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Envelope-following responses and the effects of cochlear delay

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Envelope-Following Responses and the Effects of Cochlear Delay

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Dedication

This document is dedicated to my parents. Thank you Andrea Funai and James Wall for all of your support, love, and guidance during both my undergraduate and graduate school careers that has lead to the culmination of this dissertation and subsequent Au.D. degree. Mom your humor, excellent advice, and drive is what has gotten me to this point in my life and gave me the desire to pursue this career. I know I can always count on you to tell me exactly what I need to hear. Dad, thank you for imparting in me a love for learning and desire to excel not only in my academic career but also in life. You have taught me so much. I am so blessed to have you as my parents and role models. A special thank you to my Nana who has always believed in and encouraged me to pursue my dreams. I also want to say thank you to Eddie, Deborah, Joey and the rest of my extended family who have supported and motivated me to never give up throughout these last few years. Finally, thank you to my husband, Matthew Jones, who has been along side me throughout this entire journey. Thank you for not only your dependability and words of wisdom, but also allowing me to use your brain for research. I am truly grateful for all of you.

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Abstract

There is great interest in developing clinical applications for phase-locked auditory potentials that are elicited by human speech. A common analysis of vowel-elicited responses is to analyze the envelope-following response (EFR) amplitude at the fundamental frequency (F0) of the eliciting vowel. For this study, we systematically examined the effect of modeled vowel formants on EFR amplitude. EFRs were elicited using a fundamental frequency of 103 Hz, representative of a male speaker's fundamental frequency. Stimuli consisted of two simultaneously presented sinusoidally amplitude-modulated tones with the same F0. One carrier frequency was fixed at 353 Hz, representing a first formant frequency; the carrier frequency of the other tone, representing a second formant frequency, varied across conditions. At each F0, different distances between the carrier frequencies targeted a range of cochlear phase delays (e.g., 90 to 180°). This study hypothesized that the amplitude of the EFR at the F0 of a complex sound would be affected by the cochlear travel delay related to the acoustic characteristics of the eliciting sound. The findings of this study did not show significant changes in response amplitude across stimulus conditions. Therefore, these results do not indicate that cochlear travel delay has a significant affect on envelope-following responses amplitude.

Introduction

Objective electrophysiological tests that use stimuli of pure tones, tonebursts, or clicks, such as the ABR, give an incomplete picture of the cochlea and auditory nerve's processing of speech. Therefore, there is interest in creating physiological tests using speech as the stimulus (Dajani et al., 2005). Human speech, particularly vowels, can be used to elicit phase-locked responses. These responses to the envelope of the stimulus are referred to as the envelope following response (EFR) and can be used to examine neural responses to speech within an individual. EFRs have been used to document normal processes related to neural representations of speech in young adults (Aiken and Picton, 2006; Skoe et al., 2015) and older adults (Anderson et al., 2012; Clinard and Tremblay, 2013; Vander Werff and Burns, 2011) (Appendix A). Additionally, recent research has looked at using the EFR for clinical application in hearing aid fitting and verification (Easwar et al., 2015a; Easwar et al., 2015b).

Much of the existing literature has focused on responses from one vowel (i.e., /a/) (Cunningham et al., 2001; King et al., 20002; Russo et al., 2004; Dajani et al., 2005), although recent studies have started to explore a variety of vowels and examined response amplitude at the vowel's fundamental frequency (F0) (Aiken and Picton, 2008; Bidelman et al., 2014; Easwar et al., 2015a). Studies involving multiple vowel stimuli have focused on the application of hearing aid verification by exploring the effects of sensorineural hearing loss on F0 response amplitude (Ananthakrishnan et al., 2016; Anderson and Kraus, 2013). EFRs may provide an objective measure of auditory function that goes beyond the cochlea and may give the clinician insight in how well the brainstem encodes temporal information. This information may be useful with infant and

difficult-to-fit hearing aid patients (Anderson et al. 2013). But, before clinical applications of vowel-elicited EFRs are developed, the effect of stimulus characteristics on the response amplitude must be better understood.

Brainstem responses to natural or synthetic speech, speech-like stimuli, and tones have been called auditory brainstem responses (ABRs), complex ABRs (cABRs), frequency-following responses (FFRs), and envelope-following responses (EFRs). The EFR is the focus of this paper. ABRs can be distinguished from EFRs in that the ABR is an onset response to a transient event, typically at the beginning of a stimulus, such as a click or tone burst (Moller, 1994). The cABR is similar to the ABR, but uses a complex stimulus such as speech or music that may persist for several seconds. These longer stimuli allow for the fine-structure elements such as timing, pitch, and timbre to be represented at the inferior colliculus (Moller, 1994). Complex ABRs are different than the traditional ABR in that the response waveform shows remarkable resemblance to its stimulus (Skoe and Kraus, 2010), making it more similar to the EFR. In contrast the frequency following response (FFR) is a sustained response that is synchronized to the periodicity of the stimulus and represents the temporal structure of the stimulus. The FFR reflects neural phase-locking that is most consistent with responses from multiple generator sites within the auditory brainstem, most likely involving the cochlear nucleus, trapezoid body, superior olivary complex, and the inferior colliculus (Krishnan et al.,2004). The FFR reflects the first formant, which is clearly represented in the FFR spectrum (Chandrasekaran and Kraus, 2010); this is in contrast to the EFR that represents the fundamental frequency.

The term envelope following response was first coined by Dolphin and Mountain (1991) to refer to the response from amplitude-modulated tones that followed the periodicity of the stimulus envelope. Thus, the envelope following response is a response that follows the periodicity of the fundamental frequency of the stimulus and this periodicity is what modulates the acoustic energy of the formant frequencies. The response energy for the EFR is at the modulation frequency; therefore this is where the response is analyzed. It is important to understand that the envelope frequency represents the excitation of neurons tuned to the carrier frequency, but responding to the periodicity of the modulation (fundamental) frequency; the fundamental frequency does not carry any acoustic information (Dolphin, 1997).

When using a broadband sound or complex stimulus the basal, high-frequency regions of the basilar membrane, are stimulated before the apical, lower-frequency regions, this is the cochlear traveling wave delay. Cochlear traveling wave delay refers to this process of the basal end being excited before the apical end. Phase cancellation, related to cochlear travel delays, occurs when two signals are being presented at the same time out of phase resulting in a reduction in the combined signal, this process was used in the production of the chirp stimulus (Elberling et al., 2010; Elberling and Don, 2008). From this previous research, it is known that cochlear delay affects amplitude and latency of the compound action potential and ABR waveforms. Click-evoked responses reveal that basal regions have many fibers stimulated synchronously, while apical fibers are stimulated in a less synchronous manner. Previous research has also shown that chirp stimuli in ABR recordings can be used to control the cochlear traveling wave delay

(Elberling and Don, 2010). However, the effects of phase cancellation on EFR amplitude have not yet been systematically examined.

Aiken and Picton (2006) examined EFR responses to four vowel stimuli, in the discussion section the authors mention that a possible explanation to the differences between response amplitude across their test conditions might be due to cochlear delay. They report that the responses from their data indicate that EFRs from the most extreme points of articulation seemed to have the most extreme differences in response amplitude. They hypothesized that these differences in amplitude across the vowel stimuli may be due to the formant structure of the vowels. They thought that the formants may excite the cochlea at different times, interacting across the basilar membrane to affect response amplitude, i.e. cochlear traveling wave delay may have an effect on EFR amplitude. They reported findings from a preliminary analysis showing that a model of cochlear traveling wave delay predicted amplitude differences between vowel-elicited EFR amplitudes. If similar phase cancellation effects are found for the EFR that were found for the ABR, then objective factors affecting stimulus audibility, such as degree of hearing loss and audiogram configuration, may be found to have differential effects on response amplitude as formant frequencies are modified. Therefore, the purpose of this experiment is to examine whether the acoustic characteristics of complex, vowel-like sounds interact with cochlear traveling wave delay to affect envelope-following response amplitude in young, normal-hearing adults.

Methods

Participants

Twelve young, normal-hearing subjects (ages 22 to 28, mean age of 23.8, 3 males) participated in this study. Inclusion criteria consisted of: unremarkable otoscopy, normal (type A) tympanograms, and audiometric thresholds ≤ 20 dB HL at octave frequencies between 0.25-8 kHz in each ear. All subjects completed an oral case history, ensuring they were monolingual native English speakers, had no known history of otological or neurological disease or trauma, had less than eight years of formal musical training, and were not currently taking prescription medications that were centrally-acting. These medications included those used for seizures, attention, or memory purposes. Artifact rejection and myogenic noise were monitored closely to minimize possible effects on the amplitude of the recordings. All methods and procedures used in this study were approved and in accordance with the Institutional Review Board (IRB) at James Madison University.

Stimuli

Stimuli consisted of pairs of sinusoidally-amplitude modulated tones. All stimuli were presented to the right ear at 60 dB SPL (John et al, 2003). Stimuli were presented via ER3-A magnetically shielded inserts with double length tubing. Stimulus duration was 1.024 seconds and stimuli were generated with a sampling frequency of 10 kHz. Alternating polarity was used to minimize stimulus artifact and any possible cochlear microphonic (Campbell et al., 2012). The stimuli were created to mimic vowels by using a fundamental frequency and first and second formants. It is known that the envelope following response can be examined using vowel stimuli in which the EFR is located at the fundamental frequency of the vowel (Galbraith et al., 1995; Won et al., 2016). A 103

Hz amplitude-modulation frequency, or F0, was used to approximate the average F0 of adult males (Figure 1)(Traunmüller & Eriksson, 1993). The first formant frequency remained constant in every condition at 353 Hz. The second formant frequency varied with each condition in order to target specific phase delays at the period of the fundamental frequency (Figure 2).

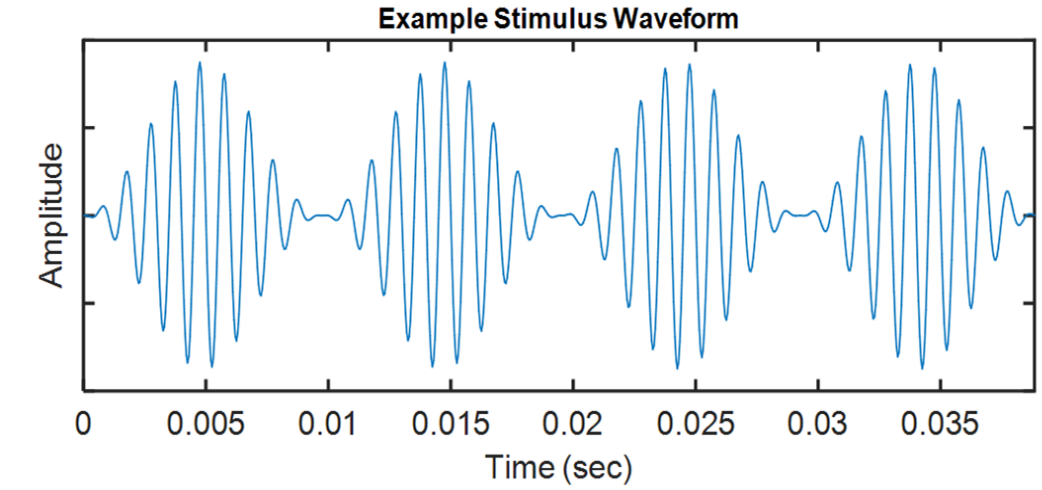

Figure 1: Example stimulus with 103 Hz fundamental frequency and carrier frequency of 1000 Hz. This example shows the first four amplitude modulated cycles of the stimulus waveform.

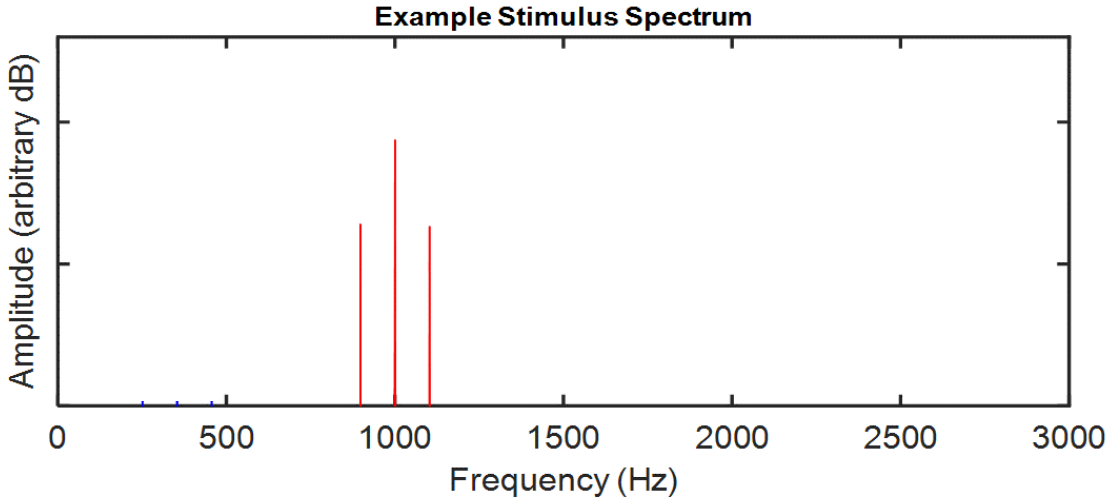

Figure 2: This is an example stimulus spectrum (digital signal from Matlab). Displayed are the first formant at 353 Hz (blue) and the second formant at 1000 Hz (red).

The phase delays used in this study were approximated after the cochlear delay model from Elberling and Don (2010). Frequencies were chosen that minimized overlap with 60 Hz electrical noise harmonics and carrier frequencies were at least one octave apart to minimize possible interaction (John & Picton, 2000). The following second formant carrier frequencies were chosen: 775, 995, 1326, 1850, and 2800 Hz which targeted phase delays of 90°, 112.5°, 135°, 157.5°, and 180°, respectively (Table 1). In addition to these five conditions there was also a sixth condition for only the 353 Hz stimulus in order to compare how response amplitude changed with the addition of the second formant. Figure 3 is a schematic representation of how the cochlear delay times between first and second formant frequencies correspond to different phase delays at the fundamental frequency. Different vowels have different formant structures and since formants carry the vowel energy, the EFR energy follows the modulation of the formants. Due to cochlear delay, the excitation along the cochlea for each formant does not occur at the same time across various vowels. Therefore, due to the different places of excitation along the basilar membrane, some formants may excite regions out of phase compared to other places. It is believed that when the formants excite regions out of phase it may result in a decrease in response amplitude. Conversely, formants that excite the cochlea in phase may result in phase summation and maximum response amplitude.

Table 1: Shows the six stimulus conditions and their estimated phase delays.

Stimulus Conditions						
	First "Formant" Only	Second "Formant" Conditions				
Frequency (Hz)	353	775	995	1329	1850	2800
Phase Delay (°)	N/A	90°	112.5°	135.2°	157.5°	180°

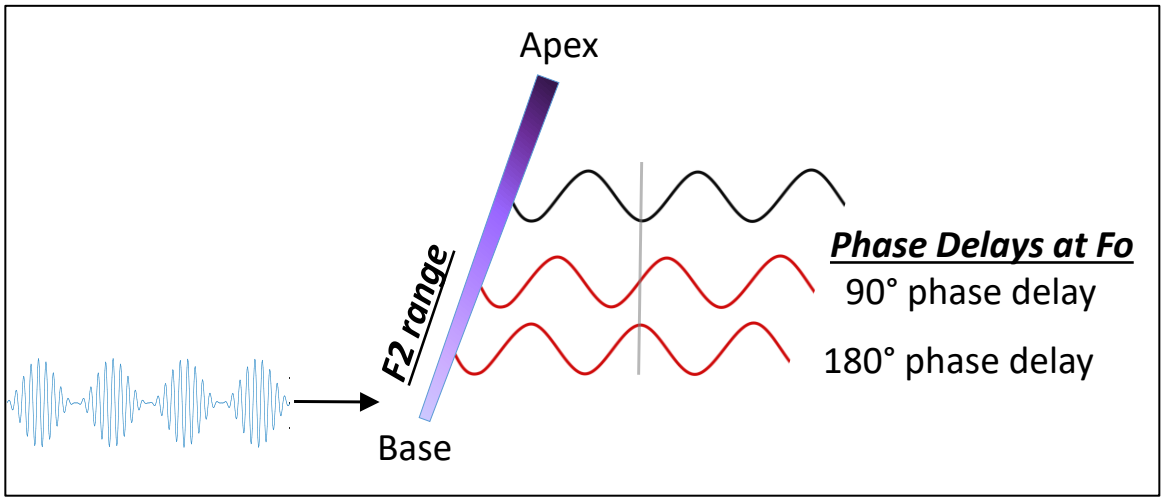

Figure 3: Schematic representation of how cochlear delay corresponds to different phase delays at F0. The black sinusoid represents the first formant condition: 353 Hz. The red sinusoids represent two of the possible second formant conditions: 775 Hz and 2800 Hz. Delay times corresponding to approximately 180° between F1 and F2 places are expected to result in minimal EFR amplitude [i.e., (1/F0)*0.5]. For this research, delay times corresponding to approximately 90° are expected to result in maximal amplitude.

Physiological Recording

A Neuroscan SynampsRT acquisition system was used to record EFRs. A single-channel electrode montage was used; the non-inverting electrode was at vertex (CZ), inverting electrode on the nape of neck, and ground electrode on forehead (Fz). Absolute

electrode impedances were below 3.5 kΩ and inter-electrode impedances were kept within 2 kΩ. Online activity was band-passed filtered from 30 to 3000 Hz with an analysis time window of 0-1.024 seconds and an analog-to-digital sampling rate of 10 kHz was employed. Artifact rejection was used to remove any sweeps with voltage exceeding ± 30 μV. A minimum of 1,050 artifact-free sweeps were collected for each condition. All testing was completed in a double-walled, sound attenuated booth. Subjects were seated in a reclining chair with feet propped up and instructed to relax, especially the muscles around their head, neck, and face. Additionally, subjects were asked to keep eyes closed and encouraged to sleep. The order of test conditions was randomized across subjects. Data collection typically consisted of one 3.5 hour-long session.

Physiological EFR Analysis

Data analysis was based on amplitude measures and occurred off-line using a custom Matlab program. The Matlab program analyzed averaged waveforms from individual subjects by performing a fast Fourier transform (FFT). Statistical analyses (i.e. F-test) were used to verify response presence with signal-to-noise ratios (SNRs) and p-values. EFR amplitude was obtained from the 103 Hz FFT bin, this bin is 1 Hz wide and centered at the 103 Hz frequency. The mean of five 1 Hz wide FFT bins, equal to ±5 Hz, above and below the response bin for a total of 10 bins were used for the noise estimate. This FFT bin was then used in order to analyze the response above the noise and give an SNR value. These results were analyzed in SPSS and a p-value of <0.05 was used as the criteria to determine if the EFR amplitude was significantly larger than the

surrounding noise bins, thus indicating response presence or absence. Signal-to-noise ratio was also measured to compare noise levels across phase delay conditions.

Normalized response amplitude was also used to compare trends across subjects. Normalized amplitude was calculated for each individual; their maximum amplitude served as their reference. Raw EFR amplitudes for that individual were divided by his or her own maximum amplitude. This procedure caused all subjects to have a maximum normalized amplitude of 1.0. Finally, amplitude change was analyzed, which refers to the response amplitude of a given condition compared to the F1-only condition response amplitude. To find the amplitude change, the response amplitude of a condition was compared to the amplitude of the F1-only condition of that same participant. By finding the difference between these two values, the amplitude change in decibels was measured. The following formula was used: *10*log10 (second formant condition/F1-only condition).*

Statistical Approach

Data analysis included a within subjects analysis with 5 levels, with the independent variables being the various stimulus conditions and the dependent variable being response amplitude. There was no between subject variable. One-way, repeated-measures analysis of variance (ANOVA) in response amplitude was used in order to determine if there were any statistically significant differences across the test conditions. Greenhouse-Geisser corrections were used when appropriate.

Results

Absolute Amplitude

A one-way repeated measures ANOVA in absolute amplitude was performed in order to compare absolute, or raw, amplitudes of each condition. This was a within subjects analysis with 6 levels, with the independent variables being the various stimulus conditions and the dependent variable being response amplitude. The main effect of phase delay was not significant [F (2.865, 31.512) = 1.911, p = 0.150, partial $\eta^2 = 0.148$]. The results from this analysis showed that amplitude across conditions did not change significantly, opposite of what was hypothesized. Within-subject quadratic and polynomial contrasts were not significant ($p > 0.05$). Figure 4 shows the average data for participants across test conditions. It is interesting that the 180° condition showed the largest amplitude, although it should be noted that this was not found to be a significant difference compared to other conditions. Two individual participants had much larger amplitudes at the 180° condition, likely increasing the average amplitude (Appendix B). Additionally, a paired samples T-test was completed in order to compare absolute amplitudes between the 90° and 180° conditions; the amplitudes were not significantly different ($t_{(11)} = -1.934$, $p = 0.792$).

Additionally, we examined the noise across the six conditions and the main effect of phase delay was not significant [F (5,55) = 0.736, p = 0.600, partial $\eta^2 = 0.063$]. It was important to monitor noise levels across conditions and participants to ensure that excessive noise was not contributing to the amplitude of the response. The average noise level across conditions was 0.0063 μV (Figure 4). As seen in figure 4, the light gray marks at the bottom of the graph are the average noise levels for each condition, these

data confirm that noise did not vary across stimulus conditions and was unlikely to influence response amplitude.

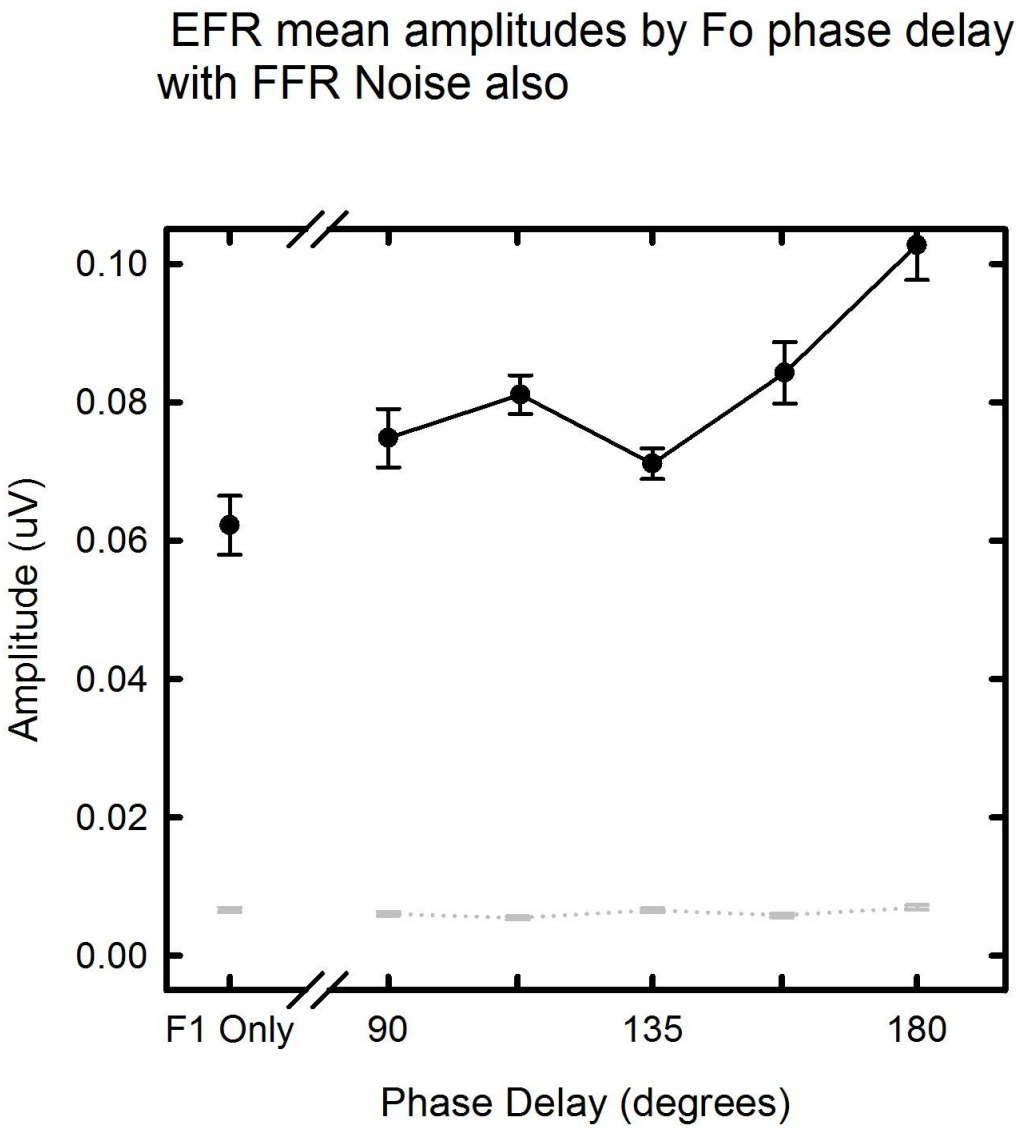

Figure 4: Average EFR absolute amplitudes across phase delay conditions. Note the broken x-axis to denote the separation between the F1-only condition and the phase delay conditions. The black line represents the average data with 1 standard error. The light gray line represents the average noise level for each condition.

Normalized Amplitude

Normalized amplitude was also examined in order to better compare response patterns across conditions and individuals. A one-way repeated measures ANOVA in normalized amplitude was completed. This also was a within subjects analysis with 6 levels, with the independent variables being the various stimulus conditions and the dependent variable being response amplitude. This analysis found that the main effect of phase delay was not significant [$F(5, 55) = 2.013$, $p = 0.091$, partial $\eta^2 = 0.155$]. By looking at figure 5, it is seen that EFR amplitude was not enhanced at shorter phase delays (closer to 90°) and actually appeared to increase at longer phase delays (closer to 180°). As mentioned previously, this is likely due to larger amplitudes from two individual participants (Appendix B). These results showed a similar data trend as the raw amplitude data above.

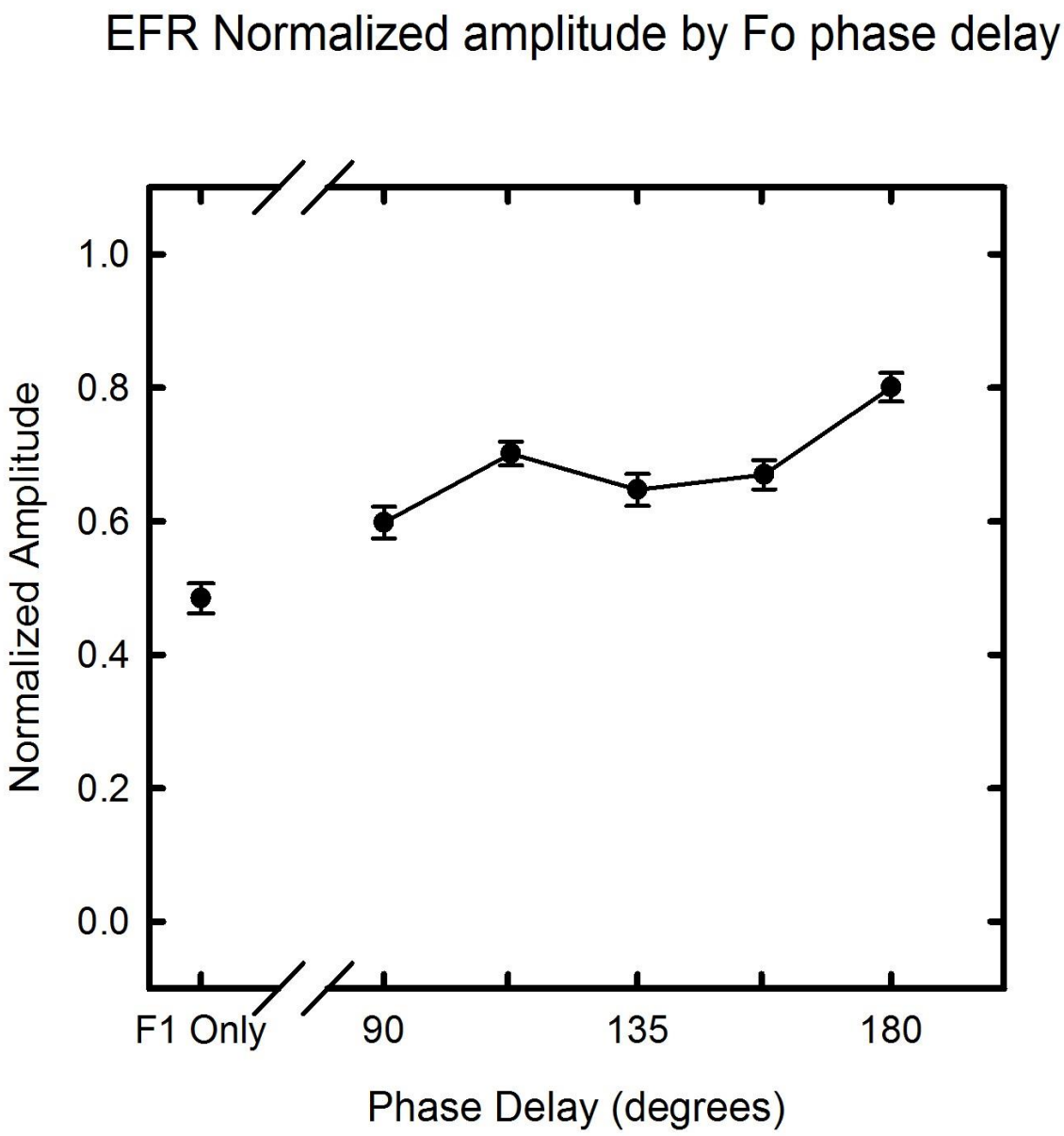

Figure 5: Average normalized EFR amplitude data across phase delay conditions with 1 standard error. Notice that there is a broken x-axis again to differentiate the F1-only condition.

Signal-to-Noise Ratio

Signal-to-noise ratio was also measured to compare noise across phase delay conditions. A one-way, repeated-measures ANOVA in SNR was completed. This was a within subjects analysis with 6 levels, with the independent variables being the various stimulus conditions and the dependent variable being response amplitude. Response SNR is shown for each stimulus condition in Figure 6. It is important to measure the level of the response above the noise floor. The main effect of phase delay for SNR was not significant [$F(5,55) = 1.293$, $p = 0.280$, partial $\eta^2 = 0.105$].

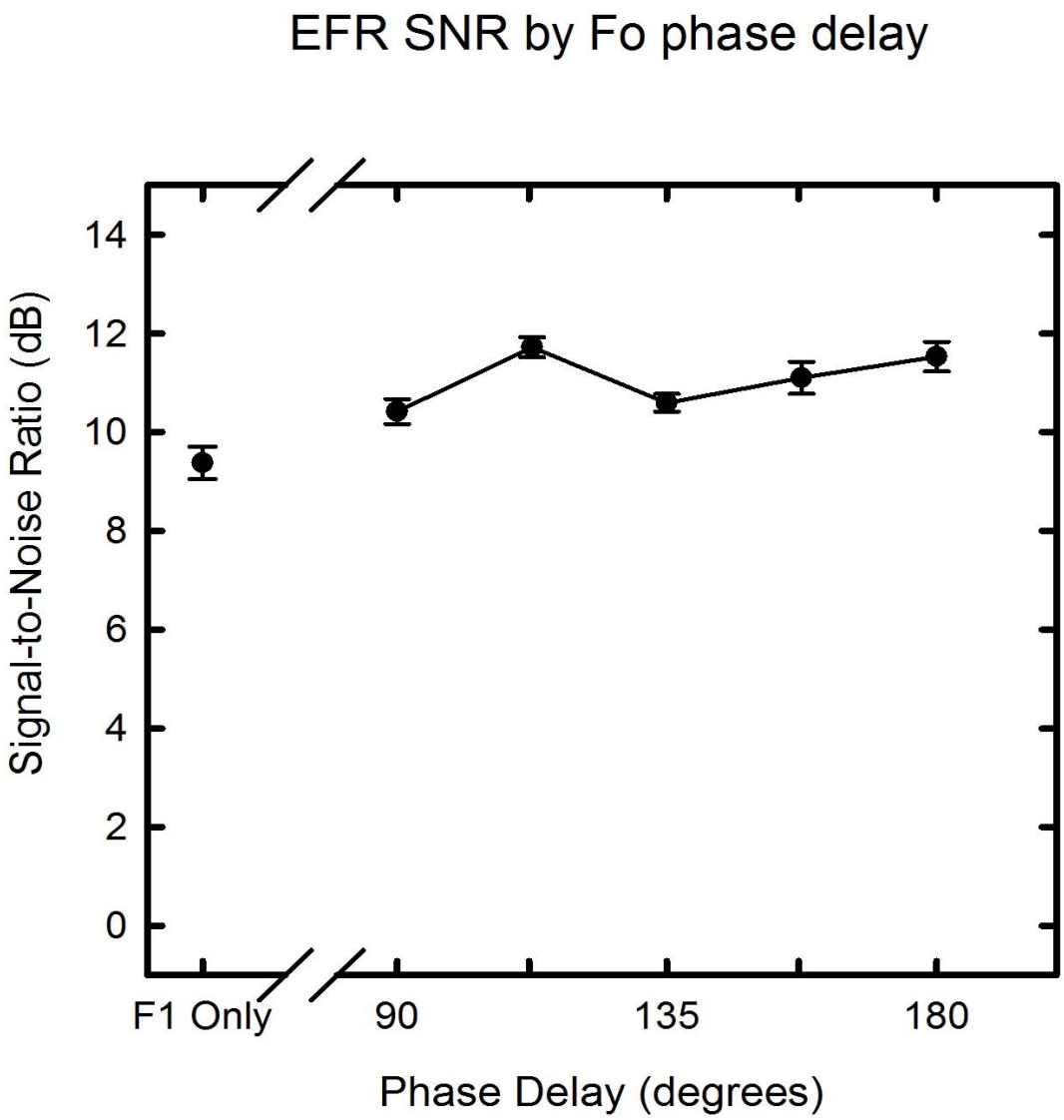

Figure 6: Average EFR amplitude across phase delay conditions. Error bars are on standard error.

Amplitude Change

Finally, amplitude change was examined in order to see how the amplitude varied between phase delays. A one-way repeated measures ANOVA in amplitude change was completed. This was a within subjects analysis with 5 levels, with the independent variables being the various stimulus conditions and the dependent variable being

response amplitude. The main effect of phase delay was not significant [$F(4, 44) = 0.908$, $p = 0.468$, partial $\eta^2 = 0.076$]. Which is consistent with previous findings indicating that amplitude was not significantly enhanced at shorter phase delays (closer to 90°) and minimum amplitudes were not observed at longer phase delays (closer to 180°) (Figure 7). It was expected that an approximate 3 dB increase in response amplitude would be seen at shorter phase delays, and that amplitude change would approach 0 dB as the phase delay reached 180°. However, those expected trends were not observed.

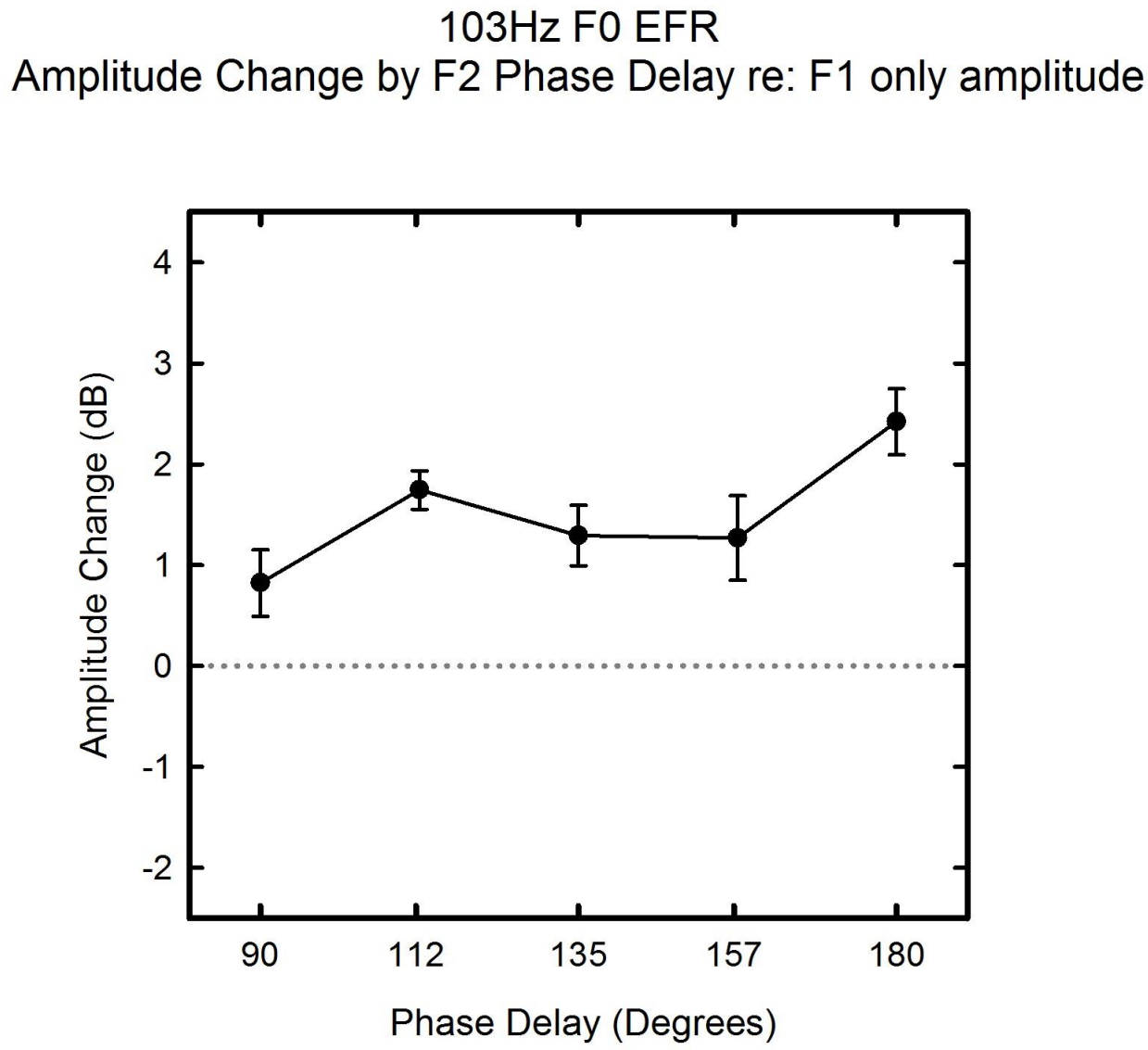

Figure 7: Relative amplitude change as a function of F2-F1 phase delay. Amplitude change (dB) is seen on the y-axis. The dashed line at zero represents no change in amplitude. Average data is shown in black with error bars representing one standard error. These data are consistent with previous figures findings.

Discussion

Phase Delay and EFR Amplitude

The present study examined the physiological EFR recordings to amplitude-modulated tones in young, normal-hearing listeners. The purpose of this study was to

establish possible cochlear delay effects on amplitude of the EFR recordings. This is important because previous research has already indicated that cochlear delay affects amplitude and latency of the click-evoked compound action potential and ABR, displayed visually in the Kiang Neurogram (Kiang, 1975). For example, click-evoked responses reveal that the basal region of the cochlea has many fibers stimulated simultaneously, while apical fibers are stimulated in a less synchronous manner. Further research has shown that controlling for cochlear traveling wave delay by using chirps enhances wave I and wave V amplitude (Don and Eggermont, 2010). Even though much attention has been given to the cochlear delay's effects on ABR amplitude, the effects on EFR amplitude have received little attention.

Aiken and Picton (2006) mentioned in their discussion section that models of cochlear delay explained EFR amplitude trends across vowel stimuli in their data. John et al (2003) mentioned that phase cancellation may reduce ASSR amplitude in broadband-noise elicited ASSRs. Therefore, this study was carried out in an effort to respond to these observations and to determine possible effects of cochlear delay time on EFR amplitude. Our proposed hypothesis prior to data collection was that EFR amplitude would be enhanced when the F1-F2 phase delay results in constructive phase summation (e.g. at approximately 90°). Conversely, we hypothesized that EFR amplitude would be reduced when phase delays result in destructive phase cancellation (e.g. at approximately 180°).

Overall, our results, using our specific stimuli, which only examined a small portion of the possible frequencies that may be examined, showed that there was not a significant finding to support the hypothesis that cochlear delay time affects EFR

amplitude. Results for raw amplitude and amplitude change analyses did not reflect significant differences across test conditions, showing that our test did not reflect the tendency for the EFR to be enhanced or reduced. These results show that EFRs elicited by the specific complex sounds we created are not influenced by cochlear delay time. Different vowels have different formant structures and since formants carry the vowel energy, the EFR energy follows the modulation of the formants. Due to cochlear delay, the excitation along the cochlea for each formant does not occur at the same time across various vowels. Due to the different places of excitation along the basilar membrane, some formants may excite regions out of phase compared to other places. Therefore, it was hypothesized that the cochlear delay time, may explain the variances in response amplitude found across various vowel stimuli from previous research (Aiken and Picton, 2006). Although our data did not reflect these findings, if the data from Aiken and Picton can be replicated it may have implications for future research and clinical applications of EFRs. Finally, it should be noted that the preliminary data for this research did not use alternating polarity. That preliminary data did show significance for changes in amplitude across the phase delay conditions (Appendix B, figure A6). Therefore a final consideration for this study is that alternating the polarity may have had an effect on the phase delay and/or response amplitude in order for the researchers to no longer find significance.

Clinical Implications

Vowel-elicited responses have been recommended for clinical use, and the analysis methods for these responses have focused on measuring the response at the

fundamental frequency (Clinard and Tremblay, 2013b; Easwar et al. 2015b). For persons with sensorineural hearing loss (SNHL), electrophysiological responses are typically assumed to be lower in amplitude. But, if using complex speech sounds, EFR amplitude may be increased even though there is decreased audibility. For example larger amplitudes may be seen in conditions where higher formants are not audible to the individual, preventing possible negative effects of the EFR phase summation which could explain results from some previous studies (Koravand et al., 2017). Thus the EFR may be enhanced in persons with high-frequency SNHL, therefore larger response amplitudes are not necessarily best.

There have been several studies that suggest that envelope coding may be enhanced in humans and animals with sensorineural hearing loss (SNHL) (Ananthakrishnan et al., 2016; Kale and Heinz, 2010; Anderson et al., 2013b). Kale and Heinz (2010) examined the physiological effects of SNHL on envelope coding in chinchillas. They found that response amplitude was actually enhanced in the chinchillas with noise induced SNHL when compared to those with normal hearing. This study also suggests the need to consider the effects of SNHL on envelope coding in evaluating perceptual deficits in the temporal processing of complex stimuli.

Additionally, other studies have examined stimuli that have been amplified. One study did this via insert earphones with stimuli that had been filtered using the NAL fitting formula and showed the same effect of larger amplitude Reponses in persons with SNHL compared to their normal hearing controls (Anderson et al., 2013b). Although, it cannot be determined whether this increase in amplitude is due to higher stimulus intensity rather than hearing loss. For example, studies have shown that simply

increasing the intensity, which is what we are doing when we fit hearing aids, increases the EFR amplitude (Easwar et al., 2015b). Therefore, there are several possible clinical applications for the EFR, but researchers and clinicians need to first understand responses and possible causes for changes in response amplitude.

Future Directions

In the present study, the majority of conditions only simulated two formants. Natural human speech is broadband and complex, with as many as five formants present in vowels. Using even more complex stimuli could provide interesting results since EFR interactions may be more complicated as the number of formants increases and their relative amplitudes are variable. (Bidelman et al., 2014; Anderson et al., 2012). By having more complex stimuli, the effects of cochlear travel delay may show significant differences in amplitude across conditions. Additionally, by completing this study by using a single polarity may also result in significant findings, as discussed previously.

Future studies could also explore the 180° to 360° phase conditions. By examining these phase delays, it will provide a more detailed picture of possible amplitude change across the entire basilar membrane. This research did not look at these further delays due to the limitations of the transfer function of the insert earphones with the fundamental frequency of 103 Hz and first formant of 353 Hz. Future studies could achieve these conditions using the fundamental frequency of 213 Hz, which would mimic the fundamental frequency of the average female voice (Traunmüller & Eriksson, 1993). Examining a thorough list of frequency conditions could also give a clearer picture of the exact delays that are being tested – since in this study no conditions showed significant

differences. By choosing phase delays that were evenly spaced, this research tried to obtain a broad picture of estimations of the phase delays, but by looking at even more phase delays, a finer and more detailed picture of phase delay may be obtained.

Conclusions

1. There were not significant changes in amplitude across conditions using vowel-modeled stimuli, as was hypothesized based on cochlear the travel delay model from Don and Elberling (2010)
2. Changes in EFR amplitude to various complex stimuli did not reflect hypotheses consistent with findings of previous research.
3. EFR amplitude did not show an increase at shorter phase delay or decrease as phase delays approached longer phase delays (approximating 180°).

Appendix A: Review of Literature

Introduction

There is a growing interest in the use of vowel-elicited auditory evoked potentials in clinical populations (Banai et al., 2009; Easwar et al., 2015). This type of test may be clinically useful for verifying hearing aids on adults, infants, and other unique

populations that do not respond well to subjective measures, such as overall patient satisfaction or Client Oriented Scale of Improvement (COSI) reports. Speech elicited ABRs, using consonant-vowel stimuli, have already been used in studies to compare response amplitudes of adults (Aiken and Picton, 2006; Anderson and Kraus, 2013). These studies also mention the importance of properly fit amplification in pediatric populations to ensure that language and cognition milestones can be reached.

Finally, an objective measure may be useful in fitting a "difficult-to-fit" patient who has been unsuccessful with hearing aids from various manufactures. By being able to objectively measure how the brain is processing the temporal structure of sound, an audiologist may be better able to adjust the hearing aid for higher patient satisfaction. The majority of audiological tests used to verify hearing aid benefit are subjective in nature. But since these tests require patient responses in order for highest benefit to be achieved, a patient who is unable to complete the task can make these subjective-based tests less valid. Thus, the need for an objective test measure to assess speech processing with these populations and their hearing aid fitting. Currently, the primary objective test used to ensure hearing aid targets are met is Real Ear, but simply making sure that speech and environmental noise is properly amplified at the output of the hearing aid does not mean that the fit will be successful.

Thus, the interests in the use of speech-evoked potentials to better test these populations. Auditory evoked responses are an objective measure and can be used in multiple ways. Similar to ABRs, which use tonebursts or clicks to measure a response, there is an interest to use vowel stimuli. This test is often referred to as a cABR (ABR to complex stimuli) and is currently being researched for the assessment of hearing aid

fittings as well as a treatment outcome measure. By having an objective brainstem measure, researchers can measure the brain's response to these speech stimuli instead of relying on subjective responses from patients. The focus of this study is the use of vowel-modeled stimuli. The vowel-like stimuli are more complex than toneburst stimuli, tonebursts excite more specific region of the cochlea whereas vowels excite multiple regions (Gorga et al., 1988). Moreover, vowels have fundamental frequencies and multiple formants that may interact in various ways and may have an effect on response amplitude. It is not yet understood how these complex stimuli excite the basilar membrane and the possible effects that this variation in excitation pattern may have on the amplitude of the response.

Envelope Following Response – An overview

The term envelope following response (EFR) was first coined by Dolphin and Mountain in 1991 to refer to the response from amplitude-modulated tones that seemed to follow the periodicity of the stimulus envelope. Since that time, the EFR has also been referred to as the amplitude-modulated following response (AMFR) and Auditory Steady State Response (ASSR) by some authors. The envelope following response is a response that follows the envelope of the speech, which is represented by the fundamental frequency. This envelope is what modulates the acoustic energy of the formant or carrier frequencies. This is a distinction from the FFR, because the FFR is thought to follow the first formant frequency (Aiken and Picton, 2006). The frequency following response is a sustained response that is synchronized to the periodicity of the stimulus and represents the temporal structure of the sound. The FFR reflects neural phase-locking that is most consistent with responses from multiple generator sites within the auditory brainstem,

most likely involving the cochlear nucleus, trapezoid body, superior olivary complex, and the inferior colliculus (Chandrasekaran and Kraus, 2010). It is important to understand that the EFR is analyzed at the envelope (modulation) frequency and that this envelope frequency represents the excitation of neurons at the carrier (formant) frequency and not due to excitation of neurons at the envelope frequency. The envelope frequency does not carry any acoustic information (Dolphin, 1997).

Conversely, the Auditory Brainstem Response (ABR) is an onset response to a transient event, typically at the beginning of the stimulus, such as a click or toneburst (Chandrasekaran and Kraus, 2010). The ABR represents the synchronous activity of the auditory nerve, cochlear nucleus , superior olivary complex, lateral lemniscus, and the inferior colliculus by the stimulus onset (Hood, 1998). Unlike click and toneburst ABR waveforms, which show no resemblance to their stimulus waveforms, EFR waveforms mimic their complex stimuli closely. As mentioned previously, the complex ABR is a measure of subcortical processing that uses complex stimuli such as speech or musical chords that may persist for several seconds. These longer stimuli allow for the representation of fine-structure elements such as timing, pitch and timbre representation with the response generator site is largely thought to be the inferior colliculus. The cABR is similar to the traditional ABR in that wave V of the traditional ABR overlaps with the response onset waveform of the cABR (Anderson and Kraus, 2013). The EFR is similar to the cABR in that they are both results of using complex stimuli, such as vowels.

As stated previously, there is an interest in developing a test to answer the problem of needing an objective measure of speech stimuli. Vowel elicited auditory

evoked potentials may be a possible solution. The vowel stimuli are similar to the stimuli used to record the auditory steady state response (ASSR) because they are more complex with different amplitude and frequency modulated tones. These modulated tones are the carrier frequency of the response and determine where on the basilar membrane the response will be excited and the frequency that it will be measured from. Speech stimuli are similar in that they have a natural carrier frequency, or fundamental frequency, which modulates all formant frequencies (Aiken & Picton, 2006).

Vowel-elicited auditory evoked potentials have already been studied in numerous other research projects for example: Akin and Picton 2006, Ananthakrishnan et al. 2016, and Easwar et al., 2015a, b, and c. These studies have shown that the neurons in the inferior colliculus are phase locked to the periodicity of the fundamental frequency, which is responsible for much of the envelope following response (Chandrasekaran and Kraus, 2010). They also eluded to how cochlear delay may explain EFR amplitude variance across vowels studied.

Cochlear Delay Affects Auditory Evoked Potentials

Aiken and Picton (2006) analyzed data from multiple conditions using various vowels. They found that when they were analyzing their data that response amplitude varied between their different vowel conditions; vowels that tended to elicit higher amplitude responses, where vowels that were in the most extreme points of articulation and thus most different in formant structure. When looking closer at the formant structure of these stimuli, it occurred to the researchers that the differences in cochlear travel delay may be the cause of the variations in response amplitude. The point of

excitation at the envelope of the vowel would be out of phase across the various points on the basilar membrane depending on the formant structure of the vowel (Aiken & Picton, 2006). By looking at the timing differences between the points of excitation across the basilar membrane certain delays can be hypothesized. For example, if the first formant frequency excites the basilar membrane's basil end and the second formant excites more apically, this could result in a time delay resulting in these stimuli exciting 180 degrees out of phase.

Chirp stimuli were created to sweep from low to high frequencies in an attempt to improve neural synchrony and maximize response amplitude (e.g., ABR) (Elberling and Don, 2008). Not only did examining the cochlear travel delay help create chirp stimuli, but it also lead to the development of the stacked ABR. The difference between the stacked and chirp ABR is that the stacked ABR attempts to compensate for cochlear delay in the output analysis of the response. Conversely, the chirp stimulus attempts to compensate at the input with a stimulus that sweeps across frequencies from low to high in order to increase neural synchrony (Elberling and Don, 2010). This same idea of cochlear delay is what Aiken & Picton (2006) were describing when they discovered that their vowel formants may have been causing differences in amplitudes between the various stimuli. There are many models of cochlear delay that use various mathematical formulas in an attempt to analyze the mechanical and physical properties of the cochlea and its effects on auditory evoked potentials. These models not only examine latency as a function of frequency, but also intensity (Elberling & Don, 2013).

Characteristics that Affect EFR Amplitude

There are a number of factors that can influence the amplitude of the EFR including changes in stimulus features as well as various patient characteristics. These variations of stimulus features include intensity, bandwidth, stimulus polarity, and modulation depth. Patient characteristics such as age, maturational changes, and inner hair cell damage have also been shown to have affects on EFR amplitude. Easwar and colleagues (2015a) examined the effects of stimulus intensity by comparing EFRs in young adults at two levels: 50 and 65 dB SPL using the /susaʃi/ stimuli. They found that there was a significant increase in response amplitude with increase of intensity for all eight carrier frequency conditions they tested. In a separate study the same group of researchers examined the combined effects of stimulus level and hearing aid amplification (Easwar et al., 2015b). They tested four conditions: 50 dB SPL via ER-2 inserts, 65 dB SPL via inserts, 50 dB SPL via hearing aids, and 65 dB SPL via hearing aids. They again confirmed the increase in response amplitude with increase stimulus via inserts, but also showed that response amplitude increased with use of amplification. Thus, an increase in level demonstrated a significant increase in response amplitude in unaided and aided conditions. Additionally, these studies examined the effects of stimulus bandwidth on response amplitude. They found that an increase in bandwidth up to 4000 Hz resulted in a significant increase in the EFR. Thus these studies confirm that the EFR is sensitive to changes in stimulus level, use of amplification, and bandwidth (Easwar et al., 2015a, Easwar et al., 2015b).

It has also been found that EFR is sensitive to the polarity of the vowel stimuli presented. Easwar and company (2015c) completed an experiment to examine individual's responses to changes in polarity of the EFR stimuli. The first part of the

study looked at the incidence and degree of differences in EFR amplitude to the /ɛ/ vowel in opposite polarities. They found that 30% of the 39 participants tested had response amplitudes that were significantly different between the two polarity recordings. Next, they examined the presence or absence of the first harmonic on the polarity sensitivity of EFRs. This time they used /u/, /a/, and /i/ vowels in two conditions: the first with the first and second (higher frequency) formants and the second with only the second formant presented. They found that there was only a significant effect of polarity with the /u/ stimuli when the first formant was present.

Dimitrijevic and colleagues (2016) looked at how monaural EFR recordings were affected by changes in amplitude modulation (AM) depth of the broadband noise stimulus. They had three groups of participants (younger, older, and a second older) in which they monitored EFR amplitude as they slowly changed the AM depth of their stimulus over time. They found that the effects of AM depth changes were larger in the younger participants when compared to the older participants. They discovered that older participants had a reduced dynamic range (which refers to how effectively they are able to physiologically differentiate between different AM depths) when compared to the younger participants. This finding shows that EFR amplitude is sensitive to changes in amplitude modulation, but it may depend on the person's age (Dimitrijevic et al., 2016). Therefore, this study suggests that aging affects the ability of the auditory system to encode subtle differences in the depth of amplitude modulation.

The second set of characteristics that affect EFR amplitude, those which are attributed to the participant. These include: aging, maturational changes, and hearing loss. As briefly discussed previously, Dimitrijevic (2016) showed that participant age

affects their physiologic ability to detect changes in AM depth of the broadband noise stimulus presented. Parthasarathy and colleagues (2016) examined differences in EFR amplitude in young verses older rat groups in two conditions: the first where the broadband noise stimulus was kept the same and the second where they varied intensity and carrier frequency. They found that there was a decrease in EFR amplitude with age. This decrease is thought to be caused by a loss of auditory nerve fibers combined with a decrease in the function of lower spontaneous rate fibers with aging (Parthasarathy et al., 2016). Therefore, there may be a reduction in temporal processing which is related to a reeducation in neural synchrony with aging.

Similar to aging, is the maturational process associated with early development. Typically we see increased amplitude of the EFR in more mature animals as a consequence of maturational processes occurring in the cochlea – these maturation processes increase the synchrony of the neural response to the stimulation, leading to greater response amplitude (Prado-Gutierrez et al., 2012). These maturational changes are most drastic during the first two years of life. Nodarse (2012) examined these maturational changes in two groups: newborns and two year olds. This study found that there are significant changes in EFR amplitude and detectability between these two groups. Other studies have also looked at the maturation process in rats to understand the changes in EFR responses and modulation frequency. They have shown that there is a "best modulation frequency" (BMF) which is defined as the modulation frequency which results in the largest amplitude response. By examining various modulation frequencies, Prado-Gutierrez et al. (2012) showed that there was a much steeper decrease in response amplitude with changes away from the BMF in younger rats compared to the older rats.

These results provided data for the development of predictor models to estimate temporal resolution of the auditory system during maturation, which may one day assist in establishing clinical norms for humans.

Hearing loss has also been shown to have an effect on EFR amplitude. Arnold and Bukard (2002) studied the effects of inner hair cell loss in chinchillas on EFR amplitude and showed that there was a decrease in amplitude at the level of the inferior colliculus but no significant change from the auditory cortex. Boettcher et al. (2001) recorded ASSRs to stimuli with high- and low-frequency pure-tone carriers and at various AM depths. They compared responses in normal hearing older adults and elderly with high-frequency hearing loss. They found that response amplitudes in the low-frequency carrier conditions were reduced compared with the normal hearing controls with no high-frequency hearing loss. Finally, Leigh-Paffenroth and Fowler (2006) examined high- and low-frequency carrier ASSRs at different amplitude modulation rates with some of the elderly subjects had some degree of high-frequency hearing loss. They found that subjects had reduced ASSR phase locking at all amplitude modulation rates tested. In conclusion, there are a number of factors that can influence the amplitude of the EFR including changes in stimulus features and patient characteristics. These include intensity, bandwidth, stimulus polarity, modulation depth, participant age, maturational changes, and inner hair cell damage have all been shown to have affects on EFR amplitude.

Vowel Elicited AEPs and Clinical Populations

As some of the previous studies mentioned above, there is a growing desire to use speech elicited auditory evoked potentials (AEPs) in clinical populations due to its

sensitivity to changes in stimulus level, bandwidth, and with use of amplification. But before these AEPs can be used for their potential clinical applications, further investigations are needed to explore stimulus and response relationship in aided conditions, especially in children (Easwar et al., 2015b). Koravand and associates (2017) examined 25 children, 13 normal and 12 with mild to moderately-severe sensorineural hearing loss and their responses to click versus speech-evoked ABRs. They discovered that responses to click ABR were the same, but when looking at speech-evoked ABR responses they found delayed latencies. This group also examined EFRs between the two groups of children; those with normal hearing and those with hearing loss. They found the children with hearing loss to have significantly larger amplitudes and longer in latencies when compared to the children with normal hearing. These results suggest that children with hearing loss may have a specific pattern of subcortical auditory processing and timing which may account for the changes in latency. Additionally, the enhancement of EFR response amplitude may be caused by a disruption in the ability of the inferior colliculus to control excitation and inhibition (Koravand et al., 2017).

Not only do speech-elicited AEPs have the clinical application of testing amplification, but there have also been studies completed which compared response waveforms of normally developing children and children with learning disabilities. It is hypothesized that children with learning disabilities, specifically those involving auditory processing, may exhibit abnormal encoding of stimuli. Therefore, it is important to continue to study the differences in response characteristics in normal hearing children, children with hearing loss, and children with developmental delays.

Summary

In summary it has been shown that there is a hole in the research of vowel elicited evoked potentials and the possible effects of cochlear travel delay on response amplitude. Variations of stimulus features and patient characteristics have been studied and shown to have affects on EFR amplitude, but stimulus interactions have not. Specifically, the EFR has been widely used in numerous studies that have confirmed the need for an explanation of the variances in response amplitude across the different conditions tested and the different vowel stimuli used; yet few researchers have examined these. This dissertation explored the question of this relationship between stimuli and the possible play on cochlear traveling wave delay. Additionally, it made an attempt to establish the feasibility of measuring the phase summation and phase cancelation associated with this delay. It is believe that there is still more work to be done on this topic and there are more conditions and vowel formants that need to be explored. It is believed that there are numerous clinical applications for speech evoked AEPs, some of which have already began to be explored, but there is more research to be done to fully understand the effects of hearing loss, maturation, and abnormal development plays on this response before clinical applications can be established.

Appendix B: Individual Data

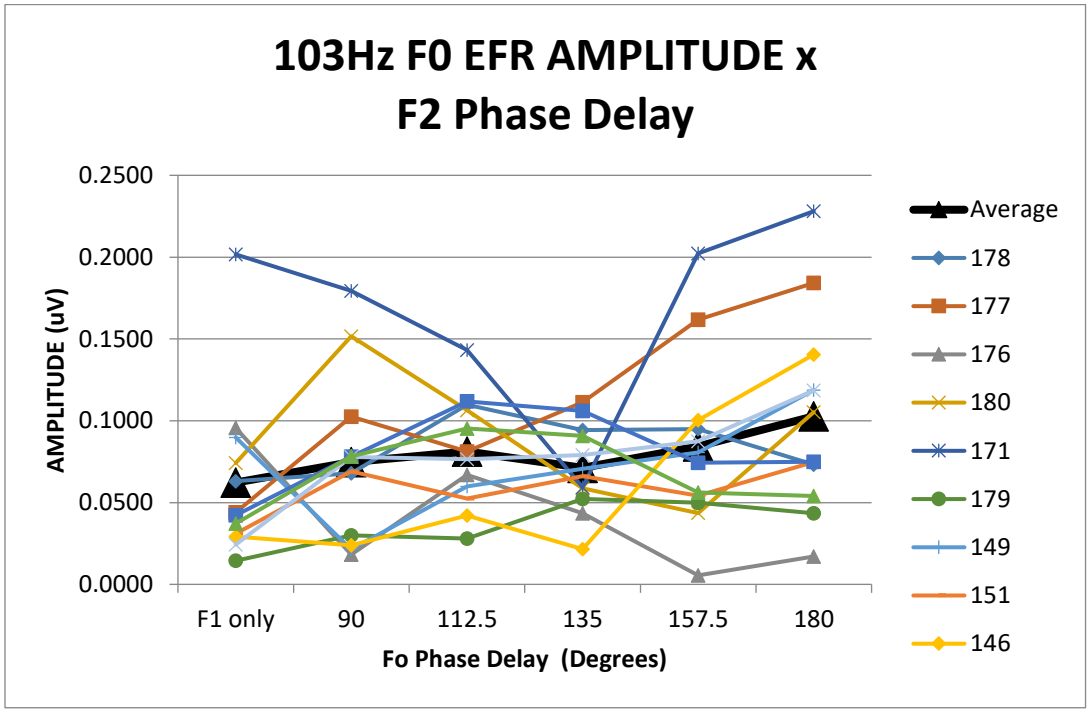

Figure A1: Average (black) and individual (color) EFR absolute amplitudes across phase delay conditions. Note the first point on the x-axis is the F1-only condition and the remainder of the x-axis is the phase delay conditions.

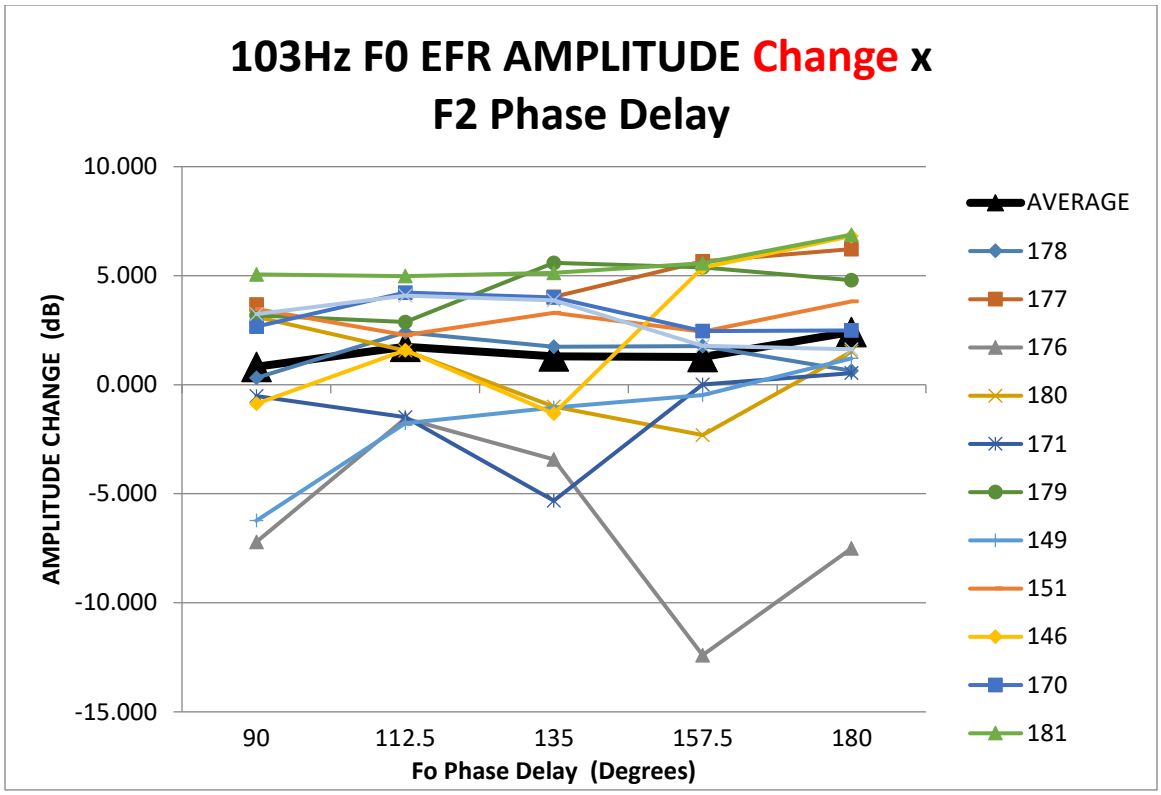

Figure A2: Relative amplitude change as a function of F1-F2 phase delay. Amplitude change (dB) is seen on the x-axis. Average data is shown in black and the individual data in colors. Again, note the first point on the x-axis is the F1-only condition and the remainder of the x-axis is the phase delay conditions.

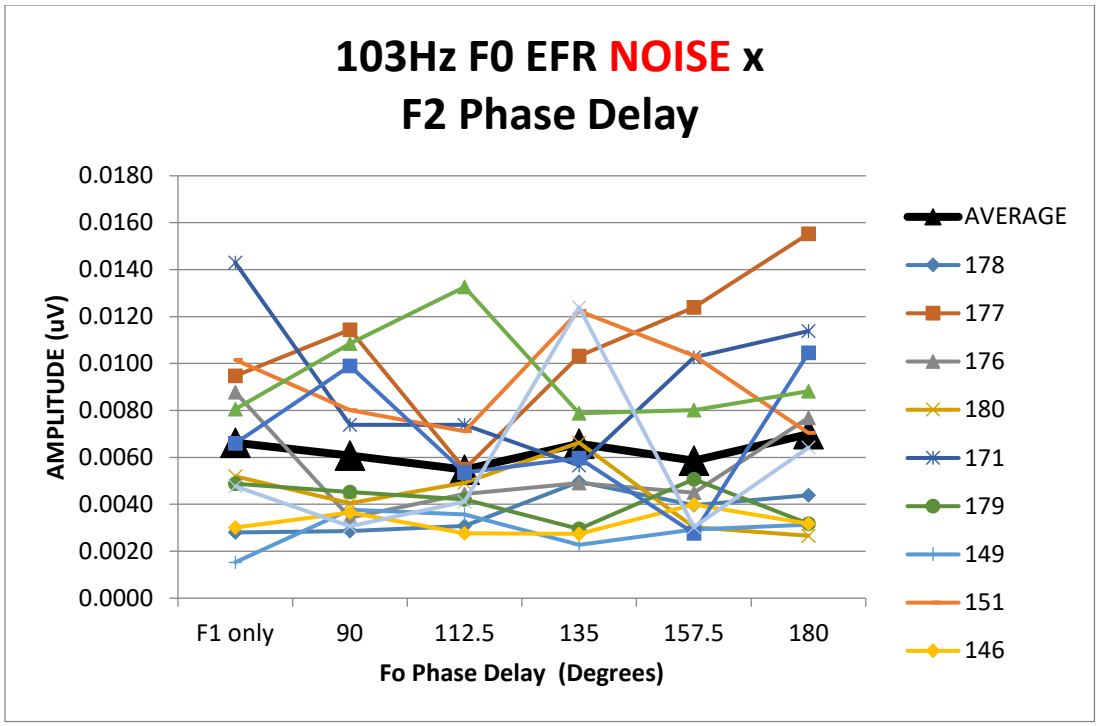

Figure A3: This graph shows the noise level (uV) across conditions. Average data is shown in black and the individual data in colors. Again, note the first point on the x-axis is the F1-only condition and the remainder of the x-axis is the phase delay conditions.

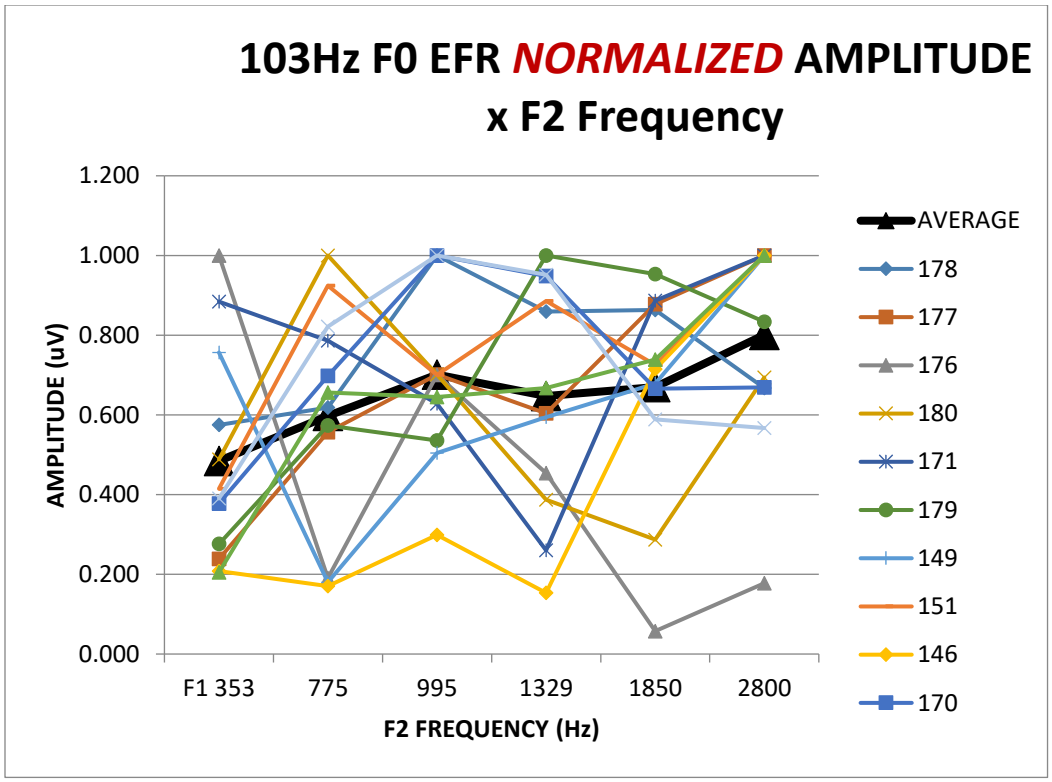

Figure A4: Average (black) and individual (color) normalized EFR amplitude data across phase delay conditions. Notice that there is the F1 only condition on the far left of the x-axis to differentiate from the other conditions.

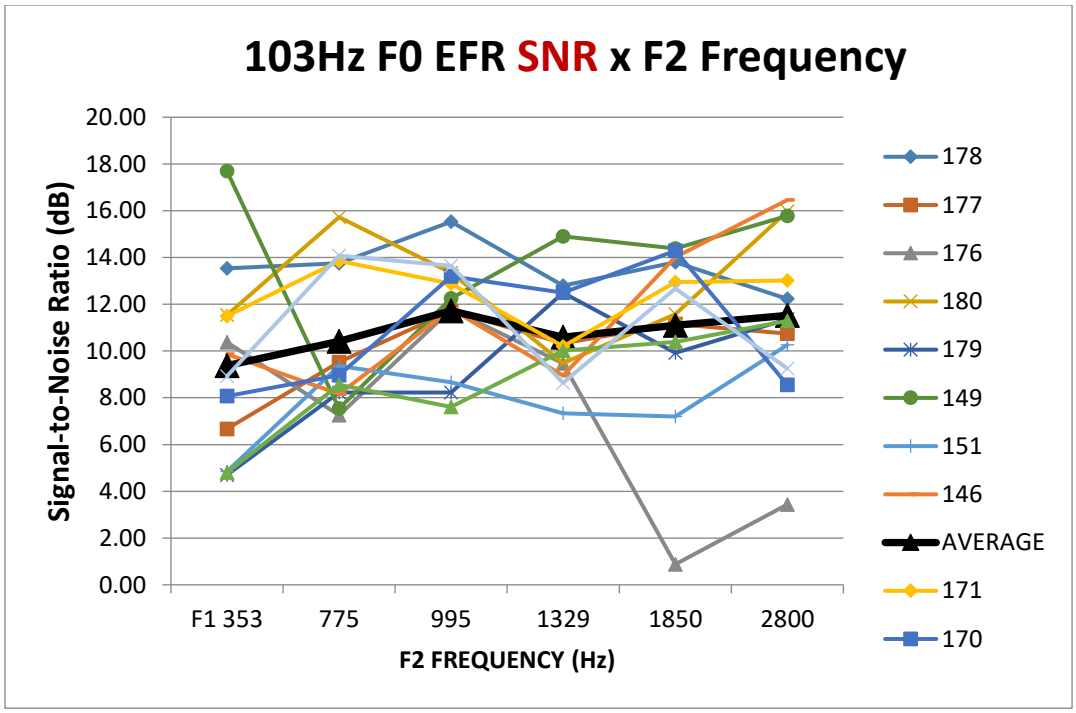

Figure A5: Average (black) and individual (color) EFR SNR values across phase conditions. Notice that the F1 only condition is separate from the phase delay conditions.

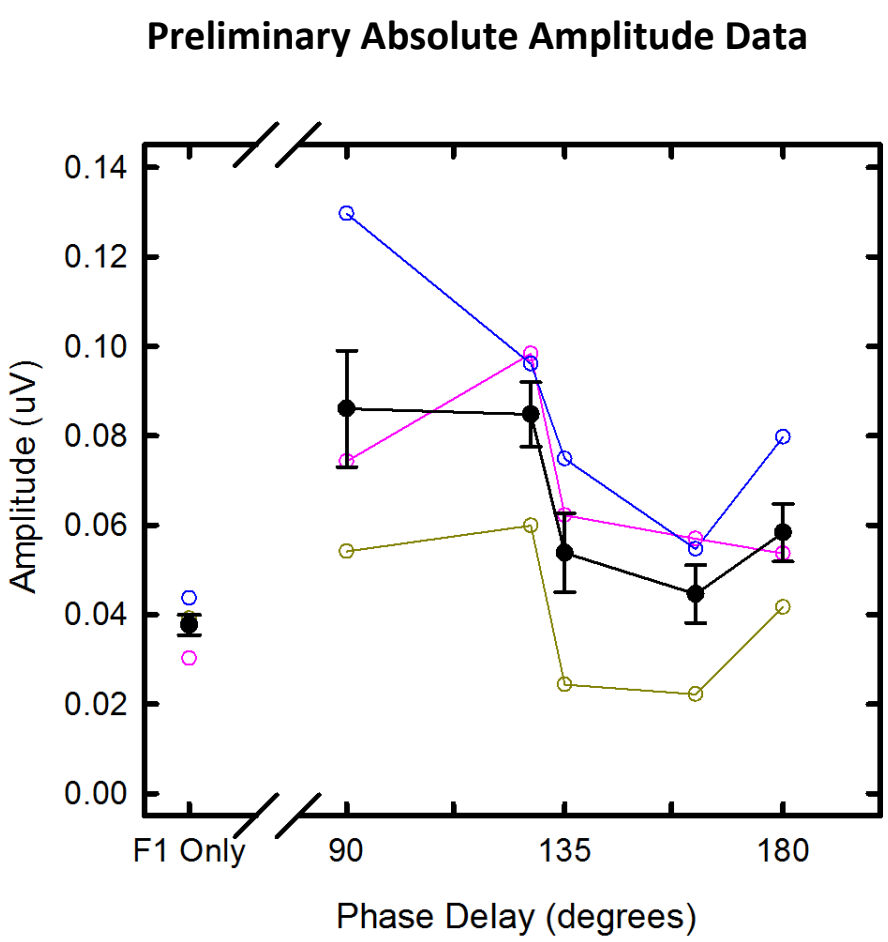

Figure A6: Preliminary data with single polarity stimuli showing individual and average EFR absolute amplitudes across phase delay conditions. Note the broken x-axis to denote the separation between the F1-only condition and the phase delay conditions. The colored lines represent the individual data. The black line represents the average data with 1 standard error. From this figure it is shown that amplitude is higher at phase delays closer to 90° and decreases as delay approaches 180°. (The main effect of phase delay was significant $F_{(5,10)} = 6.29$, $p = 0.011$ partial $\eta^2 = 0.732$)

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