valid measure of the binaural brainstem integrity of low-frequency stimuli (Ballachanda & Moushegian, 2000; Krishnan & McDaniel, 1998). Ballanchanda and Moushegian (2000) investigated the effects of interaural time and intensity differences on FFRs and FFR-BICs to 500 Hz tone bursts. The researchers used monaural and binaural FFRs from normal-hearing, young listeners. They found the monaural and binaural FFRs to stimuli with various interaural time or intensity differences that are easy to tell apart perceptually, produce distinguishable waveforms. This indicates that the FFR evoked by the stimulation of both ears shows evidence of binaural processing at the level of the brainstem. The main finding from this paper was that the FFR reflects interaural differences (Ballanchanda & Moushegian, 2000). {? No FFR to diotic stim? I think you mean FFR-BIC}

Further, Krishnan and McDaniel (1998) also examined the 500 Hz FFR with respect to interaural intensity differences. Similar to Ballachanda and Moushegian

(2000), researchers found a present FFR-BIC by subtracting the smaller binaural response from the larger summed monaural response. They also found that the FFR-BIC decreases systematically as the interaural intensity difference increases. These findings suggest that the FFR, at least for 500 Hz tone bursts, reflects the output of binaural processing (Krishnan & McDaniel, 1998). {I assume binaural still always > sum of monaural?}

Parthasarathy and Moushegian (1993) studied the effect of stimulus presentation rate, frequency, and interaural intensity on the binaural interaction component of both the auditory brainstem response (ABR) and the frequency-following response (FFR) in normal hearing adults. Researchers used tone bursts at 500, 1000, and 2000 Hz, as well as a 2000 Hz filtered click. Sounds were presented at 85 and 100 dB SPL at rates of 10 and 40/sec. The click-evoked ABR, the toneburst-evoked FFR, and the BIC waveform latencies and amplitudes are differently affected by rate, frequency and intensity of the stimulus. ABR and ABR-BIC latencies were shorter to the click-like sound than to the toneburst. Increasing the rate of the stimulus created longer latencies and reduced amplitudes of the ABR waveforms at all frequencies. In contrast, the FFR and FFR-BIC latencies of 500 & 1000 Hz tonebursts were not affected by rate, possibly due to the large number of phase locking neurons within the superior olivary complex. There were amplitude differences seen in the FFR waveforms for the different repetition rates. The frequency effect of the FFR and FFR-BIC latencies showed a shorter latency to 1000 Hz than to 500 Hz in accordance with previous literature (Parthasarathy & Moushegian, 1993). These studies illustrate that the FFR-BIC is a useful measure of binaural processing.

Although previous studies have used frequency-following responses to evaluate the binaural interaction component, the sinusoidal, neurophonic properties of the frequency-following response make BIC calculations problematic. Earlier FFR-BIC studies used short stimulus durations (e.g., 12-60 ms) and focused their BIC analysis on discrete positive or negative peaks present in the FFR-BIC waveform. Contemporary FFR research often uses stimuli of longer duration and focuses less on the time-domain waveform analysis of subjective peak picking. FFR amplitude measures, as are typically performed now in FFT output, do not lend themselves to BIC analysis as traditionally performed. If the BIC waveform (summed mono waveform minus binaural waveform) is subjected to a fast Fourier Transform, the peak response energy does not reflect whether summed monaural or binaural FFR condition had the most robust amplitude. The phase of the FFR waveform's periodicity may reverse, depending on which wave had larger amplitude, but the peak amplitude in the FFT is minimally informative. Therefore, simply obtaining FFT-based measures of response amplitude, then calculating the difference between separate summed monaural amplitudes and binaural amplitudes may be more informative than conventional BIC calculations.

Conclusion

The research has shown that age negatively affects binaural processing and these age-related declines might be related to declines in phase locking. Age-related declines are seen in perceptual detection of IPDs that are consistent with poorer phase locking (Ross et al., 2007; Grose & Mamo, 2010). Also, there is evidence of age-related physiological declines in detection of IPDs at the level of the auditory cortex (Ross et al, 2007). The FFR can be used to evaluate the physiological representation of frequencies where IPD can be measured behaviorally, allowing a comparison of perception and physiology. There is evidence of an age-related, frequency-dependent decline in the FFR (Clinard et. al, 2010) however; a systematic examination of these changes in phase locking at the higher frequencies has yet to be done.

The following hypotheses were addressed in this study:

1. Middle-aged adults will have significantly reduced FFR amplitude at higher frequencies. It is expected that a significant age x frequency interaction, indicating that FFR amplitude measure of middle-aged adults at higher frequencies, will be poorer than that of younger adults.

2. It is expected that the binaural difference amplitudes will significantly decline with aging, demonstrating an age x frequency interaction like that of FFR amplitude.

3. It is expected that the accuracy of frequency representation, as reflected by the stimulus-to-response correlations, will decline with aging, demonstrating an age x frequency interaction, indicating the correlation coefficient for middle-age adults will be poorer than that of younger adults.

Chapter II

Materials and Methods

Subjects

Seventeen subjects participated in this study. Subjects were divided into two groups: young (n = 11, mean age = 22.5 years, range = 21-24) and middle-aged (n = 7, mean age = 43.9 years, range = 37-53). All subjects had clinically normal hearing sensitivity, defined as thresholds ≤ 25 dB HL at octave frequencies from 250 to 8000 Hz. All subjects were native, monolingual English speakers, with unremarkable otoscopy findings and normal tympanometric measures. In addition, they had no history of otological or neurological disorders, and were not taking interfering prescription medications. Subjects were recruited from the community primarily through e-mail, word-of-mouth, and flyers. Subjects were compensated $10 per hour for their participation. The institutional review board at James Madison University approved all procedures in this study.

Stimuli

Stimuli consisted of tonebursts similar to those reported in the single-frequency interaural phase difference psychoacoustic task of Grose and Mamo (2010). Tonebursts had 300 ms duration with a rise time of 75 ms, a plateau of 200 ms, and a fall time of 25 ms; rise/fall times were gated with a raised cosine ramp (Figure 1).

Four frequencies were used to elicit FFRs: 500, 750, 1000, and 1125 Hz. Magnetically-shielded ER3-A insert earphones (Intelligent Hearing Systems) with extended earphone tubing delivered stimuli for the left and right monaural and binaural conditions. All stimuli were presented at 80 dB SPL. Stimulus level was calibrated with a Larson-Davis sound level meter (model System 824) and half-inch microphone (Larson-Davis model 2541) and a 2 cc coupler.

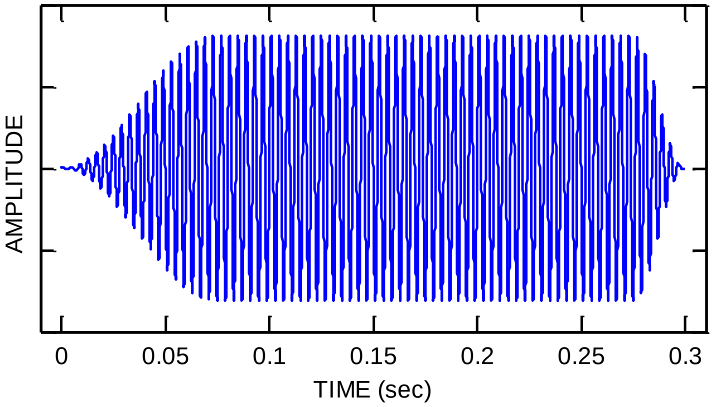

Figure 1. Example stimulus waveform for 500 Hz condition.

Physiology Recordings

FFRs were collected via a Neuroscan SynampsRT acquisition system and Neuroscan SCAN 4.3 software using a three-channel recording (Krishnan et al., 2005; Swaminathan et al., 2008). The subjects were in a double-walled, sound-attenuated booth, and were seated in a reclining chair. They were instructed to relax. The responses were recorded from Cz (vertex, inverting) to non-inverting electrodes at the nape-of-the-neck and at each earlobe with the ground electrode on the forehead. Electrode impedances were below 5 kΩ and inter-electrode impedances were within 2 kΩ.

Stimulus onset asynchrony was 633.33 ms; inter-stimulus interval was 333 ms. The online filters were 100–3000 Hz, the analysis time window was -320 to 320 ms, and the analog-to-digital sampling rate was 20 kHz. For each stimulus, one thousand individual artifact-free responses or sweeps were averaged. Artifact rejection was set to reject any sweeps with a voltage that exceeded ±30 µV.

Physiology Procedure

Stimuli were delivered via a Neuroscan SynampsRT? system. FFRs were collected in monaural-left, monaural-right and binaural conditions to each of the four frequencies: 500 Hz, 750 Hz, 1000 Hz and 1125 Hz; there was a total of 12 conditions (4 frequencies x 3 monaural/binaural conditions). A five-minute break was given between each FFR condition. Conditions were presented in a random order. Each condition lasted approximately 13 minutes, resulting in a complete session duration of approximately 3.5 hours.

Physiology Analysis

Offline FFR analyses performed in Matlab R2011b included measures of amplitude and stimulus-to-response cross correlations. Amplitude measures of response amplitude and pre-stimulus baseline noise were obtained from output of FFT analyses of their respective portions of the averaged FFR waveform. Response amplitude was obtained from an FFT of the response, or post-stimulus, time window (0 to 320 ms); an estimate of noise in the recording was obtained from an FFT on the pre-stimulus baseline (-320 to 0 ms). Response amplitude was obtained by finding the maximum amplitude within ± 50 Hz from the stimulus frequency (e.g., 500 Hz). Pre-stimulus noise was obtained by performing an FFT of the pre-stimulus baseline and averaging amplitudes of the FFT bins over the same frequency range as used to find the peak response amplitude (stimulus frequency ± 50 Hz)(e.g., noise averaged over 450 – 550 Hz). Signal-to-noise ratios were calculated from these noise and response amplitude measures. Figure 2.A illustrates an FFR waveform from an individual participant. Figure 2.B illustrates FFR amplitude, as well as pre-stimulus noise, in the FFT panels; the low level of the noise, relative to FFR amplitude, indicates robust signal-to-noise ratios for the FFR.

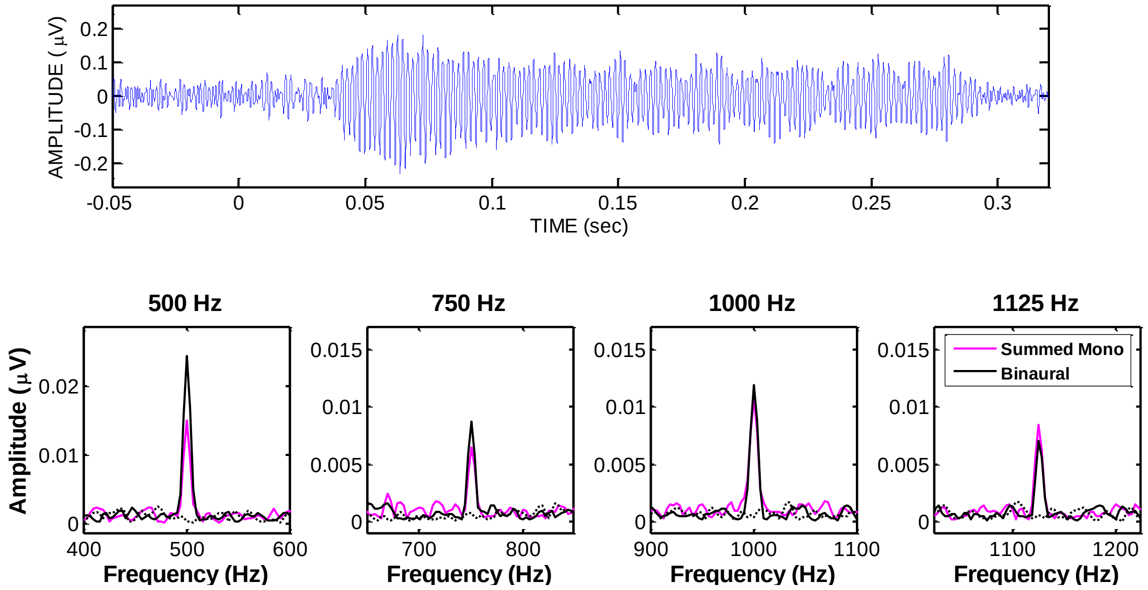

Figure 2. Individual data from a single subject (age 24) ***TOP*: ** Time-domain waveform of the FFR from the 500 Hz Binaural condition. ***BOTTOM:*** FFTs of binaural (solid, black line) and summed monaural (solid, magenta line) FFRs are shown for each frequency. The black dashed line in each panel represents the FFT of the pre-stimulus baseline from the corresponding binaural FFR recording, demonstrating robust signal-to-noise ratios for each condition.

Stimulus-to-response cross-correlations were also calculated reflecting the similarity between the stimulus waveform and the FFR waveform. These stimulus-to-response cross correlation coefficients could be said to represent the accuracy with which a frequency was encoded, as opposed to the magnitude of the response that is indicated by response amplitude. A high stimulus-to-response cross correlation coefficient would indicate that the periodicity of the response followed that of the stimulus. For each individual FFR waveform, cross correlations between the FFR waveform and the stimulus waveform of the corresponding frequency were calculated. Correlations were calculated at each lag between 0 and 15 ms, accounting for the onset latency of the neural response.

Statistical Approach

Three analyses of variance (ANOVAs) were performed. Repeated measures ANOVAs were conducted with the following dependent variables: FFR amplitude, binaural amplitude difference, and stimulus-to-response. Factors were group (between subject on 2 levels, young and middle-aged), frequency (within subjects on four levels; 500, 750, 1000, and 1125 Hz) and ear condition (within subjects on three levels: average monaural, summed monaural, and binaural). Effect size was measured using partial eta squared with small, medium, and large effect sizes defined as 0.0099, 0.0588, and 0.1279, respectively (Cohen, 1988).

Chapter III

Results

Amplitude

First, a preliminary ANOVA was performed to test whether FFR amplitude was different between left and right monaural conditions; factors were frequency (within-subjects on 4 levels: 500, 750, 1000, and 1125 Hz) and ear condition (within-subjects on two levels: left ear and right ear). FFR amplitudes between left and right ears were not significantly different (F(1,17) = 2.099, *p* = .166), therefore an average monaural FFR amplitude was used in the full factorial ANOVA by averaging FFR amplitudes from the left and right ears.

FFR amplitudes of averaged monaural, summed monaural and binaural ear conditions were evaluated using a repeated-measures ANOVA with factors of group (between-subject on 2 levels, young and middle-aged), frequency (within-subjects on 4 levels: 500, 750, 1000, and 1125 Hz) and ear condition (within-subjects on three levels: average monaural, summed monaural, and binaural). Main effects were significant for Frequency (*F(*2, 27) = 50.37, $p < .001$, partial $\eta^2 = .748$), and Ear Condition (*F(1.,24)* = 39.06, $p < .001$, partial $\eta^2 = .697$). The main effect of Group was not significant (F(1,17) = .391, $p = .540$, partial $\eta^2 = .022$). The Frequency by Ear Condition interaction was significant (F(2,40) = 8.325, $p = .001$, partial $\eta^2 = .329$). No other interactions were significant, including the Group x Frequency interaction ($p > .05$).

Pairwise comparisons for the main effect of frequency indicate that FFR amplitude at 500 Hz is significantly higher than all other frequencies. The pairwise comparisons also indicate that FFR amplitude at1125 Hz is significantly lower than all other frequencies. As shown in figure 3 (below) results are consistent with FFR amplitude being most robust for lower frequencies (Worden & March, 1968).

Pairwise comparisons for the main effect of ear condition indicate that the average monaural ear condition is significantly smaller than the summed monaural and binaural conditions. The summed monaural ear condition is significantly larger than the average monaural ear condition and significantly smaller than the binaural ear condition. Lastly, the pairwise comparisons also indicate that the binaural ear condition is significantly larger than the average monaural and summed monaural ear conditions. These findings are illustrated in figure 3, showing the monaural amplitudes recorded from the left and right ear are lower (poorer) than the binaural and summed monaural amplitudes and the binaural amplitude measures for 500 Hz are larger than the summed monaural amplitude measure for 500 Hz.

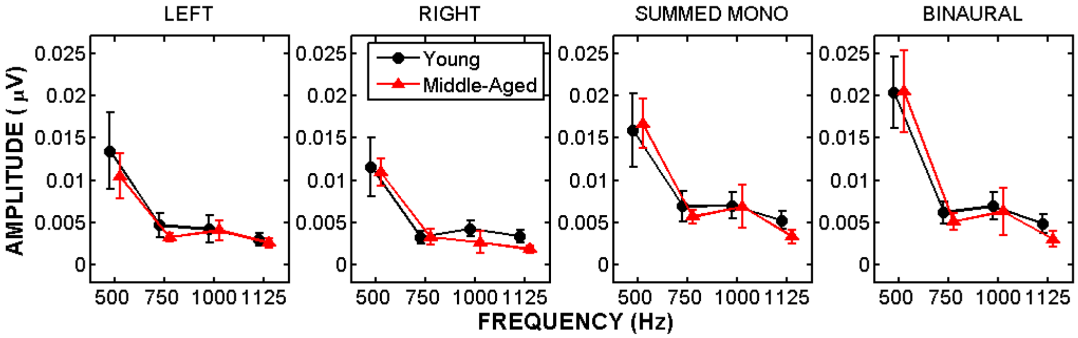

Figure 3. FFR amplitude is shown across frequencies tested for four ear conditions: Left Ear, Right Ear, Summed Monaural, and Binaural stimulus presentation. The results shown are from young (black circles) and middle-age individuals (red triangles). Dashed lines represent a noise estimate from the pre-stimulus baseline. Error bars represent one standard deviation. Data points have been slightly offset for visual clarity.

Binaural Amplitude Difference

The difference between summed monaural and binaural FFR amplitude, the binaural amplitude difference, was evaluated using a repeated-measures ANOVA with factors of Group (between subjects on 2 levels, young and middle-aged) and Frequency (within subjects on 4 levels: 500, 750, 1000, and 1125 Hz). The main effect of Frequency (F(2, 33) = 15.17, $p < .001$, partial $\eta^2 = .472$) was significant. However, the main effect of Group (F(1,17) = .020, $p = .890$, partial $\eta^2 = .001$) and the Group x Frequency interaction were not significant ($p > .05$).

Pairwise comparisons for the main effect of frequency indicate that the 500 Hz FFR binaural amplitude difference is significantly different than all other frequencies. The remaining frequencies are not significantly different from each other. Profile plots, as well as figure 4, indicate that 500 Hz, binaural FFR amplitude was greater than Summed Monaural amplitude. This indicates that, at 500 Hz, the binaural FFR amplitude represents more than the sum of its parts (summed left and right ear responses).

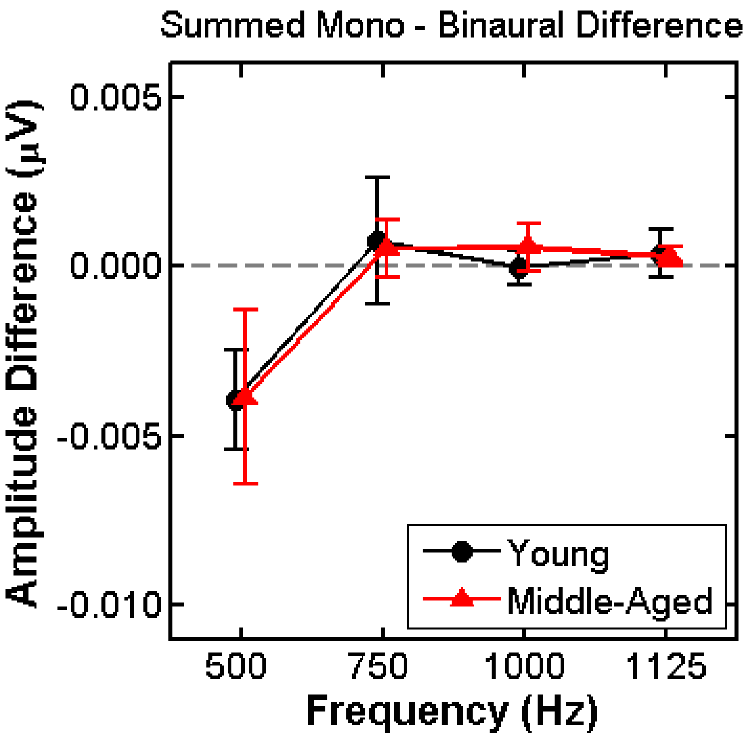

Figure 4. The difference between Summed Monaural and Binaural FFR Amplitudes (Summed Monaural Amplitude - Binaural Amplitude) is shown across frequency. The results shown are from younger (black circles) and middle-aged individuals (red triangles). Error bars represent one standard deviation. Negative values indicate that Binaural FFR amplitude was greater than Summed Monaural FFR amplitude. A dashed gray line highlights zero amplitude difference between the conditions.

Stimulus-to-Response Correlation

Prior to performing this ANOVA, a preliminary ANOVA determined that stimulus-to-response correlations between left and right ears were not significantly different. Factors were Ear Condition (within-subjects on two levels: Left and Right) and Frequency (within-subjects on four levels). The main effect of Ear Condition was not significant (*F*(1,17) = 1.166, *p* = .295) , Therefore an average monaural stimulus-to-response correlation was used in the full factorial ANOVA by averaging stimulus-to-response correlations from the left and right ears.

Stimulus-to-response correlations were evaluated using a repeated-measures ANOVA with factors of Group (between subjects on 2 levels, young and middle-aged), Frequency (within subjects on 4 levels: 500, 750, 1000, and 1125 Hz), and Ear Condition (within subjects on 3 levels; averaged monaural, summed monaural, and binaural). Main effects were significant for Frequency (F(3,51) = 24.62, $p < .001$, partial $\eta^2 = .592$) and Ear Condition (F(1,18) = 41.534, $p < .001$, partial $\eta^2 = .710$). The main effect of Group was not significant (F(1,17) = 1.419, $p = .250$, partial $\eta^2 = .077$). No interactions were significant, including the Group x Frequency interaction ($p > .05$).

Pairwise comparisons for the main effect of frequency indicate that stimulus-to-response correlations at 500 Hz are significantly greater than at all other frequencies. Comparisons also show that the stimulus-to-response correlation at 1000 Hz is significantly greater than the response correlation at 1125 Hz. Stimulus-to-response correlation at 750 Hz is not significantly different from response correlations at 1000 or 1125 Hz. Figure 5 shows that the stimulus-to-response correlations were most robust for 500 Hz and decreased at higher frequencies, similar to FFR amplitude.

Pairwise comparisons for the main effect of ear condition indicate that the stimulus-to-response correlations for the average monaural ear condition are significantly smaller than those for summed monaural and binaural ear conditions. The summed monaural ear condition was not significantly different than the binaural ear condition. This is also illustrated in figure 5 (below), showing that correlations were larger for binaural conditions than for monaural conditions.

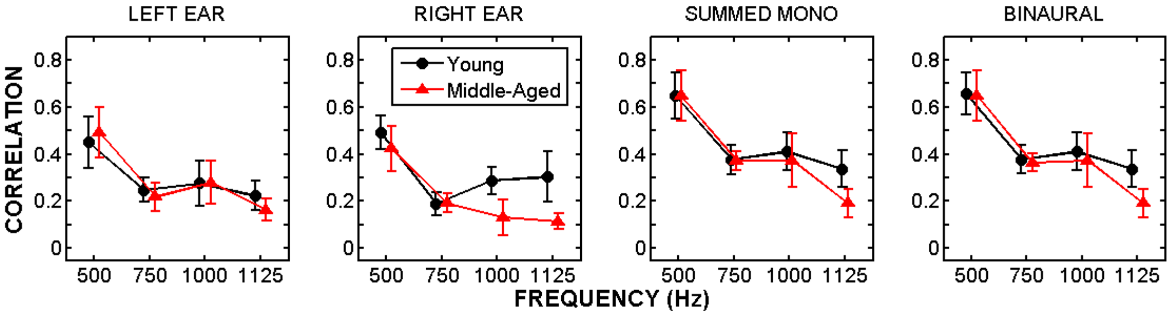

Figure 5. Stimulus-to-response cross correlation coefficients, across frequency, are shown for the left ear, right ear, summed monaural and binaural stimulus presentations. Results shown are from younger individuals (black circles) and middle-age group (red triangles). Error bars represent one standard deviation.

Chapter IV

Discussion

Age-related declines are seen on numerous behavioral measures of binaural processing such as localization, masking level differences, minimum audible angle detection and IPD detection. Grose and Mamo (2010) and Ross et al (2007) found that middle-aged and older normal-hearing listeners showed age-related changes in the perceptual and neural detection of binaural cues,. And while there have been related reports of poorer IPD processing in cortical auditory evoked potentials (Ross et al., 2007) there is a gap in the literature regarding age-related changes in phase-locked neural activity across that same frequency range (i.e., 500 – 1125 Hz). Clinard et al (2010) found a frequency-dependent decline in the amplitude and phase coherence of monaural FFR recordings with advancing age, however there is no research using a systematic approach to examining age-related changes in phase locking across frequency.

The current study examined whether recently reported age-related declines in the perception of interaural phase differences have corresponding physiological declines in phase-locked neural activity, as reflected by the frequency-following response. The aims of the study were to understand more about what physiological changes take place in aging humans related to binaural processing. The hypotheses were 1) that aging would negatively affect the neural representation of frequency, as indicated by reduced FFR amplitude at higher frequencies; 2) that aging would negatively affect binaural interaction as frequency increases, as reflected by the binaural difference amplitudes, and 3) that aging would negatively affect the accuracy of frequency encoding, as indicated by poorer correlation coefficients.

FFR Amplitude

Results showed that FFR amplitude decreases as frequency increases. FFR amplitudes for a 500 Hz stimulus were significantly larger than all other frequencies (750, 1000, and 1125 Hz). FFR amplitudes for an 1125 Hz stimulus were significantly smaller than all other frequencies (1000, 750 and 500 Hz). This was an expected finding due to the nature of the effects of continuous tone and toneburst frequency on the FFR (Glaser, Suter, Dasheiff, & Goldberg, 1976; Worden & Marsh, 1968) and from research by Clinard et al (2010) showing the same trend; that FFR amplitudes are more robust at lower frequencies.

Monaural FFR amplitude was measured from stimulating one ear. These recordings were added together to obtain the summed monaural FFR amplitude. Binaural FFR amplitude was measured from stimulating both ears simultaneously. The monaural FFR amplitude was significantly smaller than binaural and summed monaural amplitudes. These results were expected, as stimulating only one ear would produce smaller amplitudes than when stimulating two ears. Interestingly, the binaural FFR amplitude was significantly larger than the summed monaural amplitudes at 500 Hz. This is in contrast to all previous studies of the BIC for the FFR, the ABR and the AMLR. Previous ABR and AMLR research has shown that the binaural responses are smaller than the summed monaural responses (For review see Fowler, 2004). In a previous FFR study by Krishnan & McDaniel (1998) researchers used a 500 Hz toneburst and also found the opposite, where summed monaural amplitudes were larger than binaural amplitudes.

We hypothesized that aging would negatively affect the FFR amplitude at higher frequencies, however we found no significant difference in FFR amplitudes between the younger and middle-aged subjects. Perhaps a broader age range to include older adults would show the hypothesized amplitude differences between groups.

FFR Binaural Amplitude Difference

The binaural amplitude difference was calculated by subtracting the binaural FFR amplitudes from the summed monaural FFR amplitudes. Results showed that, at 500 Hz, the binaural amplitude difference is significantly different than all other frequencies for both groups. A negative number means that the binaural amplitude was larger than the summed monaural amplitude indicating that, at 500 Hz, there is a difference between summed monaural and binaural frequency processing. All other frequencies were not significantly different from each other and had binaural amplitude differences close to zero, indicating minimal-to-no difference in summed monaural and binaural frequency processing at those frequencies.

We hypothesized that the binaural amplitude difference would be significantly smaller as frequency increased for the middle-aged group when compared to the younger group, however there was no significant difference between the young and middle-age groups at all frequencies. Results may be different than expected due to very little difference noted between the binaural amplitude and summed monaural amplitude at 750, 1000, and 1125 Hz. If there were a group difference at higher frequencies, where age differences were present between summed monaural and binaural measures, those results may have indicated that binaural-specific processing was degraded in middle-aged adults.

However, the lack of group differences at those same frequencies may be consistent with the poorer upper frequency limit of behavioral IPD detection being influenced by monaural processing, rather than binaural-specific processing. Binaural processing at 500 Hz, as reflected by tone-evoked FFRs, appears to be more than the sum of its parts. At higher frequencies, binaural processing may be constrained by monaural processing.

Stimulus-to-Response Correlation

The stimulus-to-response correlation shows us how similar the frequency of the response is to the frequency of the stimulus. If they were perfectly similar they would have a correlation coefficient of 1, whereas if they were perfectly different they would have a correlation coefficient of 0. Therefore the greater number means the more accurate the response. Results show that the stimulus-to-response correlation is larger at 500 Hz than all other frequencies (750, 1000, and 1125 Hz), 1000 Hz is significantly larger than 1125 Hz but 750 Hz was not significantly different than 1000 or 1125 Hz. Results also show that the averaged monaural stimulus-to-response correlation is smaller than the summed monaural and binaural responses.

We hypothesized that aging would negatively affect the accuracy of frequency encoding and expected the middle-age group to have poorer correlation coefficients than the younger group, however we found no significant difference between the groups. When looking at the data there is a larger difference between groups at 1125 Hz and, while it is not significantly different it may be that a broader frequency range (e.g., 1250 Hz or above) may be more effective at revealing a group x frequency interaction.

Clinical Relevance.

The geriatric population is steadily increasing and it is important to better understand the underlying neural mechanisms of age-related hearing deficits. This understanding may help to find remedial therapies that could be effective in preventing and/or reversing these deficits. The FFR may help to identify older individuals who might require auditory training for temporal cues or that might benefit from signal processing devices aimed at enhancing temporal cues. Further research into the relationship of phase locked neural activity, as reflected in the FFR, and behavioral results from binaural listening tasks may provide a clearer picture of what deficits contribute to real-world listening difficulties.

Future Directions.

The FFR can be used to evaluate the physiological representation of frequencies where IPD can be measured behaviorally, allowing a comparison of perception and physiology. The intensity and duration of the stimulus used in this study is appropriate for both the FFR and for behavioral testing to facilitate an analysis of how the behavioral responses to binaural cues correlate with the physiological responses. Concurrent research involves the same participants and stimuli, however in that study, researchers are analyzing the perceptual IPD discrimination across frequencies along with speech in noise performance.

Analyzing correlations between the perceptual and physiological results from the same subject could help to better define age-related changes in hearing. While this study did not find a significant age x frequency interaction, as seen in behavioral studies of interaural phase differences, increasing the age range of our subject groups to include older participants and/or increasing the frequency range to include higher frequencies may show a significant interaction.

Continued research into the aging hearing system is essential for identifying physiological changes in the aging listener. Examination of these changes may indicate potential for future training programs for middle-aged adults to overcome these declines in central auditory function. Further, physiological responses such as the FFR-BIC may be eventually used to monitor treatment and assess outcomes.

Conclusions.

1. FFRs are most robust at lower frequencies and become poorer as frequency increases. This trend was seen across FFR metrics of amplitude and stimulus-to-response cross correlations.
2. At 500 Hz, summed monaural FFR amplitudes are smaller than the binaural FFR amplitude, indicating that binaural processing at 500 Hz may be different than at higher frequencies.
3. Age effects were not present in these data, indicating that middle-aged adults do not have significantly degraded FFRs within the frequency range tested.

References

Anderson, D. I. (1973). Quantitative model for the effects of stimulus frequency upon synchronization of auditory nerve discharges. Journal Of The Acoustical Society Of America, 54(2), 361. doi:10.1121/1.1913585

Ballachanda, B., & Moushegian, G. (2000). Frequency-following response: effects of interaural time and intensity differences. *Journal Of The American Academy Of Audiology*, *11*(1), 1-11.

Caspary, D. M., Ling, L., & Turner, J. G. (2008). Inhibitory neurotransmission, plasticity and aging in the mammalian central auditory system. Journal Of Experimental Biology, 211(11), 1781-1791.

Clinard, C., & Tremblay, K. (2013). Aging Degrades the Neural Encoding of Simple and Complex Sounds in the Human Brainstem. *Journal Of The American Academy Of Audiology*, *24*(7), 590-599. doi:10.3766/jaaa.24.7.7

Clinard, C, Tremblay, K. & Krishnan A. (2010), Aging alters the perception and physiological representation of frequency: evidence from human frequency-following response recordings. Hear Res 2010; 1-2; 48-55.

Cohen, Jacob. Applied multiple regression/correlation analysis for the behavioral sciences. 2nd ed. Mahwah, N.J.: L. Erlbaum Associates, 2003. Print.

Fowler, C. (2004). Electrophysiological evidence for binaural processing in auditory evoked potentials: the binaural interaction component. *Seminars In Hearing*, *25*(1), 39.

Fowler, C. & Beach, K. (2000). Binaural interaction in auditory evoked potentials: Effects of age, gender, and frequency. Paper presented at the annual convention of ASHA.

Gelfand, S. A. (2010). Hearing, an introduction to psychological and physiological acoustics (5 ed.). New York: M. Dekker.

Glaser E., Suter, C., Dasheiff, R., & Goldberg, A. (1976) The human frequency-following response: Its behavior during continuous tone and toneburst stimulation. *Electroencephaogr Clin Neurophysiol*; 40: 25-32

Gordon-Salant, S., & Fitzgibbons, P. (1999). Profile of auditory temporal processing in older listeners. Journal *Of Speech, Language & Hearing Research*, *42*(2), 300-311.

Grose, J.& Mamo, S. (2010). Processing of temporal fine structure as a function of age. Ear Hear, 2010; 6:755-60

Hopkins, K., & Moore, B. J. (2011). The effects of age and cochlear hearing loss on temporal fine structure sensitivity, frequency selectivity, and speech reception in noise. Journal Of The Acoustical Society Of America, 130(1), 334-349. doi:10.1121/1.3585848

Jeffress, L. (1948). A place theory of sound localization. *J. Comp. Physiol. Psychol*. 41, 35-39

Joris, P., Smith, P., & Yin, T. (1998). Coincidence detection in the auditory system: 50 years after Jeffress. Neuron, 21(6), 1235-1238.

Kelly-Ballweber, D., & Dobie, R. (1984). Binaural Interaction Measured Behaviorally and Electrophysiologically in Young and Old Adults. International Journal Of Audiology, 23(2), 181.

King, A., Hopkins, K., & Plack, C. (2014). The effects of age and hearing loss on interaural phase difference discrimination. The Journal Of The Acoustical Society Of America, 135(1), 342-351. doi:10.1121/1.4838995

Koch, U., & Grothe, B. (2000). Interdependence of Spatial and Temporal Coding in the Auditory Midbrain. Journal Of Neurophysiology, 83(4), 2300

Krishnan, A. (2007). Frequency-Following Response. In R. Burkard, M. Don, J. Eggermont, *Auditory evoked potentials: basic principles and clinical application*. (p 313-335) Philadelphia: Lippincott Williams & Wilkins.

Krishnan, A., & McDaniel, S. (1998). Binaural interaction in the human frequency-following response: effects of interaural intensity difference. *Audiology & Neuro-Otology, 3(5), 291-299.*

McAlpine, D., & Grothe, B. (2003). Sound localization and delay lines—do mammals fit the model?. Trends In Neurosciences, 26(7), 347-350.

McPherson, D., & Starr, A. (1995). Auditory time-intensity cues in the binaural interaction component of the auditory evoked potentials. Hearing Research, 89(1-2), 162-171.

Moore, B. J., Vickers, D. A., & Mehta, A. (2012). The effects of age on temporal fine structure sensitivity in monaural and binaural conditions. International Journal Of Audiology, 51(10), 715-721. doi:10.3109/14992027.2012.690079

Neher, T., Laugesen, S., So\gaard Jensen, N., & Kragelund, L. (2011). Can basic auditory and cognitive measures predict hearing-impaired listeners' localization and spatial speech recognition abilities?. *Journal Of The Acoustical Society Of America*, *130*(3), 1542-1558. doi:10.1121/1.3608122

Palmer, A. & Russell, I (1986). Phase-locking in the cochlear nerve of the guinea-pig and its relation to the receptor potential of inner hair-cells. *Hear Res 24*(1): 1-15.

Parthasarathy, T., & Moushegian, G. (1993). Rate, frequency, and intensity effects on early auditory evoked potentials and binaural interaction component in humans. Journal Of The American Academy Of Audiology, 4(4), 229-237.

Pichora-Fuller, M., & Schneider, B. A. (1992). The effect of interaural delay of the masker on masking-level differences in young and old adults. Journal Of The Acoustical Society Of America, 91(4), 2129. doi:10.1121/1.403673

Pickles, J. O. (2012). An introduction to the physiology of hearing. Bingley: Emerald Group Publishing.

Picton, T. (2013). Hearing in time: evoked potential studies of temporal processing. *Ear & Hearing (01960202)*, *34*(4), 385-401. doi:10.1097/AUD.0b013e31827ada02

Ross, B., Fujioka, T., Tremblay, K., & Picton, T. (2007) Aging in binaural hearing beings in mid-life: Evidence from cortical auditory-evoked responses to changes in interaural phase. J Neurosci 2007: 42: 11172-8

Strouse, A., Ashmead, D. H., Ohde, R. N., & Grantham, D. (1998). Temporal processing in the aging auditory system. Journal Of The Acoustical Society Of America, 104(4), 2385. doi:10.1121/1.423748

Woods, D., & Clayworth, C. (1986). Age-related changes in human middle latency auditory evoked potentials. Electroencephalography And Clinical Neurophysiology, 65(4), 297-303.

Worden, F & Marsh, J (1968). Frequency-following (microphonic-like) neural responses evoked by sound. Electrencephalography and Clinical Neurophysiology 25, 42-52.