NEUROPHYSIOLOGIC UNDERPINNINGS OF INTERAURAL ASYMMETRY IN YOUNG ADULTS WITH AND WITHOUT BINAURAL INTEGRATION DEFICITS ON DICHOTIC LISTENING TESTS.

by

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Amblyaudia is an auditory processing disorder characterized by a binaural integration deficit with poor performance in only one ear and a larger than normal interaural asymmetry (Moncrieff, et al., 2016), which responds to a deficit-specific auditory training protocol that helps to remove the asymmetry (Moncrieff, et al, 2017).

There is significant controversy in using behavioral, speech-based tests to assess children for auditory processing disorders via current diagnostic protocols, which has resulted in efforts to find alternative diagnostic methods to add to the current test battery (Jerger & Musiek, 2000). A population which previously has been shown to demonstrate binaural integration deficits is those with schizophrenia (Schubring, Popov, Miller, & Rockstroh, 2017). Their difficulties are displayed in their evoked responses to various stimulus presentation paradigms, such as those evoking the P300 responses, P50 responses, and other cortical responses. The question arises as to whether another population—i.e. those with amblyaudia—who also demonstrates binaural integration deficits will display similar patterns in their evoked responses in terms of latency and amplitude of their responses.

The purpose of this study was to identify the presence of amblyaudia in a population of young adult subjects, to measure MMN/P300, P50 (paired pulse), and Frequency Following Responses (FFR) from those individuals and other control subjects without amblyaudia, and to investigate whether any of the objective electrophysiological measures show reliable differences

in individuals with amblyaudia. Control and amblyaudia groups were determined through specific patterns of interaural asymmetry as determined by performance on the Randomized Dichotic Digits Test (RDDT) (Strouse-Carter & Wilson, 1999) and the Dichotic Words Test (DWT) (Moncrieff, 2015). The results from electrophysiological testing showed that the S3 response peak following the paired pulse paradigm was significantly longer, the amplitude of the N2 negative going response peak in the P300 paradigm was significantly larger, and the latencies of the D and E peaks in the FFR response were significantly longer in the amblyaudia group when compared to the control group. These results supported the general trends suggesting that there is increased noise and less synchrony in the central auditory nervous systems of those with amblyaudia—there was a high degree of variability in the subjects in this group, overall suggesting that there are differences in processing in those with amblyaudia as compared to the control group.

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PREFACE

I would like to thank some important people for their unrelenting support throughout my experience in writing this thesis. Without them, this would not have been possible.

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1.0 INTRODUCTION

1.1 BINAURAL INTEGRATION

Binaural integration is the process by which information from both ears is analyzed and compared to comprehend the surrounding environment. For this process to occur, signals from both ears must cross contralaterally to opposite sides to be cross-referenced with each other. In these processes, mechanisms are in place to inhibit weaker, less important signals coming from one side of the head and to boost the stronger, main input signals from the other side—this allows the auditory system to filter out distracting information, like background noise.

An auditory signal will reach both ears and initially travels through ipsilateral pathways on each side of the head. Once reaching each cochlear nucleus in the pontomedullary junction at the brainstem, the encoded information is passed on to both the ipsilateral and contralateral superior olivary complexes (SOC), located in the caudal pons region of the brainstem between the two cochlear nuclei. Thus, the SOC is first center in the central auditory nervous system (CANS) to receive information bilaterally from both ears to make comparisons using interaural cues. From the SOC and upwards throughout the CANS, cells have opportunities to create modifications to the signal based on these interaural cues, depending on the processing functions that take place at each ascending center of the CANS. One comparison that is made at the SOC is the processing of interaural level differences (ILD): incoming auditory signals from different directions reach each

ear with different intensity levels. As a sound wave propagates spherically from a sound source, the initial amount of energy from the signal becomes proportionally more spread out over larger surface areas with increasing distance from the sound source. Each ear is located at varying distances from the sound source (being about 15 cm apart), which leads to more sound energy being concentrated at the ear closer to the sound source versus the farther ear. The signal reaches each ear with differing physical intensity levels, which are encoded in the neural signals that start with the auditory nerve branch at each ear and are transmitted to the cochlear nuclei.

These neural signals from each ear must be cross-referenced with each other for their differences to become meaningful—this binaural integration first takes place at the SOC. The SOC is comprised of several nuclei, which function differently to process incoming binaural cues: the nuclei are the lateral superior olive (LSO), medial superior olive (MSO), and the medial nucleus of the trapezoid body (MNTB).

1.1.1 Processing Binaural Cues

The LSO and MNTB are involved in processing interaural level differences. As a signal comes to one side of the head, and therefore has a comparatively large sound pressure, a resulting strong neural signal excites that ipsilateral ventral cochlear nucleus. Neurons from that cochlear nucleus will in turn send a strong excitatory signal to the ipsilateral LSO. That same ventral cochlear nucleus will also send a strong excitatory signal to the contralateral MNTB, which sends a strong inhibitory signal to the contralateral LSO. A complementary verification chain of neural signals takes place starting with the side of the head opposite the side of the original auditory signal—since this is the farther ear, it receives a weaker physical signal which will manifest in a weaker neural firing chain: that side’s ventral cochlear nucleus sends a weak excitatory signal to the

ipsilateral LSO. That ventral cochlear nucleus will also send a weak excitatory signal to the contralateral MNTB, which then sends a weak inhibitory signal to the contralateral LSO.

At this point, each LSO has received a combination of strong and weak inputs from various locations and is given the opportunity to modify what information is passed on to higher CANS centers. The LSO on the side nearer to the sound source receives a strong ipsilateral excitatory signal and weak contralateral excitatory signal, signaling that the auditory signal has come from that side of the head. Meanwhile the opposite LSO receives a weaker ipsilateral excitatory signal and a strong contralateral excitatory signal, signaling that the input from that side of the head is less dominant within the auditory space.

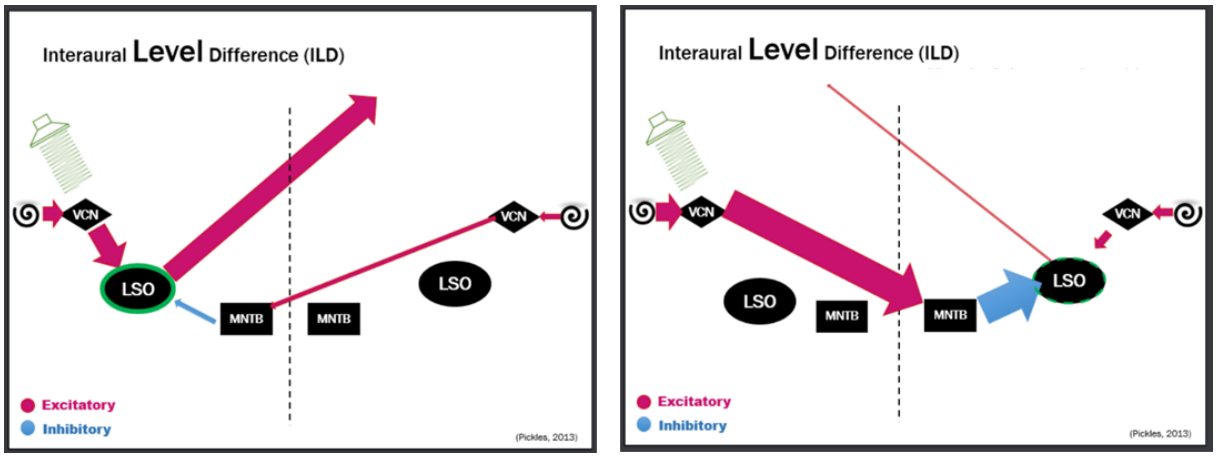

Figure 1. Processing ILDs in the SOC

1.1.2 Right Ear Advantage

Typically, the ear pathway contralateral to the language dominant hemisphere (usually the left hemisphere) of the brain does a slightly more effective job of boosting a signal coming from that dominant ear and suppressing distracting, weaker signals from the opposite nondominant ear—this is termed as the right ear advantage. Doreen Kimura (1967) asserted that a dichotic signal (i.e. a signal which simultaneously stimulates both ears with different stimuli) creates a competition between the ears, which typically results in one ear (the dominant ear) performing better than the other (the non-dominant ear). She noted that the greater number of neural fibers present in the contralateral pathway in comparison to those in the ipsilateral pathway contributes to the typical right ear advantage in individuals with left hemisphere dominance for language (Kimura, 1967).

1.2 AMBLYAUDIA

The term “amblyaudia” was coined in reference to the analogous condition in the visual system and its diagnosis, amblyopia (Kaplan et al., 2016). Amblyopia is characterized by an incongruence in processing visual stimuli. Leaving the condition uncorrected past a young age during a critical window will likely cost that person their general visual acuity in the nondominant eye into the future. Amblyaudia is characterized by a similar asymmetry in the auditory system, with one ear processing more effectively than the other and therefore leading to a binaural integration deficit that will lead to practical difficulties if left untreated (Moncrieff, Keith, Abramson, & Swann, 2016a). While the two conditions—amblyaudia and amblyopia—are parts of markedly different

peripheral and central nervous system organizations, their manifestations in asymmetrical processing are comparable. In amblyaudia, the presence of a significantly weaker ear can allow the dominant pathway to overpower the non-dominant pathway, leading to decreased contralateral suppression from the nondominant side and/or important information from the non-dominant side not being enhanced due to that side's weakness. The interaural asymmetry can then manifest in an overall difficulty in discriminating between information arriving at one ear or inappropriately analyzing information arriving during most listening situations at both ears.

Plasticity during maturation allows for neural connections to be developed adaptively with experiences. Adaptations even occur in response to physical changes (e.g. head size variation and growth) during a critical development period (Kaplan et al., 2016). However, plasticity also allows for adverse adaptations to take place when an auditory system is deprived—if any part of a nondominant pathway is consistently omitting or incorrectly relaying information in the binaural integration process during the critical period of development, the auditory system will make neural adaptations to compensate for the deficit. These unfavorable neuronal connections will remain even as any peripheral pathology has been treated. Such is the case for amblyaudia: it has been proposed that, among some children, temporary periods of unilateral hearing loss (e.g. following a bout of otitis media) during their critical period of auditory development may lead to negative compensation in the dominant ear pathway (Kaplan et al., 2016).

These pathway adaptations in those with amblyaudia can lead to struggles with processing binaural cues in both normal and difficult listening environments. In many children with amblyaudia, difficulties with listening, learning, reading, and communicating are common. "Approximately 12 percent of children less than 5 years of age are at risk for amblyaudia. Of the individuals diagnosed with auditory processing disorder, roughly half of them met diagnostic

criteria for amblyaudia. Therefore, children who are at risk for academic hearing difficulties should be screened and/or tested for amblyaudia" (Lamminen & Houlihan, 2015).

1.2.1 Amblyaudia: Diagnosis

Amblyaudia itself is technically a diagnostic category under the broader umbrella of auditory processing disorders (APD), which is assessed with a battery of tests including pattern recognition tests, dichotic speech tests, auditory discrimination tasks, and low-redundancy speech tests (Moncrieff, 2016). APD diagnoses only stipulate below normal performance on any of these two tests without specificity, meaning that poorer scores on different auditory processing skills can lead to the same diagnosis (Moncrieff, 2016). Amblyaudia, being a condition that manifests specifically with dichotic listening difficulties means that the diagnostic criteria can be tightened for a more homogenous set of results from testing that leads to its diagnosis. To diagnose amblyaudia, results from at least two dichotic listening tests must produce the same specific pattern results between the two ears. The findings allow for that person to be placed into one of four diagnostic subcategories: normal, dichotic dysaudia, amblyaudia, and amblyaudia plus (Moncrieff, 2016).

Testing within normal limits in both ears will lead to placement into the normal category. Having significantly low results in both ears without a significant interaural asymmetry leads to a dichotic dysaudia diagnosis. Normal results in the dominant ear with a significantly poorer performance in the non-dominant ear (i.e. a larger interaural asymmetry) leads to an amblyaudia diagnosis. Results that are significantly low in both ears with a large asymmetry leads to an amblyaudia plus diagnosis (Moncrieff, 2016). An idealized depiction of these patterns is shown in Figure 2, contrasting the performance on dichotic listening tasks across amblyaudia conditions.

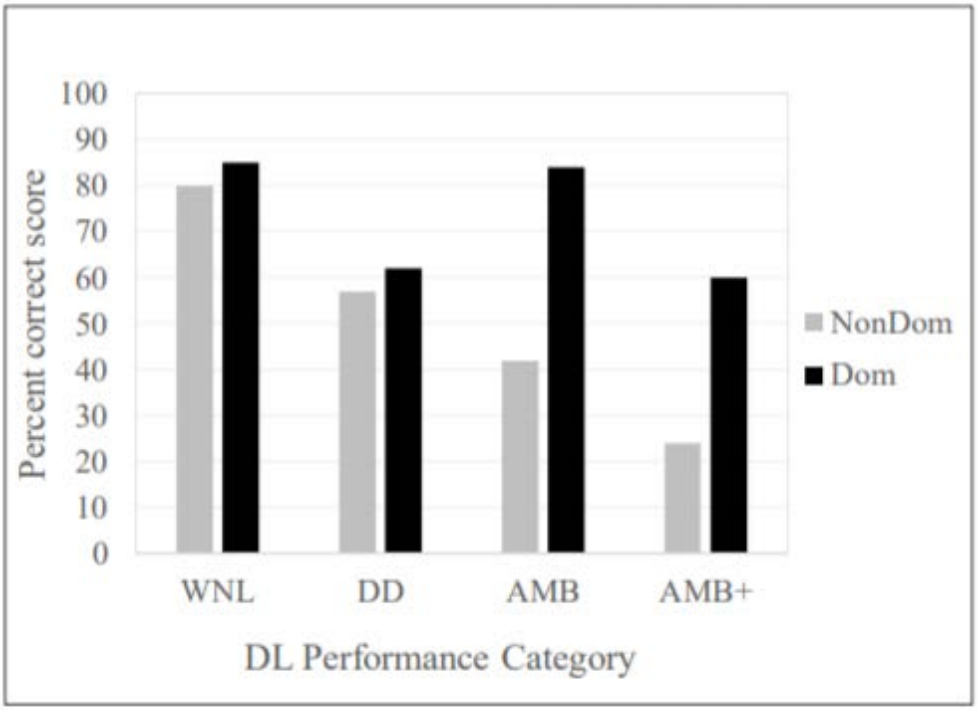

Figure 2. Dichotic listening performance categories.

In a large clinical sample across multiple sites, binaural integration was clinically assessed through two dichotic listening tests and when results were abnormal but did not match, a third test was used to ascertain whether a diagnosis could be made (Moncrieff, Keith, Abramson, & Swann, 2016b). Dichotic listening test are the most commonly used form of assessment when an individual is suspected of having an auditory processing disorder (Emanuel, Ficca, & Korczak, 2011). Significant controversy over the use of behavioral, speech-based tests to assess children for auditory processing disorders led to a recommendation that researchers find alternative methods to characterize the neurophysiology behind these deficits (Jerger & Musiek, 2000). Electrophysiologic methods could contribute to a more objective test battery if found to reliably provide supporting evidence related to the established behavioral dichotic tests.

1.3 ELECTROPHYSIOLOGIC TESTING OF DICHOTIC LISTENING

Inhibition of ipsilateral pathways is a feature of the structural model of dichotic listening. When looking for electrophysiological evidence of this effect, and early study reported no inhibition of ipsilateral pathways during dichotic stimuli (Yvert, Bertrand, Pernier, & Ilmoniemi, 1998) but another study showed an symmetry in the ascending pathway with inhibition of the left ear's ipsilateral pathway (Della Penna et al., 2007). Another feature of the structural theory is that pathways in the corpus callosum are important for dichotic listening and an imaging study led to the suggestion that weakness in the left ear during dichotic testing may be the result of poor interhemispheric transfer of information in the corpus callosum (Westerhausen, Grüner, Specht, & Hugdahl, 2009), there is no electrophysiological evidence of that failure in transmission to date.

Patients with schizophrenia often demonstrate binaural integration difficulties during dichotic listening tests. Adler et al. (1982) conducted a study comparing responses following a paired pulse paradigm in normal subjects and subjects with schizophrenia. The goal was to examine whether a sensory gating deficit in those with schizophrenia could be linked to a "more basic neuronal mechanism, such as an inhibitory neuronal circuit". The P50 response to repeated auditory stimuli had a known physiological process that examined inhibitory mechanism function. The paired pulse paradigm consists of a first stimulus (S1) and an identical stimulus (S2) following the first stimulus after a fixed period of time. Typically, the evoked response to the second stimulus is reduced due to inhibitory mechanisms from gating of repetitive sensory information. Adler et al. (1982) varied the amount of time between the two stimuli, "assessing the change in response to a second stimulus following the first at either 0.5, 1.0, or 2.0-sec intervals". The greatest amount of gating occurred at the 0.5-sec interval for which the mean decrement was over 90% in normal controls but less than 15% in schizophrenics. At longer intervals of 2-sec, responses from normal

were still 30 to 50% diminished, but those from schizophrenics showed an increased response to the stimulus compared to the base line. This early study of sensory gating demonstrated reduced inhibition in persons with schizophrenia (Adler et al., 1982), a result which has been supported by other electrophysiologic studies using the sensory gating protocol (Boutros, Zouridakis, & Overall, 1991; Schubring et al., 2017).

Reduced inhibition is also seen in those with amblyaudia, according to their results on behavioral tests (the Dichotic Words Test and Randomized Dichotic Digits Test), which suggest the presence of binaural integration deficits. With both populations experiencing binaural integration deficits, the question arises as to whether the amblyaudia population will demonstrate similar evoked responses when following the same sensory gating paradigm.

The schizophrenic population is one which is heavily studied in terms of evoked responses, with the hope that a neurophysiological marker can be determined for the disease. In addition to studies examining the paired pulse paradigm with this population, many studies have been conducted to assess differences in paradigms evoked endogenous responses (those which require cognitive processes, rather than being solely dependent on physical features of the stimulus): one of these is the P300 response. The P300 is a long-latency event-related potential (ERP), usually assessed via an "oddball paradigm," with standard and rare stimuli being presented to the subject: "the typical oddball paradigm uses a series of tones in which 20% are targets (oddballs) and 80% are standards, and on average every fifth stimulus is an oddball" (Ford, 1999). The evoked responses to the rare stimuli have larger amplitudes in comparison to those in response to the frequent standard stimuli, signifying a cognitive process indexing change. However, in an often-replicated study, persons with schizophrenia have reduced amplitude responses to the rare stimuli (Ford, 1999). This suggests an inability to discriminate between salient and non-salient auditory

stimuli, a similar characteristic to those with a binaural integration-specific auditory processing disorder (i.e. amblyaudia). Jirsa & Clontz (1990) found abnormal P300 responses in children suspected of auditory processing disorders: the study, which used the typical oddball paradigm, was conducted on children diagnosed of having possible auditory processing difficulties and controls, and found significant differences in both latency and amplitude in P300 responses of the processing-disordered group (Jirsa & Clontz, 1990). The question arises as to whether amblyaudia, an auditory processing disorder involving a binaural integration deficit similarly characteristic to schizophrenia, would also have abnormal P300 responses.

Another endogenous ERP is the mismatch negativity (MMN) response which, similar to the P300, is a cortical response that occurs when there is a change in an otherwise repetitive train of auditory stimuli which occurs whether or not the subject is focusing on the stimuli (Sharma et al., 2006)—however, the MMN occurs in response to a short-duration, less complex stimulus, while the P300 occurs in response to longer duration stimuli. Sharma et al. (2006) conducted a study investigating the MMN results (from both speech and non-speech stimuli) of children with reading disorders, based on the previous research on auditory processing deficits being linked to reading disorders. In the study, children in the auditory processing group had low scores on at least one behavioral test, which would have led them to be diagnosed with an auditory processing disorder (APD) (Sharma et al., 2006). When compared to a control group, the APD group showed significantly low (or nonexistent) MMN responses in comparison to those of the control group (Sharma et al., 2006). Again, the question arises as to whether amblyaudia, an auditory processing disorder which can lead to learning and educational difficulties, would also be associated with abnormal MMN evoked responses.

Others reported abnormal middle latency responses in children with learning difficulties, but did not relate them to auditory processing exactly (Kraus, Smith, Reed, Stein, & Cartee, 1985). Recent evidence of abnormal middle latency responses suggests that children with amblyaudia may produce shorter latencies in both ears and reduced amplitudes in their left ears (Moncrieff, Keith, Abramson, & Swann, 2017), suggesting abnormal processing through the ascending auditory pathway in children with dichotic listening deficits. Researchers have explored abnormalities in brainstem responses to speech stimuli in children with specific language impairment (Bishop, Hardiman, & Barry, 2010), but the heterogeneity of the auditory processing diagnosis has made similar studies in that population difficult to perform. Anderson and Kraus (2010) used the cABR technique to explore brainstem processing of speech stimuli in children with speech-in-noise difficulties, however, which may be related to dichotic listening deficits. These efforts suggest that differences in electrophysiological results may be present, but at this time, there is too little evidence of an electrophysiologic index of binaural integration deficits related to dichotic listening performance.

The specific aim of this study was to measure three specific electrophysiologic measures in young adults divided on the basis of their dichotic listening performance in order to explore whether significant differences in the responses would occur between individuals with normal and abnormal performance patterns. We chose to utilize measures that would explore signal processing in different regions of the auditory system, i.e. the frequency following response (FFR) to evaluate the brainstem's ability to track formant changes in a simple speech stimulus, the paired pulse paradigm to explore sensory gating to a pure tone signal, and the auditory MMN/P300 to two pure tone signals to evaluate the cortical response to a targeted change in frequency.

2.0 METHODS

2.1 SUBJECTS

Young adults were recruited for participation from the undergraduate Communication Science and Disorders program. All participants in the study had normal bilateral hearing: this was determined through a pass/fail pure-tone air conduction screening measure typically used in clinical settings: each subject was tested to see if they could hear (passing) or not (failing) at 20 dB or better at 500, 1000, 2000, and 4000 Hz in each ear. Only participants who passed were included in the study to ensure that a factor such as a conductive hearing loss would not confound findings.

All participants who passed the pure tone screening were further screened using the Randomized Dichotic Digits Test (RDDT) (Strouse-Carter & Wilson, 1999) and the Dichotic Words Test (DWT) (Moncrieff, 2015), as described in the amblyaudia diagnostic protocol (Moncrieff et al., 2016a). Subjects' scores in the 2-pairs condition were compared to normative data for the RDDT (Moncrieff & Wilson, 2009) and 12 participants whose scores fell within normal limits (WNL) were put into the control group, and 7 participants with a normal score in one ear and a significantly lower score in the other ear were placed into the AMB group—according to their RDDT scores, those in the AMB group showed difficulties with binaural integration in a form characteristic to amblyaudia (i.e. significantly poorer performance in one ear).

2.2 STIMULI AND TESTING PROCEDURES

All screening procedures (i.e. pure tone audiometry, RDDT, and DWT) took place in one of two locations, either in an audiometric booth or in a quiet room (determined using a sound level meter, with the room presenting with a sound level of 65 dB SPL or less), with the subject seated in a chair. For stimulus presentations, insert earphones were used in the audiometric booth, while over-the-ear headphones were used in the quiet room setting. Dichotic listening results would be equivalent, as comfortable interaural listening levels were used for the RDDT and DWT in both settings.

2.2.1 Behavioral Testing

2.2.1.1 Randomized Dichotic Digits Test (RDDT)

The subject was presented with a series of 27 randomized dichotic digit presentations in a free recall mode. Each presentation consisted of either 1-pair, 2-pairs, or 3-pairs of digits spoken by a male, with the order of 1-pair, 2-pairs, or 3-pairs of being randomized so that the participant could not predict the number of pairs needed for the response. The participant would recite back all the digits they could recall during the time allotted following each presentation. Raw scores were converted to percent correct and scores in the 2-pairs condition were used for comparison with normative data.

2.2.1.2 Dichotic Words Test

Four equivalent lists were available for the DWT free recall mode, with each list containing 25 pairs of common single-syllable consonant-vowel-consonant (CVC) words in the English language, spoken by a male. Each participant was randomly assigned a list and would recite back the words they could recall during the allotted time following each presentation. Raw scores were converted to percent correct. There is no currently published normative data for the DWT in young adults.

2.2.2 Electrophysiological Testing: Setup, Continuous File Acquisition, Epoching and Event Processing

Participants returned for a second session on a later date for electrophysiological testing. During this session, participants were fitted with Neuroscan Quik-Cap (based on a Montreal Neurological Institute 10/20 standard brain system). To ensure that the cap was properly fitted and the electrodes were properly positioned on the scalp, the front end of the cap was placed 4 cm above the nasion. An applicator was used to insert a salt-based gel into the electrodes from which measurements were being taken to ensure conductivity of the signals from the scalp to the electrodes. The electrodes which were filled were: FZ, CZ, C1, C3, C5, T7, C2, C4, C6, T8, PZ in addition to a ground electrode and reference electrode. An abrasive cream was applied and then cleaned away on the participant's right mastoid bone to prepare the skin, then the reference electrode was secured in this location using medical tape. The cap was then connected to the Neuroscan Synamp2 amplifier and the impedances of each electrode were monitored in the Curry Neuroimaging Suite: gel was added to each electrode until the impedance of each electrode was below 5 kOhm (kΩ).

Each participant was then moved to a chair in a soundproof booth and fitted with insert earphones through which they would receive the stimuli from the electrophysiological testing paradigms. The participant was instructed to reduce physical movements throughout the duration of the testing to prevent contamination of the sensitive electrode recordings. Each participant was given an iPad tablet and allowed to select a movie to watch silently throughout the electrophysiological testing procedures.

2.2.2.1 Paired Pulse

The first paradigm presented via earphones was the paired pulse paradigm, which takes approximately 15 minutes. The stimuli consisted of 100 presentations each of 4 identical 500 Hz tone bursts with durations of 50 msec each, spaced apart by 300 msec, followed by an inter-trial interval (ITI) of 8000 msec. The stimuli were presented through Gentask while the participant's responses were recorded through Curry Acquisition. When the raw data file (i.e. the continuous file) was acquired at the end of the testing session, event processing was done to make the file standardized and useful for comparison. In the continuous file, the event type (the one corresponding to the first stimulus in the paired pulse paradigm, evoking the S1 response) and the time frame around each time this event type was presented (-200 msec to 1800 msec) was selected for epoching (the selection of the time periods during which responses to the stimuli could be found). Several alterations were then made to each participant's epoched file: the common average reference was removed, a pre-trigger baseline correction was added, and all of the epochs were averaged. A user-defined bandpass filter from 0.5 – 35 Hz with a 6 dB/ octave slope was applied.

2.2.2.2 P300

The next testing measure presented was the P300 oddball paradigm, which takes approximately 6.25 minutes. The stimuli consisted of 200 presentations of the higher frequency standard stimulus (1122 Hz) and 50 presentations of the rare "oddball" lower frequency (880 Hz) stimulus, with all stimuli having durations of 170 msec. The rare stimuli presentations were interspersed within the standard presentations at a ratio of 1 (rare): 5 (standards), with an ITI of 1500 ms. The stimuli were presented through Gentask while the participant's responses were recorded through Curry Acquisition. When the continuous file was acquired, event processing was completed: in the continuous file, the event type (the one corresponding to the standard stimulus) and the time frame around each time this event type was presented (-100 msec to 700 msec) was selected for epoching. Several alterations were then made to each participant's epoched file: the common average reference was removed, a pre-trigger baseline correction was added, and all of the epochs were averaged. A user-defined bandpass filter from 1.0 – 30 Hz with a 6 dB/ octave slope was applied. The same type of event processing was done for the rare stimuli: the event type corresponding to the rare stimuli was selected in the continuous file, and all the same alterations were made to the resulting epoched file.

2.2.2.3 Frequency Following Response

The final testing procedure was the frequency following response (FFR) paradigm, which takes approximately 5.8 minutes. The stimuli consisted of 3000 presentations of an artificially produced 40 msec syllable /da/ with durations of 40 msec each, with an ITI of 116.67 msec to the right ear. The stimuli were presented through Gentask while the participant's responses were recorded through Curry Acquisition. When the continuous file was acquired, event processing was completed: in the continuous file, the event type and the time frame around each time this event

type was presented (-15.8 msec to 59.2 msec) was selected for epoching. Several alterations were then made to each participant's epoched file: the common average reference was removed, a pre-trigger baseline correction was added, and (average). A user-defined bandpass filter from 1.0 – 30 Hz with a 6 dB/ octave slope was applied.

2.2.3 Marker Reports

Once all the files were acquired, epoched, and processed, they were saved as files to be opened and marked in Neuroscan Scan Edit software. In Scan Edit, peaks which were relevant according to the tested electrophysiological measures were marked so that the peaks' latency and amplitude information could be extracted for analysis. Peaks were marked for the CZ electrode, where the maximum amplitudes were found for each response.

To mark a paired pulse file, the largest peak (usually around 150 msec) was found and marked as the S1 response. Then, the next largest peak along the time axis (usually about 300 msec later) was marked as the S2 response. The latency difference between the S1 and S2 responses (roughly 300 msec) was calculated and this difference was added to the S2 response latency—the largest peak around this resultant latency was marked as the S3 response. The difference would be added to the S3 response latency, and the largest peak around the resultant latency would be marked as the S4 response.

To mark a P300 file, the largest positive peak (usually around 300 msec) would be marked as positive P3 response. A large negative deflection would usually precede the P3 peak (usually around 200 msec), which was marked as the negative N2 response. This same marking process was used for both the standard and rare conditions. Earlier peaks were present in both average

files, a negative peak occurring at approximately 50 msec and a positive peak occurring at approximately 100 msec. Those peaks were also marked as N0 and P1 respectively.

In an FFR file, periodic formations in the waveform were visible. Negative peaks at certain latencies, according to previous studies (Kraus), corresponded to the oscillations that were taking place in response to the speech stimulus. The negative peak approximately between 24.2 - 34.2 msec was marked as D, the negative peak approximately around 34.2 msec was marked as E, the negative peak approximately between 34.2 – 44.2 msec was marked as F, and the negative peak approximately between 44.2 – 54. 2 msec was marked as O.

The marker reports containing amplitude and latency information corresponding to the marked peaks were imported to a Microsoft Excel sheet. This data, with behavioral data from the RDDT and DWT, were then imported into the Statistical Package for the Social Sciences (SPSS) for analysis.

2.2.4 Data Analysis

Each participant's percent correct scores from the RDDT and DWT, results from all of the marker reports, and designation of group assignment were entered into the SPSS data file. A multivariate analysis of variance (ANOVA) was performed on each participant's evoked responses with the between subject factor of group (CTRL and AMB. For the N0, P1, N2 and P3 responses, amplitudes (in μV) and latencies (in msec) were measured during both a standard and rare condition. Amplitudes and latencies were also measured for the S1, S2, S3, and S4 responses of the paired pulse and for the D, E, F, and O responses of the FFR.

3.0 RESULTS

3.1 DICHOTIC LISTENING TESTS

A multivariate ANOVA was performed on the individual ear scores and ear advantage for the 2-pairs condition of the RDDT between the two groups. As expected, there was a significant difference in performance in the non-dominant left ear, $F(1, 18) = 24.783$, $p < .001$ and in ear advantage, $F(1, 18) = 30.110$, $p < .001$ for the RDDT. Scores for that test in the right ear were not significantly different, $F(1, 18) = .779$, $p = .390$. As shown in Figure 3, participants in the AMB group scored significantly lower in their non-dominant left ears than participants assigned to the CTRL group. Ear advantage in the AMB group was 19% compared to 3% among those in the CTRL group.

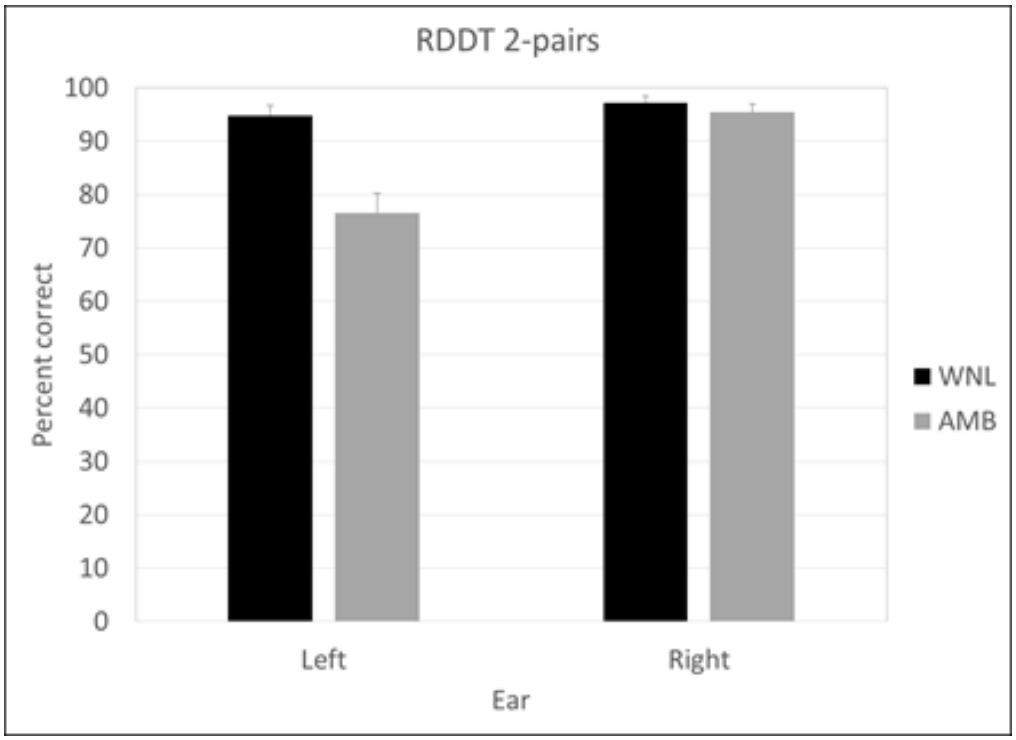

Figure 3. RDDT performance across ears by group.

3.2 PAIRED PULSE

Multivariate ANOVA revealed a significant effect of group for latency of the S3 response, F (1, 17) = 4.922, p = .041. As shown in Figure 4, AMB group participants produced longer latencies for the third stimulus than CTRL participants. The latency difference for S2 approached but did not achieve significance, F (1, 17) = 3.185, p = .093. There were no significant effects of group for amplitude of any of the paired pulse measures, but as shown in Figure 5, amplitude was lower for S1 and higher for S2, S3, and S4 in the AMB group with a high degree of variability in that group.

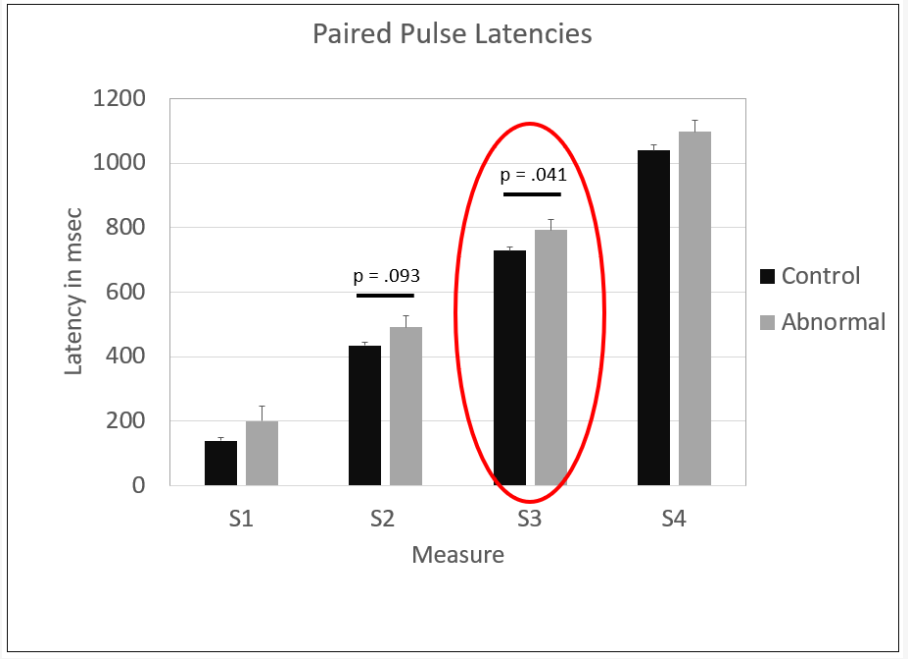

Figure 4. Mean paired pulse latencies with standard error.

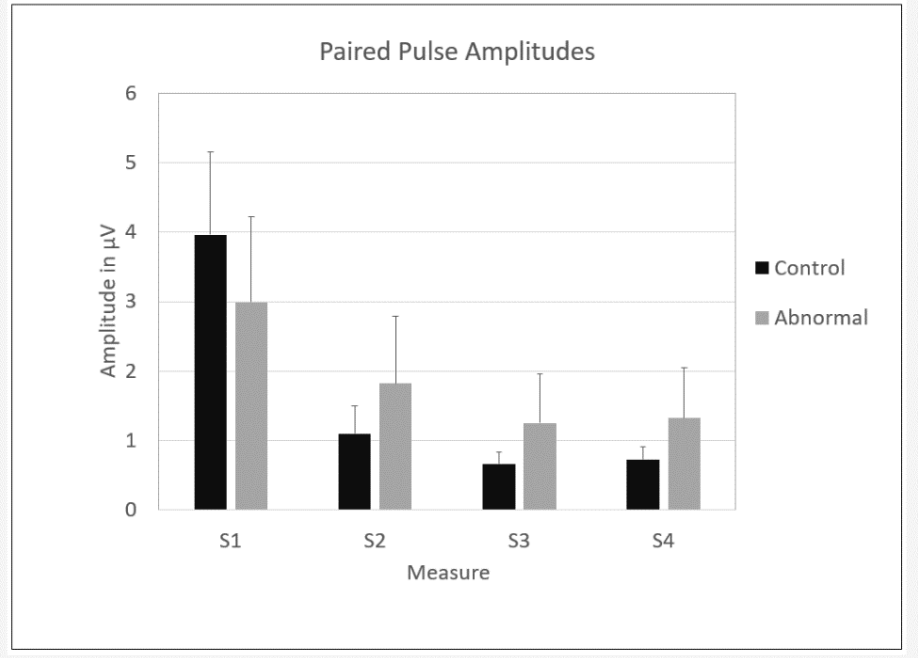

Figure 5. Mean paired pulse amplitudes with standard error.

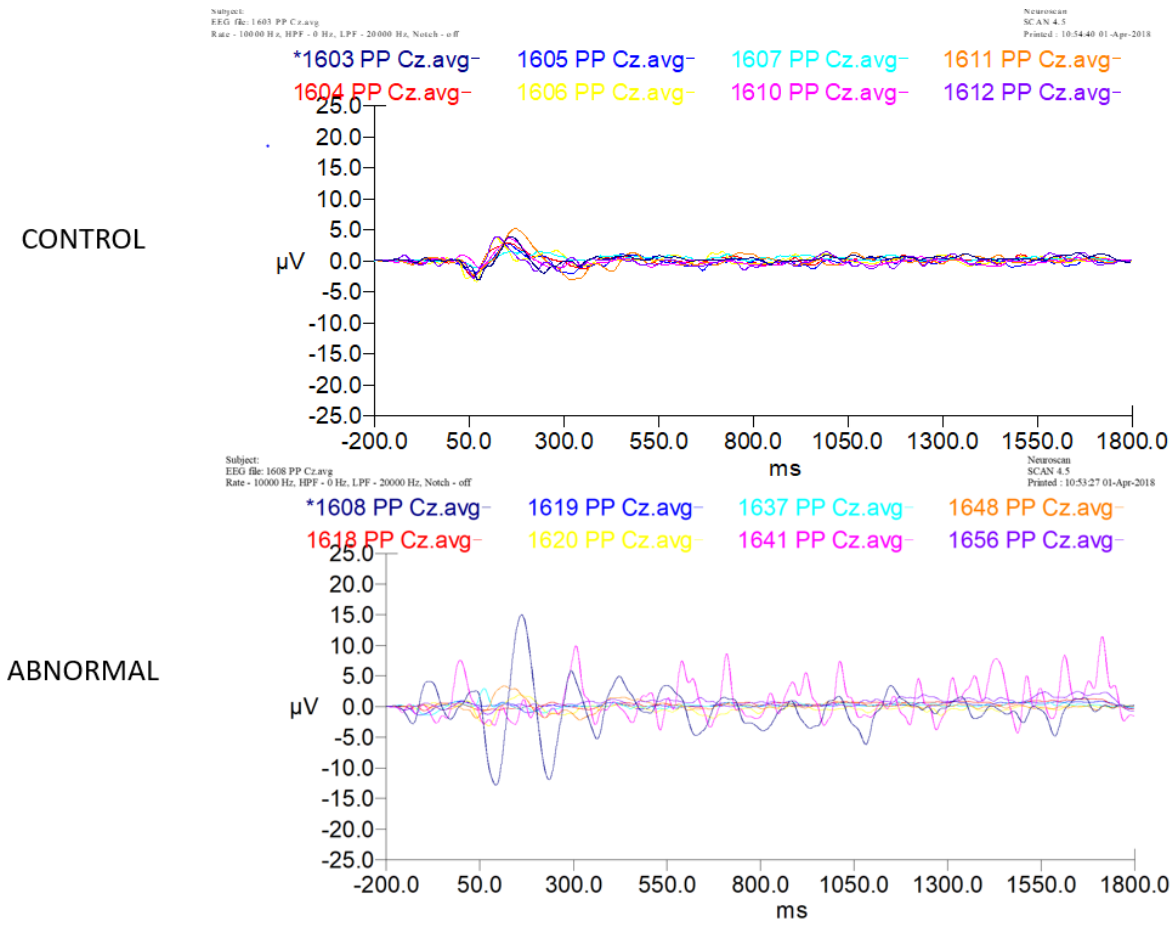

Figure 6. Comparison between control and AMB paired pulse waveforms.

In Figure 6, the control and abnormal group waveforms are juxtaposed with identical x-axis and y-axis scales to display the overall differences in amplitude. The two panels (control and AMB waveforms) are enlarged in Figure 7 and Figure 8 to display more detail in the groups' waveforms. In Figure 7, a clear cluster of S1 responses is found at a latency of approximately 150 msec, with clusters of subsequent responses (S2, S3, S4 responses) found every 300 msec from the initial S1 peak. This is contrasted to the AMB group's waveforms in Figure 8, where no clear clusters of responses can be seen.

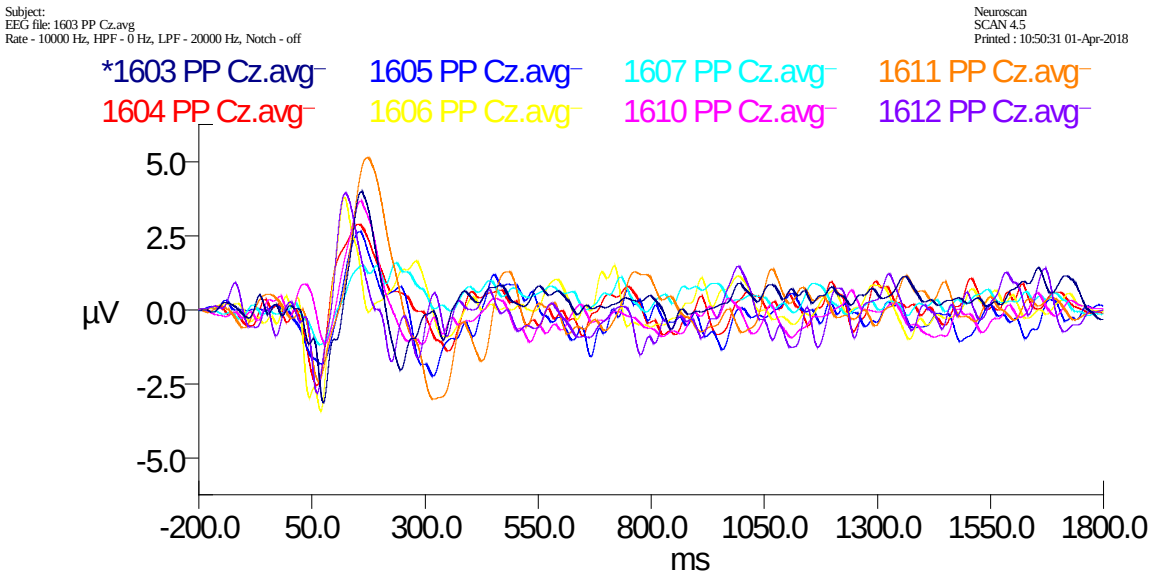

Figure 7. Control paired pulse waveforms.

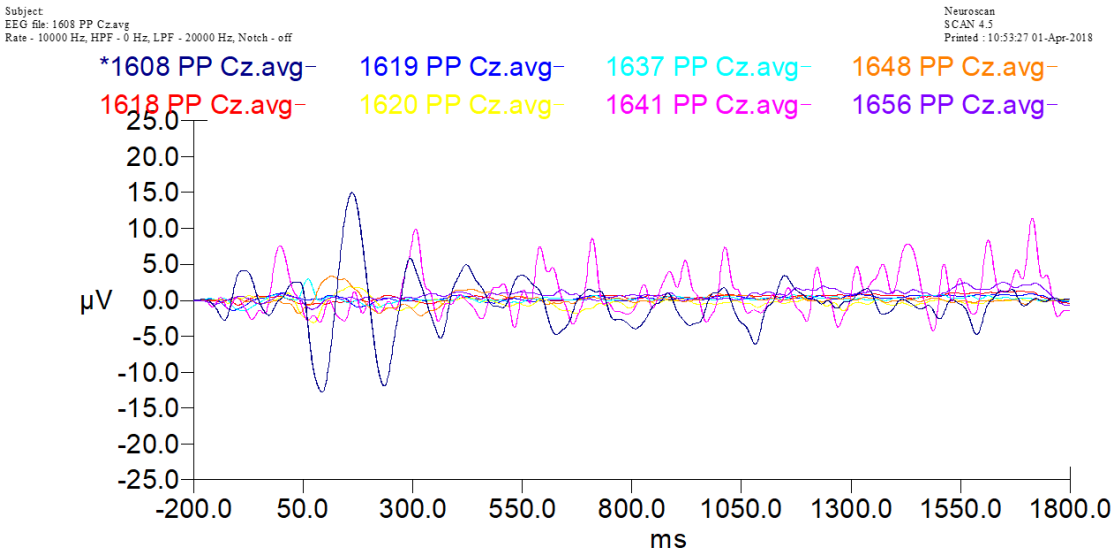

Figure 8. AMB paired pulse waveforms.

3.3 P300

The P300 was recorded with two pure tone signals, one at 880 Hz and the other at 1122 Hz (the tones used for the Frequency Pattern Test). There seemed to be earlier components present in the waveforms that are typically not observed in a standard P300 response. Pure tones are less complex than speech stimuli, which are often used in P300 oddball paradigms. It seems that, instead, we have evoked a mismatch negativity (MMN) response, which occurs with less complex stimuli. In the standard condition among the participants in the CRTL group, a negative wave appeared at an average latency of 55 msec followed by a positive wave at an average latency of 116 msec. We analyzed these responses in both the standard and rare conditions across both groups and found that they were significantly different in the participants in the ABN group. In the standard condition (when responding to the lower frequency tone), the amplitude of the earlier negative wave was significantly different, $F(1, 15) = 4.669$, $p = .050$ and the amplitude of the later positive wave was significantly different, $F(1, 15) = 7.677$, $p = .016$. The latency of the later positive wave was also approaching significance, $F(1, 15) = 4.499$, $p = .054$. These differences are shown in Figure 9.

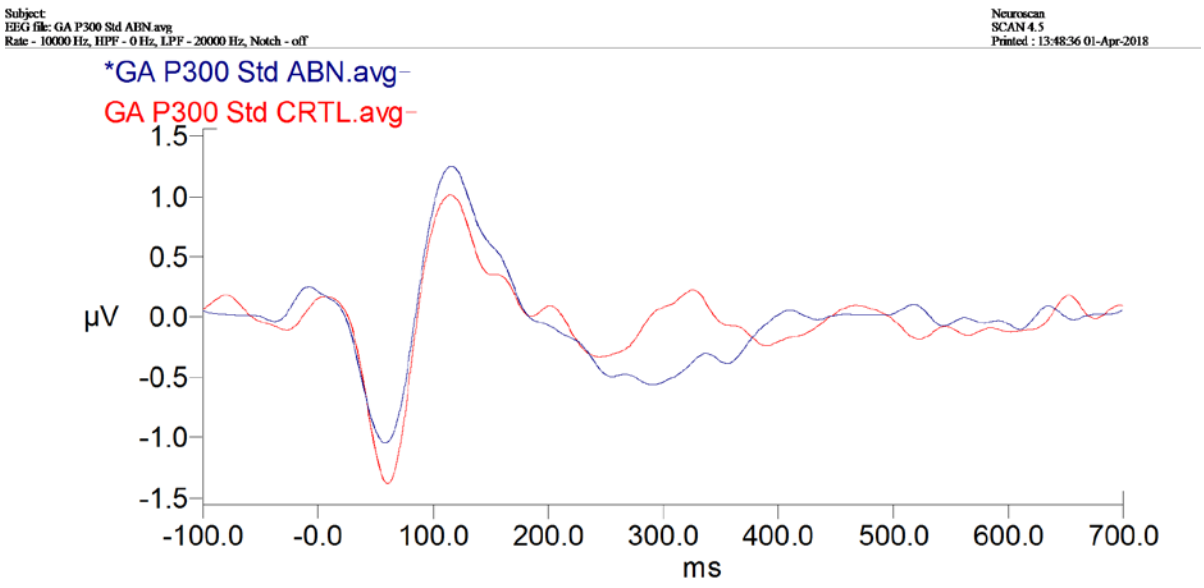

Figure 9. Control and AMB P300 grand averages in the standard condition.

In the rare condition, when responding to the less frequent higher frequency tone, the latency and amplitude of the later positive wave were both significantly different, $F(1, 15) = 5.446$, $p = .036$ and $F(1, 15) = 5.168$, $p = .041$ respectively as shown in Figure 10.

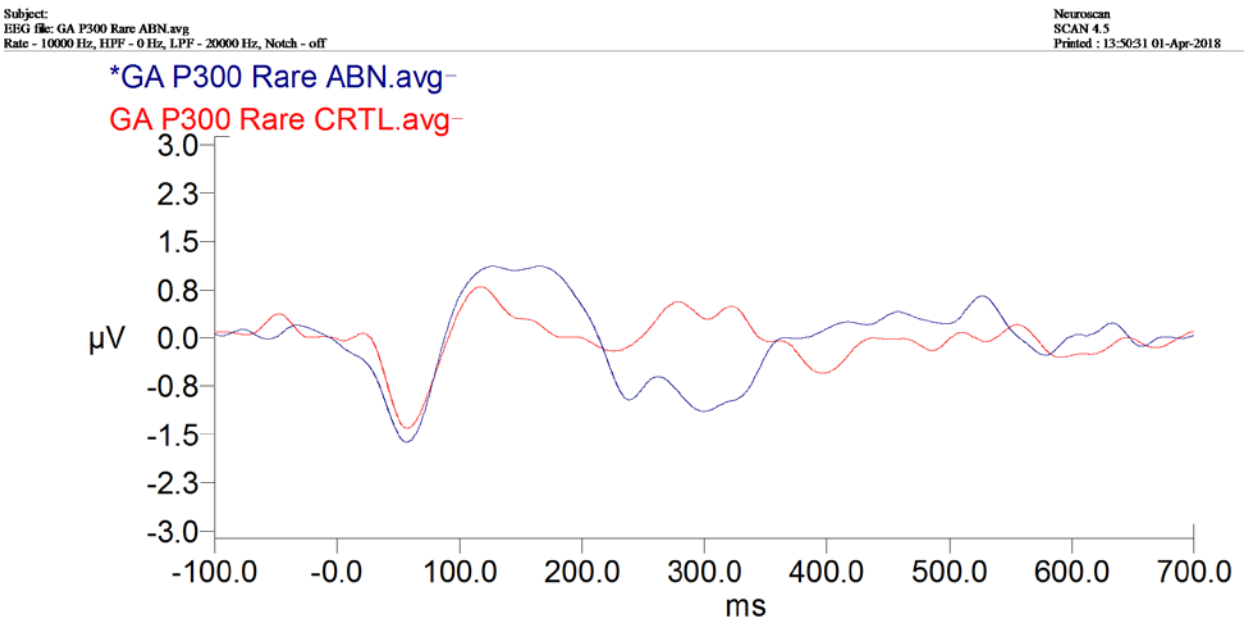

Figure 10. Control and AMB P300 grand averages in the rare condition.

Multivariate ANOVA revealed a significant effect of group for amplitude of the rare N2 response, $F(1, 17) = 5.573$, $p = .032$. As shown in Figure 12, AMB participants tests produced larger N2 amplitudes for the rare "oddball" stimulus than did CTRL participants. The amplitude difference between groups of the N2 responses to the standard condition approached but did not achieve significance, $F(1,17) = 4.090$, $p = 0.061$. As shown by Figure 12, there is a high degree of variability in the amplitudes of the AMB groups versus the CTRL group. As shown in Figures 11 and 12, there were no significant effects of group for the other measures for amplitude or latency for any of the P300 conditions.

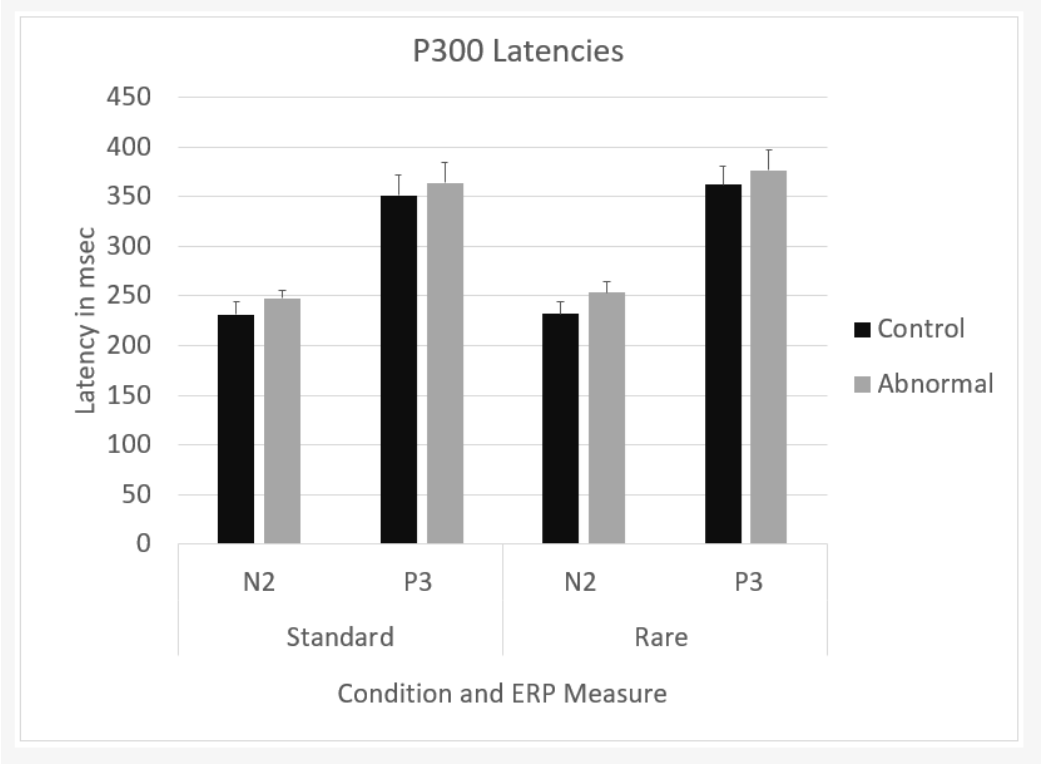

Figure 11. P300 latencies with standard error.

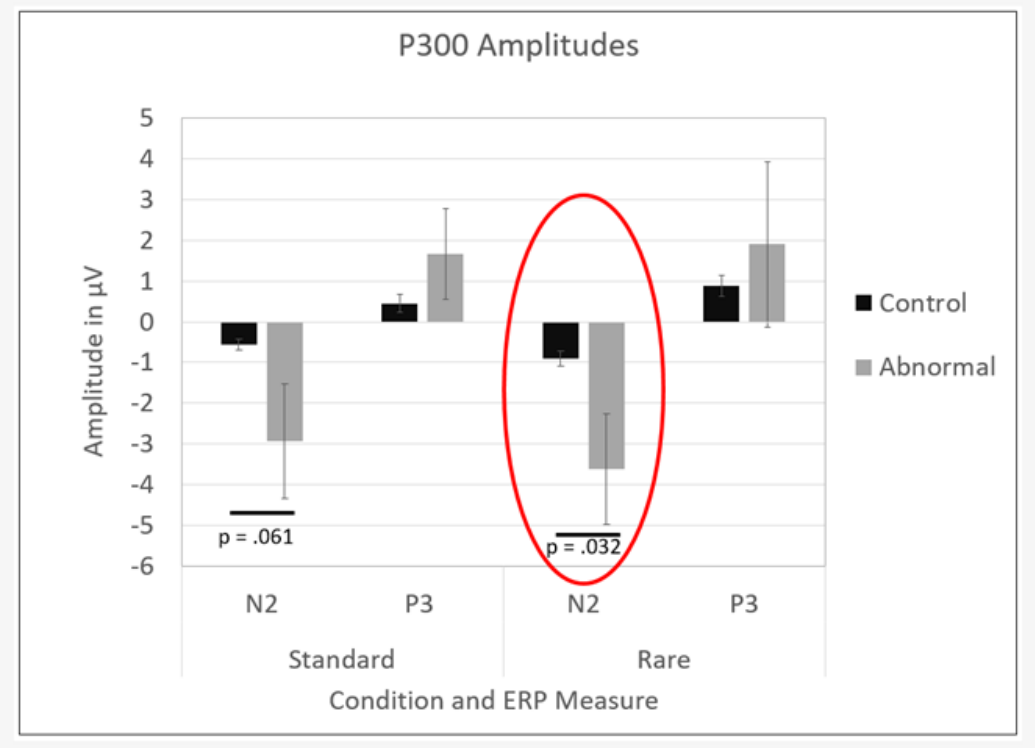

Figure 12. P300 amplitudes with standard error.

3.4 FREQUENCY FOLLOWING RESPONSE

Multivariate ANOVA revealed a significant effect of group for latency of the E response, F (1, 16) = 13.340, p = .003. As shown in Figure 13, AMB group participants produced E responses with latencies that were longer than those of CTRL participants. There was also a significant effect of group for latency of the D response, F (1, 16) = 5.174, p = .039. As shown in Figure 13, AMB group participants produced D responses with latencies that were longer than those of CTRL participants. The latency difference between groups of the F response approached but did not achieve significance, F (1, 16) = 3.831, p = .071. There were no significant effects of group for the

O latency measure or for any of the amplitude measures, but as shown in Figure 14 the amplitudes of the AMB presented with a high degree of variability.

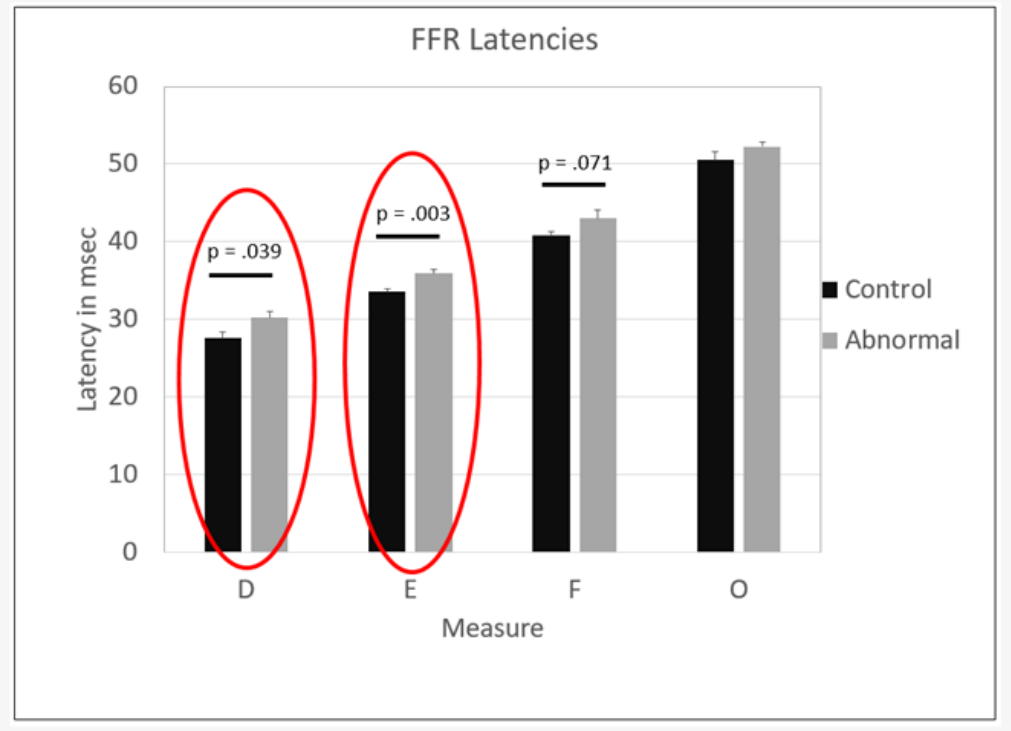

Figure 13. FFR latencies with standard error.

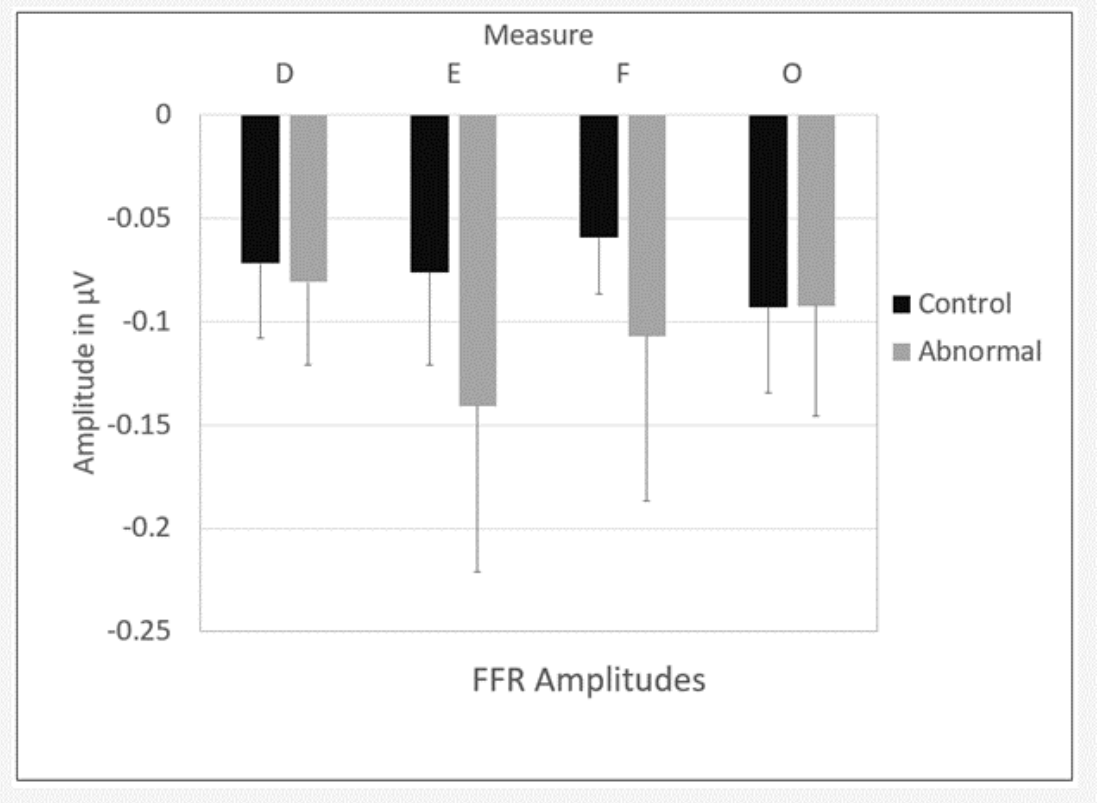

Figure 14. Mean FFR amplitudes with standard error.

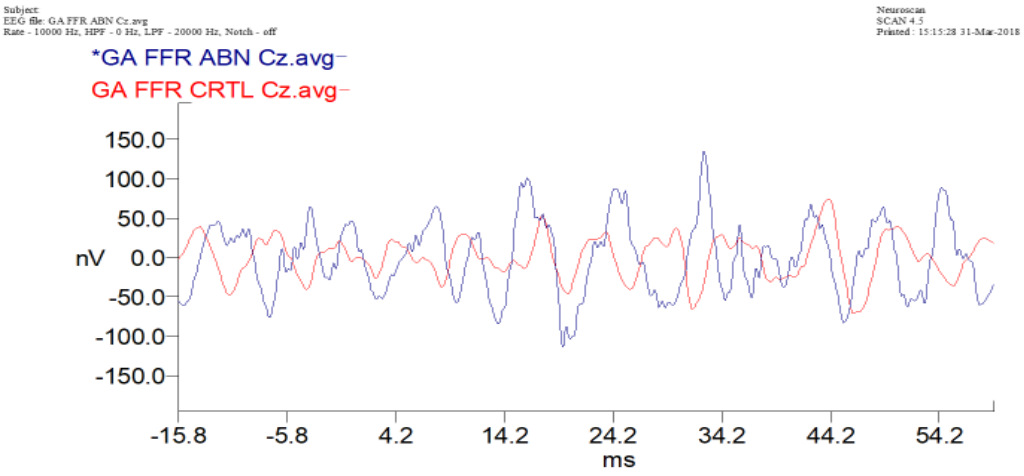

Figure 15. Control and AMB FFR grand average waveforms.

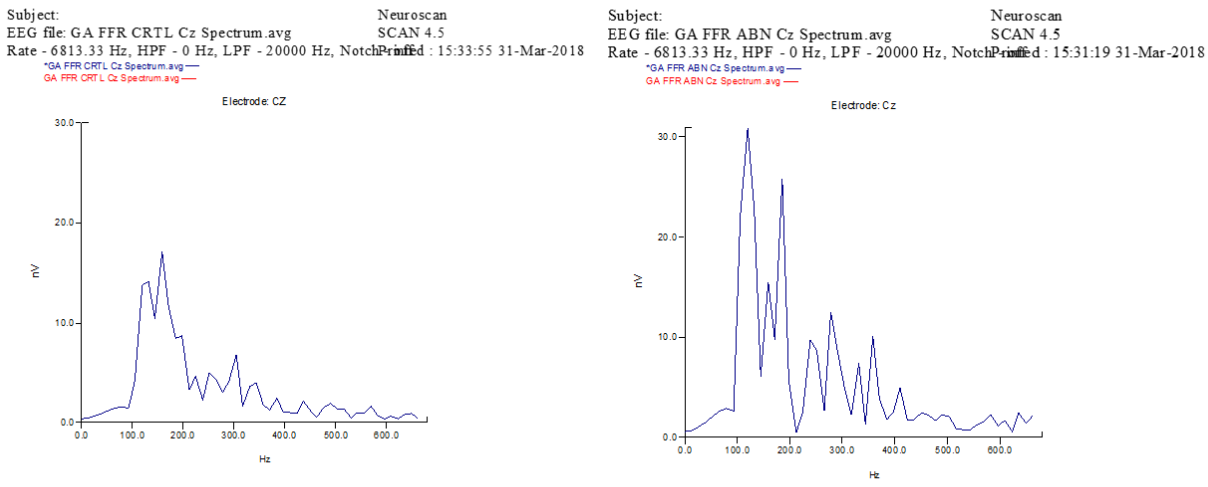

Figure 16. Control (left) and AMB (right) FFR spectral analyses.

Table 1. Significant correlations between evoked responses and dichotic listening test scores.

Evoked Response	Measure		DWT L	DWT R	RDDT L	RDDT R	DNW L	DNW R
PP: S2	Amplitude	Correlation Sig. (2-tailed)		-.598** .009				
PP: S3	Amplitude	Correlation Sig. (2-tailed)		-.726** .001			-.692* .027	
PP: S4	Amplitude	Correlation Sig. (2-tailed)		-.597** .009				
N200: Rare	Amplitude	Correlation Sig. (2-tailed)	.806** < .001					
N200: Standard	Amplitude	Correlation Sig. (2-tailed)	.725** .001	.527* .030				
FFR: E	Latency	Correlation Sig. (2-tailed)			-.516* .041			
FFR: D	Amplitude	Correlation Sig. (2-tailed)	.607* .013	.741** .001				
FFR: E	Amplitude	Correlation Sig. (2-tailed)	.752** .001	.768** .001				
FFR: F	Amplitude	Correlation Sig. (2-tailed)		.710** .002				
FFR: O	Amplitude	Correlation Sig. (2-tailed)		.743** .001				

Latencies of the S1 through S4 responses to paired pulse stimuli were not correlated with any of the dichotic listening test scores. However, amplitudes of the S2, S3, and S4 responses were negatively correlated with the dominant right ear response of the DWT and amplitude of the S3 response was negatively correlated with the non-dominant left ear response on the DNW as show in Table 1. These mean that the participants with higher dominant right-ear scores on the DWT demonstrated a generally stronger suppression of the second, third, and fourth stimuli leading to lower amplitudes of those responses following the presentation of S1. As noted in the analyses of group effects on the paired pulse responses, participants with poorer dichotic listening scores demonstrated larger amplitudes for S2, S3, and S4 that failed to reach significance, likely due to a small group size and a large amount of variability. These strong correlations suggest that the trend may be present for those individuals to demonstrate weaker suppression of the later stimuli in a manner that may warrant further investigation. Individuals with lower performance in their dominant right ear on the DWT are those who may ultimately be diagnosed with dichotic dysaudia or amblyaudia plus.

Positive correlations were observed between the non-dominant left ear score on the DWT and the amplitude of the N200 response during presentation of the rare stimulus during the P300 paradigm. Positive correlations were also observed between both ear scores on the DWT and the amplitude of the N200 response during presentation of both the rare and standard stimuli during the P300 paradigm. Because these are negative amplitudes, these results mean that the participants with better scores in their left or both ears on the DWT demonstrated smaller amplitudes for the N200 response during this task.

4.0 DISCUSSION

The nature of this study was exploratory, with the goal of looking for any electrophysiological trends when comparing the results of those with and without dichotic listening difficulties. We found several general trends that transcended specific evoked responses—that is, the tendencies could be seen in the results of multiple electrophysiological testing measures. From these tendencies, we can create some suppositions about the auditory processing that takes place in those with binaural integration deficits, which would make for worthwhile inquiry into the future.

One observation was that results from those with dichotic listening difficulties seemed to have a lot more noise. A clear example of this was in the FFR response (Figure 15): the control group's grand average waveform contains clear, smoother, periodic oscillations in response to the steady-state portion of the vowel in the stimulus. In comparison, the AMB group's grand average waveform does not seem as clear, with jagged oscillatory shapes and irregular peaks. These characteristics suggest that more noise has gotten to the level of the system which processes this signal, which manifests in these more contaminated waveforms. Typically, higher frequency information is resolved at lower, earlier levels of the CANS (towards the brainstem), meaning that cortical responses should not contain so much high frequency information—yet, the waveforms of those in the AMB still seem affected by high frequency information. This relates to the idea that there is a lack of suppression at the level of the brainstem in those with binaural integration deficits due to weak non-dominant pathways and overpowering dominant pathways.

We saw the amount of high noise present with individual epoched FFR files of those in the AMB group, which made selecting the negative deflections quite difficult in comparison to doing so with the corresponding files of those in the control group. To be able to choose peaks for

statistical analysis, we chose to use a post-hoc filter to remove some of the high frequency information—even after doing so, the waveforms of those in the AMB still seem much noisier than those of the control group. This can be seen in the spectral analysis of the average waveforms (Figure 16): more frequencies were being represented in the AMB group's spectral analysis, with larger amplitudes, in comparison to the control group.

Several of the electrophysiological testing measures resulted in significantly larger average amplitudes at certain peaks. For example, the average N2 response was larger in the AMB group in comparison to the control groups (in both conditions, significantly larger in the standard condition, and trending towards significance in the rare condition). This evokes a similar thought that there is difficulty with suppression, which is leading to a magnified amplitude from overexcitement. When looking at Figure 5, it is also evident the AMB group's S2, S3, and S4 peaks in the paired pulse response have much larger average amplitudes than those corresponding from the control group, while having a much smaller average S1 response amplitude. This also demonstrates a person with binaural integration deficit's difficulty in picking out the salient information (i.e. the stimulus preceding the S1 response) and then difficulty suppressing the information to which the CANS should be learning and adapting (i.e. the same stimulus, which precedes the S2, S3, and S4 responses), all demonstrating difficulty in using the proper excitatory and inhibitory responses.

Another way of looking at the difference between the control group and the AMB group is by considering a lack of synchrony. In several of the response measures, there were significant differences in latency: there were some places where we could pick out a peak, but its latency would be different from where we would expect to see it. For example, latencies of the D and E responses in the FFR and the S2 and S3 responses in the paired pulse were significantly later in

the AMB group than in the control group. Perhaps this means that the appropriate cells are inundated with too much information (due to a lack of suppression) and therefore struggle to receive and then send signals in a synchronous way, leading to the lag in signal transmission. Such a phenomenon can also explain why unexpected peaks are occurring at unexpected latencies with unexpected amplitudes: in the FFR grand average waveform (Figure 15), the peaks of the AMB group's waveform occur aperiodically with inconsistent amplitudes, similarly suggesting a lack of synchrony. The neurons seem unable to fire together to create neural signals with consistent amplitudes with consistent latencies, which should be happening when the stimulus remains the same (i.e. the periodicity from the steady state portion of /da/).

There also seems to be a large variability in the responses of those in the AMB group. In Figure 5, the AMB S2, S3, and S4 responses in the paired pulse have much larger amplitudes, yet the differences between the two groups are not significant. This can be elucidated by looking at the collection of AMB group waveforms in Figure 6. The large degree of variability of AMB peaks ends up averaging to represent something close to the average of the control peaks, which are much more uniform. This occurrence resulted in non-significant analysis, though when looking at the individual waveforms it is clear that there are differences between the groups. The conclusion that can be drawn here is that something different is happening while processing in those with binaural integration deficits—further investigation into the relationship between evoked potentials and binaural integration would prove to be fruitful and might contribute to discovering where in the auditory pathway any breakdowns may be occurring. The differences between the paired pulse waveforms of those with and without binaural integration deficits seem especially striking (Figure 6) in terms of both noise present and synchrony, so this would seem to be an especially interesting electrophysiological measure to investigate in the future, those any insights gained from further

study of any electrophysiological measure for binaural integration deficits could provide valuable insights.

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