A PARAMETRIC EXPLORATION OF THE PAIRED-STIMULUS SUPPRESSION PARADIGM

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As members of the Dissertation Committee, we certify that we have read the Audiology Doctoral Project prepared by ***Janette Mongelli***, titled ***A Parametric Exploration of the Paired-Stimulus Suppression Paradigm*** and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Audiology.

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ABSTRACT

The paired-stimulus suppression paradigm has been used to evaluate sensory gating in the auditory nervous system. Previous work in the AHEAD Lab has employed the paired-stimulus paradigm to investigate the perception of noise level or interference during speech perception tasks. In the present study, the effects of stimulus frequency and inter-stimulus interval were investigated as two previous experiments suggested that these could influence the amount of suppression observed. The aims of this study were to evaluate the effects of stimulus frequency and inter-stimulus interval on the latencies and amplitudes of the CAEP components evoked by each stimulus. Eleven normal hearing adults were tested using two-stimulus paradigms in which both stimuli were 500 Hz or 4000 Hz tonebursts, and the inter-stimulus intervals were varied in 100 ms steps between 100 and 500 ms. The results indicated that stimulus frequency had an effect on the CAEP onset response latencies and amplitudes, whereas inter-stimulus interval did not. Conversely, inter-stimulus interval had an effect on the CAEP response amplitude to the second stimulus (the suppressed response) whereas the effect of stimulus frequency was not significant. The results of these findings will be discussed with respect to the physiological mechanisms proposed to explain these differences and the possible translation of a two-stimulus suppression paradigm into a clinical test of acceptable noise level for those who use hearing aids.

Introduction

Cortical auditory evoked potentials and stimulus characteristics

Electrophysiologic tests, in the form of auditory evoked potentials, are used to evaluate the integrity and function of the peripheral and central auditory nervous systems. Many disciplines in addition to audiology, including psychology, psychiatry and neurology, use cortical auditory evoked potentials (CAEPs, also called late auditory evoked potentials) as a means of studying sensory, precognitive and cognitive function.

In audiology, CAEPs are used in a number of ways. Tsui et al (2001) used cortical evoked response audiometry in threshold determination in non-organic hearing loss, as it relates to disability compensation. Non-organic hearing loss is a person's report of hearing loss when no physiologic cause of hearing loss can be found. Although cortical evoked audiometry did not predict the pure-tone average for all participants in this study, the researchers concluded that it was useful as an objective measure of auditory functioning.

CAEP can also be used evaluate children with neuropathy (AN) and provide a reasonable correlate of speech perception. Rance and colleagues (2002) tested a group of 18 children with AN to see if there was a relationship between speech understanding and CAEP responses and compared their performance to an age-matched group of children with sensorineural hearing loss. In 8 of the 15 children able to complete aided and unaided speech perception testing, CAEP responses had normal latency, amplitude, and morphology; these children had word recognition abilities comparable to their peers with SNHL. Seven of 15 children had little to no open-set speech perception abilities; in those children, the CAEP response was absent. The researchers concluded that cortical evoked potentials were a good predictor of speech perception abilities for children with AN who use amplification.

There is also a significant body of literature regarding the presence of CAEP responses in cochlear implant (CI) users. Sharma, Dorman, and Spahr (2002) measured the CAEP responses of 22 congenitally deaf three-year-olds after cochlear implantation; immediately after implantation, cortical evoked responses were present with morphology similar to a newborn. After 8 months, these children's cortical responses were found to be consistent with their normal-hearing peers', thereby providing a window into the neuroplasticity and development of the auditory system following sound stimulation.

The CAEP "onset response" consists of three main components, P1, N1 and P2, illustrated in Figure 1. The main neural generator for these components is the supratemporal plane, which encompasses both Heschl's gyrus and the planum temporale; however, other neural structures likely contribute to the CAEP response as well (Picton et al., 1999; Musiek & Baran, 2020). The expected latencies of each component are as follows: P1 (~50 ms), N1 (80-100 ms), and P2 (180-200 ms) (Picton, 2011). The P1-N1-P2 complex is a robust response and can be evoked by a variety of stimuli, including clicks, rising frequency chirps, tone bursts, and speech tokens. It is well-documented that the characteristics of the stimulus are directly related to the response characteristics (amplitude and latency) of the evoked response. Frequency, intensity, and rate changes in the stimulus have been shown to affect the latency, amplitude, and morphology of the CAEP response. Jacobson et al. (1992) researched the effects of stimulus frequency on the latency and amplitude of CAEP component N1. The researchers compared responses to randomly presented 250, 1000, and 4000 Hz tone bursts presented at a rate of 0.33 Hz. They found that increasing stimulus frequency resulted in decreasing amplitude of the CAEP response, and that the amplitude of the response to the 250 Hz stimulus was significantly greater than that of the responses to 1000 and 4000 Hz. Additionally, there were effects of frequency on

latency; specifically, the average latency of N1 responses to 250 Hz was 13 ms longer than those of 1000 and 4000 Hz.

There is also a relationship between the level of the stimulus and the latency of the evoked response. Research by Antinoro, Skinner, and Jones (1969) from the Auditory Research Laboratory at the University of Arizona examined the relationship between 125, 500, 1000, 2000, 4000, and 8000 Hz tones at five intensity levels (20, 40, 60, 80, and 100 dB SPL). They found that there was a consistent growth in peak to peak amplitude with increasing intensity from 20-100 dB up to 2000 Hz, but above 2000 Hz the amplitude did not change consistently as a function of stimulus level. Additionally, the peak to peak amplitude decreased with increased frequency, independent of level, which is in agreement with previous research on the effects of stimulus frequency on AEP amplitude.

Although rate and interstimulus interval (ISI) are considered different stimulus parameters, they are often two sides of one coin, given that they both specify the onset of stimuli. Typically, rate is specified as the number of stimuli per second (1/s, 10/s), while ISI represents the length of time between presentation of subsequent stimuli. The rate of presentation of stimuli directly affects the latency, amplitude and "morphology" of the evoked potential waveform, and this is true across ABR, MLR, and CAEP testing. Jewett and Williston (1971) noted a "loss of definition of the [ABR] wave components" with an increase in stimulus rate. Not only was wave morphology affected, but replicability suffered as well. The researchers concluded that an ideal stimulus rate was 2/s. Don, Allen, and Starr (1977) examined the relationship between click rate and latency of ABR responses. The researchers measured ABR responses to click rates of 10, 30, 50, and 100/s at four intensity levels (30, 40, 50, and 60 dB SL). They found that the latency of wave V varied as a function of click rate and stimulus level but there was no interaction between

these two stimulus factors. The latency of wave V increased concomitantly with each increase in click rate; there was an approximate 0.8 ms total prolongation in wave V latency between 10/s and 100/s. This increase in latency was consistent regardless of stimulus level.

Davis and colleagues (1966) also investigated the effects of interstimulus interval on "auditory late responses" (CAEP). Although the most robust responses occur with the longest ISIs of 6-10 s, Davis et al. found that the characteristic response did not change significantly until the ISI was decreased to 0.5 s (500 ms). When the ISI was reduced past 0.5 s, clear changes in CAEP wave morphology and amplitude were seen. Additionally, the researchers noted that the overall amplitude of the CAEP response is related not only to the ISI between two stimuli, but the entire number of stimuli played over the testing duration. When stimuli were played in pairs, rather than in trains, the response to the first stimulus in a pair was larger than the response to the second (and subsequent) stimuli in a train. The researchers used tone pips but averaged across the stimulus frequency variable; they found (what we will call) a suppression ratio of 0.5.

Related to the effects of ISI on CAEP is the so-called "two-click" or "paired-click" paradigm. In the paired-click paradigm two stimuli are presented at a 500 ms interstimulus interval, with 5-10 seconds between each pair (Bruin et al., 2001; Müller et al., 2001). This paradigm has been used as a metric for the construct of sensory gating. The concept underlying sensory gating is that the brain responds less to a repetitive stimulus than to unique stimuli, or even stimuli that have not occurred recently (Picton, 2011). Thus, sensory gating is a process by which the brain filters extraneous information. Sensory gating can also be considered as the forward masking or suppression of the response to the second stimulus of the pair. Reduced sensory gating, then, manifests as decreased suppression in response to the second stimulus. In other words, the amount of latency shift and amplitude decrement of the second response relative

to the first is used as an indicator of suppression or sensory gating. The greater the latency shift and/or amplitude decrement, the greater the sensory gating. To calculate the degree of suppression, one must analyze the P50 response (in MLR), which is the same component as the P1 (in CAEP). This is calculated by dividing the amplitude of the P1 response to the second stimulus (S2) by the amplitude of the P1 response to the first stimulus (S1) of the pair. Despite this common method, there is disagreement in the literature with regard to the best way to calculate suppression. The method described above seems to dominate paired-stimulus methodologies, but some researchers have suggested that subtracting the responses (S1—S2) may be a better metric than the traditional ratio (Dalecki, Croft, & Johnstone, 2011). Dalecki and colleagues argue that the difference measure rather than the ratio is a more reliable measure of suppression, given the variability in the P50 response, the length of time required in each recording session (typically 20-60 minutes), and the number of trials presented.

Sensory gating has also been studied using these methods in special populations, particularly people with schizophrenia. Schizophrenia is a disorder marked by disturbances in sensory processing across modalities (Javitt, 2009). Auditory function in people with schizophrenia has been studied at length, particularly, suppression in the paired-stimulus paradigm (Clementz et al., 1997; Kathmann & Engel, 1990; Freedman et al., 1997; Brown et al., 2002). Researchers have hypothesized that poorer or less effective suppression would be present in schizophrenics, because of the disturbances in sensory processing including gating. Although there are conflicting conclusions regarding the extent to which gating is affected, it is generally seen that those with schizophrenia exhibit less suppression than those with typical neurologic status (for review, see citation).

Sensory gating, acceptable noise levels, and research in the AHEAD Lab

In recent years, the AHEAD lab has been researching a construct known as "acceptable noise levels" and their electrophysiologic underpinnings. The research presented in this paper is following a line of questioning started by Griffitts (2015) and continued by Everett (2017). These Audiology Doctoral Projects formed the springboard for my investigation.

The acceptable noise level (ANL) test was developed by Nabelek and colleagues (1991; 2004; 2008) as a measure of how much background noise a person can tolerate while listening to speech. Although the connection between ANL and listening with hearing loss is not immediately apparent, it is relevant because one of the primary reasons people reject hearing aids—or never adopt them—is an inability to tolerate amplified background noise while trying to understand speech (Brooks, 1985; Kochkin, 2007). As such, ANLs are proposed to be a predictor of individuals' success with hearing aids. ANLs are calculated by subtracting the amount of background noise a person can tolerate from their most comfortable level when listening to speech; thus, a higher ANL is a poorer score.

Griffitts (2015) conducted research to explore whether the ANL test does indeed have electrophysiologic correlates. Previous studies (Brännström et al., 2012; Tampas & Harkrider, 2006) examined the relationship between ANL scores and electrophysiologic measures. Tampas and Harkrider found correlations between ANLs and AEPs, with poorer ANLs associated with larger amplitudes of MLR and CAEP, and earlier latencies of waves III and V on the ABR. The researchers interpreted these findings to mean that that poorer ANL scores were indicative of poorer inhibition or suppression at the cortical level. When Brännström et al. attempted to

replicate these findings, they were unable to find any relationship between ANL and auditory evoked potentials.

In the AHEAD lab, Griffitts attempted to replicate these studies and expand upon them by addressing sensory gating and performance in quiet as well as background noise. He hypothesized that poor ANL scores would be associated with reduced suppression, measured in a two-click paradigm. He also investigated whether there was a relationship between ANL and the cognitive evoked potential, P300, evoked while listening in noise. Like ANL, an essential part of the P300 response is the participant's auditory attention to a target stimulus when presented in an oddball paradigm.

First, Griffitts determined ANLs for each participant. Following methods established by the Nabelek et al. (1991) he used a bracketing method to obtain most comfortable listening level (MCL) while listening to a story. Then, while listening to the same story, participants' maximum background noise level (BNL) was established; that is, the maximum BNL they could tolerate while still being able to follow the story. ANL was calculated by subtracting BNL from MCL for each participant. This was repeated three times, so that each participant had an ANL for their own most comfortable listening level (MCL), and for the story presented at 65 and 70 dB HL (Griffitts, 2015).

Next, click stimuli were presented to participants in the two-click paradigm. These clicks were 100 microseconds each, presented at an ISI of 500 ms, with 2 s between pairs. Participants were required to stay awake during testing, but did not have to pay attention to the stimuli. For the P300 test, tone bursts of 500, 1000, and 3000 Hz were presented in an oddball stimulus paradigm with ISI of 1800 ms +/- 30 ms. This was performed in quiet and then with the 8-talker babble background noise from the ANL test presented at the individuals measured ANL.

Participants were asked to press a specific button each time they heard the 500 or 3000 Hz tones, with no response required for the 1000 Hz tone.

Griffitts found that the CAEP amplitude in response to the second click was smaller than the response to the first click, with the mean suppression ratios for P1, N1, and P2 at 0.56, 0.42, and 0.51 (0.21, 0.16, 0.38 SD), respectively. Although there is significant variation in the literature, a suppression ratio of approximately 0.5 or greater seems to be in the normal range (Clementz, Geyer, & Braff, 1997; Dalecki et al., 2011; Müller et al., 2000; Nagamoto et al., 1989). Suppression was thus present for each component of the CAEP response; however, Griffitts did not find a strong association between suppression and ANLs.

Griffitts also found that the latency of the P300 response in noise was delayed compared to the P300 response in quiet, suggesting that auditory processing is delayed by the noise. Additionally, the amplitude of the P300 in noise was reduced compared to the response in quiet, suggesting that auditory processing resources were reduced by the noise background (i.e., masking) or that individuals were less accurate when noise was present. Overall, there were weak to moderate associations found between ANL and their potential electrophysiologic correlates. Griffitts suggested that an experiment in which two-click suppression was measured in the presence of background noise could provide more insight into an association between ANL and cortical inhibition in the presence of noise.

Building upon Griffitts' research, Everett (2017) further studied cognitive and electrophysiologic correlates of listening in noise. The goal of her research was to measure the effects of cognitive load on ANL and measure its electrophysiologic correlates. She hypothesized that the introduction of a cognitive load would result in longer latencies and smaller amplitudes, and that lower ANLs would be associated with more CAEP suppression.

To test this hypothesis, she measured ANL with and without an additional cognitive load, measured CAEP in one-chirp and two-chirp paradigms to evaluate sensory gating, with and without a cognitive load. She then correlated ANLs with CAEP results.

ANLs were obtained using the same bracketing method set out by Nabelek et al. (1991). In one condition, background noise was presented unilaterally; in a second condition, the background noise was presented bilaterally. Everett's behavioral cognitive load task consisted of participants memorizing seven random numbers after being presented with them for 15 seconds. Following that, participants were asked to recite the alphabet backwards, skipping every 1, 2, or 3 letters, as quickly as possible for two minutes. If a mistake was made during the recitation, the were asked to start over. After the two-minute recitation task, they were asked to repeat the seven numbers they initially memorized. Participants were scored on whether they repeated the numbers correctly and by how many times they restarted the alphabet task. This cognitive load task was completed in three conditions: in quiet, in multi-talker babble at their predetermined BNL, and in a third noisy situation to determine a modified BNL with respect to cognitive load.

Cortical auditory evoked potentials were measured in a 1-chirp and 2-chirp paradigm. Rising-frequency chirps were selected because they have been shown to elicit greater wave V amplitude in the ABR (Elberling, Callo, & Don, 2010; Elberling, & Don, 2008; Fobel & Dau, 2004). Further research demonstrated that rising-frequency chirps generated significantly greater Na-Pa and Pa-Nb MLR amplitudes as compared to clicks (Atcherson & Moore, 2014). There has been little research to determine whether the response evoked by the chirp at the level of the cortex will differ from that generated by a click, but this was one of Everett's areas of interest. In the 1-chirp test, stimuli were presented at the rate of 1/s. They were presented in quiet, while counting out loud (a motor control condition), in quiet while completing the cognitive load task,

and in noise presented at the participant's BNL. For the 2-chirp test, two chirps were presented at an interstimulus interval of 500 ms, with 3 seconds between pairs. The 2-chirp test was presented in quiet, at BNL, and at the participant's modified BNL obtained with the cognitive load task.

Everett found that the addition of the cognitive load task significantly impacted participants' ANLs, with a mean change of 22 dB in the unilateral condition and 14 dB in the bilateral condition. No significant effects of cognitive load on CAEP amplitude or latency were found for the 1-chirp paradigm. In the 2-chirp paradigm no significant changes in latency were noted as a function of test condition. In the 2-chirp paradigm, amplitude ratios were calculated by dividing the amplitude of each component in response to the second chirp by the amplitude of the component in response to the first chirp. Everett expected the CAEP amplitude in response to the second chirp to be reduced compared to the amplitude in response to the first chirp, as they would be for clicks, but this was not a uniform finding. In fact, the mean suppression ratio was XX in the quiet condition. Additionally, although there was a trend toward significance, there were no statistically significant differences in CAEP amplitude as a function of cognitive load condition. Everett noted that there was pronounced variability in latency and amplitude across conditions, which likely affected the ability to find significant differences across conditions.

Rationale for current study

Following Griffitts and Everett's research, we had questions about stimulus parameters and how they affect responses at the cortical level. Both Everett and Griffitts hypothesized that acceptable noise levels were related to sensory gating, but had very disparate stimulus-pair suppression ratios for click-evoked vs. chirp-evoked responses.

This research was designed as a parametric exploration of stimulus frequency and interstimulus intervals for the paired-stimuli paradigm. The hypothesis was that both frequency and ISI would have an effect on cortical evoked potentials, and that varying those parameters would result in measurable differences in the amplitude, latency, and morphology, and paired-stimuli suppression ratios of the cortical auditory evoked potential. The premises on which the hypothesis was based are the known effects of ISI and frequency on cortical evoked potentials and the not-previously-investigated possibility of frequency-rate interactions. Therefore, the aims were to systematically compare the effects of frequency and ISI on latency and amplitude of the CAEP using a paired-stimulus paradigm.

Methods

All test procedures were approved by the University of Arizona Human Subjects Protection Program (Institutional Review Board).

Participants

Eleven female, college-age adults participated in this study. Exclusion criteria included a history or presence of 1) cognitive impairment; 2) learning disability; 3) auditory processing disorder; 4) head injury resulting in loss of consciousness; and 4) other neurological conditions including migraine, or medications that cause hypo- or hyperactivity. All participants were screened for normal hearing (<20 dB HL) from 500 to 8000 Hz using pure tone stimuli. Two potential participants were excluded due to the presence of a neurological condition.

Stimuli

The stimuli were paired tone bursts that varied with respect to the interstimulus interval, varied in 100 ms steps from 100 to 500 ms. The tone burst frequencies used were 500 Hz and 4000 Hz; all interstimulus intervals were used for each tone burst pair. The tonebursts had a duration of 10 ms with a 2-ms rise-fall time. A schematic of the stimulus paradigm is provided in Figure 2. There was a 3 s inter-stimulus interval between each stimulus-pair presentation. Stimuli were played in a steady-state fashion and we measured the SPL of the continuous train.

The stimuli were created using Intelligent Hearing System's Smart-EP stimulus generation module. Stimuli were calibrated using a Larsen Davis Model 824 sound pressure level meter using a 1" microphone and H1A coupler. All stimuli were presented to the right ear at 77 dB SPL via EAR-2 insert earphones.

Procedures

Electrophysiologic testing

All recordings were made using an Intelligent Hearing System's Smart-EP system in the Advanced Research Mode. CAEPs were recorded using silver-silver chloride disposable electrodes placed at Cz (vertex, non-inverting), A2 (right mastoid, inverting), and A1 (left mastoid, ground) using electrode paste and paper tape, after cleansing each site with Nu-Prep. Electrode impedances were maintained at <10 kΩ and with <3 kΩ inter-electrode impedance. If an electrode became displaced during testing, it was replaced and electrode impedances were rechecked prior to resuming recording. The EEG was filtered at 1-30 Hz (12 dB/octave filters), amplified by 94 dB and digitized at 1000 Hz over a 1000 ms recording window. Artifact rejection was set at ± 30 μV. Each averaged response consisted of 200-250 artifact-free samples.

Test session

Participants completed all electrophysiologic testing in one session with a short break halfway through the session, if desired. Sessions began with screening for normal hearing followed by electrophysiologic testing. For electrophysiologic testing, participants were tested while awake, seated in a chair, and were given the option to read printed or electronic materials during testing. Participants were required to remain awake with their eyes open during testing. The order of toneburst pair presentation (500 Hz or 4000 Hz) was randomized among subjects, and the order of inter-stimulus interval trials was randomized within stimulus-pair frequency.

Data analysis

CAEP waveforms were analyzed using rule-based visual detection methods by the lead examiner (JM) who had been trained by the principal investigator (BC). The rules for visual detection of CAEP components included amplitude and latency criteria for each component, based upon values derived from the published literature on adult CAEPs (Wunderlich and Cone-Wesson, 2000; Cone and Whitaker, 2013; Picton, 2011). CAEP component peaks P1, N1, P2, and N2 were marked with a cursor to determine peak latency, and amplitudes were calculated as the difference between the peak and succeeding trough, or trough-to peak (e.g., P1-N1, N1-P2, P2-N2). CAEP component peaks to the second stimuli in the two-click paradigm were labeled as P1', N1', P2', and N2', with amplitudes calculated in the same manner. Descriptive and inferential statistical analyses (analyses of variance) were completed using StatView (v5.0.2) software.

Results

Presence of CAEP components for the first and second stimulus

Grand mean waveforms were created by averaging waveforms from each individual (N= 11) for each frequency (500 and 4000 Hz) and inter-stimulus interval condition. These grand mean waveforms are displayed in Figures 3a (500 Hz) and 3b (4000 Hz). Each grand mean waveform has a CAEP onset response (P1-N1-P2) within the first 300 ms following the first stimulus presentation. The waveforms also include the response to the second stimulus in the paired-stimulus paradigm that is labeled the *prime response* (P1'-N1'-P2'). The prime response is always measured from the onset of the second stimulus, which may be at 100, 200, 300, 400 or 500 ms following the first stimulus. The grand mean waveforms are presented in descending ISI order. The CAEP onset responses are evident in all stimulus frequency and ISI conditions. Indeed, analysis of the waveforms from individuals revealed that P1-N1 was present in 97/100 trials, N1-P2 was present in 96/100 trials and P2-N2 was present in 87/100 trials. When P2-N2 was absent, is was only for the trials with an ISI of 100 ms.

In contrast, there were a large number of missing components for the CAEP prime response to the second stimulus. That is, as the ISI between the first stimulus and the second decreased, the number of absent CAEP components increased. The numbers of missing components for the CAEP prime responses are summarized in Figure 4a and 4b; note the particularly large number of missing responses in the 100 and 200 ms ISI conditions for both frequencies. These bar graphs show that CAEP component P1'-N1' were most frequently absent for the 100 and 200 ms ISI conditions at both stimulus frequencies. At these ISIs, P1'-N1' was absent in 28/40 (70%) trials, N1'-P2' was absent in 22/40 (55%) trials and P2'-N2' was absent in 9/40 (23%) trials.

Effect of frequency and ISI on CAEP response latencies

The latencies of CAEP onset response components P1, N1, and P2 were measured for each stimulus frequency and ISI condition. A repeated-measures analysis of variance was performed, with P1, N1, P2 latencies as the repeated measure dependent variable and intersimulus interval and toneburst frequency as the independent variables to determine if there was a statistically significant effect of these variables on the onset response latencies. The results of this ANOVA are shown in Table 1. There was a statistically significant effect of stimulus frequency but not interstimulus interval on onset response latency, with the mean onset latencies for the 4000 Hz stimulus prolonged relative to those at 500 Hz. The mean latencies for P1-N1-P2 as a function of frequency are shown in Figure 5. P1, N1, and P2 latencies are longer for 4 kHz than for 500 Hz, by 0.3 ms, 7.26 ms, and 5.42 ms, respectively.

Similarly, a repeated measures ANOVA was used to determine the effect of ISI and stimulus frequency on the latencies of the CAEP prime response components, P1', N1' and P2'. The results are also shown in Table 1, Part B. As for the CAEP onset responses, there was also significant effect of stimulus frequency on CAEP prime component latencies, but no significant effect was observed for ISI. Note that in all cases, CAEP prime latencies were measured relative to the onset of the second stimulus. Latencies for 4 kHz were slightly longer than those for 500 Hz for all three response components. The mean latencies for these components are displayed in Figure 6. It must be kept in mind that the latency results are highly weighted towards the longer ISIs (300-500 ms) because there were so many missing components for the 100 and 200 ms ISI conditions.

Table 1, Part A. ANOVA: CAEP Onset Latency as a Function of Frequency and ISI	**DF**	**F**	***p***
Onset latency			
ISI	4	0.55	0.18
Frequency	1	5.52	0.02
Table 1, Part B. ANOVA: CAEP Prime Latency as a Function of Frequency and ISI	**DF**	**F**	***p***
Prime latency			
ISI	4	1.64	0.18
Frequency	1	5.52	0.02

Effects of frequency and ISI on CAEP response amplitudes

We also wanted to determine whether there was an effect of ISI and frequency on P1-N1-P2 response amplitude. The peak-to-trough amplitudes were measured for onset CAEP components P1-N1, N1-P2 and P2-N2. We performed an ANOVA for each component, P1-N1, N1-P2 and P2-N2, using ISI and frequency as independent variables. A significant effect of frequency on amplitude was found for each component, with greater amplitudes found in response to 500 Hz stimuli. The effect of ISI was significant only for component P2-N2, with larger amplitude evident for ISIs of 300-500 ms, compared to those at shorter ISIs. The mean amplitudes of the onset components as a function of frequency and ISI are shown in Figure 7. There was no statistically significant effect of ISI on CAEP onset response amplitude. The results of these analyses are displayed in Table 2, Part A.

Prime component amplitudes were also evaluated as a function of ISI and frequency. Recall, there were a large number of absent prime response components, summarized in Figure 4. In order to account for missing components in the data analysis, each missing amplitude was given a value of 0 μV. Analysis of variance was used to determine the statistical significance of changes in CAEP prime component amplitudes as a function of frequency and ISI. A statistically significant effect of ISI on CAEP prime amplitude components was found, with amplitudes decreasing as ISI decreased for each CAEP prime component. The analyses of variance results are summarized in in Table 2, Part B. The peak to trough amplitudes as a function of ISI are

Table 2, Part A. ANOVA: CAEP Onset Amplitude as a function of frequency and ISI	**DF**	**F**	***p***
Onset amplitude			
P1-N1			
ISI	4	0.88	0.48
Frequency	1	5.40	0.02
N1-P2			
ISI	4	0.48	0.75
Frequency	1	4.03	0.05
P2-N2			
ISI	4	2.55	0.04
Frequency	1	7.7	0.01
Table 2, Part B. ANOVA: CAEP Prime Amplitude as a function of frequency and ISI	**DF**	**F**	***p***
Prime amplitude			
P1'N1'			
ISI	4	3.12	0.08
Frequency	1	2.45	0.05
N1'P2'			
ISI	4	3.23	0.02
Frequency	1	0.01	0.94
P2'N2'			
ISI	4	3.14	0.02
Frequency	1	1.54	0.22

displayed in Figure 9. There was no statistically significant effect of frequency on response amplitude.

The amplitude of the CAEP prime components were compared to those of the onset responses by calculating an amplitude ratio. This has the effect of normalizing individual differences in CAEP amplitudes across individuals. Amplitude ratios were calculated in the following way: (Amplitude of CAEP Prime Component)/(Amplitude of CAEP Onset Component). Figure 10 displays of the mean amplitude ratios as a function of frequency, and Figure 11 summarizes the effects of ISI on the amplitude ratio for each component. Amplitude ratios appeared to increase with stimulus frequency and with increasing ISI. A repeated measures analysis of variance using the P1-N1, N1-P2 and P2-N2 as the repeated dependent variable and ISI and frequency as independent variables was used to determine if these effects were statistically significant. The results of the analysis of variance are shown in Table 3 and indicate that both frequency and ISI are significant variables affecting the amplitude ratio, although there was no interaction between the independent variables. Amplitude ratios are larger for the 4000 Hz stimulus, and also increase as ISI increases. There are no significant interactions between frequency and ISI for the amplitude ratio metric. It should be noted that there were some results in which the response to the second stimulus was larger than the onset response resulting in an amplitude ratio >1. This was evident particularly for the P1-N1 amplitude ratio that exceeded 1.0 in 13 trials, although the AR for this component only exceeded 2.0 4/100 trials.

Table 3. ANOVA: Amplitude ratio as a function of frequency and ISI	**DF**	**F**	***p***
ISI	4	5.955	0.00
Frequency	1	4.373	0.04

Discussion

The goal of this study was to evaluate how frequency and interstimulus interval affect amplitude and latency of the CAEP onset (to first stimulus) and prime (to second stimulus) responses in a paired stimulus paradigm in which the interstimulus intervals between the first and second stimulus were systematically varied. We hypothesized that there would be clear effects of frequency and ISI on the latencies and amplitudes of the CAEPs in keeping with the body of literature reviewed in the introduction. We found a statistically significant effect of stimulus frequency on onset response latencies, with the onset latencies of for the 4000 Hz stimulus prolonged relative to those at 500 Hz. Like the response to the first stimulus, there was also a significant effect of frequency on the response latencies to the second stimulus (prime) onset latencies. There were no statistically significant effects of ISI on onset latencies nor prime latencies. There were statistically significant effects of frequency on CAEP onset amplitudes, with the responses to 500 Hz stimuli having greater amplitudes, but there was no statistically significant effect of frequency for prime response amplitudes. A significant effect of ISI was found only for the P2-N2 component amplitude of the onset response, with greater amplitudes for ISIs of 300, 400 and 500 ms. There were significant effects of ISI on prime response amplitudes, with amplitudes for N1-P2 and P2-N2 decreasing as ISI decreased.

The results supported the hypotheses that ISI would affect the CAEP amplitudes in response to the second stimulus of a pair. Although stimulus frequency had effects on both latency and amplitude, there were no interactions with ISI, a question suggested by the differences between the Griffitts (2015) and Everett (2017) results, wherein suppression was found for a paired click paradigm (Griffitts) but not for a paired chirp (Everett). The effects of

ISI on second-stimulus response amplitudes were straightforward and in keeping with the well-known theory concerning neural refractory periods and rate effects.

In contrast to Everett's (2017) research, consistent evidence of suppression in the paired-stimulus paradigm was demonstrated, but only when ISIs were less than 500 ms. A main difference between her research and the present one is that the ISI was not varied in hers; the traditional paired-stimulus model was used, with an ISI of 500 ms. In the literature, there are also inconsistent findings of suppression using these parameters. Kathmann and Engel (1990) cited previous research indicating that a normal suppression ratio is approximately .2, for an 80% reduction in amplitude; that is, the amplitude of the response to the second stimulus is reduced by 80% compared to the amplitude of the first stimulus. The researchers tested P50 suppression in a group of schizophrenic patients and a control group. They used the two-click method, with clicks presented 500 ms apart. These were presented via loudspeaker and measured to have an intensity of 90 dB SPL at the participants' ear. They did not find significant suppression in either group, although the responses to the second click were generally smaller in amplitude. They found the normal group's suppression ratio (S2/S1) to be .73, for a 27% reduction in amplitude, while the schizophrenics' was .94, for a 6% reduction in amplitude.

One theme throughout the literature is that there is significant variability in the P50 response across participants and testing blocks. Smith, Boutors, and Schwarzopf (1994) conducted an analysis of seven previous P50 suppression studies. Their data analysis made them question the reliability of the P50/P1 "sensory gating ratio." They argued that the suppression ratio is not a good metric even though P50 response amplitudes (to both the first and second stimulus) were reliably evoked, because it does not reliably demonstrate normal individual differences. There were moderate correlations between both response amplitudes, but there was

greater variability in the response to the first stimulus than in the response to the second. To account for this psychometric variability, they suggest using amplitude difference scores rather than amplitude ratios, arguing that a simple difference score is better at illustrating individuals' variance. Amplitude difference scores are calculated by subtracting the response to the second stimuli (S2) from the response to the first (S1), rather than by dividing S2/S1. However, whether the responses are divided or subtracted, the effect is the same: the responses are normalized, allowing us to analyze their differences. The research reviewed here all made use of the traditional parameters of the two-click method, with an ISI of 500 ms for the paired stimuli, and the P1 amplitude ratio as the operational definition of suppression or sensory gating. A strength of the current study was the systematic variation of ISI and frequency, in order to evaluate the contribution of each of these stimulus variables.

There are some physiologic mechanisms suggested in the literature to explain the effects of frequency and ISI on CAEP. Beginning at the level of the cochlea and extending throughout the central auditory nervous system, structures involved in auditory function are tonotopically organized. They are arranged in such a way that different areas of each structure respond preferentially to different frequency stimuli. The basilar membrane is thick and stiff at its base and responds to high frequency stimuli, while the apex is wider, less thick, and more pliable, and is more responsive to low frequency stimuli. This tonotopic organization is preserved throughout the auditory system, through primary auditory cortex itself (Musiek & Baran, 2020). The primary auditory cortex is composed of a number of structures; two of the most important structures are Heschl's gyrus and the planum temporale. A significant amount of research has been undertaken in order to understand the tonotopic arrangement of these structures. Humphries et al. (2010) suggested that the medial cortical structures of Heschl's gyrus are responsive to lower

frequencies and lateral cortical structures are responsive to higher frequencies. However, research in the NeuroAudiology Lab at the University of Arizona indicates that tonotopic mapping of auditory cortex is more complex than that, with a "V" shaped tonotopic arrangement in Heschl's gyrus and the planum temporale, shown in Figure 12 (St. George, 2017) .

Jacobsen and colleagues (1992) proposed that there are both central and peripheral mechanisms that affect the cortical response as a function of frequency. Their research is consistent with the findings of Humphries et al. (2010), indicating that the cortical areas responsive to low frequencies are more lateral and thus closer to the scalp, resulting in shorter latencies and larger amplitudes of responses to low frequency stimuli when making far-field recordings. Likewise, if the neural generator of high-frequency responsiveness is located farther from the scalp, and by extension the recording electrodes, longer latencies and reduced amplitudes of the CAEP response to high frequency stimuli may be expected. Jacobson et al. also note that there is recruitment of high-frequency neurons that occurs in the peripheral auditory nervous system, and suggest that this may result in larger stimulation of cortical neurons in response to low-frequency tones. Wunderlich, Cone-Wesson, and Shepherd (2006), also demonstrated these frequency-related effects in their study of CAEP development in infants and children. Even earlier, research of Antinoro et al. (1969) and Zerlin and Naunton (1974) indicates that lower frequency tone bursts evoke CAEP waves of greater amplitude than those of higher frequencies, so the findings of this study are consistent.

As discussed earlier, it is well-documented that there are significant effects of rate and interstimulus interval on the cortical evoked response. In general, the faster the rate of stimulus presentation, the less distinct CAEP response components become (Jewett & Williston, 1971; Don et al., 1977; Davis et al., 1966). This is due at least in part to the refractory period of

auditory neurons. The refractory period occurs following an action potential, where depolarization and hyperpolarization prevent the neuron from further action potentials for a period of time. Following its return to equilibrium, the neuron is able to generate another action potential. Essentially, the number of action potentials possible in a given amount of time is limited by the physical properties of the neuron itself. Inhibition is another relevant neuroscience concept and refers to the ability of one neuron to inhibit or suppress the activity of another (Chambers, Garavan, & Bellgrove, 2009). These inhibitory neurons release the neurotransmitter GABA, which has the effect of hyperpolarizing other neurons—in effect, suppressing another action potential. The paired-stimulus paradigm is designed to investigate these processes by presenting carefully timed stimuli and recording the evoked responses. The classic paired-click paradigm presents two clicks 500 ms apart, followed by an interval between pairs; this allows the refractory period to end before the onset of the next pair. Thus, we did not see an effect of ISI on the onset responses, nor we did not expect to. However, there were clear effects of ISI on the prime responses. Although the current study did not find significant suppression of P1 in the 500 ms ISI condition, suppression of all CAEP components increased significantly as the ISI decreased, suggesting that refractoriness plays a role in suppression as well.

The refractory period of auditory neurons and CAEP responses have been studied at length and are also affected by maturational changes. Gilley and colleagues (2005) evaluated developmental changes in the refractory characteristics of cortical evoked potentials in children. They tested a group of children aged 3-12 years and compared their CAEP results to a group of young adults aged 24-26 years. The stimulus was the speech sound “uh” played four times in a train, with sequentially decreasing interstimulus intervals of 2000, 1000, 560, and 360 ms. The stimuli were presented at 70 dB SPL via soundfield. The researchers found that P1 dominated the

CAEP waveform for the youngest groups of children regardless of ISI, and that latencies were significantly delayed compared to adults. Subsequent CAEP landmarks were not seen for the youngest groups of children. The response component N1 began to emerge with maturation. The N1-P2 complex was the most robust and consistent CAEP landmark in the adult group. In keeping with the findings on ISI and latency, the latency of P1 increased with stimulation rate in the younger groups. In contrast, the mean latency for P1 in the adult group was 66 ms in all ISI conditions. There were also effects of age and ISI on the amplitude of P1, although there was no interaction between them.. Presence of the N1-P2 complex increased with age and ISIs, such that it was present in only 20% of the 3-4 year olds in the longest ISI condition, and present at all ISIs in the adult group. Gilley et al. analyzed combined N1-P2 peak-to-peak amplitudes as a metric of the refractory properties of the CAEP; their reasoning was that this is a stable indicator of the overall change in magnitude of the CAEP response elicited by trains of stimuli. They found that there were clear effects of ISI and age on the peak-to-peak amplitudes, and an interaction between ISI and age. When the response was present in the youngest age groups, there was almost no change in amplitude between ISI conditions; N1-P2 amplitudes showed an increase in the longest ISI condition as a function of increased age.

Sussman and colleagues (2008) also analyzed changes in the CAEP response as a function of age group and ISI. They worked with three age groups: children aged 8-11 years, adolescents aged 16 years, and adults aged 22-40 years. The researchers used two pure-tone stimuli (880 and 988 Hz) at a level of 75 dB SPL via insert earphones. They played the stimuli in trains with ISIs of 800, 600, 400, and 200 ms, with only one ISI in each train. Although the investigators used the term ISI, the parameter was truly rate, as they were averaging responses over a train of stimuli. In younger children, the P1-N1-P2 response was dominated by P1 and N2

regardless of stimulus rate, although the amplitudes were reduced as a function of ISI. N1 was the dominant CAEP component in the adult responses, a trend which did not emerge until adolescence. In addition, N1 amplitude was the largest in the 800 ms condition, which is in keeping with other literature indicating increased amplitude with increased ISI. The researchers also found that faster stimulus rates resulted in suppression of individual response components, with marked suppression of N1 in the adult group with decreasing ISI. They found that there was a significant decrease in the amplitude of all components, in all groups, in the 200 ms ISI condition. Sussman and colleagues concluded that both age and rate have clear effects on the morphology of the CAEP response.

The results of Gilley et al. and Sussman et al. are consistent; both saw the dominance of P1 in younger groups, increased latency with decreased ISI, and eventual emergence of the P1-N1-P2 complex with age. Gilley et al. attributed these maturational changes to myelination, synaptic refinement, and cortical fiber density. As myelination occurs throughout childhood development, neuronal transmission times decrease; this is an underlying concept in maturational causes of central auditory processing disorder. Both latency and neural synchrony are affected by myelination, resulting in shorter latencies, larger amplitudes, and more defined waveform morphology of CAEPs (Gilley et al. 2005). In addition to these changes resulting from myelination, density of axons at the cortical level continues increasing throughout childhood, reaching an adult-like state by 11-12 years old. This increased density of axonal connections allows more efficient transmission of auditory information, which, Gilley et al. point out, would likely result in faster recovery rates of the CAEP response.

Although age was not one of the parameters of the current study, our findings regarding CAEP suppression the effects of rate on CAEP landmarks are in good agreement with Sussman

and colleagues. A further research question for the AHEAD lab might be investigating the effects of frequency and ISI in the paired-stimulus paradigm on different populations, including infants, young children, and older adults. Picton (2011) also notes changes in CAEP wave morphology in older adults, where N1 and P2 waves increase in latency and decrease in amplitude as a function of aging. Interestingly, the P1 component has been found to be much larger in the elderly population, which may be related to a decline in the inhibitory connections of the auditory nervous system as we age. Tremblay and Ross (1997) discuss the aging auditory system and changes in function that may be expected. There are declines in temporal and spectral processing, which are likely related to slowing neural conduction and issues affecting neural synchrony. This is true of adults with and without hearing loss, although the functional deficits of those with hearing loss are more pronounced. Cortical evoked potentials are themselves measurements of neural synchrony and temporal integration of the central auditory nervous system, so it would be logical to use them to assess inhibitory functioning. This is certainly another avenue for study and could lend insight into sensory gating and suppression in older adults. A decrease in inhibitory function of the central auditory nervous system in the aging population could be related to speech in noise understanding and acceptance of amplification.

There are, of course, several limitations to the current study. We did not replicate Everett's two-chirp stimulus condition, as we were interested specifically in the effects of low- and high-frequency stimuli on CAEP latency and amplitude. We did not include any perceptual measures, unlike Everett and Griffitts. We were mainly interested in obligatory (acoustically-driven) CAEPs, but the addition of cognitive CAEPs could shed further light on these inhibitory processes. Perhaps a decision component while recording evoked potentials could be added, forcing participants to direct their attention to a different task; we might see less effective

suppression in that design, indicating that a cognitive component could disrupt obligatory, inhibitory processes. Additionally, our participants were all female, normal hearing, young adults; our results might have differed had we tested other populations. There is a large body of literature that demonstrates a deficit in sensory gating for people with schizophrenia, and it is hypothesized that people with tinnitus and hyperacusis may also have dysfunctional gating mechanisms. Both disorders are related to deficits in neural inhibition, so it is possible that they could demonstrate reduced suppression on the P50 measure. However, tinnitus and hearing loss are often comorbid conditions, and it would likely be difficult to determine the source of potential decrease in suppression.

Summary and next steps

Where do we go from here? Although the present research was designed as a basic parametric study, it does have implications in a larger context. Ultimately, it contributes to the foundation laid by the AHEAD lab and provides us with important information for subsequent research. Both Everett and Griffitts investigated the relationship between acceptable noise levels and its underlying electrophysiologic processes, as a means of better understanding the demands of listening in noise and hearing aid acceptance. A logical next step would be to record cortical evoked potentials in the paired-stimulus paradigm with older adults without hearing loss, to assess the degree of suppression. If indeed aging is associated with reduced inhibitory neural networks, perhaps there would be a relationship between age and suppression ratios in this context, as compared with groups of younger adults. Following that, we might be able to compare suppression ratios of older adults with and without hearing loss; and, perhaps, establish some connection between decreased inhibition and tolerance of background noise while listening to speech.

Figure 1. Cortical auditory evoked potential response in a one-stimulus paradigm (top tracing) and in a paired-stimulus paradigm (bottom tracing). Courtesy of Griffitts, 2015.

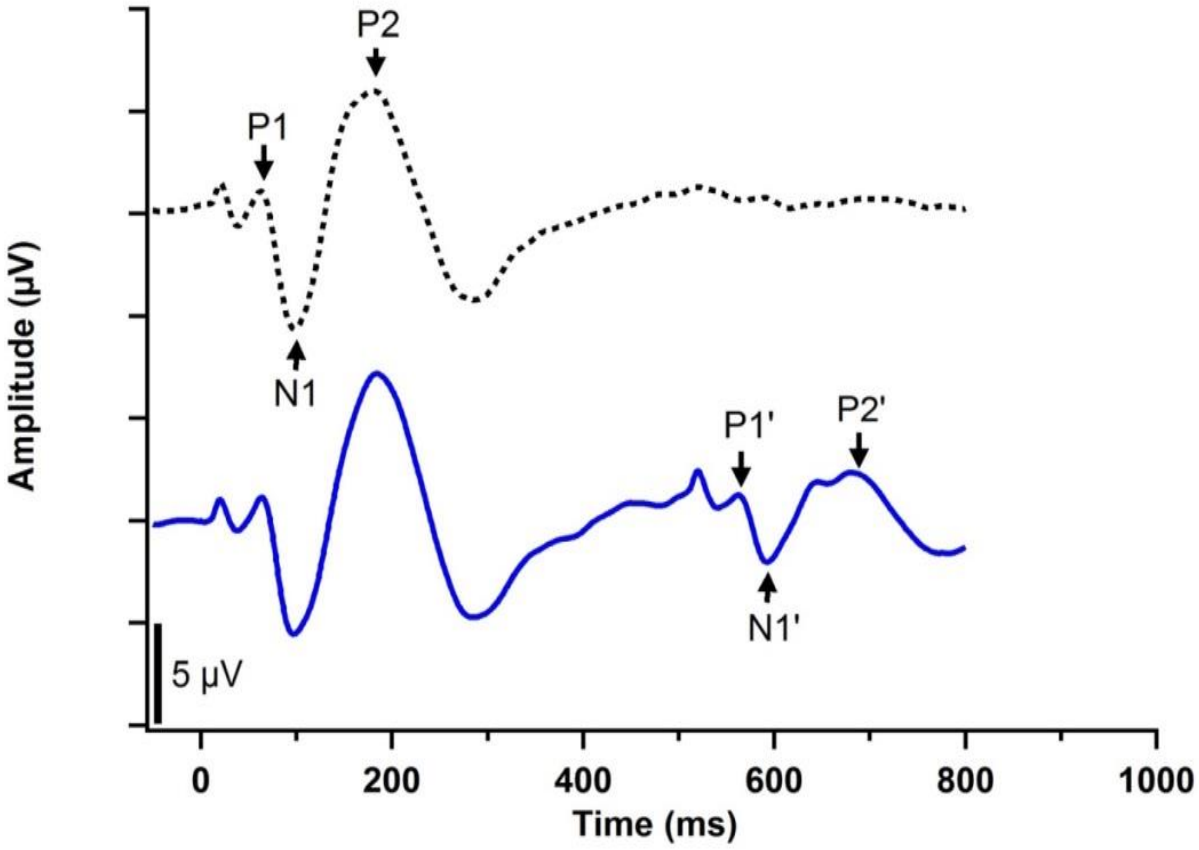


Figure 2. Schematic of paired-stimulus paradigm. The onset of the first stimulus is at 0 ms, indicated by the red line. The onset of the second stimulus is indicated by the blue lines, at interstimulus intervals of 500, 400, 300, 200, and 100 ms.

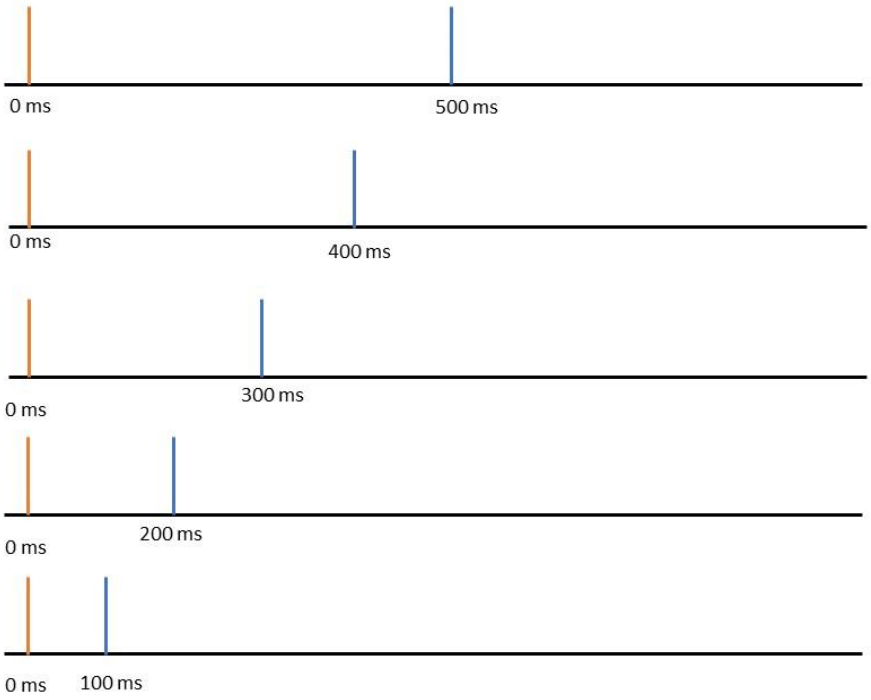


Figure 3a. Grand mean average wave forms in response to 500 Hz stimuli. Each tracing represents a 100 ms change in interstimulus interval (ISI). The red arrows denote the CAEP onset response to the first stimulus. The blue arrows denote the CAEP prime response to the second stimulus.

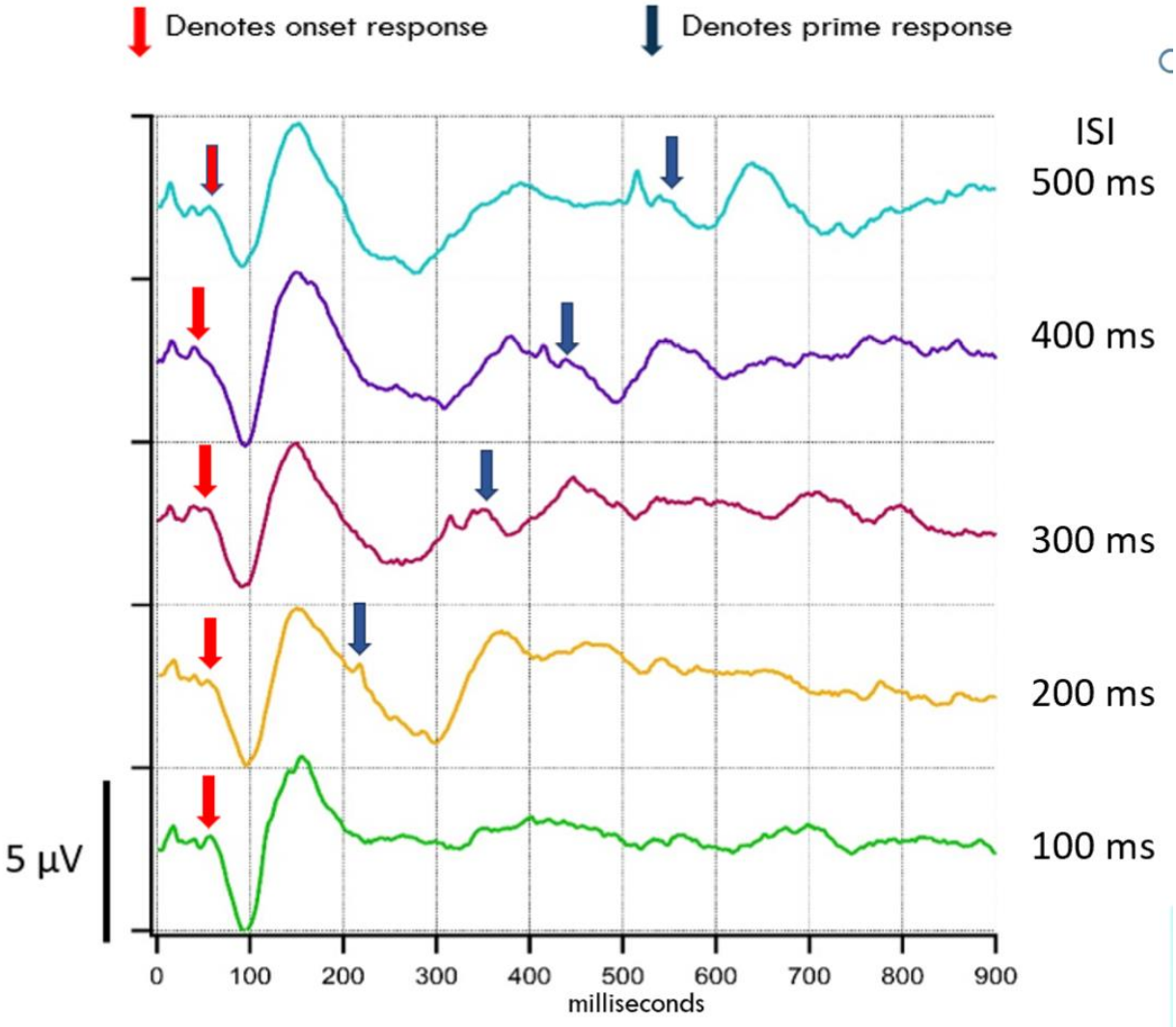
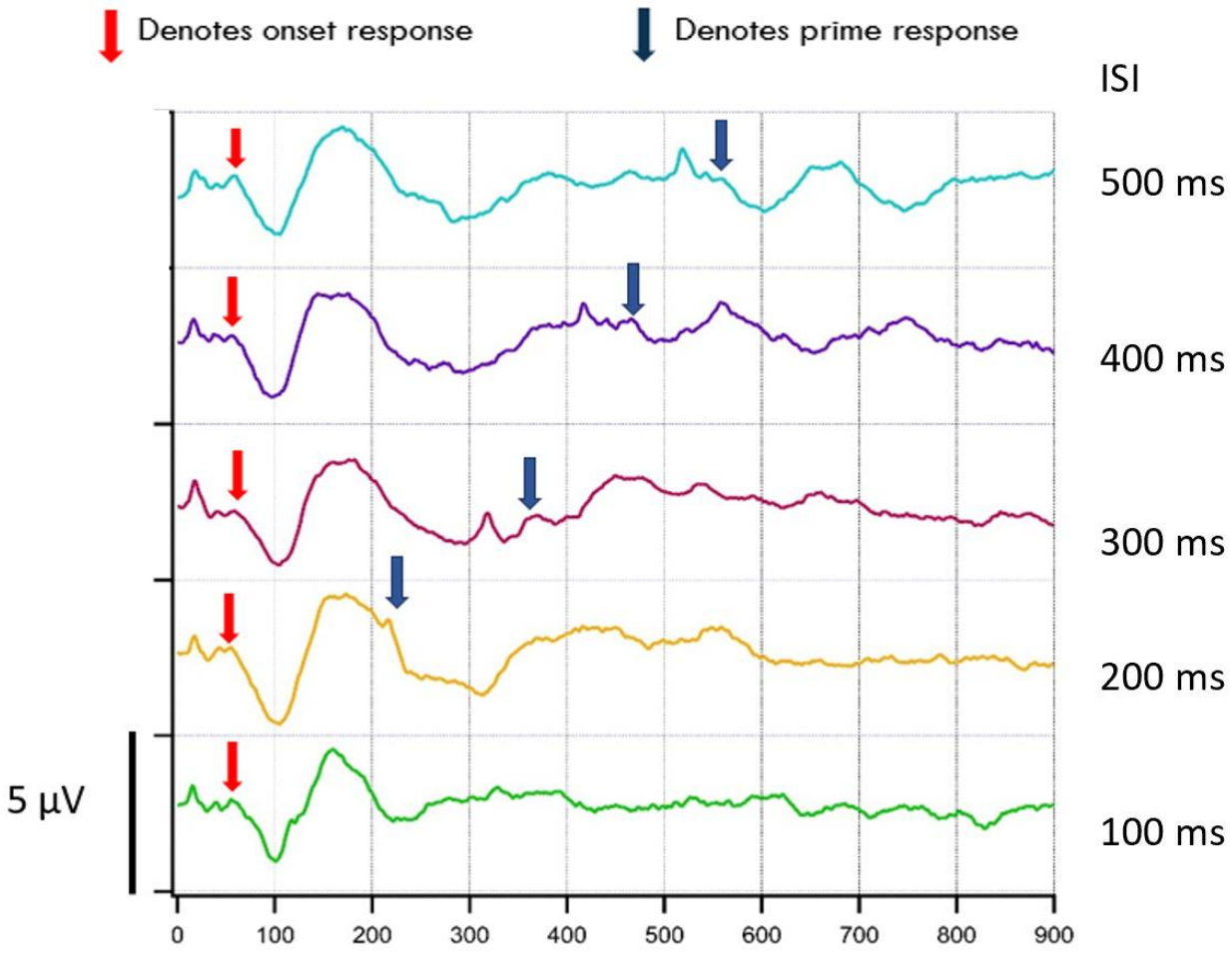
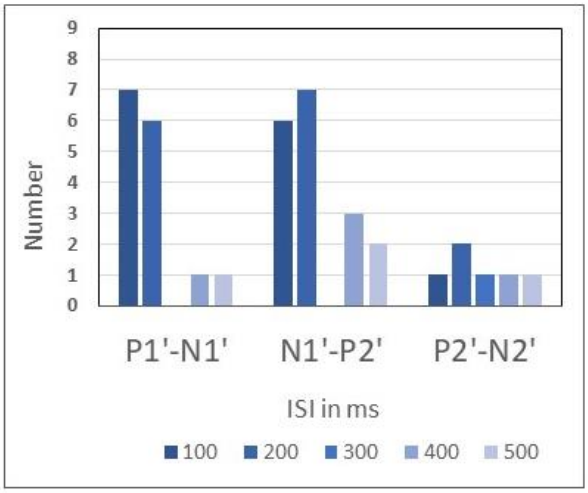


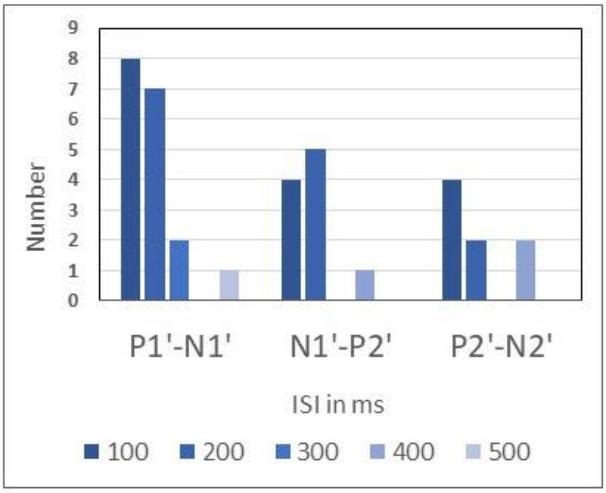
Figure 3b. Grand mean average wave forms in response to 4000 Hz stimuli. Each tracing represents a 100 ms change in interstimulus interval (ISI). The red arrows denote the CAEP onset response to the first stimulus. The blue arrows denote the CAEP prime response to the second stimulus.



Figures 4a and 4b. Number of missing P1'-N1', N1'-P2', and P2'-N2' components at 500 and 4000 Hz as a function of ISI. Note the large number of missing response components at the shortest interstimulus intervals.



4a. 500 Hz



4b. 4000 Hz

Figure 5. CAEP onset response latencies for P1, N1, and P2 components for 500 and 4000 Hz stimuli

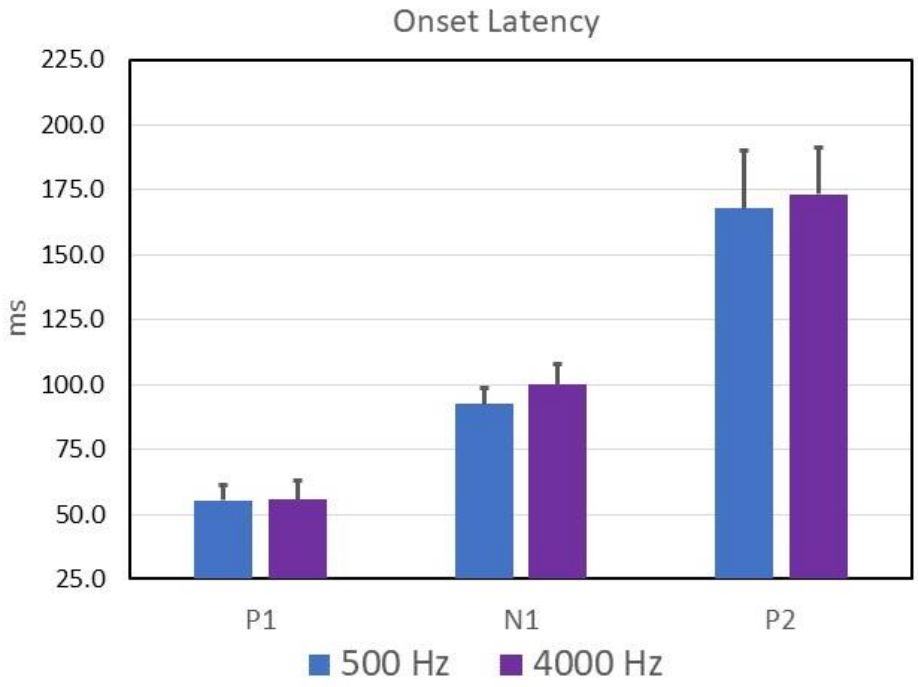


Figure 6. Latencies of P1', N1', and P2' components for 500 and 4000 Hz stimuli.

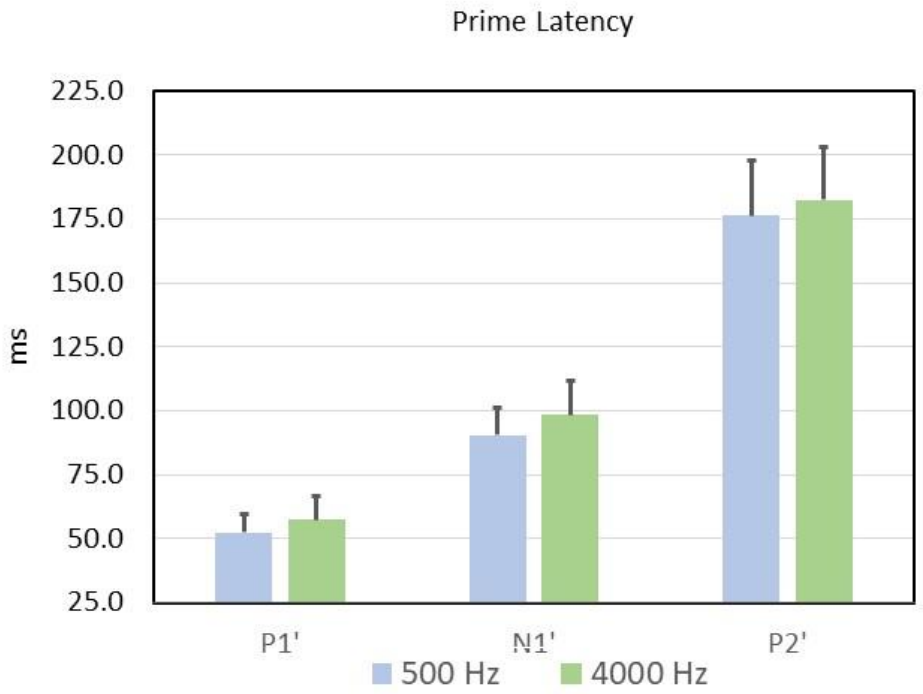


Figure 7. CAEP onset response amplitudes of P1-N1, N1-P2, and P2-N2 components for 500 and 4000 Hz stimuli. Mean amplitudes are averaged over ISIs.

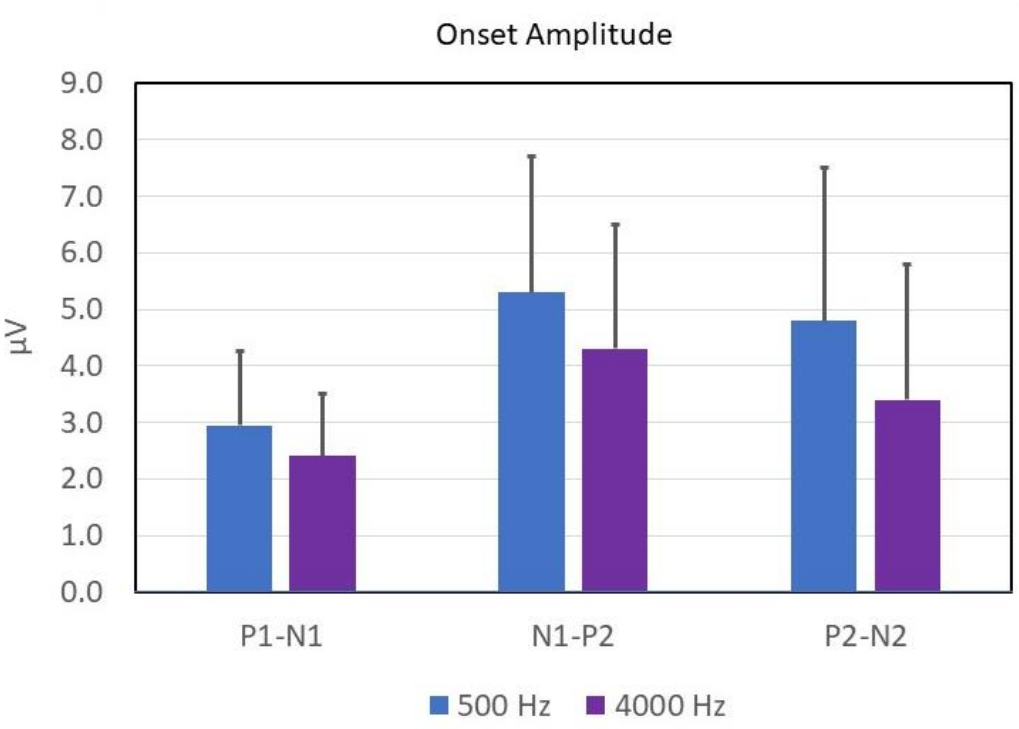


Figure 8. Amplitude of prime response components P1'-N1', N1'-P2', and P2'-N2' for 500 Hz and 4000 Hz stimuli. Amplitudes are averaged over all ISIs.

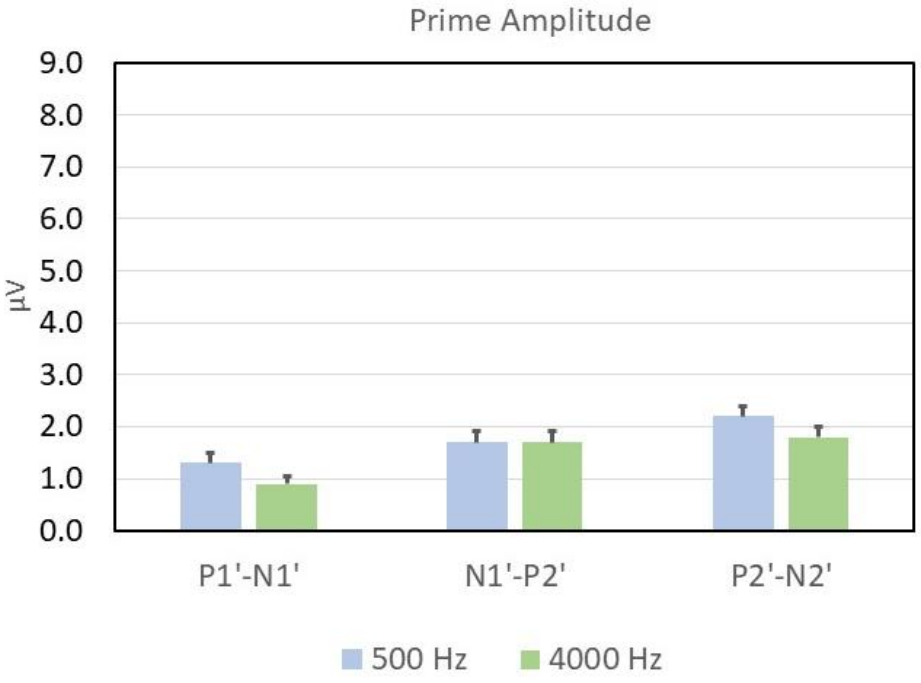


Figure 9. Peak to trough amplitudes of prime response components P1'-N1', N1'-P2', and P2'-N2' as a function of ISI. Means are averaged across frequency.

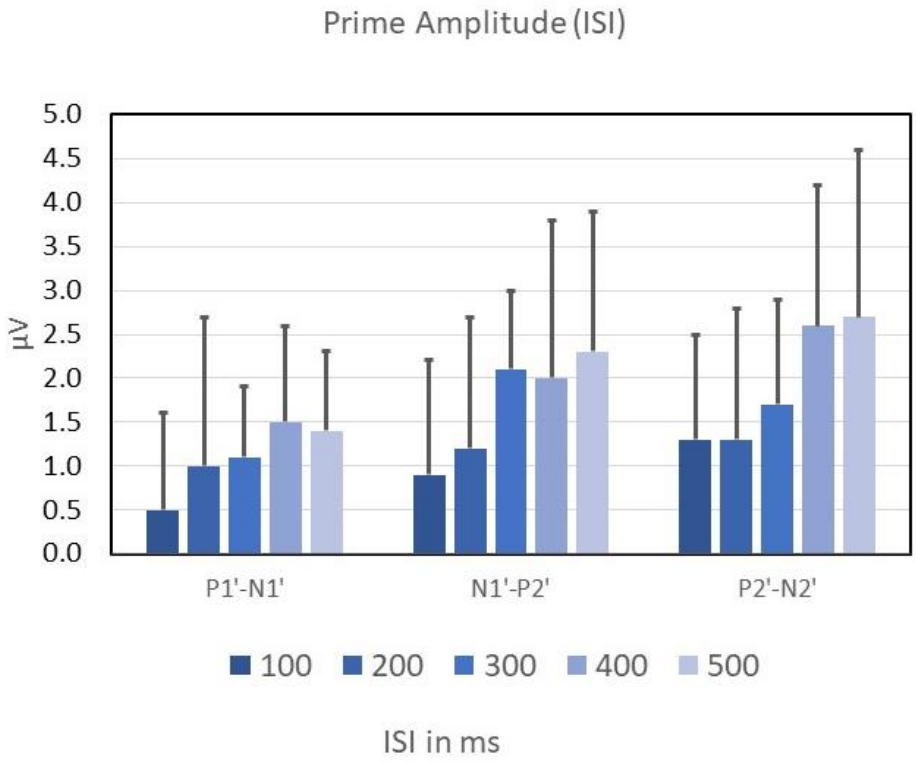


Figure 10. Amplitude ratios as a function of frequency. Means are averaged across ISI.

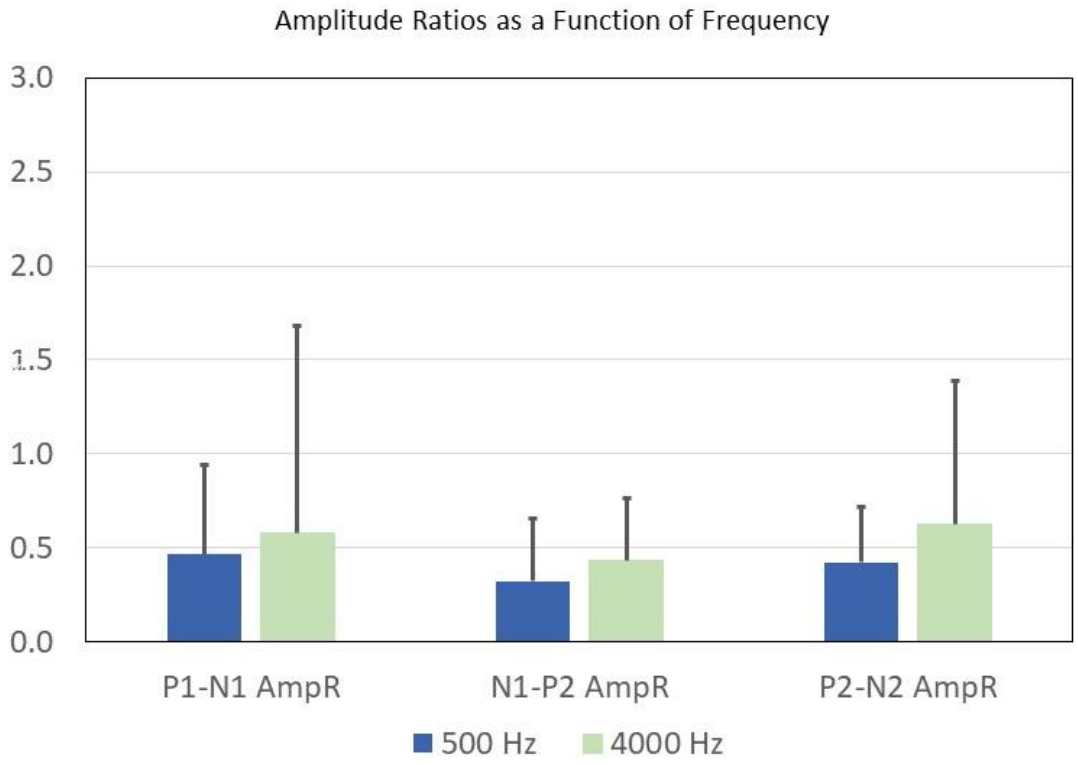


Figure 11. Amplitude ratios as a function of ISI. Means are averaged across stimulus frequency.

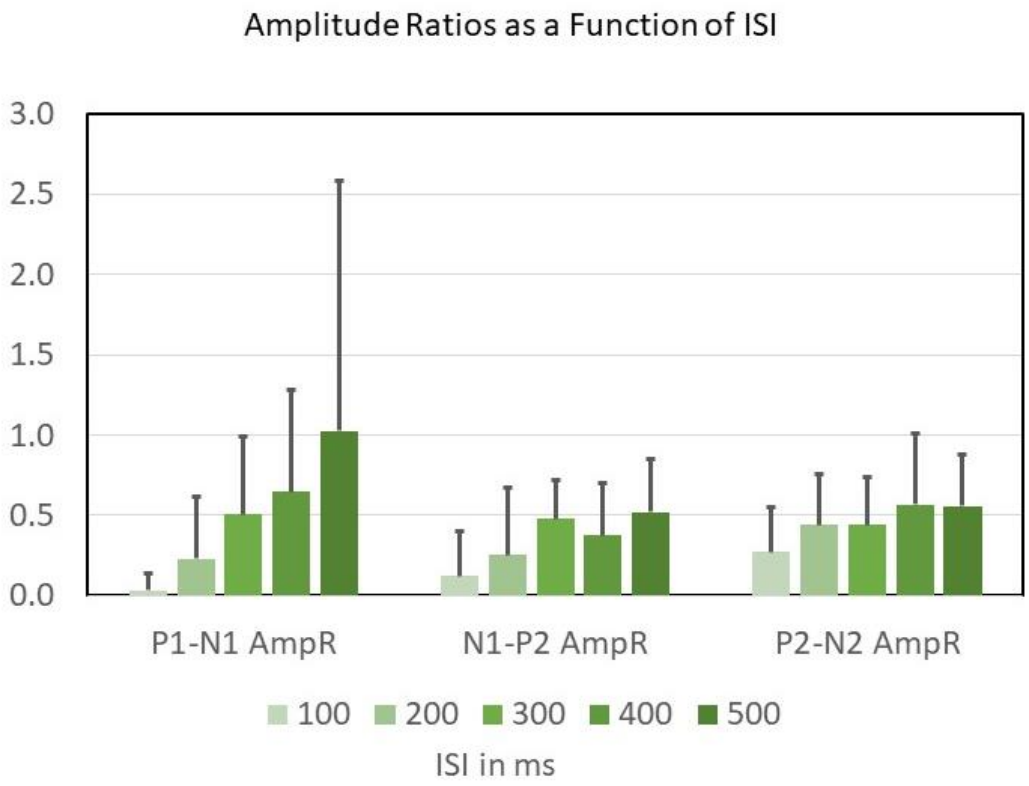
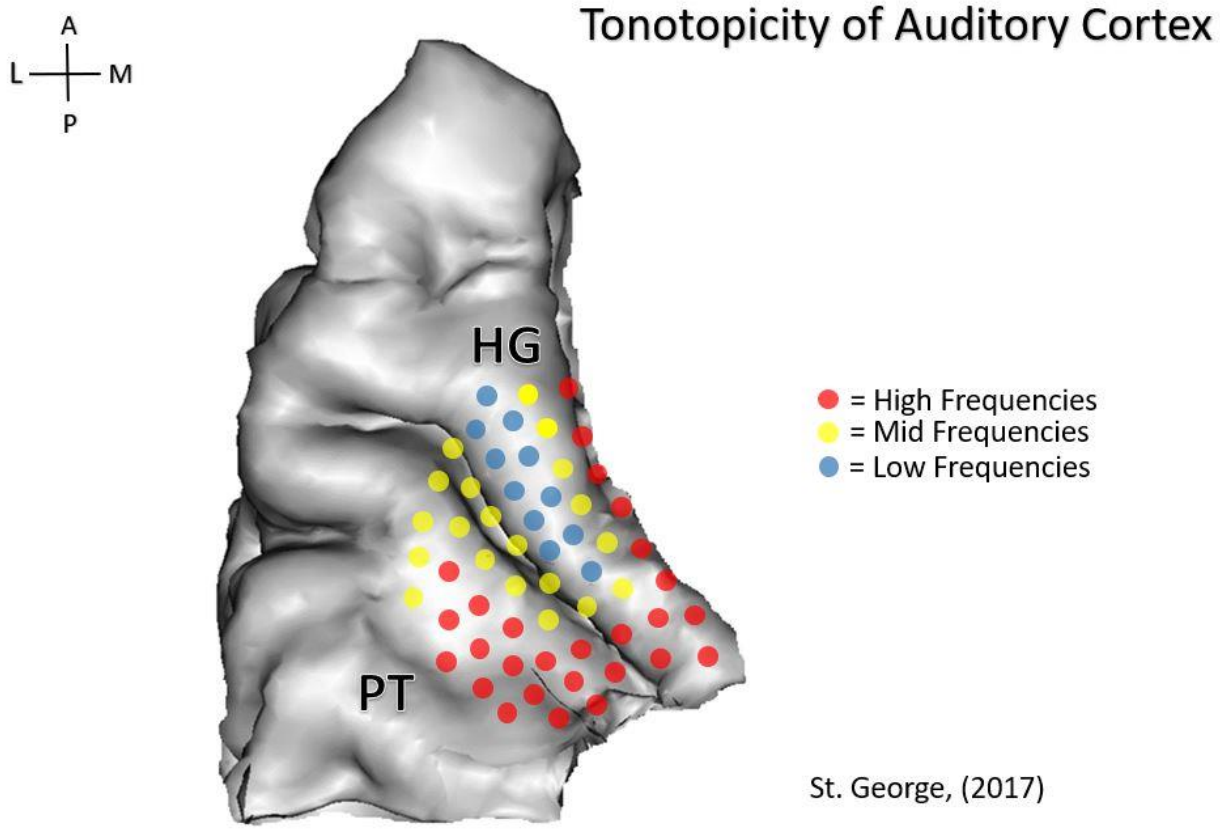


Figure 12. Tonotopic arrangement of auditory cortex. Courtesy of Barrett St. George, 2017.



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