ELECTROPHYSIOLOGIC MEASURES FOR BINAURAL MASKING LEVEL DIFFERENCE

by

Kayla Ichiba

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As members of the Dissertation Committee, we certify that we have read the dissertation prepared by ***Kayla Ichiba***, titled ***Electrophysiologic Measures For Binaural Masking Level Difference*** and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Audiology.

Barbara Cone Date: 4-8-20
Barbara Cone, Ph.D., ADP Director

David Velenovsky Date: 4/8/2020
David Velenovsky, Ph.D., Committee Member

F. E Musiek Date: 4/8/2020
Frank Musiek, Ph.D., Committee Member

Julie E. Miller Date: 4/8/2020
Julie Miller, Ph.D., Minor Area Member

Final approval and acceptance of this project is contingent upon the candidate's submission of the final copies of the doctoral project to the Graduate College.

I hereby certify that I have read this Audiology Doctoral Project prepared under my direction and recommend that it be accepted as fulfilling the project requirement.

Barbara Cone Date: 4-8-20
Barbara Cone, Ph.D., ADP Director

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ABSTRACT

This study evaluates the effect of phase change on auditory steady-state (ASSR), onset CAEP and ACC responses. The aim was to determine how phase change is encoded at lower levels of the auditory system and then processed at the cortical level. The test subjects were 23 young adults with normal hearing. ASSRs and stimulus-onset CAEPs were first recorded in a control condition using a 800 ms duration 500 Hz tone, amplitude modulated at 80 Hz, presented binaurally at 1/s. In the test condition, the phase of the 500 Hz tone was inverted 180° in one ear at 400 ms to evoke the ACC. Broad-band noise was introduced at an -5 dB SNR and the test condition repeated. Stimulus levels were varied to find the threshold of the ACC. Perceptual binaural masking level differences (BMLD) for a 500 Hz tone were also determined. At the phase change, ASSR amplitudes showed no difference between the in-phase and on-phase condition, and the ACC was 1.5-2.0 times larger than the onset CAEP response. This indicates amplification of the phase-change information in the ascending auditory pathway. These findings contribute to the development of an electrophysiological index for BMLD.

INTRODUCTION

The ability to decode and understand speech in noise relies heavily on the benefits of binaural hearing. When listening with both ears, the brain is able to summate information from the neural code provided by each auditory nerve, analyze the differences at the level of the low brainstem, and convert the neural code into meaningful information at the level of the cortex.

Anatomy of Binaural Hearing

The anatomical structure of the central auditory system provides the groundwork for binaural processing. Input to each ear travels from the peripheral auditory system via the vestibulocochlear nerve to the cochlear nucleus. Bushy and octopus cells within the cochlear nucleus demonstrate good synchronicity to specific temporal patterns; octopus cells in particular respond well to stimulus onset. This signal coherence is the neural basis behind phase-locking, an important cue for localization.

From the cochlear nucleus, information is carried to the Superior Olivary Complex (SOC). The majority of neurons decussate at this level to rostral levels of the central auditory system. It is well established that the SOC is the site for many binaural processes (Musiek & Baran, 2007). The SOC is responsible for processing differences in stimulus timing (phase) and level between ears that occur when sound is coming from a source other than directly in front of the listener. The neural bases of interaural timing and interaural level difference detection are performed by neurons that can have both excitatory and inhibitory inputs.

Jeffress (1948) proposed the coincidence detector model of binaural hearing. He defined the coincidence detector as those neurons in the medial portion of the SOC, the medial superior olive (MSO). Interaural timing differences of sound in space are mapped rostro-caudally onto the contralateral MSO. Each neuron of the MSO is tuned for a specific interaural time difference

(ITD). Information from the right ear will travel from the furthest right neuron down the line, until it meets with the information from the left ear, and vice versa. Sounds coming from directly in front of the patient will have an ITD of 0, and neural signals will be delivered simultaneously to the coincidence detector (Figure 1). A sound closer to the right ear will have to travel farther down the coincidence detector delay line, as opposed to the information coming from the left ear only traveling a short distance. These neurons appear "tuned" to certain ITDs, that is, their firing is specific to delay times between the two incoming neural signals.

Coincidence Detector (after Jeffress, 1948)

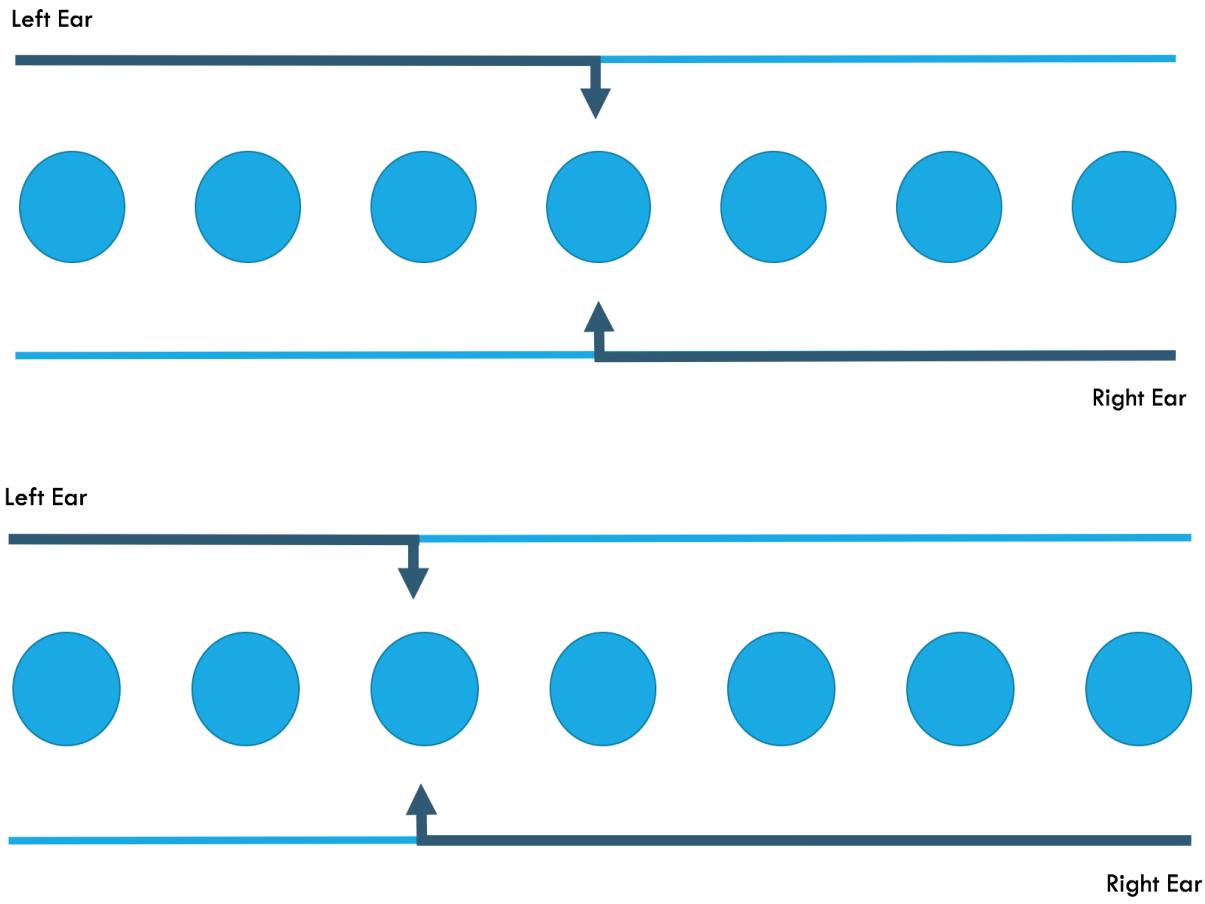

Fig 1: Diagram of coincidence detector encoding two stimuli coming from different locations along the horizontal field. The circles represent neurons in the SOC. The arrows represent the axonal pathways. The top coincidence detector is coding an ITD of 0. There is no difference in timing between left and right ears, so information arrives at the corresponding coincidence

detector simultaneously. The bottom coincidence detector is encoding a sound that is closer to the right ear. Because the sound is arriving at the right ear first, it has more time to travel along the delay line until it meets with the appropriate neuron simultaneous to information from the left ear.

Interaural level differences (ILD) are coded by neurons within the lateral superior olive (LSO). Ipsilateral input arrives at the LSO as excitatory input, whereas contralateral input is inhibitory. Information from left and right ears arrive at LSO neurons at the same time. The delay from the contralateral ear is compensated for by thicker axons and stronger synapses in the medial nucleus of the trapezoid body, for faster action potential velocity.

From the SOC, the information continues rostrally to auditory nuclei in the brainstem, most importantly, to the inferior colliculus, that also has neurons that that are sensitive to ITD and ILD (Graña et al., 2017). The inferior colliculus projects to the medial geniculate body of the thalamus, which, in turn, projects to the primary auditory cortex, where higher functioning processing can begin.

Acoustics of Binaural Hearing

In relation to the horizontal field, a sound source will have a specific ITD and ILD. The ear that is closer to the sound source will detect the sound first, because it is louder and arrives sooner than at the contralateral ear. Sounds coming from directly in front or back of an individual will have an ITD and ILD of 0 ms and 0 dB, respectively, as the sound is arriving to both ears at the same time.

Interaural Level Difference (ILD)

Sound intensity decreases with distance, explaining why the closer ear detects a sound louder than the distant ear. The head creates a shadow, and the sound wave must wrap around it in order to reach the distant ear, ultimately creating the intensity difference between ears. This mechanism is useful primarily at high frequencies because of the wavelength of the incident

sound. Smaller wavelengths, shorter than the distance between ears, are more affected by the mass of the head, and subsequently are attenuated at the opposite ear. The maximum ILDs are found for high frequency (>2000 Hz) sounds and can be as much as 20 dB (Moore, 2012).

Interaural Time Difference (ITD)

As neural information travels rostrally through the central auditory nervous system, through the lemniscal pathways, information from both ears are integrated and analyzed for their ITDs. The coincidence detector (discussed above) can resolve ITDs as small as 0.65 ms, for low frequency (<1000 Hz) sounds. Localization of low frequency information relies heavily on ITDs. The auditory system distinguishes ITDs in the low frequencies, because neurons are able to fire for each cycle of a low frequency tone up to about 1500 Hz. Above that, the interaural level differences become the dominant cue for sound localization.

ITD and ILD are cues also utilized in *lateralization*. Lateralization is the perception of sound location within the head, when stimuli are presented through headphones. Interaural timing and level differences affect the perception of the sound relative to where it is heard within the head. For example, when a sound has both an ILD and ITD of 0, the sound is perceived midline. If the stimulus presented to the left ear is more intense than from the right ear, the sound will be perceived as lateralized to the left side of the head. Similarly, if the sound is presented to the left ear first, with a slight timing lag to the right ear, the sound will be perceived as lateralized to the left.

Speech in Noise Perception

Interaural time and level differences are dependent on binaural hearing, and provide benefits to listeners as they need to localize and identify speech in noise. Binaural hearing allows the listener to selectively isolate a particular speaker and hone in on one conversation. This spatial

filtering minimizes the influence of unwanted sounds and focuses on the important communication. With the advancement of recent hearing technologies, binaurally fit hearing aids or cochlear implants are able to communicate with one another. This feature gives patients access to binaural cues that they have been missing out on because of their hearing loss. Despite the importance of binaural processes, there are relatively few clinical measures that specifically test these processes in order to form a treatment plan. Therefore, there is still a need for examining the integrity of binaural hearing mechanisms. The Binaural Masking Level Difference (BMLD) is a classic test for binaural hearing abilities.

The Binaural Masking Level Difference Test

Prior to the auditory brainstem response and the incorporation of electrophysiologic measures in clinic, The Binaural Masking Level Difference test was used to examine the integrity of the lower auditory brainstem (Kelly et al., 1994; Nicol T, 1994). This test comprises a signal (tones or speech) and masking noise, presented binaurally, with either the stimulus or noise phase varied between test conditions. First, the signal and noise are presented in-phase to both ears, this is called the S_0N_0-S_0N_0 condition. The noise level is varied until the signal becomes detectable. This is noted as the masked threshold level. Then, the phase of the signal (or the noise) is presented at 180° out-of-phase to one ear relative to the other. This is called the S_0N_0-S_π-N_0 condition for a signal that is out-of-phase. The threshold for the signal is re-established. When the signal is out of phase and the noise is in phase at the two ears, the signal is easier to detect than with both are in phase. Thus, the detection threshold is improved. The difference in threshold between the in-phase, and out-of-phase conditions is the Binaural Masking Level Difference (BMLD). This phenomenon of threshold improving with an interaural phase difference is referred to as “release from masking”.

The size of the BMLD is dependent on the listener's sensitivity to interaural timing differences and on signal and noise characteristics including signal frequency, signal-to-noise ratio and masker characteristics. BMLD varies by frequency: its effect diminishes as signal frequency increases up to about 1500 Hz. (Bourbon & Jeffress, 1965; Colburn & Durlach, 1965; Durrant et al., 1984; Hirsh, 1948; McFadden 1968; Wightman & Leshowitz, 1970). The standard frequency for clinical testing of BMLD is a 500 Hz tone.

Given the BMLD relies primarily on the brainstem's abilities to distinguish timing difference between low frequency stimuli, any peripheral or central pathologies affecting the low frequencies can produce abnormal MLDs. Previous literature has shown that individuals with conductive hearing loss produce smaller MLDs (Ferguson et al., 1998; Gravel et al., 1996; Hutchings et al., 1992). In individuals with otitis media effusion, subjects can still present with reduced MLDs directly after the course of the infection, corrective surgery and pharmacological treatment (Hall & Grose, 1993; Hall & Grose, 1996; Moore et al., 1991; Pillsbury, Grose, & Hall, 1991; Stephenson et al., 1995), but can return to normative MLDs with time (Hogan et al., 1996; Stollman et al., 1996). Jerger and colleagues (1984) performed BMLD tests in subjects with sensorineural hearing loss. BMLD values were poorer (mean = 5.3 dB) in comparison to normal controls (mean = 10.6 dB) when the hearing loss affected low frequencies. Pathologies affecting the auditory nerve or lower brainstem also produce smaller MLDs. Several studies have shown smaller MLDs in multiple sclerosis patients (Hannley et al., 1983; Henderl et al. 1990; Noffsinger et al., 1972). Binaural deficits have also been identified in those with normal hearing sensitivity but who have dyslexia Putter-Katz, 2011) and central auditory processing disorder (Moore, 2006; Sweetow & Redell, 1978).

Electrophysiologic Measures of Binaural Hearing

A brief introduction to some electrophysiologic measures is needed prior to discussing how these have been used to assay binaural hearing.

Auditory Steady-State Response

Auditory steady-state response (ASSR) is an auditory evoked potential that is phase-locked to the modulation of a carrier stimulus. The ASSR stimulus is typically a low frequency carrier tone that is either amplitude-modulated, frequency-modulated or both. ASSRs can be obtained for modulation frequencies ranging from 10-500 Hz, and evoke responses from various sites along the central auditory pathway dependent upon the modulation frequency. Modulation above 80 Hz targets the lower brainstem, while modulation below 20 Hz evokes a response from the cortex.

Acoustic Change Complex

The acoustic change complex (ACC) is a cortical auditory evoked potential to an acoustic change in a continuous steady-state signal (Martin, Tremblay & Korczak, 2008), Previous research has demonstrated its clinical potential to assess auditory discrimination, with its ability to parse changes in frequency, intensity, vowel contrast, and gap detection (Cone, 2015; Martin & Boothroyd, 1999; Martin & Boothroyd, 2000; Pratt et al., 2007; Ross et al., 2007). Any acoustic characteristic change within the continuous stimulus evokes a cortical auditory evoked potential (CAEP), consisting of the following components: P1', N1', P2', and N2'. This response differs from an onset CAEP response in that a CAEP is evoked by the stimulus onset, whereas the ACC is evoked by the neural response to detection of an acoustic characteristic change (Kim, 2015).

The ACC has obvious potential as a clinical tool, especially for pediatric and difficult-to-test populations. The ACC is evoked during passive listening; participants do not need to identify

the stimulus parameter change, or even actively listen. This suggests that the ACC is acoustically driven, rather than driven perceptually as are cognitive evoked responses such as the P300. The ACC's sensitivity for acoustic characteristic changes, particularly for speech sounds such as vowel contrasts, propel its viability as a clinical method in assessing intervention success or analyzing auditory perceptual development. This is critical, especially for later language learning (Martin et al., 2008). The ACC has good reliability in both adults and children, and has strong agreement with perceptual measures in normal hearing and hearing impaired populations (Friesen & Tremblay, 2006; Martin et al., 2010; Martin & Boothroyd, 1999; Martin & Boothroyd, 2000; Tremblay et al., 2003).

Electrophysiologic Measures of BMLD

Fowler (2017) provided a systematic review of auditory evoked potential methods used to indicate the contributions of the central auditory system to the BMLD. As the BMLD was believed to reflect neural correlates at the level of the brainstem, the ABR, ASSR and frequency following response (FFR) have been explored as potential electrophysiological markers. Several ABR studies used patients with multiple sclerosis to examine the effects of demyelination on the ABR for different BMLD conditions (Hannley, Jerger, & Rivera, 1983; Jerger, Hannley & Rivera, 1980; Noffsinger, Martinez & Schaefer, 1982). It was proposed that if the BMLD did arise from the SOC, then ABR wave III amplitude should correlate with the magnitude of perceptual BMLD. The subjects with multiple sclerosis produced smaller MLDs as well as reduced ABR wave III amplitudes, in comparison to non-affected controls.

Fowler and Mikami (1995) also examined ABRs in a BMLD paradigm, with a different method. Similar to the perceptual BMLD method, the electrophysiological BMLD (eMLD) was

reported as the difference between the S_0N_0 and the $S_\pi N_0$ ABR threshold. S_0N_0 and $S_\pi N_0$ conditions did not produce ABR threshold differences and therefore did not evidence the BMLD.

ASSR has also been evaluated as a potential electrophysiologic measure for BMLD. Wong & Stapells (2004) used an 80-Hz ASSR to target a brainstem correlate. Similar to Fowler and Mikami (1995), amplitude differences for S_0N_0-$S_\pi N_0$ waveforms were not significant and did not correlate with perceptual BMLD measures.

The brainstem generated frequency-following response could be associated with BMLD because it is a measure of neural phase-locking. However, Clinard et al. (2006) recorded FFR in S_0-S_0 and S_π-N_0 paradigms. They found that the FFR exhibited a significant *decrease* in amplitude for the S_0-S_π condition, which the researchers concluded as an effect of phase summation. This results in the opposite of a masking level difference, in other words, thresholds for the FFR are increased in the S_0-S_π condition.

Auditory middle latency potentials are generated at the level of the thalamo-cortical portion of the auditory nervous system. Fowler and Mikami (1996) measured auditory middle latency potentials using a BMLD paradigm and observed a reduction in amplitudes as interaural phase differences were varied. Again, these findings were not comparable to perceptual results. The 40-Hz ASSR, with neural generators identical to those of the middle latency potential was also tested as an electrophysiological marker of BMLD by Galambos & Makeig (1992) and Ishida & Stapells (2009). Neither study could demonstrate an eMLD for the 40-Hz ASSR, as there were no statistically significant differences between S_0-S_0 and S_0-S_π waveforms.

The longer latency auditory evoked responses demonstrate potential as a marker for BMLD. Studies with both CAEP onset (P1-N1-P2-N2) complexes, and cortically-generated slow rate ASSRs have been completed. Work by Fowler and Mikami (1992) showed P1-N1-P2-N2

eMLDs of 15 dB for 500 Hz toneburst stimuli, comparable to perceptual results. Eddins & Eddins (2018) utilized a similar BMLD paradigm to older adults using CAEP measures and found age-related decline consistent with poorer eMLDs. Wong & Stapells (2004) used ASSRs evoked by modulated tones at 7-13 Hz to obtain responses in a BMLD paradigm. They found that these slow-rate ASSRs that have primary auditory cortex generators could be used to discern an eMLD of 5.8 dB.

In summary, electrophysiologic responses from the brainstem, such as the ABR, 80-Hz ASSR and FFR do not evidence masking level differences in the way that perceptual tests do (Fowler, 2017). Cortical evoked responses, however, have response characteristics that may be similar to perceptual findings.

The effect of phase-differences such as those used to test for BMLD, have not yet been demonstrated for the cortical Acoustic Change Complex. The main objective of this study was to evaluate the effect of interaural phase differences introduced during a steady state signal to evoke the ACC, and determine if a BMLD could be derived from the ACC. A paradigm was used to simultaneously record the 80-Hz ASSR, cortical auditory evoked potential (CAEP) onset responses (P1-N1-P2) and the acoustic change complex (ACC) We hypothesized that an interaural phase difference would be detectable in the electrophysiological responses of the brainstem and cortex and that these would correlate with behavioral measures of binaural masking level difference (BMLD).

METHODS

All testing was completed at the University of Arizona. Protocols were approved by the university review board and conducted in compliance with guidelines for human subject experimentation.

Participants

Twenty-seven (27) subjects were recruited from the University of Arizona, 23 of them female, with a mean age of 24 years (range 19-51 years). There was no history of otologic disease or recent noise exposure, detailed by self-report. Otoscopy confirmed clear ear canals and the absence of any occluding cerumen or structural abnormalities. Inclusion criteria required normal bilateral hearing thresholds (<25 dB HL), established with pure-tone testing from 500-4000 Hz.

Participants were also required to demonstrate a perceptual BMLD of at least 5 dB for a 500 Hz tone before proceeding on with the electrophysiologic portion of the study. Perceptual BMLDs were measured using the DOD VA Speech Recognition CD #4, 500 Hz MLD test. The signal used was a 500 Hz pure-tone, embedded in a broadband masker presented at 70 dB. Subjects were asked to detect the presence of the tone at various SNR levels. Thresholds were found when the tone was presented in the S_OS_O and S_OS_π condition. Behavioral MLD was determined as the difference between the S_OS_O and S_OS_π thresholds.

Both pure-tone threshold and behavioral BMLD testing were administered using the Grason-Stadler Audiostar Pro (Eden Prairie, MN) and presented through EARtone 3A insert phones (Indianapolis, IN). Calibration of pure tones was verified using a Larson-Davis System 824 SPL Meter (Provo, Utah) using a 1" microphone and an H1a 2-cc coupler.

Stimuli

All stimuli for electrophysiologic tests were presented binaurally through EAR E3 Insert phones. **Stimuli:** The S_OS_O signal was 500 Hz carrier tone, modulated with an 80 Hz sinusoid at 100%. The duration of the carrier was 800 ms, and was further shaped with a 10 ms rise-fall time. The S_OS_π signal was identical to the S_OS_O signal except that the carrier tone presented to the right ear

was inverted 180º at 400 ms. The initial level of the carrier tone for testing in quiet was 70 dB SPL.

S_OS_O and S_OS_π Stimuli

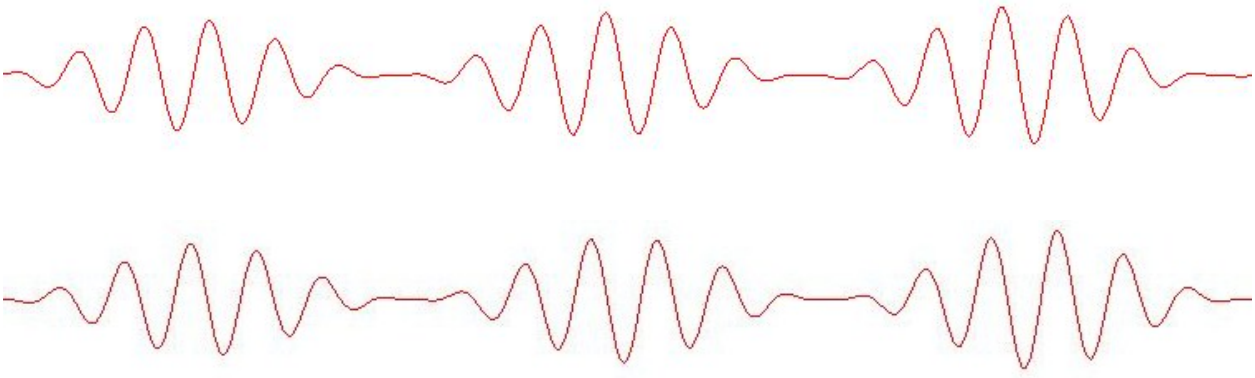

Fig 2: Diagram of S_OS_O and S_OS_π stimuli. The S_OS_π waveform is flipped 180º out of phase with the SoSo waveform at 400 ms.

Masker: The masker was broadband noise generated from a MATLAB script. When masking noise was used it was presented at 74 dB SPL in a continuous fashion.

Conditions: Two signal conditions were used, S_OS_O and S_OS_π. S_OS_O refers to when the signal is presented in phase to both ears, while S_OS_π indicates when the signal is presenting 180º out of phase. In this case, the phase difference was introduced at 400 ms after stimulus onset. Both the S_OS_O and S_OS_π conditions were presented in quiet and with masking noise.

All stimuli were calibrated using a Larson-Davis System 824 SPL Meter (Provo, Utah) using a 1" microphone and an H1a 2-cc coupler.

Electrophysiologic Testing

All electrophysiological measurements were recording using silver-silver chloride disposable cup electrodes using a Cz (non-inverting) to linked right and left mastoids (inverting) electrode montage. All participants were prepped at each site with a mild abrasive, Nu-prep, and

each electrode was secured with electrode paste and paper tape. Individual electrode impedances were ≤ 7 kΩ and inter-electrode impedances did not surpass 3 kΩ. The EEG was amplified with a gain of 34 dB and filtered at 1-1000 Hz.

Recordings were performed using the Intelligent Hearing Systems Smart-EP Advanced Research Module (Miami, FL). Each response was averaged from 512 artifact-free sweeps using a 1000 ms time window, at a sampling rate of 1.0 kHz. The artifact rejection level was set at ±30 μV.

Protocol

Participants completed both behavioral and electrophysiological testing in one session, lasting no more than 2 hours. Sessions began with the behavioral BMLD test. During CAEP recordings, subjects were required to be awake; they were seated in a chair and given the option to read printed materials. All testing was performed in a sound-treated booth.

Responses for the S_OS_O and S_OS_π were first obtained in quiet at 70 dB SPL. Broadband noise was introduced at a -4 dB SNR, and the S_OS_O and S_OS_π conditions were repeated. Stimulus levels were then incremented or decremented in 5 dB steps to find the lowest stimulus level at which an ACC was present in the masked S_OS_π condition. The difference between the SNR needed to completely mask the S_OS_π ACC and the SNR when the masked ACC was present was determined to be the electrophysiologic masking level difference (eMLD).

Data Analyses

All CAEP waveforms were analyzed using rule-based visual detection methods. Identifying CAEP amplitude and latency components were based upon values established in the literature (Picton, 2011; Wunderlich & Cone-Wesson, 2000; Cone &Whitaker, 2013). Peak latencies were identified and marked using P1, N1, P2 and N2 components for onset responses

and P1', N1' P2' and N2' components for ACC responses. Amplitudes were calculated as the difference between a peak and its subsequent trough, or trough to succeeding peak. If there was no identifiable peak, a value of 0 μV was entered for amplitude. All rule-based visual detection was performed by the lead examiner (KI) under the training of the principal investigator (BC). Descriptive and inferential statistical analyses were performed using StatView (v5.0.2) software. Off-line band-pass filtering at 60-200 Hz of the averaged responses was completed in order to extract the ASSR. Analyses of the ASSR were completed for the 400-700 ms timeframe, where the ACC was expected to take place. Statistical analyses of these waveforms was completed using Igor Pro (v 6.37) software.

RESULTS

CAEP Waveforms

Grand mean average waveforms are shown in Figure 2 for the following conditions: 1) binaural in-phase in quiet (Quiet S_OS_O); 2) binaural right-ear 180° phase shift in quiet. (Quiet S_OS_π; 3) binaural in-phase in noise (Noise S_OS_O); 4) binaural right-ear 180° phase shift in noise (Noise S_OS_π). In the first condition, the stimulus level was at 70 dB and the noise at -4 dB SNR. Waveforms in the quiet conditions demonstrate an onset response (P1-N1-P2) to the stimulus. However, when noise is introduced, the onset response is masked. The ACC is evident in S_oS_π conditions, with P1'-N1'-P2' at 50, 100 and 150 ms respectively following the phase change that occurred at 400 ms.

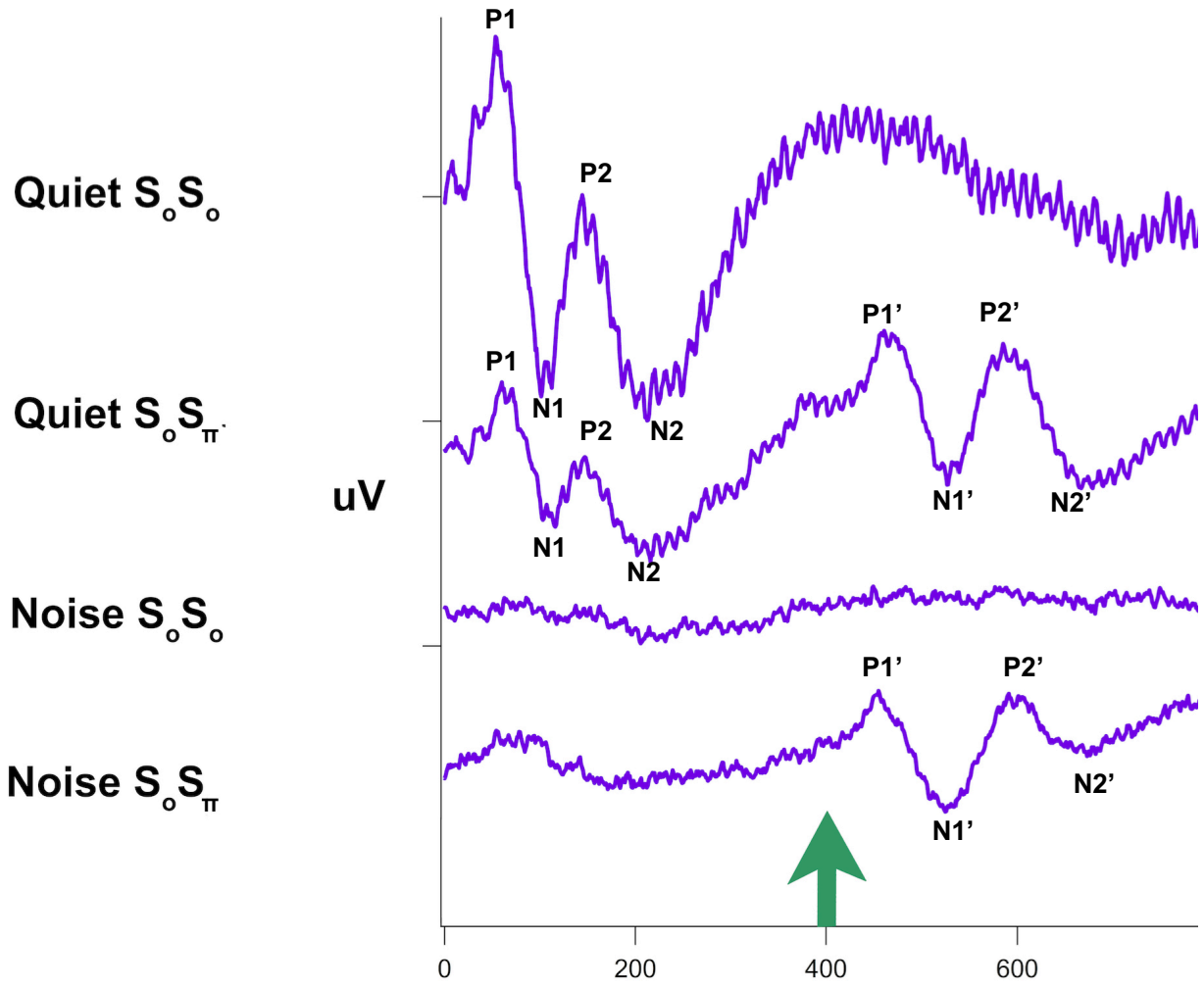

Figure 3: Grand mean average CAEP waveforms for S_OS_O and S_OS_π conditions in quiet, with stimuli at 70 dB SPL and in noise at -4 dB SNR. A robust ACC is present in S_oS_π conditions. The ASSR is evident as the "sawtooth" appearance of the traces.

Presence of Components

The presence of CAEP components P1-N1-P2 was determined. To be considered present, a component had to be visually detected within a specific latency range. The latency ranges used were 50-150 ms for P1, 100-200 ms for N1 and 150-250 ms for P2. If there was no discernible peak in that range, it was determined to be missing, and assigned an amplitude for 0 μV. Table 1

summarizes the percentage of responses in which a component had an amplitude of greater than 1 μV. There were more missing components for the $S_oS_{\pi_i}$ conditions compared to S_oS_o. Also, N1-P2 and P2-N2 were absent more often than P1-N1.

Table 1: Onset amplitudes More than 1 μV

	P1-N1	**N1-P2**	**P2-N2**
$\mathbf{S_OS_O}$	83%	60%	56%
$\mathbf{S_OS_\pi}$	61%	46%	34%

Table 1: Percentage of onset response waveforms with amplitude values of more than 1 μV by interaural phase condition.

Amplitude

CAEP onset peak-to-trough amplitudes were measured for P1-N1, N1-P2, and P2-N2. Unidentifiable components were given a value of 0.0 μV. The onset components decreased in amplitude when the phase change was introduced at 400 ms. Figure 4 illustrates the effect of binaural phase condition on component amplitude for the quiet condition. There were 1.63, .93, 1.41 μV decrements in amplitude for P1-N1, N1-P2, and P2-N2, respectively when interaural phase differences were present. P1-N1, N1-P2 and P2-N2 were combined as the repeated measure. Although components P1, N1, and P2 have different but overlapping sources, the peak-to-trough measurement of amplitude exaggerates their correlation. A repeated measures analysis of variance (see Table 2 for summary of R-ANOVA results) indicated a statistically significant difference in onset amplitude as a function of phase change, with amplitudes decreased in the S_OS_π condition in comparison to the S_OS_O condition.

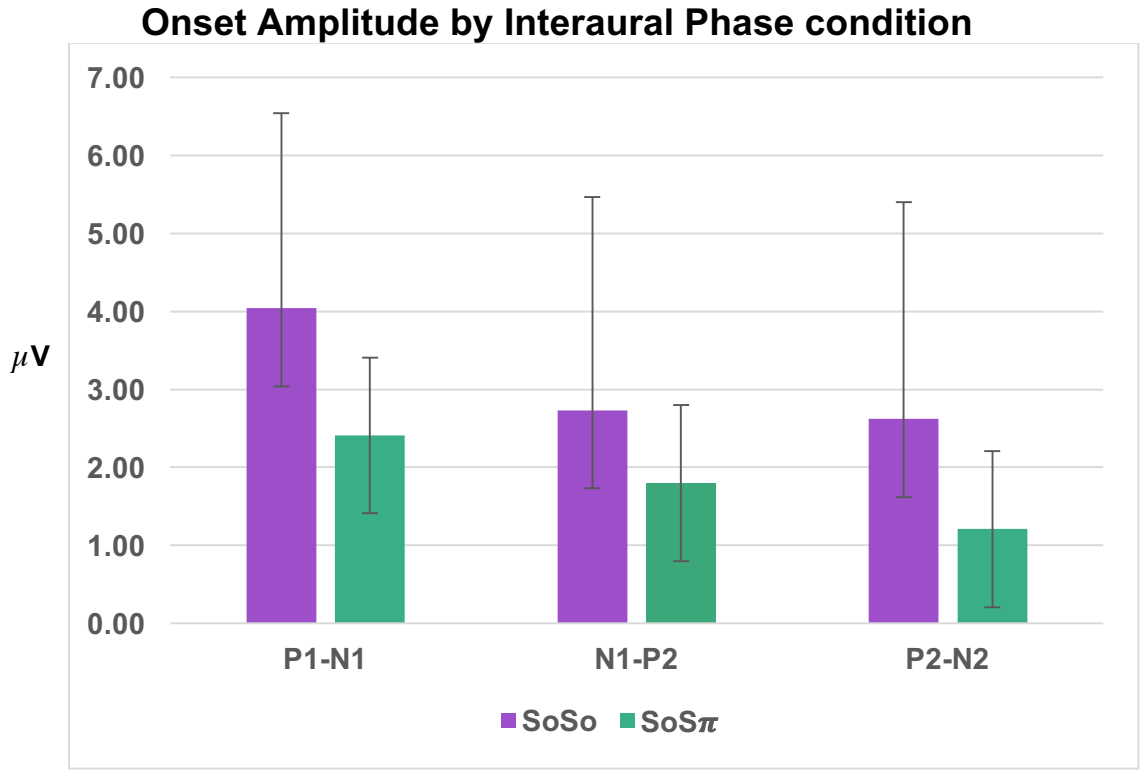

Figure 4: Mean P1-N1-P2 component amplitudes at 70 dBA are shown as a function of phase condition in quiet. Error bars indicate 1 standard deviation.

Latency

Peak latencies were measured for onset components P1, N1, P2 and N2. When measured in quiet, onset latencies did not change as a function of interaural phase, as illustrated in Figure 5. Latency differences were less than 5.2 ms for S_OS_O vs. S_OS_π conditions. A repeated measures analysis of variance was completed for onset latency as a function of interaural phase condition in quiet only. There were no statistically significant differences across phase conditions for any of the latency components.

There were, however, latency shifts when masking noise was introduced in conjunction with the tonal stimuli. Figure 6 shows the mean onset latencies in quiet compared to those when noise was introduced at -4 dB SNR. Latencies were prolonged in the noise condition compared

to the quiet condition. Repeated measures analysis of variance for the effect of noise on the onset latencies was completed, and revealed a statistically significant effect of noise (see R-ANOVA summary in Table 2.

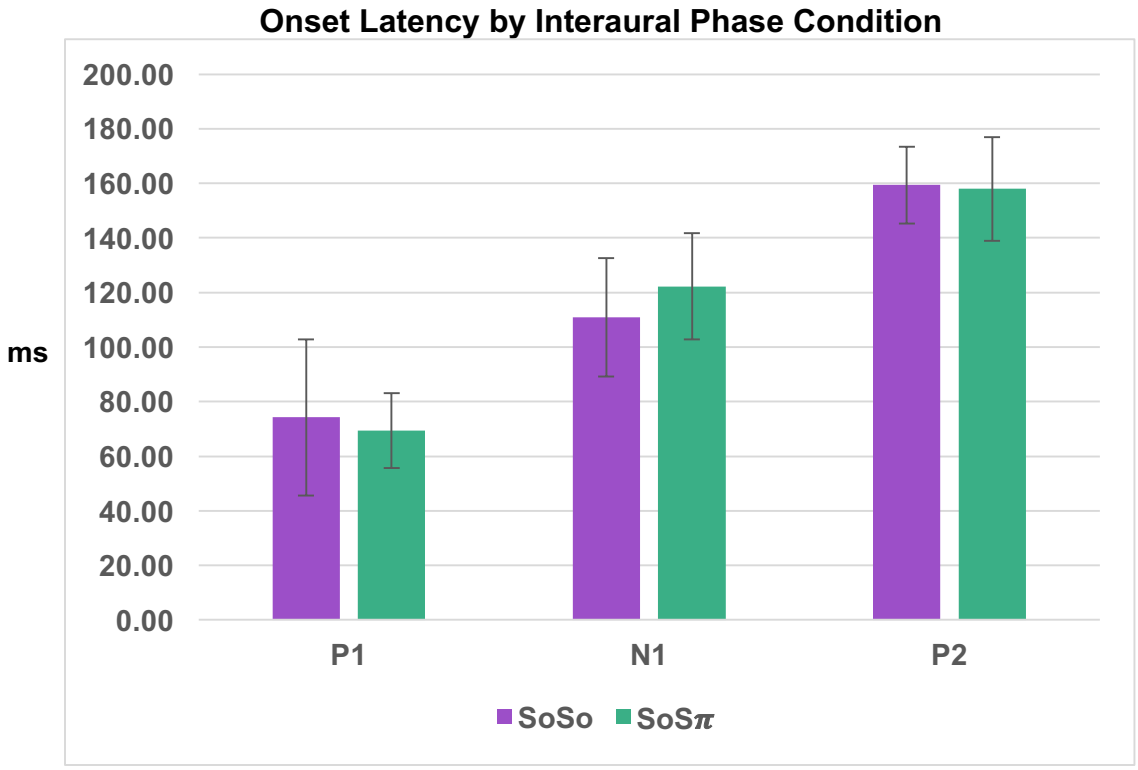

Figure 5: CAEP latencies as a function of interaural phase differences, measured in quiet. Latency differences for phase were not statistically significant.

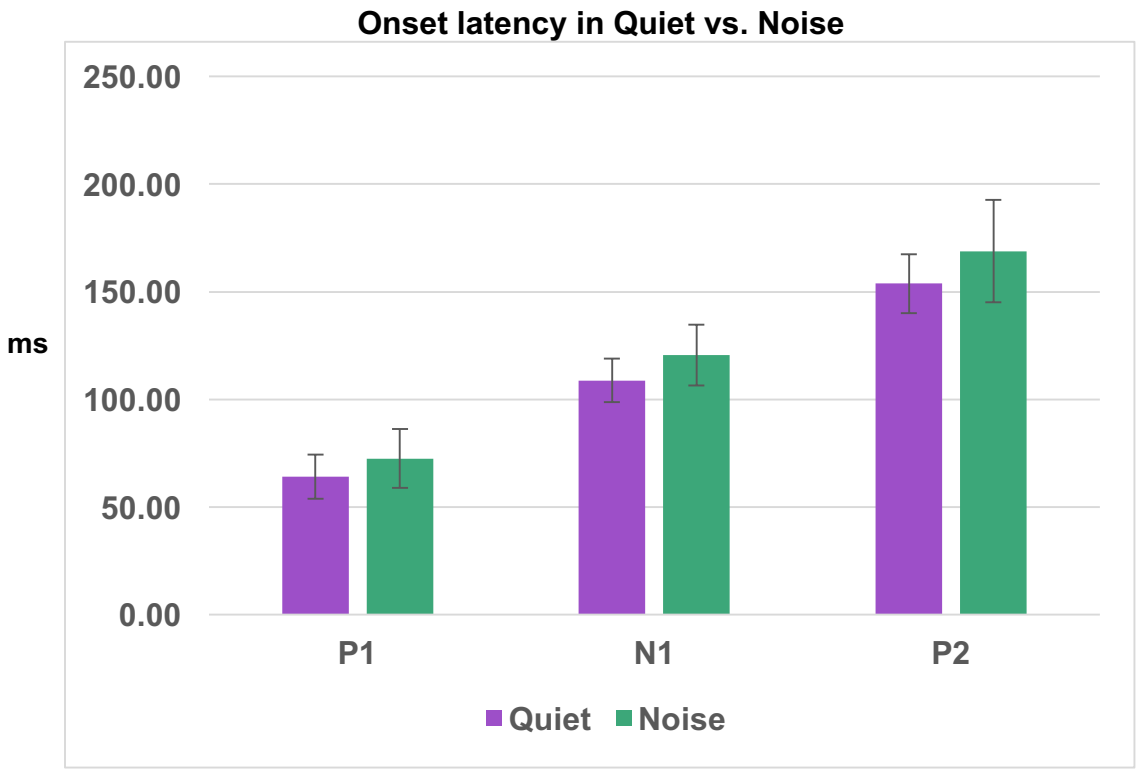

Figure 6: CAEP latencies in quiet. The differences in latencies owing to noise were statistically significant.

Table 2. Analysis of Variance for Onset Amplitude

Source	DF	Mean Square	F-Value	p
P1-N1-P2 Amplitude	1, 94	125.294	8.226	.005
P1-N1-P2 Latency	1, 70	6167.650	16.493	.000

Table 2: Results of repeated measures analyses of variance for CAEP onset components. Amplitude differences were statistically significant as a function of phase. Onset latencies were statistically significant as a function of the introduction of noise.

ACC

Presence of ACC

All participants demonstrated ACCs when the phase change was introduced at 400 ms in the S_OS_π condition. The percentage of responses demonstrating amplitudes of ≥ 1.0 μV are summarized in Table 3 as a function of component. P1' and N1' were observed more frequently than P2' and N2'.

Table 3: ACC Amplitudes More than 1 μV

	P1-N1	**N1-P2**	**P2-N2**
S_0S_π	93%	92%	82%

Table 3: Percentage of ACC response waveforms with amplitude values of more than 1 μV by interaural phase condition.

Amplitude

ACC amplitudes were measured as peak-to-trough values for the following components: P1'-N1', N1'-P2' and P2'-N2'. Mean ACC amplitudes were attenuated in the noise condition (Figure 7) relative to those obtained in quiet. A repeated measures analysis of variance for the effect of noise on ACC amplitude revealed that this was a statistically significant effect (Table 4).

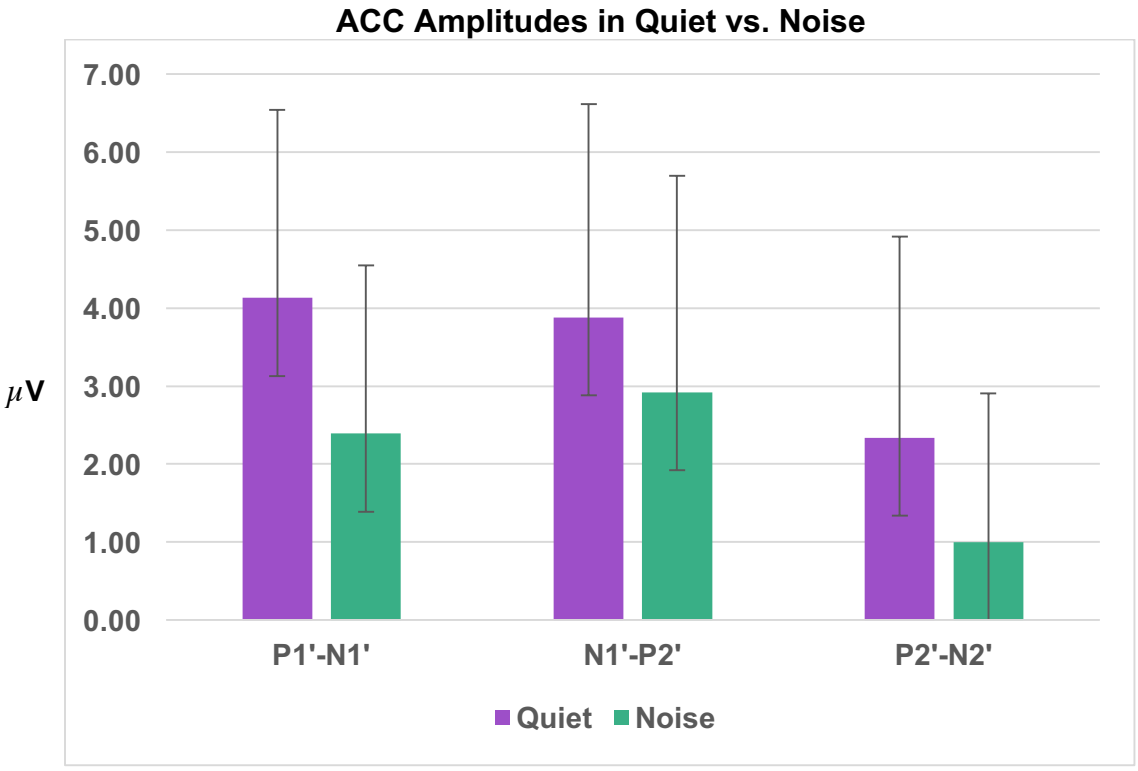

Figure 7: ACC amplitudes (evoked by interaural phase differences) in quiet and noise. The amplitude differences owing to noise were significant.

Latency

Mean ACC latencies are shown in Figure 8. These latencies are measured relative to the onset of the interaural phase difference that occurred at 400 ms. Repeated measures analysis of variance revealed that there were no statistically significant latency differences with the introduction of noise at -4 dB SNR compared to quiet conditions.

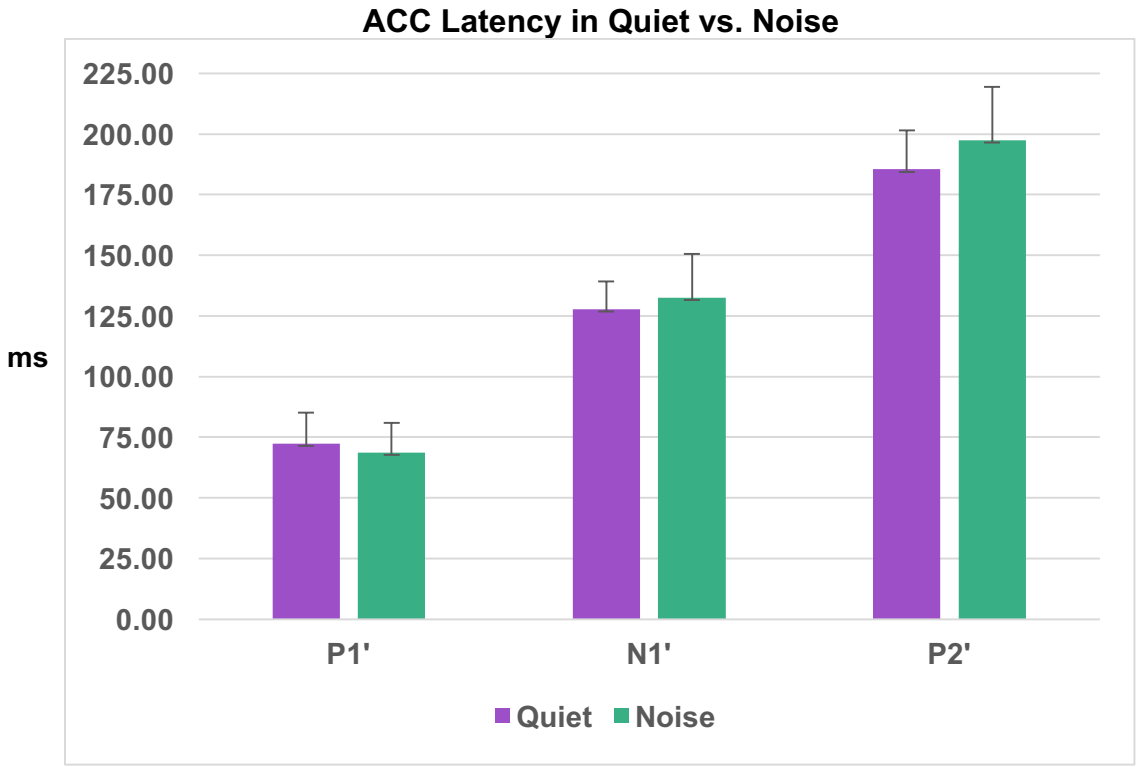

Figure 8: ACC latencies in quiet and in noise. There were no significant differences in latency due to the introduction of noise.

Table 4. Analysis of Variance for Acoustic Change Complex amplitude in quiet and noise

Source	DF	Mean Square	F-Value	p
P1-N1-P2' Amplitude	1, 286	359.996	33.857	<.000

Table 4: Results of analyses of variance for ACC components, as a function of noise.

CAEP vs. ACC

The CAEP onset amplitudes were compared to ACC amplitudes in the quiet, S_OS_π condition. Figure 9 illustrates the amplitude differences between onset and ACC components.

Amplitude differences for P1-N1, P2-N2, and N2-P2 with their ACC counterparts as 1.72 uV, 2.08 μV and 1.71 μV, respectively. Paired-sample T-tests were completed to evaluate if there were significant differences for onset vs. ACC and amplitudes. CAEP onset amplitudes were smaller than ACC amplitudes in the S_OS_π condition (t_{143}=7.1, p<.0001).

Latency differences between onset and ACC components were measured and a paired samples t-test was completed to determine the statistical significance (Figure 10). ACC latencies were prolonged relative to their onset counterpart (t_{86}=7.27, p<. 0001).

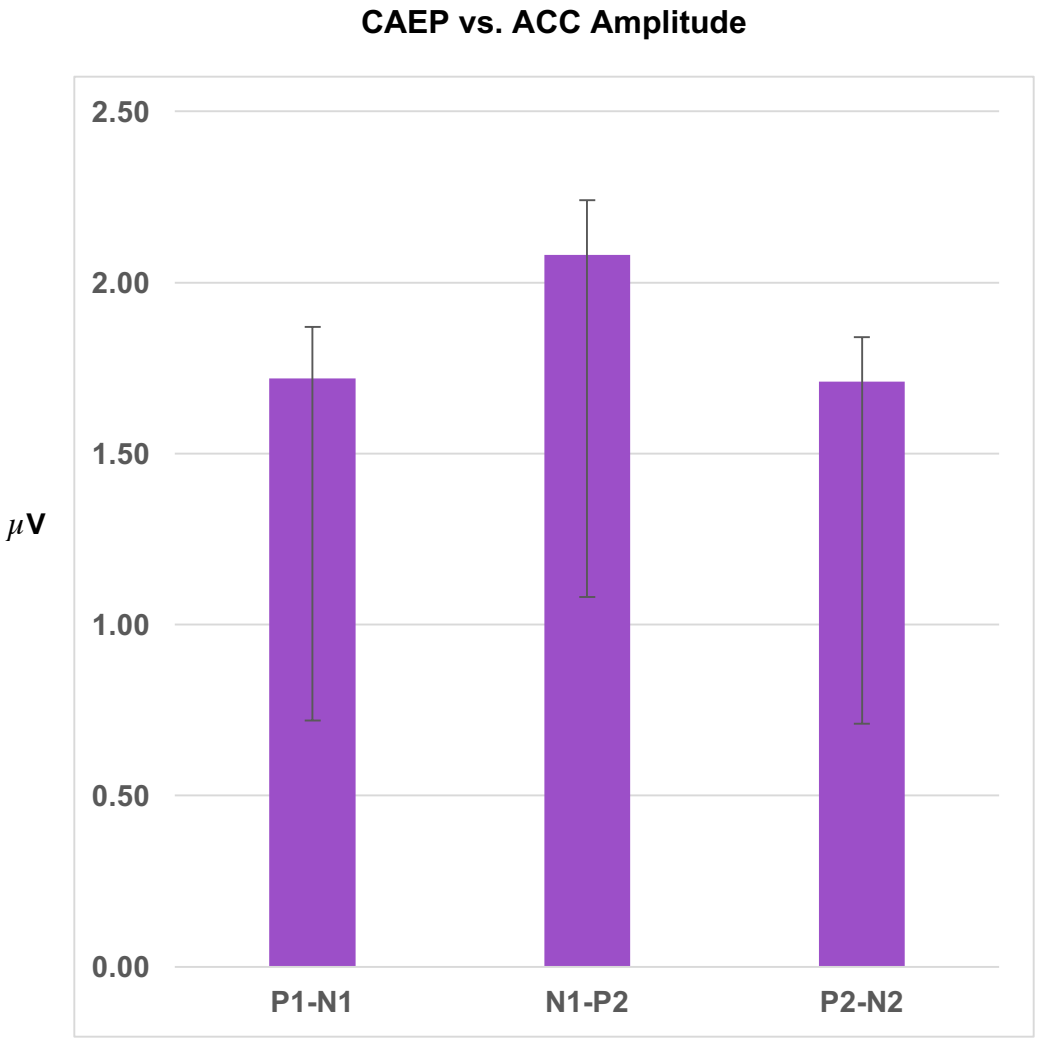

Fig 9: CAEP and ACC amplitude differences measured for the S_oS_π quiet condition.

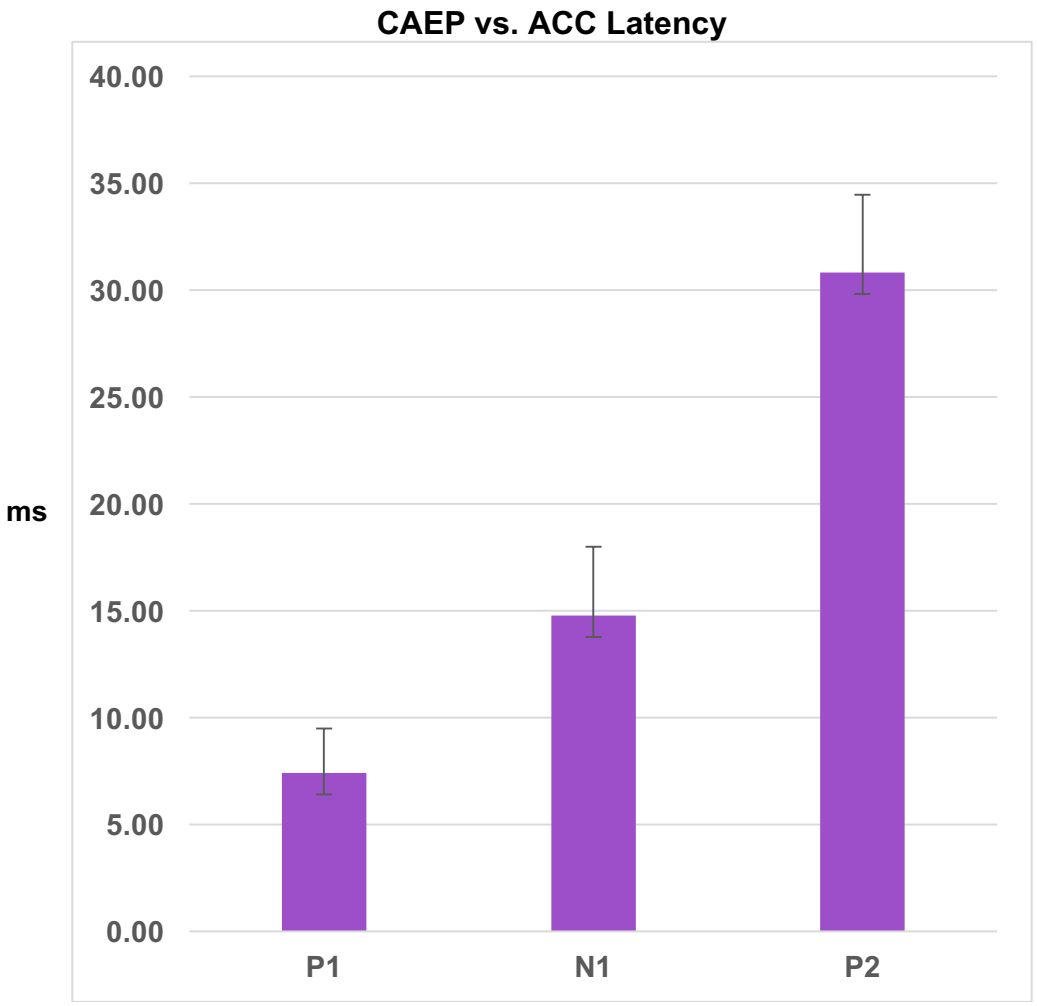

Fig 10: CAEP and ACC latency differences measured for the $S_0S_{\pi i}$ quiet condition.

vs. Perceptual BMLD

All subjects exhibited ACC in the quiet $S_0S_{\pi i}$ condition. When noise was introduced, the ACC was present in all but 3 (out of 27) participants. MLD was derived from the difference between a subject's ACC threshold and the noise level. This difference was then compared with the subject's perceptual data. The mean perceptual BMLD was 13.6 dB, and the mean electrophysiologic BMLD was 9.7 dB, resulting in a difference of 3.8 dB. The mean BMLD values for both methods are shown in Figure 11.

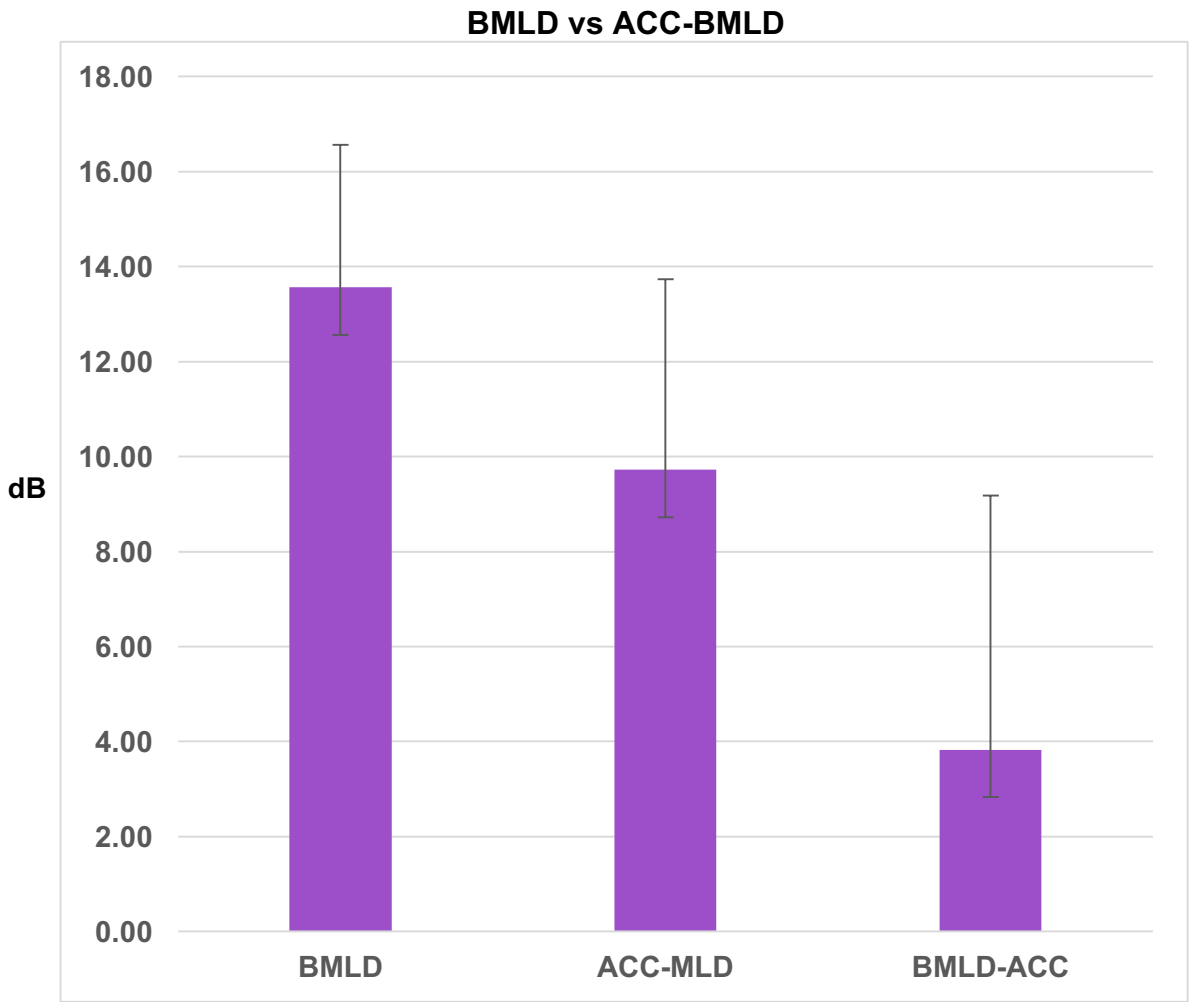

Fig 11: The mean BMLD, ACC and BMLD-ACC differences.

ASSR

The ASSR was extracted from the cortical response waveform using a 60-500 Hz bandpass filter. Grand mean average waveforms for S_OS_O and S_OS_π in quiet are shown in Figure 12 for the 400-700 ms response region. ASSR responses were analyzed in this latency range, as this is the expected latency range of the ACC. Wave statistics were determined using Igor Pro v. 6.3.7.2 (Wavemetrics Inc, 2014). The root-mean-square amplitude of the ASSR in the S_OS_O condition was 0.13 μV with a standard deviation of 0.14 μV, while in the S_OS_π condition the root-mean-square amplitude was 0.12 μV with a standard deviation of 0.12 μV. A paired

samples t-test of the S_OS_O and S_OS_π waveforms indicated that there were no statistically significant differences between them.

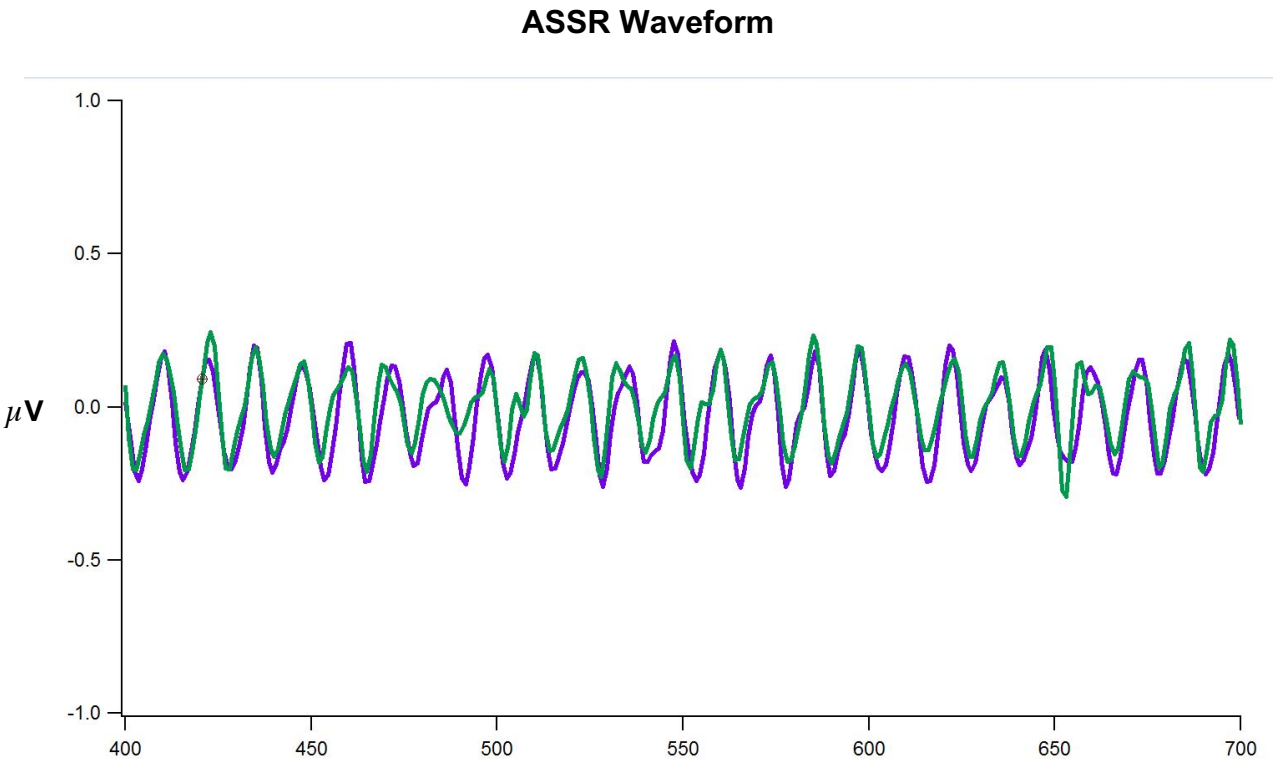

Fig 12: S_OS_O and S_OS_π in quiet grand mean average ASSR waveforms were analyzed from 400 to 700 ms. S_OS_O waveforms are depicted in purple while S_OS_π waveform is colored in green.

DISCUSSION

This study began with two overarching hypotheses: that 1) interaural phase differences (S_OS_π) would evoke a change in the electrophysiological responses from the no-phase-change (S_OS_O) condition at both the level of the brainstem and the cortex, 2) electrophysiologic BMLD (eMLD) would correlate with the perceptual BMLD.

At the level of the brainstem, 80 Hz-ASSR responses did not demonstrate a change in latency or amplitude when the interaural phase change was introduced. This is consistent with previous findings concerning binaural interaction and phase sensitivity of the ASSR completed by Wong and Stapells (2004). In their study, they utilized stimuli similar to the present study: a

500 Hz carrier tone with 80-Hz amplitude modulation. ASSR was measured with the 80 Hz-modulated tone in-phase at both ears (S_OS_O) and in a second trial, with the modulated tone out of phase (S_OS_π). Similar to results from the present study, 80-Hz ASSR amplitude differences between S_OS_O and S_OS_π conditions were not statistically significant and an eMLD was not present.

Others have utilized brainstem evoked responses to search for the effect of interaural phase differences and the MLD. Wilson & Krishnan (2005) used the FFR to test brainstem contributions to the MLD. They found that FFR amplitude increased in the $S_{\pi i}N_o$ condition compared to the S_ON_O condition. Their 9 subjects demonstrated an average FFR-MLD of 2.6 dB in the $S_\pi N_O$ condition. This did not correlate with perceptual measures of MLD, which were on the order of 9.5 dB. While Wilson & Krishnan did see an amplitude increase in the $S_\pi N_O$ condition in comparison to the S_ON_O condition, their sample size was small and perceptual measures did not correlate with eMLD, providing only weak support as an electrophysiologic BMLD measure. As previously reviewed, Clinard and colleagues (2016) measured FFR in conditions of interaural phase congruence, and interaural phase inversion. When interaural phase inversion was present (S_ON_O-$S_\pi N_O$) a decrease in response amplitude relative to the S_ON_O-S_ON_O condition was found. That is, there was a masking level difference that yielded *poorer* thresholds for the S_OS_π condition, that was on the order of -11.83 dB. The FFR results did not correlate with the perceptually measured BMLD.

These previous studies and the current study of interaural phase differences using brainstem responses 80-Hz ASSR present conflicting results. Only one study showed an increase of the amplitude in the S_OS_π condition that led to a 2.6 dB MLD (Wilson & Krishnan, 2005). All of the others, including the present one, found no change or a decrease in amplitude coincident with the

change in inter-aural phase. This decrease can be viewed as a suppressive or inhibitory mechanism. Excitatory/inhibitory response properties (Langford, 1948) and contralateral inhibitory input (Brand et al., 2002; Myoga et al., 2004) may also contribute to the decrease in amplitude.

An aspect of measuring binaural effects using the brainstem evoked responses are that the responses are quite small to begin with (sub-microvolt) and finding a change in amplitude that is smaller than the over-all amplitude is an issue of resolution of the response in the overall EEG-noise (Clinard=<.08 μV, Wilson and Krishnan = <.09μV). Given this small amplitude, and the difficulties obtaining an adequate response to noise level, it would seem unlikely that these brainstem measures could be used clinically as an electrophysiologic correlate for the BMLD.

A major finding in this study was that the ACC could be evoked by a response to change in interaural phase. Previous research has shown an ACC in response to changes in frequency (Dimitrijevic et al., 2009; Dimitrijievic et al., 2011, Harris et al., 2008), intensity (Martin & Boothroyd, 2000; Harris et al., 2007; Dimitrijevic et al., 2009; Dimitrijievic et al., 2011), vowel-token (Cone, 2015) and gap duration ((Michalewski et al., 2005; Friesen & Tremblay, 2006). This is the first demonstration of ACC evoked by interaural phase differences. The sensitivity to binaural phase is indicated by an increase in neural activity, that is, the presence of an ACC, with an amplitude that is comparable to that of the onset response. Furthermore, the ACC for interaural phase-differences is present at SNRs at which the onset response is absent. The presence and amplitude of the ACC for interaural phase change suggest an enhancement of the neural response at the level of the cortex.

In contrast to the suppression seen at the level of the brainstem, enhancement occurs at the cortex. Deburyne (1984) examined AEP binaural interaction throughout the central auditory

system using ABR, middle latency response (MLR) and cortical response (P1-N1-P2). Binaural interaction was measured as the ratio of the peak-to-peak amplitude of the binaural response divided by the amplitude of the summed right and left monaural responses. At the level of the brainstem, ABR waves I and III demonstrated ratios close to 1.0, indicating no binaural interaction. The B/R+L amplitude ratios were largest for ABR wave V, and decreased for MLR wave Pa and Pb, and cortical components (P1-N1-P2-N2). This decrease in the amplitude ratio indicated that amplitudes in the binaural condition were growing larger than the summed monaural responses at cortical levels, in contrast to the larger summed monaural responses compared to binaural at the brainstem level.

The findings of the current study are similar to those of Fowler and Mikami (1996) who measured eMLDs using onset CAEPs (P1-N1-P2) with a 500 Hz tone burst stimuli. They found eMLDs for S_0N_0-$S_\pi N_0$ of 15 dB, on average. Epp and colleagues (2013) also utilized CAEP measures to determine binaural release from masking with cortical onset responses P1-N1-P2. They found that by using an interaural phase-difference and a modulated masker, that there was a co-modulation masking release. The CAEP P2 component in particular was sensitive to both difference in interaural signal difference and masker frequency modulation, suggesting could be used as an objective measure for BMLD.

Cortical eMLD has also been used to study special populations. Eddins & Eddins (2017) used a CAEP MLD paradigm comparing young normal-hearing, older normal-hearing and older hearing-impaired adults. They found an age-related decline in release from masking. Hughes and colleagues (2014) measured cortical evoked responses in patients with progressive supranuclear palsy, a degenerative pathology that affects the upper brainstem. Even with damage to the

brainstem, an area believed to be critical for binaural hearing, these patients still evidenced BMLDs in their CAEP responses.

Perceptual MLD and eMLD

Classic studies of BMLD (Hirsh 1948 a, b; Licklider, 1948) show that lower frequency stimuli can evoke effects as large as 12-15 dB. In the present study, in which perceptual BMLD was measured using 500 Hz tones, the mean BMLD was 13.6 dB, consistent with the classic studies. For the ACC metric of MLD, there was an average eMLD of 9.7 dB. This was smaller than CAEP-MLDs from Fowler & Mikami (1996). These differences could be attributed to differences in signal duration. Fowler and Mikami used a 500 Hz tone burst (rise-fall time: 2 ms, plateau: 3 ms), in comparison with the current study's stimuli of an 800 ms amplitude modulated 500 Hz carrier tones. The responses being measured were also of different nature: Fowler and Mikami measured the cortical onset response, and not the ACC.

Differences between behavioral and electrophysiologic measures could be attributed to a variety of factors. The nature of perceptual and electrophysiologic responses and how they are measured are quite different. Ultimately, any evoked potential measure, including ACC, is one of neural synchrony. The ACC is dependent on the simultaneous firing of cortical neurons. In order for the response to be recorded at the scalp, enough neurons must fire concurrently. Perceptual responses can be present at levels lower than those required to evoke a synchronous neural response that is recorded far-field. Certainly, neural synchrony and perceptual responses are correlated, but not on a one-to-one-basis.

Clinical Relevance

While the perceptual BMLD is used as a clinical tool to assess brainstem function, there has not been an electrophysiologic correlate. Perceptual BMLD is a common test used in central

auditory processing disorder (CAPD) test battery. Developing an electrophysiologic correlate would be particularly helpful in assessing difficult to test populations that may not have the verbal skills to identify signal threshold or to avoid fatigue from the lengthy CAPD appointment.

Limitations

There are several limitations to this study. First, due to time constraints, an exhaustive search for the ACC threshold in noise was not undertaken. Stimulus levels were incremented/decremented in 5 dB steps; in contrast, perceptual BMLD levels were found in 1 dB increments. There may be more correspondence between perceptual and electrophysiologic estimates of BMLD if similar increments were used. Secondly, the recording methods were not optimized for ASSR recording. The design of the stimulus and recording paradigm was to allow ASSR and ACC to be obtained simultaneously. It is the case that the current ASSR findings are congruent with those of Wong and Stapells (2004), yet, a robust ACC for interaural phase difference was observed at the same time as ASSR showed no effect.

Future Directions

Future research should be extended to demonstrating the BMLD in CAEP using populations at risk for auditory processing deficits, such as children with specific language impairments, and children, teenagers and adults with normal hearing who complain of not being able to hear speech in noise. Also, electrophysiologic measures such as ACC for interaural phase difference could be used to investigate binaural hearing in older adults with hearing loss who use hearing aids or cochlear implants.

CONCLUSION

The results of this present study demonstrate that ACC can be evoked by interaural phase differences, and that binaural masking levels differences can be estimated using this technique.

This provides some insight into brain mechanisms of binaural hearing that could be used to assay binaural benefit from treatment strategies such as binaural hearing aids, combined electrical and auditory stimulation (cochlear implant on one side and a hearing aid on the other) or even bilateral cochlear implantation.

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