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This study aims to broaden the present understanding of the differences in cortical responses that may underlie the tendency of some people to perceive tinnitus. Participants were 30 female adults with no history of hearing loss or persistent tinnitus. Pre - and post-silence ALR and P300 recordings were obtained. After the first ALR recording they were exposed to 10 minutes of silence. They completed a Qualtrics questionnaire to report any tinnitus perception in silence. Absolute ALR and P300 waveform amplitudes and latencies were identified and were entered into an SPSS spreadsheet for data analysis. The mean age of the participants was 22.5 ± 3.9 years. When exposed to silence, eleven (36.7%) participants perceived tinnitus. Seven (63.6%) of the participants who perceived tinnitus were African American. There was no significant association between race and the perception of tinnitus. A statistically significant reduction in post-silence P300 amplitude was observed, (t_{29}= 2.2, p=0.04). Thus, the neural response in the non-auditory regions involved in modulating auditory attention and the experience of auditory stimuli appears to be affected by silence. This may explain the negative effect of silence on tinnitus perception in individuals with tinnitus as well as the tendency for some individuals to experience tinnitus emergence when exposed to silence. Therefore, clinicians can continue to advice that patients with tinnitus avoid silence. ALR and P300 waveform latencies and amplitudes did not differ significantly between the participants who perceived tinnitus in silence and those who did not ($p > 0.05$). Whites had significantly larger N1 amplitudes than African Americans ($F(1,25) = 4.4$, $p = 0.05$, effect size 0.2).

LATE AUDITORY EVOKED POTENTIALS AND P300 IN YOUNG FEMALE ADULTS WHO PERCEIVE TEMPORARY TINNITUS AFTER A BRIEF PERIOD OF SILENCE

by

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DEDICATION

Dedicated to God for this opportunity and to my family and friends, your support means the world to me.

APPROVAL PAGE

This dissertation written by Onyinyechi Ukaegbe has been approved by the following committee of the Faculty of The Graduate School at The University of North Carolina at Greensboro.

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CHAPTER I: INTRODUCTION

Tinnitus is the perception of sound in the absence of an auditory stimulus (Savage & Waddell, 2014). About 50 million Americans experience tinnitus, but it is estimated to be persistent/chronic in 16 million of these individuals (Bhatt, Lin, & Bhattacharyya, 2016; Shargorodsky, Curhan, & Farwell, 2010; Tunkel et al., 2014). Two percent of individuals with tinnitus report their tinnitus as debilitating and detrimental to their quality of life (Langguth, Kreuzer, Kleinjung, & De Ridder, 2013; Newman et al., 2011). Tinnitus has been associated with anxiety, depression, insomnia, and difficulty concentrating (Axelsson & Ringdahl, 1989; Granjeiro, Kehrle, de Oliveira, Sampaio, & de Oliveira, 2013; Langguth, 2011).

Several neural generators within the human auditory system have been proposed to be responsible for tinnitus occurrence, but the identification of the underlying neural generators for tinnitus is still under debate as these neural mechanisms reflect the heterogeneity of auditory pathologies which have been associated with tinnitus (Henry, Roberts, Caspary, Theodoroff, & Salvi, 2014; Levine & Oron, 2015; Savage & Waddell, 2014). Tinnitus has been associated with several pathologies, but chronic tinnitus can also be found in people with normal hearing (Medeiros, Sanchez, Levy, Santos, & Ramalho, 2004; Shargorodsky et al., 2010). The misconception that tinnitus was of peripheral origin was corrected after it was demonstrated that the sectioning of the auditory nerve did not always lead to tinnitus resolution (Axelsson & Ringdahl, 1989; Barrs & Brackmann, 1984; Pulec, 1984). Several neural models have been proposed as the explanation for tinnitus generation in sensory deprivation, they include the Dorsal Cochlear nucleus model, cortical tonotopic reorganization model, neural synchrony model, network model and central gain model (Henry et al., 2014; Yang & Bao, 2013). In addition to these models, tinnitus has also been postulated to be one of the many diseases that can be a direct result of auditory neuronal homeostatic plasticity.

The mechanisms behind tinnitus perception are still being investigated. As a result of the limited understanding of the neural mechanisms involved in tinnitus perception, the

management of tinnitus has remained a challenge and a definitive cure is not yet available.

Silence has been reported to increase tinnitus perception and awareness in people with chronic tinnitus; therefore, people with chronic tinnitus are counseled to avoid silence. However, it appears that most adults with no prior history of tinnitus or ear pathology report the perception of temporary tinnitus when exposed to sustained silence (Del Bo et al., 2008; Heller & Bergman, 1953; Tucker et al., 2005). There are several possible explanations for this phenomenon. First, the removal of environmental sounds may result in the perception of sounds that were previously masked by an enriched acoustic environment. Another explanation is that following a period of reduced auditory stimulation, the auditory system temporarily undergoes functional changes that manifest as tinnitus (Norena & Eggermont, 2003). Furthermore, it appears that race plays a role in the emergence of tinnitus in silence. Tucker et al., 2005 observed that 78% of the Caucasians in their study experienced tinnitus when exposed to a brief period of silence compared to only 38% of the African American participants. This difference was statistically significant (Tucker et al., 2005). They did not observe a significant difference in the perception of tinnitus when males were compared to females. Studying the perception of tinnitus in silence could improve our understanding of why it is present in some people and absent in others with similar thresholds. One method used in studying neural activity in tinnitus is by recording auditory evoked responses (AERs).

Auditory Evoked Responses (AERs) are recorded scalp neural activity from the auditory system in response to auditory stimuli (Hall, 2007; Picton, Hillyard, Krausz, & Galambos, 1974). AERs are electrophysiologic responses to sound recorded from the scalp which can be used to assess the auditory system objectively. AER waveforms represent a manifestation of intracortical currents generated by excitatory and inhibitory postsynaptic potentials (Frodl-Bauch, Bottlender, & Hegerl, 1999). AERs are time locked to sound stimuli and can be recorded from the ear, the auditory nerve, the brainstem, other sub-cortical regions of the central auditory nervous system and from regions within the cortex (Plourde, 2006). These auditory evoked signals are averaged and display a sum of electrical activity from underlying multiple neurons.

AERs can be exogenous or endogenous responses. Evoked potentials such as the Electrocochleography (ECochG), Auditory Brainstem Response (ABR), Auditory Middle Latency Response (AMLR) and the conventional Auditory Late Responses (ALR) are

exogenous responses, meaning the response does not vary markedly with subject processing abilities, level of attention or acknowledgement of the stimuli but are heavily dependent on stimulus characteristics. With exogenous AERs, the recorded waveforms can be influenced by subject and stimulus parameters. Endogenous responses such as the P300 require some level of processing and participation by the subject and thus recorded waveforms reflect the underlying cognitive activity. Therefore, exogenous responses are useful for threshold estimation and neurodiagnosis, and endogenous responses are useful for neurophysiological and psychophysiological investigations (Hall, 2007).

Auditory late responses (ALRs) are auditory evoked responses that occur between 50ms to 500ms after the presentation of a sound stimulus. The first auditory evoked responses to be recorded from the CNS were discovered by Pauline and Hallowell Davis (Hall, 2007). ALRs have both exogenous (obligatory) and endogenous (cognitive) components (Prakash, Abraham, Rajashekar, & Yerraguntla, 2016; Purdy, Kelly, & Davies, 2002). The exogenous components are named after their polarity and order of appearance. These include the P1 at 50ms to 80ms, the N1 at 100ms to 150ms, P2 at 150ms to 200ms and the N2 at 250ms to 280ms (Hall, 2007).

The P300 response can be elicited by rare or infrequent visual, somatosensory or auditory stimuli in an odd-ball paradigm format (Soltani & Knight, 2000). When the P300 is elicited by rare auditory stimuli, it is observed as an ALR waveform with an additional positive potential which is recorded at approximately 300ms post-stimulus (Melynyte, Wang, & Griskova-Bulanova, 2018). A variety of cortical regions are implicated in the generation of the P300 response region (Melynyte et al., 2018; Polich, 2007; Volpe et al., 2007). Auditory and non-auditory regions within the tempero-parietal cortex, the frontal cortex and the limbic system are believed to contribute to the generation of the P300 response.

A few studies have looked at ALR and P300 waveform patterns in subjects experiencing tinnitus. The existing literature on ALRs in tinnitus has been variable with conflicting reports. Some studies have reported longer N1, P2 and P300 waveform latencies (Azevedo, Figueiredo, & Penido, 2020; Santos Filha & Matas, 2010). However, several other studies have reported no difference in ALR latencies but rather differences in amplitude (Attias, Urbach, Gold, & Shemesh, 1993). Although some authors observed higher mean N1-P2 amplitudes in people with tinnitus, others report decreased N1, P2 and P300 amplitudes

relative to controls without a history of chronic tinnitus (Attias et al., 1993; Santos Filha & Matas, 2010). Many of the studies made use of participants with chronic tinnitus and hearing loss therefore the changes in cortical activity reported in these studies may not be wholly attributed to tinnitus but also to hearing loss and compensatory changes following chronic tinnitus. There is a paucity of data on the ALR and P300 waveform patterns in normal hearing people without tinnitus who tend to perceive tinnitus when exposed to silence.

1.1 Problem Statement

Tinnitus is a common otological symptom that can be a source of great distress to those who experience it. It is a universal problem affecting 15% to 35% of individuals worldwide. Despite the high prevalence of tinnitus, the underlying neural mechanisms behind tinnitus perception are still unknown. The recording of ALR and P300 waveforms in subjects actively perceiving tinnitus may provide researchers with a means of objectively documenting tinnitus generation. Few, if any studies have documented the differences in ALR and P300 waveforms and the emergence of temporary tinnitus after a brief period of silence.

1.2 Purpose of the Study

This study is an extension in a series of research studies on tinnitus in silence first reported by Tucker et al., 2005. These studies have compared the response of various regions of the peripheral and central auditory system in groups who do not experience tinnitus when exposed to silence and those who experience temporary tinnitus after exposure to a brief period of silence. So far, it has been observed that there is no difference in otoacoustic emissions and auditory brain stem responses between these two groups (Personal Communication). However, it has been observed that participants who perceive temporary tinnitus when exposed to a brief period of sustained silence had larger pre- and post-silence AMLR amplitudes than participants who did not perceive tinnitus while in silence (Personal Communication). There was no significant difference reported between the AMLR amplitudes before and after exposure to brief silence or AMLR latencies between both groups. This finding supports the widely held belief that tinnitus emergence has a central origin rather than peripheral origin. It also implies that people who are likely to experience temporary tinnitus in silence have an increased auditory cortical response when compared to those who do not perceive tinnitus in silence. To further explore the differences in cortical

response in tinnitus emergence, this present study investigated late latency responses and the role of auditory and non-auditory cortical regions in the emergence of tinnitus.

The purpose of this study is to compare the waveform latencies and amplitudes of scalp recorded ALR and P300 responses in normal hearing young female adults who perceive temporary tinnitus after a brief exposure to sustained silence, to the waveform latencies and amplitudes of normal hearing young female adults who do not perceive temporary tinnitus after a brief exposure to sustained silence. Results from this study will help document the neural responses of the auditory and non-auditory cortical regions associated with the emergence and perception of tinnitus. Thus, this study will broaden the present understanding of the differences in cortical responses that may underlie the tendency of some people to perceive tinnitus. This study will also improve the understanding of the role of attention in the perception of tinnitus and explore the central gain and network theories of tinnitus generation.

An improved understanding of the cortical responses that may be involved in tinnitus emergence and perception will contribute to the planning of tinnitus therapy and hopefully to the eventual arrival at an effective treatment for tinnitus.

1.3 Research Questions

This study aims to answer the following questions:

1. ALR Waveforms: Do normal hearing adults without tinnitus who perceive temporary tinnitus after a period of silence have different ALR waveform latencies and amplitudes than normal hearing adults without tinnitus who do not perceive tinnitus after a period of prolonged silence?
2. P300 Waveforms: Do normal hearing adults without tinnitus who perceive temporary tinnitus after a period of silence have different P300 latencies and amplitudes than normal hearing adults without tinnitus who do not perceive tinnitus after a period of prolonged silence?
3. Do ALR and P300 Waveform latencies and amplitudes show racial differences?

1.4 Hypothesis

1. The mean ALR amplitudes in normal hearing adults who perceive temporary tinnitus after exposure to sustained silence will be larger than the mean ALR amplitudes in normal hearing adults who do not perceive temporary tinnitus after exposure to sustained silence.
2. Mean P300 waveform amplitude in normal hearing adults who perceive temporary tinnitus after exposure to sustained silence will be significantly larger than the mean P300 waveform amplitude in normal hearing adults who do not perceive temporary tinnitus after exposure to sustained silence.
3. Waveform latencies will not be affected by silence and tinnitus perception. Waveform latencies and amplitudes will not differ by race.

CHAPTER II: LITERATURE REVIEW

The following review of the current literature will examine the epidemiology as well as the current theoretical models of tinnitus generation. Current treatments of tinnitus and the effect of silence on tinnitus perception will be reviewed. The different kinds of AERs and the associated underlying neural generators will be described. Finally, research addressing ALRs in people with tinnitus will be reviewed.

2.1 Epidemiology of Tinnitus

Tinnitus is the perception of sound in the absence of an auditory stimulus (Langguth et al., 2013; Savage & Waddell, 2014). It is often reported as the perception of sound in the ears or the head and this perception can be unilateral or bilateral (Baguley, McFerran, & Hall, 2013). Tinnitus can be perceived as noise or tones such as ringing, buzzing, humming, whistling, hissing, roaring, cricket-like or like water falling from a height (Hoffman & Reed, 2004; Langguth, 2011; Schlee et al., 2011). These can be persistent or intermittent.

Tinnitus is estimated to affect 12% to 15% of the adult population, with a male preponderance (Axelsson & Ringdahl, 1989; Bhatt et al., 2016; Tunkel et al., 2014). The worldwide prevalence of tinnitus varies from 5.1% to 42.7%. This variability in reported prevalence is related to the use of differing definitions of tinnitus by authors, however, it is estimated that 25.3% of Americans are likely to be experiencing tinnitus at any point in time and that it is persistent in 7.9% of individuals(McCormack, Edmondson-Jones, Somerset, & Hall, 2016; Shargorodsky et al., 2010). The CDC estimates that one out of every ten Americans experiences tinnitus whereas a National Health and Nutrition Examination Survey which ran from 2005–2008 estimated that 2.5 million youths aged 12–19 years reported having tinnitus (CDC, 2018; Mahboubi, Oliaei, Kiumehr, Dwabe, & Djalilian, 2013). The incidence of tinnitus rises with age and is highest amongst persons between 40 to 70 years, but peaks between 60 and 69 years, after which the incidence reduces (Bhatt et al., 2016; McCormack et al., 2016; Shargorodsky et al., 2010).

The five-year incidence of tinnitus is estimated to be 18% while the prevalence is estimated to be as high as 12.7% in older adults within the United States (Gopinath, McMahon, Rochtchina, Karpa, & Mitchell, 2010; Nondahl et al., 2010). Studies in the United States indicate that it is seen more in Caucasians than Blacks, and is reported more in the Southern part of the United States in comparison to the North (Seidman, Standring, & Dornhoffer, 2010). In the 2007 National Health survey sponsored by the National Institute of Health, 9.6% of the participants reported experiencing tinnitus within 12 months of the study, 36% of these had constant symptoms (Bhatt et al., 2016). Higher rates of tinnitus were reported in those exposed to occupational and leisure noise and the incidence was positively related to the length of exposure to loud noise. Tinnitus is regarded as a significant problem by 7.2% of those who experience it and 2% of individuals with tinnitus find it debilitating and detrimental to their quality of life (Bhatt et al., 2016; Langguth et al., 2013; Newman et al., 2011). Tinnitus has been associated with anxiety, depression, insomnia, and difficulty concentrating (Axelsson & Ringdahl, 1989; Granjeiro et al., 2013; Langguth, 2011).

2.2 Etiopathogenesis of Tinnitus

Tinnitus can be objective or subjective. In objective tinnitus, the examiner is able to confirm the tinnitus sound while in subjective tinnitus, the patient is the only one that perceives the tinnitus.

Objective tinnitus may present as a clicking sound in palatal myoclonus and temporomandibular joint disorders, fluttering sound in stapedius muscle myoclonus (Bernhardt et al., 2011). A vascular murmur (bruit) may be picked up in cases of pulsatile tinnitus resulting from arterial bruits, venous hums and from glomus tumors of the middle ear, vagus nerve or the jugular bulb (Crummer & Hassan, 2004; Levine & Oron, 2015; Sismanis, 2011). Arterio-venous malformations of the carotid, jugular bulb or dural vasculature can also result in objective pulsatile tinnitus (Borton & Hicks, 1989; Sismanis, 2011)

Subjective tinnitus is seen more frequently and is commonly associated with tinnitus of various qualities seen after exposure to loud sounds and in association with hearing loss (Langguth et al., 2013; Levine & Oron, 2015). This type of tinnitus may also occur in patients with cerebellopontine angle tumors. Pulsatile subjective tinnitus is often associated with

hyperdynamic states such as anemia and thyrotoxicosis, as well as in otosclerosis while blowing tinnitus is often reported in patients with patulous eustachian tubes (Bailey, Johnson, & Newlands, 2006).

Lesions of the peripheral and/or central auditory pathway can often lead to the perception of tinnitus (Langguth et al., 2013). Tinnitus has been associated with sudden sensorineural hearing loss, noise induced hearing loss, age related hearing loss, Meniere's disease, autoimmune inner ear disease, ototoxicity, non-syndromic familial hearing loss and various forms of conductive hearing loss, however, the relationship between tinnitus and hearing loss is complex because not everyone with hearing impairment will report tinnitus and some people with tinnitus have normal audiometric thresholds (Langguth et al., 2013; Levine & Oron, 2015). Some studies have shown that despite normal audiometric thresholds, people with tinnitus may have some form of auditory abnormalities that are not detected by conventional audiometry but may be evident in distortion product otoacoustic emission tests, threshold equalizing tests and pitch scaling tasks (Ami, Abdullah, Awang, Liyab, & Saim, 2008; Park et al., 2013; Weisz, Hartmann, Dohrmann, Schlee, & Norena, 2006).

Tinnitus can also be classified as primary or secondary. Primary tinnitus is tinnitus that has no associated specific underlying cause except perhaps sensorineural hearing loss whereas secondary tinnitus is tinnitus associated with some underlying condition except for sensorineural hearing loss (Tunkel et al., 2014)

2.3 Mechanisms Behind Tinnitus Generation

Several mechanisms have been proposed for tinnitus generation, the most common ones are the dorsal cochlear nucleus model, cortical tonotopic reorganization model, neural synchrony model, central gain model and network model (Henry et al., 2014; Yang & Bao, 2013).

2.3.1 The Dorsal Cochlear Nucleus (DCN) Mechanism

The DCN mechanism proposes that auditory sensory deprivation is associated with hyperactivity in the DCN and that this hyperactivity may initiate or maintain tinnitus generation (Brozoski,

Bauer, & Caspary, 2002; Wang et al., 2009). Although this model may explain the maintenance of tinnitus it does not explain its initiation because this hyperactivity is only observed days after the onset of tinnitus. Ablation of the DCN also does not lead to tinnitus resolution but may result in a worsening of tinnitus symptoms (Brozoski & Bauer, 2005). This implies that the DCN plays some sort of modulatory role on tinnitus but is not responsible for the initial generation of tinnitus.

2.3.2 Cortical Tonotopic Reorganization Mechanism

The cortical tonotopic reorganization mechanism proposes that tinnitus may be a consequence of the reorganization of the cortical tonotopic map which occurs in the primary auditory cortex following sensory deafferentation (Muhlnickel, Elbert, Taub, & Flor, 1998). This reorganization results in the expansion of the cortical response and representation to intact frequency regions at the expense of the deprived frequencies and is thought to be similar to that seen after amputation in patients with phantom limb sensation and phantom limb pain (De Ridder, Elgoyhen, Romo, & Langguth, 2011; Seki & Eggermont, 2002, 2003). The neurons with characteristic frequencies above the trauma frequencies become tuned to the lower frequencies at the edge of the hearing loss zone. Sometimes a broadening of the frequency tuning within the hearing loss zone and adjacent zones is seen instead (Seki & Eggermont, 2002, 2003). Yang et al, 2011 observed that adult rats with induced persistent high frequency threshold shifts developed a significant increase in the elicited auditory cortical response (spikes per tone) from the unaffected low frequencies, as well as an enlarged cortical representation of these low frequencies when compared with normal hearing controls (Yang, Weiner, Zhang, Cho, & Bao, 2011) The cortical remapping model proposes that cortical remapping results in the generation of tinnitus from within the intact remapped zone or at the edge of its boundary with the hearing loss zone (Engineer et al., 2011; Muhlnickel et al., 1998). However, tinnitus pitch-matching shows that most tinnitus is perceived in the frequencies affected by hearing loss, therefore, cortical remapping may be a consequence of hearing impairment but not the initiator of tinnitus (Langers, de Kleine, & van Dijk, 2012; Yang et al., 2011) To further support this fact, Langers et al, 2012 studied the tonotopic maps generated from imaging studies of some human tinnitus sufferers with near normal hearing and compared these with those of healthy normal hearing controls. They did not observe a significant

difference in the cortical tonotopic maps in these two groups and concluded that cortical map reorganization is not required for tinnitus generation in the auditory cortex (Langers et al., 2012). Yang et al., 2011 also demonstrated that tinnitus in high frequency hearing loss was associated with the sensory deprived cortical region which lacked map reorganization rather than the region with normal afferent input which had undergone cortical remapping.

2.3.3 The Central Gain Mechanism

The central gain mechanism proposes that tinnitus is the result of homeostatic plasticity, an attempt by the neurons to maintain their activity level during auditory deprivation or injury (Henry et al., 2014; Wang et al., 2009; Yang et al., 2011). The central gain model implies that auditory neurons develop increased excitability and undergo homeostatic synaptic plasticity. This mechanism could account for the widespread changes seen in neurons within the auditory pathway and other non-auditory associated regions after auditory injury or deprivation. It appears to tie all the other models together and focuses on an imbalance between excitation and inhibition within the auditory pathways and their non-auditory connections.

Several animal studies have looked at the role of homeostatic plasticity in auditory sensory deprivation and tinnitus. Whiting et al, 2009 demonstrated an increase in the expression of GluR3 α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) at excitatory auditory nerve synapses on the bushy cells and fusiform cells of the dorsal cochlear nucleus in rats after 24 hours of unilateral ear plugging. They observed a concomitant decrease in the expression of GlyR∝1, a prominent receptor subunit for the inhibitory neurotransmitter glycine. This change in the excitatory and inhibitory expression in the synapses of cochlear neurons was only observed in synapses affected by sensory deprivation but was not observed in synapses whose afferent input was unaffected by the ear plugging (Whiting, Moiseff, & Rubio, 2009). This implies that the neurons in the cochlear nucleus adjust the inhibitory and excitatory inputs at their synapses in response to auditory deprivation. This redistribution of AMPAR subunits was seen after just 4 hours of unilateral ear plugging and was shown to return to the baseline levels observed prior to the ear plugging 24 hours after the removal of ear plugs. Their results also show that the compensatory synaptic upregulation of AMPAR subunits at excitatory

synapses and the compensatory downregulation of GlyR∝1 at inhibitory synapses occurred in contralateral homologous regions of the cochlear nucleus in response to the decreased afferent auditory input from the plugged ear. Wang et al, 2009 also observed tinnitus related changes in glycine receptor (GlyR) composition and decrease in the number of GLyR binding sites within the DCN while Wu et al, 2018 demonstrated a relationship between tinnitus and the increase in the excitation in neurons of the auditory cortex as evidenced by increased AMPAR expression and altered gamma-Aminobutyric acid (GABA) receptor activity in excitatory neurons of the auditory cortex following long-term administration of salicylate (Wang et al., 2009; Wu et al., 2018).

Yang et al., 2011 measured the miniature excitatory and inhibitory post-synaptic currents (mEPSCs and mIPSCs) and observed an increase in the amplitude and frequency of the mEPSCs in the auditory pyramidal neurons tuned to the unaffected frequencies. They also observed that although there was an increase in the amplitude of the mIPSCs in the neurons within the unaffected frequency regions, the neurons in the affected high frequency regions of the primary auditory cortex showed a decrease in the frequency of mIPSCs. This is indicative of a reduction in GABA neurotransmitter release probability. They were able to show that this down-regulation of neuronal inhibition in the auditory cortex was responsible for the generation of tinnitus.

2.3.4 Neural Synchrony Mechanism

The neural synchrony mechanism postulates that the changes in frequency tuning seen in the deafferented neurons results in the broadening of the response region and a tendency for neuronal synchrony. Deafferented auditory cortical neurons become tuned to the characteristic frequency of adjacent neurons within the intact frequency bands. In addition to the changes in tuning, alteration in the timing and pattern of firing have been observed as well as an increase in the spontaneous firing rate and burst frequencies (Norena & Eggermont, 2003). Norena & Eggermont, 2003 observed an immediate change in the characteristic frequencies of central auditory neurons and an immediate increase in burst firing rate, number of spikes per burst and burst duration in cats exposed to a loud 5KHz tone. They also observed an increase in spontaneous firing rate, but this was a delayed response seen after some hours. These changes

were maximal in neurons with characteristic frequencies one or more octave above the frequency region of the trauma tone. They observed that these affected high frequency neurons showed a characteristic frequency shift towards lower frequencies. This alteration in brain rhythms and increase in synchronous activity is postulated as the reason for tinnitus generation (Eggermont & Tass, 2015; Henry et al., 2014; Munguia, Pienkowski, & Eggermont, 2013). This mechanism is very similar to the central gain model and may in fact work synchronously with it especially as it has been postulated that the increase in spontaneous firing rate may be due to a release from inhibition as a consequence of the reduction in GABAergic input (Yang et al., 2011).

Tinnitus thus appears to the result of a complex set of events set in motion by a reduction in auditory stimulation and resulting in a downregulation of auditory neuronal inhibition, a redistribution of glutamate receptors on the neurons, an increase in burst firing and an increase in spontaneous firing rate which are all part of an increase in gain which is perceived as tinnitus (Schaette & Kempter, 2006; Sedley, 2019). This may explain why studies have consistently shown that more than 60% of normal hearing subjects who have no previous history of tinnitus are likely to perceive tinnitus when left in silence for a minimum duration of 5 minutes, an activity that simulates auditory deprivation (Del Bo et al., 2008; Heller & Bergman, 1953; Tucker et al., 2005).

These compensatory changes demonstrated in the primary auditory cortex have also been observed in other regions of the central auditory nervous system. Increased spontaneous activity has been observed in the neurons of the dorsal and ventral cochlear nucleus after noise damage and has been linked to tinnitus generation (Brozoski et al., 2002; Robertson, Bester, Vogler, & Mulders, 2013; Zhang & Kaltenbach, 1998). Some studies have observed this increased activity in inferior colliculus which showed a correlation to the frequency of the tinnitus (Bauer, Turner, Caspary, Myers, & Brozoski, 2008; Ma, Hidaka, & May, 2006; Robertson et al., 2013). This increase in gain extends all the way to the primary auditory cortex (Norena, 2011; Norena & Eggermont, 2003; Seki & Eggermont, 2003) . Consequently, this hyperactivity within various levels of the central auditory nervous system may make them more likely to generate action potentials in response to spontaneous afferent input from the cochlear (Robertson et al., 2013).

2.3.5 Network Model

The network model attempts to explain the emotional response to tinnitus and its interaction with attention by elucidating that the spread of neuronal activation seen in tinnitus is widespread and extends to the thalamus, limbic system, frontal cortex, parietal cortex and the parahippocampal region (Knobel & Sanchez, 2008; Lanting, de Kleine, & van Dijk, 2009; Muhlau et al., 2006; Rauschecker, Leaver, & Muhlau, 2010). Increased fluorodeoxyglucose (FDG) uptake has been observed in the hippocampus, Inferior Colliculus, and the auditory cortex of rats with tinnitus (Yi et al., 2016). Increased functional connectivity between the limbic system and the auditory cortex have also been observed (Cai, Li, Yang, & Zhang, 2019). These non-auditory areas may modulate attention to tinnitus which may amplify its perception. These non-auditory cortical regions may also be responsible for the differing emotional responses seen in patients with tinnitus as reported in patients who underwent frontal leucotomy as part of therapy for tinnitus. These patients showed reduced annoyance from tinnitus despite the fact that there was no reported change in the loudness of their tinnitus (Beard, 1965). Some authors have reported that resting state Magnetoencephalography (MEG) and resting state Functional Magnetic Resonance Imaging (fMRI) show increased connectivity between the medial temporal cortex and the prefrontal cortex, parahippocampus and inferior parietal cortical regions (Kim et al., 2012; Paraskevopoulos et al., 2019). It appears that these regions may contribute to the modulation of tinnitus perception as well as to the regulation of emotional processing, auditory memory, awareness and attention in tinnitus subjects (Kim et al., 2012; Paraskevopoulos et al., 2019). It is postulated that following the increased gain seen in an effort to achieve homeostasis in the auditory pathway, a breakdown in the control of the perception of this gain as tinnitus occurs in these non-auditory regions and results in persistent attention to the sensation generated by the increase in auditory gain (Rauschecker et al., 2010). Even though the exact nature of the breakdown is still being investigated, this mechanism may account for the variance in the response to tinnitus and why some people find it more disturbing than others.

2.4 Tinnitus in Silence

Several authors have reported that more than 50% of individuals without ongoing tinnitus are likely to perceive temporary tinnitus if they are exposed to sustained silence for a few minutes.

The first of such studies was by Heller and Bergman, 1953. They observed that after exposure to five minutes of silence, 94% of the participants with self-reported normal hearing and 73% of those with hearing loss perceived temporary tinnitus (Heller & Bergman, 1953). They concluded that tinnitus may be a physiological phenomenon which is present in everyone but not audible because of environmental sounds. Tucker et al., 2005, observed that 64% of the 120 participants in their study perceived temporary tinnitus when exposed to 20 minutes of silence. They observed this in normal hearing young adults aged between 18 years to 30 years. Although they made use of 20 minutes of silence, the majority of the participants in their study perceived tinnitus within the first five minutes (Tucker et al., 2005). The participants were younger than those in the Heller & Bergman, 1953 study and were confirmed to have hearing loss, which may account for the lower proportion of those who perceived tinnitus in this study. They also observed that Caucasians (78%) were more likely to perceive tinnitus than African Americans (38%), but no gender differences were observed.

Knobel and Sanchez, 2008 explored the influence of auditory attention on the perception of temporary tinnitus in silence and observed that although only 19.7% of their participants perceived temporary tinnitus while engaged in a cognitive task, 45.5% of the participants perceived temporary tinnitus when their visual attention was engaged and this increased to 68.2% when their auditory attention was engaged (Knobel & Sanchez, 2008). Their findings imply that attention and cognitive mechanisms have an influence on the perception of tinnitus. A study by Del Bo et al., 2008 questioned the role of attention and anticipation in tinnitus perception. Their participants were exposed to two sessions of brief silence. In both sessions, they remained in silence for 4 minutes in an anechoic chamber, but they added a loudspeaker during the second session to test for the effect of auditory suggestion on tinnitus perception. They observed a slight increase in the perception of temporary tinnitus from 83% to 92% when a loudspeaker was placed in the testing booth, but this increase was not statistically significant (Del Bo et al., 2008). The participants in this study underwent tests to confirm that they had

normal audiometric thresholds, high frequency thresholds and outer hair cell function, therefore, the high proportion of reported tinnitus perception in this study may be a consequence of the instruction given to the participants in which they were asked to listen for tinnitus sounds. Although they concluded by saying that auditory suggestion may not play a significant role in the perception of phantom sounds when exposed to silence, this study confirms that a large proportion of normal hearing individuals will perceive temporary tinnitus when exposed to silence.

The emergence of tinnitus in subjects exposed to silence as reported in these studies may be attributed to the perception of internally generated sounds previously masked by environmental sounds, however, another explanation could be that the reduced auditory stimulation in silence results in compensatory activity in the auditory system which is perceived as tinnitus(Heller & Bergman, 1953; Norena & Eggermont, 2003; Tucker et al., 2005; Whiting et al., 2009). The findings by Knobel and Sanchez, 2008 and Del Bo et al., 2008 imply that attention plays a key role in the perception of emergent tinnitus in normal hearing individuals without tinnitus.

2.5 Effect of Tinnitus on Quality of Life

Several studies have reported that a proportion of people with chronic tinnitus find that it has a detrimental effect on their quality of life and is associated with psychiatric symptoms such as depression and anxiety (Gopinath et al., 2010; Langguth, 2011; Martines, Bentivegna, Martines, Sciacca, & Martinciglio, 2010). De Ridder et al.,2011, observed increased activity in all frequency bands in the anterior and posterior cingulate cortex, insula, parahippocampus and frontal gyrus in the participants with tinnitus compared to controls without tinnitus. The activity within these cortical networks were similar to the network activity in patients being managed for pain and post-traumatic stress disorder and may reflect that the tinnitus group shared a similar distress network as those with pain and post-traumatic stress disorder (De Ridder, Vanneste, & Congedo, 2011).

Individuals with chronic tinnitus may experience anxiety, depression, concentration difficulties, sleep difficulties and in some cases suicidal ideation (Axelsson & Ringdahl, 1989; Langguth, 2011). Malakouti et al., 2010 observed a greater prevalence of psychiatric disorder when they

compared a group of adults with tinnitus to a control group without tinnitus. This was a large study of 400 tinnitus patients. They observed that females had greater levels of handicap and distress than did males (Malakouti, Nojomi, Mahmoudian, Alifattahi, & Salehi, 2010). A similar finding was reported by Granjeiro et al., 2013, in which subjects with ongoing tinnitus were observed to have a higher prevalence of anxiety and depression than controls. They also observed a positive correlation between the scores from the Beck Depression and Anxiety Inventory and the Tinnitus Handicap Inventory (Granjeiro et al., 2013).

Some authors have reported sleep disturbances and difficulties with carrying out daily activities in participants with tinnitus (Martines et al., 2010). Interestingly, in the study by Martines et al., 2010, even though a greater proportion of participants with hearing loss reported handicap from tinnitus, participants who had normal hearing were more likely to report catastrophic levels of handicap (Martines et al., 2010). Thus, there appears to be a positive relationship between tinnitus severity and quality of life, and the negative effect of tinnitus on the quality of life has been widely reported (Härter, Maurischat, Weske, Laszig, & Berger, 2004; Negrila-Mezei, Enache, & Sarafoleanu, 2011; Ukaegbe, Orji, Ezeanolue, Akpeh, & Okorafor, 2017).

2.6 Tinnitus Treatment

There is no single approved treatment for tinnitus as designated by the US Food and Drug Administration. Some treatment modalities have been used in an attempt to improve tinnitus symptoms but most have been reported to show no advantage over placebo (Seidman et al., 2010). Lifestyle modifications such as the avoidance of silence and the reduction in caffeine, alcohol and aspartame intake have been reported to be beneficial in those with mild symptoms. Antidepressants such as Amytriptyline and Benzodiazepam are often part of the prescription for tinnitus and have been reported to be beneficial but their use is not recommended by the American Academy of Otorhinolaryngology because there is no strong evidence for their use and they may have serious adverse effects (Seidman et al., 2010; Tunkel et al., 2014). Tinnitus retraining therapy, cognitive behavioral therapy and mindfulness therapy have been successfully used in managing tinnitus and can help reverse the negative thoughts and emotions that can worsen the response to tinnitus (Seidman et al., 2010; Tunkel et al., 2014). These are often

combined with sound therapy using tinnitus maskers and hearing devices. Transcranial Magnetic Stimulation seems to be successful in some people with tinnitus and is gaining in popularity (Kreuzer et al., 2017; Seidman et al., 2010).

Neural stimulation to promote plastic changes have been combined with auditory stimulation using stimuli centered around the hearing loss frequencies. Sound therapy combined with Vagus nerve stimulation may be used to selectively improve auditory neuronal response in deafferented auditory cortical neurons (Engineer et al., 2011; A. Noreña & Eggermont, 2005). This has the potential to improve cortical frequency selectivity and reverse cortical remapping as well as homeostatic plasticity driven increased burst firing rate, increased synchronization and increased excitability of the auditory cortical neurons which will likely result in tinnitus relief (Engineer et al., 2011). In a study by Yang er al. 2011, they were able to reverse noise induced tinnitus in rats with the use of drugs that enhance neuronal inhibition, in an effort to reverse the downregulation of inhibition which is proposed to be responsible for tinnitus (Yang et al., 2011).

2.7 Auditory Late Response (ALR) and the P300 Waveform

Two late AER waveforms that can be recorded in the late epoch timebase (between 50 and 500ms) after the presentation of an auditory stimulus are the Auditory Late Response (ALR) and the P300 response. Intracranial electrode studies in animals and in man seem to imply that the ALR is generated from the region of the Sylvian fissure and the superior portion of the temporal lobe with some contributions from the parietal and frontal cortices.

The ALR waveform consists of several exogenous positive and negative peaks. They are the P1, N1, P2 and N2 waveforms (See Figure 1). The P1 wave corresponds to Pb wave of the AMLR and is believed to be generated from the primary auditory cortex with some contribution from the reticular activating system. The N1 wave seems to be generated from the auditory cortex with contributions from the frontal cortex and sub-cortical structures that form part of the limbic system such as the thalamus, the hippocampus and the RAS (Picton et al., 1999). The P2 also has some contributions from the RAS as well as the planum temporale and auditory association areas such as Brodmann area 22. The N2 waveform is dependent on activity within the limbic system and the reticular activating system

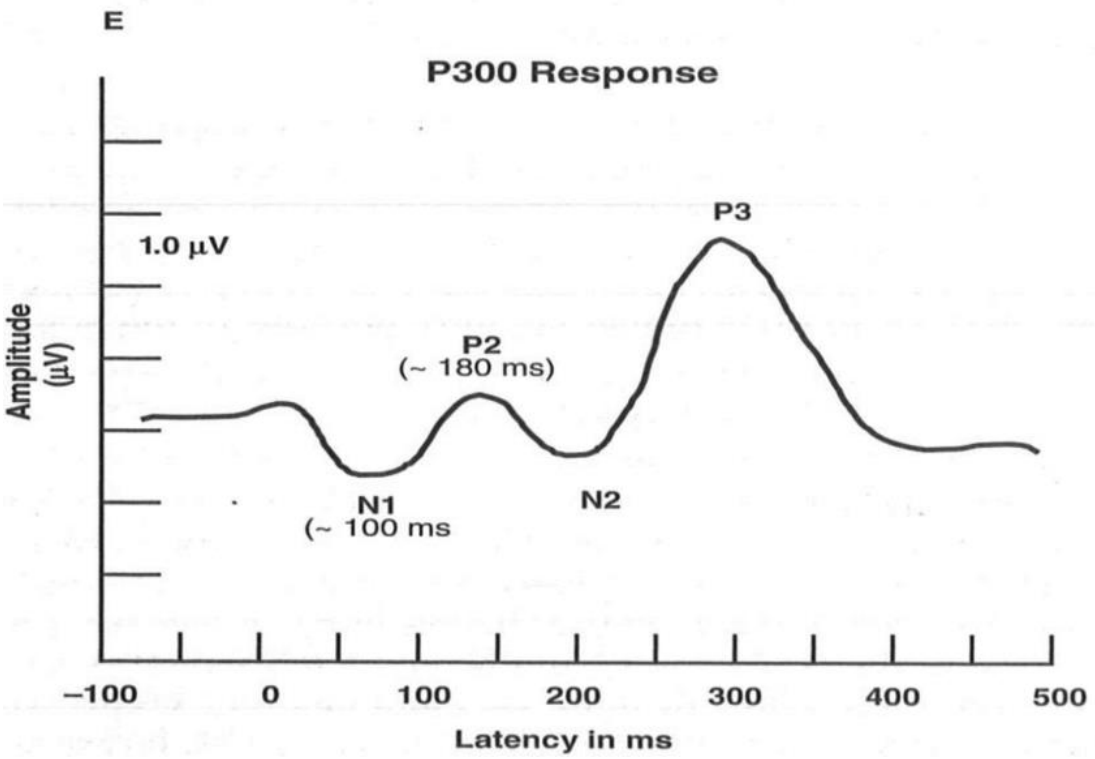

Figure 1: ALR Waveform (Hall, 2007)

The P300 is an endogenous waveform which is not as dependent on stimulus characteristics as the earlier waves but is more dependent on stimulus context and subject state and central or cognitive processing abilities (Hall, 2007; Prakash et al., 2016). Cortical regions implicated in the generation of the P300 waveform include the temporal cortex, temporal-parietal cortical regions, the hippocampus, para-hippocampus, amygdala, frontal cortical regions, thalamus, and the parieto-occipital junction. Functional magnetic imaging studies have been used to show activity in the peri-sylvian region, the supramarginal gyrus, the frontal operculum and medial frontal gyrus, the insular, thalamus and the inferior parietal regions (Linden et al., 1999). The corpus callosum also plays a role in interhemispheric processing of attention, therefore it has some influence on the characteristics of the P300 wave form. The amplitude of the P300 response shows a reduction in those with medial temporal and temporo-parietal lesions (Polich, 2007).

Multiple perceptual and cognitive processes seem to be involved in the generation of a P300 response, the most common being memory, attention, discrimination, and response inhibition (Melynyte et al., 2018; Polich, 2007). The P300 response is believed to either be a consequence of context-updating or context -closure. The former hypothesizes that it is due to information processing in which there is continuous updating of response to encountered stimuli, whereas the context-closure hypothesis contends that it reflects the conclusion of a sensory response (Melynyte et al., 2018; Polich, 2007).

2.7.1 ALR/P300 AND GENDER

ALR and P300 waveforms are affected by sex and handedness. Females show similar P300 latency as males but have greater P300 amplitudes in comparison to males (Melynyte et al., 2018). Females also tend to have higher ALR waveforms and steeper amplitude-intensity functions than males. This has been attributed to differences in cortical anatomy and physiology. Females tend to have thicker corpus callosum and higher grey matter volume in the parietal lobe than do males.

2.7.2 ALR/P300 AND HANDEDNESS

Left handed individuals have shorter P300 latencies and larger amplitude in anterior scalp recordings than their right-handed counterparts(Alexander & Polich, 1997). They also have larger N1 and N2 amplitudes and shorter N1, P2 and N2 latencies compared to right-handed subjects. It has also been reported that P1 amplitude seems to show a left ear disadvantage when compared to P1 elicited with binaural stimulation (Purdy et al., 2002).

2.7.3 ALR/P300 AND RACE

The effect of race on AERs have not been extensively studied. Zakaria et al., 2016 investigated the effect of ethnicity on speech ABR by comparing ABR waveform latencies and amplitudes in Malay and Chinese participants. They did not observe any significant differences in speech-ABR waveform latencies and amplitudes between these two groups and they attributed this to

anatomical similarities between the two groups (Zakaria, Jalaei, Aw, & Sidek, 2016). However, when they compared the data obtained in these subjects to the data obtained in a group of Caucasians, they observed shorter latencies and higher amplitudes in the Asian subjects and attributed this difference to anatomical differences between both groups such as the smaller head sizes of the Asian participants (Zakaria et al., 2016). They also considered the possibility that the tonal nature of the Chinese language may contribute to the differences observed.

2.7.4 ALR/P300 AND AGE

The ALR shows a lot of variability based on stimuli pattern, subject characteristics and arousal state (Hall, 2007). It can be recorded from children and adults, as well as preterm infants (Didoné, Garcia, & da Silveira, 2014). The amplitude of P2 increases with age especially throughout childhood, while its latency decreases (Hayes, Warrier, Nicol, Zecker, & Kraus, 2003; Wunderlich & Cone-Wesson, 2006; Wunderlich, Cone-Wesson, & Shepherd, 2006). N1, P2 and P3 waveform amplitudes increase steadily throughout childhood till the early twenties after which a steady decrease in amplitude is seen in adults (Goodin, Squires, Henderson, & Starr, 1978).

Conversely, the peak amplitude of N2 and its latency decreases with age and this is considered a sign of maturation. The ALR waveform typically looks adult like by the age of twelve. The shortest ALR and P3 latencies are seen in teens and those in their early twenties, prior to that, the P3 latency decreases steadily in children while a significant increase in latency is seen in adults after their teens (Goodin et al., 1978).

2.7.5 ALR/P300 AND ACOUSTIC STIMULUS

Amplitudes of the N1 and P2 waves are often larger for low frequency tonal stimuli in comparison to high frequency stimuli(Wunderlich et al., 2006). They are also larger for speech stimuli than for simple tonal stimuli, however, latency is shorter for single frequency tonal stimuli. N1 and P2 amplitudes also show an increase with increasing sound duration. (Ostroff, McDonald, Schneider, & Alain, 2003). Longer duration signals elicit P2 waves with larger amplitudes in young and middle-aged adults than older adults and may indicate an age-related

impairment in temporal processing (Ostroff et al., 2003). A nonlinear decrease in latency and increase in amplitude is observed with increasing stimulus intensities (Prakash et al., 2016).

2.7.6 ALR/P300 AND THE EFFECT OF ATTENTION

Attention affects the P300 waveform, attention to the target stimuli results in an increase in P300 amplitude, furthermore, the target signal results in an increase in N1 and N2 amplitude and a decrease in P2 amplitude probably due to the presence of the P300 waveform (Polich et al., 1997). With decreasing arousal there is an enhancement of the N2 wave while the NI wave shows an increase in latency and a decrease in amplitude (Picton et al., 1974). During sleep the intensity needed to elicit the ALR increases, and the waves are differentially affected but amplitude of the waves becomes highly variable (Cote, Etienne, & Campbell, 2001; Hall, 2007). Cote et al 2001 report reduced N1 waves and enlarged P2 waves relative to wakefulness but Picton et al., 1974 reported a decrease in P2 amplitude often preceded by a transient increase in amplitude in the early moments of sleep. Sedation therefore results in marked variability of the ALR and should be avoided in ALR assessment.

2.8 Resting State Functional Connectivity in Tinnitus

Several authors have looked at the resting state cortical activity in people with tinnitus using various imaging techniques. The studies on resting state cortical activity appear to give a glimpse into the typical cortical activity in tinnitus patients since they are not often engaged in any task, auditory or otherwise.

Studies using functional Magnetic Resonance Imaging (fMRI) based on resting state fluctuations in blood oxygen level-dependent (BOLD) signals have shown increased connectivity between the auditory cortex and non-auditory regions such as the frontal cortex, amygdala, hippocampus and parahippocampus (Chen et al., 2017; Kim et al., 2012). The increased connectivity between the auditory cortical region and the areas involved with the updating and consolidation of memory such as the hippocampus and parahippocampus could explain the problems with habituation experienced by some people with tinnitus (Chen et al., 2017). Increased functional connectivity has also been observed between the auditory cortex and cortical regions involved in

the modulation of attention, response inhibition and behavior such as the frontal cortex and the cingulate cortex (Chen et al., 2017; Kim et al., 2012; Maudoux et al., 2012). This implies that the frontal and cingulate cortices may play a role in the regulation of the emotional and attentional response to tinnitus. Furthermore, the increased functional connectivity demonstrated between the amygdala and the auditory cortex implies that the amygdala has a significant role to play in the interpretation of the tinnitus sound and any negative connotations (Chen et al., 2017; Kim et al., 2012). However, Hofmeier et al., 2018 observed reduced sound evoked auditory cortical activity and reduced resting state functional connectivity in auditory and non-auditory cortical regions in tinnitus subjects and Davies et al., 2014 did not observe a difference in cortical functional connection between the amygdala and the auditory cortex (Davies, Gander, Andrews, & Hall, 2014; Hofmeier et al., 2018). This may be a consequence of the differences in patient selection and signal acquisition methods used in these studies, while subjects in the studies by Kim et al., 2012 and Chen et al., 2017 had normal average pure tone thresholds, the subjects, and the controls in the study by Davies et al., 2014 had mild to moderate hearing loss. Furthermore, Maudoux et al., 2012 reported increased resting state connectivity in areas of the limbic system such as the basal ganglia, nucleus accumbens, parahippocampus and in regions of the frontal, parietal and temporal cortices in tinnitus subjects with varying degrees of hearing loss and tinnitus handicap. Issa et al., 2016 observed that while silence led to a decrease in activity in the temporal cortical regions of control participants, it led to increased activity in the auditory and non-auditory regions in tinnitus subjects (Issa, Bisconti, Kovelman, Kileny, & Basura, 2016).

Studies in which Magnetoencephalography (MEG) was used in monitoring cortical resting state functional connectivity have the advantage of having a better temporal resolution as well as a quieter test environment. Researchers using the MEG to investigate resting state functional connectivity in tinnitus patients have reported increased functional connectivity between the auditory cortex and the prefrontal cortex, the parahippocampus and the inferior parietal region responsible for processing of auditory memory and awareness (Paraskevopoulos et al., 2019).

Leaver et al., 2011 demonstrated the presence of functional and structural markers of chronic tinnitus. Using fMRI recorded while subjects listened to tinnitus frequency matched sounds, they observed that tinnitus patients exhibited hyperactivity in the Heschl's gyri and in parts of the

limbic system (Leaver et al., 2011). They also report that tinnitus subjects appear to have structural differences in the white matter and gray matter concentration within the prefrontal cortex. These findings were not related to the age of the participant or to their hearing profile. The authors suggest that the structures involved in a network that appraises the importance of incoming sensations and determines how they are experienced differs in those with chronic tinnitus. They also postulate that the reduction in gray matter within the prefrontal cortex implies that tinnitus patients have less functional output from the prefrontal cortex.

These imaging studies in tinnitus subjects imply that there is altered functional connectivity between the auditory cortical regions and regions of the brain involved in the regulation of emotion, attention, auditory awareness, auditory memory and behavioral response. These areas therefore play a modulatory and regulatory role in tinnitus perception. The degree of alteration in functional connectivity has been shown to have some correlation to the level of distress from tinnitus, the perception of tinnitus loudness and to the duration of the tinnitus (Chen et al., 2017; Paraskevopoulos et al., 2019).

2.9 Auditory Evoked Response in Tinnitus

The latencies and amplitudes of auditory evoked potentials provide researchers with information about the timing and the strength of auditory neural discharge in response to sound stimuli (Azevedo et al., 2020).

The evoked response most investigated in patients with chronic tinnitus is the Auditory Brainstem Response (ABR), and those reports are conflicting. Researchers such as Said (2012) reported a higher prevalence of ABR abnormalities in tinnitus subjects with sensorineural hearing loss compared to subjects with sensorineural hearing loss but no tinnitus (Said, 2012). Tinnitus patients had longer III-V interpeak latencies and larger V/I amplitude ratio. Dadoo et al., 2019 observed that normal hearing subjects with tinnitus had prolonged wave I latencies but they did not report any other significant abnormalities in other components of the ABR (Dadoo, Sharma, & Sharma, 2019). Although the participants were described as having normal hearing after undergoing pure tone audiometry and otoacoustic emissions screening of frequencies between 2KHz and 6KHz, this was not confirmed with high frequency audiometry. Although the

studies by Said, 2012 and Dadoo et al., 2019 imply that abnormalities in neuronal synchrony may exist in the brainstem in tinnitus, some authors report that there were no significant differences in the ABR thresholds and latencies when tinnitus patients were compared to controls (Attias et al., 1993; Barnea, Attias, Gold, & Shahar, 1990; Konadath & Manjula, 2016). Although Konadath & Manjula, 2016 did not observe any significant difference in ABR latencies and amplitudes when a group with tinnitus was compared to controls without tinnitus, they observed that despite having normal hearing, the tinnitus group had reduced waves I and V amplitudes: an indication of alterations in the cochlear nerve and brainstem. However, they did not confirm that the high frequency thresholds of the tinnitus group were within normal limits, therefore, the decreases in wave I and V amplitudes may have resulted from high frequency hearing loss. They also observed an increase in P1 amplitude in the tinnitus group and they mention that this P1 enhancement may be an indication of an increase in central gain (Konadath & Manjula, 2016). Barnea et al., 1990 looked at the difference in high frequency audiometry and ABR in normal hearing participants with tinnitus and compared this to a control group without tinnitus. They did not observe any significant differences in the ABR of both groups and concluded that the cochlear and brainstem auditory pathways do not seem to be significantly affected in tinnitus patients (Barnea et al., 1990). A systematic review by Milloy et al., 2017 shows that there is sparse evidence that tinnitus patients have abnormal ABR latencies and amplitudes when compared with controls that are matched in age, sex and hearing thresholds. The most consistent finding in the reviewed articles was that normal hearing subjects with tinnitus were likely to have prolonged wave I latencies and smaller wave I amplitudes compared to controls, and this was significant in only three of the ten studies that investigated ABR latencies in tinnitus patients with normal hearing (Milloy, Fournier, Benoit, Noreña, & Koravand, 2017).

The Auditory middle latency response (AMLR) has not been as widely investigated in tinnitus as has the ABR. When participants with tinnitus and mild hearing loss were compared to controls without tinnitus in a study by Theodoroff et al., 2011, no differences were observed in the latencies and amplitudes of the AMLR. However, the controls were poorly matched in gender, age and hearing thresholds which presents some reservation in the interpretation of the results in that study (Theodoroff, Chambers, & McMillan, 2011). Gerken et al., 2001 report that 59% of

the participants with tinnitus in their study had large AMLR waves about three standard deviations larger than the waves in the control group with normal hearing. The AMLR waves showed a lot of variability in the participants with tinnitus when compared to a normal hearing group, an elderly group and a hearing loss group without tinnitus (Gerken, Hesse, & Wiorkowski, 2001). The tinnitus group were a heterogenous group with a wide age range extending from 26 years to 68 years. The control subjects in this study were poorly matched for age and hearing thresholds. However, the researchers concluded that the fact that these large AMLRs were only present in some tinnitus subjects and not in all of them may indicate that there are subgroups within the tinnitus group who have abnormalities along the auditory pathway in the midbrain and central auditory regions (Gerken et al., 2001).

2.9.1 Auditory Late Response in Tinnitus

Few studies have looked at the relationship between chronic tinnitus and ALRs. Most studies have investigated ALRs in tinnitus patients with hearing loss or with a history of noise exposure, but few have looked at tinnitus patients with normal hearing. Some authors report that tinnitus patients are likely to have lower N1, P2 and P300 amplitudes while others have reported larger amplitudes. Attias et al.,1993 examined tinnitus patients with noise induced hearing loss and observed that they had significantly lower amplitudes than controls who had noise induced hearing loss without tinnitus. They did not observe any significant differences in the latencies of N1, P2 and P300 between tinnitus patients and controls (Attias et al., 1993). They concluded that tinnitus patients do not appear to have disturbances in the speed of their cognitive processes but may exhibit decrease in neuronal activity and increased desynchronization in neuronal activity within auditory and non-auditory cortical neurons (Attias et al., 1993). The study by Attias et al (1993) looks at participants with hearing loss and it is difficult to know to what extent the result was affected by their hearing pathology. Jacobson et al., 2003 also observed smaller N1 amplitudes in participants with tinnitus with no significant differences in N1 latencies and attributed this to adaptive processes within the auditory cortical neurons in response to tinnitus (Jacobson & McCaslin, 2003). However, the tinnitus subjects in that study had varying degrees of hearing loss and were not matched in hearing thresholds to their normal hearing control subjects. Vasudevan et al., 2019 studied tinnitus subjects with normal hearing to mild hearing

loss and compared them to controls matched in hearing as well as in age and gender. They observed larger N1 and P300 amplitudes in the tinnitus group and longer P300 latencies in comparison to the control group (Vasudevan, Palaniswamy, & Balakrishnan, 2019). They concluded that since N1 reflects conscious detection of acoustic stimuli within the environment, the increased N1 amplitude in tinnitus may be a reflection of breakdown in habituation or a result of enhanced neural synchrony from the reorganization of tonotopic maps and increased baseline activity responsible for tinnitus perception in the tinnitus group (Vasudevan et al., 2019).

Other researchers have reported that tinnitus subjects have altered ALR waveform latencies possibly in association with altered amplitudes in comparison to controls without tinnitus. Although Houdayer et al., 2015 observed shorter N1 latencies in normal hearing subjects with tinnitus, dos Santos et al., 2010 observed that when they compared two groups of subjects who had been exposed to occupational noise, the group with bilateral tinnitus had significantly longer N1, P2 and P300 latencies while the group with unilateral tinnitus was observed to have larger N1-P2 amplitudes in the tinnitus ear (dos Santos Filha & Matas, 2010; Houdayer et al., 2015). They did not observe any differences in P300 amplitude between the tinnitus group and the controls without tinnitus and they conclude that the larger N1-P2 amplitudes in the subjects with tinnitus may reflect a disturbance with habituation, while the longer latencies may reflect problems with attention in tinnitus subjects. Both the tinnitus group and the control were confirmed to have normal audiometric thresholds, but high frequency hearing loss and outer hair cell function were not examined as part of the inclusion criteria so some of the participants may still have had some auditory pathology. Said, 2012 also reported significantly longer N1, P2 and P300 latencies in tinnitus subjects as well as reduced P2 and P300 amplitudes when subjects with tinnitus and sensorineural hearing loss were compared to subjects with sensorineural hearing loss but no tinnitus and controls with normal hearing (Said, 2012). This implies that cortical activity is altered in tinnitus patients independent of their hearing thresholds. In addition to the alteration in cortical activity, there seems to be an impairment in attention and cognitive performance in tinnitus patients as evidenced by longer P300 latencies and smaller P300 amplitudes. In some studies, P300 amplitudes and latencies did not differ significantly between subjects with tinnitus and controls without tinnitus (Abdeltawwab & Elmorsy, 2013; Houdayer et al., 2015; Najafi, 2020).

Although these studies give some insight into the alteration of cortical networks in tinnitus, the reports have been inconsistent probably due to the differences in subject characteristics and testing protocol as well as the heterogeneity in the tinnitus group involved in these studies. The existing studies of evoked potentials in tinnitus still do not improve our understanding of cortical differences that may precede the emergence of tinnitus because it is unclear to what extent these results reflect the cortical changes that result in tinnitus. The altered neuronal activity in people with chronic tinnitus may reflect compensatory cortical activity in response to prolonged exposure to tinnitus rather than a direct reflection of cortical changes that may explain the presence of tinnitus. These changes may give some insight into the level of cortical adaptation to tinnitus and may be explored as a measure of handicap and therapeutic monitoring. In addition, more investigation is needed about how differences in auditory and non-auditory cortical activity may result in an individual's susceptibility to tinnitus. Therefore, the aim of this present study is to investigate if there are differences in the latencies and amplitudes of the N1, P2, N2 exogenous waveforms and the P300 endogenous waveforms when adults without ongoing tinnitus who perceive temporary tinnitus after exposure to prolonged silence are compared to age-matched individuals who fail to perceive temporary tinnitus under similar conditions. This will document any underlying differences in neural activity which may predispose some people to tinnitus.

CHAPTER III: METHODS

3.1 Study Design

This was a prospective cross-sectional study. Convenience sampling was employed. Forty potential participants, and after hearing screenings and ALR recordings, thirty female participants were recruited for the study, in order to control for the effect of gender on ALRs (Melynyte et al., 2018). While there are no reported gender effects have been reported in the perception of temporary tinnitus in silence, there are differences in the ALR and P300 waveforms due to gender. Thus, only female participants were recruited for this study (Tucker et al., 2005). The age range was limited to young adults aged 18 to 35 years to control for the potential effect of age on tinnitus and hearing (Bhatt et al., 2016; McCormack et al., 2016; Shargorodsky et al., 2010). The use of young adults was also done to control for the changes in ALRs due to aging (Goodin et al, 1978). This study made use of ten minutes of silence based on the time it took participants to perceive tinnitus in previous studies (Tucker et al., 2005).

3.2 Participants

Participants were recruited by means of fliers, email messages and in-person. Minimum study sample size was twenty-five. Female participants without a history of chronic tinnitus aged 18-35 years, were admitted to this study. National Institutes of Health (NIH) racial classifications were used (NIH, 2015)

3.2.1 Inclusion Criteria

Additional criteria for inclusion in the study were pure tone hearing thresholds 25dBHL or less in octave frequencies 250Hz to 8000Hz, normal findings on otoscopy, Type A tympanograms bilaterally with peak pressure between -100 and +100 daPa.

3.2.2 Exclusion Criteria

No participant with a history of chronic ear infections, tinnitus, sound sensitivity, ear surgeries, concussions, head trauma, attention deficit disorder, attention deficit hyperactivity disorder, learning disability, speech-language disorder, central auditory processing disorder, seizures, or neurological disease was admitted to the study. Additionally, participants who were taking anti-depressants, sedatives, or anticonvulsant medications during the period of the study were excluded from the study.

3.3 Institutional Review Board (IRB) Approval and COVID-19 Safety Protocol Approval

Approval for the study was obtained from the UNCG IRB. All participants read and signed an informed consent form approved by the UNCG Institutional Review Board. Approval for the COVID-19 safety protocol used in this study was obtained from the UNCG Ramp-up committee.

3.4 Instrumentation

Hearing assessments, questionnaires and Evoked Response Audiometry will be part of the study protocol.

3.4.1 Hearing Assessment

All subjects who gave their consent to participate in the study underwent otoscopy, tympanometry, and audiometry in 327A lab to determine the conditions of their outer ears, middle ears, and their hearing sensitivity.

- Otoscopy was performed with the use of a Heine Otoscope.
- Middle ear function was assessed using a Grason Stadler (GSI) Middle Ear Analyzer calibrated 01/21/2021. A 226 Hz probe tone was used and pressure sweeps -200daPa through +200daPa. Participants with Modified Jerger type A tympanograms were admitted to the study.

- Hearing thresholds were assessed using a Grason Stadler (GSI) 61 clinical audiometer calibrated 01/21/2021 in a double-wall sound booth. Air conduction thresholds in octave frequencies 250 Hz to 8000Hz were assessed. Participants with thresholds ≤ 25 dBHL were admitted to the study.

3.4.2 Late Auditory Evoked Response (ALR) and P300 Recording

Intelligent Hearing Systems (IHS) Smart EP was used in recording the Late Auditory Evoked Potentials and P300 waveforms. A protocol was created for right monoaural P300 recording with a timebase of 512 ms using tone bursts with 10ms rise and fall times and 50ms durations.

ALR and P300 waveforms were elicited using 1000Hz (frequent) and 2000 Hz (rare) stimuli in an odd-ball paradigm (Hall, 2007). Two hundred and fifty artefact free tone bursts were presented at 80dBHL intensity with 50ms duration and 10ms rise-fall time through the intelligent hearing systems Smart EP. Eighty percent of the tones were 1000Hz tones, and 20% of the tones were 2000Hz tones. The stimuli were presented monoaurally at a rate of 1.1/sec through 3A Etymotic ear inserts and was calibrated in dB HL (Hall, 2007). Amplification was set at 1000 and filters at 1hz to 30Hz. The scalp EEG activity was averaged over a 512 ms time base.

For skin preparation alcohol wipes, Nuprep skin preparation gel and normal saline were used. Non-inverting electrodes were placed at the vertex (Cz), with the use of the Ten20 Conductive electrode paste, according to the international 10-20 system of electrode placement. The ground electrode was placed at the high forehead (Fpz), electrodes placed on the left and right mastoid (M1 and M2) were linked and served as reference electrodes (Abdeltawwab & Elmorsy, 2013; Najafi, 2020). Impedances at each electrode site was maintained below 5k Ohms.

3.4.3 Questionnaires

Two questionnaires were administered to the participants in this study (See Appendix A and B).

- A General History questionnaire was completed by all participants to assess eligibility for the study. This questionnaire was developed for the study and covered questions

addressing the inclusion criteria for the study. Questions about participants' demographics and history of head trauma, ear disorders and medications.

- A Tinnitus in Silence questionnaire with ten questions asking about their experience in silence was completed by participants who completed the study. Questions were developed on Qualtrics, they were multiple choice questions addressing any perception of tinnitus and the properties of any sound heard in silence.

3.5 Study Procedure

3.5.1 Consent

This study took place at the Department of Communication Sciences and Disorders, University of North Carolina Greensboro in 327A Neuro Lab located on the third floor of the Ferguson building. On arrival to the lab, participants were given a verbal and written description of the study and completed the COVID information form and the consent form. A signed copy of the consent form was given to the subject and a second copy was kept in the subject's de-identified file which was securely locked in a file cabinet. Participants who gave their consent to participate in the study were asked to fill a general history questionnaire to help determine that they met the inclusion criteria.

3.5.2 Hearing Assessments

Participants underwent otoscopy, tympanometry, and pure tone audiometry in the lab to determine that they met the normal hearing inclusion criteria. Participants who had normal outer ears, middle ear pressures and normal hearing thresholds were invited to participate in the study.

3.5.3 First ALR Measurement

Each participant's scalp was cleaned with an alcohol pad to remove excess oil or make up at the intended electrode placement locations. After the electrode placement sites had been cleaned, Nuprep skin preparation gel which is a mild abrasive solution was applied on the cleaned areas

before a final application of normal saline solution to the electrode placement sites to improve the electrode impedance.

Tin-cup scalp EEG electrodes were used to acquire the ALR and P300 potentials with enough Ten20 conductive gel and was secured in place using a small piece of surgical tape. The electrodes were placed on the following locations: 1) non-inverting electrode on the vertex (Cz); 2) inverting electrode on the mastoid (M1 and M2); and 3) ground electrode on the forehead (Fpz). Measured electrode impedance was kept below 5000 ohms.

Participants were then seated in a soundproof booth on a comfortable reclining chair and asked to relax and keep their eyes open. Participants were informed that they will have two P300 tests and will be directed to ignore the frequent stimuli, silently keep count of the rare stimuli and to tap the arm of the reclining chair each time they hear the rare stimuli. They were also informed that they would be left in silence for 10 minutes after the first P300 test. Disposable ear tips were placed in the participant's ear canals for stimulus delivery. After impedance verification across the electrodes, both the frequent and rare rarefaction tone burst stimuli were presented through the right ER-3A insert transducer using the oddball paradigm in a pseudorandom order. The computer recorded and saved the electrophysiological potentials obtained from the electrodes.

3.5.4 SILENCE

Participants were asked to sit in silence for ten minutes within the soundproof booth after the initial ALR/P300 test was recorded. They were asked to take note of any experiences in silence, but they were not told to expect any sound. Prior to the first ALR recording, the investigator instructed each participant as follows; "At some point the tones will stop and you will be required to stay in silence for ten minutes. You may lie back and close your eyes but try to stay awake. Take note of any experiences within this period because at the end of ten minutes, and after you have completed another set of recordings from your electrodes, you will need to fill out a questionnaire in which you will answer some questions about your experience in silence."

3.5.5 Second ALR Measurement

Immediately after the ten minutes of silence, a second ALR measurement was recorded. The second ALR measurement followed the same protocol as the first. Once the second ALR was concluded, the electrodes were removed, and the electrode locations cleaned with a wet wipe.

3.5.6 Tinnitus in Silence Questionnaire

On completion of the second ALR, participants were asked to fill a ten-item Qualtrics questionnaire in which they indicated if they heard any sounds in their head or ears while in silence and if they did, they described the type of sounds heard.

3.6 ALR and P300 Statistical Analysis

Raw ALR and P300 waveforms were analyzed for latency and amplitude measures. Any recordings with a high signal-to-noise ratio (indicating the potential of muscle artifact contaminating the AEP waveforms) were rejected from the data analysis. Peak amplitude for the N1 wave was measured from the peak of the preceding P1 wave to the lowest point on the N1 wave. Peak amplitude for the P2 wave was measured from the trough of the preceding N1 wave to the highest point on the P2 wave. Peak amplitude for the N2 wave was measured from the peak of the preceding P2 wave to the lowest point on the N2 wave. The peak amplitude for the P300 was measured from the baseline to the peak latency. Absolute peak latencies of the ALR and P300 waveforms were measured. Amplitudes and latencies were entered into SPSS statistical software.

The mean/averaged latencies and amplitudes of the N1, P2 and P300 waveforms were compared pre- and post- silence using t-test. The mean/averaged latencies and amplitudes of the N1, P2 and P300 waveforms were compared between the group that perceived tinnitus in silence (Tinnitus in Silence group) and the group that did not perceive tinnitus in silence (No tinnitus group) and analyzed using Analysis of Variance (ANOVA) statistical test. The mean/averaged latencies and amplitudes of the N1, P2 and P300 waveforms were compared between the racial groups using ANOVA statistical test. The independent variables were the participant groups and

the time points while the dependent variables were the mean latencies and amplitudes of the ALR and P300 potentials. Descriptive statistics and qualitative analysis were used in analyzing the tinnitus in silence questionnaire.

All statistical tests were two-tailed, and level of significance set at $P \leq 0.05$.

CHAPTER IV: RESULTS

4.1 Recruitment

Forty female participants were seen for hearing screening prior to being admitted to the study to determine that they met the inclusion criteria. Thirty-three females met the eligibility criteria and were initially admitted to the study. However, only thirty of the participants had ALR and P300 waveforms with good signal to noise ratios. Therefore, this study reports the findings of thirty young adult females.

4.2 Demographics

The mean age of the participants was 22.5 ± 3.9 years. Their age ranged from 19 years to 35 years. Table 1 shows the race of the participants. Sixteen (46.7%) of the participants identified as White while 12 (40%) identified as African American.

Table 1: Racial distribution

Race	Frequency	Percent
White	16	53.4
African American	12	40.0
Asian	1	3.3
Other	1	3.3
Total	30	100.0

4.3 Tinnitus Perception

When exposed to silence, a total of eleven (36.7%) participants perceived tinnitus while sitting in silence. Seven (63.6%) of the participants who perceived tinnitus were African American while 4 (36.4%) were White (Table 2). There was no significant association between race and the perception of temporary tinnitus (χ^2 (3, N=30) = 4.5, p = 0.2). The participants who heard tinnitus perceived the tinnitus sounds within five minutes of sitting in silence. The majority (54.5%) of the participants reported that they perceived tinnitus sounds in their head, 18.2% of the subjects that perceived tinnitus did so in both ears, a further 18.2% perceived the tinnitus sound in the left ear and 9.1% perceived the tinnitus sounds in their right ear. Five (45.5%) of the participants that perceived tinnitus described their tinnitus as having one sound while 2(18.2%) of the participants that perceived tinnitus heard three or more sounds. The majority (72.7%) of the participants who perceived temporary tinnitus in silence described their tinnitus as pulsatile followed by buzzing and humming (see Figure 2). Half of those who reported hearing pulsatile tinnitus were African American.

Table 2: Perception of tinnitus in different racial groups

		Tinnitus perception		
		Yes	No	Total
Race	White	4	12	16
	African American	7	5	12
	Asian	0	1	1
	Other	0	1	1
Total		11	19	30

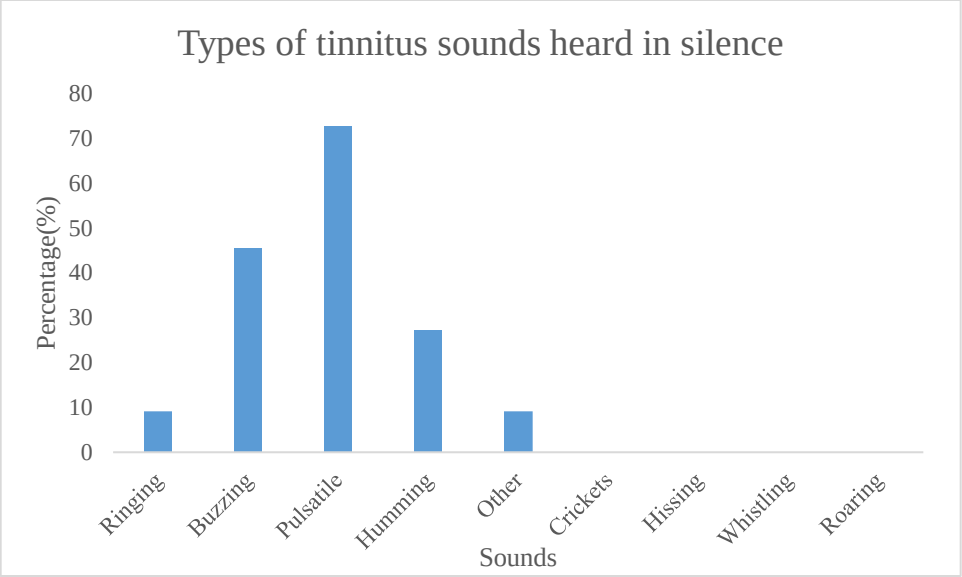

Figure 2: Types of tinnitus sounds heard in silence

Six (54.5%) of those who perceived tinnitus while sitting in silence described their tinnitus as having a pitch and 50% of these had mid-pitched tinnitus. Only 1(16.7%) participant reported that their tinnitus was high-pitched.

4.4 Effect of Silence on N1, P2 and P300 Waveforms

The mean N1, P2 and P300 waveform amplitudes and latencies pre- and post-silence for all the participants were compared to examine the effect of silence on ALR and P300 neural responses.

4.4.1 Grand Average Waveforms and Wave Morphology

Figure 3 shows pre-silence and post-silence grand averages for the participants and groups. A decrease in P300 waveform amplitude is seen post-silence; there appears to be a slight decrease in P300 latency post-silence. The ALR waveform in both test conditions appear similar in latency and amplitude.

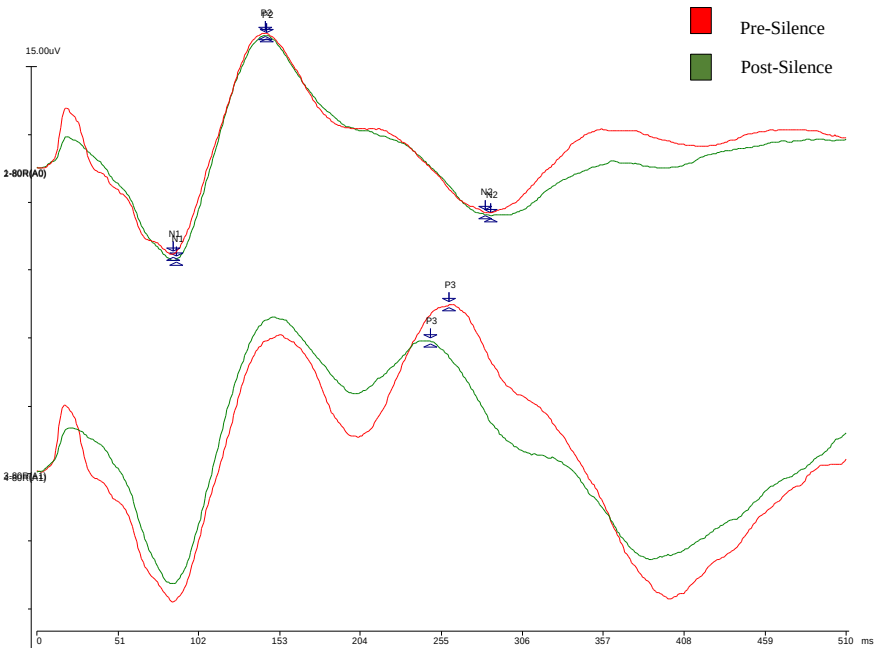

Figure 3: Grand average of pre- and post-silence ALR and P300 waveforms

4.4.2 Effect of Silence on N1, P2, N2, and P300 Waveforms

Figure 4 shows the means for the pre-and post-silence exposure on the ALR and P300 waveform amplitudes, and Figure 5 shows the means for the pre- and post-silence exposure on the ALR and P300 waveform latencies.

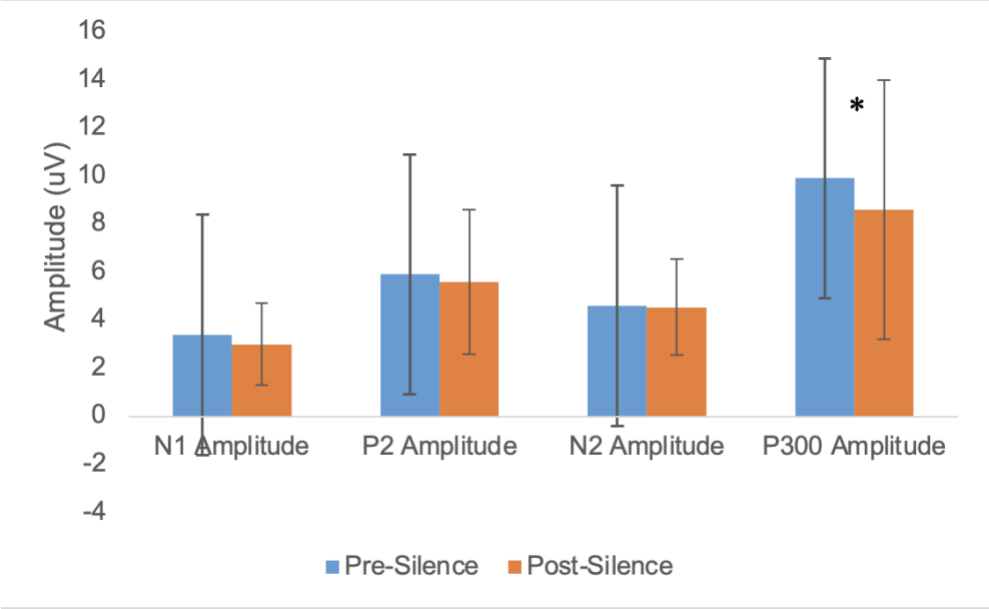

Figure 4: Mean pre- and post-silence N1, P2 and P300 amplitudes. (Error bars=Standard Deviation, *=P<0.05)

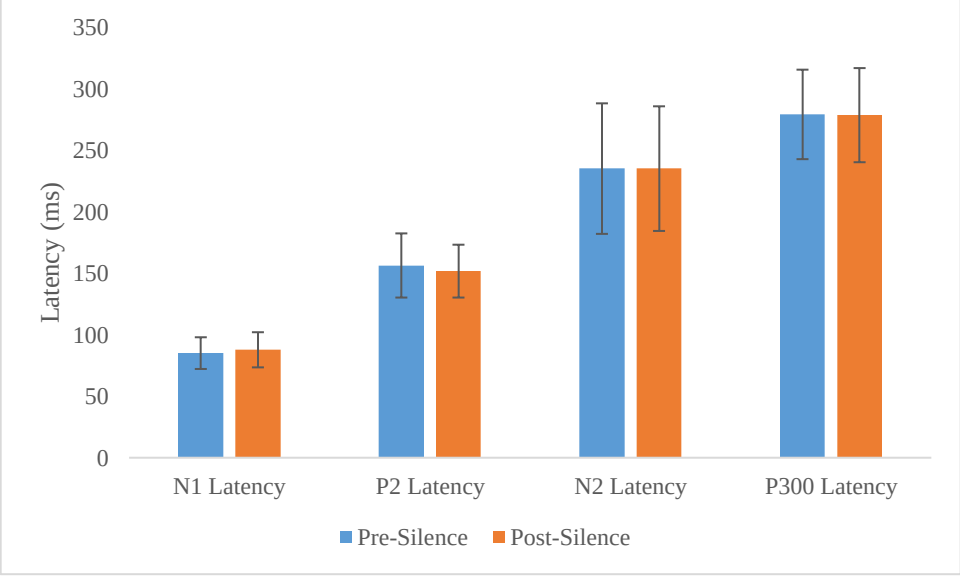

Figure 5: Mean pre- and post-silence N1, P2 and P300 latencies. (Error bars=Standard Deviation)

4.4.2.1 N1 Waveform

The mean pre-silence N1 amplitude for all the participants in this study was 3.4 ± 2.3 μV, while the mean post-silence N1 amplitude was 3 ± 1.7 μV. The mean pre-silence N1 latency was 85.1 ± 12.9 ms while the mean post-silence N1 latency was 87.8 ± 14.3 ms. The differences in pre- and post-silence waveform N1 amplitudes (t_{29}= 1.4, p=0.2) and latencies (t_{29}= -1.6, p=0.1) were not statistically significant.

4.4.2.2 P2 Waveform

The mean pre-silence P2 amplitude was 5.9 ± 3 μV while the mean post-silence P2 amplitude was 5.6 ± 3 μV. The mean pre-silence P2 latency was 156.4 ± 26.1 ms while the mean post-silence P2 latency was 151.8 ± 21.5 ms. The differences in pre- and post-silence waveform P2 amplitudes (t_{29}= 1.1, p=0.3) and latencies (t_{29}= -1, p=0.3) were not statistically significant.

4.4.2.3 N2 Waveform

The mean pre-silence N2 amplitude was 4.6 ± 1.9 μV while the mean post-silence N2 amplitude was 4.5 ± 1.99 μV. The mean pre-silence N2 latency was 235.2 ± 53.1 ms while the mean post-silence N2 latency was 235.2 ± 50.7 ms. The differences in pre- and post-silence N2 waveform amplitudes (t_{28}= 0.2, p=0.9) and latencies (t_{28}= 0.01, p=1) were not statistically significant.

4.4.2.4 P300 Waveform

The mean pre-silence P300 amplitude was 9.9 ± 5.6 μV while the mean post-silence P300 amplitude was 8.6 ± 5.4 μV. This reduction in post-silence P300 was statistically significant (t_{29}= 2.2, p=0.04), Hedges' *g* was 0.3. The mean pre-silence P300 latency was 279.3 ± 36.4 ms while the post-silence P300 latency was 278.7 ± 38.3 ms. The difference in pre- and post-silence P300 waveform latencies was not statistically significant (t_{29}= 0.2, p=0.9).

4.5 Tinnitus Perception Group Differences in ALR and P300 Waveforms

Figures 6 and 7 show pre-silence and post-silence grand averages for the tinnitus in silence and non-tinnitus in silence groups. The P300 waveform amplitude in the tinnitus in silence group is smaller than that of the non-tinnitus in silence group in the pre-silence and post-silence test conditions. The tinnitus group shows faster N1 latency and larger N2 amplitude pre-silence. Post-silence, the tinnitus group appears to have a slightly smaller P2 amplitude.

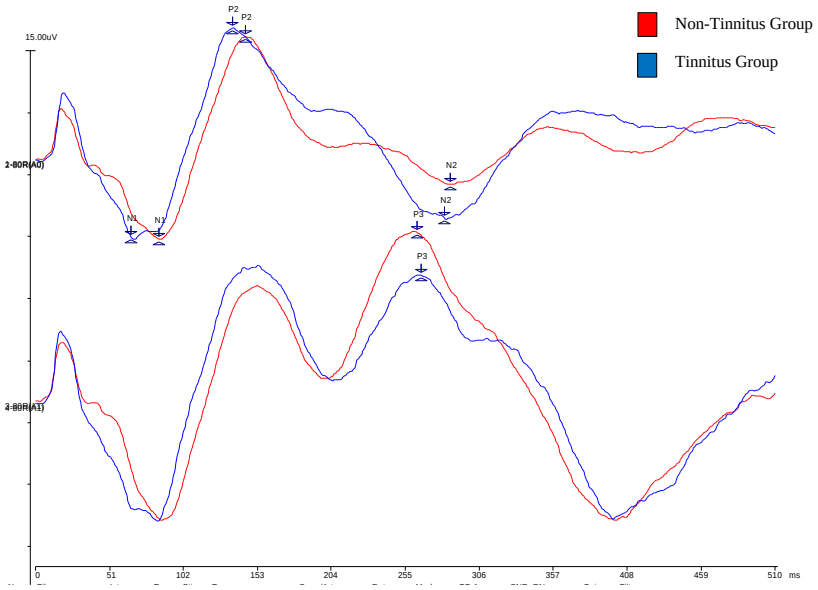

Figure 6: Pre-silence ALR and P300 grand average for the tinnitus in silence group and the non-tinnitus in silence group

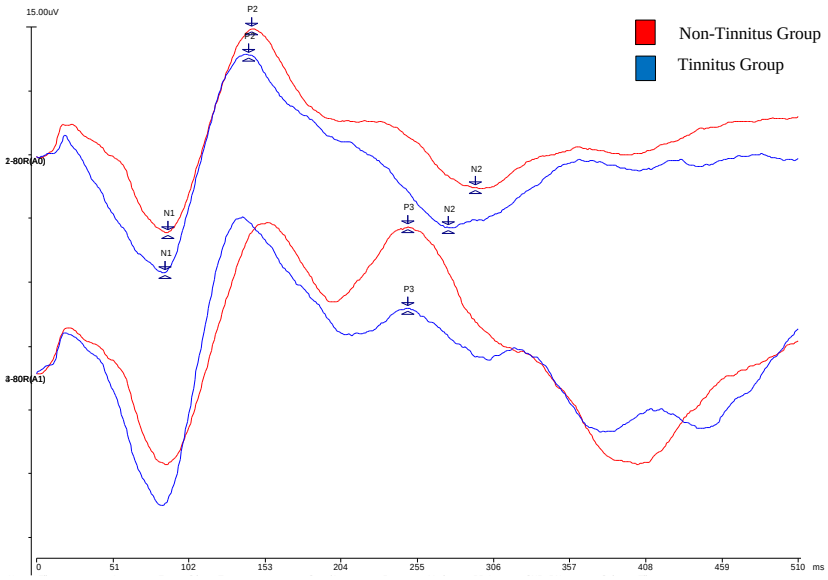

Figure 7: Post-silence ALR and P300 grand average for the tinnitus in silence group and the non-tinnitus in silence group

4.5.1 Tinnitus Perception Group Differences in Mean Pre-Silence and Post-Silence N1 Waveform Amplitudes

In comparison to the non-tinnitus in silence group, the tinnitus in silence group had a larger mean N1 amplitude pre-silence but a smaller mean N1 amplitude post-silence. The mean pre-silence N1 amplitude for the tinnitus in silence group was 3.8 ± 2.8 μV and their post-silence N1 amplitude was 2.97 ± 1.7 μV, while the mean pre-silence N1 amplitude for the non-tinnitus in silence group was 3.2 ± 1.97 μV and their post-silence N1 amplitude, 3.1 ± 1.8 μV (Figure 8). There was no significant difference in the pre-silence and post-silence N1 waveform amplitudes when the tinnitus group was compared to the non-tinnitus group ($F(1,28) = 0.12$, $p = 0.73$). Although the tinnitus in silence group showed a slight decrease in amplitude post-silence, there was no significant interaction between tinnitus perception groups and the points in time at which measurements were obtained ($F(1,28) = 1.45$, $p = 0.24$).

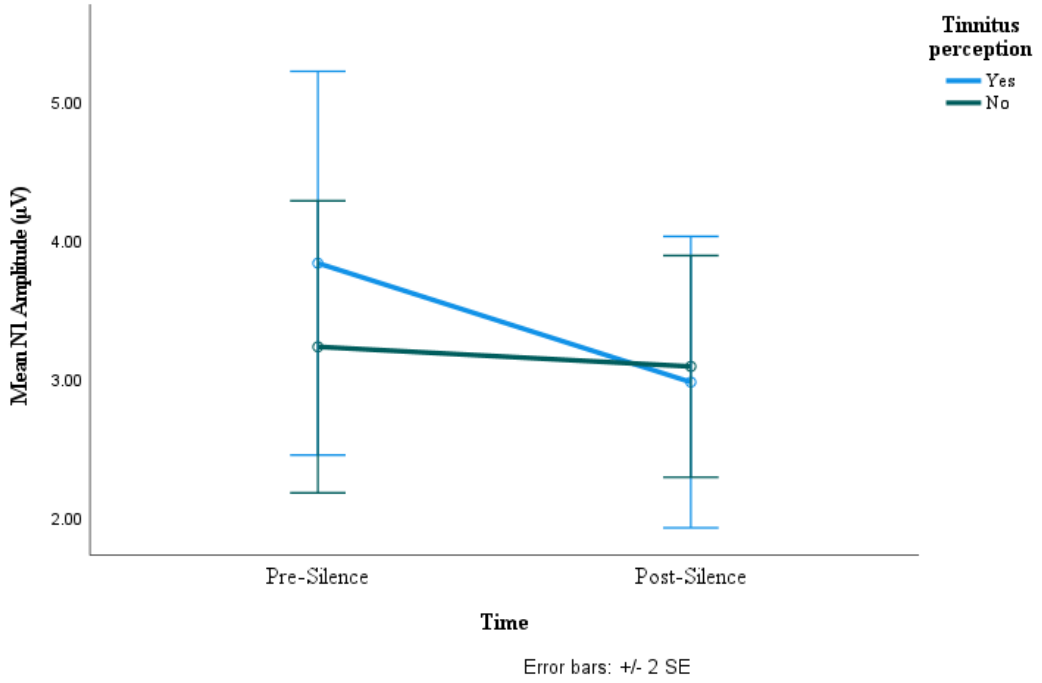

Figure 8: Mean N1 pre- and post-silence N1 waveform amplitudes for both groups

4.5.2 Group Differences in Mean Pre-Silence and Post-Silence N1 Waveform Latencies

Mean N1 latencies were shorter in the tinnitus in silence group pre- and post-silence. An increase in N1 latency was observed in both groups post-silence. The mean pre-silence N1 latency for the tinnitus in silence group was 81.7 ± 12.9 ms and their post-silence N1 latency 86 ± 11.1 ms, while the mean pre-silence N1 latency for the non-tinnitus in silence group was 87.1 ± 12.8 ms and their post-silence N1 latency was 88.9 ± 16.1 ms (Figure 9). A repeated measures ANOVA revealed that there was no significant difference in the pre-silence and post-silence N1 waveform latencies when the tinnitus group was compared to the non-tinnitus group ($F(1,28) = 0.72$, $p = 0.41$). Although the tinnitus group showed a larger difference between pre- and post-silence mean latencies, there was no significant interaction between tinnitus perception groups and the points in time at which measurements were obtained ($F(1,28) = 0.52$, $p = 0.48$).

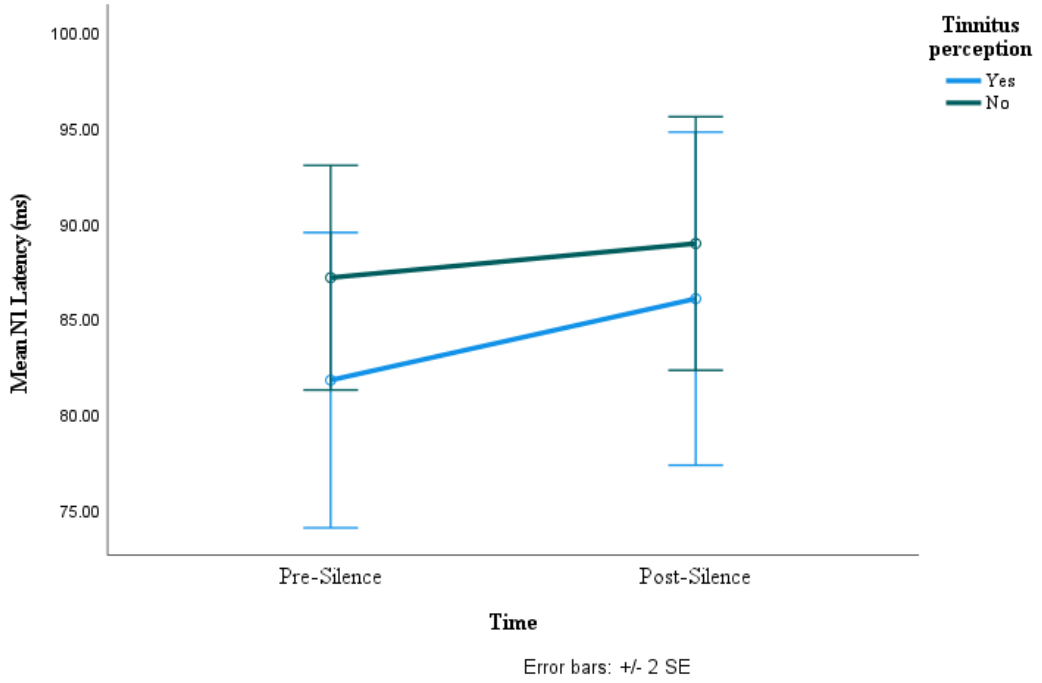

Figure 9: Mean N1 pre- and post-silence waveform latencies for both groups

4.5.3 Tinnitus Perception Group Differences in Mean Pre-Silence and Post-Silence P2 Waveform Amplitudes

The non-tinnitus group had a larger mean P2 amplitude than the tinnitus in silence group pre-silence but a smaller mean amplitude than the tinnitus in silence group post-silence. The mean pre-silence P2 amplitude for the tinnitus in silence group was 5.8 ± 2.7 μV and their post-silence P2 amplitude, 5.8 ± 2.6 μV, while the mean pre-silence P2 amplitude for the non-tinnitus in silence group was 5.9 ± 3.3 μV and their post-silence P2 amplitude was 5.6 ± 3.3 μV (Figure 10). There was no significant difference in the pre-silence and post-silence P2 waveform amplitudes when the tinnitus group was compared to the non-tinnitus group ($F(1,28) = 0$, $p = 1$). There was no significant interaction between the groups and the points in time at which measurements were obtained ($F(1,28) = 0.78$, $p = 0.38$)

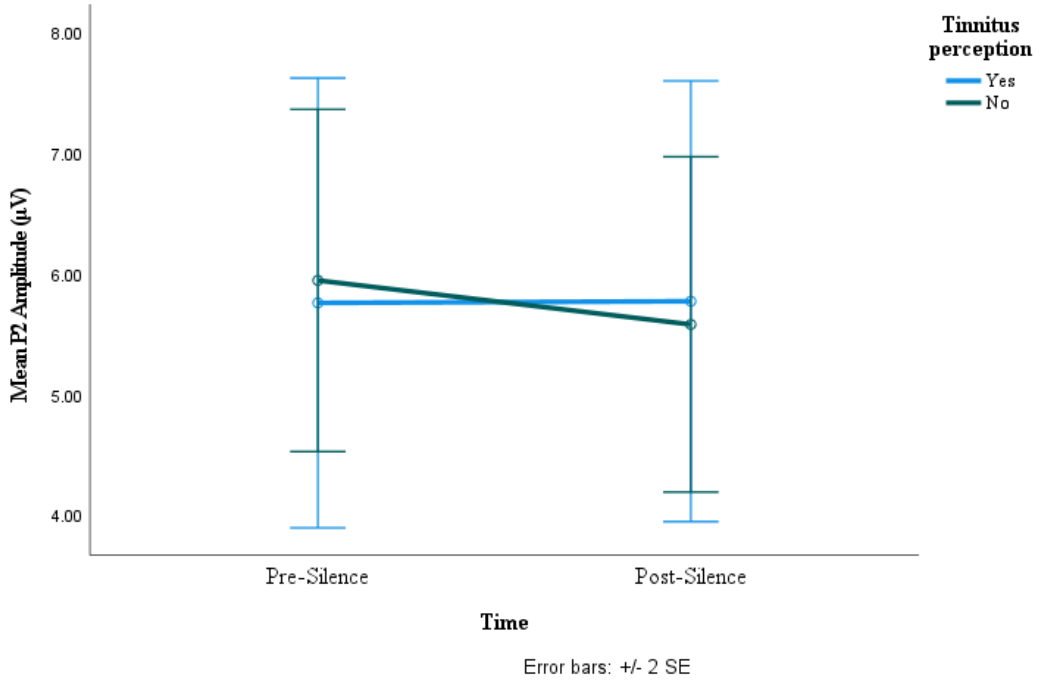

Figure 10: Mean P2 pre- and post-silence waveform amplitudes for both groups

4.5.4 Tinnitus Perception Group Differences in Mean Pre-Silence and Post-Silence P2 Waveform Latencies

The tinnitus in silence group showed shorter P2 latencies pre- and post-silence. The mean pre-silence P2 latency for the tinnitus in silence group was 151.6 ± 24.6 ms and their post-silence P2 latency was 149.1 ± 25.7 ms, while the mean pre-silence P2 latency for the non-tinnitus in silence group was 159.1 ± 27.1 ms and their post-silence P2 latency, 153.3 ± 19.3 ms (Figure 11). A repeated measures ANOVA revealed that there was no significant difference in the pre-silence and post-silence P2 waveform latencies when the tinnitus group was compared to the non-tinnitus group ($F(1,28) = 0.49$, $p = 0.49$). There was no significant interaction between participant groups and the points in time at which measurements were obtained ($F(1,28) = 0.19$, $p = 0.66$).

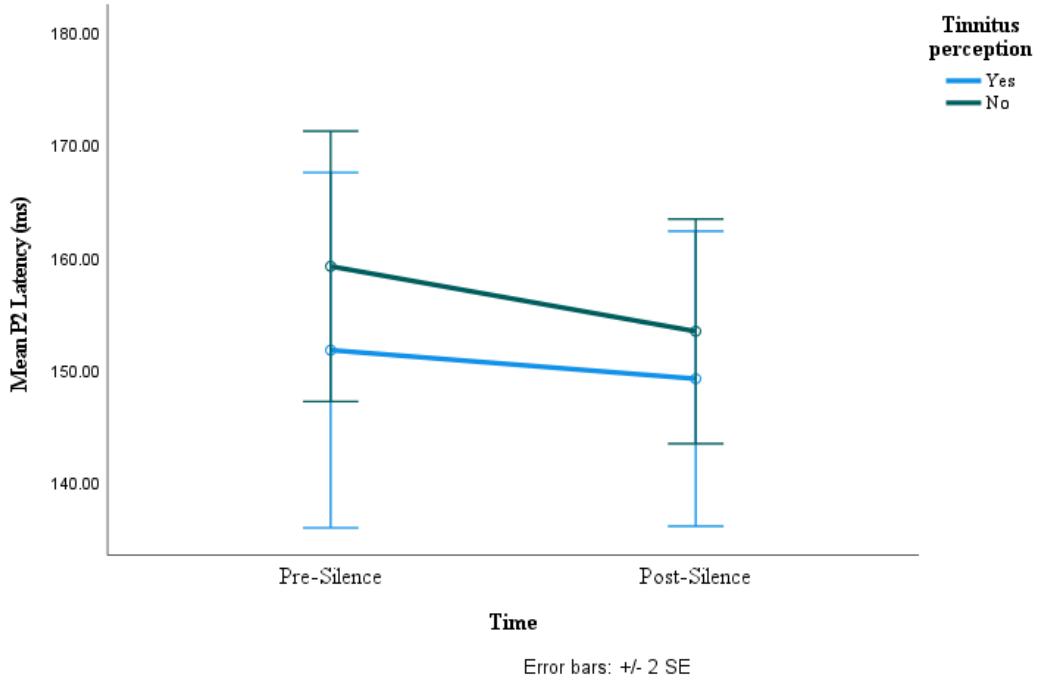

Figure 11: Mean P2 pre- and post-silence waveform latencies for both groups

4.5.5 Tinnitus Perception Group Differences in Mean Pre-Silence and Post-Silence N2 Waveform Amplitudes

The tinnitus in silence group had smaller pre- and post-silence N2 amplitudes. The mean pre-silence N2 amplitude for the tinnitus in silence group was 4.2 ± 1.7 μV and their post-silence N2 amplitude 4.2 ± 1.6 μV, while the mean pre-silence N2 amplitude for the non-tinnitus in silence group was 4.8 ± 2 μV and their post-silence N2 amplitude 4.7 ± 2.2 μV (Figure 12). There was no significant difference in the pre-silence and post-silence N2 waveform amplitudes when the tinnitus group was compared to the non-tinnitus group ($F(1,27) = 0.81$, $p = 0.38$). There was no significant interaction between the tinnitus perception groups and the points in time at which measurements were obtained ($F(1,27) = 0.01$, $p = 0.91$).

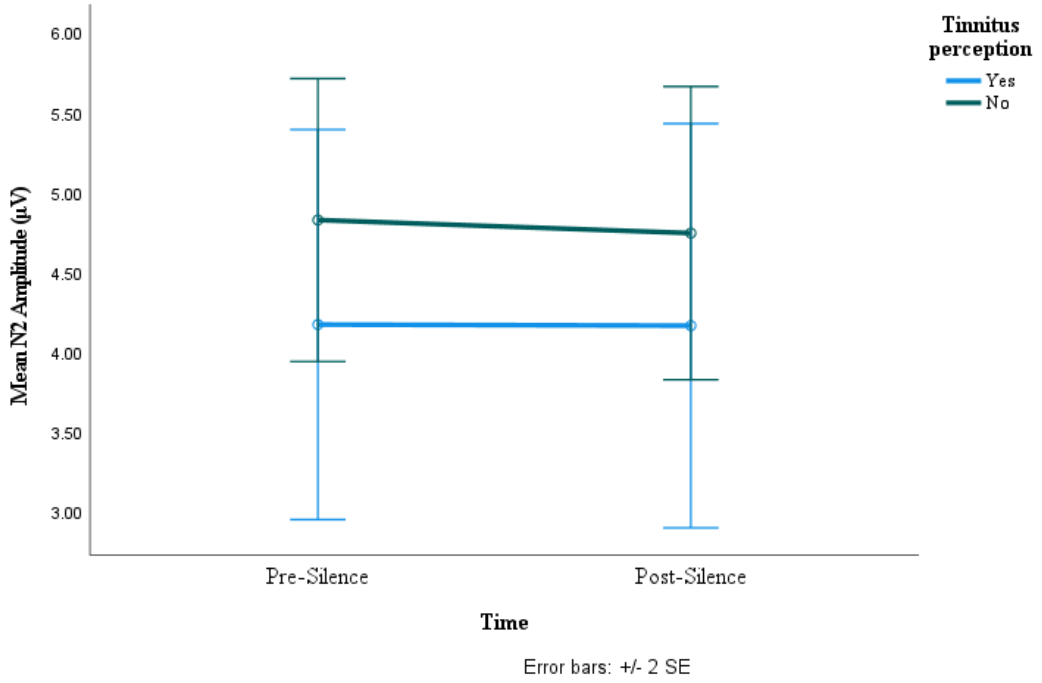

Figure 12: Mean N2 pre- and post-silence waveform amplitudes for both groups

4.5.6 Tinnitus Perception Group Differences in Mean Pre-Silence and Post-Silence N2 Waveform Latencies

The mean pre-silence N2 latency for the tinnitus in silence group was 239.1 ± 45.4 ms and their post-silence N2 latency 233.2 ± 40.6 ms, while the mean pre-silence N2 latency for the non-tinnitus in silence group was 233.2 ± 57.8 ms and their post-silence N2 latency 236.3 ± 56.3 ms (Figure 13). A repeated measures ANOVA revealed that there were no significant main effects of group on N2 waveform latencies ($F(1,27) = 0.01$, $p = 0.9$). Although the post-silence N2 latency showed a decrease in the tinnitus in silence group and an increase in the non-tinnitus group, there was no significant interaction between tinnitus perception group and the time points at which measurements were obtained ($F(1,27) = 0.79$, $p = 0.38$).

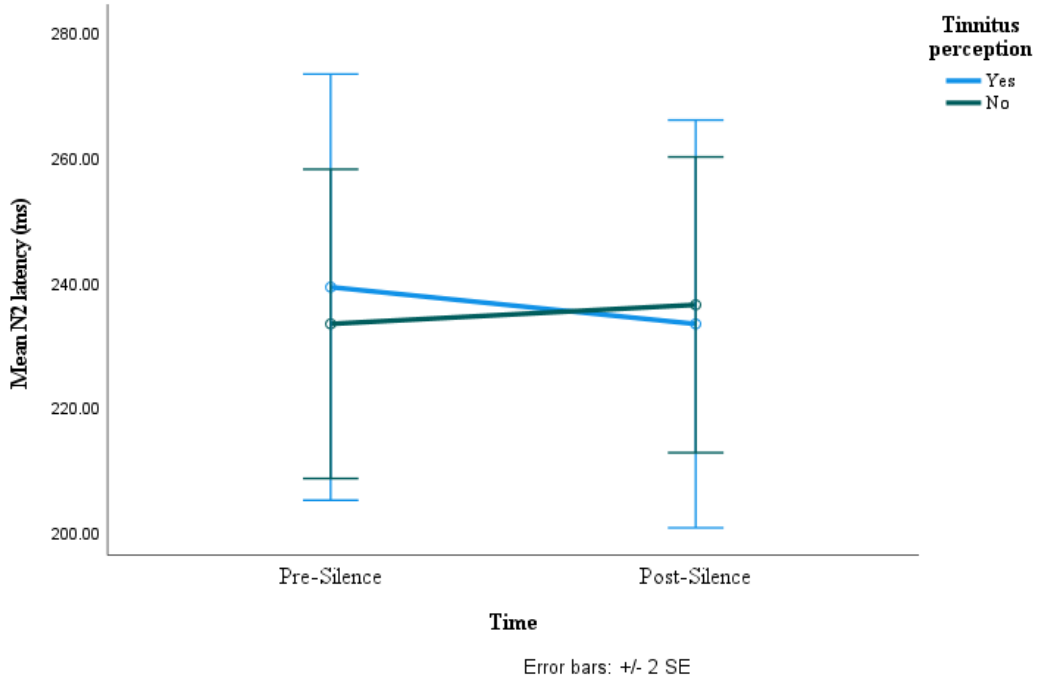

Figure 13: Mean N2 pre- and post-silence waveform latencies for both groups

4.5.7 Tinnitus Perception Group Differences in Mean Pre-Silence and Post-Silence P300 Waveform Amplitudes

The tinnitus in silence group had smaller mean P300 amplitudes pre- and post-silence. The mean pre-silence P300 amplitude for the tinnitus in silence group was 9.3 ± 4.3 µV and their post-silence P300 amplitude was 7.4 ± 5.6 µV, while the mean pre-silence P300 amplitude for the non-tinnitus in silence group was 10.3 ± 6.3 µV and their post-silence P300 amplitude 9.3 ± 5.2 µV (Figure 14). There was no significant difference in the pre-silence and post-silence P300 waveform amplitudes when the tinnitus group was compared to the non-tinnitus group ($F(1,28) = 0.57$, $p = 0.46$). There was no significant interaction between group and ALR measurement time points ($F(1,28) = 0.48$, $p = 0.49$).

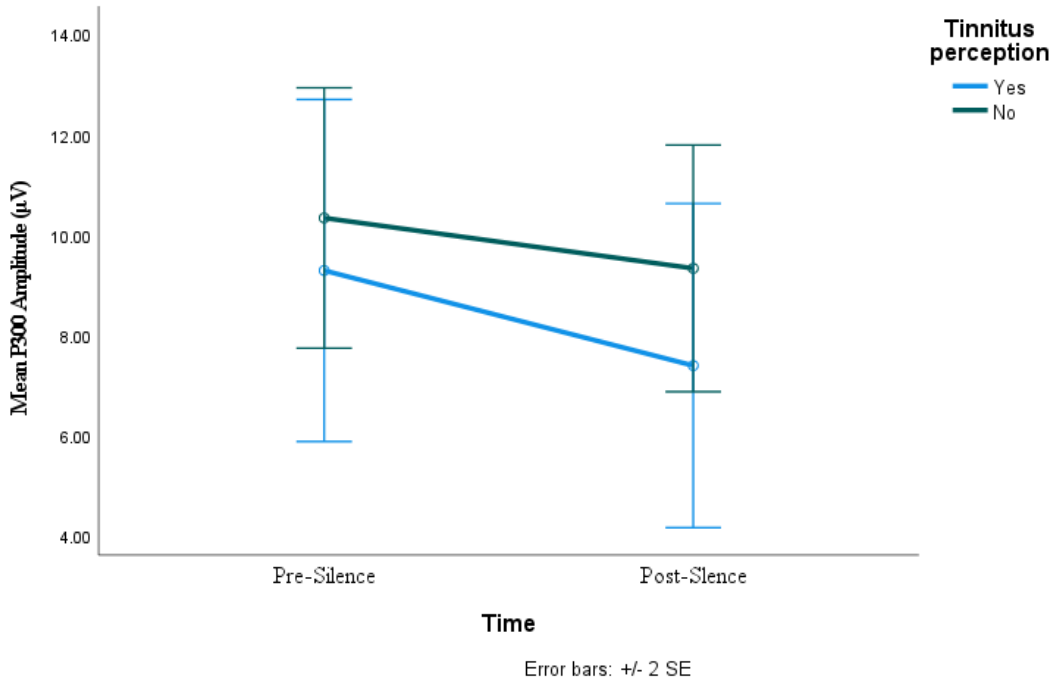

Figure 14: Mean P300 pre- and post-silence waveform amplitudes for both groups

4.5.8 Tinnitus Perception Group Differences in Mean Pre-Silence and Post-Silence P300 Waveform Latencies

The tinnitus in silence group had longer latencies pre- and post-silence. The mean pre-silence P300 latency for the tinnitus in silence group was 292.6 ± 38.7 ms and their post-silence P300 latency was 289 ± 41.3 ms, while the mean pre-silence P300 latency for the non-tinnitus in silence group was 271.7 ± 33.7 ms and their post-silence P300 latency, 272.7 ± 36.3 ms (Figure 15). A repeated measures ANOVA revealed that there was no significant difference in the pre-silence and post-silence P300 waveform latencies when the tinnitus group was compared to the non-tinnitus group ($F(1,28) = 1.98$, $p = 0.17$). Although the tinnitus group showed a slightly faster P300 response post-silence, there was no significant interaction between the tinnitus perception group and the time points at which ALR measurements were obtained ($F(1,28) = 0.26$, $p = 0.62$).

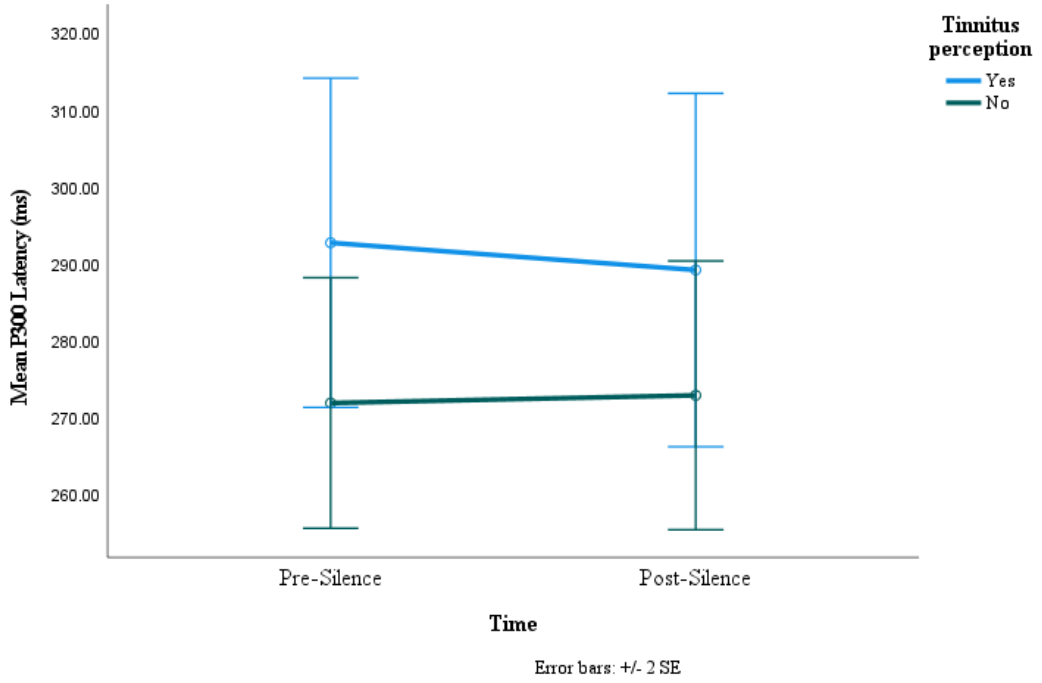

Figure 15: Mean P300 pre- and post-silence waveform latencies for both groups

4.6 Effect of Race on the ALR and P300 Waveforms: Analysis of Mean Pre-silence and Post-silence ALR and P300 Waveforms for Racial Groups

Whites had slightly larger P2 amplitudes in comparison to African Americans' pre- and post-silence P2 amplitudes (Figures 16 and 17). The amplitude of the P300 endogenous response was smaller in African Americans in both the pre-silence test condition and the post-silence test condition.

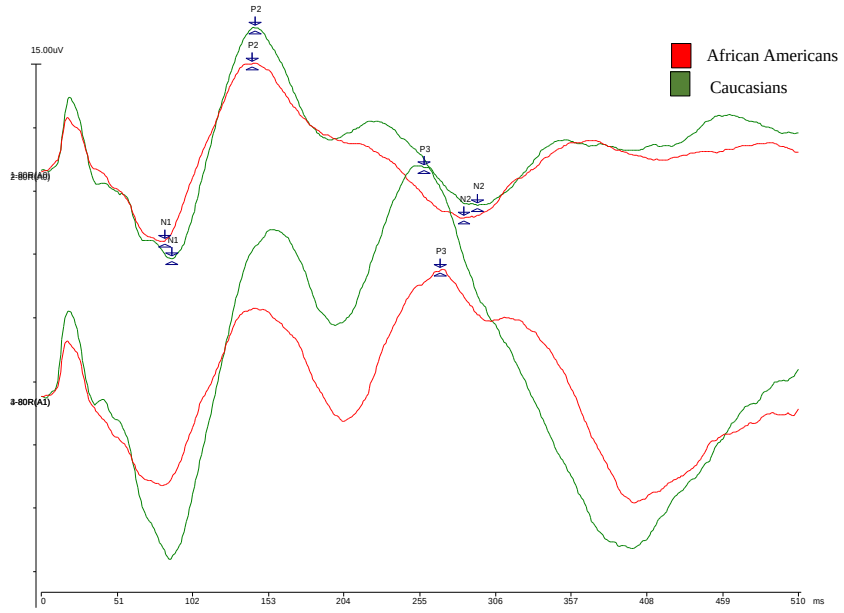

Figure 16: Pre-silence grand average of ALR and P300 in Whites and African Americans

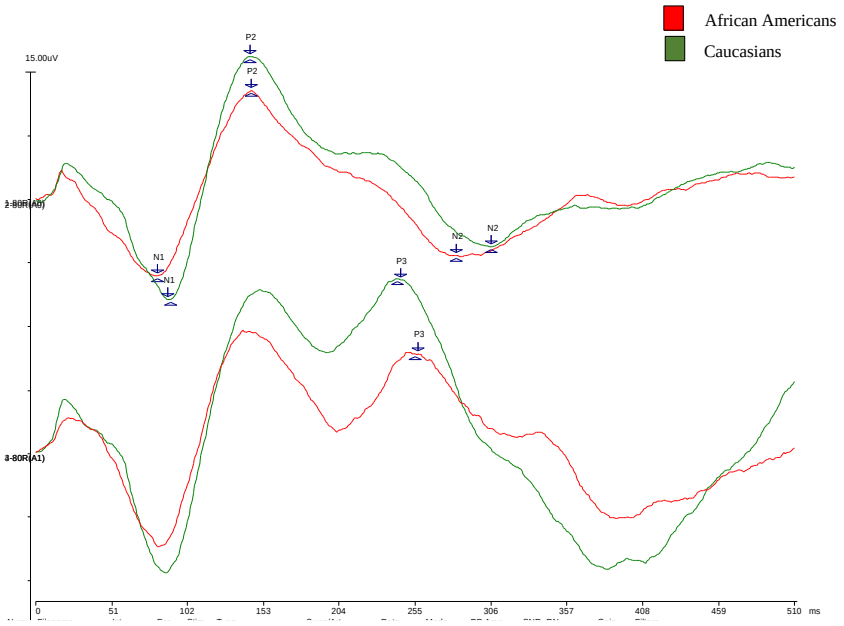

Figure 17: Post-silence grand average of ALR and P300 in Whites and African Americans

4.6.1 Mean Pre-Silence and Post Silence N1 Waveform Amplitude in Racial Groups

Table 3 and Figure 18 show the mean Pre-silence and Post-silence N1 waveform amplitudes for the racial groups. There was no significant main effect of Test period (pre- or post-silence) ($F(1,26) = 1$, $p = 0.3$) or racial group ($F(3,26) = 0.6$, $p = 0.6$) and no significant interaction between Race and Time of ALR test ($F(3,26) = 0.4$, $p = 0.7$). When the White and African American groups were compared, there was no significant main effect for racial group ($F(1,26) = 1.1$, $p = 0.3$) and time of test $F(1,26) = 1.8$, $p = 0.2$) or interaction between Test period (pre- or post-silence) and racial group $F(1,26) = 0.8$, $p = 0.4$).

Table 3: Mean N1 pre- and post-silence waveform amplitude for racial groups

	Race	Mean	Std. Deviation	N
PreAmplitudeN1	White	3.7181	2.85600	16
	African American	3.2317	1.49787	12
	Asian	2.1500	.	1
	Other	2.9100	.	1
	Total	3.4443	2.27985	30
PostAmplitudeN1	White	3.5863	1.96938	16
	African American	2.5267	1.19959	12
	Asian	2.0000	.	1
	Other	1.4700	.	1
	Total	3.0390	1.71694	30

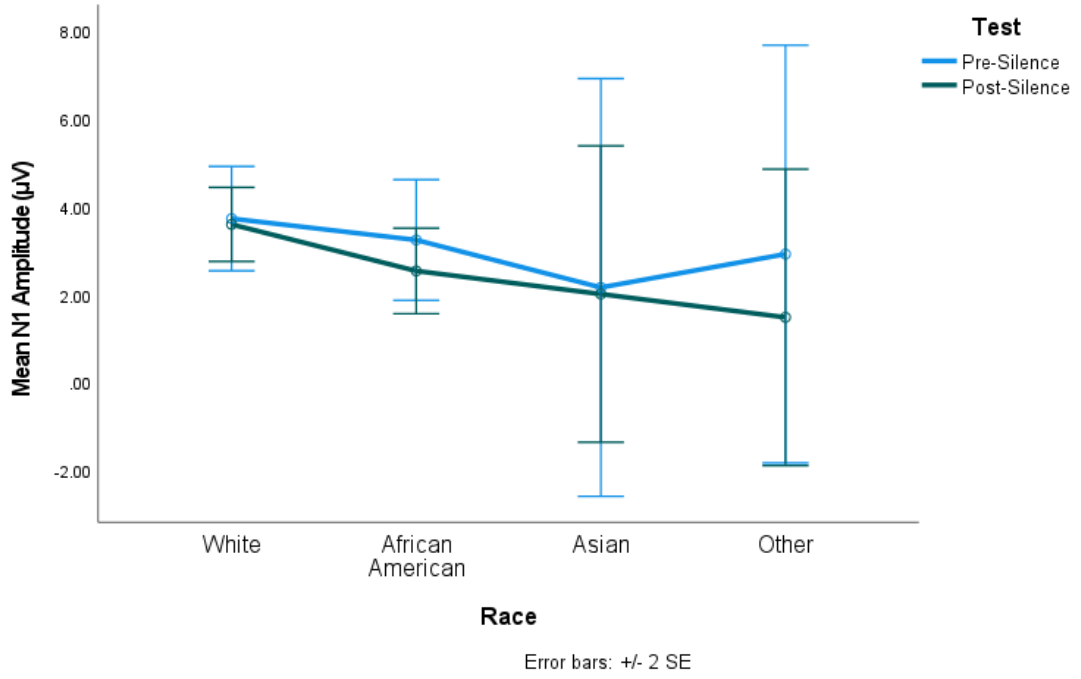

Figure 18: Mean N1 pre- and post-silence waveform amplitudes for racial groups

4.6.2 Mean Pre-Silence and Post-Silence N1 Waveform Latency in Racial Groups

Table 4 and Figure 19 show the mean Pre-silence and Post-silence N1 waveform latencies for the racial groups. There was no significant main effect of Test period (pre- or post-silence) ($F(1,26) = 2.1$, $p = 0.2$) or racial group ($F(3,26) = 1.3$, $p = 0.3$) but there was a significant interaction between Race and Time of ALR test ($F(3,26) = 3.4$, $p = 0.03$ effect size 0.3). When the White and African American groups were compared, there was a significant main effect for Test period $F(1,26) = 5.1$, $p = 0.03$, effect size 0.2) but no significant main effect for racial group ($F(1,26) = 3.3$, $p = 0.08$) or interaction between Test period (pre- or post-silence) and racial group $F(1,26) = 1.6$, $p = 0.2$).

Table 4: Mean N1 pre- and post-silence waveform latencies for racial groups

	Race	Mean	Std. Deviation	N
PreLatencyN1	White	87.8125	14.08176	16
	African American	81.0000	11.66970	12
	Asian	90.0000	.	1
	Other	87.0000	.	1
	Total	85.1333	12.89141	30
PostLatencyN1	White	93.2500	14.36895	16
	African American	82.5000	12.15431	12
	Asian	85.0000	.	1
	Other	68.0000	.	1
	Total	87.8333	14.30477	30

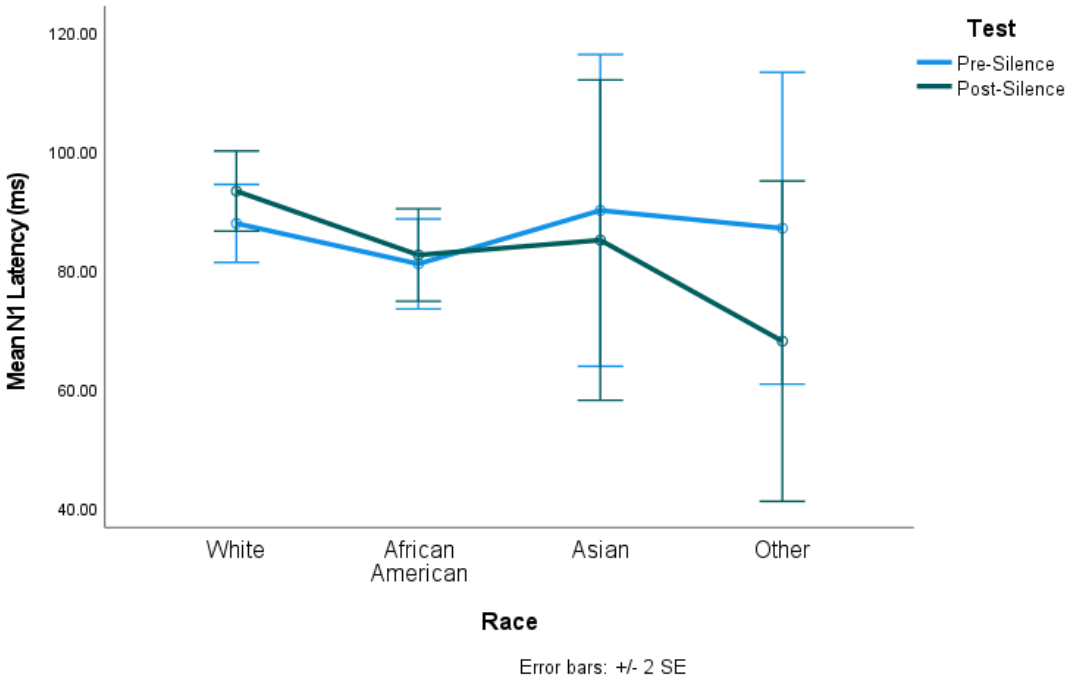

Figure 19: Mean N1 pre- and post-silence waveform latencies for racial groups

4.6.3 Mean Pre-Silence and Post-Silence P2 Waveform Amplitude in Racial Groups

Table 5 and Figure 20 show the mean Pre-silence and Post-silence P2 waveform amplitudes for the racial groups. There was no significant difference in pre- and post- silence P2 amplitude between the racial groups ($F(3,26) = 1.6$, $p = 0.2$), no significant main effect of Test period (pre- or post-silence) ($F(1,26) = 0.1$, $p = 0.7$) and no significant interaction between Race and Time of ALR test ($F(3,26) = 0.9$, $p = 0.5$). When the White and African American groups were compared, there was no significant main effect for racial group ($F(1,26) = 3.8$, $p = 0.06$) or Test period (pre- or post-silence), ($F(1,26) = 1.2$, $p = 0.3$) and no significant interaction between Test period and racial group $F(1,26) = 1.7$, $p = 0.2$).

Table 5: Mean P2 pre- and post-silence waveform amplitudes for racial groups

	Race	Mean	Std. Deviation	N
PreAmplitudeP2	White	7.0644	3.18711	16
	African American	4.6600	2.39723	12
	Asian	2.6400	.	1
	Other	4.4800	.	1
	Total	5.8690	3.04188	30
PostAmplitudeP2	White	6.5406	3.49819	16
	African American	4.7058	2.00998	12
	Asian	3.2600	.	1
	Other	4.9000	.	1
	Total	5.6427	2.98075	30

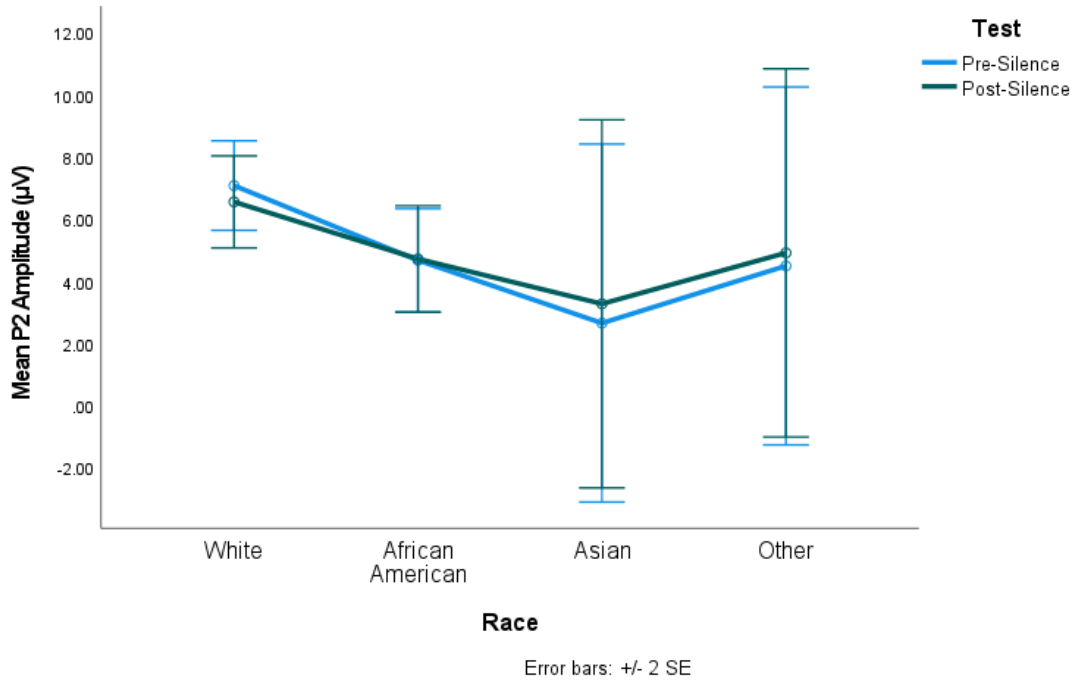

Figure 20: Mean P2 pre- and post-silence waveform amplitudes for racial groups

4.6.4 Mean Pre-Silence and Post-Silence P2 Waveform Latency in Racial Groups

Table 6 and Figure 21 show the mean Pre-silence and Post-silence P2 waveform latencies. There was no significant difference in pre- and post- silence P2 latencies between the racial groups (F (3,26) = 0.7, p = 0.6) but there was a significant main effect Test period (pre- or post-silence) (F (1,26) = 17.2, p = <0.001, effect size 0.4), and a significant interaction between Race and Time of ALR test (F (3,26) = 13.5, p = <0.001, effect size 0.6). When the White and African American groups were compared, there was no significant main effect of Test period (pre- or post-silence) (F (1,26) = 0.8, p = 0.4) or racial group (F (1,26) = 0.4, p = 0.6) and no significant interaction between ALR test period (pre- or post-silence) and racial group F (1,26) = 0.2, p = 0.6).

Table 6: Mean P2 pre- and post-silence waveform latencies for racial groups

	Race	Mean	Std. Deviation	N
PreLatencyP2	White	153.6875	24.17359	16
	African American	157.5833	24.47804	12
	Asian	214.0000	.	1
	Other	127.0000	.	1
	Total	156.3667	26.04569	30
PostLatencyP2	White	150.3750	18.48919	16
	African American	156.5833	25.83324	12
	Asian	131.0000	.	1
	Other	137.0000	.	1
	Total	151.7667	21.51773	30

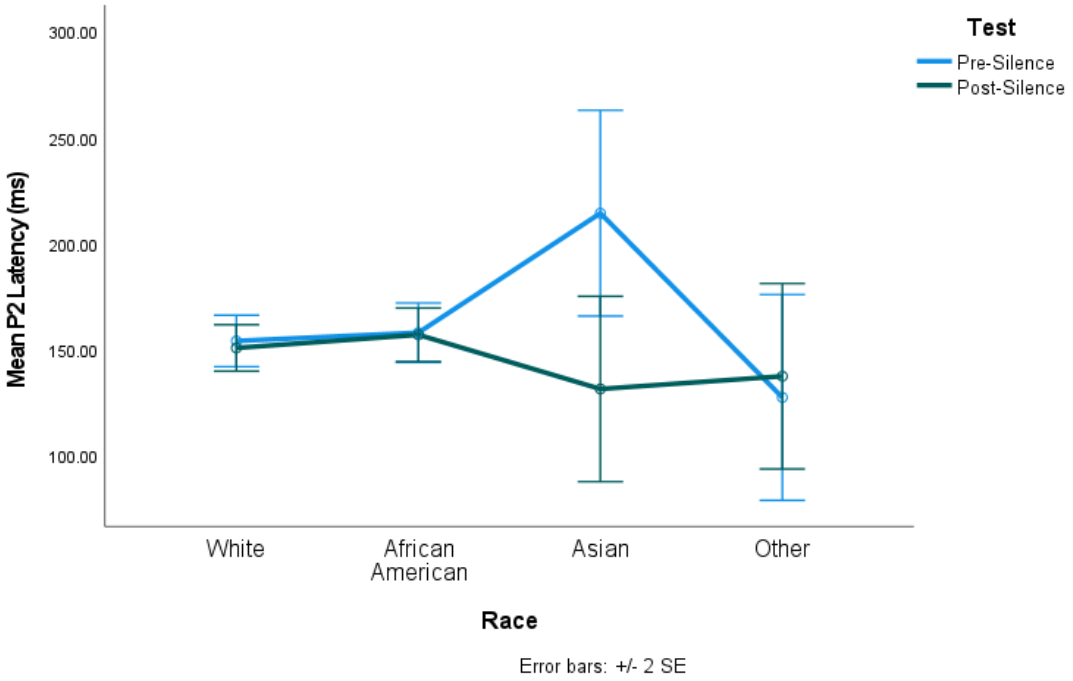

Figure 21: Mean P2 pre- and post-silence waveform latencies for racial groups

4.6.5 Mean Pre-Silence and Post-Silence N2 Waveform Amplitude in Racial Groups

Table 7 and Figure 22 show the mean Pre-silence and Post-silence N2 waveform amplitudes. There was no significant difference in pre- and post- silence N2 amplitude between the racial groups ($F(3,25) = 1.7$, $p = 0.2$), no significant main effect of Test period (pre- or post-silence) ($F(1,25) = 0.08$, $p = 0.8$). and no significant interaction between Race and Time of ALR test ($F(3,25) = 1$, $p = 0.4$). When the White and African American groups were compared, there was a significant main effect of racial group ($F(1,25) = 4.4$, $p = 0.05$, effect size 0.2) but there was no significant main effect for Test period (pre- or post-silence) ($F(1,25) = 0.006$, $p = 0.9$) and there was no significant interaction between ALR test time and racial group $F(1,25) = 2.3$, $p = 0.1$).

Table 7: Mean N2 pre- and post-silence waveform amplitude for racial groups

	Race	Mean	Std. Deviation	N
PreAmplitudeN2	White	5.4860	1.91408	15
	African American	3.5983	1.56346	12
	Asian	3.4100	.	1
	Other	4.4000	.	1
	Total	4.5959	1.92215	29
PostAmplitudeN2	White	5.0007	2.44151	15
	African American	4.1333	1.31772	12
	Asian	4.0300	.	1
	Other	3.0100	.	1
	Total	4.5397	1.98497	29

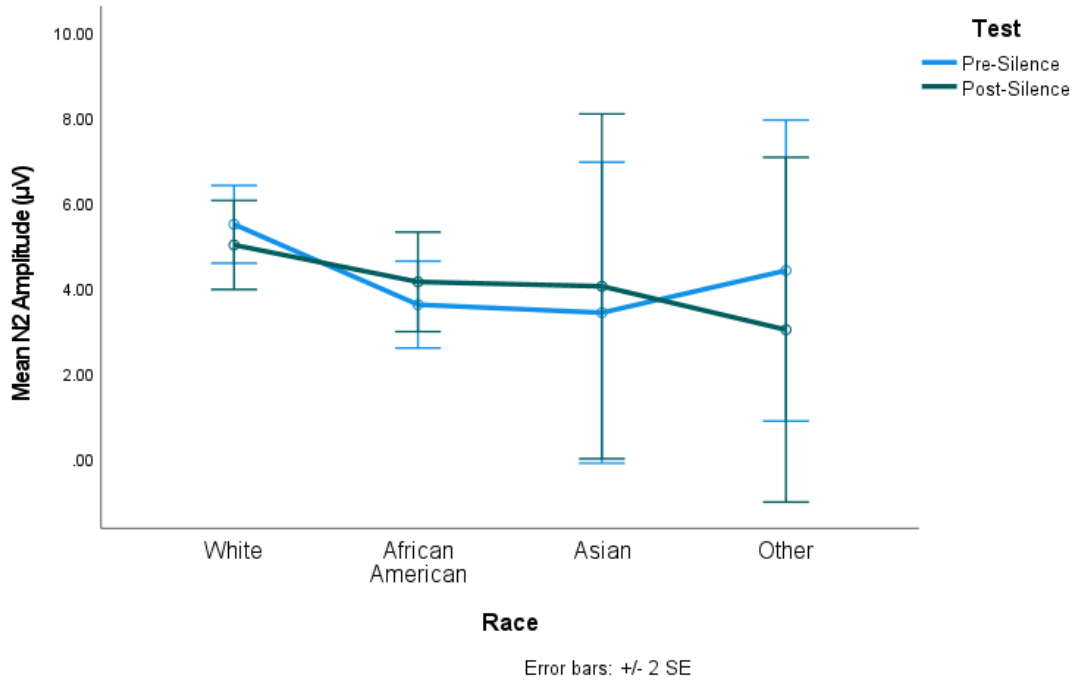

Figure 22: Mean N2 pre- and post-silence waveform amplitude for racial groups

4.6.6 Mean Pre-Silence and Post Silence N2 Waveform Latency in Racial Groups

Table 8 and Figure 23 show the mean Pre-silence and Post-silence N2 waveform latency. There was no significant difference in pre- and post- silence N2 latencies between the racial groups ($F(3,25) = 1.3$, $p = 0.3$). There was no significant main effect of Test period (pre- or post-silence) ($F(1,25) = 2.7$, $p = 0.1$) and no significant interaction between Race and ALR Test period ($F(3,25) = 2.4$, $p = 0.09$). When the White and African American groups were compared, there was no significant main effect for Test period (pre- or post-silence) ($F(1,25) = 0.2$, $p = 0.6$) and racial group ($F(1,25) = 1.8$, $p = 0.2$). There was no significant interaction between Test period (pre- or post-silence) and racial group $F(1,25) = 0.001$, $p = 0.97$).

Table 8: Mean N2 pre- and post-silence waveform latencies for racial groups

	Race	Mean	Std. Deviation	N
PreLatencyN2	White	225.2000	40.44785	15
	African American	251.0000	64.17873	12
	Asian	268.0000	.	1
	Other	164.0000	.	1
	Total	235.2414	53.06778	29
PostLatencyN2	White	227.6000	39.26249	15
	African American	253.0833	60.23357	12
	Asian	205.0000	.	1
	Other	165.0000	.	1
	Total	235.2069	50.72149	29

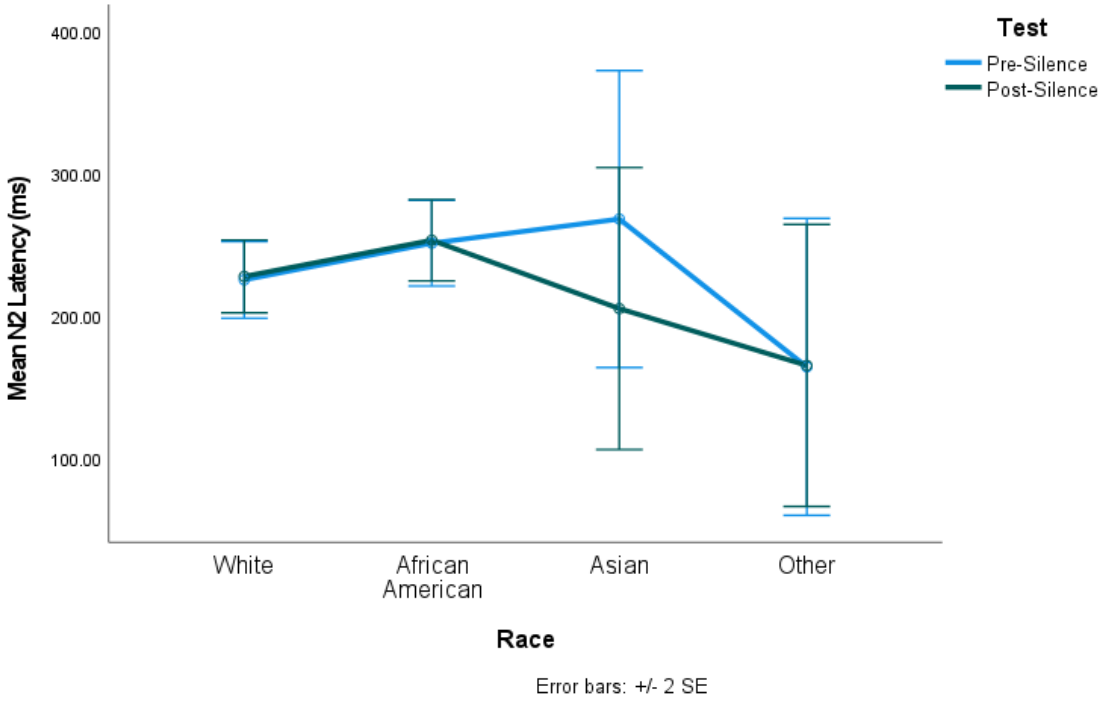

Figure 23: Mean N2 pre- and post-silence waveform latencies for racial groups

4.6.7 Mean Pre-Silence and Post-Silence P300 Waveform Amplitude in Racial Groups

Table 9 and Figure 24 show the mean Pre-silence and Post-silence P300 waveform amplitudes for the racial groups. There was no significant main effect for Test period (pre- or post-silence) ($F(1,26) = 0.02$, $p = 0.97$) and no significant interaction between Race and Test period (pre- or post-silence) ($F(3,26) = 1$, $p = 0.4$). There was no significant difference in pre- and post- silence P3 amplitude between the racial groups ($F(3,26) = 1.6$, $p = 0.2$). When the White and African American groups were compared, there was a significant main effect for Test period (pre- or post-silence) ($F(1,26) = 5.8$, $p = 0.02$, effect size 0.2) but no significant main effect for racial group ($F(1,26) = 3.6$, $p = 0.07$) or interaction between Test period (pre- or post-silence) and racial group $F(1,26) = 0.07$, $p = 0.8$).

Table 9: Mean P300 pre- and post-silence waveform amplitude for racial groups

	Race	Mean	Std. Deviation	N
PreAmplitudeP3	White	11.5038	6.91646	16
	African American	7.6825	2.24073	12
	Asian	7.2200	.	1
	Other	14.7300	.	1
	Total	9.9400	5.58142	30
PostAmplitudeP3	White	9.8025	6.44346	16
	African American	6.3100	2.72046	12
	Asian	11.5200	.	1
	Other	14.1900	.	1
	Total	8.6090	5.34989	30

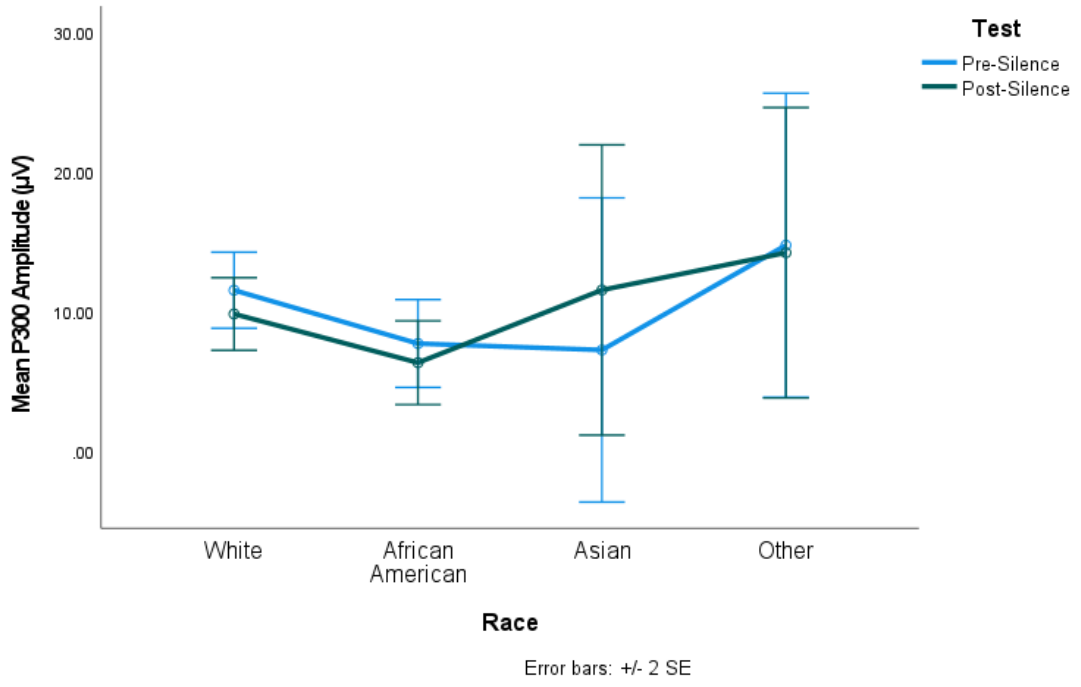

Figure 24: Mean P300 pre- and post-silence waveform amplitude for racial groups

4.6.8 Mean Pre-Silence and Post-Silence P300 Waveform Latency in Racial Groups

Table 10 and Figure 25 show the mean Pre-silence and Post-silence P300 waveform latencies for the racial groups. There was a significant difference in pre- and post- silence P3 latencies between the racial groups ($F(2,26) = 3$, $p = 0.05$, Effect size 0.3). There was no significant main effect of Test period (pre- or post-silence) ($F(1,26) = 0.03$, $p = 1$) and no significant interaction between Race and Test period (pre- or post-silence) ($F(3,26) = 1.2$, $p = 0.3$). When the White and African American groups were compared, there was no significant main effect for racial group ($F(1,26) = 3.5$, $p = 0.07$), no significant main effect for Test period (pre- or post-silence) ($F(1,26) = 0.2$, $p = 0.6$) or interaction between Test period (pre- or post-silence) and racial group $F(1,26) = 3.3$, $p = 0.08$).

Table 10: Mean P300 pre- and post-silence waveform latencies for racial groups

	Race	Mean	Std. Deviation	N
PreLatencyP3	White	264.6250	28.21554	16
	African American	295.9167	35.08550	12
	Asian	350.0000	.	1
	Other	245.0000	.	1
	Total	279.3333	36.39660	30
PostLatencyP3	White	270.6250	38.02258	16
	African American	285.7500	35.91182	12
	Asian	346.0000	.	1
	Other	255.0000	.	1
	Total	278.6667	38.32829	30

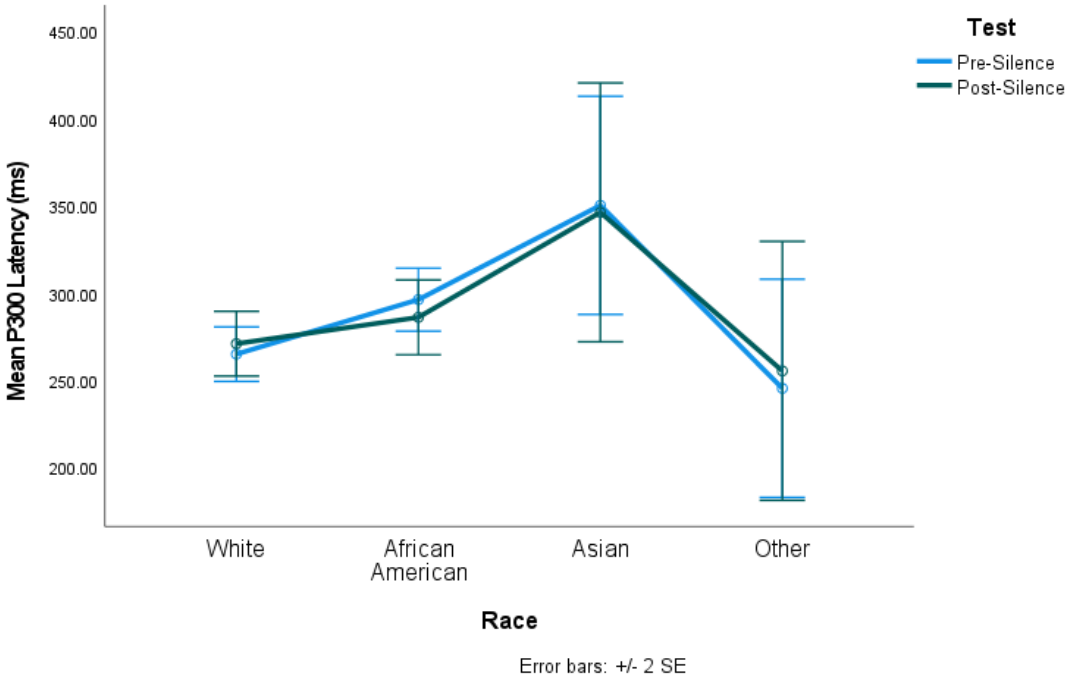

Figure 25: Mean P300 pre- and post-silence waveform latencies for racial groups

CHAPTER V: DISCUSSION

5.1 Perception of Tinnitus in Silence

The current study found that 36.7% of the participants perceived tinnitus in silence. The proportion of those who perceived tinnitus in this study is less than the number reported in the study by Tucker et al., 2005 (64%) and Heller and Bergman, 1953 (94%). This may be because of differences in subject demographic as well as differences in study protocol and instructions given to the participants. The participants in Heller and Bergman, 1953 were older and were not confirmed to have normal hearing (Heller & Bergman, 1953). The participants in Tucker et al. 2005 sat in a soundproof booth for 20 minutes, but the participants in this study stayed in silence for 10 minutes in a soundproof booth wearing ear plugs (Tucker et al., 2005). The proportion of those who perceived tinnitus in this study was also less than the number reported by Knobel and Sanchez, 2008 and Del Bo et al., 2008. Both studies documented the role of auditory attention in the perception of temporary tinnitus in silence and they observed that a greater proportion of people without chronic tinnitus are likely to perceive tinnitus in silence when their attention is drawn to their auditory system (Del Bo et al., 2008; Knobel & Sanchez, 2008). In the present study, participants were not given any indication that they might perceive sounds in silence, and the lack of auditory attention may explain the number of participants who perceived temporary tinnitus in silence.

The results from this current study show that the association between race and tinnitus perception was not significant. This finding does not agree with the results of the study by Tucker et al., 2005 and this may be attributed to a smaller sample size as well as the differences in protocol used in both studies. Additionally, there was a slightly greater percentage of African American participants in the current study (40%) than in the Tucker et al. 2005 study (33%). Thus, additional research is needed to understand the role of race in the emergence of tinnitus.

5.2 Effect of Silence on ALR and P300 Waveforms

Silence did not have a significant effect on the N1, P2 and N2 waveform amplitudes or the N1, P2, N2 and P300 latencies in the present study. However, the post-silence P300 waveform amplitude was significantly smaller than the pre-silence P300 amplitude. The reduction in P300 amplitude post-silence may reflect a reduction in attentional capacity and memory processing during the second round of ALR and P300 testing (Melynyte et al., 2018; Polich, 2007). It may also reflect a response of the neurons to reduced sensory input during the preceding ten minutes of exposure to silence. A reduction in stimulus locked responses has been reported after auditory sensory deprivation, and it appears that this reduction in neural response may extend to the non-auditory neuronal network proposed to have a modulatory effect on tinnitus perception (Blatchley, Williams, & Coleman, 1983; Coleman, Blatchley, & Williams, 1982; Teichert, Liebmann, Hubner, & Bolz, 2017). This response to silence seen in the modulatory non-auditory cortical regions may explain the negative effect of silence on tinnitus perception, and further reiterates the importance of advising tinnitus patients to avoid silence. The reduction in P300 amplitude post-silence as found in this present study, may indicate decreased synchronicity and strength of neural response after a period of reduced auditory stimulation and this agrees with the fMRI study by Wolak et al., 2016 in which reduced active cluster sizes were observed in study participants immediately after exposure to 15 minutes of silence (Wolak et al., 2016). They observed this reduced activity in the superior temporal lobe, and they reported a recovery to pre-silence levels ten minutes later.

5.3 Effect of Tinnitus Perception on ALR and P300 Waveform

The tinnitus in silence group had a smaller mean P300 amplitude and longer mean P300 latency than the non-tinnitus in silence group. The difference in P300 amplitude was not statistically significant and implies that the response of the non-auditory regions responsible for regulating auditory attention, auditory memory and response inhibition may not be different in people who tend to perceive tinnitus. Further research is needed on the network theory which postulates that non-auditory regions within the frontal, parietal and hippocampal regions have a role to play in tinnitus perception and the response to tinnitus. Although the differences in amplitude and

latency were not significant, and there is a paucity of studies documenting cortical responses that may underlie the emergence of tinnitus, studies in people with chronic tinnitus such as the studies by Said, 2012 and Attias et al., 1993 have observed smaller P300 amplitudes in subjects with chronic tinnitus. This may imply that people with chronic tinnitus or people with a tendency to experience emergent tinnitus, are likely to experience altered neuronal response in the auditory and non-auditory regions believed to be involved in the modulation of tinnitus and the response to tinnitus (Attias et al., 1993; Henry et al., 2014; Said, 2012). The reduced P300 amplitude observed in participants who perceived tinnitus in silence differs from the findings of Vasudevan et al., 2019 who reported larger P300 amplitudes in subjects with tinnitus and mild hearing loss (Vasudevan et al., 2019). The results from this present study agree with those of Houdayer et al., 2015 and Abdeltawwab & Elmorsy, 2013 who observed that there was no significant difference in the P300 amplitude in tinnitus and non-tinnitus subjects (Abdeltawwab & Elmorsy, 2013; Houdayer et al., 2015).

With respect to P300 latency differences, Vasudevan 2019, dos Santos 2010 and Said 2012 also observed longer P300 latencies in people with chronic tinnitus but unlike in the present study, the observed differences were statistically significant (dos Santos Filha & Matas, 2010; Said, 2012; Vasudevan et al., 2019). However, much like the present study, Attias 1993, Abdeltawwab & Elmorsy, 2013 and Houdayer et al., 2015 did not observe a significant difference in P300 latencies when they compared subjects with chronic tinnitus to normal controls without tinnitus and this may imply that there may be no significant deficits in processing speed in the fronto-tempero-parietal regions involved in auditory attention and auditory memory in people with chronic tinnitus and in those who are susceptible to tinnitus emergence (Abdeltawwab & Elmorsy, 2013; Attias et al., 1993; Houdayer et al., 2015). Most of the studies investigated ALR and P300 responses in tinnitus patients with HL and this may explain why their findings were different from those of the study. However, participants in the study by Houdayer et al., 2015 and Abdeltawwab & Elmorsy, 2013 were normal hearing tinnitus subjects and the researchers did not observe a significant difference in the P300 amplitudes or latencies when they compared the group with chronic tinnitus to normal controls without tinnitus. Abdeltawwab & Elmorsy, 2013 observed longer P300 latencies and smaller P300 amplitudes in tinnitus participants but this difference did not achieve statistical significance. There are limitations to comparing the results

of the present study to the ALR and P300 studies done with participants with chronic tinnitus but there is a paucity of studies documenting the ALR and P300 waveform patterns in normal hearing people who tend to perceive tinnitus under certain conditions such as silence.

Although a larger mean N1 amplitude was observed in the tinnitus group pre-silence, they experienced a larger reduction in amplitude post-silence than the non-tinnitus group. The tinnitus group also showed shorter latencies pre-silence and a greater increase in N1 latency than the non-tinnitus group after exposure to silence, however, these interactions between group and test time were not significant. The N1 wave is believed to be a marker of conscious detection of a sound signal and a large N1 wave may reflect problems with auditory habituation (Vasudevan et al., 2019). The N1 waveform is believed to originate from areas of the auditory cortex with contributions from the frontal cortex and the reticular activating system (Hall, 2007; Vasudevan et al., 2019). However, group differences observed in the N1 waveform were not statistically significant, which seems to imply that the auditory and non-auditory cortical neurons responsible for the generation of the N1 response may not have a significant role to play in the emergence of tinnitus. The findings from the present study agrees with those of Said, 2012 and dos Santos, 2010, who did not observe any significant differences in N1 amplitudes in the tinnitus and non-tinnitus group. Larger N1 amplitudes were also observed in the tinnitus group in the study by Vasudevan et al., 2019 but unlike the findings in the present study, they observed a significant difference between the N1 amplitude in the group with chronic tinnitus and controls without tinnitus. Contrary to the findings in the present study, Jacobson, 2003 and Attias, 1993 reported smaller N1 amplitude in tinnitus subjects compared to controls. The tinnitus subjects in the study by Attias, 1993 had hearing loss and although the subjects in the study by Jacobson 2003 had normal hearing they made use of an older subject population who had been exposed to occupational noise. Several studies have documented similar N1 latency findings as in the present study. Jacobson et al., 2003, Vasudevan, 2019 and Attias et al., 1993 did not observe a significant difference in N1 latency when they compared tinnitus patients with normal hearing to controls. Shorter N1 latencies have been observed in tinnitus subjects in studies by Houdayer et al., 2015 while some studies have reported longer N1 latencies in subjects with tinnitus (dos Santos Filha & Matas, 2010; Houdayer et al., 2015; Said, 2012).

The P2 amplitude did not show much difference between the two groups but the tinnitus group showed a tendency to have faster P2 latency responses in both the pre-silence and the post-silence test conditions. Although this difference was not significant, it aligns with previous findings of increased firing rates and neuronal reactivity in the auditory cortical neurons after a few minutes of auditory sensory deprivation (Norena & Eggermont, 2003; A. J. Noreña, Tomita, & Eggermont, 2003). Both groups showed a decrease in latency post-silence, but the non-tinnitus group showed a greater decrease after silence. These findings seem to imply that the processing speed and strength of neuronal response in the secondary auditory cortical neurons are not significantly different in those with tinnitus or people who tend to experience tinnitus emergence. It is curious that the tinnitus group showed higher neuronal reactivity in the auditory cortical neurons, but this was not mirrored in the non-auditory network regions believed to play a modulatory role in tinnitus detection. The decreased reactivity and response speed observed in the network regions of the tinnitus group is unlikely to be attributed to a lack of attention since participants maintained a count of the rare signal and tapped the arm of the reclining chair for the pre- and post-silence tests. Additional research is needed to understand if the emergence of tinnitus is linked to a mismatch between the neuronal response in auditory cortical regions and the neuronal response in non-auditory modulatory regions. The differences in N2 amplitude and latency observed when the tinnitus in silence group was compared to the non-tinnitus in silence group were not statistically significant. However, the tinnitus group tended to have longer N2 latencies and smaller amplitudes. Since the N2 waveform is believed to be generated from the reticular activating system (RAS), this raises further questions about the role of the RAS in the emergence of tinnitus. There doesn't appear to be much research on the role of the RAS in tinnitus perception, however, some studies on ALR in tinnitus patients have reported similar P2 waveform findings as the present study (Houdayer et al., 2015; Vasudevan et al., 2019).

5.4 Effect of Race on ALR and P300 Waveform

The participants were mainly Whites and African Americans with one Asian and one participant that identified as "other". Comparison of the ALR and P300 waveforms in the four racial groups showed some group differences in the latency of the N1, P2 and the P300 waveforms. The N1 latencies of the four racial groups varied dependent on whether the test was pre- or post-silence.

hence the significant interaction between race and the time of the ALR test. Most of the racial groups showed a reduction in P2 latency after the exposure to silence, especially the Asian participant and the White group hence the interaction between the racial group and the speed of the response observed in the pre- and post-silence ALR tests. The speed of the P300 response was observed to be slower in the Asian participant when compared to the other racial groups. The ALR and P300 waveform amplitudes and the N1 and N2 waveforms latencies did not vary significantly between the four racial groups.

When the White and African American groups were compared, the White group had larger mean P3 waveform amplitudes and shorter P300 latencies in both the pre-silence and post-silence test conditions, but this difference did not attain statistical significance. Racial differences in ALR and P300 waveforms have not been extensively studied but Zakaria et al., 2016 observed significant differences in speech-ABR amplitudes and latencies when they compared results obtained from the Chinese participants to data obtained from Caucasians (Zakaria et al., 2016).

In the present study, no significant differences in ALR and P300 waveforms were observed when the White and African American groups were compared, and differences observed when the four racial groups were compared did not show a strong effect. However, this implies that there may be racial differences in the speed of the neuronal responses that generate the ALR and P300 waveforms, therefore, additional research is needed to further document differences in ALR and P300 waveforms due to race. These documentations will help clinicians and researchers to accurately interpret ALR and P300 results obtained from patients of various racial groups. Racial differences in ALR and P300 waveforms are likely to be the result of differences in Inner Ear (Cochlea) and cortical anatomy and physiology. AEP differences have been attributed to variations in head size, skull thickness grey or white matter volume and the thickness of the corpus callosum (Hall, 2007; Melynyte et al., 2018). Furthermore, people with darker skin tones are likely to have greater quantities of inner ear melanin and perhaps different concentrations of neuromelanin and this may explain some of the differences in neuronal responses (Bonaccorsi, 1965; Breathnach, 1988; Wolff, 1931). Several studies have observed that Caucasians and those with lighter eye colors are more susceptible to noise induced hearing loss and tinnitus (Da Costa, Castro, & Macedo, 2008; Shargorodsky et al., 2010).

5.5 Limitations

The limitations of the present study include a small sample size and the dependence on subjective reports of tinnitus perception in silence.

5.6 Suggestions for Future Research

Additional research comparing the pre-silence and post-silence neural responses in the auditory cortex documented with the AMLR test and the non-auditory modulatory regions documented with the P300 auditory response in individuals who experience chronic tinnitus and in those who experience tinnitus in silence will help explore the concept of tinnitus emergence due to a dysregulation in the auditory cortex. The comparison of the AMLR waveform to the P300 waveform will improve our understanding of the central gain theory and its relationship to the network theory of tinnitus generation. There is need for a longitudinal study to document if there is a link between the emergence of temporary tinnitus in silence and the actual development of tinnitus later in life, this would clarify if tinnitus can be predicted by the emergence of temporary tinnitus in silence.

A larger study documenting ABR, AMLR, ALR and P300 waveform latencies and amplitudes in diverse racial groups will be clinically beneficial. Additional research will also be necessary to understand the underlying anatomical and physiological variations that may contribute to any racial differences observed in AER amplitudes and latencies.

There is a need for continued research in tinnitus to understand the underlying mechanisms behind tinnitus perception and the distress from tinnitus. This will contribute to the existing knowledge on tinnitus and improve the odds of arriving at an effective therapy for tinnitus.

5.7 Conclusion

There was a significant reduction in the P300 amplitude after 10 minutes of silence. Thus, the neural response in the non-auditory regions involved in modulating auditory attention and appraisal as well as the experience of auditory stimuli appears to be affected by silence and this

may explain the negative effect of silence on tinnitus perception in individuals with tinnitus. It may also explain the tendency for some individuals without chronic tinnitus to experience tinnitus emergence when exposed to silence. Therefore, clinicians can continue to advice that patients with tinnitus avoid silence by explaining that the non- auditory networks that regulate auditory perception are affected by silence and may not show optimal control of auditory cortical activity in situations where they are exposed to silence. Furthermore, clinicians can explain the need for cognitive behavioral therapy to modify the activity and the response in these non-auditory network regions such as the limbic system.

ALR and P300 waveform latencies and amplitudes were not significantly different when normal hearing young adults without chronic tinnitus who perceived temporary tinnitus in silence were compared to normal hearing young adults without tinnitus who did not perceive temporary tinnitus in silence. Thus, ALR and P300 responses do not seem to be significantly different in those individuals who tend to experience temporary tinnitus emergence in silence and those who do not experience temporary tinnitus in silence. Further research is needed to understand the differences in cortical responses that may predispose normal hearing individuals to the emergence of tinnitus or that may occur in individuals who perceive tinnitus.

There is a need to document factors that may affect ALR and P300 waveform latencies and amplitudes, such as race and trauma. Racial differences may exist in ALR and P300 waveform latencies and amplitudes, therefore, further research is needed to further document ALR and P300 waveforms in various racial groups and to understand the underlying anatomical and processing variations that may account for any differences observed in ALR and P300 responses. Furthermore, additional research is needed to understand how general health, emotional and physical trauma affects the P2 and P300 waveform latencies and amplitudes. This will enable clinicians to interpret ALR and P300 recordings accurately in patients.

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APPENDIX A: MEDICAL HISTORY FORM

Subject Number: _____ Date: _____

Provide answers to the following questions. These answers will help us to determine if you are to be included in this study.

1. Age: _____
2. Gender: Female _____ Male _____
3. Which hand is your dominant hand? Right _____ Left _____
4. Race: Circle your answer

    - Non-Hispanic White or Euro-American
    - Black, Afro-Caribbean, or African American
    - Asian
    - American Indian or Alaska Native
    - Native Hawaiian or Other Pacific Islander.
    - Multiracial
    - Other

5. Do you experience ringing in your ears? Yes/No

    If yes, what does it sound like? _____
    Is it temporary or continuous?

6. Do you have a history of ear infections or ear drainage?
7. Are you currently experiencing pain in your ears?
8. Do you have a medical history of a head injury or suffered from a concussion?
9. Do you have a medical history of any related neurological problems, like seizures?
10. Have you had any ear surgeries?
11. Are you on antidepressants, sedatives, or anticonvulsants? Yes/No

Thank you

APPENDIX B: TINNITUS IN SILENCE QUESTIONNAIRE

Late Auditory Evoked Potentials and P300 in Young Female Adults who Perceive Temporary Tinnitus after a Brief Period of Silence

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Start of Block: Default Question Block

Q1 Click to write the question text

- ○ Yes, I agree to complete the Survey (1)
- ○ No, I do not agree to complete the Survey (2)

Skip To: End of Survey If Click to write the question text = No, I do not agree to complete the Survey

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Q2 What is your age?

_____

Q3 What is your birth gender?

- ○ Male (1)
- ○ Female (2)

Q4 Did you begin to hear sounds (not generated from outside sources but from within your ears or head) while sitting in silence?

- ○ Yes (1)
- ○ No (2)

Skip To: End of Survey If Did you begin to hear sounds (not generated from outside sources but from within your ears or hea... = No

Q5 How soon did you begin to hear the sounds, which we call Tinnitus?

- ○ Immediately (1)
- ○ around 30 seconds (2)
- ○ about 1 minute (3)
- ○ around 3-5 minutes (4)
- ○ Near the end of 10 minutes (5)

Q6 List where you perceived this sound, which we call Tinnitus?

- ○ right ear (1)
- ○ left ear (2)
- ○ Both ears (3)
- ○ Head (4)

Q7 How many sounds did you hear?

- ○ one sound (1)
- ○ two sounds (2)
- ○ three or more sounds (3)

Q8 Check all types of Tinnitus Sounds that you heard in the silent condition.

- ☐ Ringing (1)
- ☐ Buzzing (2)
- ☐ Heartbeat/Pulsing (3)
- ☐ Crickets (4)
- ☐ Roaring (5)
- ☐ Humming (6)
- ☐ Hissing (7)
- ☐ Whistling (8)
- ☐ Other (9)

Q9 Did the tinnitus sound you heard seem to have a Pitch?

- ○ yes (1)
- ○ No (2)

Skip To: End of Survey If Did the tinnitus sound you heard seem to have a Pitch? = No

Q10 Describe the Frequency of the Pitch that you heard.

- ○ low frequency (1)
- ○ mid frequency (2)
- ○ high frequency (3)

Q11 Thank you so much for completing this survey and for participating in our Tinnitus and Silence Experiment. You will receive a copy of your hearing test before leaving the lab today.

End of Block: Default Question Block

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