ELECTROPHYSIOLOGICAL AUDITORY MEASURES TO IDENTIFY POTENTIAL CORTICAL MARKERS OF TINNITUS

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Dissertation Prepared for the Degree of

DOCTOR OF PHILOSOPHY

UNIVERSITY OF NORTH TEXAS

December 2022

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Caldwell, Joshua. *Electrophysiological Auditory Measures to Identify Potential Cortical Markers of Tinnitus*. Doctor of Philosophy (Health Services Research), December 2022, 105 pp., 11 tables, 15 figures, 1 appendix, references, 177 titles.

Tinnitus, or the perception of sound in the absence of external acoustic stimuli, is a common condition that impacts approximately 10-15% of the United States population, with similar prevalence rates reported in other countries. Current diagnosis of tinnitus relies on case history and audiometric testing, which depend on responses provided by the patient. To date, there is no objective test that can be used for tinnitus diagnosis, despite the high prevalence and significant financial impacts of this condition. Cortical auditory evoked potentials have shown promise in their ability to assess not only the integrity of the auditory system, but also higher level preattentional and cognitive processing. For this study, the pitch-matched tinnitus frequency was used to evoke an auditory late response. Double oddball paradigms with the tinnitus frequency as the deviant stimuli were also used to evoke a mismatch negativity and P300 to determine where along the auditory pathway biomarkers of tinnitus may exist. The results of this study suggest that when the tinnitus frequency is incorporated into paradigms designed to produce cortical auditory evoked potentials, differences exist between participants with tinnitus and matched controls without tinnitus. Individuals with tinnitus exhibit smaller MMN amplitudes and area under the curve and have a more parietal distribution in their P300 responses on topographic maps compared to non-tinnitus participants. Evaluation of relationships between perceived tinnitus severity and electrophysiological measures also revealed that P2 latency was a significant predictor of tinnitus severity, with longer latencies indicating greater severity. Findings of this study have clinical implications for test paradigms that may be used in an objective tinnitus test battery and for measures that can predict tinnitus severity.

ACKNOWLEDGEMENTS

This work would not have been possible without my invaluable support system, particularly during the challenging times of the COVID-19 pandemic. I first must thank my mentor, Dr. Kamakshi Gopal, for all the time and energy she invested into making this research possible. Without her guidance and support I would not have been able to pursue a Ph.D. in conjunction with a doctorate of audiology. I also would like to acknowledge the time, expertise, and support provided by my committee members Dr. Daniele Ortu and Dr. Sharon Miller. Dr. Ortu very generously provided the electrophysiological equipment used in the study, agreed to this collaborative study between the audiology and behavioral analysis department, and was instrumental in the development of the EEG protocols. Dr. Sharon Miller was also instrumental in this study's success, and her time and expertise were greatly appreciated. Dr. Miller provided the base Matlab code and Excel formulas used for analysis, for which I am very grateful. A special thanks also goes to the Beatrice Barrett Neuro-Operant Research endowment through the Department of Behavior Analysis for funding this study and to the numerous UNT faculty and staff who aided in participant recruitment.

I also want to thank my colleagues, Jacy Manning and Chelsea Anderson, for their support and encouragement. Lastly, I must also thank my wife, Erin Caldwell, for her unfaltering support, especially with proofreading and caring for a new baby, through this entire process.

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LIST OF ABBREVIATIONS

AIC	Akaike information criterion
ALR	Auditory late response
ANOVA	Analysis of variance
AUC	Area under the curve
CAEP	Cortical evoked auditory potential
DCN	Dorsal cochlear nucleus
EEG	Electroencephalography
EPSP	Excitatory postsynaptic potential
GFP	Global field power
IPSP	Inhibitory postsynaptic potential
LDL	Loudness discomfort level
LME	Linear mixed effect
MGN	Medial geniculate nucleus
MMN	Mismatch negativity
Nd	Negative difference
NMDA	N-methyl-D-aspartate
PM	Pitch-matching
RMS	Root mean square
SL	Sensation level
SOAE	Spontaneous otoacoustic emission
THI	Tinnitus Handicap Inventory
TRQ	Tinnitus Reaction Questionnaire

CHAPTER 1

INTRODUCTION

1.1 Review of Proposed Tinnitus Mechanisms

Tinnitus, originating from the Latin word *tinnire* which means ringing, tinkling, or jingling, is a form of auditory dysfunction that results in an auditory percept even though no corresponding external stimulus is present. Tinnitus has been documented for thousands of years, with early depictions being found in Egyptian artwork (Stephens, 1984). There are two broad categories of tinnitus: objective tinnitus, which can often be traced to a physiological generator, and subjective tinnitus, which presently can be neither objectively measured nor quantified. Objective tinnitus can be classified into three major groups: (1) pulsatile, which is caused by vascular etiologies, such as stenosis of the carotid or jugular veins; (2) muscular, which is caused by myoclonus of palatal or middle ear muscles; and (3) spontaneous, which is the result of robust spontaneous otoacoustic emissions that can be measured in the ear canal. Approximately 10% of individuals who report tinnitus symptoms describe experiencing a "pulsatile" quality to their tinnitus that can often be traced to a physiologic source (Kircher, Standring, & Leonetti, 2008). Subjective tinnitus is much more common than objective tinnitus and provides an excellent area for further research, as there is currently no objective test nor treatment for subjective tinnitus (Henry, Roberts, Caspary, Møller, 2011; Theodoroff, & Salvi, 2014).

Early research on tinnitus focused on the peripheral auditory system as the primary generator of tinnitus (Møller, 2011). This approach seemed logical as tinnitus is an auditory phenomenon, and individuals with tinnitus often can lateralize their tinnitus to the right or left ears or hear it in both ears. It was initially theorized that the mechanical generators of the cochlea responsible for producing spontaneous otoacoustic emissions (SOAEs) could underly the tinnitus

percept (Penner & Burns, 1987). SOAEs result from the activation of the cochlear partition in the absence of external acoustic stimuli. Outer hair cells in the inner ear provide increased amplification and more selective frequency tuning for lower intensity stimuli by drawing the basilar membrane closer to cilia located on the apical surface of inner hair cells. This action mechanically increases the magnitude of the traveling wave through the basilar membrane, increasing sensitivity to softer intensity stimuli. This function, termed the cochlear amplifier, is likely responsible for the generation of SOAEs. Two models have been proposed to explain the mechanisms behind SOAEs (Shera, 2003). The original theory, first suggested by Gold (1948) and demonstrated by Kemp (1979a), postulates that SOAEs are generated by a particular portion of the cochlea that has suffered a disruption to the normal feedback control, resulting in a frequency specific response being generated through the oscillatory activity of the outer hair cells. The specific portion of the cochlea that is experiencing dysfunction in its feedback control mechanisms would determine the frequency of the emission measured in the ear canal. Conversely, the global standing wave resonance model suggests SOAEs are generated via standing wave interactions from either environmental acoustic stimuli or physiologic noise and involve complex interaction between the entire cochlear, middle, and outer ear structures (Shera, 2003).

Because SOAEs are measurable sounds produced by the cochlea, it was initially believed those with tinnitus may have larger than normal SOAEs (Kemp, 1981). However, studies have documented that only a small percentage of individuals show a correlation between their perceived tinnitus symptoms and SOAE values (Coles & Hallam, 1987; Penner, 1990) Moreover, salicylate, which obviates SOAEs (Long & Tubis, 1988; Martin, Lonsbury-Martin, Probst, & Coats, 1988), often induces tinnitus (McFadden, 1982). Previous work has also found

the prevalence of tinnitus caused by SOAEs is approximately 1-2%, as evidenced by elimination of the tinnitus through either the use of salicylate or the presentation of a tone located near the emitted frequency of the SOAE, both of which eliminate SOAEs, (Penner and Coles, 1992).

Low levels of calcium in the cochlear fluid have also been proposed to be a contributing factor to the tinnitus percept, as calcium is involved in numerous electromechanical functions of the cochlear sensory organs (Jastreboff, 1989). Calcium metabolism becomes altered with age via decreased uptake by terminal neurons, which may explain the higher prevalence of tinnitus in older individuals (Gibson & Peterson, 1987), although there are likely many other contributing factors. Low calcium levels can lead to the cilia of the outer hair cells becoming decoupled from the tectorial membrane. Jastreboff (1989) proposed that this decoupling underlies the findings first by Harris (1968) who suggested that loose connections between the outer hair cell cilia and tectorial membrane can produce up to 30 dB of thermal noise, and second by Tonndorf (1981) who suggested that decoupling can produce a tinnitus percept. Abnormal calcium levels can also lead to a loosening of the connections of the cilia's rootlets and impact neurotransmitter release (Jastreboff, 1989).

While the peripheral auditory system is likely involved in the initial generation of most subjective tinnitus symptoms, as evidenced by the large percentage of individuals with tinnitus who also have some measure of cochlear damage (Nondahl et al., 2002; Weisz, 2006), current theories suggest the central nervous system plays a major role in the perception and maintenance of tinnitus (Eggermont, 2003). This theory is supported by instances in which individuals with tinnitus have their auditory nerves sectioned, yet the tinnitus remains (Berliner, Shelton, Hitselberger, & Luxford, 1992; House & Brackman, 1981). Because of animal models of tinnitus (Brozoski & Bauer, 2016), we now know that changes to neural firing rates and patterns at the

peripheral level caused by damage from noise exposure, medications, and the aging process result in a type of maladaptive neural plasticity, which gives rise to changes in neural firing patterns in higher-level auditory and cortical structures (Roberts et al., 2010).

One of the first structures to demonstrate this plasticity is the dorsal cochlear nucleus (DCN). A decrease in input from the peripheral auditory system can result in hyperactivity at the level of the DCN, which is then preserved through the auditory pathway (Eggermont & Roberts, 2003; Henry, 2014; Roberts et. al., 2010). One of the first studies examining the role of the DCN in tinnitus found that stimulating the DCN with electrical current could impact the perceived tinnitus quality in patients with Neurofibromatosis II who had received an auditory brainstem implant following damage to the auditory nerve caused by tumor removal (Soussi & Otto, 1994). These effects were temporary, however, and only lasted as long as the stimulation was provided. While this study provided more qualitative information, it suggested that the DCN may play a role in tinnitus perception.

Subsequent animal studies have found that exposure to ototoxic substances (Kaltenbach et al., 2002) and prolonged intense noise exposure (Kaltenbach & McCalsin, 1996; Kaltenbach et al., 1998), resulting in tinnitus behavior, are accompanied by increases in spontaneous activity in the DCN. Increases in the firing rates and synchronous firing of neurons in the DCN typically result from activation of more peripherally located structures, such as inner hair cells and auditory nerve fibers, which leads to a sound percept in the auditory cortex. Spontaneous increases in the neural firing rates in the DCN or increases in neural synchrony without concurrent sensory stimulation may then falsely be interpreted as an activation of the peripheral auditory system and is transferred to the auditory cortex where it is perceived as sound. However, for this spontaneous activity to be recognized by higher-level structures as sound, it

needs to have a neural pattern similar to that evoked by a physical acoustic stimulus (Kaltenbach, 2006). One previous study found increased spontaneous activity in the DCN resulting from prolonged exposure to an intense 10,000 Hz stimulus for several hours. This spontaneous activity matched the activity profile of the DCN induced by presentation of a non-damaging 10,000 Hz stimulus. However, the spontaneous activity profile caused by the noise exposure to the 10,000 Hz stimulus had a broader area of activation and was centered on edge neurons that encoded the 12,000 Hz frequency region instead of the center 10,000 Hz frequency region (Kaltenbach, 2006). Increases in spontaneous firing rates have been found in the ventral cochlear nucleus (VCN) as well, suggesting the mechanisms responsible for increases in the DCN are also present in the VCN (Berliner, Shelton, Hitselberger, & Luxford, 1992; Wickesberg & Oertel, 1990). The increased spontaneous activity is maintained through the inferior colliculus, which then propagates the increased activations further up the central auditory system (Henry, Roberts, Caspary, Theodoroff, & Salvi, 2014; Robertson & Mulders, 2012).

It is well documented that peripheral deafferentation in the auditory system induces cortical map reorganization both in animal models and humans (Dietrich et al., 2001; Weisz et al., 2005). Given the close connection between damage of the auditory periphery and tinnitus, it is not surprising that cortical reorganization has been found in humans with tinnitus (Mühlnickel et al., 1998; Weisz et al., 2005; Wienbruch et al., 2006). However, one previous MRI study did not find significant differences in cortical reorganization between tinnitus and non-tinnitus participants who were matched for hearing loss (Langers, de Kleine, & van Dijk, 2012). This tonotopic reorganization in the cortex has been proposed as a neural correlate of tinnitus (Eggermont, 2003; Eggermont & Roberts, 2004). One proposed mechanism for this tonotopic reorganization is that a lack of lateral inhibition from damaged peripheral neural structures

results in an overrepresentation of frequencies located on the edge of the hearing loss (Roberts et al., 2010). Since neurons encoding the frequencies located in the region of hearing loss are not being stimulated, they are unable to suppress surrounding neurons, resulting in increased spontaneous firing rates of these edge neurons. There are several features of tinnitus that are not accounted for by this model, however. First, if tinnitus was caused by increased neural activation of edge frequencies, then tinnitus pitch-matching procedures should result in individuals identifying frequencies located on the edge of their maximal hearing loss. While some studies have found this to be the case (König et al., 2006), others have found that the tinnitus frequency typically falls within the maximal region of hearing loss (Schecklmann et al., 2012), or does not have a strong relation to audiometric thresholds (Henry, Flick, Gilbert, Ellingson, & Fausti, 2004). This theory also does not explain why many people experience tinnitus consisting of multiple tones or that is broadband in nature.

Another theory suggests that increases in spontaneous firing rates in the central auditory system are the result of a homeostatic mechanism attempting to maintain a baseline state, referred to as "central gain" (Jastreboff, 1990; Schaette & Kempter, 2006 Noreña & Farley, 2013). Alteration to this set level of activity caused by damage from peripheral structures results in homeostatic mechanisms in higher level structures becoming activated, thereby resulting in an increase in spontaneous firing rates, increased neural synchrony, and increased bursting activity (Noreña & Farley, 2013). This model would explain why individuals who are deprived of auditory stimulation, either through conductive hearing losses (Kim et al., 2011) or in silent environments such as anechoic chambers (Heller & Bergman, 1953), may experience tinnitus despite the lack of apparent damage to auditory system.

One perplexing aspect of tinnitus is that most individuals who experience chronic tinnitus are not severely affected by it; however, there is a small subset of individuals for whom the tinnitus causes a significant decrease in quality of life (Henry, Dennis, & Schechter, 2005). This discrepancy would suggest that while tinnitus may be generated and maintained in the auditory structures, it is likely other cortical structures contribute to increased perception and annoyance of the tinnitus (Jastreboff et al., 1996; Rauschecker et al., 2010). Rauschecker et al. (2010) propose the thalamic reticular nucleus may act as a gate that prevents the tinnitus signal generated in the auditory periphery from reaching the auditory cortex where it is perceived by the individual. Their model suggests when neural activity that represents sound reaches the medial geniculate nucleus (MGN) it gets sent simultaneously to the auditory cortex and the amygdala. From the amygdala, the activity is then sent to the nucleus accumbens in the ventral striatum and the ventral medial prefrontal cortex. These subcallosal structures evaluate the emotional context of the stimulus, and if found to be irrelevant, they activate the thalamic reticular nucleus, which exhibits a strong inhibitory effect on the MGN (Yu et al., 2009), thereby acting as a selective gating mechanism. According to the model, dysfunction in this system allows the tinnitus signal to be transmitted through the MGN to the auditory cortex.

The thalamocortical dysrhythmia model has also been proposed as an underlying mechanism for tinnitus generation (Llinás et. al., 1999). According to this model, deafferentation at the peripheral level leads to a lack of excitatory responses in the thalamus for these regions, resulting in an over-inhibition that leads to an increase in slow wave activity in the theta band (4-8 Hz) (Adjamian et al., & Palmer, 2012). Increased theta activity results in a lack of lateral inhibition for beta and gamma oscillations located on the edge of the differentiated region, which may, in turn, cause the tinnitus percept (Llinás et al., 2005).

To date, the exact underlying mechanisms responsible for the generation of tinnitus are not fully understood. The heterogeneity of tinnitus symptoms and impact on quality of life suggests that there are likely multiple dysfunctional pathways involved.

1.2 Need for Electrophysiological Auditory Measures to Identify Tinnitus

Subjective tinnitus is a phenomenon that currently lacks an objective test for diagnosis or quantification (Hall et al., 2016; Jackson et al., 2019; McFerran et al., 2019). Current diagnostic batteries typically involve tests such at pitch-matching, loudness matching, loudness discomfort levels, residual inhibition, and questionnaires such as the Tinnitus Handicap Inventory (THI) and Tinnitus Reaction Questionnaire (TRQ), all of which depend upon subjective responses provided by the patient (Henry et al., 2005; Henry, 2016). The ramifications of using purely subjective tests are particularly evident in the Veterans Affairs system, where tinnitus is the number one service-connected disability, costing hundreds of millions of dollars annually in compensation, with this number expected to increase (Henry et al., 2004; Henry et al., 2005; Yankaskas, 2013). As of 2018, nearly two million veterans were receiving treatment for their service-connected tinnitus (Henry, 2018). Workers' compensation cases involving tinnitus could also benefit from the development of an objective test for tinnitus, as 29 out of the 50 states provide workers compensation for tinnitus symptoms, although the criteria vary from state to state (Dobie, 2001). Unfortunately, a national database of the number of workers compensation cases for tinnitus has not been created, making it difficult to track data pertaining to workplace-induced tinnitus. While not directly related to workers compensation, a study by Goldstein et al., 2015 suggests the annual medical cost per tinnitus patient is $2,110 annually while Maes et al. (2013) suggest the cost in lost productivity per tinnitus patient is $5,605 annually, highlighting the need for tests and treatments to address this problem. Developing an objective test for tinnitus would also help

bridge the gap between animal and human research. If specific patterns can be identified in individuals with tinnitus compared to those without, then these areas can be further examined in animal models and potential innovative new therapies developed.

Auditory evoked potentials have been utilized in the past for their evaluative capability to differentiate between individuals with and without tinnitus and have been proposed as a possible cornerstone upon which an objective test battery may be built. (Attias et al., 1993; Gopal et al., 2017; Jacobson et al.,1996). Auditory evoked potentials can be divided into two broad categories: exogenous and endogenous. Exogenous potentials are influenced by external factors, such as the characteristics of the stimulus being presented while being relatively unaffected by intrinsic factors, such as the attentional state of the participant (Cardon et al., 2020). Changing the stimulus parameters, such as the intensity, duration, frequency, and rate will have an impact on the variability of exogenous potentials. As exogenous potentials are not affected by higher order cognitive processes, they may be particularly useful for clinical testing, especially when malingering is suspected, since they are dependent upon the stimulus characteristics and are not heavily influenced by the attentional state of the patient. Examples of exogenous auditory potentials include Waves I through V of the auditory brainstem response (ABR), the middle late responses, and P1, N1, and P2 of the auditory late response (ALR), although these later potentials may be affected by intrinsic factors to some extent.

Endogenous potentials, while influenced to some extent by stimulus characteristics, are primarily generated by task-dependent neural activity and are susceptible to internal participant factors, such as attentiveness, alertness, and psychological state (Cardon et al., 2020). These potentials occur later after stimulus onset than exogenous potentials and include N2, P300, and N400. Donchin et al. (1978) proposed three criteria that an evoked potential must meet to be

considered endogenous. First, the response to the stimulus needs to be non-obligatory. This means the stimulus may or may not evoke the response depending on the state of the participant and the task required. In addition, the lack of a stimulus may also cause the same response, such as when a stimulus is occasionally deleted from a train of stimuli. The second criterion is that amplitude, latency, and scalp distribution of endogenous potentials should be relatively immune to differences in stimulus characteristics. For example, the presentation of a high frequency and low frequency stimulus should produce a similar endogenous potential as the cognitive state of the participant is going to play a larger role in the response compared to the physical characteristics of the stimulus. Finally, variation in the endogenous potential can be mostly explained by the paradigm utilized. Changes to the tasks required of the participant will lead to larger changes in the endogenous potential than changes to the stimulus characteristics; however, this is not to say that changes to the physical aspects of the stimulus will have no effect on the endogenous potential produced. The distinction between endogenous and exogenous potentials is often not completely apparent. Donchin et al. (1978) categorize potentials as endogenous or exogenous based on what can produce variance in the potential. If changes to the stimulus result in changes to the evoked potential, then it is exogenous or mostly exogenous. If changes to the task result in more variance in the potential, then it may be considered endogenous or mostly endogenous.

A plethora of research has shown tinnitus is not solely confined to the auditory networks as there are other cortical networks involved as well (Rauschecker et al., 2010). Endogenous potentials, like the P300, are more appropriately suited to assess the effects of tinnitus on other modalities such as attention while exogenous potentials allow for evaluation of stimulus characteristics on lower-level auditory structures. When combined, exogenous and endogenous

potentials may be able to provide us with a more complete picture of tinnitus. Of the auditory evoked potentials that have been well established, the auditory late response (Gopal et al., 2017; Noreña et al., 1999), mismatch negativity (Li et al., 2016; Mahmoudian et al., 2013; Mohebbi et al., 2019; Weisz et al., 2004; Yang et al., 2013), and P300 (Cardon et al., 2020) have been studied in tinnitus populations and show promise in their ability to differentiate between individuals with and without tinnitus.

1.3 Electrophysiological Measures of Tinnitus

1.3.1 Electroencephalography (EEG)

While many different tools are available to measure cortical responses to auditory stimuli, each with their advantages and disadvantages, EEG is a relatively strong and feasible method that offers excellent temporal resolution on the order of milliseconds. Originally recorded in animals in 1875 by Richard Canton and in humans in 1924 by Hans Burger, the EEG approach uses electrodes on the scalp to measure the summed excitatory and inhibitory postsynaptic potentials generated by a minimum of 10,000-50,000 synchronously firing pyramidal neurons (Murakami & Okada, 2006) whose dipoles are oriented perpendicular to the scalp. While changes to the electric potential of single neurons are the result of an action potential, these potentials are too brief to form a summed response detected by EEG. The postsynaptic potentials (PSP), on the other hand, have a longer duration of tens to hundreds of milliseconds, providing enough time for the electrical activity of synchronously firing neurons to summate and be detected by EEG. A PSP is generated whenever a presynaptic terminal has an influx of either a positive ion, such as Na+ or Ca 2+ that results in an excitatory postsynaptic potential (EPSP) or a negative ion, such as Cl-, that results in an inhibitory postsynaptic potential

(IPSP). During an EPSP the influx of positive ions from the extracellular fluid into the cell results in a negative sync in the extracellular fluid that can be detected by EEG. A superficial EPSP is detected as a negative polarity by the EEG, while an EPSP that is deeper in the cortex is detected as a positive polarity. The inverse is true for an IPSP. Superficial IPSPs are detected as a positive polarity by the EEG while deep IPSPs are detected as a negative polarity. Given the increased distance from deep PSPs to the scalp where the EEG electrodes are placed, EEG responses are dominated by superficial PSPs. While the EEG reading is the sum of both the IPSPs and EPSPs, the influx of Na+ and Ca2+ results in an EPSP that produces a stronger gradient than the influx of Cl– and outflux of K+ that result in an IPSP, resulting in EPSPs contributing more to the generation of EEG waves.

Cortical pyramidal neurons contain long apical dendrites that travel perpendicularly to the surface of the cortex, thus generating dipoles that can be detected by EEG. However, the cortex contains many gyri and sulci that can change the orientation of the dipoles generated by cortical pyramidal neurons. Pyramidal neurons located on the tops of gyri or bottoms of sulci (although to a lesser extent given the increased distance between the bottom of the sulcus and the scalp) produce postsynaptic potentials (PSPs) that can be detected by EEG while pyramidal populations located on the walls of gyri and sulci produce horizontal dipoles that EEG is much less sensitive to.

EEG uses a differential amplifier to record electrical activity from populations of neurons. Each differential amplifier has two inputs with an electrode connected to each. The differential amplifier takes the electrical activity generated at one electrode and adds it to the inverse waveform of a second reference electrode that ideally does not contain electrical activity caused by cognitive processes. Linked mastoids or midline electrodes are common references,

although digital EEG allows for re-referencing offline. The similarities between the two electrodes are cancelled out while the differences between the two are accentuated. However, the noise measured by two different amplifiers is only moderately correlated, and thus does not cancel out entirely (Hyde, 1994). Filtering is an additional tool that is utilized to help improve the signal to noise ratio. High and low pass filters can help reduce the noise not associated with the neurological region of interest and can be applied to both online recordings and offline recordings. Care must be taken when applying filters, however, as filtering can affect the shape and temporal structure of the recorded waveforms (Widmann & Schröger, 2012). Signal averaging provides another means of increasing the signal to noise ratio of an EEG recording. As noise is not time locked to a particular stimulus, presenting more stimuli will result in the noise further cancelling out while the time locked response will sum together (Hyde, 1994).

Equipment capable of recording EEG activity is readily available commercially, making it a promising avenue for tinnitus evaluation. There are disadvantages to EEG, however. The first is that while the temporal resolution is excellent, the spatial resolution is poor compared to other methods such as MEG and fMRI. Another is that EEG measures far field potentials, which makes precise measurement of specific neural generators impossible. Despite these disadvantages, the clinical applicability of EEG makes it a promising venue to explore.

1.3.2 Auditory Late Response

An ALR consists of a series of peaks labeled P1, N1, P2, and N2 that are generated in response to an auditory stimulus (Figure 1). The ability of cortical evoked auditory potentials (CAEP) to assess both bottom up and top-down processes makes them particularly well suited to assessing tinnitus. The equipment required to collect auditory evoked potentials is readily available, relatively cheap, and many commercially available systems can collect CAEPs. The

ALR peaks P1, N1, P2, and N2 have been shown to have good test-retest reliability and are clinically utilized to assess central auditory processing, hearing in populations for which behavioral testing is not feasible, such as infants, and neural encoding of speech for potential cochlear implant candidates (Hossain et al., 2013; Picton et al., 1977). These measurements are obligatory and primarily exogenous, although the patient's state can have some influence on their magnitude (Donchin, 1978).

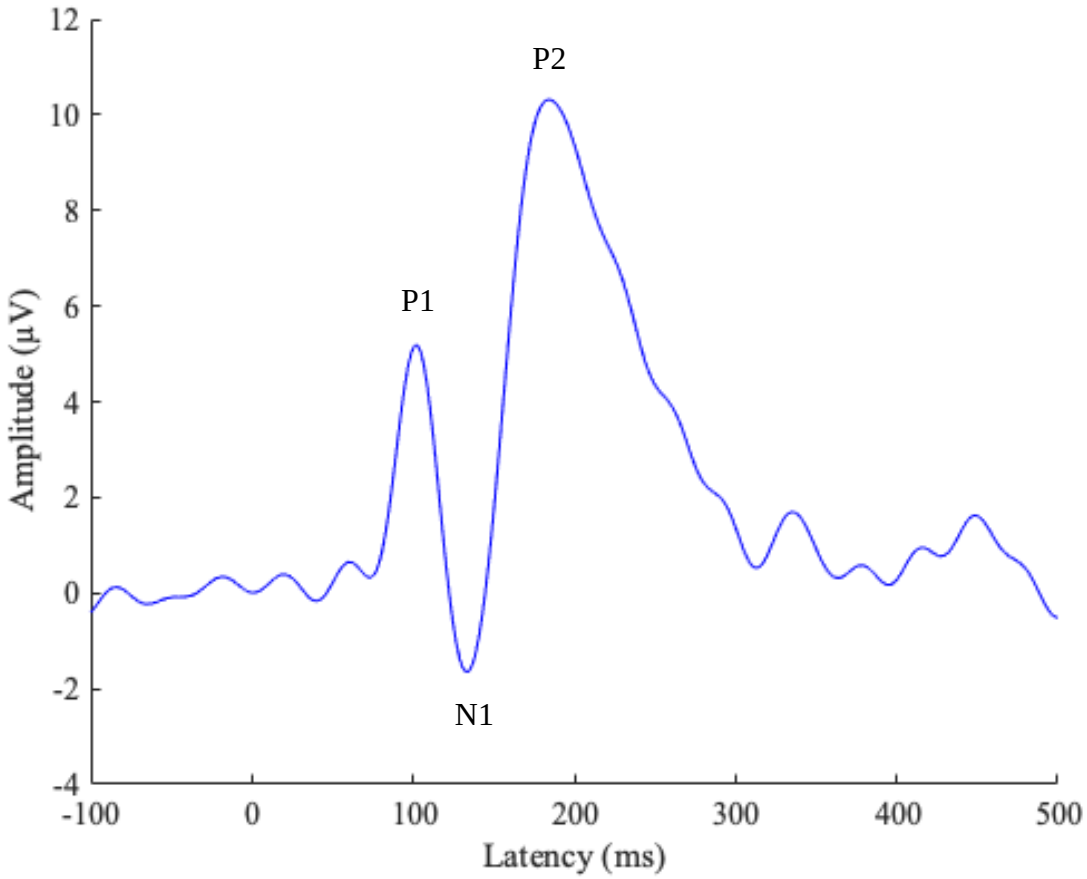
The primary outcome measures of the ALR are the latencies of the maximum peaks in the specified time range for P1, N1, P2, and N2; the absolute amplitude values of the peaks relative to baseline; and the peak-to-peak amplitudes values, i.e., the peak-to-peak amplitude of P1N1. The amplitude of a peak is determined by the amount of neural activation that is occurring in response to a stimulus. For earlier auditory evoked components, such as the ABR, the action potentials (AP) of groups of neurons contribute to the measured responses. However, for later evoked potentials, such as the ALR, the time course of the AP is too short to be measured and distortion of the electrical signal occurs. Post synaptic potentials, both excitatory and inhibitory, have a much slower time course and are what generate the peaks measured in the ALR. As more neurons that have similar spatial orientations are synchronously activated, the amplitude of the peak becomes larger (Olejniczak, 2006). Amplitudes of the peaks are significantly impacted by stimulus intensity, with higher stimulus intensities producing larger amplitudes and lower stimulus intensities producing smaller amplitudes (Billings et al., 2007). For exogenous potentials, attention can also modulate amplitude values (Picton & Hillyard, 1974). Latency values reflect the transmission speed that a signal is neurally encoded. Stimulus characteristics, such as intensity for endogenous potentials, or task difficulty for exogenous potentials, have an impact on latency as does neural synchrony, with greater neural synchrony manifesting in shorter

latencies (Billings et al., 2007; Ritter et al., 1972). In adults, P1 occurs around 50 ms and is thought to be generated primarily by the auditory cortex, although there may be other minor contributors as well (Liegeois-Chauvel, 1994). The N1 peak is produced by multiple neural generators and occurs around 100 ms after stimulus presentation (Näätänen & Picton, 1987). Initial stimulus onset activates the frontocentral portion of the cortex. The second generator of the N1 response, known as the T-complex, is thought to occur in the auditory association cortex located within the superior temporal gyrus. The third component of the N1 may be more susceptible to the state of the patient as it reflects diffuse transient arousal to the stimulus (Näätänen & Picton, 1987). P2 likely has multiple neural generators located within the primary and secondary auditory cortices (Lightfoot, 2016), while N2 is also likely to have multiple neural generators located in the bilateral supratemporal auditory cortices, thalamus, and brainstem (Fitzroy et al., 2015).

While the ALR is primarily an exogenous response, it can be influenced by the state of the patient to some extent. The best ALR responses will be obtained when the patient is awake and engaged in an activity that keeps their attention away from the stimulus and prevents them from becoming drowsy, such as reading or watching a silent movie (Picton et. al., 2000). Since the N2 component of the ALR occurs several hundred milliseconds after the stimulus onset, an epoch length of 500 ms is recommended to ensure that there is not overlap in responses to two different stimulus presentations (Duncan et al., 2009).

Figure 1

A Typical ALR Waveform



P1 = first positive peak; N1 = first negative peak, P2 = second positive peak

Given that tinnitus very likely involves the central auditory system, the ALR has been assessed in individuals with tinnitus, although results have been mixed. Jacobson et al. (1996) utilized a dichotic auditory selective paradigm to evaluate the N1, P1, and negative difference (Nd) wave in tinnitus and non-tinnitus participants. Participants were asked to respond to duration deviants consisting of 500 or 1,000 Hz tones in the "attend" ear while ignoring deviants in the "non-attend" ear. There were stimulus blocks with four recording conditions summarized in Table 1. The authors found tinnitus participants had significantly longer latencies for N1 in the

attend condition, but not in the non-attend condition, compared to non-tinnitus participants. They suggested that this may have been due to the difficulty of the task, which engaged a selective auditory attention mechanism, suggesting that these selective attention mechanisms were responsible for the changes in latency for this task. N1 amplitude differences, P2 amplitude and latency differences, and Nd onset time between the two groups were not statistically significant. Given the heterogeneity in findings of N1 amplitude and latency differences, or lack thereof, the authors suggest that selective auditory attention may be able to modulate the latency of N1. As differences between the controls without tinnitus and the tinnitus participants were only present in the selective attention condition, the ability of tinnitus participants to attend to stimuli presented in one ear while ignoring stimuli presented in the opposite ear may be hampered by their internally perceived tinnitus, suggesting deficits in selective auditory attention.

Table 1

Stimulus Blocks used in Jacobson et al. (1996)

	Left ear	Right ear	Instruction
Condition 1	500 Hz	1,000 Hz	Attend to deviants in the left ear
Condition 2	500 Hz	1,000 Hz	Attend to deviants in the right ear
Condition 3	1,000 Hz	500 Hz	Attend to deviants in the left ear
Condition 4	1,000 Hz	500 Hz	Attend to deviants in the right ear

Adapted from *Electrophysiological indices of selective auditory attention in subjects with and without tinnitus* (Jacobson et al., 1996, p.68).

In a previous EEG and fMRI study, Gopal et al. (2017) presented 1,000 Hz tones at 60 dB nHL and 80 dB nHL to evaluate the amplitude response growth between tinnitus and non-tinnitus controls. Findings indicated N1 amplitude growth had a disproportionate increase in tinnitus subjects compared to control participants, although this result failed to reach significance after a Bonferroni multiple significance *t*-test correction was applied (p=.0007). However, in a LASSO (Least Absolute Shrinkage and Selection Operator) regression model, N1 amplitude

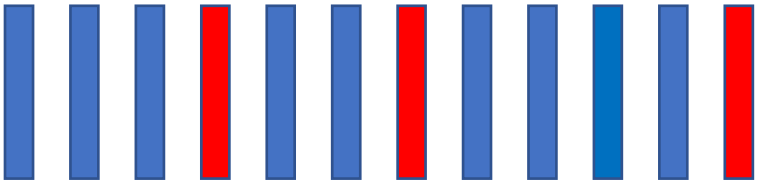
growth was the second top predictor of tinnitus group membership. In their regression model, elevated frontal cortex activity in response to the pitch-matched tinnitus frequency compared to controls was the top predictor. These results agreed with earlier studies which found increased N1-P2 amplitude growth in tinnitus subjects (Noreña et al., 1999; Lee et al., 2007). Gopal et al. (2017) suggested the N1 amplitude growth could be due to hyperactivity in attentional regions in the cortex that result in a disproportionately stronger cortical response to stimuli of higher intensity. dos Santos Filha & Matas (2010) found significantly delayed latencies for N1 and P2 for tinnitus participants compared to non-tinnitus participants, which contrasts with Noreña et al. (1999) who found earlier N1 latencies in tinnitus patients and no difference in P2 latencies across groups. Comparing findings across studies is made difficult by the different methodologies utilized to evoke cortical responses. Further research and standardization of methods is needed to tease apart the differences in ALR responses between tinnitus and non-tinnitus individuals.

1.3.3 Mismatch Negativity

The MMN is a primarily exogenous response that can be evoked using an oddball paradigm without the active participation of the patient. In its simplest form, an oddball paradigm consists of a train of identical stimuli that are infrequently interrupted in some fashion, either by the insertion of a stimulus differing along some parameter, the deletion of an expected stimulus, or breaking an expected pattern. An example of a simple oddball paradigm is provided in Figure 2. The MMN is the product of subtracting the evoked potential generated by the standard stimulus from that generated by the deviant stimulus. The MMN peaks in the 100-250ms time range (Schröger, 1998).

Figure 2

Oddball Paradigm



Blue bars represent commonly presented "standard" stimuli while red bars represent infrequently presented "deviant" stimuli.

The MMN (demonstrated in Figure 3), first described by Näätänen et al. (1978), is thought to assess pre-attentive cortical responses to stimuli presented in an oddball paradigm. It has contributions from both the auditory and frontal cortices and is activated when a change in a stimulus characteristic is detected (Näätänen et al., 2012). This neural change detection mechanism appears to be correlated with behavioral discrimination abilities, which has led to the interpretation that the MMN is the result of a memory trace violation (Näätänen et al, 2007). Evidence of this interpretation is summarized in a review by Näätänen et al. (2007). The first evidence they present in support of this claim is that the MMN is not generated by the first presentation of a stimulus, regardless of whether it is a standard or deviant. Several presentations of the standard are required before the MMN can be evoked. The MMN also occurs when there are decreases to stimulus presentation parameters, such as duration, interstimulus interval, and intensity. If differences in the responses to the standard and deviant stimuli were due to the refractory period of the neural populations being activated, then decreasing these parameters should only produce acute differences in peak amplitude. If an MMN was simply a reflection of new neural populations being activated in response to a deviant stimulus, then one would not expect softer intensity deviants, stimulus omissions, or decreased stimulus durations to evoke a waveform with a larger amplitude than that of the standard stimulus. The MMN spans over a

long duration, so differences must be due to other neural processes (Näätänen et al., 2007). This is further implicated by MMNs that are evoked by deletions in a train of presentations despite no new neural populations being activated during the period of deletion.

Imaging studies have also found that the MMN and N1 components have different neural generators (Näätänen, 1995). A recent study by Takasago et al. (2020) looked for spatiotemporal differences between N1 and MMN in three participants who had their lateral cortices covered with high density electrodes to identify sources of seizure activity. The authors found the MMN and N1 had spatially distant neural generators, with the N1 being localized to the superior temporal gyrus close to the superior temporal plane and the MMN being diffusely present in the superior and middle temporal gyrus, frontal lobe, and parietal lobe. The authors also found that N1 adaptation and the MMN occurred at different latencies within the same electrode, which they interpreted as meaning that N1 adaptation cannot be responsible for the negative difference wave of the MMN. This is further supported by studies that examined auditory evoked cortical potentials in newborns. The N1 response is not present in this population, but the MMN can reliably be evoked (Alho et. al., 1990). The same is true for comatose patients and for those who are in the REM stage of the sleep cycle (Atienza & Cantero, 2001; Fischer et al., 1999). Differentiation between N1 and MMN generators can also be seen by the effects of medications such as N-methyl-D-aspartate (NMDA) blockers phencyclidine, CGS-19755, and MK-801 (Javitt et al., 1996) and lesions in the dorsolateral prefrontal cortex (Alho et al., 1994) that can reduce or abolish the MMN response while leaving the N1 response intact (Näätänen et al., 2007).

Other theories regarding the underlying nature of the MMN also exist. Perhaps the most widely cited theory that competes with Näätänen's (1978, 1995, 2007) explanation for the origin

of the MMN is the adaptive hypothesis put forth by Jääskeläinen et al. (2004). They suggest the MMN is not a distinct process from the elicitation of N1 but is instead an artifact produced when subtracting the waveform generated by the standard stimulus from the waveform generated by the deviant stimulus. They divide the N1 component into two major parts: the posterior N1, which occurs around 85 ms, and the anterior N1, which occurs around 150 ms and reportedly has similar source generators as the MMN. Changes in the amplitudes between these two separate generators in response to a novel stimulus could change the center of gravity of the N1 response, and thus produce a negative wave form generated by adaption of the neural populations as opposed to being generated by a population of change specific neurons postulated to be responsible for the generation of the MMN.

In their study, Jääskeläinen et al. (2004) hypothesized an MMN could be generated after only a single standard stimulus, which contrasts with previous suggestions that several standard presentations are necessary to form a memory trace (Näätänen et al., 2007). The authors also posited that the posterior N1 component is more attenuated by repetitive stimuli than the anterior N1 component. This difference in susceptibility to habituative effects of repetitive stimuli between the two N1 components would therefore change the center of gravity of the N1 source generators, causing them to appear shifted from the traditional N1 source loci (Jääskeläinen et al., 2004). To determine if a single preceding standard stimulus could produce a negative response consistent with the latency of the MMN, the authors presented subjects with groups of stimuli containing either one, two, or three standard stimuli preceding the deviant stimulus. The interval between presentations of novel stimuli was held constant at 3.5 seconds regardless of whether one, two, three, or four standard stimuli were presented before each deviant stimulus. The authors argue that this paradigm protects against the suppression of N1 responses to novel

tones that are presented at shorter intervals. There was also a control condition where the groups of stimuli consisted only of standard stimuli. They found that larger negative difference waves were produced when the deviant was preceded by only a single standard compared to two to four standards and suggest that previous studies failed to have similar findings due to short intervals between novel stimuli. Single equivalent current dipole results from MEG recordings indicated that the posterior N1 response was more affected by decreasing sound novelty relative to the anterior N1 response and that the anterior N1 response increased in latency with decreasing sound novelty.

Friston (2005) also provides another view of the MMN. This theory describes the sensory brain as a hierarchical structure that works to minimize the free energy generated by a stimulus by predicting the most likely cause of the stimulus. Higher order cortical structures compare sensory input received from lower-level sensory structures and their afferent pathways resulting in predictive coding. Whenever there is a mismatch between what is expected and what is present, a prediction error is generated. This is possible through both forward connections, which drive cortical responses, and backward connections, which both drive and modulate cortical responses. In this view, the MMN can be viewed as a direct measure of predictive error detection at the pre-attentive level (Hofmann-Shen et al., 2020). Higher order cortical structures predict the source of an incoming stimulus based on previous exposure to that stimulus. In the case of the MMN, these higher-level cortical structures are attempting to minimize the free energy required in identifying these stimuli, which results in an attenuation to the cortical response to these stimuli. An infrequently presented deviant stimulus violates the predictive coding of the sensory brain and results in a prediction error. Friston (2005) suggests that error suppression, or the minimization of free energy, is the basis for the MMN. This hypothesis is similar to the adaptive

hypothesis proposed by Jääskeläinen et al. (2004) but differs in that both backward and lateral connections are required for minimizing free energy. Friston (2005) defends his hypothesis by noting that compromising plasticity through the blocking of NMDA receptors reduces the MMN response by approximately 20 percent (Umbricht et al., 2000). Neural plasticity is thought to play an important role in the formation of neural traces and NMDA receptors play an important role in synaptic plasticity (Friston, 2005). NMDA channel blockers, such as Ketamine, act to prevent the flow of ions through the NMDA receptor, and thus block, to some extent, the progression of neural synaptic plasticity.

There are several factors that can influence the strength of the MMN response. The first is increasing the number of standards that are presented between deviant stimulus presentations (Haenschel et al., 2005). This presumably allows a stronger memory trace to be developed, which then leads to a greater prediction error (Näätänen et al., 2007). The duration of the interstimulus interval can also play a role. While the MMN trace can last several seconds in healthy subjects, decreasing the interval leads to an increase in MMN elicitation, likely because after a few seconds the memory trace formed by the standard stimuli begins to decay, thereby weakening the template to which the deviant stimuli are being compared (Sabri & Campbell, 2001). However, as Jääskeläinen et al. (2004) suggest, if the length of time between the presentation of the novel stimuli is reduced, regardless of the number of standard stimuli between each deviant, the MMN will be attenuated, possibly because the frequent presentation of deviant stimuli presentation within short time periods results in a neural adaption that reduces the response of feature specific neural populations. The probability of a deviant stimulus presentation also influences the strength of the MMN response. Similar to increasing the number of standards between deviant presentations, decreasing the probability of deviant presentations

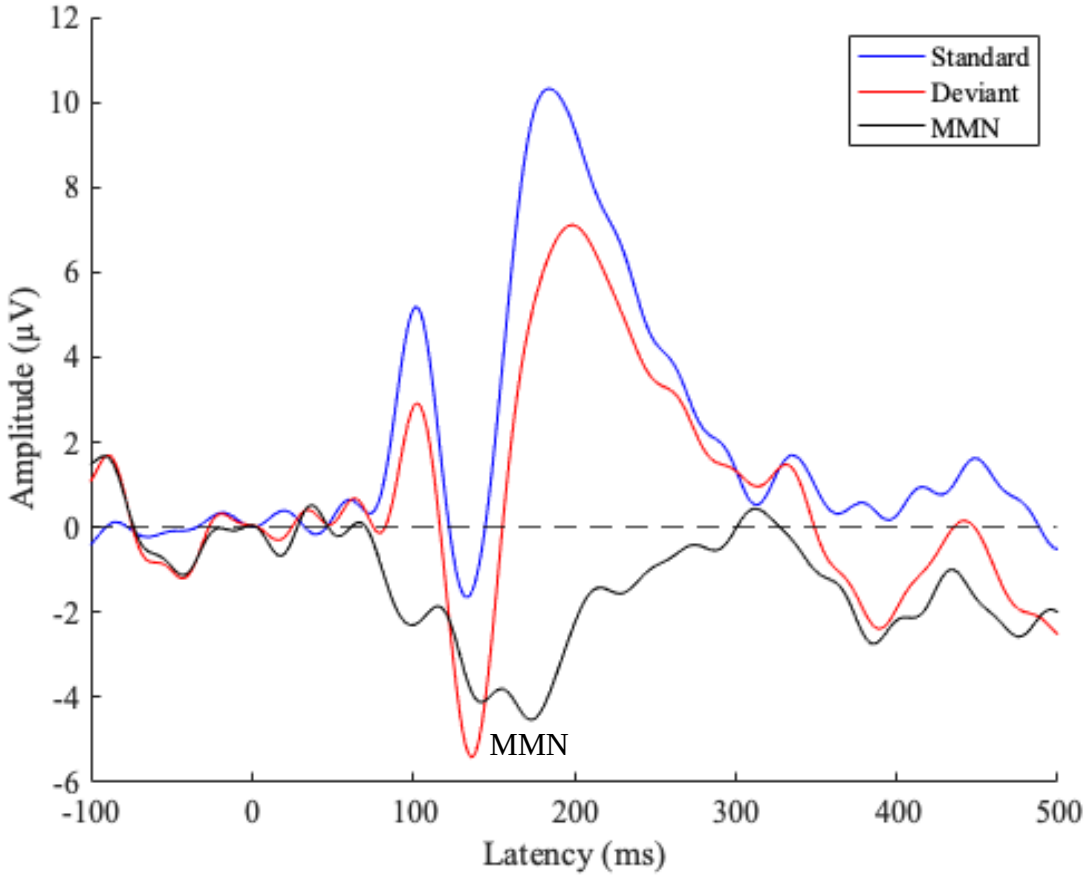
allows for a stronger memory trace of the standard, which then results in larger prediction errors when the deviant is presented (Sabri & Campbell, 2001). Conversely, increasing the number of deviant presentations relative to the standards results in the deviant stimuli developing a memory trace of their own, thereby interfering with the error prediction mechanism of the MMN (Sabri & Campbell, 2001). This is also evidenced by the significant reduction in MMN strength when two deviant stimuli are presented consecutively (Müller et al., 2005).

The MMN was originally obtained by subtracting the evoked response potential (ERP) waveforms evoked by a commonly presented standard stimulus from those generated by a rarely presented deviant stimulus (Näätänen, 1978). However, if this method is used, differences in the N1 peak caused by activation of different neural populations responding to the different frequency stimuli may contaminate the true MMN response (Kraus, McGee, Carrell, & Sharma, 1995). One way to control for this is to present the deviant stimulus in a block by itself, thus resulting in the deviant stimulus serving as its own standard. This guarantees that the neural populations being activated by the two CAEPs to be subtracted are the same, thereby reducing the "N1 effect" (Hillyard, 1973). However, the interstimulus interval between the stimulus when presented as a standard and when presented as a deviant likely has an impact on the amplitude of the N1 response, as there is less time for recovery in the standard condition. Differences in N1 response between the two conditions are therefore unlikely to be entirely eliminated (Martin et al., 2008.) Martin et al. (2008) also provides two additional measures that can be modified to reduce the impact of the N1 response on the MMN. As the interstimulus interval decreases, the N1 response begins to attenuate (Pereira et al., 2014). This likely has to do with the refractory period of the neural populations being activated, with longer ISI times allowing for more complete recovery (Pereira et al., 2014). Decreasing the difference between the standard and

deviant stimulus also separates out the MMN response from the N1 response. As the stimulus difference begins to increase, the latency of the MMN decreases, bringing it closer to the average latency range of the N1 response (Schröger, 1998) and making it more likely that the MMN is contaminated.

Figure 3

A Typical MMN Response Derived from Standard and Deviant Waveforms



1.3.4 P300

First described by Sutton et al. (1965), the P300 is an endogenous response that is evoked by a paradigm very similar to that of the MMN, except that the participants are asked to respond in some way whenever they detect a deviant stimulus. If the participant is able detect the deviant stimulus from standard stimulus, then a large positive inflection of 10-20 μV occurs in the 300

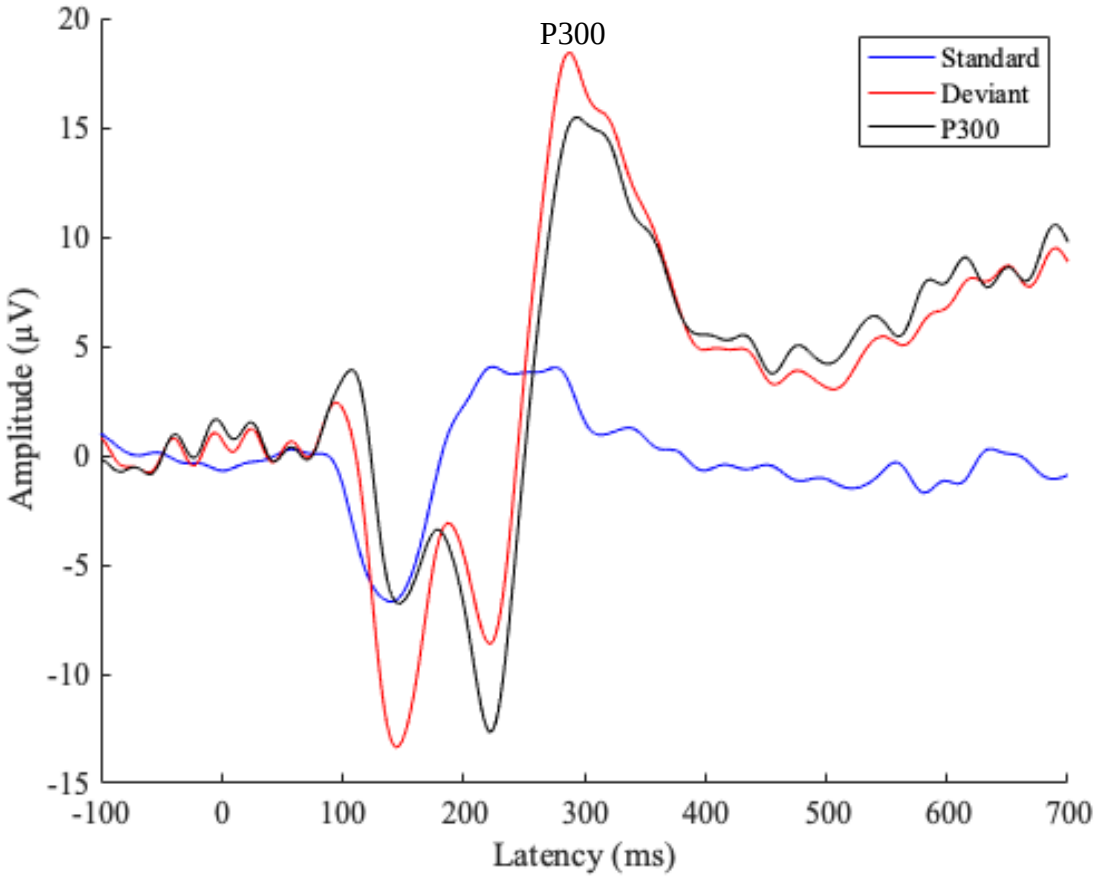
ms time window with a maximal distribution over midline electrodes (Polich & Kok, 1995). An example of a P300 response is shown in Figure 4. As with the MMN, the amplitude of the P300 increases as the probability of the deviant stimulus being presented decreases (Johnson & Donchin, 1978). The P300 is thought to reflect cognitive processes; however, after decades of research and thousands of publications on the topic, the exact cognitive processes that the P300 is assessing remain unknown (van Dinteren et al., 2014). Neural generators of the P300 have also not been concretely identified. Since the P300 is a higher order cognitive response, a diffuse cortical network has been found to be involved (Duncan et al., 2009). Results from P300 research in tinnitus participants suggest that these individuals may have reduced P300 amplitudes (Asadpour et al., 2018; Attias et al., 1993; Attias et al., 1996; Hong et al.,2016; Majhi et al., 2019; Mannarelli et al., 2017) and increased latencies (Attias et al., 1993; Attias et al., 1996; Gabr et al., 2011; Majhi et al., 2019; Zuraida et al., 2016) compared to non-tinnitus controls, although these findings have not been reported in other studies (Shiraishi et al., 1991; Houdayer et al., 2015). Of these studies, only three have incorporated the pitch-matched tinnitus frequency, or frequencies close to the average tinnitus frequency (Asadpour, et al., 2018; Attias, et al., 1993; Hong, et al., 2016).

Attias et al. (1993) used two oddball paradigms in their study to elicit a P300 response. The first paradigm utilized a standard oddball protocol with a 2,000 Hz non-target (standard) and 1,000 Hz target (deviant) stimuli while the second paradigm used a modified oddball paradigm in which a 1,000 Hz tone was used as the target and 5,000 Hz, 6,000 Hz, and 7,000 Hz tones were used as non-targets. Each tone had a 25% probability of occurrence. They found that the standard oddball paradigm produced smaller N1 and P300 amplitudes in response to the target stimuli in the tinnitus group compared to the non-tinnitus group. The N1 amplitude evoked by

the non-target stimulus was also significantly reduced in the tinnitus group compared to the controls. The modified oddball paradigm produced significantly smaller N1, P2, and P300 amplitude responses to the target stimulus in the tinnitus group compared to the non-tinnitus group. As there were no significant differences in brainstem auditory evoked potentials, reaction times in identifying the target stimuli, nor in correct percent identification of the target stimuli, the authors suggest that individuals with tinnitus have deficits in cognitive processing of auditory stimuli due to either a decrease in the number or activity of responding neurons or an increased desynchronization in response to the stimuli. As latencies were not significantly different between the groups, the authors posit that the speed of these processes is not affected by tinnitus.

Figure 4

A Typical P300 Response Derived from Standard and Deviant Waveforms



Hong et al. (2016) utilized a standard oddball paradigm to evoke a P300 in the tinnitus and control groups. They also used the same oddball paradigm in a passive listening task where participants were watching a silent movie. For the control group, the non-target (standard) stimulus was a 500 Hz tone while the target (deviant) stimulus was an 8,000 Hz tone. The tinnitus group was presented with a 500 Hz non-target tone and a target tone located at the individual's tinnitus frequency. Ten participants had a pitch-matched tinnitus frequency located at 8,000 Hz, one at 2,000 Hz, one at 250 Hz, and two at 125 Hz. The authors found that the tinnitus group had significantly smaller N1 and P300 amplitudes and shorter P170 and N200 latencies compared to the non-tinnitus controls. The authors then divided the tinnitus group into two separate subgroups based on P300 amplitude size, which they labeled as a higher attentional resourcing group (T1 had the highest P300 amplitudes in the tinnitus group) and a lower attentional resourcing group (T2 had the lowest P300 amplitudes). They found that the T2 group (group with the smaller P300 amplitudes) was the driving force in the differences between the collective tinnitus group and non-tinnitus group. When the T1 group was compared to the non-tinnitus group in isolation, there were not significant differences in P300 amplitude. Interestingly, the T1 group was significantly more annoyed by their tinnitus, as measured by a visual analog scale and the Korean THI. They suggest this could be attributed to the fact that all of the T1 participants had unilateral tinnitus while three of the T2 participants had bilateral tinnitus, leading to the conclusion that having an "unbalanced" tinnitus may contribute to increased distress. The authors interpret these results as suggesting that tinnitus involves both bottom-up (evidenced by differences in N1 amplitudes) and top-down (evidenced by differences in P300 amplitudes) processes. As there were no differences between the two tinnitus groups for

N1, the authors posit that differences between the two groups begin to come into play at the junction between where top-down and bottom-up processes merge.

Asadpour et al. (2018) utilized a standard oddball paradigm with a target stimulus consisting of narrow band noise centered around 6,000 Hz (the predominant tinnitus frequency), a non-target stimulus of 4,000 Hz, and infrequent novel stimuli consisting of environmental sounds. They found that the tinnitus group exhibited significantly smaller P300 amplitudes, but only in the FT7, FT8, and T7 channels. Care should be taken when interpreting these results, as two sample *t*-tests were used to compare the groups at each of the 32 channels which significantly increases the chance of making a Type 1 error.

A recent meta-analysis by Cardon et al. (2020) examined studies that utilized late auditory evoked potentials in tinnitus groups. They concluded the amplitude of the P300 response was significantly reduced in tinnitus groups compared to controls and that P300 latencies were significantly longer. No other amplitude or latency measures for P1, N1, or P2, were found to be significantly different, although tinnitus groups did on average have a larger P2 amplitude. The MMN was not able to be included in the meta-analysis due to the heterogeneity of the studies using an MMN paradigm.

Since tinnitus is an auditory perception heard by the individual, despite the lack of external stimulus, the tinnitus frequency could play an important role in the objective diagnosis of individuals with tinnitus, particularly for electrophysiological tests that involve attentional or pre-attentional mechanisms. If individuals are constantly attending to their tinnitus, then the presentation of an acoustic stimulus located at the tinnitus frequency may not be detected as a novel stimulus, and thus will result in a decreased amplitude and area under the curve for the

mismatch negativity and P300 when compared to age-, sex-, and hearing-matched controls presented with the same paradigms.

1.4 Objectives

The first objective of this study was to determine if there are differences in auditory evoked potentials between participants with tinnitus and controls matched for hearing, age, and gender. Specific aims of this objective were to determine if there are differences between tinnitus and non-tinnitus controls in (a) the peak-to-peak amplitudes or latencies of the P1N1, N1P2, and P2N2 of the ALR, (b) MMN amplitude and area under the curve, and (c) P300 amplitude and latency.

The second objective of this study was to determine if there is a relationship between the objective auditory evoked potentials and the subjective responses to the Tinnitus Handicap Inventory (THI) and Tinnitus Reaction Questionnaire (TRQ). Specific aims of this objective were to determine if scores on the TRQ and THI are correlated with ALR amplitudes and/or latencies, MMN amplitude and/or area under the curve, and P300 amplitude and latency.

1.5 Hypotheses

1. When the pitch-matched tinnitus frequency is used as the deviant stimulus, subjects with and without tinnitus will exhibit differences in ALR peak P1N1, N1P2, P2N2 peak-to-peak amplitude and latency, MMN amplitude and area under the curve, and P300 amplitude and latency due to the interference of their tinnitus percept.

2. Perceptions of tinnitus severity as measured by the TRQ and THI will show correlations with ALR, MMN, and P300 amplitude and latency measures and MMN area under the curve.

CHAPTER 2

MATERIALS AND METHODS

2.1 Participants

Behavioral and electrophysiological data were obtained from 10 participants with tinnitus (seven women; mean age 34.8 years; age range 24-59 years) and 10 non-tinnitus control participants (seven women; mean age 35.1 years; age range 24-53 years) matched for age, gender, and hearing status. The first group (tinnitus group) consisted of adults with a history of constant tinnitus for at least the last six months, and no greater than a moderate hearing loss in the region of their pitch-matched tinnitus frequency. To be included in the study, the participant's tinnitus had to have a tonal quality and be present bilaterally most of the time, particularly in quiet situations. A second group of adult participants without tinnitus were also recruited. This group served as the control group, and each subject was matched with a tinnitus participant based on sex, age, and hearing status from 250-12,500 Hz. Inclusion criteria for both group of participants included no contraindications to EEG testing, such as pacemakers, the use of central nervous system depressants or stimulants that could impact EEG responses or have middle ear pathology that affected hearing.

2.2 Audiological Test Battery

All participants signed an informed consent form approved by the university IRB prior to participating in the study. All participants completed a Tinnitus Case History while tinnitus participants also completed the TRQ and THI. All participants then completed a series of audiological tests in a sound attenuated booth to assess the integrity of their auditory system. First, otoscopy and tympanometry were performed to ensure the absence of outer or middle ear

pathologies that could impact subsequent audiological and EEG testing. Next, participants completed pure tone testing to assess their hearing thresholds using a GSI AudioStar Pro (Eden Prairie, MN) with extended high frequency capability. Using a modified Hughson-Westlake technique, thresholds were measured in half octave intervals from 250 Hz through 12,500 Hz using RadioEar DD450 circumaural headphones. This concluded audiological testing for the control participants.

All tinnitus participants were assessed using the exact protocol as above. If tinnitus participants exhibited a hearing loss that was greater than 45 dB HL at the pitch-matched tinnitus frequency, they were excluded from the study. Tinnitus participants that met the criteria then underwent a tinnitus test battery to assess the psychophysical perception of their tinnitus. First, a tinnitus pitch-matching procedure was used to determine the perceived frequency of the tinnitus participant (Vernon & Meikle, 1981). This test was performed by presenting a 1,000 Hz pure tone for several seconds, followed by a 2,000 Hz pure tone for approximately the same period of time at 10 dB sensation level (SL) relative to the individual's hearing threshold at each presented frequency. The participant then indicated which tone, tone one or tone two, seemed more similar to their perceived tinnitus. The frequencies of the tones were then bracketed up or down depending on the participant's response. The order of the tones was presented pseudorandomly so that the lower frequency was not always the first tone of the set that was presented. The test concluded whenever the participant broke the pattern of tone selection. For example, for tinnitus frequencies located above 1,000 Hz, the test concluded whenever the participants indicated that the lower of the two tones presented was more similar to their perceived tinnitus, and vice versa for individuals with lower-pitched tinnitus below 1,000 Hz. Due to equipment and physiological

limitations, participants were not eligible for the EEG portion of the study if they pitch-match a frequency that was greater than 10,000 Hz or lower than 500 Hz.

After the pitch-matching procedure, the perceived loudness of the participant's tinnitus was assessed using a loudness matching procedure (Vernon & Meikle, 1981). For this test, the participant was presented with two different frequency pure tones in each ear. The first tone was located at their tinnitus frequency while the second tone was located at 1,000 Hz, or at 3,000 Hz if the participant's tinnitus was located at 1,000 Hz. Both tones were initially presented at an intensity level that was below their hearing threshold at that frequency. The intensity was then increased in 2 dB steps until the participant indicated that the tone was just as loud as their tinnitus. This was repeated for each frequency tone and the two responses at each frequency were averaged together. The last test in the tinnitus test battery was a loudness discomfort level (LDL) obtained using Neuromonics Tinnitus Treatment Clinician's Guidelines (2008). The same tones used in the loudness matching procedure were used to obtain LDLs. The stimulus was initially presented at an intensity level below the participant's hearing threshold and was gradually increased in five dB steps until the participant indicated that the tone was just beginning to become uncomfortably loud. At this point the intensity was decreased by 10 dB and further increased in 2 dB steps until the participant indicated it had just become uncomfortably loud. Each LDL was repeated, and the responses averaged. After successful completion of the audiological test battery, participants then completed EEG portion of the study.

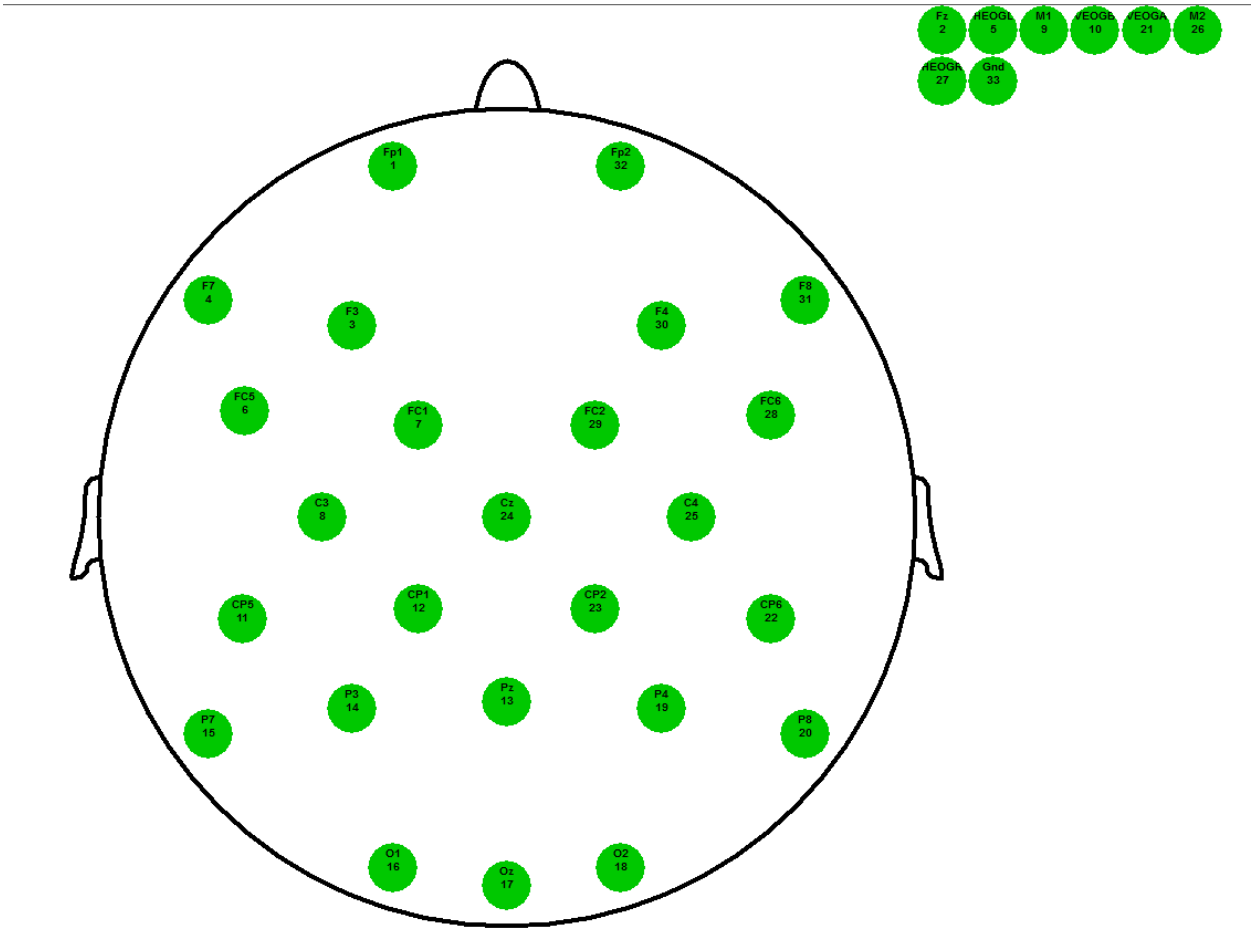
2.3 Electrophysiological Testing

EEG was recorded continuously (500 Hz sampling rate, online filter 0.01-100 Hz) in a quiet room using an actiCAP electrode cap (Brain Products, Germany) and BrainVision actiCHamp amplifier (Brain Products, Germany). 28 Ag/AGCL electrodes (Figure 5), each with

their own individual amplifier, were placed using the conventional 10-20 system. Two electrodes were placed at the outer canthi of the left and right eyes while an additional two electrodes were placed above and below the left eye to record eye movements. Impedances were kept below 10 kOhms using SuperVisc HighViscosity electrolyte gel. CAEPs were recorded with an online reference to FCz.

Figure 5

Electrode Montage



The EEG stimuli used were pure tones (sampling rate 44,100 Hz), created using Audacity software, with a 5 ms rise and fall time, 80 ms duration, and intensity level of 70 dB SPL. Stimuli intensities were calibrated using a Larson Davis 824 sound level meter and Knowles

Electronic Manikin for Acoustic Research and were presented through ER3A insert earphones. Each control participant completed the electrophysiological testing using the same parameters as their matched tinnitus counterpart.

Three custom test protocols were designed using EPrime 2.0 software (Psychology Software Tools, Pittsburgh, PA). For the first protocol, participants sat comfortably in a chair and were told to ignore the stimuli while watching a silent movie or TV show of their choice with subtitles. An auditory late response was elicited using 400 stimuli located at the tinnitus participant's pitch-matched frequency, presented binaurally at a rate of 1.1/s. The duration of this test was approximately 10 minutes. Each control matched for age, gender, and hearing thresholds underwent the same protocol as their paired tinnitus participant. The waveform generated by this protocol was then used as the standard waveform for the MMN calculation. This allowed for elimination of potential differences in the waveforms generated in the standard and deviant stimuli caused by activation of different neural populations by ensuring all the waveforms used were generated by the same frequency stimulus.

For the next protocol, a simple oddball paradigm was used to evoke an MMN response. The standard stimulus was located at a frequency that was 10% lower than the pitch-matched tinnitus frequency, while the deviant stimulus was located at the tinnitus frequency. This relation between the standard and deviant stimulus was recommended by Duncan et al. (2009) and has been used by multiple studies utilizing the MMN paradigm (Holdefer et al., 2013; Mahmoudian et al., 2013; Mohebbi et al., 2019). A total of 1010 stimuli were pseudorandomly presented binaurally so that the first 10 stimuli were standards and there were at least two standards presented between every deviant stimulus in an 80/20 standard to deviant ratio. This portion of the test took approximately 20 minutes to complete.

The final test protocol utilized an oddball paradigm to evoke a P300 response. 400 stimuli were presented in an 80/20 standard-to-deviant ratio with the standard located at 1,000 Hz, unless the tinnitus frequency was located at 1,000 Hz, in which case 3,000 Hz was used. Using a higher frequency as the standard stimulus allowed for a greater degree of separation from the standard stimulus, thus decreasing the difficulty of distinguishing between the two tones. The deviant stimulus frequency was set at the tinnitus subject's pitch-matched tinnitus frequency. Participants were instructed to push the '3' key on a keyboard whenever they heard the deviant stimulus. All subjects were tested on their ability to successfully discriminate between the two tones prior to testing. Participants were instructed to look at a '+' fixation cross on a computer directly in front of them to help minimize unwanted eye movements. This portion of the test lasted approximately 15 minutes.

2.4 CAEP Data Analyses

CAEP data were processed offline using the EEGLAB toolbox (Delorme & Makeig, 2004) in the MATLAB (Mathworks, Natick, MA) software. First, VEOG and HEOG channels were removed from the analysis. CAEPs were then filtered using a 0.1-30 Hz bandpass filter. Blind source separation Independent Component Analysis in EEGLAB (Bell & Sejnowski, 1995) using both temporal and spatial component maps. Data were then re-referenced to linked mastoids and artifact rejection set at +/- 50 µV for the processing of ALR and MMN waveforms and +/- 100 µV for P300 waveforms. Channels not located in the frontocentral or parietal regions of interest were interpolated as needed to help improve the number of averaged waveforms. Epochs of 600 ms duration with a 100 ms pre-stimulus baseline were extracted and baseline corrected for the ALR and MMN waveforms. An MMN difference wave was calculated by subtracting the CAEP waveform generated when only the deviant is present (the ALR

waveform) from the CAEP waveform generated by the deviant stimuli in the oddball paradigm. This helped reduce the exogenous effects caused by differences between the standard and deviant stimuli (Kujala et al., 2007), resulting in a more accurate MMN. Epochs for the P300 responses were 800 ms in duration with a 100 ms pre-stimulus baseline. The P300 difference wave was calculated by subtracting the waveforms generated by the standard stimuli from those generated by the deviant stimuli.

The MMN is the largest over the central midline and parasagittal electrodes (Lang et al., 1995; Schröger, 1998), so this region was selected for analysis of the ALR and MMN responses. Based on previous literature reporting P300 being largest at Cz (Johnson, 1993) and findings from the current study, Cz was selected for analysis of the P300 waveform. Peak latencies, amplitudes, and area under the curve were identified on the processed data using custom Matlab scripts. P1 was labeled as the largest positive peak in the 50-80ms region, N1 was the most negative peak in the 80-120ms region, P2 was the most positive peak in the 160-200ms time region, N2 was the most negative peak in the 200-250ms time regions, the MMN amplitude was the most negative peak in the difference waveform in the 100-250ms time region, and the P300 was the most positive peak in the 250-400 ms time region (Duncan et al., 2009; Moore, 1983). In the event of a triple peak P300 response, the middle of the peaks was selected.

2.5 Statistical Analyses

Statistical analysis was performed using SPSS v.28 (Armonk, NY). Separate linear mixed-effect (LME) regression analyses were used to examine the relationships between perceived tinnitus impact, as measured by the THI, TRQ, and tinnitus perception measures, and electrophysiological responses. As there is a high degree of correlation between the subjective tests, which violates the assumption of independence of data required for simple Pearson

correlations, a linear mixed-effect regression analysis is the preferred method of analysis (Koener & Zhang, 2017). Tinnitus participant group was included as the random variable while electrophysiological and behavioral data were included as the fixed variables. The data were split into blocks that were then further evaluated with LME models, with the electrophysiological measures serving as the independent variables and the behavioral measures acting as the dependent variables. Dividing the data into the three blocks reduced the degrees of freedom of the model, which was needed due to the relatively small number of subjects. A separate LME model was run for each dependent variable in each block. The first block evaluated the relationship between ALR latency measures for P1, N1, P2, and N2 and behavioral tinnitus measures. The second block evaluated the relationships between ALR amplitude measures and behavioral tinnitus measures. The third block evaluated the relationships between MMN and P300 amplitudes and latencies and behavioral tinnitus measures. An Akaike Information Criterion (AIC) was then calculated using the maximum likelihood ratio to determine which independent variables best modeled the dependent variable. The model that had the lowest AIC value and was at least two points lower than the previous model was further evaluated (Burnham & Anderson 2004).

Amplitudes for P1N1, N1P2, and P2N2 components of the ALR were measured from peak to trough. The amplitude data for P1N1, N1P2, and P2N2 were analyzed using a repeated-measures analysis of variance (ANOVA; Cheek & Cone, 2020). Separate one-way analyses of variance tests were used to determine if there were group differences between tinnitus and non-tinnitus groups for MMN amplitude, MMN area under the curve, and P300 amplitude and P300 latency. Equality of variance was assessed using Levene's test for equality of variance.

A global field power (GFP) analysis comparing MMN difference waveforms was also completed. The most used references for examining the MMN are the nose and linked mastoids (Duncan et al., 2009). However, the reference electrode chosen can impact the overall morphology and amplitudes values of the ERP (Lehman & Skrandies 1984). A GFP addresses this problem by examining the entire cortical response to the stimulus across all electrodes simultaneously at each time point (Lehman & Skrandies, 1980). Differences in GFP between MMN and P300 waveforms for tinnitus and non-tinnitus subjects were compared via methodology utilized previously by Miller & Zhang (2014). Root mean square (RMS) values were calculated for the tinnitus and control MMN waveforms utilizing the responses from all electrodes at each time point (500 ms post stimulus baseline and 100 ms prestimulus baseline). From these values z scores were calculated for the post stimulus baseline relative to the prestimulus baseline. Each data point in the post stimulus baseline was compared using a Bonferroni correction factor to account for the number of samples in the poststimulus response ($p < .01$). Given the large number of comparisons that are being made, a minimum of 10 consecutive points with p values of less than .01 were required before differences between the two waveforms were considered significant (Miller & Zhang, 2014; Zhang et al., 2011).

CHAPTER 3

RESULTS

3.1 Introduction

The primary objective of this study was to determine if a series of electrophysiological tests incorporating the participants' pitch-matched tinnitus frequency could be used to differentiate between participants with tinnitus and controls matched for age, gender, and hearing loss who did not have tinnitus. A secondary objective was to evaluate potential relationships between subjective perceptions of tinnitus, as measured by questionnaires and self-reports, and objective electrophysiological measures. The third tinnitus participant was noted to have significant alpha wave activity in the raw EEG data for all conditions, which was confirmed using topographic maps and on subsequent processed waveforms. Large fluctuations of more than 4 μV were present in the deviant prestimulus baselines. To assess if the presetimulus baseline for the third tinnitus participant for the MMN deviant condition significantly deviated from the group average, the RMS was calculated for the prestimulus baseline for the T3 participant and for the group average, not including T3. These were then compared using an independent two sample *t*-test and found to be significantly different $t(50) = 108$, $p < .001$. The mean of the group average RMS values was then treated as a population mean, and a one sample *t*-test was used to compare the RMS values for the third tinnitus participant. The third tinnitus participant exhibited higher RMS values ($M = .939$, $SD = .434$) than the group average $t(50) = 13.2$, $p < .001$. This, in combination with visual inspection of the data resulted in the third tinnitus participant being treated as an outlier and subsequently removed from further analyses. The range of trials after EEG artifact rejection for the tinnitus and control groups for each condition are listed in Table 2.

Table 2

Range of Trials Remaining for Each Condition After Artifact Rejection

	S2	S3	S4	S5
Total possible trials	322	200	78	400
Control	197-321	181-200	52-78	292-399
Tinnitus	211-372	96-199	60-89	252-399

S2 = the standard P300 trials, S3 = the MMN deviant trials, S4 = the P300 deviant trials, S5 = the ALR and MMN standard trials.

3.2 Demographic Measures, Case History, and Behavioral Measures

Demographic and tinnitus survey information are described in Table 3. There were seven females and three males in the tinnitus group who were matched with seven males and three females in the control group, for a total of twenty participants in this study; however, one subject pair was removed from analysis. Subjects ranged in age from 24-59 years (M=34.8, SD = 12.9) for the tinnitus group and 24-53 years (M = 35.1, SD = 13.3) for the control group. A paired t-test indicated there was no significant difference in age between the tinnitus and control groups [$t(9)$= -0.312, p = 0.763]. For the tinnitus participants, on average, tinnitus symptoms were noticed 56% of the time they were awake, and the average percentage of time the tinnitus was considered bothersome was 19%. 70% of the tinnitus participants reported their tinnitus preventing sleep at least once.

As depicted in Table 3, tinnitus participants' scores on the TRQ ranged from 0-44 (M = 19.4, SD = 14.9) while scores on the THI ranged from 8-64 (M = 28.7, SD = 19.1). For the TRQ, a score of 0-16 indicates slight perceived handicap, 18-36 indicates a mild perceived handicap, 38-56 indicates a moderate perceived handicap, 58-76 indicates a severe perceived handicap, and a score of 78-100 indicates a catastrophic perceived handicap (McCombe et al., 2001). The THI operates on a nearly identical scale, with scores of 0-16, 18-36, 38-56, 58-76, and 78-100

indicating a perceived tinnitus handicap of not bothersome/slight, mild, moderate, severe, and catastrophic, respectively (Wilson et al., 1991). Based on these criteria, for the TRQ, five participants classified their tinnitus as none to slight, four classified their tinnitus as mild, and one classified their tinnitus as moderate. For the THI, five participants described their tinnitus as causing none to slight handicap, two classified their tinnitus as causing a mild handicap, two described their tinnitus as causing a moderate handicap, and one described their tinnitus as causing a severe handicap.

Table 3

Demographic Information for all Participants and Tinnitus Information for Tinnitus Participants

Gender	Control participants age (yrs)	Tinnitus participants age (yrs)	Has tinnitus prevented sleep	TRQ scores	THI scores
F	28	29	No	7	14
F	25	26	No	4	10
F	26	25	Yes	25	36
M	54	59	Yes	44	64
F	22	25	No	0	8
F	25	24	Yes	31	38
M	45	40	Yes	29	32
F	53	49	Yes	9	12
M	49	47	Yes	26	44
Average	36.3	36.0		19.4	28.6
SD	13.5	13.1		14.9	19.0

F = female, M = male. TRQ = Tinnitus Reaction Questionnaire; THI = Tinnitus Handicap Inventory; SD = 1 standard deviation from the average

Table 4 describes case history information collected on patients' tinnitus characteristics. The range of tinnitus duration for the tinnitus participants was 2-50+ years, with two participants reporting they had experienced tinnitus as long as they can remember. Most participants found

their tinnitus disturbing at least some of the time (n = 7), and 2 participants did not provide a response to this question. Noise exposure was the most perceived etiology of the participants' tinnitus (n = 5), followed by stress/anxiety, genetics, hearing loss, and idiopathic etiology (n = 1 for each). Exacerbating factors were variable from person to person and included emotions, stress, loud noises, environments, lack of sleep, quiet situations, and alcohol; the most common alleviating factor was some type of competing acoustic stimulus, such as masking noises or music (n = 6), while three participants reported there were no factors that were able to alleviate their tinnitus.

Table 4

Descriptive Characteristics of the Tinnitus as Reported by Participants on the Case History

Subject	Tinnitus duration	Is the tinnitus disturbing	Perceived Etiology	Exacerbating factors	Alleviating factors
T1	"Always"	In quiet	Stress/anxiety	Emotions	Noise, music
T2	8-9 years	N/A	Noise exposure	Loud noises, congestion	None
T4	"Always"	"Always"	Genetics	None	Other sounds
T5	50+years	In quiet	Unknown	Loud environments	Masking, relaxation
T6	4 years	N/A	Noise exposure	Alcohol, lack of sleep	None
T7	11 years	Yes	Noise exposure	Stress	Sleep
T8	11 years	Yes	Noise exposure	Emotions, stress, exhaustion, alcohol, loud environments	None
T9	7-8 years	Occasionally	Hearing loss	Caffeine, salt, lack of sleep, stress	Masking
T10	2 years	Yes	Noise exposure	Depression	Background noise

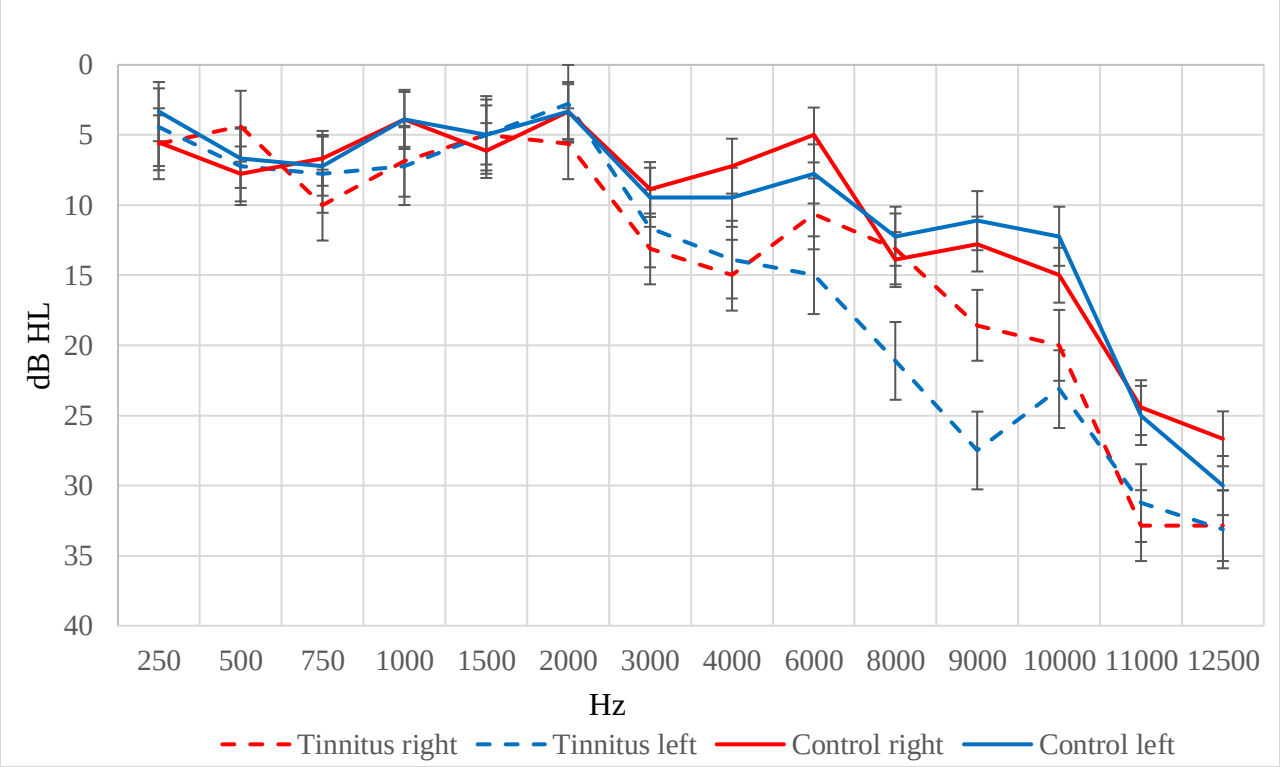
3.3 Audiometric Thresholds

Audiometric thresholds were obtained for frequencies from 250-12,500 Hz in each ear separately at inter-octave intervals and are shown in Figure 6. There were no significant differences between right ear and left ear audiometric thresholds within the two groups, as

indicated by a two-way repeated measures ANOVA utilizing a Bonferroni correction factor for multiple comparisons ($p > .05$ for all frequencies), so the two ears were collapsed for further analysis. A two-way repeated measures ANOVA, utilizing a Bonferroni correction factor, comparing the average left and right ear thresholds for each frequency between the tinnitus and control groups did not reveal any significant differences for any frequency ($p > .05$ for all frequencies).

Figure 6

Average Audiograms for Tinnitus and Control Participants



Error bars represent 1 standard deviation of the mean

3.4 Pitch and Loudness Matching

Pitch and loudness matching data as well as the percentage of time tinnitus was noticed and was bothersome are listed in Table 5. The pitch-matched tinnitus frequency ranged from 1,000-10,000 Hz (Left ear: M = 4,844 Hz, SD = 3,907 Hz; Right ear: M = 4,778, SD = 3,598)

among the nine tinnitus subjects. Loudness matching (calculated by subtracting the audiometric threshold at the loudness matching frequency from the perceived loudness level) ranged from 5-26 dB SL (*M* = 11.3 dB, *SD* = 6.5 dB). The percentage of the time that the tinnitus participants noticed their tinnitus when awake ranged from 10% to 100% (*M* = 59%, *SD* = 38%) while the percentage of the time that the tinnitus was bothersome to the tinnitus participants ranged from 0-50% (*M* = 19%, *SD* = 19%).

Table 5

Pitch-Matching and Percentage of the Time the Participant's Tinnitus was Bothersome

Participant	Pitch-match left (Hz)	Pitch-match right (Hz)	Percent of time tinnitus is noticed	Percent of time tinnitus is bothersome	LM at dominant tinnitus frequency (SL)
1	3,000	3,000	20%	10%	17.5 dB
2	10,000	10,000	20%	3%	10 dB
4	750	1,000	30%	25%	10 dB
5	1,000	1,000	100%	50%	26 dB
6	10,000	10,000	100%	0%	6.5 dB
7	2,000	3,000	60%	10%	10.5 dB
8	4,000	3,000	90%	50%	8.5 dB
9	Variable	4,000	100%	13%	8 dB
10	8,000	8,000	15%	10%	5 dB
Average	4,844	4,778	59%	19%	11.3 dB
SD	3,907	3,598	38%	19%	6.5 dB

SD = 1 standard deviation from the average, PM AS = left ear pitch-match, PM AD = right ear pitch-match, LM = loudness match.

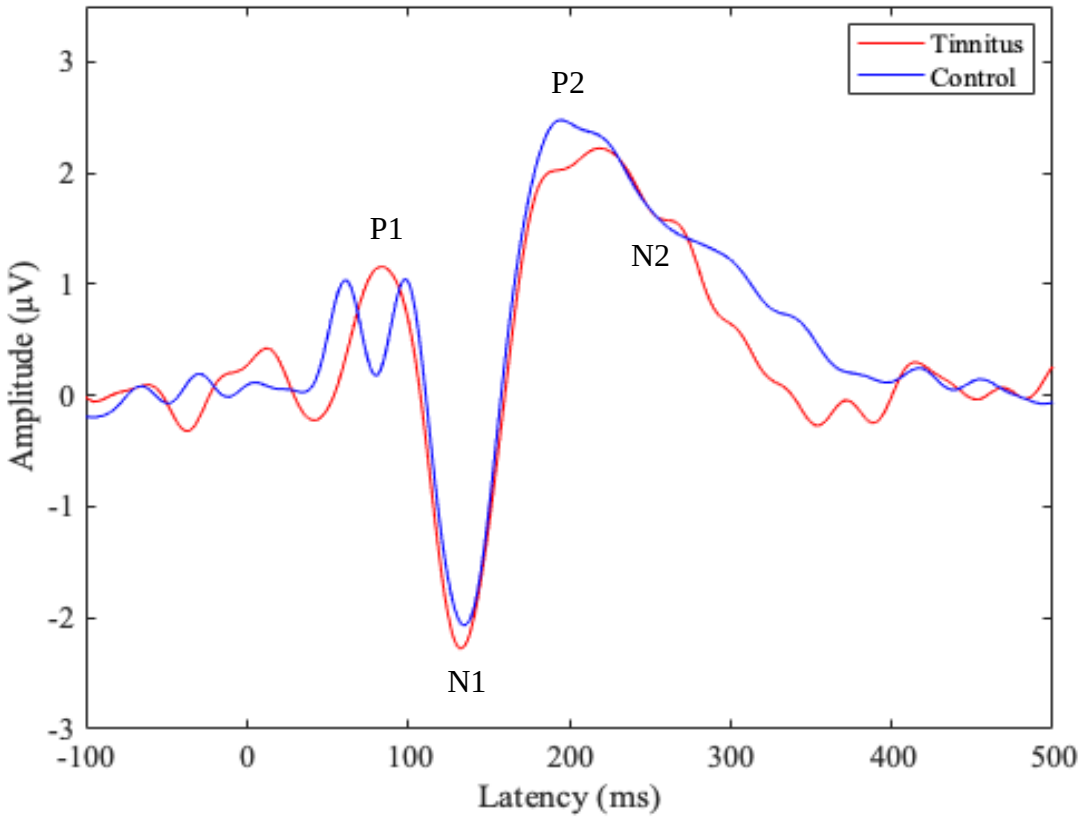
3.5 Auditory Late Responses

The grand average waveforms for the tinnitus and control groups that were evoked in the ALR paradigm are shown in Figure 7. Individual peak latency and amplitude values are listed in Table 6. In general, control participants exhibited larger peak-to-peak amplitudes for P1N1,

N1P2 and P2N2. A two-way repeated-measures ANOVA was performed to compare the effect of peak-to-peak amplitude of P1N1, N1P2, and P2N2 on group membership. Mauchly's test of sphericity indicated that the assumption of sphericity had not been violated $X^2(2) = 5.85$, $p = .054$. There was not a statistically significant difference between groups with respect to peak-to-peak amplitudes $F(1, 2) = .170$, $p = .686$, $n_p^2 = .10$. A One-way ANOVA was used to compare latency measures between the two groups. The groups were not significantly different for P1 $F(1, 16) = .719$, $p = .409$, $n_p^2 = .043$, N1 $F(1, 16) = .730$, $p = .406$, $n_p^2 = .044$, P2 $F(1, 16) = .031$, $p = .863$, $n_p^2 = .002$, or N2 $F(1, 16) = .274$ $p = .608$, $n_p^2 = .017$.

Figure 7

Average ALR Waveforms at Cz



P1 = the first positve peak, N1 = the first negative peak, P2 = the second positive peak, N2 = the second negative peak

Table 6

Amplitude and Latency Values at Cz for P1N1, N1P2, and P2N2 Measures for the Tinnitus and Control Groups

Subject	C_P1N1 amp	T_P1N1 amp	C_N1P2 amp	T_N1P2 amp	C_P2N2 amp	T_P2N2 amp	C_P1 lat	T_P1 lat	C_N1 lat	T_N1 lat	C_P2 lat	T_P2 lat	C_N2 lat	T_N2 lat
1	6.4	9.0	5.7	9.1	1.3	4.2	58	100	146	138	244	204	221	229
2	2.3	1.2	3.1	2.3	2.4	2.2	66	94	114	140	250	192	187	211
4	9.3	7.2	12	10	15	6.6	106	86	136	138	188	226	249	297
5	4.0	5.4	8.1	6.0	3.4	6.0	94	98	140	150	230	232	261	259
6	2.2	1.9	1.2	0.6	1.2	1.1	100	78	146	52	220	204	241	231
7	4.4	5.5	6.4	8.0	9.0	5.0	110	72	136	126	184	236	231	289
8	6.8	3.4	5.8	4.8	2.9	2.2	64	90	148	136	222	250	239	199
9	4.1	2.4	6.5	4.1	2.3	2.1	66	76	130	142	196	200	263	255
10	1.3	1.6	2.6	2.7	2.3	2.1	54	86	130	124	214	220	257	243
Average	4.5	4.2	5.7	5.3	4.4	3.5	80	87	136	127	216	218	239	246
Standard deviation	2.5	2.7	3.2	3.3	4.5	2.0	22	10	11	29	23	19	24	33

C = control, T = tinnitus, SD = standard deviation, amp = amplitude, lat = latency, amplitude measures are in microvolts, latency measures are in milliseconds.

3.6 Mismatch Negativity

Group average MMN waveforms are shown in Figure 8. Individual MMN latency and amplitude measures are shown in Table 7. The general trends observed in the tinnitus group included smaller amplitude and AUC values as well as shorter latencies compared to the control group. A One-way ANOVA was used to compare MMN amplitude, area under the curve, and latency between the two groups.

Table 7

Amplitude and Latency Values for the MMN Measures at Cz for the Tinnitus and Control Groups

Participant	C_MMN amp (µV)	T_MMN amp (µV)	C_MMN lat (ms)	T_MMN lat (ms)	C_AUC	T_AUC
1	-6.6	-4.2	210	192	389	245
2	-2.8	-1.7	256	236	267	83
4	-4.5	-3.5	176	228	401	117
5	-3.7	-1.2	238	176	228	66
6	-2.9	2.1	222	208	189	75
7	-5.7	-2.7	220	136	554	82
8	-4.3	-4.0	216	220	263	359
9	-1.9	-0.6	290	168	63	32
10	-4.6	-3.8	234	224	255	301
Mean	-4.1	-2.7	229	198	290	151
SD	1.4	1.2	30	31	134	112

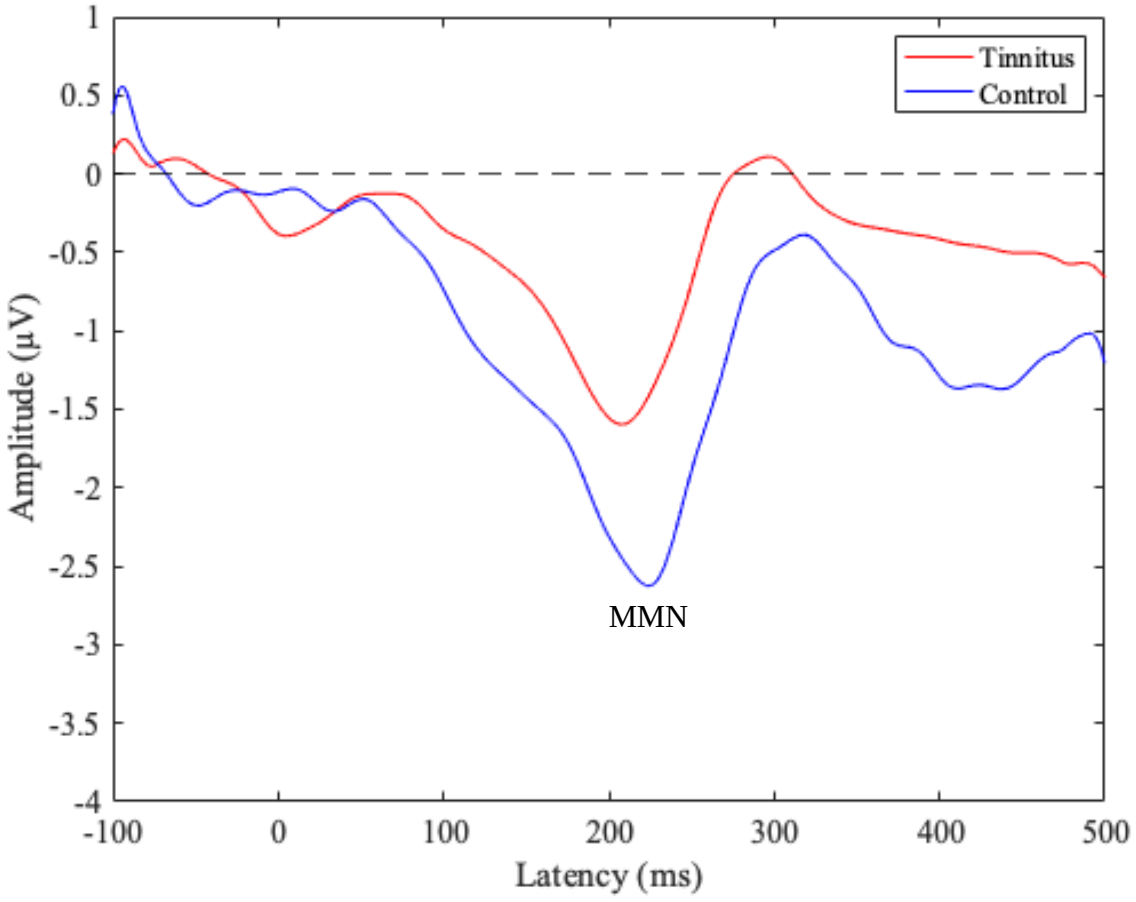
T = tinnitus group, C = control group, amp = amplitude, lat = latency, AUC = area under the curve, µV = micro volts, ms = millisecond, SD = 1 standard deviation from the mean

Levene's test of homogeneity of variance was not significant for any of the measures, indicating homoscedasticity of the data. Differences in MMN amplitudes were found to be statistically

significantly different between the two groups [$F(1, 16) = 4.803$, $p = .044$, $\eta^2 = .231$] as well as differences in MMN area under the curve [$F(1, 16) = 4.773$, $p = .044$, $\eta^2 = .230$]]. Average MMN latency was earlier for the tinnitus group, but the difference just failed to reach significance [$F(1, 16) = 3.951$, $p = .064$, $\eta^2 = .198$]. Between the three measures, 65.9% of the variance in the model was explained.

Figure 8

Average MMN Waveforms at Cz

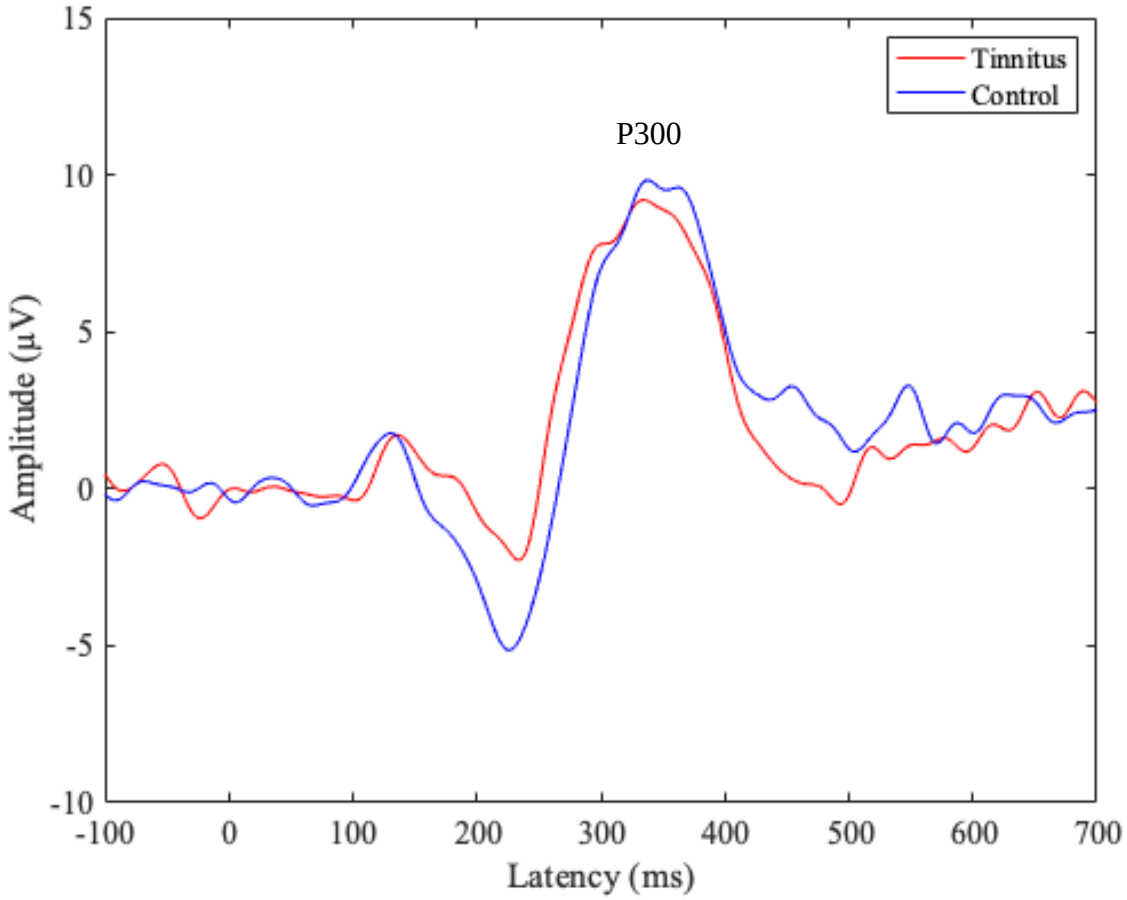


3.7 P300

Group average P300 waveforms are shown in Figure 9. Individual P300 latency and amplitude measures are shown in Table 8. In general, P300 amplitude values were smaller for the tinnitus group compared to the control. No discernable trends were present in the latency values. A one-way ANOVA was used to compare P300 amplitude and latency between the two groups.

Figure 9

Average P300 Waveforms at Cz



Levene's statistics was not significant for either measure, indicating homoscedasticity of the data. There was not a statistically significant difference for P300 amplitude [$F(1, 16) = .669$, $p = .425$, $\eta 2 = .040$] nor P300 latency [$F(1, 16) = .043$, $p = .838$, $\eta 2 = .003$], and these measures only accounted for 4.3% of the variance in the model.

Table 8

Amplitude and Latency Values for the P300 measures at Cz for Tinnitus and Control Groups

Participant	T_P300 amp (µV)	C_P300 amp (µV)	T_P300 lat (ms)	C_P300 lat (ms)
1	3.5	16.9	364	362
2	13.1	18.2	330	376
4	22.2	4.3	366	306
5	10.8	15.5	384	296
6	15.2	19.3	302	362
7	5.2	11.3	314	448
8	10.0	10.8	336	310
9	11.6	11.3	384	336
10	10.6	12.3	376	396
Mean	11.4	13.3	351	354
SD	5.14	4.40	29.12	46.1

T = tinnitus group, C = control group, amp = amplitude, lat = latency, AUC = area under the curve, µV = microvolts, ms = millisecond, SD = 1 standard deviation from the mean

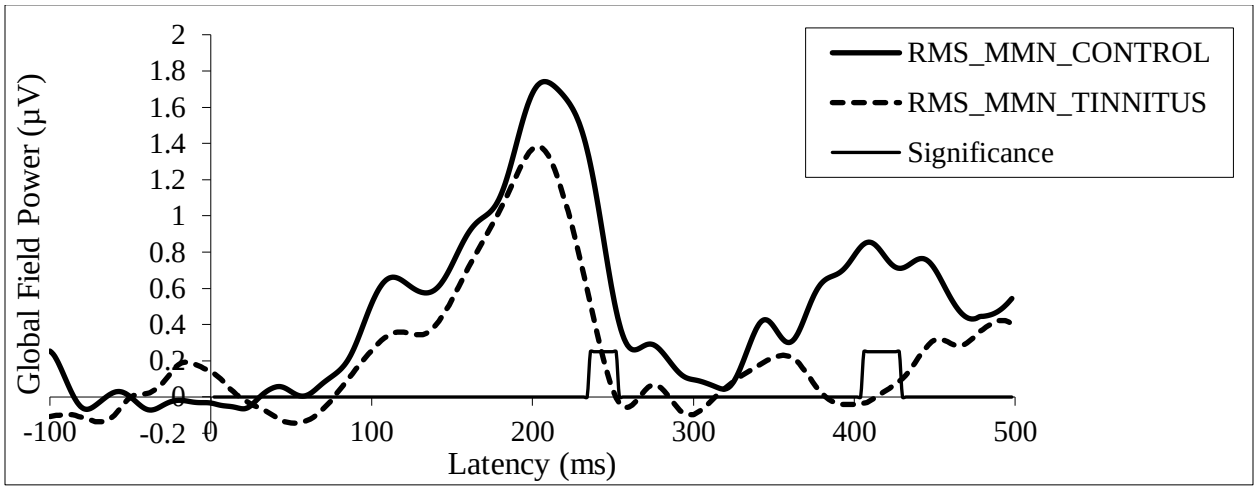
3.8 Global Field Power Analysis

GFP analysis of the grand average ALR waveforms (see Appendix) did not reveal any significant differences in RMS values between the two groups as defined by the criteria in the methods section. GFP analysis of the grand mean MMN waveforms in each group (Figure 10)

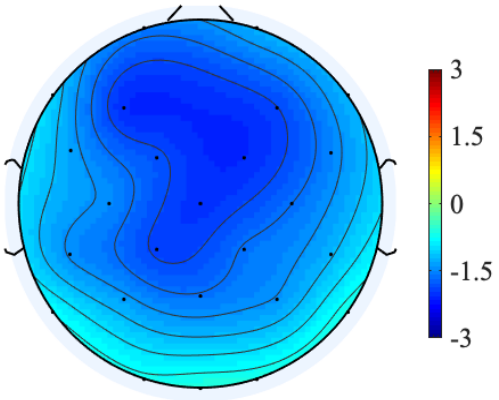
revealed significant differences in the 250 ms time region, which agrees with the ANOVA results. Significant point-by-point differences in MMN amplitude ($p<.01$) between the two groups were observed in the 236-252 ms time window, with the control group exhibiting larger point-by-point amplitudes; however, after baseline correction, only nine consecutive sample points were significantly different, which was just shy of the required 10 sample points needed for the point-by-point analysis to be considered significant in that time region. Point-by-point MMN GFP amplitudes were also significantly different in the 406-428 ms region, with the control group exhibiting significantly greater amplitudes. Topographic maps of the MMN in the 250 ms time region, which contained the largest differences between the two groups in the GFP, demonstrate a higher, broader area of frontocentral activation in the control group compared to the tinnitus group. GFP analysis of the average P300 waveforms and topographic maps (Figure 11) revealed significant differences between the two groups in the 182-238 ms time window, with the control group exhibiting larger amplitudes; the 256-302 ms time window, with the tinnitus group exhibiting larger amplitudes; and the 460-484 ms time window, with the tinnitus group exhibiting larger amplitudes. Topographic maps demonstrated differences in the spatial neural activity between the two groups at multiple time points in the cortical responses, with the tinnitus group exhibiting more parietal neural activity in the 260 ms and 350 ms time windows compared to the control group.

Figure 10

MMN GFP and Topographic Maps



Latency 250 ms from MMN Control Group



Latency 250 ms from MMN Tinnitus Group

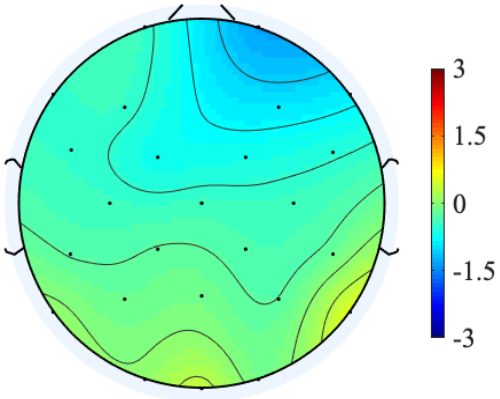
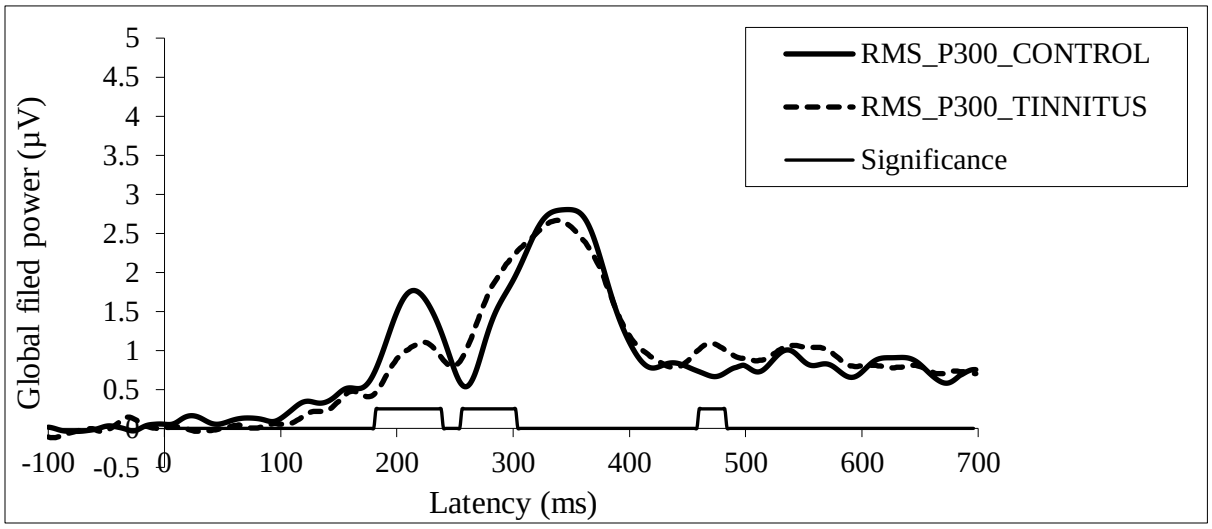
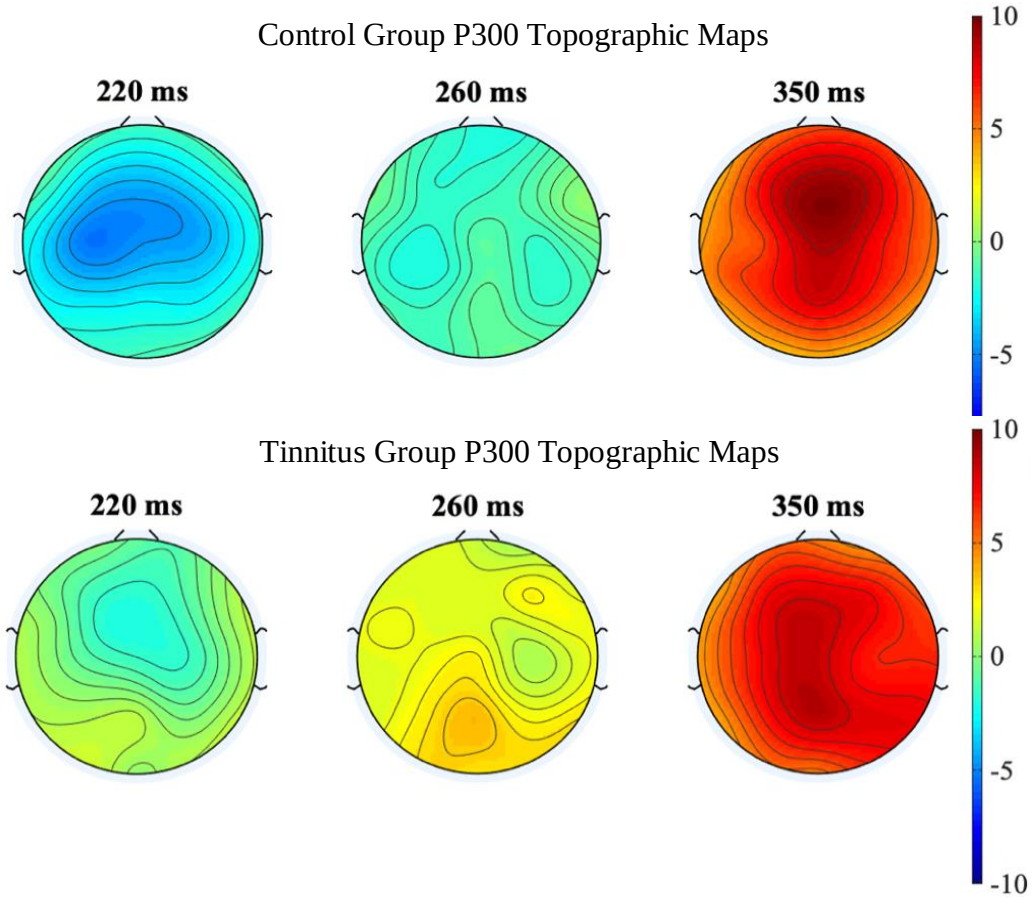


Figure 11

P300 GFP and Topographic Maps





3.9 Relationships Between Behavioral and Electrophysiological Data

As concrete relationships between electrophysiological data and perceived tinnitus severity have not been found, an exploratory approach was used to assess which of the independent variables in each block best modeled the dependent variable. LME regression models were used to evaluate the relationships between behavioral and electrophysiological data in the tinnitus group. The data were split into blocks that were then evaluated with separate LME models. Dividing the data into the three blocks reduced the degrees of freedom of the model, which was needed due to the relatively small number of subjects. The behavioral tinnitus outcome data were the dependent variables in the models tested. Regression weights and significance values for each LME regression analysis evaluating the relationship between ALR latencies and THI scores, TRQ scores, percent of the time tinnitus is noticed, and percent of the time tinnitus is bothersome are listed in Table 9.

For prediction of THI and TRQ, after performing an LME fit by maximum likelihood, the N1 latency was removed from each of the models. In the best reduced model, P2 latency was a significant predictor of THI score [$F(1,5)= 10.5$, $p =.02$] with a β value of 0.64, indicating an increase in THI score of 0.64 points for every 1ms increase in latency. Likewise, P2 latency was also a significant predictor of TRQ score, [$F(1,5)= 23.2$, $p =.005$] with a β value of 0.60, indicating an increase in TRQ score for every 1 ms increase in latency. For prediction of percent of the time the tinnitus was bothersome, P2 was a significant [$F(1,5)= 9$, $p =.04$] with a β value of 0.01, indicating an increase of 1% of the time the tinnitus is bothersome for every 1 ms increase in P2 latency. P2 latency was not a significant predictor of the time the tinnitus is noticed [$F(1,5)= .42$, $p =.55$], $\beta = 0.01$. Scatter plots depicting the relationship between P2

latencies and THI, TRQ, and percentage of the time the tinnitus is bothersome are shown in Figures 12, 13, and 14.

Table 9

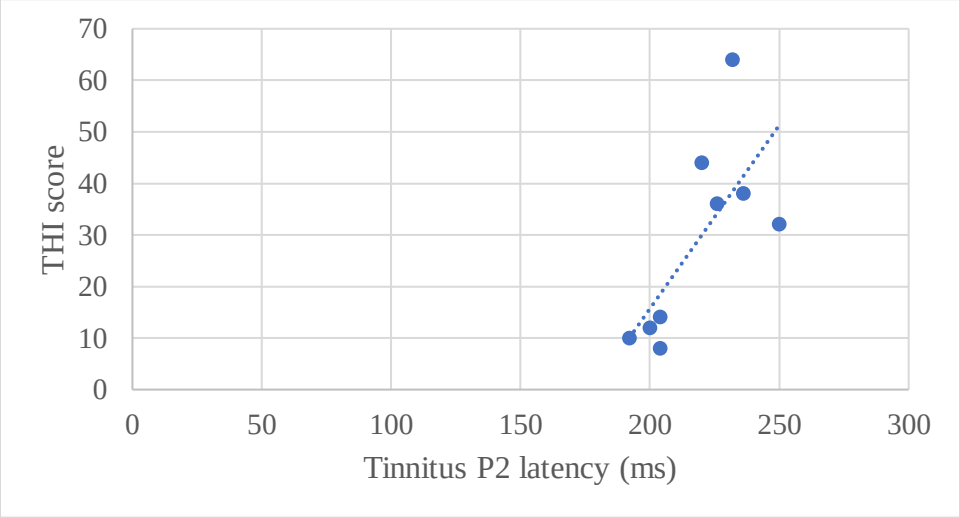
LME Model for Prediction of ALR Latencies on Subjective Measures

Variable	THI			TRQ			% Noticed			% Bothersome		
	F	*β*	*p*	*F*	*β*	*p*	*F*	*β*	*p*	*F*	*β*	*p*
Intercept	49.5			61.4			14.3			20.3		
P1_lat	0.7	0.81	.44	0.41	0.47	.55	0.57	-0.01	.49	2.7	0	.18
N1_lat	-	-	-	-	-	-	0.09	0	.78	2.1	0	.22
P2_lat	10.5	0.64	.02*	23.2	0.6	<.01**	0.42	0.01	.55	9	0.01	.04*
N2_lat	3.3	0.27	.13	3.5	0.17	.11	0.22	0	.67	0.08	0	.79

* = significance at the .05 level, ** = significance at the .01 level, THI = Tinnitus Handicap Inventory, TRQ = Tinnitus Reaction Questionnaire, Amp = amplitude, P1N1 = Peak to peak amplitude from P1 to N1, N1P2 = peak to peak amplitude from N1 to P2, P2N2 = peak to peak amplitude from P2 to N2.

Figure 12

Scatterplot of THI vs Tinnitus P2 Latency

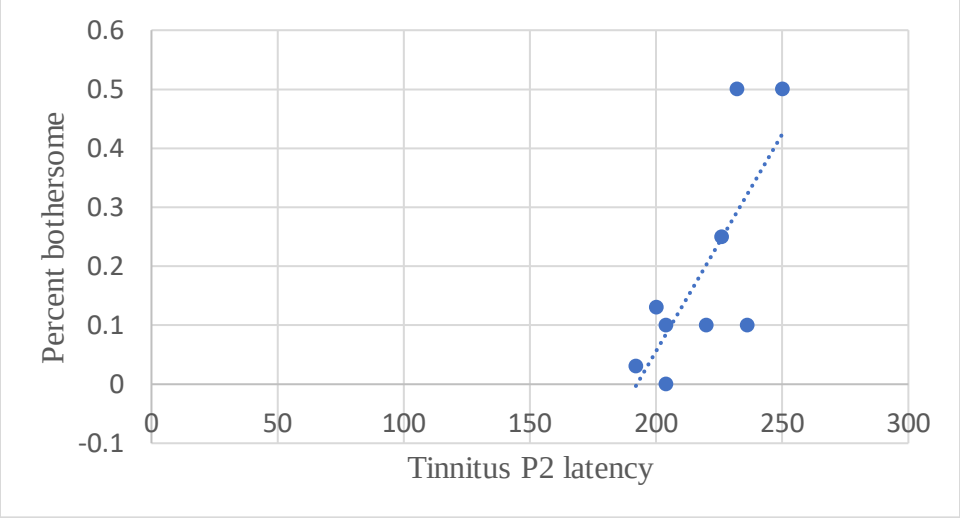


P1 and N2 latency were also included as fixed effects in the final reduced models because they explained additional variance and minimized the AIC. Results indicated P1 latency was not a significant predictor of THI scores [$F(1,5)= 0.81$, $p = .44$; $\beta = 0.01, .81$], TRQ scores [$F(1,5)= .41$, $p = .55$; $\beta = 0.47$], percent of the time tinnitus is noticed [$F(1,5)= .57$, $p = .49$; $\beta = -0.01$], or percent of the time the tinnitus was bothersome [$F(1,5)= 2.7$, $p = .18$; $\beta = 0$]. N2 latency was not a significant predictor of THI scores [$F(1,5)= 3.29$, $p = .13$; $\beta = 0.27$], TRQ scores [$F(1,5)= 3.5$, $p = 0.11$; $\beta = 0.17$], percent of the time tinnitus is noticed [$F(1,5)= .22$, $p = .67$; $\beta = 0$], or percent of the time the tinnitus was bothersome [$F(1,5)= 0.08$, $p = .79$; $\beta = 0$].

The second block of LME models evaluated the relationship of ALR amplitude measures for prediction of behavioral tinnitus data. Regression weights and significance values for the LME regression model with the lowest AIC value that was at least two points lower than the previous model for each dependent variable are listed in Table 10.

Figure 13

Scatterplot of Percent Tinnitus Bothersome vs Tinnitus P2 Latency

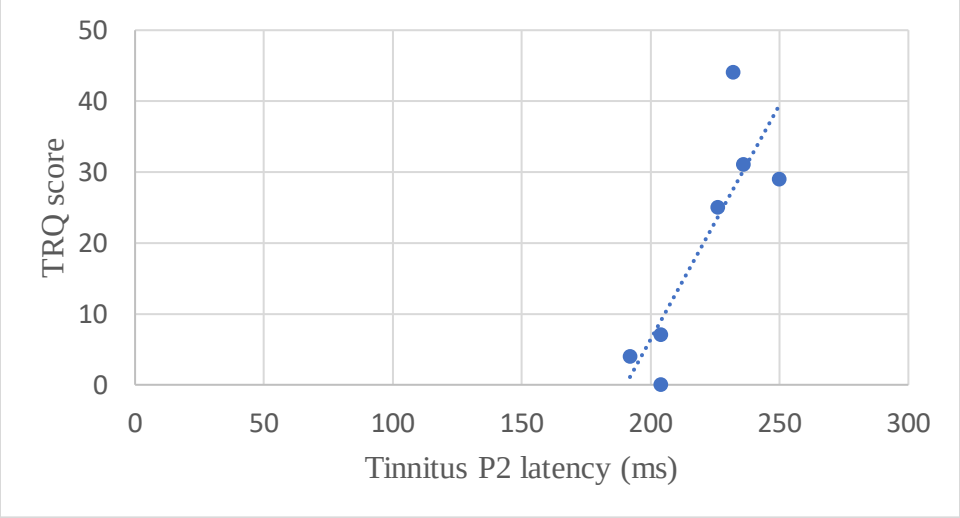


After performing the LME fit by maximum likelihood, the model with the lowest AIC dropped the N1P2 amplitude variable for the LME evaluating the relationship between ALR amplitudes

and THI scores. Results of the model indicate P2N2 amplitude being a significant predictor of THI scores [$F(1,6)= 6.68$, $p =.04$, $\beta = 11.0$], while P1N1 amplitude was not a significant predictor [$F(1,6)= 0.70$, $p =.43$, $\beta = -4.74$]. Scatter plots depicting the relationship of P2N2 amplitude and THI score are shown in Figure 15. The P1N1 amplitude measure was not a significant predictor of TRQ [$F(1,5)= 0.72$, $p =.43$], $\beta = 4.0$, nor was N1P2 amplitude [$F(1,5)= 2.0$, $p = .22$], $\beta = 0.9$, or P2N2 amplitude [$F(1,5)= 0.2.77$, $p = .16$], $\beta = 7.7$. The P1N1 amplitude measure was not a significant predictor of percent of the time tinnitus symptoms are noticed [$F(1,5)= 0.62$, $p = .62$], $\beta = 0.04$, nor was N1P2 amplitude [$F(1,5)= 0.24$, $p = .65$], $\beta = -0.10$, or P2N2 amplitude [$F(1,5)= 17$, $p = .70$], $\beta = 0.07$. The P1N1 amplitude measure was not a significant predictor of percent of the time tinnitus symptoms are bothersome [$F(1,5)= 0.37$, $p = .57$], $\beta = -0.01$, nor was N1P2 amplitude [$F(1,5)= 0.37$, $p = .67$], $\beta = -0.00$, or P2N2 amplitude [$F(1,5)= 0.55$, $p = .49$], $\beta = 0.06$.

Figure 14

Scatterplot of TRQ vs Tinnitus P2 Latency

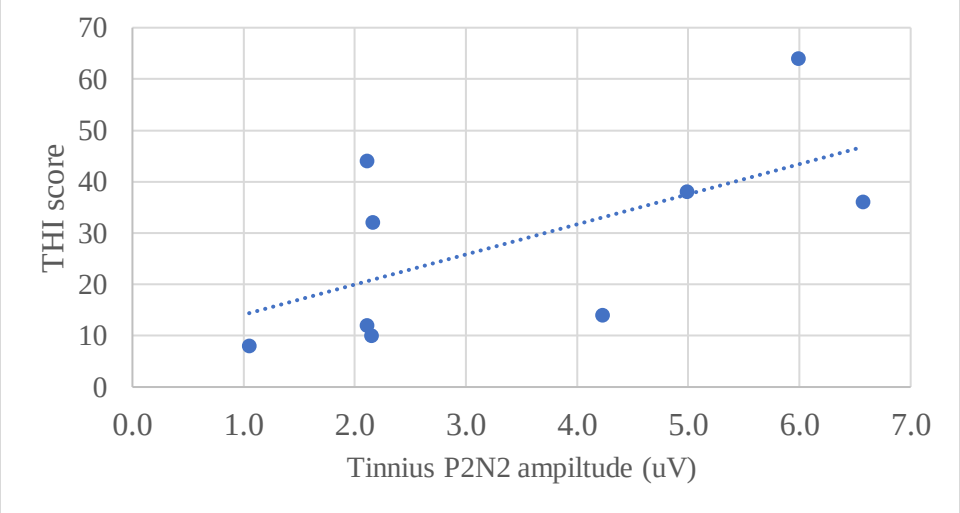


The third block evaluated the relationship of MMN and P300 amplitude and latency measures on behavioral tinnitus data. Regression weights and significance values for the LME

regression model with the lowest AIC value that was at least two points lower than the previous model are listed in Table 11. The MMN amplitude measure was not a significant predictor of the THI [$F(1,5)= 0.05$, $p = .84$], $\beta = -5.1$, TRQ [$F(1,5)= 0.07$, $p = .80$, $\beta = -4.7$, percent of the time tinnitus symptoms are noticed [$F(1,5)= 2.1$, $p = .22$], $\beta = -0.01$, or percent of the time tinnitus symptoms are bothersome [$F(1,5)= 0.03$, $p = .88$], $\beta = 0$. While not significant, the MMN amplitude did show a trend of decreased THI and TRQ scores and percent of the time tinnitus is noticed with increases in MMN amplitudes. MMN latency measure was not a significant predictor of the THI [$F(1,5)= 0.33$, $p = .59$], $\beta = -0.28$, TRQ [$F(1,5)= 0.67$, $p = .46$, $\beta = -0.27$, percent of the time tinnitus symptoms are noticed [$F(1,5)= 0.41$, $p = .55$], $\beta = 0$, or percent of the time tinnitus symptoms are bothersome [$F(1,5)= 0.01$, $p = .93$], $\beta = 0.01$.

Figure 15

Scatter Plot of THI Score vs. Tinnitus P2N2 Amplitude



The P300 amplitude measure was not a significant predictor of the THI [$F(1,5)= 0.27$, $p = .63$], $\beta = 1.0$, TRQ [$F(1,5)= 0.31$, $p = .61$, $\beta = 0.86$, percent of the time tinnitus symptoms are noticed [$F(1,5)= 0.14$, $p = .73$], $\beta = 0.01$, or percent of the time tinnitus symptoms are bothersome [$F(1,5)= 0.06$, $p = .81$], $\beta = 0.01$. The P300 latency measure was not a significant predictor of the

THI [$F(1,5)= 1.0$, $p = .37$], $\beta = 0.26$, TRQ [$F(1,5)= 0.76$, $p =.43$, $\beta = 0.18$, percent of the time tinnitus symptoms are noticed [$F(1,5)= 0.15$, $p = .71$], $\beta = 0$, or percent of the time tinnitus symptoms are bothersome [$F(1,5)= 0.67$, $p =.46$], $\beta = 0$.

Table 10

LME Model for Prediction of ALR Amplitudes on Subjective Measures

Variable	THI			TRQ			Percent Noticed			Percent Bothersome		
	F	*β*	*p*	*F*	*β*	*p*	*F*	*β*	*p*	*F*	*β*	*p*
Intercept	34.1			20			15.3			6.97		
P1N1_amp	0.7	-4.7	.43	0.72	-4	.43	0.28	0.04	.62	0.37	-0.01	.57
N1P2_amp	-	-	-	2	0.9	.22	0.24	-0.1	.65	0.21	0	.67
P2N2_amp	6.7	11	.04*	2.8	7.7	.16	0.17	0.07	.7	0.55	0.06	.49

* = significance at the 0.05 level, THI = Tinnitus Handicap Inventory, TRQ = Tinnitus Reaction Questionnaire, Amp = amplitude, P1N1 = Peak to peak amplitude from P1 to N1, N1P2 = peak to peak amplitude from N1 to P2, P2N2 = peak to peak amplitude from P2 to N2

Table 11

LME Model for Prediction of MMN and P300 Amplitudes and Latencies on Subjective Measures

Variable	THI			TRQ			Percent Noticed			Percent Bothersome		
	F	*β*	*p*	*F*	*β*	*p*	*F*	*β*	*p*	*F*	*β*	*p*
Intercept	14.5			11.1			18.2			5.43		
MMN_amp	0.05	-5.1	.84	0.07	-4.7	.80	2.1	-0.01	.22	0.03	0	.88
MMN_lat	0.33	-0.28	.59	0.67	-0.27	.46	0.41	0	.55	0.01	0	.93
P300_amp	0.27	1	.63	0.31	0.86	.61	0.14	0.01	.73	0.06	0.01	.81
P300_lat	1	0.26	.37	0.76	0.18	.43	0.15	0	.71	0.67	0	.46

THI = Tinnitus Handicap Inventory, TRQ = Tinnitus Reaction Questionnaire, Amp = amplitude, P1N1 = Peak to peak amplitude from P1 to N1, N1P2 = peak to peak amplitude from N1 to P2, P2N2 = peak to peak amplitude from P2 to N2

CHAPTER 4

DISCUSSION

4.1 Introduction

The primary goal of this study was to determine if a battery of electrophysiological measures elicited by tinnitus subjects' pitch-matched tinnitus frequency could be used to differentiate between individuals with tinnitus from those without when controlling for age, gender, and hearing loss. A secondary goal was to evaluate the relationships between reported tinnitus characteristics, perceived severity and impact, and collected electrophysiological data. To date, this is the first study that has used the participants' pitch-matched tinnitus frequency to evoke the ALR, MMN and P300 in the same individuals to determine where along the auditory pathway biomarkers of tinnitus may be located. It is also the only study thus far that has used linear mixed analyses to determine if ALR, MMN, and P300 measures are good predictors of perceived tinnitus severity. Tinnitus has been proposed to not be solely confined to the auditory system, but also involves other cortical networks, particularly those involved in attention and emotions (Jastreboff, 1990).

One of the primary strengths of this study was the use of the tinnitus frequency to evoke cortical potentials located along multiple points of auditory processing within the same individuals. The hypothesis was that individuals with constant, bilateral tinnitus would exhibit some form of dysfunction in their auditory processing in response to stimuli located at their tinnitus frequency. Numerous studies have examined the role of attention in the perception and modulation of tinnitus and suggest an important relationship between the two (Roberts et al., 2013). The results of this study suggest that individuals with tinnitus exhibit differences in electrophysiological responses compared to their matched controls. Specifically, these

differences were found in the MMN responses, with tinnitus participants on average exhibiting smaller MMN amplitudes and decreased MMN area under the curve than their matched controls. Tinnitus participants also exhibited decreased MMN latencies, although this was just shy of significance. Interestingly, the differences in electrophysiological measures were not significant for the P300 amplitudes and latencies between the two groups at Cz, although tinnitus participants in general exhibited smaller P300 amplitudes. Examination of the P300 GFP and topographic maps did reveal differences in scalp distribution of the P300, however. Also, the P2 latency was found to be a good predictor of the THI and TRQ scores and percent of the time that the tinnitus was bothersome, with longer latencies being associated with higher scores and higher percentages of bothersome tinnitus. P2N2 amplitude was also found to be a significant predictor of THI score, with larger amplitudes being associated with higher THI scores.

4.2 The use of Auditory Evoked Potentials for the Measurement of Tinnitus

Auditory evoked potentials are a well-established and relatively cost-efficient means of assessing the peripheral and central auditory system (Picton et al., 1977). CAEPs have been studied in the tinnitus population and have the advantage of being able to measure pre-attentional and attentional processing in addition to central auditory function (Näätänen, 1975). Tinnitus is not only influenced by bottom-up processing but can also be modulated by top-down processing, making it important to utilize tests that are able to assess both pathways (Cardon et al., 2020). Previous findings using ALRs in the tinnitus population have been mixed, with some studies finding differences in peak amplitudes and latencies in these measures between tinnitus and non-tinnitus individuals, while others have not. These seemingly contradictory findings can in part be explained by the heterogeneity of tinnitus. While damage to the peripheral auditory seems to be a driving force in tinnitus, the etiology of the damage can vary, which may result in differences in

the generation and sustaining of the tinnitus percept. Perceived severity also greatly varies, with most individuals not experiencing significant distress caused by their tinnitus. Tinnitus may also be unilateral, bilateral, or perceived in the head and has been described with a plethora of adjectives, including ringing, buzzing, chirping, and roaring to name a few. In this study there were no significant differences in P1N1, N1P2, or P2N2 amplitudes or P1, N1, P2, and N2 latencies between the two groups in the Cz electrode nor in the GFP analysis, which is in agreement with numerous previous studies (Gopal et al., 2017; Lee, Jaw, Pan, Lin, & Young, 2007; Morse & Vander Werff, 2019), but contrasts with others (Jacobson et al., 1996; Noreña et al., 1999; dos Santos Filha et al., 2010). Topographic maps of the P1, N1, and P2 time ranges for each group also did not exhibit differences in distribution of the cortical response (see Appendix).

In addition to confounding effects of tinnitus participant selection criteria, methodological differences may also account for seemingly contradictory findings between results in this study and others, with one of the largest methodological considerations being the use of the tinnitus frequency in each paradigm. Few studies examining CAEPs in the tinnitus population have incorporated the pitch-matched tinnitus frequency into their paradigms, and of those that do, only one included tinnitus participants that have different pitch-matched tinnitus frequencies (El-Minawi et al., 2018). Studies examining AEPs in the tinnitus population often only include individuals with tinnitus who have normal hearing, whereas in this study participants could have up to a moderate hearing loss at their pitch-matched tinnitus frequency. Another important consideration when comparing late auditory evoked potentials between two groups is ensuring that hearing thresholds are similar, as hearing loss can impact both latency and amplitude measures, although the extent to which hearing loss impacts CAEP latencies and

amplitudes has not been concretely established (Alain et al., 2013). Wall et al. (1991) compared latencies and amplitudes for N1, P2, and P3 in a group of individuals with symmetrical sensorineural hearing loss compared to a control group with normal hearing matched for age. Both pure tones and speech stimuli were used to evoke the ALR and P300 with a presentation level of 40 dB SL. The authors did not find any significant differences in latencies for any of the peaks. They also did not find significant differences in P3 amplitudes. They did, however, find that the hearing-impaired group exhibited decreased N1 amplitudes. These findings would suggest that CAEPs, when stimuli presented at sufficient intensity levels, are relatively robust to hearing impairments, particularly for endogenous potentials. It could also be that since the stimuli were presented at 40 dB relative to hearing thresholds, this helped reduce the impact of differences in hearing thresholds.

Another study by Oates et al. (2002) investigated the effects of different degrees of hearing loss on N1, MMN, N2, and P300 measures evoked by speech stimuli. They found that individuals with hearing loss exhibited decreased CAEP amplitudes, but this only became evident when 60 dB HL of hearing loss was present at 1,000 and 2,000 Hz. Effects of hearing loss on latency were more sensitive, with prolongations in latency occurring with mild hearing losses (25-49 dB HL) compared to normal hearing participants. Effects of hearing loss were more pronounced for the later CAEP components, N2 and P300, than for the earlier ERP components N1 and MMN. As many individuals with tinnitus also have some degree of hearing loss, any test battery that is to be used in diagnosis must be resilient to the effects of hearing loss, and any comparisons that are made between tinnitus and non-tinnitus groups should control for hearing loss. Encouragingly, auditory evoked potentials seem to show a resilience to at least mild and moderate levels of hearing loss.

Findings of this study would suggest that an ALR paradigm alone evoking a P1, N1, P2, N2 complex using the pitch-matched tinnitus frequency would not be sufficient for objectively differentiating the tinnitus group from the control group, even when hearing loss, age, and gender were matched between the two groups. Given the neurophysiological complexities of tinnitus stemming from the interactions between hearing, cognition, attention and emotional regulation, and the likelihood of multi-system involvement, any measures used as potential biomarkers of tinnitus will need to be able to assess higher order cortical processes.

4.3 Use of the MMN as an Objective Assessment of Tinnitus

First described by Näätänen (1978), the MMN is another electrophysiological test that has been shown to have good test-retest reliability and validity when elicited using frequency deviants (Frodl-Bauch et al., 1997). The MMN has been used to assess several conditions across multiple fields including hearing status in newborns, development disorders such as dyslexia, schizophrenia, coma, and drug effects to name a few (Näätänen & Escera, 2000). The MMN is thought to reflect a change detection mechanism and can be evoked with double oddball paradigm utilizing standard and deviant stimuli that differ along some physical parameter, and it is sensitive enough to be evoked by changes in stimuli that are close to the behavioral detection threshold (Sharma et al., 1993).

One challenge in eliciting CAEPs is the impact that the stimulus parameters have on the morphology of the exogenous components of these measures. As stimulus frequency begins to change, differences in latency and amplitude measures appear. Wunderlich & Cone-Wesson (2001) examined the impact of stimulus frequency on latency and amplitude measures of P1, N1 and the MMN. They used tone bursts located in the speech frequency range (400-3,000 Hz) to evoke these responses in normal hearing individuals. They found that as the stimulus frequency

began to increase, N1 and P2 amplitudes began to decrease and the N1 latency decreased, likely due to the tonotopic organization of the auditory system. The P2 latency was not affected. This agrees with other studies that have found decreases in amplitudes with increasing stimulus frequency, although P1, N1, and P2 can still be evoked by stimuli at least as high as 8,000 Hz (Antinoro et al., 1969). There are several reasons for this. The first is that as the stimulus frequency is increased, activation of the basilar membrane becomes more basal. The cochlea is organized such that higher frequencies are encoded in the basal portion while lower frequencies are encoded more towards the apical portion. This results in less activation of the basilar membrane for higher frequency stimuli compared to lower frequency stimuli due to the shorter distance required for higher frequency acoustic stimuli to travel before they reach their resonant area on the basilar membrane. Less basilar membrane activation in turn produces a smaller transfer of neural activity propagating through the auditory system (Wunderlich & Cone-Wesson, 2001). A second is that higher frequencies are thought to be encoded by neural populations located deeper in the auditory cortex while lower frequencies are encoded by neural populations located more superficially (Wunderlich & Cone-Wesson, 2001). This results in less attenuation of the electrical signal since there is less medium through which to propagate.

The orientation of the neural populations also plays a role. Neural activity can only be detected by surface electrodes if the pyramidal neurons and axons are in a perpendicular orientation to the skull (Olejniczak, 2006). This finding would initially seem problematic, as most individuals with tone-like tinnitus pitch-match at frequencies at 3,000 Hz or above (Tyler, 2000). However, as the time from stimulus onset begins to increase, the extent to which the CAEP is influenced by stimulus characteristics begins to decrease as more endogenous components come into play. The MMN contains both exogenous and endogenous influences

(Näätänen, 2007). Wunderlich & Cone-Wesson (2001) found that as stimulus frequency begins to increase, the area of the MMN decreases, but is still present, although they did not test standard or deviant frequencies above 3,000 and 3,300 Hz. An advantage of the MMN over earlier auditory evoked components is its ability to be "elicited by any discriminable change of a repetitive sound…", (Näätänen, 1995, p. 6), making it less susceptible to degradative effects of increased stimulus frequency. MMN amplitude has been shown to have good intrasubject and intrasubject variability (Frodl-Bauch et al., 1997). The MMN area under the curve (AUC) is an additional measure that has been used to increase the interpretability of the MMN (Sharma et al., 1993). As the onset and offset times as well as the general shape of the MMN are variable from individual to individual, the AUC provides an additional means to assess this response (Pekkonen et al., 1993).

In the current study, the MMN amplitude and AUC were found to be smaller for the tinnitus group compared to the control group. This agrees with previous studies comparing the MMN between tinnitus and non-tinnitus individuals (Mahmoudian et al., 2013; Sendesen et al., 2022). As the MMN is likely a measure of pre-attentive auditory processing, it has been suggested that the internal tinnitus percept interferes with the detection change mechanisms responsible for the generation of the MMN (Mahmoudian et al., 2013). While not significant, the tinnitus group exhibited shorter MMN latencies than the control group, similar to findings of El-Minawi et al. (2018), who reported that their tinnitus group had significantly shorter MMN latencies than their non-tinnitus control group before being administered Tinnitus Retraining Therapy. MMN latency has been shown to be affected by task relevance (Schlossmacher et al., 2021). Reduced latencies in the tinnitus groups may be suggestive of increased relevance of the deviant stimuli, located at the tinnitus frequency. Whereas those without tinnitus do not have an

associated relevance to the deviant stimulus, those with constant tinnitus may have categorized the deviant stimulus as having a higher relevance due to the similarity between the internally perceived tinnitus, resulting in faster categorization of the deviant stimuli.

4.4 Use of the P300 as an Objective Assessment of Tinnitus

The P300 is a powerful tool that has been used to assess cognitive function, including age-related cognitive decline, schizophrenia, alcoholism, epilepsy, and depression (Sowndhararajan, et al., 2018). The P300 has also been used in assessment of cognitive function in individuals with tinnitus, as this condition has been found to be associated with impairment to executive control of attention and increased rates of depression and anxiety (Tegg-Quinn et al., 2016). It has been found to be as reliable as clinical assays and is relatively cost efficient compared to other assessment techniques, such as magnetic resonance imaging, magnetoencephalography, and positron emission tomography (Polich & Herbst, 2000). Cardon et al. (2020) performed a systematic review and meta-analysis of studies collecting AEPs in individuals with tinnitus. They found that of the P50, P1, N1, P2, N2 amplitudes and latencies, contingent negative variation, and P300 amplitudes and latencies, only the P300 amplitude and latency showed differences between tinnitus and non-tinnitus subjects. Four of the eight studies included in the analysis found significantly decreased P300 amplitudes in tinnitus participants while three of the eight found significantly prolonged P300 latencies in tinnitus participants.

The results of the current study did not find significant differences in cognitive processing speed or function, as measured by the P300 at Cz, between the tinnitus and control group, as evidenced by lack of significant differences in absolute P300 amplitude or latencies. While Cz was selected for P300 analysis due to this electrode containing the largest P300 amplitudes, there are implications for only examining this late potential at only one electrode.

The first is that the P300 can contain the subcomponents P3a and P3b. The P3a occurs earlier than the P3b and has a more frontocentral scalp distribution. The P3b occurs later and has a more parietal distribution. These different topographical distributions suggest different neural generators responsible for these to P300 subcomponents, although the exact neurophysiological mechanisms are not fully understood (Polich, 2007). The P3a, also referred to as the novelty P300, is generated by a deviant stimulus inserted in a train of frequent standard stimuli when no task is assigned to the paradigm, or the task does not contain relevance (Polich, 2007). This could include a paradigm similar to an MMN paradigm in which the participant is asked to ignore the deviant stimuli, or in a three-stimulus oddball paradigm consisting of a standard, a deviant that the participant is asked to respond to, and a distractor stimulus that the participant ignores. The distractor stimulus evokes a P3a while the task relevant deviant stimulus evokes a P3b. The P3b is generated whenever the participant is asked to respond to the stimulus in some way. As the task becomes more difficult, the P3b amplitude begins to decrease (Kimura et al., 2008).

Despite a lack of differences in P300 amplitudes or latencies between the two groups at Cz, there were significant differences in several time ranges in the GFP analysis prior to the P300, which has the advantage of taking all electrodes into account. Differences between the two groups existed in the 182-238 ms and 256-302 ms time windows, with tinnitus participants exhibiting smaller amplitudes in the 182-238 ms window and larger amplitudes in the 256-302 ms window. Evaluation of the topographic maps revealed a more negative distribution in the left frontal region in the control group compared to the tinnitus group at 220 ms, which was in the middle of the first significantly different time window in the P300 GFP. Informal evaluation of the standard and deviant waveforms (see Appendix) revealed that this difference in neural

activity was primarily driven by differences in the N2 time region in the deviant waveforms, with control groups exhibiting a larger N2 just prior to the P300 than the tinnitus group. N2 has been proposed to reflect a preattentive general stimulus classification mechanism while the P300 reflects processing that occurs after the behavioral response has been determined (Ritter et al., 1983). A smaller N2 in the tinnitus group would indicate that they were not able to classify the deviant stimulus located at the tinnitus frequency as well as their non-tinnitus counterparts, presumably because of the interference to this classification system caused by the tinnitus precept. This finding, in conjunction with reduced MMN latencies in the tinnitus group indicate that while the deviant stimulus located at the tinnitus frequency is more relevant in a non-attentive task, presumably due to the internal tinnitus relevance, individuals with tinnitus have more difficulty classifying the stimulus when asked to differentiate between a stimulus located at their tinnitus frequency from a stimulus located far away from their tinnitus frequency.

Interestingly, the topographic maps at 260 ms show that the tinnitus group had greater positive neural activity in the center parietal region, which could correspond with the beginning of a P3a, whereas the control did not exhibit this same neural activity. Evaluation of the 350 ms topographic maps, which is approximately where the maximal P300 amplitude was located, shows a more frontocentral activation in the control group whereas the tinnitus group showed a greater parietal activation. The P3a is generally evoked by deviant stimuli with low task relevance while the P3b is associated with attended deviant stimuli with high task relevance. Differences in the P300 scalp distribution between the two groups would suggest that the tinnitus frequency is modulating the perceived relevance of the deviant stimulus in the tinnitus group.

Taken together, the electrophysiological results of this study indicated that more central mechanisms are responsible for the perception of tinnitus. If tinnitus were maintained by more

peripheral mechanisms, such as increased spontaneous or synchronous neural activity in the auditory nerve, dorsal cochlear nucleus, or primary auditory cortex, it would be expected that these differences would manifest themselves in exogenous evoked potentials. This was not the case in this study, as evidenced by a lack of differences in ALR measures and a similarity in topographic distribution between the two groups. A deficit in the MMN in the tinnitus group indicates a dysfunction in the pre-attentional processing. A study by Campbell et al. (2018) found that participants with tinnitus exhibited deficits in auditory gating in the Pa component of the cortical auditory evoked potential compared to participants without tinnitus, indicating reduced central inhibition. Results of the current study and the Campbell et al. (2018) study would suggest that individuals with hearing loss, but no tinnitus are able to gate out the increased neural activity more effectively before it is able to reach the cortex and become perceived as sound. In individuals with tinnitus, the aberrant peripheral neural activity caused by reduced sensory input is not effectively gated out and is passed along to higher order auditory and attentional structures, where it is then perceived as sound. The perception of sound in turn interferes with multiple endogenous responses dealing with preattentional processing and stimulus classification. Individuals with tinnitus have also been found to exhibit cognitive deficits (Mohamad et al., 2016). This would suggest that a network model that involves multiple cortical systems may be the most likely source of tinnitus.

4.5 Correlations Between Electrophysiological Measures and Tinnitus Severity

Few studies have evaluated potential correlations between reported tinnitus severity, as measured by questionnaires, and electrophysiological data. Results from these studies have been mixed, with no consistent relationship between AEP components in tinnitus sufferers and tinnitus severity, as reported in a recent meta-analysis of CAEPs in tinnitus by Cardon et al.

(2020). Mannarelli et al. (2017) used a Pearson correlation to examine potential relationships between electrophysiological measures (N1 and P300 amplitudes and latencies) and THI scores. They did not find any significant correlations. A recent study by Schoisswohl et al. (2021) collected continuous EEG in individuals with tinnitus before and after exposure to sounds designed to induce residual inhibition. They then used Pearson correlations to examine potential relationships between rated tinnitus loudness and pre- and post-power spectra. They did not find any significant correlations between the EEG and behavioral measures. Sendesen et al., (2022) evaluated potential relationships between MMN amplitude and latency with scores on the THI. As in the study by Mannarelli et al. (2017), they used a Pearson correlation and did not find significant correlations between the aforementioned measures. Campbell et al. (2018) found that increased tinnitus severity, as measured by the THI, was correlated with decreased Pa gating ability, with reduced gating predicting higher THI scores. Campbell et al. (2019) used one-tailed Spearman ranked correlations to assess relationships between THI scores and amplitude difference gating indices at P1, P50, N1, and P2. They found that the Pa gating indices were moderately-negatively correlated with higher THI scores and N1 gating indices were moderately-positively correlated with higher THI scores. No correlations between peak latencies and THI scores were reported.

Given the lack of consensus and research into relationships between electrophysiological measures and perceived tinnitus severity, exploratory LME analyses using the AIC to determine best fit models were used to evaluate relationships between the two classes of variables. Results from this study demonstrated that P2 latency was a significant predictor of tinnitus severity, as indexed by THI and TRQ scores and the percentage of the time tinnitus symptoms were considered bothersome.

P2 has not been as extensively studied as the N1, MMN, and P300 potentials, although it is thought to be involved in stimulus classification (Crowley & Colrain, 2004; Garcia-Larrea et al., 1992). For earlier auditory evoked potentials, latencies are known to be influenced by stimulus characteristics and neural transmission efficiency (Näätänen, 1990), while for later evoked potentials, latencies are influenced by task relevance, cognitive performance, attentional state, and efficiency of neural synchronization of multiple cortical networks (Cardon et al., 2020). Prolonged latencies in later evoked auditory potentials are indicative of dysfunction in "auditory selective attention processing" and decreased cognitive processing speed (Attias et al. 1996, p. 331). Individuals who have greater levels of perceived tinnitus severity may have more difficulty classifying the stimulus located at their tinnitus frequency used in this study due to competition from their internally perceived tinnitus, as indicated by increased P2 latencies. Hoke, Feldmann, Pantev, Lütkenhöner, & Lehnertz (1989) found that individuals with tinnitus exhibited delayed P2 and M2 (the magnetic counterpart to P2) latencies and that P2 and M2 were significantly reduced or absent compared to non-tinnitus controls. They posited that the internal tinnitus precept was affecting endogenous components of the P2 and M2 generators, thereby interfering with those generators' ability to respond to the presented stimuli. As with this study, these findings point towards a more central origin of tinnitus, with endogenous factors being the primary driving force behind tinnitus.

While ALR amplitudes have been found to be sensitive to stimulus frequency, P2 latency is robust against this stimulus characteristic (Wunderlich & Cone-Wesson, 2001), indicating that differences in P2 latency were not due to differences in stimulus frequency presented.

Differences between findings in this study and previous could be the result of different statistical tests used. An important assumption in the Pearson correlation is independence of the

data collected. Often in electrophysiological testing this assumption is violated because electrophysiological measures often have a high degree of correlation (Cheek & Cone, 2020; Koerner & Zhang, 2017), making a simple Pearson correlation an inappropriate assessment tool. An LME analysis, on the other hand, can account for fixed and random effects, as well as correlational relationships, between the measures collected (Koerner & Zhang, 2017).

4.6 Implications

Results of this study suggest there are deficits in auditory processing in individuals with tinnitus that can be assessed using MMN and P300 paradigms incorporating the pitch-matched tinnitus frequency. A lack of differences in P300 measures evaluated at Cz demonstrates that a single electrode analysis may not be effective in differentiating between individuals with and without tinnitus. The presence of differences in primarily endogenous driven potentials in conjunction with a lack of differences in latencies or amplitudes of exogenous potentials suggest a network model may be responsible for constant tinnitus. Several different models of tinnitus generation and sustaining of the tinnitus precept have been proposed (Henry et al., 2014). These include tonotopic reorganization that results due to peripheral deafferentation caused by damage to cochlear structures, increases in central neural firing, known as central gain, and increases in neural synchrony in central structures encoding peripheral deafferented neurons. One common underlying theme for these proposed mechanisms of tinnitus is the presence of damage to peripheral auditory structures resulting in negative maladaptive plasticity. However, these models do not explain why individuals may have hearing loss but do not experience tinnitus or why individuals with normal hearing develop tinnitus. A recent review by Hu et al. (2021) on MRI imaging in tinnitus participants concluded that in addition to the auditory system, there are numerous other cortical regions that exhibit differences in the tinnitus population, including the

limbic system, default mode network, which exhibits increased activity during the resting state and decreased activity during a task-oriented state, and in attention and control networks. The authors concluded that while tinnitus may initially be generated in the auditory periphery, non-auditory systems are crucial for the maintenance of tinnitus and very likely have an influence on the perceived characteristics of tinnitus. While tinnitus is traditionally thought of as an auditory phenomenon, non-auditory cortical centers may hold be the key to discovering tinnitus biomarkers.

4.7 Limitations

There were several limitations in this study that should be considered. Perhaps the largest of which was the small sample sizes for each group. While results from the electrophysiological data and linear mixed models are encouraging, a larger sample size would increase the power of these measures and perhaps elucidate further subtle differences between the two groups.

Another limitation was the method used to pitch-match the tinnitus frequency. While the pitch-matching procedure used was able to approximate the tinnitus frequency, it is likely that the exact tinnitus frequency fell outside of the half octave intervals used. However, this method is commonly used clinically and provides the benefit of using readily available equipment in addition to providing a quick means of assessing an individual's tinnitus.

A third limitation of this study was the exclusion of participants who had more than a moderate hearing loss at the pitch-matched tinnitus frequency. Equipment and physiologic limitations prevent the methodologies used in this study from being applied to individuals with severe to profound hearing losses. Also, only a subset of individuals with tinnitus, specifically, bilateral, constant, tone like were recruited for this study. Tinnitus is a very heterogenous condition, with different subtypes likely exhibiting differing underlying mechanisms. Recruiting

controls that were matched for age, gender, and hearing status also proved challenging, especially during the COVID-19 pandemic.

4.8 Future Research

If different subtypes of tinnitus are to be assessed, future studies will need to include larger sample sizes that allow for analysis and possible categorization of CAEPs in individuals with different types of tinnitus. Given the large number of individuals experiencing tinnitus, if an objective test is to be developed, it will also need to be able to be conducted using readily available, relatively inexpensive equipment, such as auditory evoked potential systems commonly used in the field of audiology. Futures studies should compare findings between clinical and research equipment to determine if differences in CAEPs in tinnitus persist when simpler equipment and less advanced data processing are used.

4.9 Conclusion

Results from this study indicated that there are electrophysiological differences between individuals with tinnitus and matched controls without tinnitus. Specifically, significant reductions in the mismatch negativity amplitude and area under the curve were present and a trend towards shorter MMN latencies for individuals with tinnitus. Results of the GFP analysis appear to support these findings and indicate differences in spatial distribution of P300 responses in tinnitus participants. This would suggest that any test that is developed for tinnitus diagnosis needs to examine cortical networks extending beyond the traditional afferent auditory system, as evidenced by a lack of significant differences in ALR amplitudes and latencies between the two groups. Including AUC measures in addition to amplitude measures may increase the sensitivity and specificity of an electrophysiological test for tinnitus, especially for a measure like the MMN

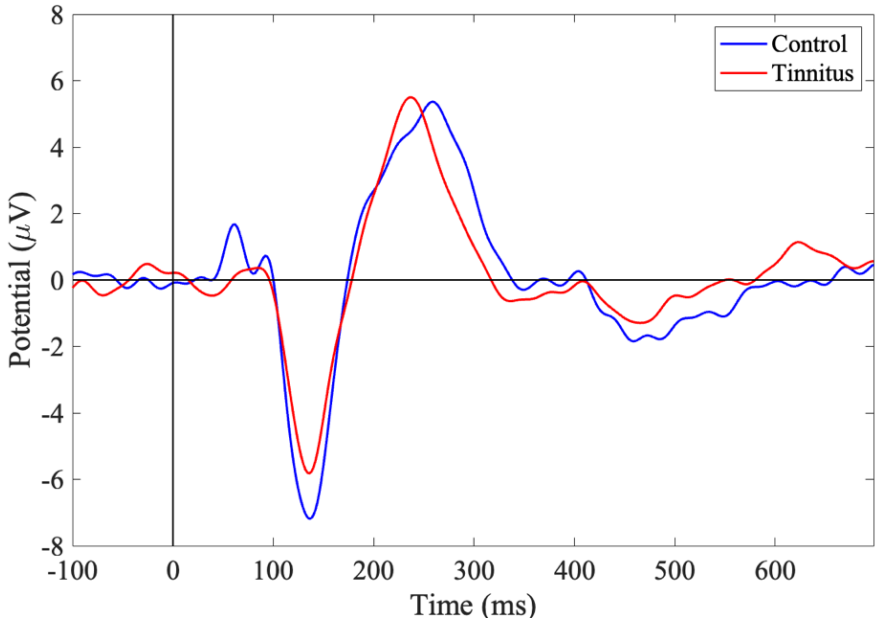
which can have variable onset and offset times. Protocols and equipment used to evoke and measure the MMN and P300 can be performed using commonly available audiological equipment that is used for collecting shorter latency evoked potentials. Differences in MMN between the two groups was the most pronounced at Cz, so a two-channel setup could feasibly be used instead of an EEG cap containing multiple electrodes, however, analysis of P300 responses may require a higher number of electrodes. Further, results from this study showed relationships between P2 latencies and perceived tinnitus severity as measured by questionnaires and self-reported percentage of the time the tinnitus is considered bothersome, with longer P2 latencies results in higher (worse) scores. In addition to current tinnitus assessment techniques, namely questionnaires and audiological testing, the MMN and P300 may provide a useful measure for determining the presence or absence of tinnitus, while the P2 latency may provide insight to the perceived severity of the tinnitus.

APPENDIX

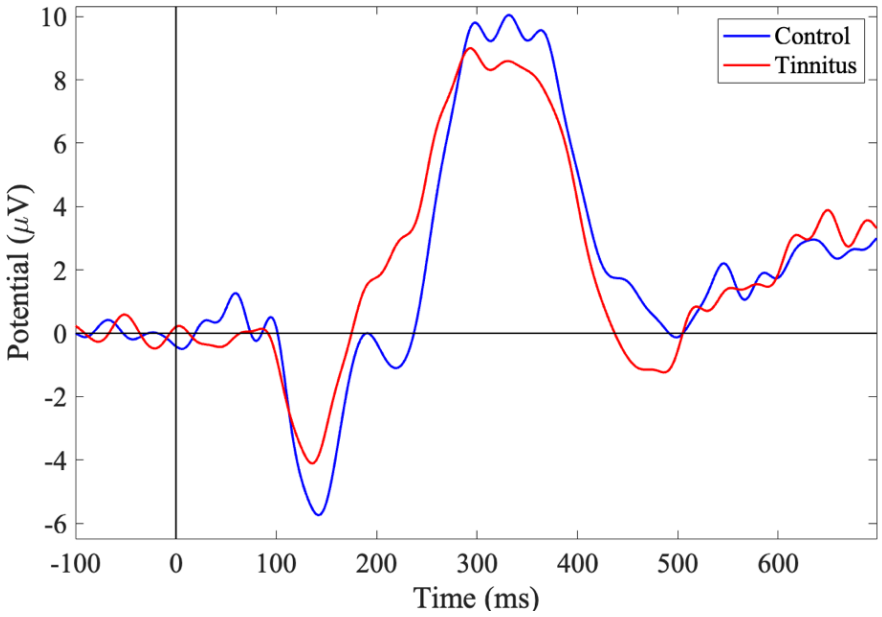
SUPPLEMENTAL FIGURES

A. 1

Average P300 Standard Waveforms



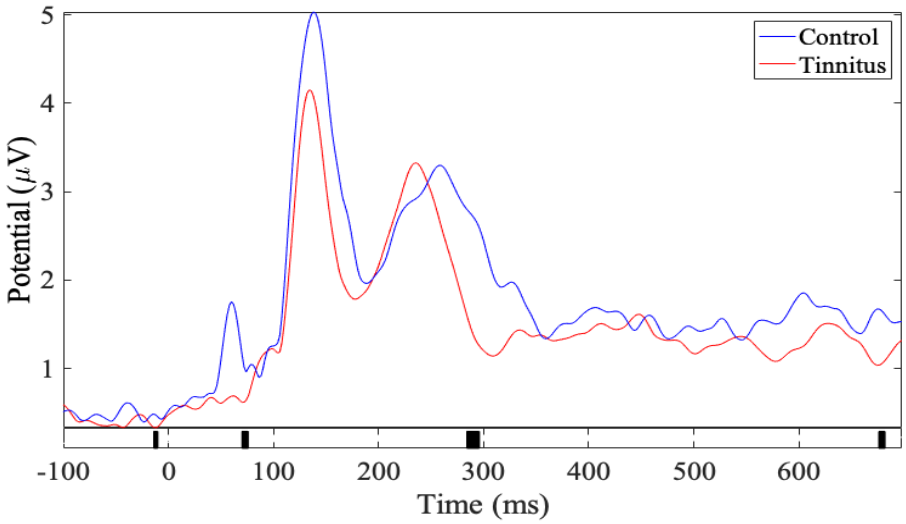
Average P300 Deviant Waveforms



Waveforms generated by the standard stimulus (top) and deviant stimulus (bottom) in the P300 protocol for tinnitus and control groups.

A. 2

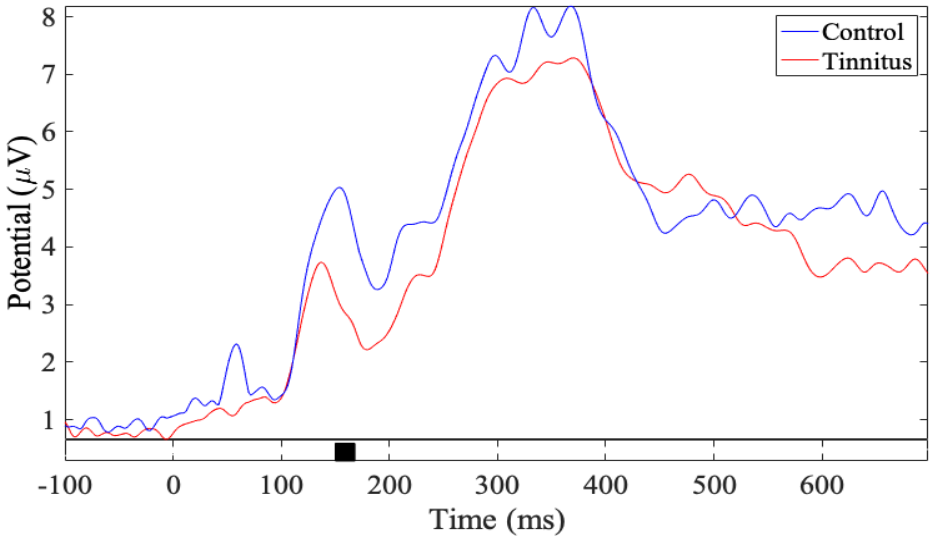
GFP Analysis for P300 Standard Waveforms



Black rectangles on the x-axis represent areas of statistical significance at p <.05

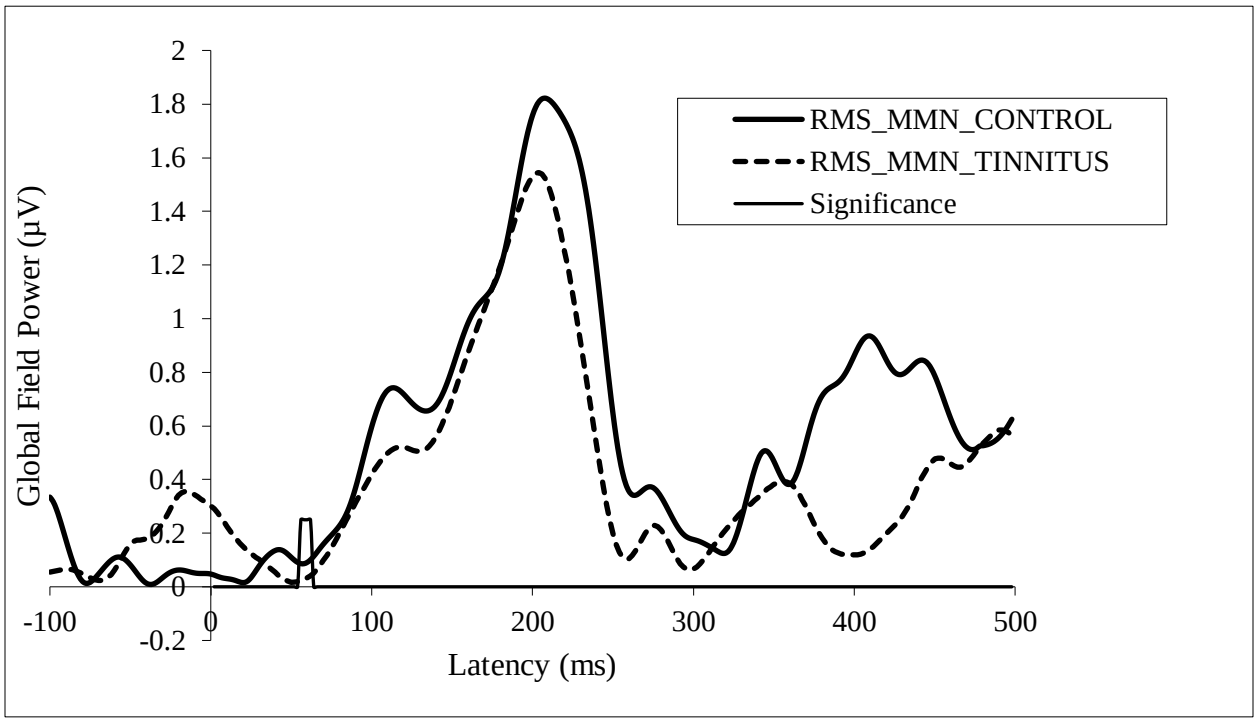
A. 3

GFP Analysis for P300 Standard Waveforms



Black rectangles on the x-axis represent areas of statistical significance at p <.05

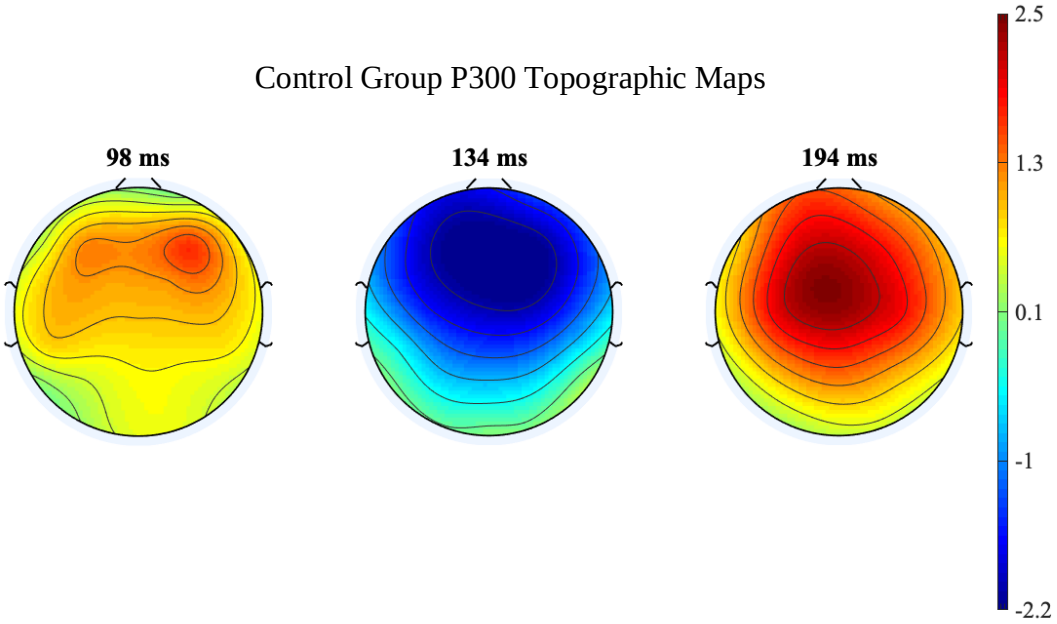
A. 4
GFP Analysis for the ALR

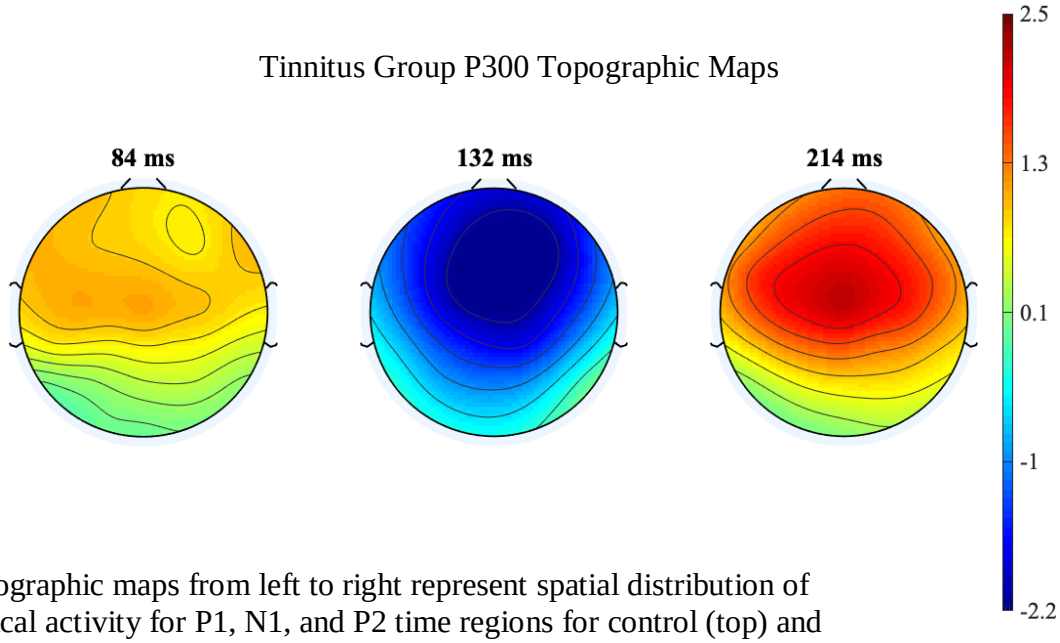


Black rectangles on the x-axis represent areas of statistical significance at $p < .05$

A. 5

Topographic Maps for the ALR for Tinnitus and Control Groups





Topographic maps from left to right represent spatial distribution of cortical activity for P1, N1, and P2 time regions for control (top) and tinnitus (bottom) groups.

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