Summer 7-16-2021

Tinnitus and Decreased Subcortical and Cortical Inhibition

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Abstract

Background: The perception of tinnitus may be triggered by a reduction in inhibitory function in the central auditory nervous system. Evidence, primarily from invasive studies of animal models of tinnitus, indicates that these changes occur at both the subcortical and cortical level. Auditory evoked potential (AEP) indices of subcortical inhibition [auditory brainstem response (ABR) $V/I_{amp\ ratio}$] and cortical inhibition [cortical auditory evoked potential (CAEP) sensory gating ratios] may provide an objective index of whether reduced subcortical and/or cortical inhibition is associated with tinnitus perception in humans. The aims of this study were to assess whether ABR and/or CAEP indices of subcortical and cortical inhibition distinguish between a group with constant tinnitus and matched non-tinnitus controls, and whether tinnitus presence and/or other factors [age, noise exposure history, hearing loss, speech perception in noise (SPIN)] predicted ABR and/or CAEP outcomes related to inhibition.

Methods: Individuals with tinnitus and control counterparts matched for sex, age, and hearing thresholds completed the study (n = 18 per group). ABRs were recorded with a tiptrode in response to high intensity click ABRs to determine the $V/I_{amp\ ratio}$. CAEPs were recorded in response to two successive high intensity 10 ms clicks. A ratio of the amplitude or area of the first (conditioning CAEP) and second (test CAEP) click response was determined ($\frac{\text{test CAEP}}{\text{conditioning CAEP}}$) as the primary measure of sensory gating. The latency ratio was also determined as a secondary outcome which may relate to sensory gating. For both the ABR $V/I_{amp\ ratio}$ and CAEP sensory gating ratios, a larger value indicated reduced inhibition. Ratios were compared between the

two groups using independent t-tests. The relative predictive value (proportional reduction in error, *PRE*) of tinnitus, age, noise exposure history, hearing loss, and SPIN on ABR and CAEP outcome variables related to inhibition was analyzed using regression.

Results: Individuals with tinnitus, relative to controls, exhibited similar ABR $\mathrm{V/I}_{\mathrm{amp\ ratio}}$, and significantly larger sensory gating $\mathrm{P1}_{\mathrm{lat\ ratio}}$. None of the variables assessed significantly predicted the ABR $\mathrm{V/I}_{\mathrm{amp\ ratio}}$. Tinnitus significantly predicted $\mathrm{P1\text{-}N1}_{\mathrm{amp\ ratio}}$, but not when taking into account age, noise exposure history, hearing loss, and SPIN. The $\mathrm{P1}_{\mathrm{lat\ ratio}}$ was significantly predicted by both tinnitus and age, however, best predicted by age.

Conclusions: Tinnitus-related reduced inhibition was not evident at the subcortical level based on the ABR $\mathrm{V/I}_{\mathrm{amp\ ratio}}$. At the cortical level, the predictive influence of tinnitus on the $\mathrm{P1\text{-}N1}_{\mathrm{amp\ ratio}}$ supports the association between reduced sensory gating with tinnitus presence in humans. The significantly larger $\mathrm{P1}_{\mathrm{lat\ ratio}}$ in the tinnitus group may also support reduced sensory gating and/or a change in the recovery time, or refractoriness, of auditory evoked responses in individuals with tinnitus. The strong predictive influence of age on the $\mathrm{P1}_{\mathrm{lat\ ratio}}$ indicates that increasing age reduced sensory gating above and beyond the effects of tinnitus. Potential limitations to the current study, including the non-normally distributed participant characteristics and AEP methodologies, as well as considerations for future research aiming to improve the reliability and validity of tinnitus AEP assessments are discussed.

Tinnitus and decreased subcortical and cortical inhibition

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Dissertation
Submitted in partial fulfillment of the requirements for the degree of
Doctor of Philosophy in Audiology.

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July 2021

Acknowledgments

Thanks to the individuals who participated in the research study, both those with and those without tinnitus. Thanks also to my colleagues and friends in the field who helped with recruitment, including the audiologists and employees at the Syracuse Veterans Affairs Hospital and, in particular the progressive tinnitus management audiologist, Dr. Leah Valensi, who went above and beyond the recruitment call of duty.

Thanks to my dissertation committee members, Dr. Karen Doherty, Dr. Beth Prieve, Dr. Marc Fagelson, and Dr. Sara Burke – the time, effort, and thoughtful feedback you have provided for me contributed to an overall better dissertation. A special thanks is due to my advisor, Dr. Kathy Vander Werff, without whose diligent commitment and thorough guidance, this research would not have been possible.

This dissertation was funded with support from the American Academy of Audiology/American Academy of Audiology Foundation Research Grants Program which was awarded to the author in 2020.

Table of Contents

1.0: Introduction

Tinnitus is a phantom auditory perception in that a person with tinnitus perceives a ringing, buzzing, roaring or other auditory sensation without the presence of any external stimulus. Tinnitus perception can be temporary, such as following loud noise exposure, intermittent, or constant. An epidemiological study of data collected from the 2007 National Health Survey identified that up to 25% of adults are estimated to perceive tinnitus during the course of their lifetime (Bhatt et al., 2016). Among survey responders with tinnitus, 83% experienced tinnitus for longer than 5 years and 27% believed their tinnitus was between a moderate and very big problem. Especially when problematic, tinnitus is associated with distress, depression, anxiety, mood swings, sleep disturbances, irritability, poor concentration, pain, and in severe cases suicide (American Tinnitus Association, 2015; Lewis et al., 1994).

Even with treatment, tinnitus can be a debilitating condition affecting an individual's health and wellbeing, including ability to work and participate in social activities. The United States Veterans Administration (VA) reported that tinnitus was the most prevalent compensated disability among service-connected veterans followed by hearing loss, a commonly co-occurring problem (Department of Veterans Affairs Benefits Administration, 2018). In addition to the high tinnitus prevalence among veterans, being a male and having a history of loud noise exposure is associated with an increased likelihood of having tinnitus (Bhatt et al., 2016). Among the respondents from the 2007 National Health Survey, an individual with a history of work related noise exposure was 3.3 times more likely to have tinnitus and an individual with recreational noise exposure was 2.6 times more likely to have tinnitus compared to an individual who did not report those respective noise exposures.

Further, as the number of years of work-related noise exposure increased, tinnitus prevalence also increased from 12.9% (0-2 years) to 25.7% (15+ years). In general, as humans age cumulative noise exposure, hearing loss, and tinnitus prevalence all increase (Bhatt et al., 2016; Gates & Mills, 2005).

In addition to the individual impact, tinnitus costs society an estimated $26 billion annually (American Tinnitus Association, 2015). In 2018, the VA awarded disability compensation for tinnitus to 1,971,201 veterans (Department of Veterans Affairs Benefits Administration, 2018). In 2012, when the number of service connected veterans for tinnitus was approximately half (972,000 veterans) of what it was reported in 2018, the annual aggregate cost of these disability payments was estimated to be nearly $1.5 billion (American Tinnitus Association, 2015). Thus, the cost of tinnitus to society is presumably rising. Furthermore, while about one in five adults, both veterans and non-veterans, with tinnitus (about 10 million people), are estimated to need clinical intervention for their tinnitus, only 10-15% of those actually seek medical evaluation (Tunkel et al., 2014). The societal cost may therefore be greatly underestimated.

Despite the high prevalence, individual impact, and societal cost of tinnitus, the available treatment options are not effective for everybody. Currently, a multidisciplinary approach to tinnitus management including auditory and psychological intervention strategies is recommended for patients with problem tinnitus (Cima et al., 2019; Henry & Manning, 2019; Tunkel et al., 2014). Typically, a tinnitus patient would initially receive an auditory and medical evaluation to identify the type and severity of hearing loss, if present, and identify any potential treatable sources of tinnitus generation, such as an VIIIth cranial nerve tumor or Meniere's

disease. Following this evaluation, auditory or medical interventions would be carried out as indicated, such as fitting the patient with hearing aids or sound generating machines. For some patients these interventions provide sufficient tinnitus relief. If, however, tinnitus is still problematic for the patient following these steps, counseling techniques such as tinnitus retraining therapy (TRT) or cognitive behavioral therapy (CBT) are often the next recommended interventions utilized to help a patient coexist with their tinnitus. CBT has been recommended as a clinically effective tinnitus intervention strategy and has been shown to reduce tinnitus distress, anxiety, and depression (Cima et al., 2014; Tunkel et al., 2014). However, there is no standardized CBT approach to treat tinnitus. CBT approaches vary in the number of treatment sessions, time spent per session, group or individual formats, in-person or internet-based formats, and tinnitus diagnostic and outcome assessments. Further, although audiologists are typically the healthcare professional an individual with tinnitus will end up being treated by, CBT approaches to treating tinnitus are not taught at most programs offering audiology degrees and thus many audiologists do not have the required training to administer CBT to tinnitus patients (Henry et al., 2019). These factors all likely contribute to the varying success of current tinnitus intervention options.

The goal of these current clinical tinnitus intervention recommendations is to mitigate an individual's adverse tinnitus reaction. Alternatively, treatments aimed at addressing the underlying cause of, rather than reaction to, tinnitus may lead to the development of more successful tinnitus interventions. Studying the pathophysiological cause of tinnitus generation has been an important goal of tinnitus research. However, the *specific* pathophysiological mechanisms underlying tinnitus generation are complex and remain poorly understood. That

said, evidence suggests that the major risk factor for acquiring tinnitus is peripheral auditory insult or cochlear damage. While cochlear damage could be caused by aging, ototoxicity, head injury, or a combination of factors, it may be most commonly caused by noise exposure. Although much is known about cochlear damage, the resulting hearing loss from noise exposure, and the association between hearing loss and tinnitus, not everyone with a damaged auditory periphery or hearing loss has tinnitus. This suggests that peripheral auditory damage alone is insufficient to generate tinnitus. Rather, it is likely that tinnitus generation results from central auditory nervous system (CANS) changes beyond the cochlea. No matter the cause of peripheral insult, when the peripheral auditory sensory end organ housed in the cochlea and the connecting auditory nerve fibers (ANFs) that propagate neural information downstream are damaged, the cochlear output to the CANS is reduced. This reduction in cochlear output can cause neuroplastic changes throughout the CANS. Such neuroplastic changes can have a substantial functional impact by altering the normal integration and processing of neural signals within the CANS and the central pathways the CANS communicate with.

Several hypotheses regarding the relationship between CANS neuroplastic changes and tinnitus generation have been proposed. The predominant theory of the majority of these hypotheses is that peripheral auditory insult triggers *reduced inhibition* and consequently, increased spontaneous auditory subcortical and cortical hyperactivity which leads to the perception of tinnitus (Baguley & Fagelson, 2016; Caspary & Llano, 2017; De Ridder et al., 2015; Eggermont, 2012; Henry et al., 2014; Kaltenbach, 2011; Norena & Farley, 2013; Rauschecker et al., 2010; Sedley, 2019; Shore & Wu, 2019). Although reduced inhibition is widely theorized to relate to tinnitus, a direct relationship between tinnitus perception and specific inhibitory

differences have not yet been well demonstrated in human studies. This may relate to the challenges of quantifying auditory inhibition in humans and difficulty controlling for tinnitus-related variables such as noise exposure history, hearing loss, or age. These limitations may be contributing to the lack of direct evidence of reduced inhibition in humans with tinnitus. Studying inhibitory function in humans with tinnitus would potentially contribute to our understanding of tinnitus mechanisms and, ultimately, the ability to provide tinnitus intervention that more directly targets the underlying pathology.

1.1: Normal Auditory Neurotransmission

The auditory pathway can be divided into peripheral and central (i.e. the CANS) auditory structures. Peripheral structures including the outer, middle, and inner ear function to transduce external sound waves into neural signals. The neural signals are processed by the CANS structures to be consciously perceived as sound. The CANS structures include the ANFs, auditory brainstem nuclei [cochlear nucleus (CN), superior olivary complex (SOC), and inferior colliculus (IC)], thalamus [medical geniculate body MGB)], and primary auditory cortex (AC). Communication through the CANS is achieved with neural signals called action potentials sent between presynaptic (the sending) and postsynaptic (the receiving) neurons. Action potentials are all-or-nothing signals such that a presynaptic neuron either will or will not send a message to a receiving postsynaptic neuron. The message sent, dictated by the chemical neurotransmitters released by the presynaptic neuron, can be either inhibitory or excitatory. The sum total and temporal incidence of the excitatory and inhibitory signals received by postsynaptic neurons along the pathway will govern whether or not a subsequent action potential will be triggered, and transmission continued to higher auditory centers.

The rate and probability that an action potential, or "spike", will fire never drops to zero in the auditory system (Clark & Ohlemiller, 2008). In other words, there is a spontaneous firing rate (SFR) present in the auditory neurons of all mammalian species and the auditory system is active even when no sound is stimulating it. When a stimulus is presented, an excitatory or inhibitory signal will respectively cause the spike rate and spike probability to increase or decrease relative to the SFR. Specific characteristics of the stimulus, such as the frequency, intensity, or location of the sound will dictate which neurons maximally respond, or, maximally change in firing rate. These neural response properties can be studied by recording the spike rate from neurons in different locations throughout the CANS during periods of no stimulation or following stimulation by sounds with specific characteristics. By studying the neural response properties in this way, scientists have described normally functioning auditory processing features of the CANS such as frequency, intensity, and temporal tuning of auditory neurons. Especially at higher-level central structures, the complexity of neural inputs increases such that individual neurons may receive many excitatory and inhibitory auditory and non-auditory signals that dictate whether or not a subsequent action potential will fire. Normal functioning auditory signal processing throughout the CANS is dependent on the integrity of the peripheral neural signal available to the CANS and, particularly at more centrally located auditory nuclei, the appropriate integration of many auditory and non-auditory neural signals through a balance of excitatory and inhibitory connections.

1.1.1: Inhibition and Sensory Gating in the Normal Auditory Nervous System

In the normally functioning CANS, inhibitory regulation of auditory signals is an important component of the preparation of auditory information for conscious perception

(Bartlett, 2013). For example, the CN receives afferent information from ANFs and functions as the first stage of sound processing in the brainstem. The CN is composed of several different neuron types, distinguished by their unique structures, connections, and functions. The CN is also the first stage of the auditory pathway where inhibitory synapses are found. Recordings from neurons within the CN exhibit intensity tuning identified by an increased firing rate with increased stimulus intensity to a given point and then a decreased firing rate with further increases in stimulus intensity. This reversal in firing rate, referred to as a non-monotonic function, is achieved through inhibitory connections acting on the neuron to suppress its continued response to further increases in stimulus intensity yielding a neuron "tuned" to a particular stimulus intensity (Clark & Ohlemiller, 2008). Beyond this encoding of a wide range of sound intensity levels, the balance of excitatory and inhibitory inputs in the CN play a role in processing of complex temporal and spectral information. Fusiform neurons, for example, are the principal cells in the dorsal cochlear nucleus (DCN) that integrate multiple excitatory and inhibitory auditory and non-auditory inputs and send an output signal to receiving postsynaptic neurons in the contralateral inferior colliculus, or midbrain in the opposite hemisphere. In relationship to tinnitus specifically, some of these DCN neurons receive non-auditory somatosensory inputs that can modulate the response properties of auditory neurons through inhibition (Shore et al., 2008), as reviewed further in *Introduction* section 1.2.2. These examples of inhibitory modulation are also present beyond the CN, throughout the CANS.

The auditory thalamus, or MGB, also functions to inhibit auditory cortical projections, which likely improves the perception of acoustic information at the conscious cortical level by filtering out irrelevant or unwanted auditory information (Cope et al., 2005; Goard & Dan,

2009; Hughes et al., 2008; Wafford et al., 2009). Like the CN, the MGB receives both afferent auditory signals, non-auditory inputs, and top-down efferent inputs (Clark & Ohlemiller, 2008). These neural projections to the MGB contribute to the thalamocortical inhibition, or "gating", of select auditory information (De Ridder et al., 2015; Rauschecker et al., 2015). Specifically, irrelevant information that is not driven by external auditory stimuli, such as spontaneous neural activity (the auditory SFR), may be inhibited from reaching higher-level conscious auditory cortical pathways. This process is referred to as *sensory gating,* or the ability to inhibit irrelevant sensory information (Braff et al., 2001; Swerdlow et al., 2001). A model of the normal sensory gating pathway is depicted in Figure 1A. As all multisensory information (e.g. visual, auditory, somatosensory) must pass through the thalamus as the last subcortical structure before cortical processing, the thalamus plays a major role in gating processes. Sensory gating can be considered a protective mechanism in that it keeps higher cortical centers that govern perception from being flooded with irrelevant and unwanted sensory information (Cromwell et al., 2008). Sensory gating occurs across sensory systems and impaired or decreased sensory gating has been well described in several clinical populations that exhibit inhibition deficits, most notably individuals with schizophrenia (Jones et al., 2016), but also those with Bipolar Disorder (Olincy et al., 2006), Post-Traumatic Stress Disorder (PTSD) (Ghisolfi et al., 2004), epilepsy (Boutros et al., 2006), Alzheimer's Disease (Jessen et al., 2001), traumatic head injury (Arciniegas et al., 2010), obsessive compulsive disorder (OCD) (Rossi et al., 2005), and Huntington's Chorea (Uc et al., 2003). Although these populations with sensory gating disorders may not experience exclusively *auditory* sensory gating deficiencies, in the context of this paper, sensory gating will refer to the ability to inhibit unwanted *auditory* information. Thus,

inhibition is a necessary component of successful auditory processing, such as the intensity tuning observed in the CN and sensory gating regulated by the thalamus.

1.1.2: Abnormal Auditory Neurotransmission, Inhibition, and Sensory Gating

Following peripheral auditory insult, cochlear output is reduced, and the peripheral neural signal sent to the CANS becomes altered. For example, fundamental changes in neural cochlear output, including elevated ANF thresholds and abnormally broad ANF tuning curves (Salvi et al., 1990), can over time alter the anatomy and physiology of downstream subcortical and cortical auditory structures. These changes are commonly referred to as neural plasticity (Purves, 2008), and can occur over the short-term or long-term. Long-term plasticity can be subdivided into two inverse types, long-term potentiation (LTP), or a strengthening of synapses, and long-term depression (LTD), or weakening of synapses. LTP is defined by an increase in excitatory postsynaptic membrane receptors increasing the net excitatory post-synaptic potential (EPSP), or, an increased likelihood of an action potential firing. LTD is defined by the inverse physiological process, a decreased net EPSP, and decreased likelihood of an action potential firing. Depending on the pattern in which typical communication between pre- and postsynaptic neurons is altered, neuroplastic changes (LTP and LTD) can yield increases or decreases in spontaneous or stimulus-evoked spike rate and probability and ultimately a change in the excitatory or inhibitory properties of a neural system.

When cochlear damage occurs and the peripheral auditory signal sent to the CANS is reduced, the typical communication between the auditory periphery and CANS becomes altered. As a result of this, long-term neural plasticity may occur and alter processing at various subcortical and cortical levels throughout the CANS. Discussed throughout this *Introduction*,

neuroplastic changes following peripheral auditory insult and reduced cochlear output to the CANS that have been associated with tinnitus generation include reduced auditory inhibition yielding hyperactivity in the brainstem and compromised auditory sensory gating in the thalamus. This model of tinnitus generation is depicted in Figure 1B and can be compared to Figure 1A, depicting normal auditory inhibition and normal sensory gating.

In animals, tinnitus-related neuroplastic changes have been objectively studied using highly controlled and invasive methods, such as comparing single-unit neural response properties throughout the CANS before and after tinnitus induction. In humans, such invasive cellular level studies are not possible, and objective evidence of neuroplastic changes due to tinnitus requires more largescale measurement of inhibitory processes through methods such as electroencephalographic (EEG) scalp recordings. Information from animal models and a small number of human studies have so far been consistent with theories that there are long-term neuroplastic changes triggered by peripheral auditory insult, specifically *decreases in inhibition,* that are related to tinnitus perception. Evidence suggests that these neuroplastic changes in individuals with tinnitus include: (1) decreased subcortical inhibition yielding an increase in auditory SFR and SFR synchrony, and (2) decreased thalamocortical inhibition causing a sensory gating failure to prevent the subcortical hyperactive auditory SFR from being consciously perceived as tinnitus. The evidence for these neuroplastic changes in inhibitory function and their relationship to tinnitus are reviewed in the following sections.

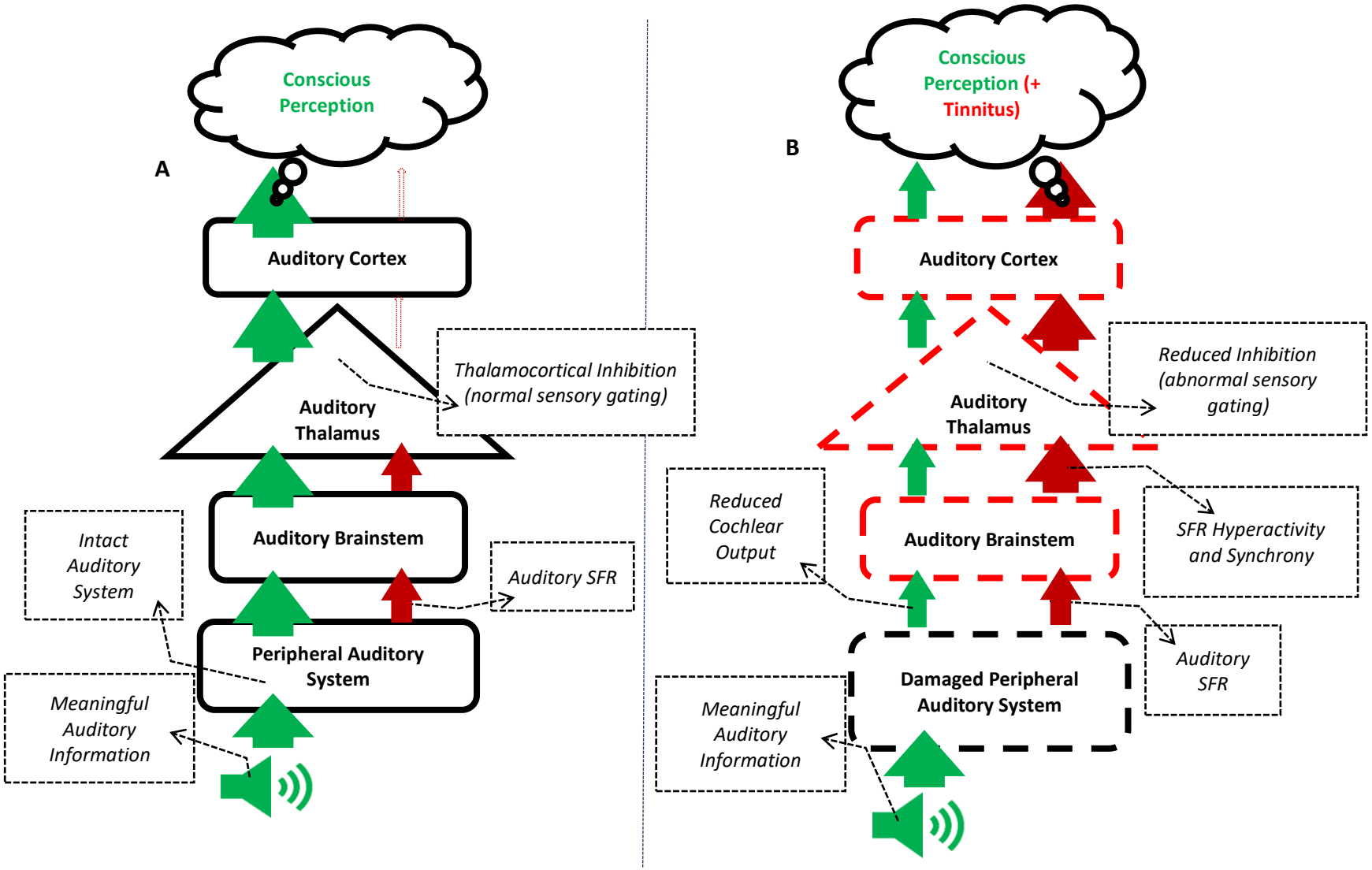


Figure 1. (A) Normal auditory inhibition (normal sensory gating), and normal perception of meaningful external auditory information, cdored in green. (B) Proposed mechanism of abnormal inhibition and reduced sensory gating of meaningless auditory SFR, colored red, related to tinnitus generation.

1.2: Animal Models of Tinnitus

The evidence gathered from animal models of tinnitus has largely directed the current state of tinnitus pathophysiological knowledge. In animal models, like in humans, noise exposure causes tinnitus in some, but not all individuals. In noise-exposed animals, between 40 to 70% will show evidence of tinnitus, as described below (Kalappa et al., 2014; Li et al., 2015; Longenecker & Galazyuk, 2011; Wu et al., 2016). In other words, pathophysiological mechanisms crucial to the development of tinnitus occur only in 40-70% of animals while the other 30-60% remain unaffected despite both groups having the same baseline, receiving the same dose of noise exposure, and exhibiting the same auditory thresholds (a common measure of hearing loss) following noise exposure. Identifying the differences between animals that do and do not develop tinnitus has contributed to the understanding of tinnitus-specific pathophysiological indices as opposed to effects confounded by noise exposure, hearing loss, or age.

1.2.1: Behavioral Evidence of Reduced Inhibition

Prior to drawing conclusions from animal models of tinnitus, it is important to consider whether or not animals actually hear tinnitus. Unlike humans, animals cannot verbally confirm or describe their perception of tinnitus. Researchers screen for tinnitus presence using two behavioral methods. First is behavioral conditioning, which was originally developed for tinnitus application by Jastreboff et al. (1988) and later refined into reproducible models that can be used over longer periods of time (Bauer & Brozoski, 2001; Bauer et al., 1999). Behavioral conditioning involves training animals to associate silence with a shock. This conditioning paradigm results in the animals associating silence with fear. Once silence has been conditioned

to elicit fear, the animals will stop behaviors that may bring about silence (and thus fear and a shock), such as eating or drinking. Then tinnitus is induced, typically with noise exposure, and the animals are tested to see if they respond to silence in the same manner as before. Presumably, if the animals perceive tinnitus and no longer experience silence, they would continue to engage in eating or drinking even in a silent environment where they would otherwise anticipate a shock.

The second tinnitus screening method in animals is called gap prepulse inhibition of the acoustic startle reflex (GPIAS). GPIAS reflects *sensory gating* in that it is a measure of how well a *sensory* event (a silent gap in noise prepulse) *gates* (inhibits) the acoustic startle reflex. Animals with tinnitus exhibit reduced inhibition, or reduced sensory gating, and thus greater acoustic startle reflexes relative to baseline or no-tinnitus animals. GPIAS is an attractive alternative to behavioral conditioning because it does not require food or water deprivation, shocks, or prior animal training (Turner et al., 2006). Animal models of tinnitus from many different species exhibit decreased acoustic startle inhibition, which is most evident when a silent gap prepulse is present in noise presumably similar in frequency to the tinnitus perception (Galazyuk & Hebert, 2015). As the GPIAS sensory gating effect was shown to be most prominent when the stimulus frequency was presumably acoustically similar to the tinnitus perception, it was originally hypothesized that the mechanism by which tinnitus influenced GPIAS was that tinnitus perception “filled in” or “masked” the silent gap prepulse, rendering it ineffective (Turner et al., 2006). However, frequency non-specific GPIAS deficits (Fournier & Hebert, 2013) and similar silent-gap evoked neural responses (Morse & Vander Werff, 2019) identified in humans with tinnitus compared to controls do not substantially support the “fill-in-the-gap” hypothesis. It

may be more likely *compromised inhibition* that yields GPIAS deficits in animals with tinnitus, as well as in humans. Regardless, behavioral and GPIAS methods are widely accepted as reliable indicators confirming the presence of tinnitus in animal studies that provide evidence of neuroplastic changes as reviewed below.

1.2.2: Subcortical Evidence of Reduced Inhibition

Evidence from animal models has indicated that tinnitus-specific neuroplastic changes within the auditory system may "begin" with subcortical auditory brainstem neurons located in the CN, specifically the fusiform cells of the DCN. Research has shown that following tinnitus induction, DCN fusiform cells demonstrate auditory hyperactivity represented by increased SFRs and increased SFR synchrony relative to pre-tinnitus baseline levels (for a review, see: Shore & Wu, 2019). For example, studies have shown that DCN fusiform cells exhibit increased SFRs within the frequency region of the noise exposure immediately following (Gao et al., 2016) and weeks after noise exposure (Kaltenbach et al., 2000). These SFR changes in animals are consistent with human experiences of both temporary and chronic presence of tinnitus following noise exposure. Not only have these general hyperactive responses been found, they have also been associated with tinnitus characteristics in animals. Increased DCN SFR has been identified in neurons tonotopically tuned to behaviorally identified tinnitus frequencies (Wu et al., 2016) and DCN SFR increases have been shown to correlate with the severity of animals' tinnitus, indexed by a behavioral conditioning suppression ratio of eating or drinking behaviors (Kaltenbach et al., 2004). In addition to an overall increased SFR, increased SFR synchrony, indexed by cross-unit spike correlations across DCN fusiform cells, has also been found in tinnitus models following noise exposure (Wu et al., 2016).

DCN hyperactivity identified in animal models of tinnitus is likely a result of reduced inhibition. Reviewed by Caspary et al. (2005), DCN fusiform cells receive inhibitory input from D-multipolar cells in the ventral cochlear nucleus (VCN) (Doucet et al., 1999), and frequency-specific (tonotopic) inhibitory input from vertical cells (Rhode, 1999). These inhibitory inputs normally function to, for example, reduce the DCN response to high intensity stimuli at or near the characteristic frequency yielding the aformentioned non-monotonic intensity functions indicative of CANS neural intensity tuning. Inhibition, such as this, is facilitated by synaptic receptors and ionic currents. For example, GABA-B receptors, when activated, open potassium (K^+) channels, which function to inhibit excitatory signals (Gonzalez et al., 2012). An in vitro analysis of the excitatory and inhibitory neural contributions to tinnitus-related DCN hyperactivity reported that the auditory pathway of mice with behavioral evidence of tinnitus exhibited hyperactivity due to decreased GABAergic inhibition (Middleton et al., 2011). This decrease in GABAergic inhibition likely relates to reduced DCN K^+ currents (reduced inhibition) also identified in animal models of tinnitus (Pilati et al., 2012). Another neural channel that may be related to decreases in inhibition and increases in SFR and SFR synchrony in animal models of tinnitus is the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel. The opening of HCN channels allows positively charged sodium (Na^+) and K^+ ions to flow into the neuron yielding a membrane depolarization, increasing the likelihood of an action potential (Benarroch, 2013). Decreased HCN channel activity has been associated with decreased synchronous oscillatory activity in the thalamocortical system (Zobeiri et al., 2019). Noise exposed animals that *did not* show evidence of tinnitus exhibited reduced HCN channel activity (less synchrony) in addition to greater K^+ currents (greater inhibition) relative to baseline (Li et

al., 2015). Thus, hyperactivity identified by invasive intracellular recordings from animal models of tinnitus is likely secondary to reduced inhibition.

Studies of animal models of tinnitus have also indicated that tinnitus may be related to excitatory and inhibitory activation from multisensory or bimodal connections in the DCN. DCN fusiform cells normally integrate auditory and somatosensory (motor) inputs. The somatosensory inputs, which can modulate the response properties of fusiform auditory neurons in the DCN, may be involved in some forms of tinnitus. This is supported by the motor abnormalities indicative of GPIAS (inability to inhibit the acoustic startle reflex) and the ability of some humans to modulate the psychoacoustic properties of tinnitus by moving parts of their face or neck. Following cochlear damage, cochlear output to the DCN is reduced and somatosensory input to the DCN is increased (Han et al., 2019). The net result of this neuroplasticity is change in the balance between auditory and non-auditory excitatory and inhibitory signals acting upon fusiform cells in the DCN and ultimately changes to the SFR of the DCN fusiform cells. Specifically, hyperactive DCN fusiform cells observed in some animal models of tinnitus may be a result of LTP, or long-term increases in postsynaptic DCN activation by presynaptic somatosensory input (Koehler & Shore, 2013). Therefore, at least “somatosensory tinnitus”, or tinnitus that can be modulated by motor activity, may be related to increased neural activation due to LTP observed between somatosensory inputs and DCN fusiform cells. This has been demonstrated in animal models of tinnitus, where increased LTP of somatosensory-auditory connections was associated with increased DCN SFR (Dehmel et al., 2012). That is, there was a long-term enhancement of DCN auditory responses from somatosensory input. Conversely, in other research, animals that were noise-exposed but did

not develop tinnitus exhibited LTD, or a long-term decrease in DCN auditory responses from somatosensory input (Koehler & Shore, 2013). In other words, noise exposed animals that did *not* show evidence of tinnitus exhibited a decrease in auditory SFR whereas noise exposed animals that *did* show evidence of tinnitus exhibited an increase in auditory SFR due to changes in the balance of excitatory and inhibitory DCN postsynaptic receptors.

The above evidence suggested to researchers that counteracting the LTP of the somatosensory-auditory connections may decrease the excitability of DCN fusiform cells and thus decrease the perception of somatosensory tinnitus. In other words, counteracting the specific neural processes leading to subcortical DCN hyperactivity and tinnitus generation may decrease the psychophysical perception of tinnitus. In a study designed to test this theory, Marks et al. (2018) delivered repeated bimodal somatosensory-auditory stimulation known to induce a net decrease in DCN auditory activation by somatosensory input in guinea pigs that already had noise-induced tinnitus. In other words, Marks et al., (2018) aimed to induce LTD to counteract the LTP that may be related to tinnitus generation. Over the course of 25 days, tinnitus in the animal models decreased based on physiological (reduction in DCN SFR and synchrony) and behavioral (GPIAS) evidence. These findings in animals led the researchers to apply the same bimodal stimulation to 20 humans with somatosensory tinnitus using a double-blinded, sham-controlled, crossover study. Their results indicated that the bimodal stimulation reduced both self-reported tinnitus loudness and intrusiveness scores whereas unimodal auditory stimulation did not yield either benefit for humans.

Findings from the Marks et al., (2018) study firstly suggest that conclusions drawn from animal models of tinnitus likely translate well to humans. Therefore, evidence from animal

models, reviewed above, indicating that tinnitus presence is associated with increased subcortical SFR and SFR synchrony (i.e. subcortical hyperactivity) secondary to reduced inhibition suggests that the perception of tinnitus in humans may result from the same mechanisms. Namely, humans with tinnitus likely have decreased subcortical auditory inhibition that manifests as auditory hyperactivity. Secondly, Marks et al., (2018) provide initial evidence that by identifying pathophysiological mechanisms of tinnitus, targeted neuroplastic therapies aimed at reversing those mechanisms may provide tinnitus relief for humans. Specifically, identifying in humans with tinnitus where in the auditory pathway (e.g. subcortical vs. cortical) inhibition is reduced, how inhibition is reduced and, in the future, targeting those neural mechanisms may reduce the psychophysical perception and emotional impact of tinnitus. Achieving these goals depend on our ability to assess neuroplastic changes related to tinnitus in humans. As we cannot assess such changes at the cellular levels in the DCN or MGB in humans, non-invasive and inexpensive objective assessments of auditory function at multi-level sites throughout the CANS may be an imperative step towards linking tinnitus perception in humans to pathophysiological tinnitus mechanisms, such as reduced inhibition. Differentiating between groups of individuals with tinnitus compared to those without tinnitus based on non-invasive and inexpensive objective measures of inhibition is an important initial step towards the assessment of pathophysiological tinnitus mechanisms in humans.

1.3 Studying Tinnitus in Humans

In humans, the diagnosis of tinnitus itself relies almost exclusively on self-report and functional behavioral performance. Subjective measures provide a good indication for how tinnitus impacts an individual functionally or emotionally, but little can be learned regarding the

pathophysiological mechanisms related to tinnitus. Typical subjective tinnitus measures include audiometry, behavioral auditory performance tests, psychoacoustic tinnitus estimations, and self-report questionnaires. Individuals with tinnitus may demonstrate varying degrees of sensorineural, mixed, or conductive hearing loss on standard audiometric threshold testing. Individuals with tinnitus have also been shown to have poorer performance on functional behavioral measures, such as poorer speech perception in noise (SPIN) compared to normal hearing non-tinnitus controls of the same age (Ryu et al., 2012). These characteristics are not specific to individuals with tinnitus. Rather, many individuals with hearing loss and other auditory processing deficits exhibit such audiometric threshold and behavioral auditory performance outcomes. Therefore, based on standard audiometric testing or behavioral auditory performance testing alone, it is difficult to distinguish an individual who has tinnitus.

Characteristics of an individual's tinnitus can vary widely and be difficult to assess and quantify. Psychoacoustic assessments of tinnitus perception require the individual to estimate features of their tinnitus such loudness, pitch, laterality, maskability, and residual inhibition. However, the measures used in psychoacoustic tinnitus evaluation require validation, and the most reliable laboratory measures for tinnitus quantification are generally time consuming and their clinical relevance can be questionable (Tunkel et al., 2014). For example, to be reliable for research studies, tinnitus pitch and loudness matching procedures often use multiple adaptive forced-choice trials requiring difficult subjective comparisons for participants (Henry, 2016). Clinically, these methods are typically not feasible and may be of minimal utility in providing intervention. However, providing a patient with information based on brief tinnitus pitch and

loudness matching evaluations that can be conducted with a standard audiometer may be of counseling benefit by providing the patient with data regarding their tinnitus perception.

Self-report questionnaires that quantify the perceived severity and quality of life impact of an individual's tinnitus are also of counseling utility. Most self-report tinnitus questionnaires focus on the emotional impact of tinnitus and include lifestyle questions such as how tinnitus impacts sleep habits. Self-report questionnaires may help to distinguish between patients that do or do not require interventions and can document changes in distress over time. For example, a retrospective analysis of treatment outcomes following tinnitus masking coupled with TRT indicated that self-report questionnaires could differentiate between patients who did and did not respond well to treatment (Theodoroff et al., 2014). Subjective measures are also commonly used to quantify hyperacusis, or decreased sound tolerance, a problem identified in between 30-40% of tinnitus patients (Sheldrake et al., 2015). Like tinnitus, the psychoacoustic properties of hyperacusis can be estimated by finding, for example, a patient's uncomfortable loudness level (UCL) and the quality of life impact can be determined with self-report questionnaires. Examples of commonly used questionnaires to evaluate the quality of life impact on tinnitus and hyperacusis are the Tinnitus Functional Index (TFI; Meikle et al., 2012) and Hyperacusis Questionnaire (HQ; Khalfa et al., 2002), respectively.

1.3.1: Peripheral Objective Measures of Tinnitus in Humans

Objective measures, as opposed to subjective, may potentially provide information regarding the site and extent of tinnitus pathology in humans. However, to date, objective measures of peripheral or central auditory function, like otoacoustic emissions (OAEs) or evoked potentials, have generally not proven to be reliable indicators of the presence or

severity of tinnitus. Variability in findings across studies of individuals with tinnitus may relate to lack of control for related factors such as noise exposure history, hearing loss, or age. The objective measures used may also not be directly measuring the appropriate site of lesion or specific mechanisms of tinnitus generation. For example, peripheral objective measures such as OAEs, which assess the function of cochlear outer hair cells (OHCs), have been shown to yield lower amplitudes (reduced OHC function and reduced cochlear output) in people with tinnitus compared to those without tinnitus (Ozimek et al., 2006). However, noise exposure predominantly damages the stereocilia of OHCs and inner hair cells (IHCs) in the cochlea and is also associated with decreased OAE amplitude (Le Prell, 2019). The direct relationship between tinnitus and decreased OAE amplitude may, therefore, be confounded by the amount of noise exposure and the resulting peripheral auditory damage. Regardless, measuring OHC function is still an important component of a full assessment of peripheral auditory integrity and can help differentiate between cochlear and auditory nerve damage.

Objective measures of central auditory processing beyond the cochlea, including measures of the auditory nerve, brainstem, thalamus, and cortex, may have the potential to provide more evidence of the specific pathophysiological differences related to tinnitus. Consistent with the research in animal models, studies using objective measures in humans have provided some initial evidence linking the perception of tinnitus and compromised inhibition, as reviewed below. However, evidence directly identifying specific compromised anatomical sites or physiological processes related to tinnitus perception is lacking. It may be that more substantive evidence of specific compromised sites or processes related to tinnitus generation can be learned by studying the presumed mechanism of tinnitus generation,

compromised inhibition, at different levels (subcortical and cortical) of CANS processing and by addressing previous limitations, including accounting for the influence of related characteristics on variability in outcome measures presumed to relate to tinnitus.

1.3.2: Objective Evidence of Reduced *Subcortical* Inhibition in Humans with Tinnitus

Animal models have provided direct evidence of reduced inhibitory processes at the level of the auditory brainstem, particularly in the CN. While the same single-neuron and near-field measures can't be made in humans, the auditory brainstem response (ABR) is an auditory evoked potential (AEP) that reflects the integrity of the subcortical vestibulocochlear nerve and auditory brainstem. Reviewed by (Luck, 2005), AEPs are tools that can be utilized to non-invasively study the electrical potentials generated by neurons from far-field electrodes placed on the scalp. When the activity from many spatially arranged neurons simultaneously occurs, the summed electrical potentials can be recorded as a voltage from scalp electrodes. The amplitude of the AEP provides information regarding the size of the active neural population while the latency of the AEP provides information regarding the timing, or speed, of processing. AEPs that are elicited by and time-locked to specific stimuli, such as the ABR, can provide us with an index of the biological processes underlying auditory processing.

Relative to peripheral auditory measures, the ABR may be a more suitable tool to study tinnitus given its more central, albeit still subcortical, generators. Further, the ABR can provide an index of the biological processes underlying auditory activity at a pre-attentive level and averaged responses are highly sensitive to temporal patterns of neural discharge in the auditory nerve and brainstem. The typical adult ABR is characterized by five major component peaks,

labeled I through V. The generation of ABR wave I is well established, and this wave is analogous to gross measures of synchronous afferent neural activity generated at the most distal portion of the VIIIth cranial nerve by the spiral ganglion cell bodies. The probable generating source of wave II is the proximal portion of the VIIIth cranial nerve, closer to the brainstem. Wave III has been associated with primary generators at the CN and wave IV may be generated by fiber tracts leaving the CN, the SOC, and neural fibers along the lateral lemniscus, a tract of brainstem fibers that carry auditory information towards the IC. The most prominent peak of the ABR is wave V, which is likely generated by activity in the lateral lemniscus and the IC, the primary convergence site for afferent brainstem auditory and non-auditory signals. It is notable that the neural contributors to more centrally generated ABR components are more complex and less well defined than the more peripheral waves I and II (Atcherson & Stoody, 2012).

Based on the theory that the perception of tinnitus may be a result of reduced inhibition secondary to peripheral auditory damage, relative amplitude differences in the peripheral ABR waves compared to the later, more centrally generated waves, may provide an objective indication of tinnitus. Specifically, wave I amplitudes may be reduced due the peripheral damage at the synapse between the cochlear hair cells and ANFs, while later waves that reflect activity in the brainstem nuclei and pathways including the CN (primarily wave III) and IC (primarily wave V) may be enhanced due to reduced inhibition yielding auditory hyperactivity. As previously discussed, animal studies have identified tinnitus-specific hyperactivity localized to the CN. Auditory nuclei downstream of the CN in animal models of tinnitus, such as the IC, have also exhibited both increased SFR (Ma et al., 2020; Manzoor et al., 2012) and increased

SFR synchrony (Bauer et al., 2008). Therefore, the ABR waves III and V in humans may also reasonably exhibit an increased amplitude reflecting auditory hyperactivity secondary to reduced subcortical inhibition. As wave V is the largest ABR component and most reliable on an inter- and intra-individual basis (Picton, 2011), many human studies focus solely on wave V indices of the activity of the CN and beyond. Therefore, in humans, the coinciding observation of a reduced wave I amplitude (peripheral auditory insult) and increased wave V amplitude (auditory hyperactivity secondary to reduced inhibition), or an overall increase in the $\frac{\text{wave V}}{\text{wave I}}$ amplitude ratio, denoted $\text{V/I}_{\text{amp ratio}}$, in the scalp-recorded ABR may be a good indication of reduced subcortical inhibition and its relationship to tinnitus status. Note that in many of the subsequent studies, the measured ABR outcome was a $\text{I/V}_{\text{amp ratio}}$, a reduction of which is equivalent to an increased $\text{V/I}_{\text{amp ratio}}$. The $\text{V/I}_{\text{amp ratio}}$ was chosen for the current study to remain consistent with the later discussed sensory gating ratio, where an increase in the ratio is also indicative of a decrease in inhibition.

An overall increase in the ABR $\text{V/I}_{\text{amp ratio}}$ was identified by Schaette and McAlpine (2011), who compared click-evoked ABRs between 15 females with tinnitus (36.3 $\pm$ 2.6 years) and 18 females without tinnitus (33.2 $\pm$ 1.9 years), all with clinically normal pure tone thresholds [<25 dB hearing level (HL) 0.125-8 kHz]. The researchers observed that the tinnitus group exhibited a decreased wave I amplitude, similar wave V amplitude, and overall larger $\text{V/I}_{\text{amp ratio}}$ relative to the control group. Despite the finding that wave V amplitude itself was not larger in the tinnitus group relative to control, because of the difference in the amplitude ratio, or the relative central versus peripheral effects, Schaette and McAlpine (2011) concluded that these results may indicate the presence of reduced cochlear output leading to reduced

subcortical inhibition and auditory hyperactivity. Although Schaette and McAlpine (2011) provided initial evidence that the ABR $V/I_{amp\ ratio}$ may be an indication of tinnitus status, variability accounted for by other characteristics that may have also influenced the $V/I_{amp\ ratio}$, such as age or variation in pure tone thresholds, were not analyzed.

Gu et al. (2012) similarly reported an overall larger click-evoked ABR $V/I_{amp\ ratio}$ in 15 men with tinnitus (42 $\pm$ 6 years) relative to 21 men without tinnitus (43 $\pm$ 7 years). Gu et al. (2012) also observed a decrease in wave I amplitude, increase in wave V amplitude, and overall larger $V/I_{amp\ ratio}$ in the tinnitus group relative to control. Although Gu et al. (2012) measured high frequency audiometric thresholds of their participants (up to 16 kHz) and matched the tinnitus and control groups based on having similar thresholds, details regarding the specific pure tone audiograms and degree of hearing loss within the sample were not reported or accounted for in the analysis. They did, however, also include a younger control group of 11 younger men without tinnitus (23 $\pm$ 2 years) who had less hearing loss, represented by the pure tone audiogram, relative to the older group without tinnitus. The younger group without tinnitus exhibited larger amplitudes for all ABR components, however, the specific influence of age versus differences in pure tone audiometric thresholds on ABR outcomes was not analyzed. The study also did not include a similar younger group with tinnitus to better establish the relative influence of these factors.

Bramhall et al. (2018) compared ABR outcomes in 74 participants, all between 19-35 years old and with clinically normal audiometric thresholds (<20 dB HL 0.25-8 kHz). The participants were originally grouped based on veteran status and noise exposure history. However, Bramhall et al. (2018) observed a relationship between wave I amplitude and the

presence of tinnitus and reported group ABR outcomes between 15 participants (13 males, 26.3 $\pm$ 2.1 years) with tinnitus and 59 participants (22 males, 26.7 $\pm$ 4.5 years) without tinnitus. Of note, a history of high noise exposure was strongly associated with tinnitus presence in this study, such that 14 out of 15 participants reporting a high noise exposure history also reported tinnitus. Unlike the previously discussed studies, Bramhall et al. (2018) recorded ABRs in response to a 4 kHz toneburst rather than a click stimulus. They also recorded ABR responses using a tiptrode, an electrode placed in the ear canal that decreases the physical distance between the generation site of ABR wave I and the recording electrode and may enhance the amplitude of wave I. The Bramhall et al. (2018) study showed that the tinnitus group exhibited a decreased wave I amplitude, similar wave V amplitude, and overall larger $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ relative to the control group. Therefore, despite some methodological differences, the results of Bramhall et al. (2018) were also generally consistent with an association between tinnitus presence and reduced subcortical inhibition and auditory hyperactivity secondary to reduced peripheral output.

These studies associating tinnitus with an increased $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ recruited participants of predominantly (or entirely) the same sex and with normal hearing based on the audiogram. However, Valderrama et al. (2018) recruited young and middle-aged participants evenly split by sex (*M* = 43.36 years, *SD* = 6.94, range = 29 – 55 years; 37 females, 37 males). 84% of the participants had normal hearing (≤ 20 dB HL from 0.25 to 6 kHz), however, the remaining 12% had "near-normal" hearing (≤ 25 dB HL to 2 kHz, ≤ 30 dB HL to 3 kHz, ≤ 35 dB HL to 4 kHz, and ≤ 40 dB HL to 6 kHz). Despite these differences in sex and hearing, Valderrama et al. (2018) also associated tinnitus presence with a significantly larger $\mathrm{V/I}_{\mathrm{amp\ ratio}}$. Further, Valderrama et al.

(2018) also identified a significant relationship between increased noise exposure history with decreased wave I and wave V amplitudes.

Although these studies (Bramhall et al., 2018; Gu et al., 2012; Schaette & McAlpine, 2011; Valderrama et al., 2018) provide initial evidence that the ABR $V/I_{amp\ ratio}$ may be a good reflection of subcortical inhibitory processes related to tinnitus, other studies have not shown reduced wave I amplitudes and increased $V/I_{amp\ ratio}$ in groups with tinnitus (Guest et al., 2017) and increased noise exposure histories (Couth et al., 2020; Prendergast et al., 2017). In a review of ABR studies in individuals with tinnitus, Milloy et al. (2017) reviewed outcomes and discussed factors that may lead to variability in ABR outcomes associated with tinnitus across studies including methodological differences such as the stimulation parameters (e.g. click versus tone burst stimuli, intensity levels), recording parameters (e.g. tiptrode versus mastoid electrode), participant factors such as including individuals with varying tinnitus characteristics (e.g. constant versus intermittent perception), and poor consideration of tinnitus-related variables such as noise exposure history, hearing loss, or age on ABR outcomes. In summary, evidence from some human studies suggest that the ABR may provide an objective index of subcortical neuroplastic changes related to the presence of tinnitus that is consistent with abnormal inhibitory processes. Specifically, larger ABR $V/I_{amp\ ratio}$, interpreted as being consistent with decreases in wave I amplitude due to peripheral auditory damage and a similar or enlarged wave V amplitude due to reduced inhibition and auditory hyperactivity in the brainstem, have been reported. However, not all studies have agreed, and it remains in question whether changes in the ABR $V/I_{amp\ ratio}$ are associated with the perception of tinnitus or other tinnitus-related factors such as noise exposure history, hearing loss, and age. By using specific ABR

stimulus and recording techniques that may improve outcomes, recruiting research groups with and without constant tinnitus, who have varying and matched degrees of hearing loss (up to a moderate degree), matched sex, varying noise exposure history, and a range of age may help to describe these relationships and contribute to a better understanding of tinnitus and decreases in subcortical inhibition as indicated by objective ABR measures.

1.3.3: Objective Evidence of Reduced *Cortical* Inhibition in Humans with Tinnitus

In addition to differences in inhibitory processes at the subcortical level, studies of animal models of tinnitus have identified neuroplastic inhibitory differences at higher levels, including the MGB and AC (Shore & Wu, 2019). Because the *conscious* perception of tinnitus is likely to relate to a higher level of processing than the pre-attentive brainstem, it is also important to objectively evaluate whether there is evidence of reduced cortical inhibition in humans who perceive tinnitus.

Differences in higher-level auditory neural processing can be objectively studied in a few ways. One method is using cortical imaging techniques such as functional magnetic resonance imaging blood-oxygen-level dependent (fMRI BOLD) imaging. BOLD signals are an indirect measure of neural activity and have been used in some studies to demonstrate hyperactivity from the CN to the AC of people with tinnitus (Boyen et al., 2014; Lanting et al., 2008; Melcher et al., 2009). These findings are consistent with those from single unit recordings in animal models of tinnitus, which also exhibited increased SFR and increased SFR synchrony in the animal AC following noise exposure (Basura et al., 2015; Zhang et al., 2016). BOLD fMRI has also been used to examine whether tonotopic map reorganization, as has been demonstrated in some animal studies, was present in humans with tinnitus, but findings have so far not been

consistent with this type of reorganization (Langers et al., 2012). Although the resolution of current fMRI technology may limit the ability to observe such neuroplastic differences due to tinnitus, advances in fMRI scanners including increased resolution (7T scanners) may prove to be useful for application of tinnitus study in the future. A recent analysis of functional and structural differences between a tinnitus and hearing-matched control group using an ultra-high field 7T fMRI scanner identified reduced thalamocortical and cortico-cortical connectivity in the tinnitus group, which the researchers concluded to be indicative of reduced thalamocortical inhibition (Berlot et al., 2020).

Previous MRI studies, consistent with the findings of Berlot et al. (2020), have also demonstrated evidence of central neuroplastic differences in humans with tinnitus. Such findings include differences in cortical tissue volume in people with tinnitus that may be indicative of thalamic inhibition deficits like that observed in people with chronic pain (Rauschecker et al., 2015). Specifically, individuals with tinnitus, relative to controls, have exhibited a reduction in grey matter in the ventromedial prefrontal cortex (vmPFC; Muhlau et al., 2006) and hyperactivity in the nucleus accumbens (NA) in response to sounds frequency-matched to the tinnitus (Leaver et al., 2011). These imaging findings have led to the "frontostriatal gating hypothesis" (Rauschecker et al., 2015), which states that the NA and vmPFC, which indirectly inhibit the auditory thalamus, function to gate (inhibit) irrelevant auditory SFR from passing through the thalamus to the conscious auditory cortex. The reduction in vmPFC grey matter and NA hyperactivity suggest that this inhibitory circuit is compromised and thus the vmPFC/NA mediated gate effectively opens, allowing irrelevant auditory SFR to pass from thalamus to cortex and thus from an individual's subconscious to

conscious perception. Thus, the frontostriatal gating hypothesis suggests that individuals with tinnitus have a *sensory gating impairment*. However, this specific hypothesis has not been directly supported by other MRI studies (Husain et al., 2011). Further, high costs and low access to imaging instrumentation limit the current utility of these imaging studies.

EEG measures have also been used to study cortical function in people with tinnitus. The measured timing and amplitudes of oscillations in ongoing EEG recorded from scalp electrodes are influenced by firing rate, synchrony, and the spatial alignment of current flowing through neurons. Thus, resting state EEG measures may provide a good indication of tinnitus related differences in auditory SFR and SFR synchrony. EEG studies in people with tinnitus have been interpreted as consistent with decreased thalamocortical inhibition as reflected by increased amplitude of low-frequency oscillations as compared to non-tinnitus controls (Llinas et al., 1999; Moazami-Goudarzi et al., 2010; Weisz et al., 2005; Weisz et al., 2007). These findings from resting state EEG studies in people with tinnitus led to a hypothesis referred to as "thalamocortical dysrhythmia" (TCD; De Ridder et al., 2015). Whereas the frontostriatal gating hypothesis is based on the compromised vmPFC/NA gate, the TCD hypothesis is based on compromised MGB inhibition, indicated by differences in thalamocortical rhythmicity. Specifically, the TCD hypothesis states that increases in low frequency oscillations (decreased thalamocortical inhibition) trigger increases in high frequency oscillations (hyperactive and synchronous cortical auditory SFR). The synchronous auditory cortical hyperactivity is presumed to be perceived as tinnitus. Therefore, the TCD hypothesis, like the frontostriatal gating hypothesis, also suggests that individuals with tinnitus have *impaired sensory gating* such that decreased thalamic inhibition allows irrelevant auditory SFR to pass from subcortical

unconscious to cortical conscious auditory processing centers. Like the frontostriatal gating hypothesis, more evidence is needed to confirm this specific pathology in the context of tinnitus generation as these mechanisms have not been confirmed in other studies (Adjamian et al., 2012). Regardless, both hypotheses have some support from imaging and EEG studies and are consistent with differences in inhibitory processes in individuals with tinnitus, specifically, a sensory gating impairment.

AEPs, as compared to resting state EEG, have the advantage of reflecting stimulus-specific processing with fine temporal resolution within the auditory system as well as being non-invasive and relatively easy to obtain. Specifically, cortical auditory evoked potentials (CAEPs), which reflect auditory stimulus processing primarily at the level of the AC (Martin et al., 2008), can also be used to study the relationship between central neuroplastic changes and the perception of tinnitus in humans. The CAEP is dominated by the P1-N1-P2 waveform complex (also known as the P50, N100, and P200) and can be evoked by a change in the auditory environment, for example, an onset, offset, or change in stimulus. CAEPs are sometimes referred to as obligatory or sensory, meaning that the participant does not need to actively attend and respond to the stimulus in order to record the response. However, some studies have indicated that when the subject is attentive to the stimulus, later components of the CAEP (N1 and P2) may exhibit increased amplitudes (Picton & Hillyard, 1974). Reviewed by Picton (2011), these later CAEP components likely reflect activity generated within the AC including the connections between the AC and non-auditory cortical regions. Whereas the later CAEP components reflect widespread activity across the AC and it's neural projections, the largely pre-attentive earlier component of the CAEP (P1) may reflect afferent thalamocortical

connections, or, information flow from thalamus to cortex (Jerger et al., 1992). Thus, the temporal incidence of the CAEP components (P1, followed N1, and lastly P2) can be thought of as reflecting the flow of information from thalamus to AC, to AC projections to non-auditory regions while the amplitude of each component can be thought of as a reflection of the size of the active neural population at that discrete time.

Basic features of auditory processing can be studied with the CAEP by manipulating stimulus parameters. For example, temporal processing, the ability to process changes in frequency and intensity over time, can be studied using stimuli that vary in onset properties or include an abrupt change in these properties. For example, the CAEP can be evoked when an ongoing stimulus changes from 1 kHz to 2 kHz, reflecting that this stimulus change is detected and encoded at the level of the auditory cortex. Similarly, a CAEP can be evoked by a silent gap in ongoing background noise, due to the change from noise to silence. Based on the theory that tinnitus may be associated with impaired gap detection, or that tinnitus "fills in the gaps", the author conducted a study comparing CAEPs evoked by silent gaps of varying duration in broadband noise between a tinnitus group (n = 13, 6 male, M = 52.9 $\pm$ 19.3 years) and hearing, age, and sex matched control group (n = 13, 6 male, M = 54.4 $\pm$ 18.0 years) (Morse & Vander Werff, 2019). We hypothesized that the tinnitus group, relative to controls, would exhibit gap-evoked CAEP components with decreased amplitude and increased latency in response to silent gaps below, slightly above, and well above individual behaviorally established gap-detection thresholds. While none of the component amplitudes or latencies were significantly different between the tinnitus and control groups overall, there was a significant interaction between group and silent gap duration. Specifically, in the tinnitus group, P1 latency decreased as gap

duration increased (more salient gap) while for the control group, the relationship was the opposite. These results, therefore, only partially supported tinnitus related gap-evoked CAEP abnormalities.

One possible explanation for this outcome was the predominantly high-frequency tinnitus experienced by the participants, which may not have been similar enough to the broadband noise stimulus to adequately mask gap perception. It is also possible that our hypothesis was only partially supported because tinnitus may not "fill in the gaps" perceptually, and the responses did not reflect the proposed mechanism of tinnitus, reduced inhibition. As suggested by the previously discussed ABR, MRI, and EEG indications of tinnitus status as a reflection of reduced inhibition, it may be that a CAEP paradigm that specifically reflects inhibitory processing may be a better reflection of tinnitus mechanisms in humans. As discussed in the following section, the CAEP can be used in a sensory gating paradigm as an indication of inhibitory function on the cortical neural response.

1.3.4: Objective Evidence of Impaired *Cortical Sensory Gating* in Humans with Tinnitus

CAEP paradigms that reflect sensory gating may be particularly well-suited to studying tinnitus pathophysiology because sensory gating reflects the central nervous system's ability to inhibit irrelevant sensory information and tinnitus is a pathology characterized by the perception of irrelevant sensory information (presumably poorly inhibited auditory subcortical and cortical SFR and SFR synchrony). In humans, cortical sensory gating can be assessed using a paired auditory stimulus CAEP paradigm that reflects inhibition. The sensory gating CAEP paradigm is characterized by the successive presentation of two identical auditory stimuli with

an interval of about one-half to one second between them, where the first stimulus is a "conditioning" stimulus and the second a "test" stimulus. As such, the response to the first sound can be referred to as the conditioning CAEP and the response to the second sound as the test CAEP. In the normal central auditory system, there is a reduction in test CAEP amplitude relative to conditioning CAEP amplitude, which is indicative of normal inhibitory function. This is thought to be the result of the conditioning stimulus exciting auditory neurons that subsequently activate inhibitory hippocampal interneurons responsible for the suppression of auditory cortical neural activation (Jones et al., 2016; Vlcek et al., 2014). This is demonstrated by pilot data from one healthy (young, normal hearing, non-tinnitus) control subject collected by the author shown in Figure 2. The waveform represents an average of 200 responses to paired clicks separated by 500 ms recorded at C_z and exhibits the expected CAEP response pattern, or normal sensory gating/normal inhibitory function with a reduced test, relative to conditioning, CAEP amplitude.

Sensory gating inhibition is typically quantified either as an amplitude ratio ($\frac{\text{test CAEP}}{\text{conditioning CAEP}}$) or amplitude difference ($\text{conditioning CAEP} - \text{test CAEP}$) between the test and conditioning response for an individual CAEP component. Poorer sensory gating (reduced inhibition) is indicated by a ratio closer to 1 or a difference closer to 0, both of which reflect equivalent conditioning and test CAEP amplitudes, or a lack of inhibitory function. To account for potential baseline shifts in the CAEP response over time, peak-to-trough or trough-to-peak amplitudes can be analyzed as opposed to baseline to peak amplitudes. Sensory gating ratios or differences can be calculated for any of the amplitude measures. For example, the pilot subject in Figure 2 has a sensory gating ratio of 0.804 for P1-N1 amplitude ($= \frac{2.384\mu V}{2.966\mu V}$) and 0.451 for N1-

P2 amplitude ($= \frac{2.250\mu V}{4.994\mu V}$). Comparing between these two sensory gating ratios, the pilot subject exhibited reduced sensory gating inhibition for the P1-N1 amplitude relative to the N1-P2 amplitude, as indicated by the larger sensory gating ratio for P1-N1 amplitude.

While there is a lack of normative data for what values constitute "normal" and "impaired" sensory gating, paired click CAEP sensory gating has been well studied in psychiatric clinical populations. A meta-analysis of 84 studies comparing schizophrenic and control groups reported that average P1 (sometimes referred to as P50) component sensory gating ratios from control subjects were between 0.25 to 0.57, however, the range extended from about 0.1 to 0.8 (Patterson et al., 2008). Across studies of schizophrenic groups, the grand average sensory gating ratio was 0.80 (*SD* = 0.24). In this meta-analysis, sensory gating ratios for the N1 and P2 components were not reported. This may be because the most commonly studied CAEP

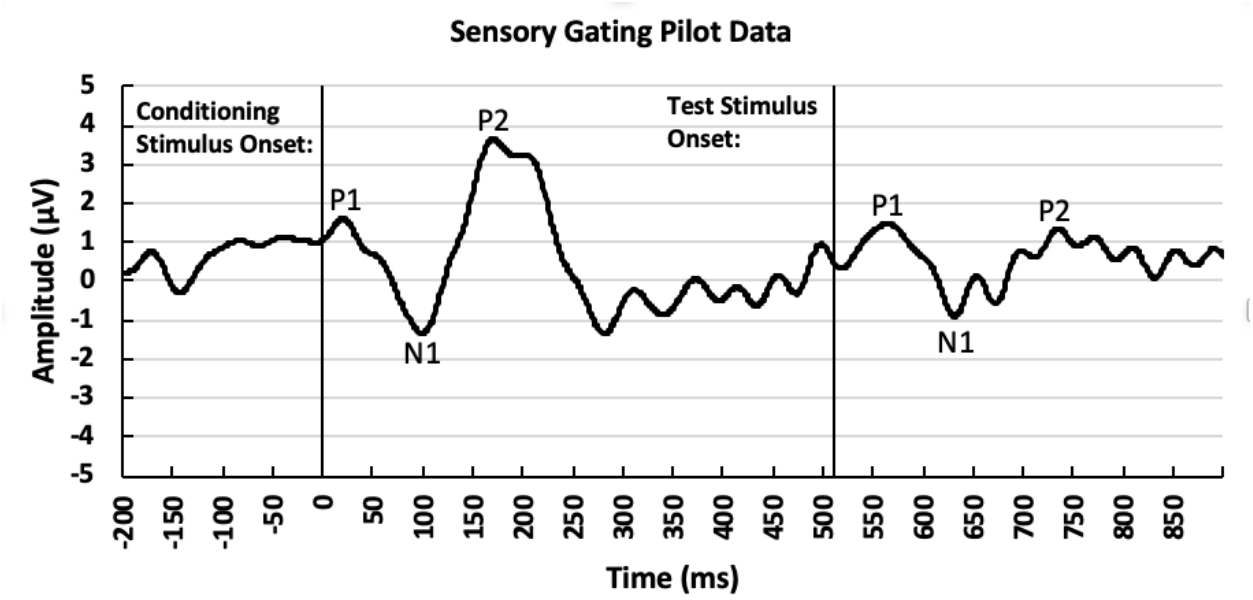


Figure 2. Sensory gating CAEP response recorded from a healthy control subject collected as pilot data in the Syracuse University Auditory Electrophysiology Lab. The figure depicts an average response to 200 presentations of paired high-intensity clicks recorded from the C_z electrode (mastoid reference). CAEP components elicited to the first conditioning click and the second test click presented 500 ms later are labeled.

component for sensory gating applications is the preceding trough-to-peak P1 amplitude. As P1 predominantly reflects pre-attentive thalamocortical activity, the component may more closely relate to the sensory gating model (Lijffijt et al., 2009a). However, N1 and P2 sensory gating may also apply to the study of tinnitus given the relationship to auditory processing and attentional contributions to these later components.

Two recent studies by Campbell and colleagues demonstrated initial evidence of differences in sensory gating using a paired 250 Hz stimulus CAEP sensory gating paradigm in individuals with tinnitus compared to controls without tinnitus (Campbell et al., 2018; Campbell et al., 2019). Campbell et al., (2018) compared sensory gating outcomes between young adults (18-30 years) with (n=15) and without (n=18) tinnitus. Results showed that the tinnitus group, relative to control, exhibited poorer sensory gating of the CAEP P1 component. They also analyzed the earlier Pa component associated with the auditory middle latency response (MLR) and found a moderate negative correlation between sensory gating of the Pa component and tinnitus handicap inventory (THI) scores. This finding suggested that as sensory gating got worse, or inhibition decreased, tinnitus severity also got worse. Due to this identified correlation, Campbell et al., (2018) further divided the tinnitus group into two subgroups based on the median sensory gating difference of the Pa component, a common secondary analysis in sensory gating literature (Knott et al., 2009). In other words, the tinnitus group was split into one subgroup that exhibited poorer sensory gating and one subgroup that exhibited better sensory gating. Predictably, the poor sensory gating tinnitus subgroup was found to have significantly worse sensory gating of the Pa and P1 component compared to the better sensory

gating tinnitus subgroup and no-tinnitus control group, while the responses of the better sensory gating tinnitus subgroup were not significantly different from the controls.

While this secondary analysis suggested that tinnitus severity was associated with poorer sensory gating, it's important to consider that THI scores in the tinnitus sample ranged only from 0-14 (on a scale from 0-100), suggesting the presence of slight or no tinnitus handicap within the entire sample (Newman et al., 1996). The narrow range of tinnitus handicap scores limits the external validity of the correlation and brings into question the conclusion that poorer sensory gating is associated with greater tinnitus distress. Further, of the tinnitus participants in the sample, 4 had constant tinnitus, 4 had intermittent tinnitus, and 5 participants did not state the duration or consistency of their tinnitus. This suggests that the participants within the sample had different subtypes of tinnitus and therefore could potentially exhibit different sensory gating outcomes. Although the researchers did not specifically state the tinnitus characteristics of the poor sensory gating tinnitus subgroup, demographics reported in their data table indicated that the participants with constant tinnitus had worse THI scores, *suggesting constant tinnitus was related to poorer sensory gating*. Lastly, it's also important to note that Campbell et al., (2018) only recruited individuals with behavioral pure-tone thresholds better than 20 dB HL from 0.25-16 kHz. The researchers stated that these extended high frequency thresholds were inclusionary criteria to rule out peripheral auditory insult. However, given the proposed necessity of peripheral auditory insult to trigger changes in inhibition and tinnitus generation, the lack of clinically significant peripheral hearing loss, even beyond the range of the clinical audiogram, may suggest peripheral damage was not sufficient to cause sensory gating changes across individuals in their sample. Despite these limitations,

the evidence from this study at least preliminarily suggests that constant tinnitus may be associated with poorer sensory gating, even in individuals with clinically normal audiograms.

In a follow-up study using the same CAEP paired 250 Hz stimulus sensory gating protocol, Campbell et al., (2019) aimed to address the contribution of hearing loss, at least in the extended high-frequency pure tone threshold range, on sensory gating in individuals with and without tinnitus. In this follow up study, sensory gating in adults (17-43 years) with (n=21) and without (n=45) tinnitus was compared and the relationship between sensory gating, pure-tone thresholds and THI scores was assessed. The only inclusion criteria for the follow-up study were clinically normal standard pure tone thresholds (≤20 dB HL, 0.25-8 kHz) and high frequency thresholds ≤ 40 dB HL from 10-16 kHz. In contrast with their previous study, sensory gating outcomes for all CAEP components (P1, N1 and P2) were not significantly different between the tinnitus and control group and there was not a significant correlation between extended high-frequency PTA (average threshold from 10-16 kHz) and the sensory gating difference. There was, however, a significant correlation between tinnitus distress and sensory gating, in that greater tinnitus distress was associated with poorer sensory gating of the Pa component.

It is notable that all participants included in the initial Campbell et al., (2018) study were also included in the follow-up Campbell et al., (2019) study. Thus, the same limitations of the initial research may have influenced the results of the follow-up study. In particular, the positive correlation between greater tinnitus distress and poorer sensory gating is questionable as the data is largely made up of the same participants in the original study who had a limited range of tinnitus handicap. Further, 6 control participants and 3 tinnitus participants in the

2019 study reported contraindicating neurological or psychological diagnoses, including attention-deficit/hyperactivity disorder and migraines, and 1 tinnitus participant reported smoking nicotine. All of these factors may impact sensory gating (Cromwell et al., 2008).

Regarding the confounding effect of hearing loss on sensory gating results, Campbell et al., (2019) suggest that CAEP measures of sensory gating may be independent of pure tone thresholds, up to a point. This assumption is supported in the sensory gating literature, in that stimulus intensity has not been a variable that is highly controlled across studies. In the previously discussed meta-analysis comparing sensory gating between schizophrenic patients and controls, sensory gating CAEP stimulus intensities ranged from 52 – 110 dB and, in some studies, the stimulus intensity varied from subject to subject (Patterson et al., 2008). Thus, sensory gating outcomes may not be strongly related to the hearing sensitivity of the participant or the intensity of the auditory stimulus, at least if the stimulus is audible and evokes a measurable response, as the outcome is related to the amplitude ratio or difference between conditioning and test CAEP within the same individual.

The Campbell et al., (2018, 2019) studies provide some initial evidence that *constant* tinnitus may be related to poorer cortical sensory gating. However, the relationship between tinnitus and reduced inhibition, as indicated by neural responses reflecting sensory gating, is not yet established in individuals who perceive tinnitus due to noise exposure. Further, the lack of clinically significant peripheral hearing losses, even beyond the clinical audiogram range, and the use of a 250 Hz toneburst stimulus, rather than a paired click paradigm, to evoke the sensory gating response in Campbell et al. (2018, 2019) may have contributed to the inconsistent findings. As will be discussed in the following section, it is important to address

additional potentially confounding variables and sources of individual variability when studying AEP outcomes presumed to relate to tinnitus.

1.4: Potential Sources of Variability in Objective Human Tinnitus Studies

One of the difficulties in studying tinnitus and the underlying pathophysiological processes that lead to its perception is in attempting to control for potentially confounding individual characteristics related to tinnitus such as noise exposure history, hearing loss, and age. All these factors may be interrelated and associated with the amount of peripheral auditory damage (and reduced cochlear output) an individual has and the associated neuroplastic changes in the CANS leading to decreased inhibition. It can therefore be difficult to determine whether outcomes indicating reduced inhibition are actually related to the perception of tinnitus rather than the degree of hearing loss or amount of noise exposure, for example.

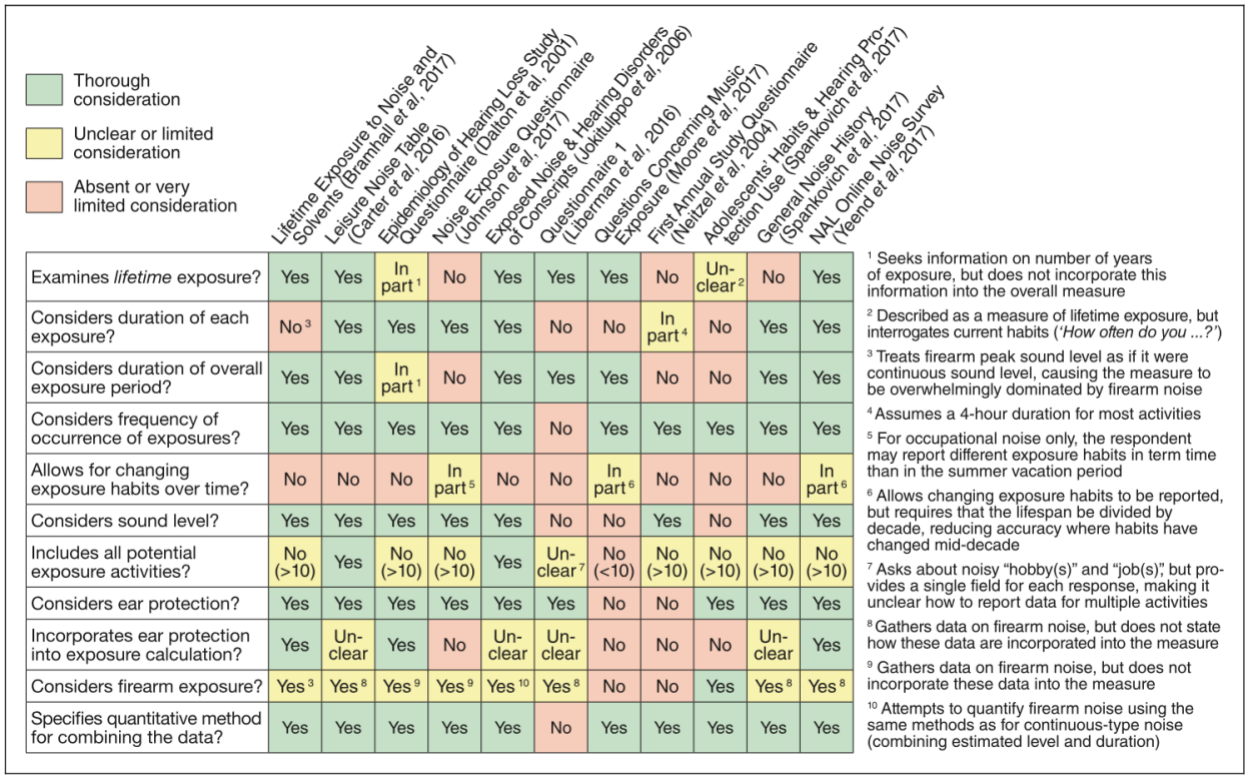
Confounding variables in tinnitus research are often addressed by limiting participant recruitment to individuals with predetermined characteristics such as young adults of the same sex with clinically normal pure tone thresholds. While this helps reduce the potential confounds of peripheral hearing loss, sex, and age on outcome measures, the population of young adults with clinically normal hearing and tinnitus is limited and difficult to recruit in large enough numbers. Even if this kind of recruitment can be achieved, participants with clinically normal pure tone thresholds may not have the degree of peripheral auditory insult that is sufficient to cause neuroplastic changes and reduced inhibition that may relate to tinnitus perception. Including participants with a range of noise exposure history, hearing loss, and age may be

essential when studying tinnitus to improve the external validity of the conclusions that can be drawn.

1.4.1: Noise Exposure History

Noise overexposure may be the most common precipitating factor of tinnitus in humans. In animal models of tinnitus, noise overexposure is commonly utilized to induce tinnitus. However, in animal models the baseline hearing level is known, and the amount of noise exposure can be administered in a controlled manner. This is not possible in humans, who exhibit variable baseline levels of hearing and noise exposure histories that are not objectively quantified. In humans, noise exposure questionnaires are typically administered to estimate how much noise a person has been exposed to throughout their lifetime. The relationship between these questionnaires and auditory processing can be assessed to study how noise exposure history influences auditory processing in humans. However, the validity and reliability of noise exposure questionnaires are dependent upon an individual's ability to recall their personal histories over years. To address this, noise exposure history questionnaires have been extensively researched to maximize the quality of the data collected and standardize data collection procedures (Guest et al., 2018). Several recently published noise exposure history questionnaires are summarized in Figure 3, originally published by Guest et al. (2018). Some questionnaires have limitations such as mathematically treating impulse noise exposure as continuous noise, not including all potential noise exposure activities, or not allowing for changing habits over time. Despite these limitations, quantification and control for noise exposure history is an important component of tinnitus research. A questionnaire specifically designed to address some of these limitations, such as the Noise Exposure Structured Interview

(NESI) (Guest et al., 2018), may provide the most comprehensive quantification of individual cumulative noise exposure currently available. The NESI may be the most appropriate method to estimate noise exposure history, in the absence of actual lifetime noise dosimetry measurements, as the measure allows for the quantification of noise exposure history after taking into account different sources of noise exposure (e.g. recreational, occupational, firearm), over different time periods throughout the lifetime, the use of hearing protection, and the different impact of continuous and high-impulse noise exposure (e.g., concert music versus firearms). Studies relating tinnitus perception and inhibition have thus far not incorporated control and quantification of noise exposure history across tinnitus and control groups. There is a possible indication that CAEP measures of sensory gating may be affected in individuals with at least high impulse noise exposure. A recent study by Papesh et al. (2019) found evidence of



	Lifetime Exposure to Noise and Solvents (Bramhall *et al.*, 2017)	Leisure Noise Table (Carter *et al.*, 2016)	Epidemiology of Hearing Loss Study Questionnaire (Dalton *et al.*, 2001)	Noise Exposure Questionnaire (Johnson *et al.*, 2017)	Exposed Noise & Hearing Disorders of Conscripts (Jokitulppo *et al.*, 2006)	Questionnaire 1 (Liberman *et al.*, 2016)	Questions Concerning Music Exposure (Moore *et al.*, 2017)	First Annual Study Questionnaire (Neitzel *et al.*, 2004)	Adolescents' Habits & Hearing Protection Use (Spankovich *et al.*, 2017)	General Noise History (Spankovich *et al.*, 2017)	NAL Online Noise Survey (Yeend *et al.*, 2017)
Examines *lifetime* exposure?	Yes	Yes	In part [1]	No	Yes	Yes	Yes	No	Un-clear [2]	No	Yes
Considers duration of each exposure?	No [3]	Yes	Yes	Yes	Yes	No	No	In part [4]	No	Yes	Yes
Considers duration of overall exposure period?	Yes	Yes	In part [1]	No	Yes	Yes	Yes	No	No	Yes	Yes
Considers frequency of occurrence of exposures?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Allows for changing exposure habits over time?	No	No	No	In part [5]	No	No	In part [6]	No	No	No	In part [6]
Considers sound level?	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes
Includes all potential exposure activities?	No (>10)	Yes	No (>10)	No (>10)	Yes	Un-clear [7]	No (<10)	No (>10)	No (>10)	No (>10)	No (>10)
Considers ear protection?	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Incorporates ear protection into exposure calculation?	Yes	Un-clear	Yes	No	Un-clear	Un-clear	No	No	No	Un-clear	Yes
Considers firearm exposure?	Yes [3]	Yes [8]	Yes [9]	Yes [9]	Yes [10]	Yes [8]	No	No	Yes	Yes [8]	Yes [8]
Specifies quantitative method for combining the data?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes

[1] Seeks information on number of years of exposure, but does not incorporate this information into the overall measure

[2] Described as a measure of lifetime exposure, but interrogates current habits (*'How often do you ...?'*)

[3] Treats firearm peak sound level as if it were continuous sound level, causing the measure to be overwhelmingly dominated by firearm noise

[4] Assumes a 4-hour duration for most activities

[5] For occupational noise only, the respondent may report different exposure habits in term time than in the summer vacation period

[6] Allows changing exposure habits to be reported, but requires that the lifespan be divided by decade, reducing accuracy where habits have changed mid-decade

[7] Asks about noisy "hobby(s)" and "job(s)", but provides a single field for each response, making it unclear how to report data for multiple activities

[8] Gathers data on firearm noise, but does not state how these data are incorporated into the measure

[9] Gathers data on firearm noise, but does not incorporate these data into the measure

[10] Attempts to quantify firearm noise using the same methods as for continuous-type noise (combining estimated level and duration)

Figure 3. Comparison of the features of several noise exposure history questionnaires.

impaired sensory gating, or reduced inhibition using a paired click CAEP in a group of 16 blast-exposed (24-58 years) compared to 13 non-blast exposed control veterans (19-66 years). Blast exposure is a type of severe high impulse noise exposure that can severely damage the middle and inner ear (Clark & Ohlemiller, 2008). Importantly, however, the relationship between noise exposure and sensory gating was likely confounded by the presence of mild traumatic brain injury and PTSD in the blast-exposed sample (Cromwell et al., 2008). Further, tinnitus was not accounted for in this study. Therefore, while the results of this study suggest that at least in high intensity blast-exposed contexts, noise exposure may potentially influence measures of inhibition, including sensory gating indices.

1.4.2: Hearing Loss and Behavioral Auditory Performance

Reduced cochlear output due to peripheral auditory insult, whether noise-induced or otherwise, is typically measured using pure tone thresholds of audibility across a range of frequencies. The measured pure tone thresholds are compared to the average hearing of a normal hearing adult to assess the presence and degree of hearing loss. This is a common clinical measure, and it is generally accepted that for adults, thresholds better than or equal to 25 dB HL from 0.25 to 8 kHz constitutes “clinically normal hearing”. However, clinically normal hearing does not rule out peripheral auditory damage. For example, cochlear synaptopathy has become a topic of interest due to the potential implication that humans do indeed experience permanent peripheral auditory damage in the absence of pure tone threshold changes. Thus, it is sometimes referred to as “hidden hearing loss” (Schaette & McAlpine, 2011). The hallmark of cochlear synaptopathy is a loss of auditory synapses between IHCs and Type I afferent ANFs (Kujawa & Liberman, 2006). Auditory thresholds remain relatively unaffected due to the

susceptibility of high threshold low- and medium-SFR ANFs (Furman et al., 2013). These low- and medium-SFR ANFs maximally respond to higher intensity stimuli as opposed to lower intensity, near-threshold, stimuli. Thus, audibility near threshold remains unaffected and individuals present with hearing within normal limits on the audiogram. Presumably, these peripheral auditory changes, independent of clinical hearing loss, may lead to decreases in inhibition similar to that related to tinnitus. It has been reported that even slight reductions of cochlear output to the CN can result in decreased levels of inhibitory neurotransmitters and increased levels of excitatory neurotransmitters (Barker et al., 2012; Heeringa et al., 2016; Zeng et al., 2009).

Hearing loss is associated not just with reduced audibility and reduced sensory gating, but with a range of functional deficits including decreased frequency discrimination and poorer sound localization (Takesian et al., 2009). Behavioral auditory performance deficits have also been identified in individuals with tinnitus (Ryu et al., 2012), high noise exposure histories (Papesh et al., 2019), and age (Lister et al., 2007; Lister et al., 2011). Among individuals with hearing loss, one of the most commonly reported functional deficits is difficulty perceiving signals in the presence of background noise. This may potentially be due to a decreased ability to inhibit the unwanted background noise. It has previously been proposed that the neural basis for a decline in the ability to utilize spectrotemporal auditory information to distinguish speech signals from unwanted noise may be, in part, due to degraded auditory inhibition (Anderson et al., 2011).

In another study, it has been reported that hearing loss was associated with a decreased ability to process signals in noise and differences in auditory cortical activity, reflected by

auditory evoked fields (AEFs), recorded using a technique similar to the aforementioned AEPs, known as magnetoencephalography (MEG) (Alain et al., 2014). Specifically, the researchers identified AEF components with larger amplitudes and more posterior and inferior generating sources, suggesting the hearing loss group exhibited neuroplastic differences in the AC that may be related to decreased inhibition. Reviewed by Alain et al., 2014, enhanced amplitudes of sensory evoked responses (e.g. AEFs and AEPs) such as was observed in the hearing loss group of their study, may be related to impaired inhibition of task-irrelevant information, in this case, inhibiting external auditory noise. Specifically, the larger amplitudes may be indicative of more, and potentially different, neural generators involved in auditory processing, possibly in a compensatory manner.

As variations in the amount of hearing loss, indicated by pure tone thresholds, may yield variations in objective and behavioral outcomes related to inhibition, it is important to consider these effects when studying tinnitus. Specifically, recruiting subjects with and without tinnitus who have varying degrees of hearing loss within groups and similar hearing loss across groups, may help to identify whether it is variability in tinnitus, hearing loss, or both that contribute to variability in objective measures that reflect inhibition. Campbell et al. (2019) identified an unexpected significant correlation between greater (*poorer*) pure tone thresholds and *better* sensory gating across individuals with and without tinnitus, but all with normal hearing. However, the participants in the study had clinically normal hearing (≤20 dB HL from 0.25 - 8 kHz). In a follow-up study, Campbell et al. (2020a) identified the more expected relationship between greater (*poorer*) pure tone thresholds with *poorer* sensory gating in a group of participants (none of whom had tinnitus) who exhibited a mild-moderate high frequency

sensorineural hearing loss. In this case, variability in hearing loss between the groups may have led to the differing outcomes.

Related to hearing loss, as SPIN deficits may be a functional indicator of auditory inhibition deficits, it may also be important to consider how behavioral auditory performance varies in relation to objective measures of inhibition in people with and without tinnitus, varying degrees of hearing loss, and noise exposure history. Indeed, poorer SPIN has been reported to significantly correlate with poorer sensory gating in a group of young and normal hearing (≤20 dB HL from 0.25 - 8 kHz) participants without tinnitus (Campbell et al., 2020b). However, whether poorer SPIN influences sensory gating above and beyond the effects of tinnitus and/or hearing loss is unknown. Understanding these associations may help to clarify the relationship between the behavioral performance deficits, particularly SPIN, and objective indicators of auditory inhibition in individuals with tinnitus. Thus, it may be important to consider both variations in the amount of hearing loss, measured by pure tone thresholds, and the functional impact of behavioral performance, measured by a speech in noise test, when studying auditory inhibition, particularly in the context of tinnitus.

1.4.3: Age

Increased age is associated with increased hearing loss, cumulative noise exposure, and tinnitus prevalence. Age-related hearing loss is referred to as presbycusis and may be due to several factors including noise exposure over the lifetime and the general ageing process (Gates & Mills, 2005). Older adults, both with and without hearing loss, commonly report difficulty with behavioral auditory performance similar to younger individuals with high noise exposure

history, hearing loss, and tinnitus. Specifically, older adults report difficulty understanding speech in the presence of background noise, which may be related to impaired inhibition.

Two studies examining gap-evoked CAEPs in older adults with at most minimal hearing loss (mean age = 63 years) compared to younger adults with similar hearing status (mean age = 25.8 years) aimed to describe the effect of aging, independent of hearing loss, on temporal processing (Lister et al., 2007; Lister et al., 2011). Auditory temporal processing is important for SPIN. Similar to the research conducted in our own laboratory (Morse & Vander Werff, 2019), Lister et al., (2007, 2011) assessed the CAEP evoked by very short silent gaps in noise in the older and younger groups. They identified that the older adults exhibited longer P2 latencies that may be associated with slower neural propagation. Further, the older group exhibited broader P1 components with larger P1 amplitudes relative to younger adults. The larger P1 components, similar to the results observed by Alain et al., (2014) in the hearing loss group, suggest that older adults exhibited an impaired ability to inhibit irrelevant stimuli relative to the younger group. This study suggests that age, above and beyond the influence of hearing loss, may contribute to CANS neuroplastic changes related to decreased inhibition. While these studies do not address or control for tinnitus, they highlight the importance of considering age-related differences in central auditory processing and the influence on the proposed outcome measures of inhibition.

1.5: Specific Aims

Pathophysiological animal and human tinnitus studies provide supporting evidence that peripheral auditory insult *triggers a reduction in inhibitory function* that may be related to tinnitus generation. There is substantial evidence from noise-induced animal models of tinnitus

and human tinnitus studies suggesting that tinnitus-related neuroplastic changes secondary to peripheral auditory insult and reduced cochlear output include: (1) decreased subcortical inhibition yielding an increase in auditory SFR and SFR synchrony, and (2) decreased thalamocortical inhibition causing a sensory gating failure to prevent the subcortical auditory SFR and SFR synchrony from being consciously perceived as tinnitus.

While there is significant evidence supporting these mechanisms in animal models of tinnitus, research linking the perception of tinnitus in humans to differences in inhibitory processes is currently limited. Reviewed above, some preliminary evidence of tinnitus presence in humans from EEG and imaging studies has suggested that reductions in cochlear output are linked with subcortical brainstem auditory hyperactivity secondary to reduced inhibition as measured by ABR (Bramhall et al., 2018; Gu et al., 2012; Schaette & McAlpine, 2011; Valderrama et al., 2018), and disruptions to thalamocortical auditory inhibition as measured by structural and functional MRI (Rauschecker et al., 2015) and resting state EEG oscillatory activity (De Ridder et al., 2015). While these studies provide some support for the hypothesized pathophysiological mechanisms of tinnitus, there is considerable variation in findings and not all studies have found differences in inhibitory function between groups with and without tinnitus. The relationship between reduced inhibition and tinnitus perception has therefore not been conclusively established in humans, particularly in terms of objective measures that are clinically feasible. Potential reasons for the lack of evidence more conclusively linking inhibitory differences to tinnitus perception include both variability in the methods and control for individual subject factors. First, there is a need for research using objective measures that may be sensitive to differences in inhibitory processes at both subcortical and cortical levels, both of

which may be subject to neuroplastic change following peripheral auditory damage and could be associated with tinnitus perception. Combining subcortical and cortical AEP measures, specifically the subcortical ABR $\mathrm{V/I}_{\text{amp ratio}}$ and cortical sensory gating $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratios, which may reflect differences in inhibitory status across groups, will add to our knowledge about the association between tinnitus and the pathophysiological changes in the CANS. Because such measures are within-subject comparisons, non-invasive, inexpensive, and clinically available, the outcomes have the potential to exhibit low intra-individual variability, be translated to future use in assessing inhibitory function on an individual basis, and in studying neuroplastic change following tinnitus intervention.

Further, to determine whether group differences in these outcome measures are actually associated with the perception of tinnitus, there is a need to consider potentially confounding related variables. These critical variables include hearing thresholds, quantified noise exposure history, age, and SPIN. Because all these factors could, independent of tinnitus perception, be associated with neuroplastic changes in auditory function, it is important to control them to the extent possible or factor them into the analyses in order to make conclusions about the link between tinnitus perception and outcomes reflecting subcortical and cortical inhibitory status.

The goals of the current study, therefore, were to: (1) objectively determine whether there was evidence of compromised <u>subcortical and/or cortical inhibition</u> in people with constant tinnitus and, (2) to describe the effects of potentially related variables to tinnitus on subcortical and cortical inhibition to determine whether it is tinnitus, another characteristic, or a combination thereof that influences differences in inhibition. In the short term, defining

the relationship between these objective outcomes and tinnitus status will improve our pathophysiological understanding of constant noise-induced tinnitus in humans. In the long term, this line of research may lead to more effective tinnitus management, for example, by distinguishing between different tinnitus subgroups, such as those with subcortical inhibition deficits and cortical inhibition deficits, who respond best to distinct interventions.

1.5.1: Specific Aim 1

To objectively determine and quantify whether individuals with constant noise-induced tinnitus have evidence of reduced inhibition at the <u>subcortical</u> level as compared to non-tinnitus controls using auditory brainstem response (ABR) measures.

To accomplish this aim, ABR was recorded using stimulus and recording parameters including high intensity click stimuli presented at a slow rate and recording with a reference electrode in the ear canal (tiptrode) to enhance wave I. The primary measured outcome was the amplitude (peak to following trough) ratio of ABR $\frac{\text{wave V}}{\text{wave I}}$, denoted $\text{V/I}_{\text{amp ratio}}$. **It was hypothesized** that the tinnitus group, relative to control, would exhibit an increased ABR $\text{V/I}_{\text{amp ratio}}$, indicative of decreased peripheral auditory output and increased subcortical auditory hyperactivity secondary to *reduced subcortical inhibition*.

1.5.2: Specific Aim 2

To objectively determine and quantify whether individuals with constant noise-induced tinnitus have evidence of reduced inhibition at the <u>cortical</u> level as compared to non-tinnitus controls using a CAEP sensory gating paradigm.

To accomplish this aim, CAEPs were recorded to a paired click stimulus paradigm using a multiple electrode montage. Paired click stimuli were presented at a high and audible stimulus level using parameters consistent with the sensory gating literature. A decreased response to the second click in the pair, the test stimulus, relative to the first click in the pair, the conditioning stimulus, is indicative of normal inhibitory function. The primary outcome measure was the $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude ratio of the P1-N1, N1-P2, and $P1_{T\text{-}P}$ components and the $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ area ratio, a measure of amplitude across the entire P1-N1-P2 CAEP response. The secondary outcome measure which may relate to sensory gating was the $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ latency ratio of the P1, N1, and P2 peak components. **It was hypothesized** that the tinnitus group, relative to controls, would exhibit larger $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratios that are closer to or greater than 1 (less of a change, or increase, in amplitude/area/latency of the test, relative to conditioning, response), indicative of poorer sensory gating and *reduced cortical inhibition*.

1.5.3: Specific Aim 3

To estimate the extent to which tinnitus presence and tinnitus-related factors, including noise exposure history, peripheral hearing loss, SPIN, and age predict objective outcomes of reduced subcortical and cortical inhibition in individuals with and without constant tinnitus.

To accomplish this aim, a multiple linear regression model was used to determine the amount of variability in outcome measures of subcortical and cortical inhibition (ABR $\text{V/I}_{\text{amp ratio}}$ and sensory gating $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratios) predicted by five tinnitus-related characteristics (Table 1). The reduction in multiple linear regression model error for each

predictor variable above and beyond the effect of all other predictor variables was analyzed to determine variables that are influential (Judd et al., 2009). **It was hypothesized** that the presence of tinnitus would be the major predictive factor, but other characteristics would also influence subcortical and cortical inhibition.

Table 1. Multiple regression predictor and dependent variables.

Predictor Variables	Subcortical and Cortical Inhibition: Dependent Variables
Tinnitus (Present/Absent)	1. Subcortical ABR $V/I_{amp\ ratio}$
Hearing Loss (Pure tone average 0.25-20 kHz)	2. Cortical Sensory Gating $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratios
Noise Exposure History (NESI)	
Behavioral Performance (SPIN score)	
Age	

2.0: Design and Methodology

2.1: Design

For Specific Aim 1 and Specific Aim 2, a quasi-experimental independent groups design was used to establish the effect of presence versus absence of the perception of constant tinnitus on subcortical and cortical measures of inhibition. The independent variable for both aims was group (further described under the *Participants* section 2.2.1). The experimental group had constant tinnitus and the control group counterparts (without tinnitus) were matched by sex, age, and hearing thresholds [clinical pure tone average ($PTA_{0.5\text{-}2\ kHz}$) within 20 dB HL of counterpart]. Dependent variables related to inhibition included the subcortical ABR $V/I_{amp\ ratio}$ and cortical sensory gating $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratios for Specific Aim 1 and Specific Aim 2, respectively.

For Specific Aim 3, an observational multiple correlational design was used to establish the relationship between tinnitus and tinnitus-related variables with subcortical and cortical measures of inhibition. Pearson correlations and regression models were used to analyze the associations among predictor variables including tinnitus presence versus absence, noise exposure history, hearing loss, SPIN, and age with the subcortical ABR $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ and cortical sensory gating $\frac{\mathrm{test\ CAEP}}{\mathrm{conditioning\ CAEP}}$ ratios, the dependent variables of Specific Aims 1 and 2.

2.2: Methodology

2.2.1: Participants

To accomplish the aims of this study, participants in two groups, with and without constant tinnitus, were recruited. All participants were aged 18-55 years. The age inclusion criteria was chosen to provide a wide age range within the study sample while also attempting to limit the impact of auditory degradation due primarily to the aging process (Gates & Mills, 2005). This was done in an effort to avoid recruiting a study sample that may yield outcomes primarily related to age, as opposed to tinnitus, noise exposure history, or hearing loss (although age was included as one of the predictor variables in Aim 3). As the mechanism of tinnitus (being secondary to peripheral auditory insult) is also associated with hearing loss, individuals with a range of peripheral hearing thresholds were recruited. The degree of hearing loss was necessarily limited to a moderate loss, however, in order to ensure that ABR and sensory gating stimuli were audible and evoked measurable neural responses. All participants had no greater than a moderate sensorineural hearing loss as defined by audiometric thresholds $\leq$ 55 dB HL from 0.25-4 kHz. Recruiting individuals with no greater than a moderate

hearing loss ensured that ABR and sensory gating stimuli were audible and safe for all participants and allowed for a range of hearing loss in the sample which contributed to a better analysis of the role of hearing loss on measures of inhibition. Average pure tone thresholds across the entire range of tested frequencies ($PTA_{0.25\text{-}20\ kHz}$) were included as a predictor variable in Aim 3.

Participants in the experimental group had *constant* tinnitus perception, as constant tinnitus has been associated with poorer sensory gating (Campbell et al., 2018). Constant tinnitus was determined by self-reported unilateral or bilateral tinnitus present on a daily basis for longer than 6 months. In addition, individuals with tinnitus were excluded if the onset of their tinnitus was attributable to specific factors other than noise exposure such as medications or illness/disease.

Further exclusion criteria included a history of middle ear surgery, or the presence of middle ear dysfunction as indicated by self-report, an abnormal 226 Hz tympanogram, or a 1000 Hz acoustic reflex inconsistent with the participant's hearing thresholds. Factors known to affect CAEP responses were also exclusionary including daily nicotine smokers (Friedman & Meares, 1980), history of diagnosed learning, psychiatric or neurological disorders, and current prescription of categories of medications (e.g. benzodiazepines, prescription sedatives, anticholinergics, antipsychotics) (Polich & Kok, 1995). Participants with self-reported diagnoses that are known to influence sensory gating were also excluded (e.g. schizophrenia, bipolar disorder, PTSD, epilepsy, Alzheimer's Disease, traumatic head injury, Huntington's Chorea, and OCD).

Participants were recruited from the Central New York population around Syracuse, New York. Participants with tinnitus were recruited from several sources, including the Syracuse Veterans Affairs Medical Center (SVAMC). Patients enrolled in the Progressive Tinnitus Management program at the SVAMC who met the inclusion criteria were given a flyer so they could contact the researcher if they were interested in participating. Flyers were also posted throughout the SVAMC hospital. Participants were recruited from the general Syracuse University community as well, who were reached through advertisement postings in the Syracuse University News and listserv e-mails. For example, a listserv e-mail was sent to all members of the Syracuse University Band, who provided a range of tinnitus status, age, and noise exposure histories relative to the recruited individuals from the SVAMC. Further, individuals who have previously participated in tinnitus research studies at the Syracuse University Auditory Electrophysiology Lab and met the inclusion criteria were contacted for recruitment. Control group participants were recruited from the same sources to match the age, sex, and hearing thresholds of recruited tinnitus group participants to the extent possible.

To determine sample size for Specific Aim 1 and 2, power analyses for an independent t-test between groups with an alpha = 0.05 and a power of 80% based on ABR $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ (Bramhall et al., 2018; Gu et al., 2012; Schaette & McAlpine, 2011) and sensory gating $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ (Papesh et al., 2019) comparisons between individuals with tinnitus or high noise-exposure history and controls was conducted using G*Power (Erdfelder et al., 1996). ABR $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ amplitude ratios comparing tinnitus and control groups from the previously cited studies are reported by Bramhall et al. (2018). Averaged across studies, the estimated ABR $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ amplitude ratio in response to a 100 dB ppe SPL click for the tinnitus group is 2.9

and the control group is 2.0. Based on these averages, the estimated sample size required to provide sufficient power for the ABR outcome measures in Aim 1 is a minimum of 9 per group.

Regarding sensory gating, the studies measuring cortical sensory gating in individuals with and without tinnitus using a paradigm similar to that proposed in the current study did not report sufficient data, including means and standard deviations, necessary to conduct a power analysis (Campbell et al., 2018; Campbell et al., 2019). Thus, a power analysis based on a significant difference in P2 amplitude sensory gating percent change from the Papesh et al. (2019) study including blast-exposure participants using a similar paradigm as proposed in the current study was conducted. Using the aforementioned power analysis criteria, the estimated required sample size for an independent samples t-test between groups for Aim 2 based on the reported results was 16 participants per group.

To determine the number of predictor variables that could be incorporated into the multiple regression model for Specific Aim 3, a power analysis for a multiple regression assessing the effects of a single predictor was computed using G*Power. Maintaining an alpha = 0.05, a power of 80%, and a medium effect size (f^2 = 0.2), a total of five predictor variables yielded a total sample size of 33. The model was limited to these predictor variables to avoid overfitting by including too many terms for the number of observations, reducing generalizability.

For the study, therefore, the largest required sample size of the power analyses, 16 participants per group, was used to provide adequate power to detect differences in inhibition between groups with and without tinnitus and to provide the necessary power for the regression predictions. Two additional participants per group were added to account for

possible attrition, resulting in a minimum recruitment target of 18 participants per group, or 36 participants total. This sample size is consistent with auditory electrophysiological research and provided sufficient power to achieve all 3 Specific Aims.

2.2.2: Data Sources and Measurement

2.2.2.1: Audiometric Assessment

All audiometric testing adhered to the best practices described by The American Speech-Language-Hearing Association (American Speech-Language-Hearing Association, 2019) and was conducted in a double-walled sound treated booth. Air conduction pure tone audiometry and SPIN in the monaural test ear was determined and used as predictor variables for Specific Aim 3. Note that for individuals with unilateral tinnitus, the test ear was the ear with tinnitus perception. For all other participants (individuals with bilateral tinnitus and controls) the test ear was the ear with the PTA across all tested frequencies ($PTA_{0.25\text{-}20\ kHz}$) that most closely matched the counterpart's PTA, or if no counterpart was yet recruited, the ear with a greater history of reported noise exposure that still fell within the inclusion criteria. The test ear was the same across all audiometric and electrophysiological tests.

Behavioral air conduction thresholds were obtained for standard audiometric frequencies from 0.25 to 8 kHz, via a Grason-Stadler GSI-61 audiometer coupled to Etymotic ER-3A insert earphones. Extended high frequency thresholds (9-20 kHz) were obtained using the same audiometer coupled to Sennheiser Radioear DD450 headphones. The predictor variable for Specific Aim 3 was the PTA in the test ear across all frequencies tested ($PTA_{0.25\text{-}20\ kHz}$).

To determine SPIN, methodology similar to that previously used in our laboratory was adapted for the current study (Niemczak & Vander Werff, 2019). Specifically, female spoken

IEEE English sentences (IEEE, 1969) were presented to the test ear at the most comfortable loudness level (MCL) in the presence of concatenated 2-talker female English babble, also presented to the test ear, at multiple signal-to-noise ratios (SNRs; 10, 5, 0, and -5 dB SNR). A 10 dB SNR, for example, indicates that the target IEEE sentences were 10 dB louder than the 2-talker babble noise. Sentence recognition in babble, as opposed to single word in white or speech-shaped noise testing, tasked the participant with a functional test that better represents real-world listening situations, such as conversing in a noisy restaurant. The IEEE sentences included 72 lists of 10 sentences in each list and 5 keywords in each sentence. The MCL was determined as the level (in dB HL) that the participant most preferred listening to the IEEE sentences in quiet. A previous study examining sentence recognition in two-talker babble noise using -5 dB SNR indicated variable performance (median = ~38%, 1st quartile = ~22%, 3rd quartile = ~51% correct) in normal hearing young adults (Calandruccio et al., 2013). As the current study recruited older individuals with varying degrees of hearing loss, more favorable SNRs (10, 5, and 0 dB SNR) were presented, in addition to -5 dB SNR, to maximize the opportunity to identify each participant's SNR-50, or, the dB SNR that corresponds to a 50% correct response rate. At each SNR level, 5 sentences were presented, totaling a percent correct score out of 25 keywords per SNR. The SNR-50 was determined based on the Spearman-Kärber equation (Wilson & McArdle, 2007; Wilson et al., 1973). The SNR-50 was a predictor variable for Specific Aim 3.

Additional non-primary audiometric and peripheral hearing outcomes that were measured included psychoacoustic tinnitus measures, uncomfortable loudness levels (UCLs), loudness contour slopes, and otoacoustic emissions (OAEs). To determine tinnitus pitch and

loudness, a common clinical two-alternative forced-choice tinnitus pitch- and loudness-matching procedure was performed. Perceived tinnitus pitch was assessed first by presenting audible pairs of audiometric tones across the range of frequencies tested (0.25–20 kHz). The participant was asked to indicate which sound in each tone pair was most similar to their tinnitus perception. The tone pair was then increased or decreased in frequency in the same direction as the participant's response. The process was repeated until the participant reported a single tone as being most similar to their tinnitus perception. Then, the half- and double-octaves were presented to avoid octave confusion. For example, if 4 kHz was the initial pitch match, pairs of 2 and 4 kHz as well as 4 and 8 kHz were presented to ensure the participant still indicated that the 4 kHz sound was most similar to their tinnitus perception and was not confusing their tinnitus pitch with the sound an octave above or below it. The tinnitus loudness match was subsequently determined by presenting the pitch-matched stimulus in ascending 1 dB steps, starting below the participant's audiometric threshold for that frequency. The level was slowly increased until the participant responded that the perceived loudness was equivalent to his or her tinnitus. The loudness level was recorded in dB SL.

Loudness sensitivity, which may be related to hyperacusis and tinnitus, was assessed using the Contour Test of Loudness Perception (Cox et al., 1997) which yielded a UCL and loudness contour slope. To quantify these, the participant was asked to make judgements regarding how loud sounds of varying intensity were based on 7 categories ranging from *very soft* to *uncomfortably loud*. The 1000 Hz stimuli presented ascended in loudness in increments of 5 dB. The decibel level at which the participant indicated the sound was *uncomfortably loud* was documented as the UCL. The loudness contour slope was determined by the participant's

perceived loudness category (from *very soft* to *uncomfortably loud*) plotted as a function of stimulus intensity. A higher loudness contour slope was indicative of greater sensitivity to increases in intensity. In other words, a higher loudness contour slope was the result of less of an increase in stimulus intensity required for the participant to perceive a greater change in loudness discomfort. Previous research utilizing similar procedures to quantify maximum loudness discomfort (UCL) and loudness sensitivity across the range of hearing (loudness contour slope) has shown that tinnitus is associated with greater loudness sensitivity of both measures (Hebert et al., 2013). Finally, as an additional measure of the peripheral auditory integrity that may be indicative of cochlear degradation prior to auditory thresholds, distortion product OAEs (DPOAEs) were measured (f2/f1 ratio = 1.22, 55/65 dB SPL, 0.5-10 kHz). Although psychoacoustic tinnitus features, loudness sensitivity, and DPOAEs were not exclusionary or analyzed as a primary outcome measure, these outcomes may be analyzed as a potential source of inter-individual variability.

2.2.2.2: Self-Report Questionnaires

Each participant completed self-report questionnaires to collect demographic history, and tinnitus-related information. The demographic questionnaire asked the participant to provide information regarding their age, sex, details regarding factors that may confound sensory gating including substance use (nicotine, alcohol, and marijuana), handedness, and aforementioned exclusionary criteria. As dominant left-handedness has been reported to affect CAEP responses (Hoffman & Polich, 1999; Polich & Hoffman, 1998), the handedness of participants was assessed using the Shortened Edinburgh Handedness Inventory (Veale, 2014). Further, individuals in the tinnitus group were asked if they have ever received tinnitus

treatment, and if so, what kind of treatment, who the treatment was administered by, how long ago the treatment was, and how successful they felt the treatment was.

Although not the primary outcome measures under study, additional tinnitus-related subjective reports of tinnitus functional impact and the presence and degree of hyperacusis were collected. To quantify a person's tinnitus-related emotional impact, the Tinnitus Functional Index (TFI) was administered (Meikle et al., 2012). The TFI was designed to provide a comprehensive set of items with high construct validity for scaling tinnitus severity and to document changes to tinnitus-related problems. The 25-question TFI categorizes tinnitus distress into 8 subscales including intrusiveness, feelings, thinking, hearing, relaxing, sleeping, managing, and quality of life. The total score for the TFI ranges from 0 to 100, with severity categories interpreted as none to mild (0-25), moderate (26-50), and severe (51+). For descriptive purposes, the degree to which participants experience hyperacusis was also assessed with the Hyperacusis Questionnaire (HQ), designed to gauge an individual's reaction to sound sensitivities based on three factors: attention, social, and emotional effects (Khalfa et al., 2002).

2.2.2.3: Noise Exposure Structured Interview

Research relating noise exposure to hearing loss and tinnitus in humans, unlike animals, relies on retrospective self-report. Quantifying lifetime noise exposure can be difficult and available instruments are of variable quality and comprehensiveness. Guest et al., (2018) published the NESI in an attempt to design a widely available and comprehensive noise exposure history questionnaire that draws on the strengths and addresses the pitfalls of its predecessors (Figure 3) in an effort to improve the validity and reliability limitations inherent of

retrospective noise exposure history questionnaires. Advantages of the NESI include providing data on the intensity and duration of an individual's noise exposure history throughout the lifespan after taking into account hearing protection devices, changing habits over time, no restriction on participant responses, and provided open source instructions on administering the interview and determining noise exposure history. The interview itself is designed to be flexible while still maintaining the following interview structure; (1) identification of exposure activities, (2), segmentation of the lifespan, (3) estimation of exposure duration, (4) estimation of exposure level, (5) consideration of hearing protection, (6) quantification of firearm noise exposure, and (7) quantification of overall noise exposure units (NEUs). Each single NEU is equivalent to one working year of noise exposure at 90 dBA. Detailed instructions and an Excel spreadsheet to calculate NEUs are available in the Supplementary material from Guest et al., (2018). Therefore, in order to have a comprehensive and defined quantification of noise exposure, the total NEU score calculated from the results of the NESI was used as a predictor variable for Specific Aim 3.

2.2.2.4: Electrophysiological Testing

2.2.2.4a: ABR

Ipsilateral and contralateral ABRs were recorded using parameters found most sensitive in recording a robust wave I using a Bio-Logic Auditory Evoked Potentials system version 6.1.0. Participants were seated in a comfortable reclining chair and asked to try to relax and sleep during the recording. 100 dB ppe SPL click stimuli with a duration of 100 μS were unilaterally presented to the test ear at a rate of 27.7 clicks/second with an insert delay of 0.80 ms. The active electrode was C_z. A gold-foil ER3-26A tiptrode served as the reference electrode to

improve recording of wave I by decreasing the distance between the wave I generation site and the recording electrode in the test ear. A traditional mastoid electrode served as the reference electrode for the contralateral recording. For each ABR, a minimum of two replications were conducted to confirm waveform quality and response presence or absence. Each recording was averaged over a minimum of 2000 sweeps, band-pass filtered from 30-3000 Hz, and amplified 100,000X. Artifact rejection was set at ±15μV over an epoch time window of 16 ms starting at -1.5 ms re: stimulus onset with 256 samples per time window, or a sampling rate of 16 kHz. The component peaks of the ipsilateral recording were manually determined by the experimenter as the final point before the component decreased in amplitude to the component trough within the expected latency range. Contralateral recordings were referenced to aid in ipsilateral peak determination. For the two most consistent sweeps, peak to following trough ipsilateral amplitudes and latencies were determined for waves I, III, and V. For each participant, amplitudes and latencies were averaged across the two sweeps. For Specific Aim 1 and Specific Aim 3, the dependent variable was the ipsilateral $\mathrm{V/I}_{\text{amp ratio}}$.

2.2.2.4b: Sensory Gating

The sensory gating procedure for the current study was based on previously validated and published methodology (Grunwald et al., 2003; Lijffijt et al., 2009a). Participants were asked to avoid caffeine, cigarettes, and marijuana for at least 2 hours prior to the sensory gating procedure as these substances can impact sensory gating outcomes. Stimuli were presented using Neuroscan Stim2. Recordings were made with disposable electrodes placed along the midline (F_z, C_z, P_z) and referenced to the average mastoid response ($\frac{M1+M2}{2}$). Electrodes were also placed above and below the left eye to record eyeblink artifact. Curry

Neuroimaging Suite 7.0.2 was used to record, average, and analyze responses (Neuroscan, 2014). During the recording, participants were seated in a reclining chair and asked to watch a muted closed caption video of their choice or read while ignoring the sensory gating stimuli. Stimuli were presented to the test ear at 100 dB ppe SPL via ER-3A insert earphones. A minimum of 200 trials (1 trial = 1 conditioning and 1 test stimulus) were recorded. Stimuli were a pair of identical 10 ms broadband clicks (interstimulus interval of 500 ms between the conditioning and test click, intertrial interval of 7000 ms, intertrial interval range of 700 ms). The click stimulus is commonly utilized for sensory gating research. This specific methodology was piloted in normal hearing controls in our own laboratory and resulted in waveforms with good morphology and amplitudes demonstrating typical sensory gating patterns showing an inhibited response to the second (test) click presentation (Figure 2).

The recording window for each pair of stimuli was -200 to 1200 ms in reference to the conditioning stimulus onset. Recordings were amplified 10X with an A/D rate of 1 kHz. Eyeblink artifact in excess of 200 µV between -200 and 1200 ms re: conditioning stimulus onset was corrected based on a covariance analysis computed between the eye channel and all other channels. Based on the covariance analysis, a proportion of the voltage was subtracted from each data point during the artifact time interval. Artifact in all other channels in excess of 200 µV between -200 and 1200 ms re: conditioning stimulus onset was rejected. Recordings were baseline corrected relative to the 200 ms prestimulus interval. The recordings were bandpass filtered from 0.1 to 30 Hz. These filter settings are consistent with previous auditory research (Campbell et al., 2018; Campbell et al., 2019; Campbell et al., 2020a; Campbell et al., 2020b) and recommended for CAEP research (Luck, 2005). Peaks were confirmed by comparing

responses across channels. C_z yielded the most robust responses and response metrics were measured from C_z recordings.

P1, N1, and P2 CAEP components were picked automatically using Neuroscan software according to the following criteria (Liegeois-Chauvel et al., 1994; Luck, 2005; Muller et al., 2001) and confirmed by an experimenter:

- P1 was identified as the largest positive deflection occurring between 20 and 120 ms following stimulus (conditioning or test) onset.
- N1 was identified as the largest negative deflection following P1 and occurring between 50 and 150 ms following stimulus (conditioning or test) onset.
- P2 was identified as the largest positive deflection following N1 and occurring between 80 and 300 ms following stimulus (conditioning or test) onset.

Amplitude outcome measures included the peak-to-trough (P1-N1) and trough-to-peak (N1-P2) amplitudes, which were calculated as the total voltage difference between the peaks. Latency outcomes measures included P1, N1, and P2 peak latencies, which were considered as the time difference between stimulus onset with the component peak. Additionally, the rectified area of the entire P1-N1-P2 complex was determined as the total area under the curve from 20 to 300 ms re: stimulus onset to provide a comprehensive measure of amplitude. Amplitude (P1-N1 and N1-P2), latency (P1, N1, and P2), and area (P1-N1-P2) $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ within-individual comparisons were made for each participant. For Specific Aim 2, the primary dependent variables which best represent sensory gating were the $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratios for measures of amplitude (denoted $\text{P1-N1}_{\text{amp ratio}}$ and $\text{N1-P2}_{\text{amp ratio}}$) and area (denoted $\text{P1-N1-P2}_{\text{area ratio}}$). As

a secondary outcome measure which may relate to sensory gating, the $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ latency ratios (denoted $\text{P1}_{\text{lat ratio}}$, $\text{N1}_{\text{lat ratio}}$, and $\text{P2}_{\text{lat ratio}}$) were also analyzed. For Specific Aim 3, the $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratios which best differentiated between the tinnitus and control group were analyzed.

Across the broader sensory gating literature, including psychiatry and psychology research, the most common sensory gating outcome measure is the P1 amplitude (sometimes referred to as P50). For comparative purposes, individual results were also analyzed in a fashion more consistent with this sensory gating literature. Specifically, raw EEG was bandpass filtered from 10 to 50 Hz in order to maximize the resolution of the P1 component, which has been shown to be composed of primarily 40 Hz frequency content (Boutros et al., 2004). All other aforementioned CAEP processing details described above otherwise remained the same. For each individual, the amplitude of the P1 component for the conditioning and test CAEP was then measured from the preceding trough-to-peak (denoted $\text{P1}_{\text{T-P}}$) within the aforementioned specified P1 time window and the sensory gating $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ $\text{P1}_{\text{T-P}}$ amplitude was determined for each participant (denoted $\text{P1}_{\text{T-P}_{\text{amp ratio}}}$). The $\text{P1}_{\text{T-P}_{\text{amp ratio}}}$ was also included as a dependent variable for Specific Aim 2.

2.2.3: Statistical Methods

Statistical analyses were conducted using R studio and Jamovi (Fox & Weisberg, 2018; jamovi, 2020; Lenth, 2018; R Core Team, 2019; Signmann, 2018). For all tests, *p*-values less than 0.05 were considered statistically significant. For all tested variables, statistical assumptions

were assessed including the presence of outliers, having a normal distribution, and homogeneity of variances.

To check the matched characteristics between the tinnitus and control groups, independent groups t-test with the null hypothesis, H_0: $\mu_{Tinnitus}=\mu_{Control}$, were used to identify the presence of group differences in age and PTAs in the test ear. Independent groups t-test with the null hypothesis H_0: $\mu_{Tinnitus}=\mu_{Control}$ were also used to assess group differences of DPOAEs, SNR-50, UCLs, loudness contour slopes, HQ scores, and NESI scores.

For Specific Aim 1 and Specific Aim 2, independent groups t-tests with the null hypothesis, H_0: $\mu_{Tinnitus}=\mu_{Control}$, were used to identify group differences in subcortical (ABR $V/I_{amp\ ratio}$) and cortical ($\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ sensory gating ratios) inhibitory function between the tinnitus and control groups. For ABR and CAEP measures of inhibition, the data was not normally distributed. Therefore, a $\log_{10}$ transformation of the raw data was performed to yield a more normal dependent variable distribution across the multiple statistical analyses conducted on these AEP measures of inhibition.

For Specific Aim 3, multiple regressions were conducted according to the principles described by Judd et al. (2009) to determine which predictor variables significantly influenced subcortical and cortical inhibition. For all regression models, assumptions including a test for autocorrelation (Durbin-Watson test), collinearity (variance inflation factor), and normality of residuals (Shapiro-Wilk test) were assessed. The predictor variables included tinnitus (present versus absent), age, noise exposure history (total NEUs), hearing loss ($PTA_{0.25\text{-}20\ kHz}$), and SPIN (SNR-50). These variables were chosen due to the potential influence they may have on the relationship between tinnitus with subcortical and cortical inhibition. Additional predictor

variables in the model were not included as that substantially increased the likelihood of a Type I error.

The predictor variables that significantly reduced model error above and beyond the effect of all other variables were considered influential. This was determined by assessing if the multiple regression model was improved by adding the predictor variable of interest. In other words, a comparison between two regression models was made. The first model included all predictor variables *except* for the predictor of interest (reduced model) and the second model includes all predictor variables *with the addition of* the predictor of interest (overall model). If the overall model significantly reduced model error, then it was concluded that the predictor of interest substantially influenced the dependent variable when all other predictor variables were held constant. For example, if our variable of interest was the presence of tinnitus then the following two models were compared:

$$Y_1 = \beta_0 + \beta_{PTA}X_{PTA} + \beta_{NEU}X_{NEU} + \beta_{SNR\text{-}50}X_{SNR\text{-}50} + \beta_{Age}X_{Age}$$

$$Y_2 = \beta_0 + \beta_{PTA}X_{PTA} + \beta_{NEU}X_{NEU} + \beta_{SNR\text{-}50}X_{SNR\text{-}50} + \beta_{Age}X_{Age} + \beta_{Tin}X_{Tin}$$

The models are the same except the overall model, Y_2, includes the tinnitus (present versus absent) variable. The null hypothesis that tinnitus has no influence on the outcome variable (H_0: $\beta_{Tin}=0$) was tested based on the proportional reduction in error [$PRE=\frac{SSE(Y_1)\text{-}SSE(Y_2)}{SSE(Y_1)}$] of the overall model ($Y_2$) relative to the reduced model (Y_1) and the associated *F*-statistic [$F=\frac{PRE/(\#Variables_{Y_2}\text{-}\#Variables_{Y_1})}{(1\text{-}PRE)/\left(n\text{-}\#Variables_{Y_2}\right)}$]. If *PRE* or *F* exceeded their respective critical values, the null hypothesis was rejected and it was concluded that, with all other variables held constant, tinnitus influenced the dependent variable. Further, the $\sqrt{PRE}$ equals the partial correlation, or,

the extent to which the variable of interest and the outcome correlate after "partialing out" the other predictor variables and could be compared across predictor variables. Therefore, this methodology determined which predictor variables significantly influenced subcortical and cortical inhibition and the extent of that influence.

Additional statistical analyses included independent groups t-tests with the null hypothesis, H_0: $\mu_{Tinnitus}=\mu_{Control}$ to identify group differences in ipsilateral ABR waves I, III, and V amplitudes and latencies between the tinnitus and control groups [Mann-Whitney U non-parametric alternatives to the independent groups t-test were reported in cases where the assumptions of normality (Shapiro-Wilk test) and equality of variances (Levene's test) were violated]. While both parametric and non-parametric tests were run in all cases, in order to be conservative, non-parametric alternatives are reported in the tables for cases where assumptions were not met. In cases where the statistical result differed between the non-parametric and parametric tests, both results are reported. A 2x2 mixed-model ANOVA was also used to assess the main effects of and interactions between *group* (tinnitus and control) and *stimulus* (conditioning and test) on CAEP amplitudes, areas, and latencies. As the repeated measures in these mixed-model ANOVA analyses have only two levels, the assumption of sphericity was always met. Lastly, Pearson correlations and simple linear regressions were determined between predictor variables (tinnitus, $PTA_{0.25\text{-}20\ kHz}$, NEUs, SNR-50, and age) with dependent variable measures of subcortical and cortical inhibition to aid in visualization of the trends described by the multiple regression analyses used to achieve Specific Aim 3.

3.0: Results

3.1: Participant and Group Characteristics

This study was approved by the Syracuse University Institutional Review Board, and all participants provided written or oral informed consent prior to participating. A total of 42 participants were recruited. Of the 42 recruited, four individuals with tinnitus were excluded due to not meeting hearing threshold criteria (n = 2) or having abnormal middle ear function (n = 2) and two control group counterparts to disqualified tinnitus participants were also excluded from the final data analysis. The final participant sample analyzed included a total of 36 participants, 18 in the tinnitus group matched to 18 in the control group based on having similar age, hearing ($PTA_{0.5\text{-}2\ kHz}$), and sex (10 females, 8 males in both groups). This exceeded the targeted sample size of 16 per group estimated by the power analyses described in *Methods* section 2.2.1.

Effectiveness of group matching to the extent possible by age and hearing are shown by the distributions of age and audiometric thresholds in Figure 4 and Figure 5. Age ranges for the two groups were similar, with participants ranging in age from 19 to 54 years. Age ranges were not normally distributed in either group, skewed such that younger ages were more common

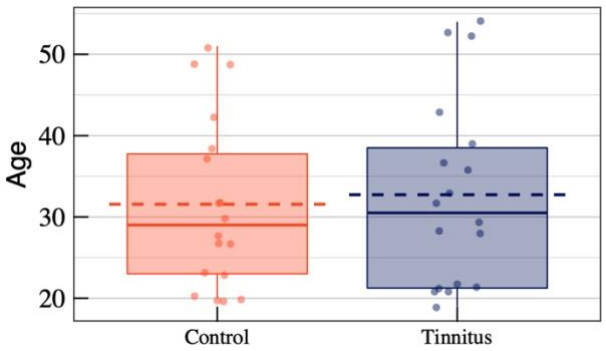


Figure 4. Age in years for the control (in orange) and tinnitus (in blue) groups. Individual participant data points are circles, mean is horizontal dotted line, median is solid horizontal line within boxplot, lower and upper hinges correspond to the first and third quartiles (25^{th} and 75^{th} percentile). Lower and upper whiskers extend to minimum or maximum observed values within 1.5x the first or third quartile. Data points beyond the whiskers are outliers.

than older ages. About one-third of the participants (12 out of 36) were between 19 and 23 years old. Although a broader strategy was attempted to recruit participants from outside of the Syracuse University community, it was difficult in the recruitment timeframe, which occurred during the COVID-19 pandemic. Therefore, in order to achieve the targeted number of participants determined by the power analysis, a large number of younger tinnitus participants were recruited from a pool of musicians in the Syracuse University band. Despite this, the tinnitus and control groups were well matched by age with an average age of 32.7 years (*SD* = 11.69) for the tinnitus group and 31.6 years (*SD* = 10.58) for the control group. A Mann-Whitney U test verified that age did not significantly differ between groups ($U = 148$, $p = 0.657$, $r_{rb} = 0.090$).

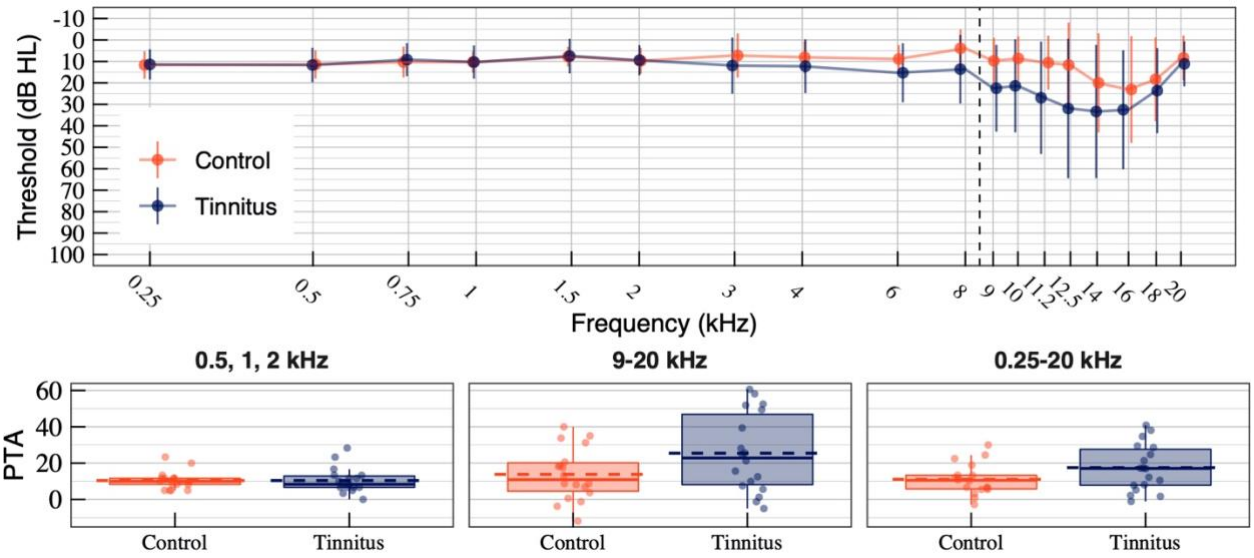


Figure 5. Top Row: Mean (± 1 standard deviation) pure tone audiometric thresholds across standard (0.25-8 kHz) and extended high-frequency (9-20 kHz) ranges for the test ear for the control (in orange) and tinnitus (in blue) groups. Bottom row: Distribution of pure tone averages (PTAs) for three different frequency ranges, denoted above each box plot, for each group. For boxplots: Individual participant data points are circles, mean is horizontal dotted line, median is solid horizontal line within boxplot, lower and upper hinges correspond to the first and third quartiles (25th and 75th percentile). Lower and upper whiskers extend to minimum or maximum observed values within 1.5x the first or third quartile. Data points beyond the whiskers are outliers.

Control group counterparts were matched to have clinical pure tone averages ($PTA_{0.5\text{-}2\ kHz}$) within 20 dB HL of their tinnitus counterpart. As shown by the audiogram in Figure 5, mean audiometric thresholds for the test ear were similar between the two groups from 0.25 through 2 kHz. Thresholds were slightly poorer on average for the tinnitus group from 3 kHz through 8 kHz. In the extended high frequency range from 9 to 20 kHz, mean thresholds were also poorer for the tinnitus group compared to controls. Three different PTAs were calculated and depicted by the boxplots in Figure 5; (1) standard clinical ($PTA_{0.5\text{-}2\ kHz}$), (2) extended high frequency ($PTA_{9\text{-}20\ kHz}$), and (3) full audiogram ($PTA_{0.25\text{-}20\ kHz}$). The average standard clinical PTA ($PTA_{0.5\text{-}2\ kHz}$, the matching criteria) was the same for the tinnitus (*M* = 10.5 dB HL, *SD* = 6.88) and control group (*M* = 10.5 dB HL, *SD* = 4.88). However, the tinnitus group had poorer average extended high-frequency hearing thresholds ($PTA_{9\text{-}20\ kHz}$ tinnitus *M* = 25.4 dB HL, *SD* = 21.7; control *M* = 13.8 dB HL, *SD* = 14.4). Average thresholds across the entire frequency range were also slightly poorer for the tinnitus group ($PTA_{0.25\text{-}20\ kHz}$ tinnitus *M* = 17.5 dB HL, *SD* = 12.9; control *M* = 11.1 dB HL, *SD* = 8.47). As shown in Table 2, none of these three PTA differences between groups were statistically significant by independent t-tests or Mann-Whitney U tests in cases of violation of normality. None of the threshold differences for any individual frequencies were significant, with the exception that the tinnitus group was found to have significantly poorer thresholds at 8 kHz. Note that the measure of effect size for the independent groups t-test was Cohen's *d* [interpreted as small $|d|$ = 0.2–0.49), medium $|d|$ = 0.5–0.79, and large $|d|$ > 0.8 (Cohen, 2013)]. The measure of effect size for the Mann-Whitney U test was the rank biserial correlation [ranging from -1 to 1, interpreted the same as other correlational measures of association; weak $|r_{rb}| < 0.29$, medium $|r_{rb}|$ = 0.3–0.49, and large $|r_{rb}| > 0.5$) (*APA Dictionary*

of Psychology, 2007)]. Therefore, although the tinnitus group only exhibited statistically significantly poorer thresholds at 8 kHz, there was a medium effect size for poorer thresholds in the tinnitus group for both the $PTA_{9\text{-}20\ kHz}$ and $PTA_{0.25\text{-}20\ kHz}$ as well as for individual frequencies from 3 kHz through 16 kHz.

Table 2. Pure tone average (PTA) and individual frequency independent t-test comparisons between groups. Statistically significant outcomes at $\alpha = 0.05$ indicated with cell shading. Mann-Whitney U statistic reported for cases where assumptions of normality or homogeneity of variances were not met. Measure of effect size for t-test is Cohen's *d* and for Mann-Whitney U test is rank biserial correlation.

Pure Tone Averages (PTAs)				
kHz	*Statistic*	*df*	*p*	Effect Size
0.5-2	152	-	0.762	0.062
9-20	-1.90	34	0.066	-0.632
0.25-20	-1.78	34	0.085	-0.592
Individual Frequencies				
0.25	0.124	34	0.902	0.041
0.5	-0.113	34	0.910	-0.038
0.75	0.448	34	0.657	0.149
1	<0.001	34	1.00	<0.001
1.5	0.127	34	0.900	0.042
2	0.127	34	0.900	0.042
3	-1.20	34	0.237	-0.401
4	-1.21	34	0.234	-0.404
6	115	-	0.138	0.287
8	99.0	-	0.044	0.389
9	104	-	0.067	0.358
10	111	-	0.107	0.315
11.2	107	-	0.083	0.340
12.5	102	-	0.059	0.370
14	-1.46	34	0.153	-0.487
16	-1.08	34	0.290	-0.358
18	-0.804	34	0.427	-0.268
20	-0.796	34	0.432	-0.265

DPOAE results resembled audiometric threshold results in that the two groups had similar lower frequency DPOAEs but diverged slightly in the higher frequencies such that the tinnitus group had reduced DPOAE levels above 1.5 kHz compared to the control group (Figure 6). DPOAE levels were significantly lower for the tinnitus group relative to controls at F2 = 4 kHz, 6 kHz, and 8 kHz, with medium (6 kHz and 8 kHz) and large (4 kHz) effect sizes. None of the other individual F2 frequencies tested or the average across all tested frequencies significantly differed between groups (Table 3).

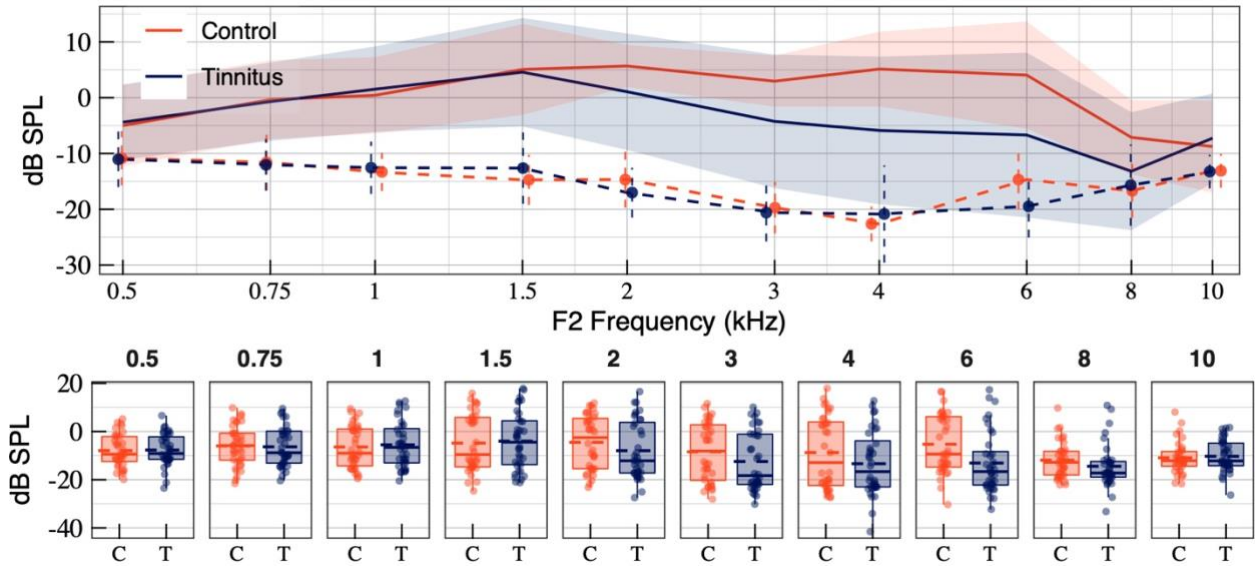


Figure 6. Distortion product otoacoustic emissions (DPOAEs) for the control (in orange) and tinnitus (in blue) groups. Top row: Solid line and shading denotes mean ± 1 standard deviation DPOAEs, dotted line denotes mean ± 1 standard deviation noise floor, both from F2 = 0.5 to 10 kHz in the test ear. Bottom row: DPOAEs at each F2 frequency tested. For boxplots: Individual participant data points are circles, mean is horizontal dotted line, median is solid horizontal line within boxplot, lower and upper hinges correspond to the first and third quartiles (25^{th} and 75^{th} percentile). Lower and upper whiskers extend to minimum or maximum observed values within 1.5x the first or third quartile. Data points beyond the whiskers are outliers.

Table 3. DPOAE independent t-test comparisons between groups. Statistically significant outcomes at $\alpha = 0.05$ indicated with cell shading. Mann-Whitney U statistic reported for cases where assumptions of normality or homogeneity of variances were not met. Measure of effect size for t-test is Cohen's *d* and for Mann-Whitney U test is rank biserial correlation.

DPOAEs				
F2 kHz	*Statistic*	*df*	*p*	Effect Size
0.5	-0.261	34	0.796	-0.087
0.75	-0.158	34	0.876	0.053
1	-0.449	34	0.656	-0.150
1.5	158	-	0.913	0.025
2	129	-	0.308	0.204
3	109	-	0.097	0.327
4	69.0	-	0.003	0.574
6	90.0	-	0.022	0.444
8	2.06	34	0.047	0.686
10	-0.551	34	0.585	-0.183
0.5-10	120	-	0.192	0.259

There were also some group differences in functional auditory tests of SPIN and loudness perception (Figure 7). The average SNR-50 for the tinnitus group was -2.47 dB (*SD* = 4.18), which was significantly higher (poorer) than the control group average of -5.36 dB (*SD* = 3.03) with a medium effect size (Table 4, Figure 7A). In other words, the tinnitus group required a more favorable signal to noise ratio condition compared to the controls, to achieve 50% correct sentence recognition. The tinnitus group had a slightly steeper mean loudness contour slope (*M* = 0.071, *SD* = 0.012) than the control group (*M* = 0.067, *SD* = 0.010), indicating a trend towards greater sensitivity to intensity increments in the tinnitus group, although this difference was not statistically significant (Table 4). Mean UCLs, however, were significantly different between groups, with a medium effect size (Table 4), such that the tinnitus group perceived uncomfortable loudness at significantly lower levels (*M* = 95 dB HL, *SD* = 9.7) compared to the control group (*M* = 103 dB HL, *SD* = 10.3). As expected, there was a significant

correlation between UCLs and loudness contour slope (r = -0.765, p < 0.001), such that participants with the steepest loudness contour slopes also had the lowest UCLs.

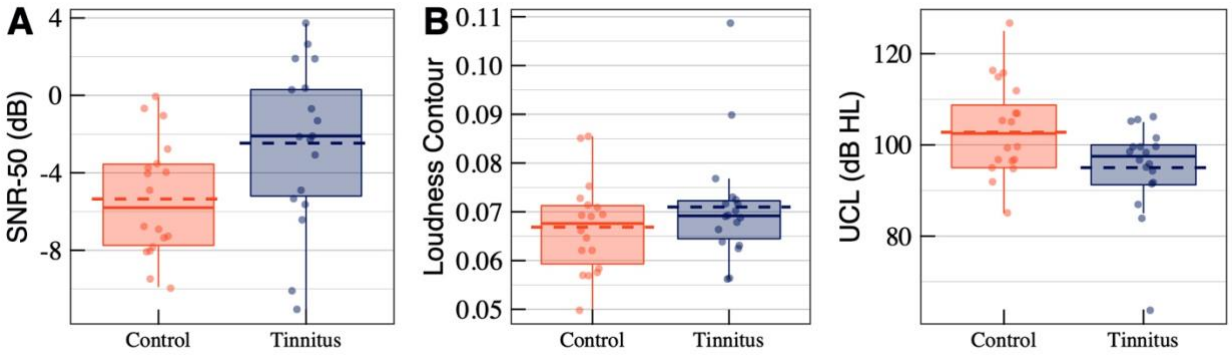


Figure 7. Comparisons of SNR-50 (in A) and Loudness Contour Test results (in B) between the control (in orange) and tinnitus (in blue) groups. In A: SNR-50 is the signal to noise ratio in dB at which participants were correctly identifying words in noise at a rate of 50%, lower is better. In B: Loudness contour slope, on left, is a measure of loudness growth perception (a higher slope indicates greater sensitivity to increases in loudness), and uncomfortable loudness level (UCL), on right, the maximum decibel level tolerable (lower level is greater sensitivity to loud sounds). Individual participant data points are circles, mean is horizontal dotted line, median is solid horizontal line within boxplot, lower and upper hinges correspond to the first and third quartiles (25th and 75th percentile). Lower and upper whiskers extend to minimum or maximum observed values within 1.5x the first or third quartile. Data points beyond the whiskers are outliers.

Table 4. SNR-50 and Loudness Contour Test independent t-test results. Statistically significant outcomes at α = 0.05 indicated with cell shading. Mann-Whitney U statistic reported for cases where assumptions of normality or homogeneity of variances were not met. Measure of effect size for t-test is Cohen's *d* and for Mann-Whitney U test is rank biserial correlation.

SNR-50				
	Statistic	*df*	*p*	Effect Size
SNR-50	-2.38	34	0.023	-0.778
Loudness Contour Test				
	Statistic	*df*	*p*	Effect Size
Loudness Contour	133	-	0.376	0.176
UCL	2.33	34	0.026	0.777

Self-reported perceptions of tinnitus, hyperacusis, and noise exposure history were also obtained. The Tinnitus Function Index (TFI) was administered to the tinnitus group only, while the Hyperacusis Questionnaire (HQ) and Noise Exposure Structured Interview (NESI) were administered to both groups. As shown in Figure 8 (note change in y-axis scales between panels), TFI subscale scores out of 100 indicated that participants with tinnitus in the current study perceived their tinnitus to be difficult to control, intrusive, and interfering with relaxation, based on the highest scores (greatest distress) on these subscales (Table 5). The subscales with the lowest average scores (lowest distress) were the sleep and quality of life (QOL) subscales, suggesting that the tinnitus participants did not perceive their tinnitus to influence their sleep or impact their overall quality of life. According to published guidelines (Meikle et al., 2012), total TFI scores (average of all subscale scores) below 25 indicate mild tinnitus, scores between

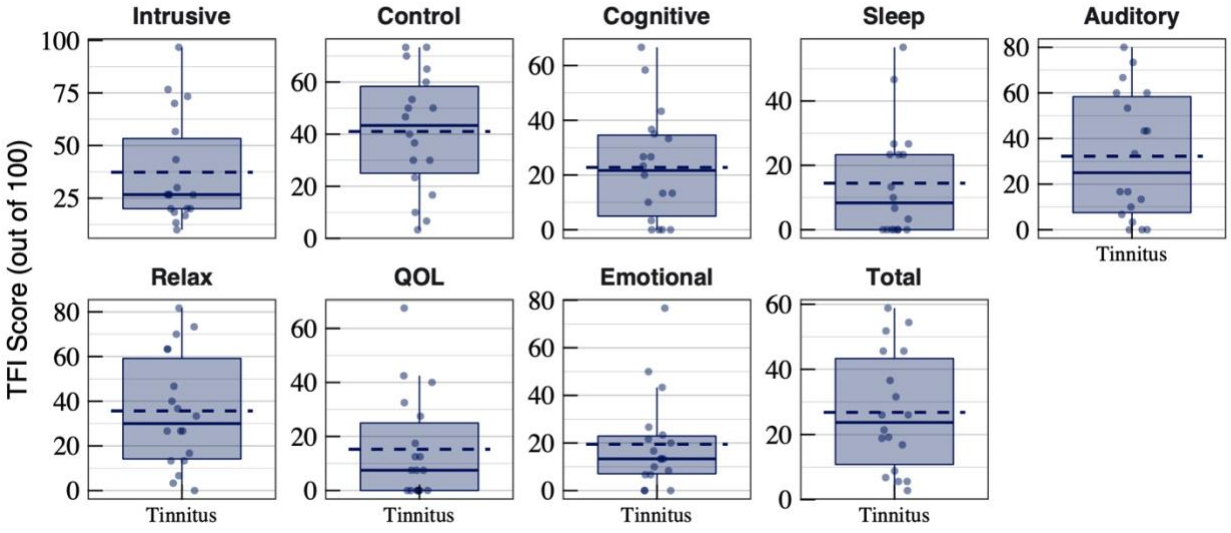


Figure 8. Tinnitus Functional Index (TFI) results for tinnitus group (TFI not administered to control group). TFI scores for each category are out of 100. TFI subscale listed at the top of each boxplot. Individual participant data points are circles, mean is horizontal dotted line, median is solid horizontal line within boxplot, lower and upper hinges correspond to the first and third quartiles (25^{th} and 75^{th} percentile). Lower and upper whiskers extend to minimum or maximum observed values within 1.5x the first or third quartile. Data points beyond the whiskers are outliers.

Table 5. Tinnitus Functional Inventory (TFI) mean (out of 100 for each category) ± 1 standard deviation for each subscale and the total score. Administered to participants in the tinnitus group only.

Intrusive	Control	Cognitive	Sleep	Auditory	Relaxation	QOL	Emotional	Total
37.3 ± 25.9	41.0 ± 22.9	22.8 ± 20.1	14.4 ± 17.2	32.2 ± 28.0	35.6 ± 25.6	15.3 ± 19.3	19.4 ± 19.8	26.8 ± 18.3

25 and 50 indicate significant problems with tinnitus, and scores above 50 indicate severe tinnitus. Nine of the 18 participants in the tinnitus group had total scores greater than a 25, with three of those having scores higher than a 50, suggesting that half of the experimental group had tinnitus that would be classified as having a significant or a severe problem. The remaining nine participants primarily found their tinnitus to be mildly, if at all, problematic.

Self-reported distress related to hyperacusis, as assessed by scores on the HQ, was greater for the participants with tinnitus compared to controls (Figure 9; note change in y-axis scales between panels). Across both groups, participants reported greater hyperacusis distress related to social factors as opposed to attentional or emotional factors as shown by the distributions of the three subscale scores. Total HQ scores (sum of all subscales) ranged from 8 to 31 in the tinnitus group and 0 to 11 in the control group. The published cutoff for significant hyperacusis based on the total HQ score is 28 out of a total of 42 (Khalfa et al., 2002). Across all participants, only two out of 36 (both with tinnitus) had total scores greater than 28, suggesting that in general the participants did not report strong hypersensitivity to sound. Between groups, however, HQ scores were significantly higher for the tinnitus group compared to controls on all three subscales as well as for the total score (Table 6), indicating that the tinnitus group had significantly greater attentional, emotional, social, and overall hyperacusis related

distress. These group differences had large effect sizes, except for the attentional subscale, which was a small effect.

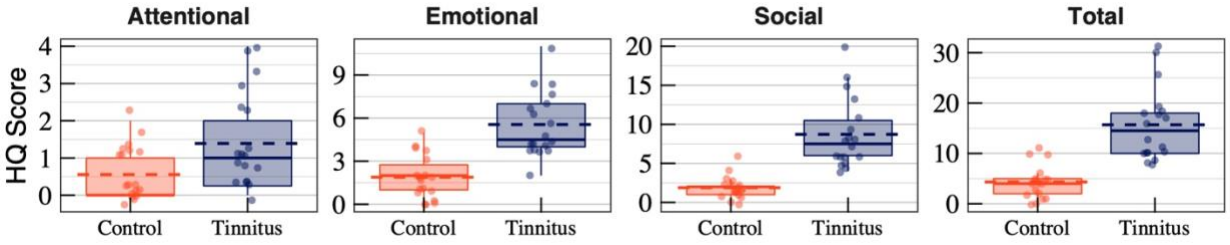


Figure 9. Hyperacusis Questionnaire (HQ) results for the control (in orange) and tinnitus (in blue) groups. HQ subscale listed at the top of each boxplot. Attentional subscale out of 6, emotional out of 12, social out of 24, and the total score is out of 42. Individual participant data points are circles, mean is horizontal dotted line, median is solid horizontal line within boxplot, lower and upper hinges correspond to the first and third quartiles (25th and 75th percentile). Lower and upper whiskers extend to minimum or maximum observed values within 1.5x the first or third quartile. Data points beyond the whiskers are outliers.

Table 6. Hyperacusis Questionnaire (HQ) Mann-Whitney U between group comparisons. Statistically significant outcomes at $\alpha = 0.05$ indicated with cell shading. Measure of effect size is rank biserial correlation.

	Statistic	*df*	*p*	Effect Size
Attentional Subscale	102	-	0.045	0.370
Emotional Subscale	28	-	<0.001	0.827
Social Subscale	7	-	<0.001	0.957
Total Score	17.5	-	<0.001	0.892

Because peripheral damage due to noise exposure is a likely contributor to the hypothesized mechanism of reduced inhibition and perception of tinnitus, lifetime noise exposure was quantified for all participants by self-report using the NESI. Results of this interview were calculated and expressed in noise exposure units (NEUs), for which one NEU is equivalent to one working year of exposure at a daily level of 90 dBA. As shown in Figure 10 (note change in y-axis scales between panels), across all participants, and within the tinnitus and control group separately, NEUs across each subscale and total NEUs were not normally distributed (Shapiro-Wilk $p < 0.05$ for all). This was because most participants reported relatively little noise exposure, particularly for firearm and occupational noise sources, while a few participants reported very high noise exposure histories. Only eight participants reported firearm noise exposure, which ranged from 0 to 6.35 NEUs, indicating very little self-reported lifetime exposure to firearms. Only nine participants reported occupational noise exposure which ranged from 0 to 48.6 NEUs. Further, only three out of 36 participants had over 40 total NEUs. These outliers exhibited high noise exposure histories due to motorcycle riding (recreational), working on a naval cruise ship (occupational), and working on an army airfield

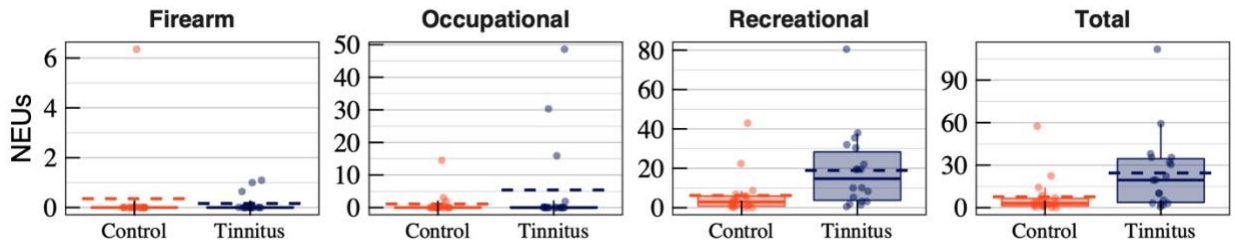


Figure 10. Noise Exposure Structured Interview (NESI) for the control (in orange) and tinnitus (in blue) groups. NESI subscale listed at the top of each boxplot. Individual participant data points are circles, mean is horizontal dotted line, median is solid horizontal line within boxplot, lower and upper hinges correspond to the first and third quartiles (25th and 75th percentile). Lower and upper whiskers extend to minimum or maximum observed values within 1.5x the first or third quartile. Data points beyond the whiskers are outliers.

Table 7. Noise Exposure Structured Interview (NESI) Mann-Whitney U between group comparisons. Statistically significant outcomes at $\alpha = 0.05$ indicated with cell shading. Measure of effect size is rank biserial correlation.

	Statistic	*df*	*p*	Effect Size
Firearm NEUs	120	-	0.084	0.259
Occupational NEUs	143	-	0.459	0.117
Recreational NEUs	77	-	0.008	0.525
Total NEUs	77	-	0.006	0.525

(occupational). Two of these three outliers were military veterans recruited from the SVAMC. Recreational noise exposure (which typically included activities such as listening to music or attending concerts) was higher for both groups, particularly the participants in the tinnitus group. The tinnitus group had significantly greater recreational NEUs (*M* = 18.9 NEUs, *SD* = 19.7) and total NEUs (*M* = 24.5 NEUs, *SD* = 27.3) compared to controls (*M* = 6.22 NEUs, *SD* = 10.6; *M* = 7.7 NEUs, *SD* = 13.6 for each, respectively). These effect sizes were of medium strength (Table 7).

In summary, the two groups were similar in age and standard audiometric hearing thresholds, although a trend for greater high frequency hearing loss and significantly smaller higher frequency DPOAES was observed in the tinnitus group, suggesting poorer high-frequency peripheral auditory function for the tinnitus group. The tinnitus group also had poorer sentence recognition in noise (greater SNR-50) and greater sensitivity to loud sounds (lower UCLs). About half of the tinnitus group reported tinnitus that would be considered significantly problematic, while scores for the other half indicated mildly, if at all, problematic tinnitus. The tinnitus group also had greater hyperacusis-related distress than the control group. Both groups reported noise exposure that was primarily recreational, and the tinnitus group had significantly greater self-reported noise exposure in this category as well as the overall total. The possible influence

of these participant characteristics and group differences on the primary ABR and CAEP outcome measures of inhibition are described below in the *Results* and *Discussion*.

3.2: Auditory Evoked Potentials

3.2.1: Tinnitus and Subcortical Inhibition (ABR)

The objective of Specific Aim 1 was to determine whether ABR outcomes reflecting the mechanisms leading to tinnitus perception in humans would differentiate between a tinnitus and control group. Specifically, reduced cochlear output and subcortical hyperactivity secondary to reduced inhibition would be expected in individuals who perceive tinnitus, compared to controls. The hypothesis for this aim, therefore, was that the tinnitus group would exhibit reduced cochlear output (reduced wave I amplitude) and subcortical hyperactivity secondary to reduced inhibition (increased wave V amplitude) – together leading to an overall larger $\mathrm{V/I_{amp\ ratio}}$ within an individual. Grand mean ipsilateral and contralateral ABRs from the control and tinnitus groups are shown in Figure 11. Morphology of grand mean ABRs was similar between groups. As expected, for most individual subjects, wave V amplitude was larger than wave I, which can also be observed in the grand mean. Grand mean waveform amplitudes for wave I and V visually appear slightly smaller in the tinnitus group compared to controls, with greater between-subject variability in the tinnitus group as indicated by the wider 1 *SD* shaded range.

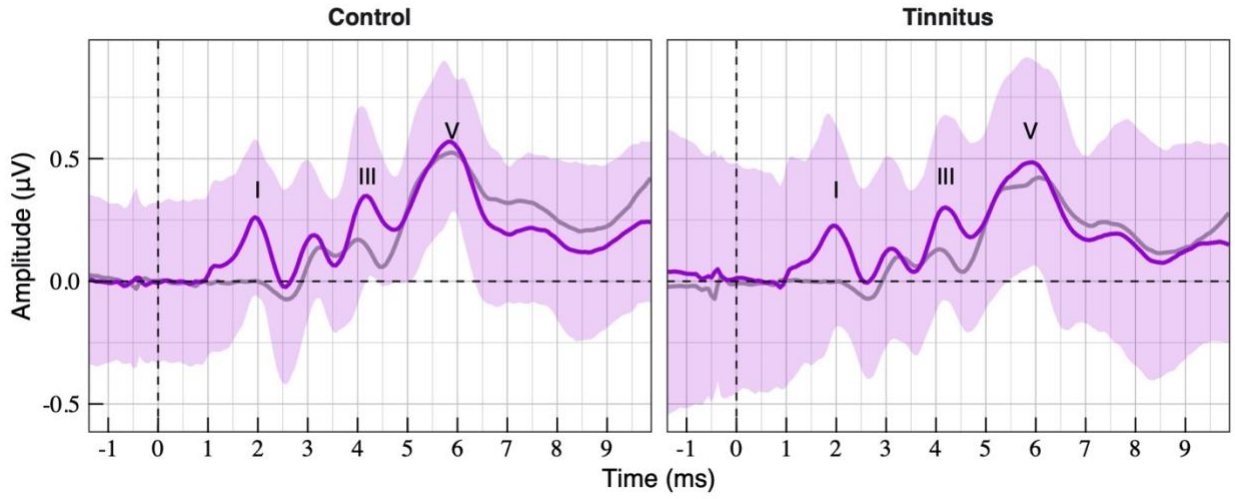


Figure 11. Grand mean ABR waveforms (solid lines) ± 1 standard deviation (shading) for the control (left panel) and tinnitus (right panel) groups. Ipsilateral responses are purple, contralateral responses are gray. Waves I, III, and V are labeled on the ipsilateral grand means.

Individually picked ABR component amplitudes and latencies were generally in agreement with the trends seen in the grand mean waveforms. The tinnitus group had smaller mean amplitudes within a narrower range for waves I, III, and V as compared to the control group (Figure 12A). By contrast peak latency was more variable in the tinnitus group (larger range), and slightly prolonged on average compared to the control group, at least for waves I and V (Figure 12B). However, none of these amplitude or latency differences between groups for wave I, III, or V reached statistical significance (Table 8).

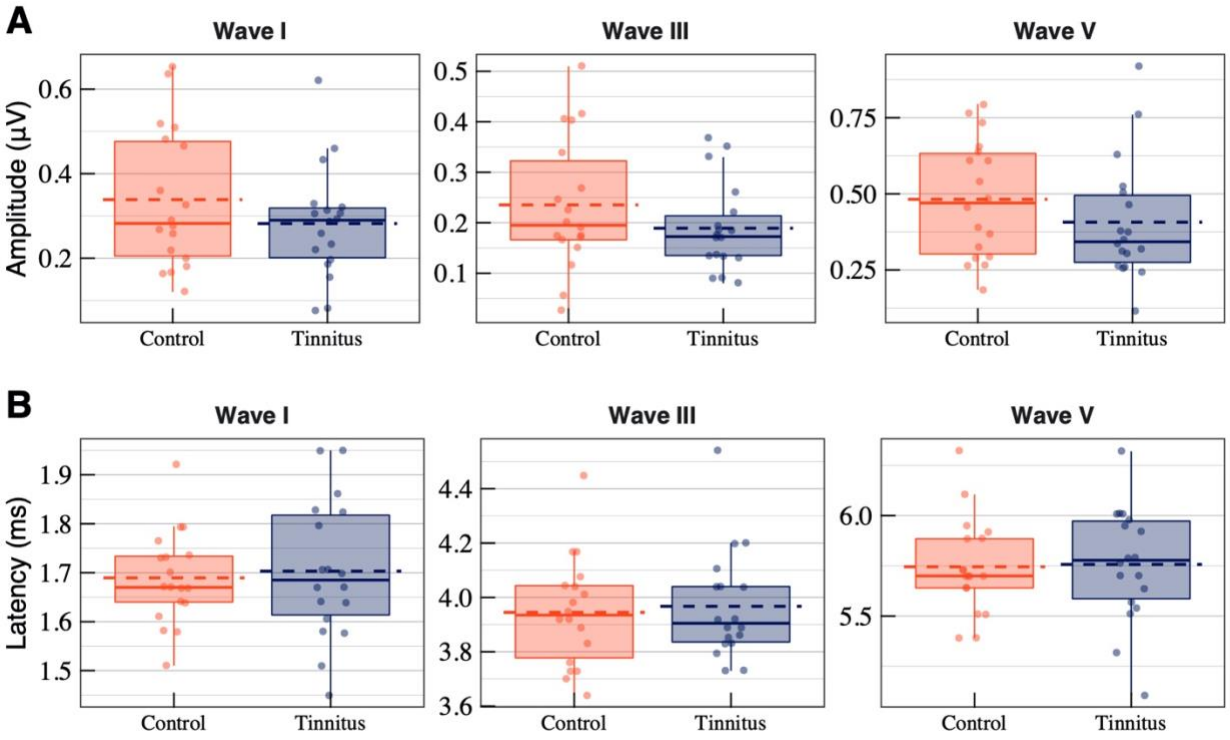


Figure 12. Ipsilateral ABR amplitudes (in A) and latencies (in B) for the control (orange) and tinnitus (blue) groups. Individual participant data points are circles, mean is horizontal dotted line, median is solid horizontal line within boxplot, lower and upper hinges correspond to the first and third quartiles (25th and 75th percentile). Lower and upper whiskers extend to minimum or maximum observed values within 1.5x the first or third quartile. Data points beyond the whiskers are outliers.

Table 8. Ipsilateral ABR wave I, III, and V amplitude and latency independent t-test comparisons between groups. Statistically significant outcomes at $\alpha = 0.05$ indicated with cell shading. Mann-Whitney U statistic reported for cases where assumptions of normality or homogeneity of variances were not met. Measure of effect size for t-test is Cohen's *d* and for Mann-Whitney U test is rank biserial correlation.

Amplitude				
	Statistic	*df*	*p*	Effect Size
I	1.11	34	0.276	0.369
III	125	-	0.241	0.232
V	1.16	34	0.255	0.388
Latency				
	Statistic	*df*	*p*	Effect Size
I	-0.358	34	0.722	-0.119
III	157	-	0.874	0.034
V	-0.132	34	0.896	-0.044

To account for potential inter-individual variability and to better evaluate and quantify whether individuals with tinnitus exhibited evidence of reduced inhibition at the subcortical level as compared to controls, the $V/I_{amp\ ratio}$ was calculated for each participant. The mean $V/I_{amp\ ratio}$ was similar between the tinnitus (*M* = 1.69, *SD* = 0.97) and control groups (*M* = 1.59, *SD* = 0.64), although the tinnitus group had greater variability due to the presence of some large outliers (Figure 13). Most individuals, as expected, had larger wave V than wave I, resulting in a $V/I_{amp\ ratio}$ greater than one. However, due to the use of a tiptrode recording electrode to enhance wave I amplitude (as compared to a mastoid reference electrode), some participants exhibited relatively large wave I amplitudes and $V/I_{amp\ ratio}$ less than one. A $V/I_{amp\ ratio}$ less than one was observed for three participants in the control group and two participants in the tinnitus group.

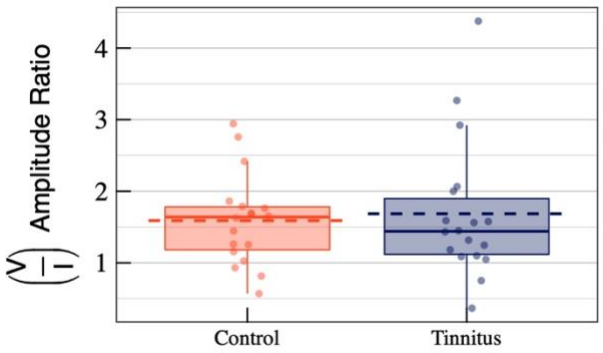


Figure 13. ABR $V/I_{amp\ ratio}$ for the control (orange) and tinnitus (blue) groups. Individual participant data points are circles, mean is horizontal dotted line, median is solid horizontal line within boxplot, lower and upper hinges correspond to the first and third quartiles (25^{th} and 75^{th} percentile). Lower and upper whiskers extend to minimum or maximum observed values within 1.5x the first or third quartile. Data points beyond the whiskers are outliers.

There were also a few outliers with larger $V/I_{amp\ ratio}$ in both groups. For example, T06, a 21-year-old female in the Syracuse University marching band with high pitched ringing tinnitus in her left ear had a $V/I_{amp\ ratio}$ of 4.38, which can be seen as the highest outlier in Figure 13. This large value, relative to the rest of the sample, was due to a relatively small wave I amplitude (0.08 µV). As a result of these outliers, the $V/I_{amp\ ratio}$ was not normally distributed

(*W* = 0.898, *p* = 0.003). To account for the non-normal distribution, $\mathrm{V/I_{amp\ ratio}}$ were $\log_{10}$ transformed as described in *Methods* section 2.2.3. The distributions of $\log_{10}(\mathrm{V/I_{amp\ ratio}})$ for both groups are shown in Figure 14. A subsequent Shapiro-Wilk test was not significant, indicating the $\log_{10}$ transformed data now met the assumption of having a normal distribution (*W* = 0.974, *p* = 0.529). Note that although the $\log_{10}(\mathrm{V/I_{amp\ ratio}})$ now ranged between approximately -0.5 to 0.75, a larger $\log_{10}(\mathrm{V/I_{amp\ ratio}})$ was still consistent with reduced subcortical inhibition. Further, whereas a raw (not $\log_{10}$ transformed) $\mathrm{V/I_{amp\ ratio}}$ less than one indicated a larger wave I than wave V, the equivalent $\log_{10}$ transformed ratio was a negative value. This is because a $\mathrm{V/I_{amp\ ratio}}$ = 1 is equivalent to a $\log_{10}(\mathrm{V/I_{amp\ ratio}})$ = 0. Thus, more negative $\log_{10}(\mathrm{V/I_{amp\ ratio}})$ indicated a greater wave I relative to wave V and a more positive $\log_{10}(\mathrm{V/I_{amp\ ratio}})$ indicated a greater wave V relative to I, consistent with reduced subcortical inhibition.

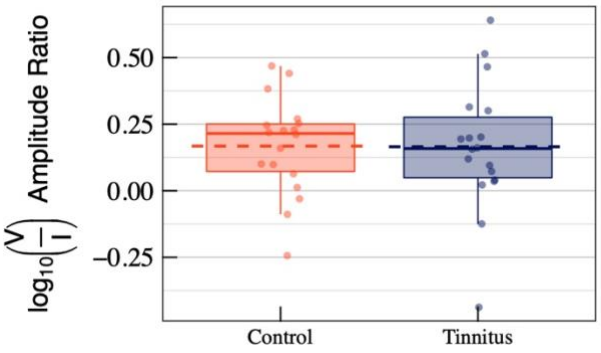


Figure 14. ABR $\log_{10}(\mathrm{V/I_{amp\ ratio}})$ for the control (orange) and tinnitus (blue) groups. Individual participant data points are circles, mean is horizontal dotted line, median is solid horizontal line within boxplot, lower and upper hinges correspond to the first and third quartiles (25^{th} and 75^{th} percentile). Lower and upper whiskers extend to minimum or maximum observed values within 1.5x the first or third quartile. Data points beyond the whiskers are outliers.

The tinnitus group had slightly lower mean $\log_{10}(\mathrm{V/I_{amp\ ratio}})$ compared to the control group, but with a larger range of variability (tinnitus *M* = 0.165, *SD* = 0.242; control *M* = 0.168, *SD* = 0.183) (Figure 14). Although larger $\log_{10}(\mathrm{V/I_{amp\ ratio}})$ would be consistent with the

Table 9. $\log_{10}(\mathrm{V/I_{amp\ ratio}})$ independent t-test results. Measure of effect size is Cohen's *d*.

	Statistic	*df*	*p*	Effect Size
$\log_{10}(\mathrm{V/I_{amp\ ratio}})$	0.036	34	0.972	0.003

hypothesis of reduced cochlear output (smaller wave I amplitude) and subcortical hyperactivity (increased wave V amplitude), the $\log_{10}(\mathrm{V/I_{amp\ ratio}})$ was not significantly different between groups (Table 9). Further, even if outliers (and their matched counterparts) with $\log_{10}(\mathrm{V/I_{amp\ ratio}})$ less than zero were removed, indicating a larger wave I than wave V, there was still no significant difference in the $\log_{10}(\mathrm{V/I_{amp\ ratio}})$ between groups [$t(24) = 0.278$, $p = 0.783$, $d = 0.109$].

In summary, the tinnitus group relative to controls exhibited on average smaller wave I, III, and V amplitudes and longer wave I and V latencies. However, none of these group differences were statistically significant. The primary outcome measure for Specific Aim 1 was the $\mathrm{V/I_{amp\ ratio}}$. No significant group difference was observed, however, for this measurement proposed to reflect subcortical inhibition. Therefore, the results for Specific Aim 1 did not provide supporting evidence of the proposed mechanisms of tinnitus-related reduced subcortical inhibition, at least as objectively measured based on the paradigm used to record the ABR $\mathrm{V/I_{amp\ ratio}}$ in the current study.

3.2.2: Tinnitus and Cortical Inhibition (CAEP)

The objective of Specific Aim 2 was to determine whether the sensory gating CAEP paradigm, which reflects cortical inhibition of irrelevant auditory information, was sensitive to tinnitus presence or absence at the group level. Based on the proposed poor thalamocortical inhibition of irrelevant subcortical auditory hyperactivity in individuals with tinnitus, it was

expected that the tinnitus group would exhibit reduced sensory gating (poorer inhibition). As described in *Methods* section 2.2.2.4b, sensory gating is quantified by a comparison of the change in amplitude or area from the conditioning to test CAEP where less of a change is indicative of poorer sensory gating (mathematically equal to a larger $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude or area ratio). Therefore, it was hypothesized that the tinnitus group would exhibit larger $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude or area ratios relative to the control group. As a secondary measure which may relate to sensory gating, the $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ latency ratios were also determined within each individual.

Grand mean waveforms in response to the paired click sensory gating paradigm for the tinnitus and control groups are shown in Figure 15. A large P1-N1-P2 complex was observed in both groups in response to the first (conditioning) click, and a reduced P1-N1-P2 complex to the second (test) click, consistent with an inhibited neural response to repetitive stimuli as

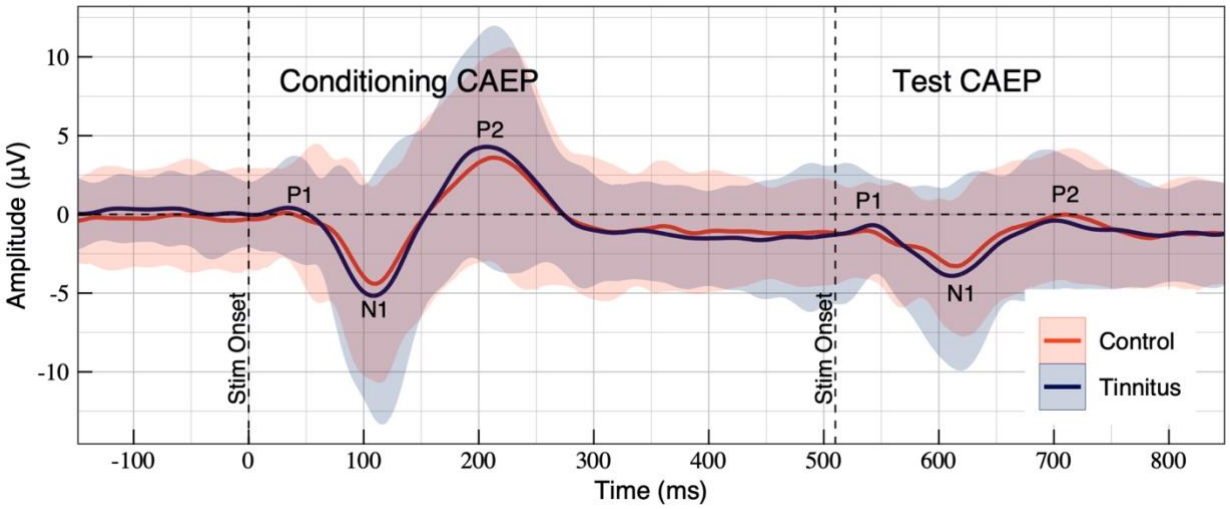


Figure 15. Grand mean sensory gating CAEP waveforms (solid line) ± 1 standard deviation (shading) for the control (orange) and tinnitus (blue) groups. Conditioning stimulus onset at 0 ms and test stimulus onset at 510 ms (vertical dotted lines), followed by the conditioning and test CAEP responses. P1, N1, and P2 component peaks for the conditioning and test CAEPs are labeled.

expected due to sensory gating. Visually, the tinnitus group average conditioning CAEP was larger than the control group in terms of P1-N1 and N1-P2 amplitudes. For the test response, the P1-N1 amplitudes are, again, slightly smaller for the control group but the N1-P2 amplitudes are more similar between groups.

To better depict the sensory gating effect, grand means for the conditioning and test CAEP responses within each group are shown in the same panel, with the response to each click zeroed to stimulus onset in Figure 16. In these grand means, both groups show reduced amplitudes for all component peaks of the test CAEP relative to conditioning CAEP. The magnitude of the sensory gating effect appears similar between groups. At the whole group level, therefore, at least visually the grand mean waveforms are not consistent with tinnitus-related reduced cortical inhibition.

To evaluate the sensory gating effect on an individual level, conditioning and test CAEP amplitudes (P1-N1, N1-P2, $P1_{T-P}$), latencies (P1, N1, and P2), and area (P1-N1-P2) were

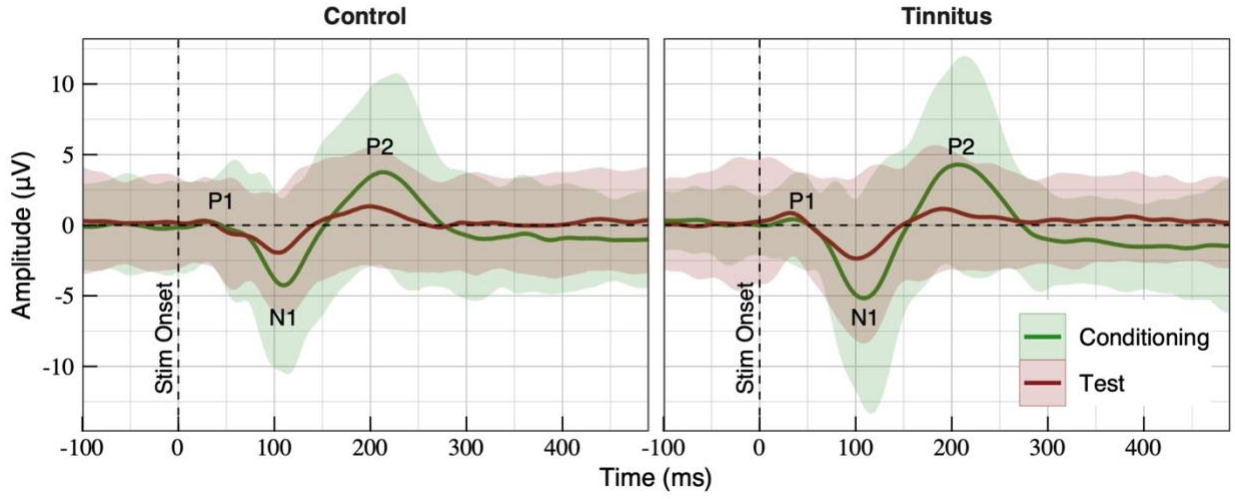


Figure 16. Grand mean CAEP waveforms (solid lines) ± 1 standard deviation (shading) for the control (left panel) and tinnitus (right panel) groups. Conditioning responses are green and test responses are red. Both CAEPs are zeroed relative to stimulus onset, represented by the vertical dotted line at 0 ms. P1, N1, and P2 component peaks are labeled.

identified and measured for each individual's recorded conditioning and test CAEP as described in *Methods* section 2.2.2.4b. In Figure 17A, distributions of P1-N1 and N1-P2 amplitudes are shown within each group and for each stimulus response. As expected, both P1-N1 and N1-P2 amplitudes decreased from conditioning to test CAEP for participants in both groups. The tinnitus group, relative to controls, exhibited larger conditioning CAEP amplitudes and, particularly for the P1-N1 amplitude, larger test CAEP amplitudes. For the tinnitus group, the reduction in N1-P2 amplitude was similar from conditioning to test CAEP (conditioning *M* = 6.75 µV, *SD* = 3.48; test *M* = 2.71 µV, *SD* = 1.46) relative to the control group (conditioning *M* = 5.86

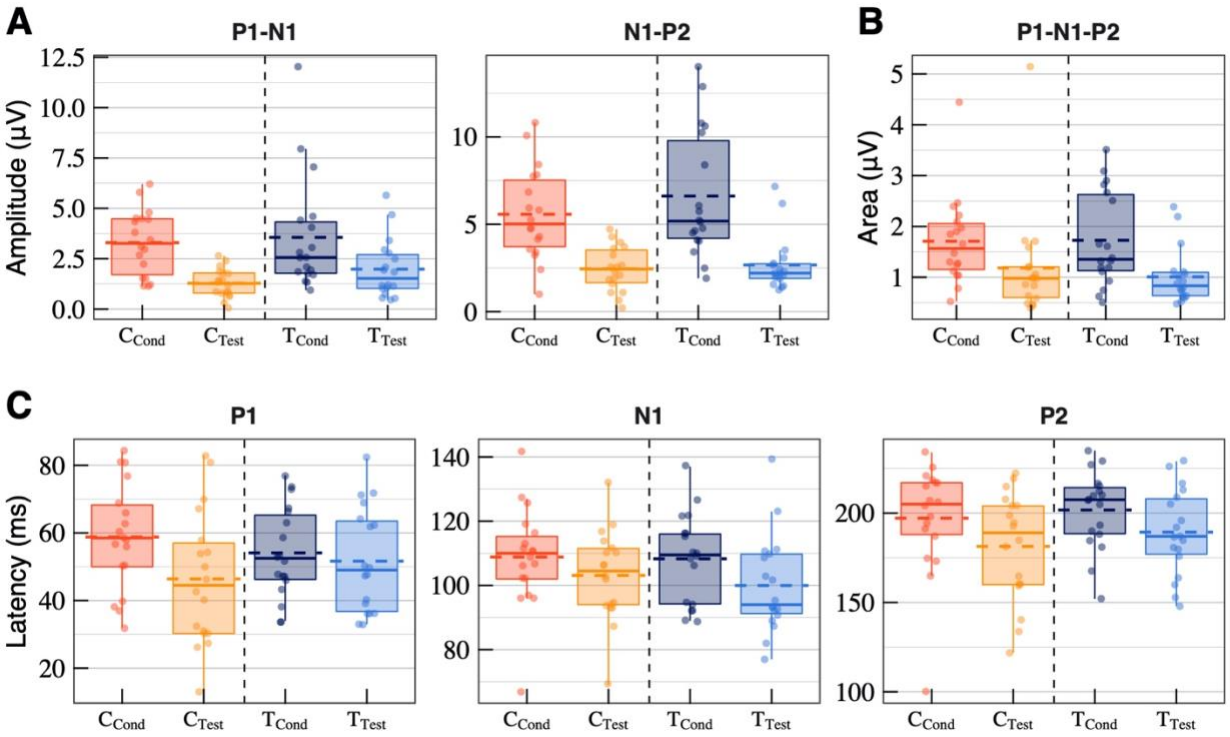


Figure 17. CAEP amplitudes (in A), areas (in B), and latencies (in C) for the control (orange) and tinnitus (blue) groups. Conditioning responses are the darker color (on left for each group) and test responses are the lighter color (on right for each group). Individual participant data points are circles, mean is horizontal dotted line, median is solid horizontal line within boxplot, lower and upper hinges correspond to the first and third quartiles (25th and 75th percentile). Lower and upper whiskers extend to minimum or maximum observed values within 1.5x the first or third quartile. Data points beyond the whiskers are outliers. C_{Cond} = Control, Conditioning; C_{Test} = Control, Test; T_{Cond} = Tinnitus, Conditioning; T_{Test} = Tinnitus, Test.

μV, *SD* =2.53; test *M* = 2.60 μV, *SD* = 1.33). This is consistent with similar sensory gating of the N1-P2 amplitude between groups. By contrast, the reduction in P1-N1 amplitude from conditioning to test for the tinnitus group (conditioning *M* = 3.56 μV, *SD* = 2.86; test *M* = 1.98 μV, *SD* = 1.46) was less than that of the control group (conditioning *M* = 3.30 μV, *SD* = 1.61; test *M* = 1.18 μV, *SD* = 0.776). This is consistent with reduced sensory gating in the tinnitus group relative to the control group, which could be the result of decreased cortical inhibition.

Two way mixed model ANOVAs (group x stimulus) in Table 10 indicated that the effect of stimulus (conditioning vs. test) was significant for the P1-N1 and N1-P2 amplitudes (Figure 17A) and overall P1-N1-P2 area (Figure 17B). That is, across groups, the reduction in amplitude from conditioning to test CAEP was significant. However, there were no significant main effects for group for any of the amplitudes or the overall area. Further, there were no significant interactions between group and stimulus for these outcomes. Although not a main outcome related to sensory gating, P1, N1 and P2 latencies were also measured (shown in Figure 17C) and analyzed by two-way mixed model ANOVAs with results also shown in Table 10. Latencies were significantly shorter for the response to the test stimulus compared to the conditioning stimulus for all peaks. There were no significant group effects or interactions for latencies. The measure of effect size for these two way mixed model ANOVAs was partial eta squared ($\eta 2_p$) which can be interpreted as the proportion of variation accounted for by the effect being tested (Lakens, 2013). For example, for the significant main effect of N1-P2 amplitude, $\eta 2_p = 0.706$, indicating that 70.6% of the variation in N1-P2 amplitude can be accounted for by stimulus (conditioning vs. test).

Table 10. 2x2 RMANOVA results for CAEP amplitudes, area, and latencies. Statistically significant outcomes at $\alpha = 0.05$ indicated with cell shading. Post-hoc tests not shown for main effects as comparisons were between 2 groups. Measure of effect size is partial eta squared ($\eta 2_p$). $P1_{T\text{-}P}$ = trough-to-peak P1 amplitude.

Main Effect: Stimulus (Conditioning, Test)

	Amplitude			Latency		
	F (df)	*p*	$\eta 2_p$	*F* (df)	*p*	$\eta 2_p$
P1-N1	49.9 (1, 34)	<0.001	0.595	-	-	-
N1-P2	81.8 (1, 34)	<0.001	0.706	-	-	-
$P1_{T\text{-}P}$	42.2 (1, 34)	<0.001	0.554	-	-	-
Area	26.2 (1, 34)	<0.001	0.435	-	-	-
P1	-	-	-	8.76 (1, 34)	0.006	0.205
N1	-	-	-	5.37 (1, 34)	0.027	0.136
P2	-	-	-	12.8 (1, 34)	0.001	0.273

Main Effect: Group (Tinnitus, Control)

	Amplitude			Latency		
	F (df)	*p*	$\eta 2_p$	*F* (df)	*p*	$\eta 2_p$
P1-N1	0.92 (1, 34)	0.343	0.026	-	-	-
N1-P2	0.86 (1, 34)	0.360	0.025	-	-	-
$P1_{T\text{-}P}$	0.76 (1, 34)	0.388	0.022	-	-	-
Area	0.09 (1, 34)	0.767	0.003	-	-	-
P1	-	-	-	<0.01 (1, 34)	0.950	<0.001
N1	-	-	-	0.22 (1, 34)	0.644	0.006
P2	-	-	-	0.60 (1, 34)	0.444	0.017

Interaction

	Amplitude			Latency		
	F (df)	*p*	$\eta 2_p$	*F* (df)	*p*	$\eta 2_p$
P1-N1	1.08 (1, 34)	0.305	0.031	-	-	-
N1-P2	0.89 (1, 34)	0.354	0.025	-	-	-
$P1_{T\text{-}P}$	0.11 (1, 34)	0.744	0.003	-	-	-
Area	0.62 (1, 34)	0.436	0.018	-	-	-
P1	-	-	-	3.94 (1, 34)	0.055	0.104
N1	-	-	-	0.18 (1, 34)	0.675	0.005
P2	-	-	-	0.18 (1, 34)	0.676	0.005

The lack of group differences or interactions could relate to inter-individual variability in CAEP amplitudes, areas, and latencies. To quantify whether individuals with tinnitus exhibited reduced cortical inhibition represented by sensory gating, therefore, within individual $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude, area, and latency ratios were determined for each participant. Thus, primary outcome measures for Specific Aim 2 were the amplitude and area $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ sensory gating ratios. Latency $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratios were also analyzed as a secondary within-individual outcome measure that may reflect sensory gating. It was hypothesized that decreased cortical inhibition would result in larger sensory gating ratios, a result of less amplitude/area reduction of the response to the repetitive second (test) stimulus. Distributions of $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude, area, and latency ratios for each group are shown in Figure 18. A ratio of one would indicate no change in the response from the conditioning to the test stimulus, suggestive of abnormal or impaired sensory gating. For each of the ratio measures, data were not normally distributed due to the presence of outliers (all Shapiro-Wilk *p*-values < 0.05). Therefore, the ratios were $\log_{10}$ transformed as described in the *Methods* section 2.2.3. The distribution of individual $\log_{10}$ transformed amplitude, area, and latency $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$

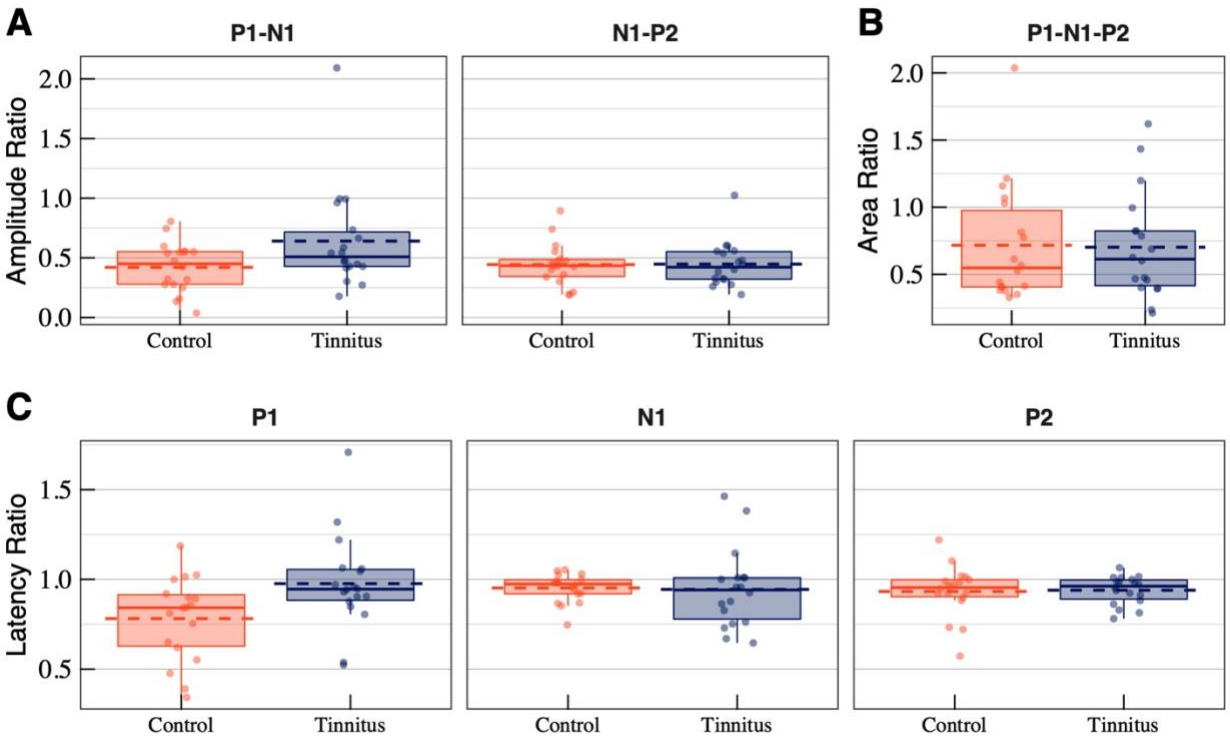


Figure 18. CAEP test/conditioning amplitude ratios (in A), area ratios (in B), and latency ratios (in C) for the control (orange) and tinnitus (blue) groups. Individual participant data points are circles, mean is horizontal dotted line, median is solid horizontal line within boxplot, lower and upper hinges correspond to the first and third quartiles (25^{th} and 75^{th} percentile). Lower and upper whiskers extend to minimum or maximum observed values within 1.5x the first or third quartile. Data points beyond the whiskers are outliers.

ratios are shown in Figure 19A, 19B, and 19C, respectively. As seen in the ABR $\log_{10}(\mathrm{V/I}_{\mathrm{amp\ ratio}})$ data, outliers still existed even after applying a $\log_{10}$ transformation. The $\log_{10}(\mathrm{P1\text{-}N1}_{\mathrm{amp\ ratio}})$, $\log_{10}(\mathrm{N1}_{\mathrm{lat\ ratio}})$, and $\log_{10}(\mathrm{P2}_{\mathrm{lat\ ratio}})$, were still not normally distributed (Shapiro-Wilk $p < 0.05$). Note that due to the $\log_{10}$ transformation, $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratios ranged between approximately -1.5 and 0.25. However, poorer sensory gating was still indicated by a larger $\log_{10}$ transformed $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratio. Further, whereas a raw (not $\log_{10}$ transformed) ratio of one indicated no change in the response from the conditioning to test CAEP, the equivalent $\log_{10}$ transformed ratio was equal to zero. In other words, a $\mathrm{P1\text{-}N1}_{\mathrm{amp\ ratio}} = 1$ is

equivalent to a $\log_{10}(\text{P1-N1}_{\text{amp ratio}})$ = 0. Thus, more negative $\log_{10}$ transformed ratios indicated a greater decrease in amplitude, area, or latency for the test, relative to conditioning response (better sensory gating).

Relative to the other $\log_{10}$ transformed $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratios, the $\log_{10}(\text{P1-N1}_{\text{amp ratio}})$ was on average larger, meaning there was a smaller sensory gating effect, or less of a reduction in P1-N1 amplitude from conditioning to test responses within participants for both groups. The $\log_{10}(\text{P1-N1}_{\text{amp ratio}})$ was larger for the tinnitus group compared to the control group (tinnitus

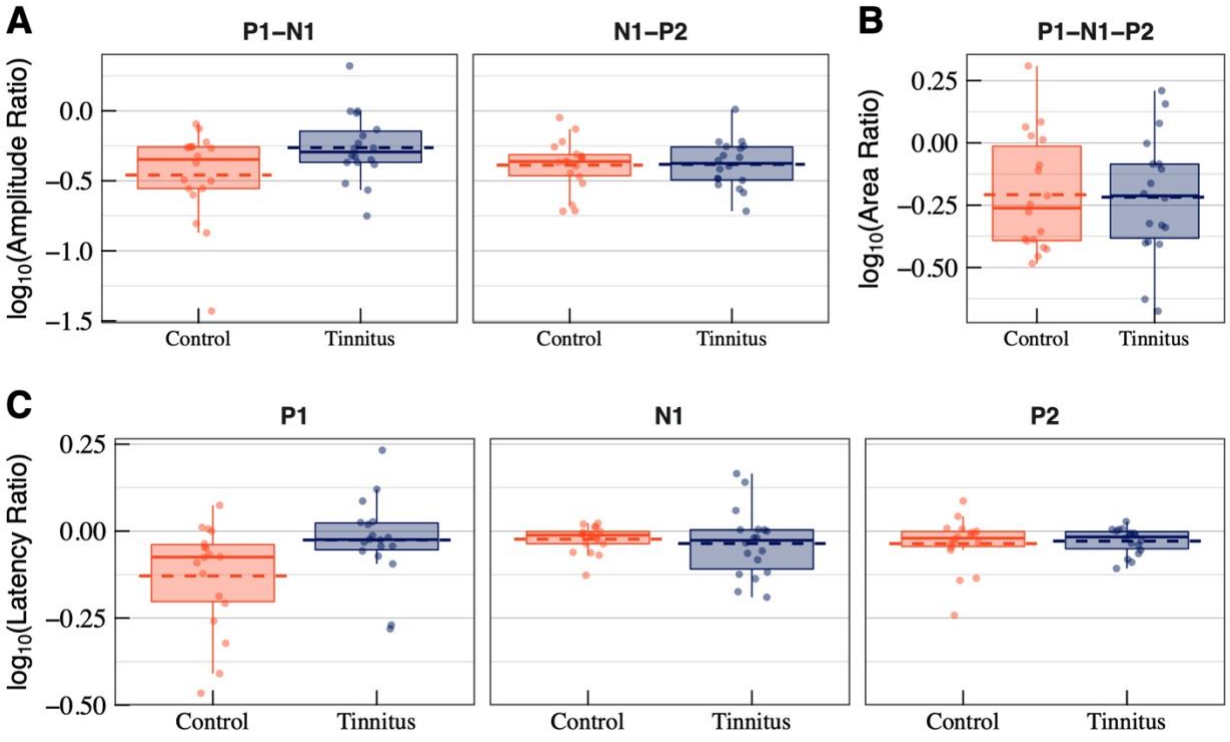


Figure 19. CAEP $\log_{10}(\text{test}/\text{conditioning})$ amplitude ratios (in A), area ratios (in B), and latency ratios (in C) between the control (orange) and tinnitus (blue) groups. Individual participant data points are circles, mean is horizontal dotted line, median is solid horizontal line within boxplot, lower and upper hinges correspond to the first and third quartiles (25^{th} and 75^{th} percentile). Lower and upper whiskers extend to minimum or maximum observed values within 1.5x the first or third quartile. Data points beyond the whiskers are outliers.

M = -0.263, *SD* = 0.244; control *M* = -0.458, *SD* = 0.325). By contrast, $\log_{10}(\text{N1-P2}_{\text{amp ratio}})$ were similar for the tinnitus and control groups (tinnitus *M* = -0.382, *SD* = 0.171; control *M* = -0.388, *SD* = 0.183). Between-group comparisons indicated that there was not a statistically significant difference in either of these $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude ratio measurements between groups (Table 11). However, when comparing the $\log_{10}(\text{P1-N1}_{\text{amp ratio}})$ between groups by independent groups t-test rather than the Mann-Whitney U test, the difference was statistcally significant due to the less conservative statistical consideration of outlier values rather than rank-order [$t(34) = -2.04$, $p = 0.049$, Cohen's $d = -0.681$]. This was the only case in which the parametric and non-parametric statistical outcome differed.

In this study, P1-N1 and N1-P2 amplitudes were used to as outcomes due to being more stable and robust amplitude measures than baseline to peak P1, N1, and P2 amplitudes.

Table 11. $\log_{10}$(test/conditioning) amplitude, area, and latency ratio independent t-test results. Statistically significant outcomes at $\alpha = 0.05$ indicated with cell shading. Mann-Whitney U statistic reported for cases where assumptions of normality and homogeneity of variances were not met. Measure of effect size for *t*-test is Cohen's *d* and for Mann-Whitney U test is rank biserial correlation. $\text{P1}_{\text{T-P}}$ = trough-to-peak P1 amplitude.

Amplitude Ratio				
	Statistic	*df*	*p*	Effect Size
$\log_{10}(\text{P1-N1}_{\text{amp ratio}})$	117	-	0.161	0.278
$\log_{10}(\text{N1-P2}_{\text{amp ratio}})$	-0.103	34	0.919	-0.006
$\log_{10}(\text{P1}_{\text{T-P}_{\text{amp ratio}}})$	158	-	0.913	0.025
Area Ratio				
	Statistic	*df*	*p*	Effect Size
$\log_{10}(\text{P1-N1-P2}_{\text{area ratio}})$	0.123	34	0.903	0.041
Latency Ratio				
	Statistic	*df*	*p*	Effect Size
$\log_{10}(\text{P1}_{\text{lat ratio}})$	-2.28	34	0.029	-0.761
$\log_{10}(\text{N1}_{\text{lat ratio}})$	139	-	0.467	0.145
$\log_{10}(\text{P2}_{\text{lat ratio}})$	162	-	1.00	0.003

However, across the broader sensory gating literature, including in other fields such as psychiatry and psychology research, the most common sensory gating outcome is P1 amplitude (also called P50). As a more direct comparison to the wider sensory gating literature and to further evaluate whether there were any group differences in P1 sensory gating, individual results were re-analyzed as described in *Methods* section 2.2.2.4b to determine trough-to-peak P1 amplitudes (denoted $P1_{T\text{-}P}$) and a $P1_{T\text{-}P_{amp\ ratio}}$ for each participant. Figure 20 shows the distribution of $P1_{T\text{-}P}$ amplitudes, $P1_{T\text{-}P_{amp\ ratio}}$, and $\log_{10}\left(P1_{T\text{-}P_{amp\ ratio}}\right)$. Like the other measures of amplitude, two way mixed model ANOVAs (group x stimulus) in Table 10 indicated that the effect of stimulus (conditioning vs. test) was significant for the $P1_{T\text{-}P}$ amplitude such that amplitude significantly reduced from conditioning to test CAEP. However, there was no significant main effect of group or interaction between group and stimulus. For the tinnitus group, the reduction in amplitude from the conditioning to test CAEP (conditioning *M* = 1.23 µV, *SD* = 0.564; test *M* = 0.746 µV, *SD* = 0.301) was similar to the control group (conditioning *M*

= 1.39 µV, *SD* = 0.670; test *M* = 0.850 µV, *SD* = 0.402). This indicated similar sensory gating between groups based on this measure. This was supported by a similar $\mathrm{P1}_{\mathrm{T\text{-}P}_{\mathrm{amp\ ratio}}}$ between the tinnitus and control group. However, as this measure, like the other $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude ratios, was not normally distributed (*W* = 0.864, *p* < 0.001), the $\log_{10}\left(\mathrm{P1}_{\mathrm{T\text{-}P}_{\mathrm{amp\ ratio}}}\right)$ was assessed [notably, outliers in both groups remained and this measure was still not normally distributed (*W* = 0.917, *p* = 0.01)]. Supporting the similar change in $\mathrm{P1}_{\mathrm{T\text{-}P}}$ amplitude from conditioning to test CAEP observed between groups, there was no significant difference in $\log_{10}\left(\mathrm{P1}_{\mathrm{T\text{-}P}_{\mathrm{amp\ ratio}}}\right)$ between the tinnitus and control groups (tinnitus *M* = -0.220, *SD* = 0.252; control *M* = -0.215, *SD* = 0.216) (Table 11).

The $\log_{10}(\mathrm{P1\text{-}N1\text{-}P2}_{\mathrm{area\ ratio}})$, the ratio of the area of the entire waveform complex, was also similar between groups as shown in Figure 19B, and there was not a significant difference between the $\log_{10}(\mathrm{P1\text{-}N1\text{-}P2}_{\mathrm{area\ ratio}})$ for the tinnitus and control group (tinnitus *M* = -0.218,

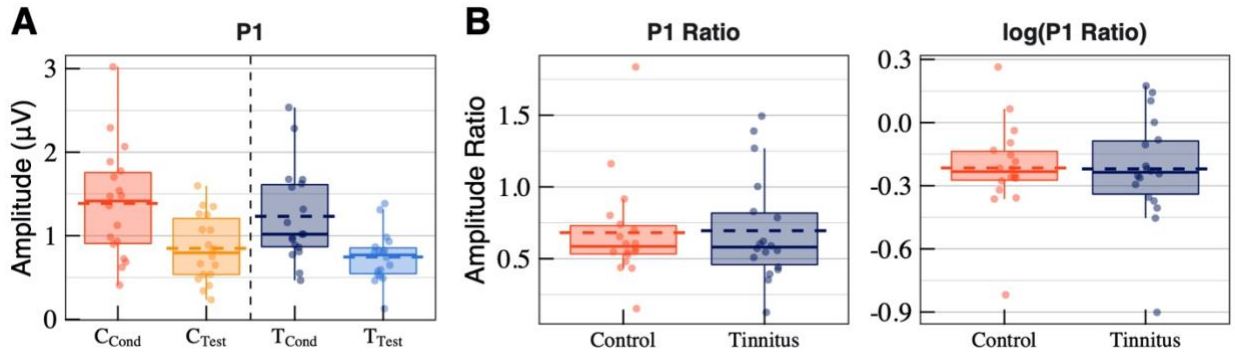


Figure 20. CAEP filtered from 10-50 Hz, preceding trough-to-peak P1 (denoted in-text $\mathrm{P1}_{\mathrm{T\text{-}P}}$) amplitude response metrics for the control (orange) and tinnitus (blue) groups. In (A), conditioning P1 amplitude are the darker color (on left for each group) and test P1 amplitude are the lighter color (on right for each group). In (B), raw test/conditioning amplitude ratios and $\log_{10}$ transformed amplitude ratios. Individual participant data points are circles, mean is horizontal dotted line, median is solid horizontal line within boxplot, lower and upper hinges correspond to the first and third quartiles (25^{th} and 75^{th} percentile). Lower and upper whiskers extend to minimum or maximum observed values within 1.5x the first or third quartile. Data points beyond the whiskers are outliers. $\mathrm{C}_{\mathrm{Cond}}$ = Control, Conditioning; $\mathrm{C}_{\mathrm{Test}}$ = Control, Test; $\mathrm{T}_{\mathrm{Cond}}$ = Tinnitus, Conditioning; $\mathrm{T}_{\mathrm{Test}}$ = Tinnitus, Test.

SD = 0.246; control *M* = -0.208, *SD* = 0.231) (Table 11). Regarding latency, the tinnitus group exhibited similar $\log_{10}(\text{N1}_{\text{lat ratio}})$ and $\log_{10}(\text{P2}_{\text{lat ratio}})$ (N1 *M* = -0.036, *SD* = 0.097; P2 *M* = -0.029, *SD* = 0.037) relative to the control group (N1 *M* = -0.023, *SD* = 0.038; P2 *M* = -0.036, *SD* = 0.074). However, the tinnitus group did exhibit a larger $\log_{10}(\text{P1}_{\text{lat ratio}})$ relative to controls (tinnitus *M* = -0.026, *SD* = 0.119; control *M* = -0.129, *SD* = 0.150). Only the $\log_{10}(\text{P1}_{\text{lat ratio}})$ was significantly different between groups such that tinnitus group had a larger $\log_{10}(\text{P1}_{\text{lat ratio}})$, the effect size was of medium strength (Table 11). As the sensory gating effect is traditionally indicated by measures of amplitude or area, this secondary outcome measure might indicate poorer sensory gating in the tinnitus group, as described *Discussion* section 4.2.

In summary, both groups exhibited the expected sensory gating response such that amplitude and area reductions were observed from conditioning to test CAEP. Although some trends were observed, such as larger mean conditioning CAEP amplitudes in the tinnitus group, statistical results showed that none of the absolute measures of conditioning and test CAEP amplitude, latency, and area distinguished between the tinnitus and control groups. Within-individual sensory gating $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude and area ratios, the primary outcomes for Specific Aim 2, showed some trends for larger ratios in the tinnitus group, specifically the $\log_{10}(\text{P1-N1}_{\text{amp ratio}})$, a possible indication of poorer sensory gating. However, none of the amplitude and area $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratio group differences reached statistical significance. There was a significant difference in the $\log_{10}(\text{P1}_{\text{lat ratio}})$, such that the tinnitus group exhibited significantly larger $\log_{10}(\text{P1}_{\text{lat ratio}})$. This secondary outcome measure may be indicative of poorer sensory gating related to tinnitus. Taken together, the results for Specific Aim 2 did not

strongly support the hypothesis that individuals with tinnitus would exhibit poorer cortical inhibition represented by poorer sensory gating (larger $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude or area ratios).

Altogether, neither subcortical (ABR) nor cortical (CAEP) outcomes strongly supported the hypotheses, that individuals with tinnitus would exhibit reduced subcortical and cortical inhibition represented by larger ABR $\text{V/I}_{\text{amp ratio}}$ and $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude or area ratios. It is possible that other tinnitus-related characteristics, such as hearing loss or noise exposure history, had more influence on the ABR and CAEP outcomes than the presence of tinnitus alone. In *Results* section 3.2.3, outcomes are discussed for the analyses used to address Specific Aim 3, which was to estimate the extent to which other individual characteristics beyond the presence of tinnitus alone predicted the subcortical ABR and cortical CAEP outcomes related to inhibition.

3.2.3: Other Predictors of Primary AEP Outcomes

One of the challenges in tinnitus and AEP research is that multiple individual characteristics are likely to affect the dependent variable. It was hypothesized that the presence of tinnitus would affect the primary outcome measures of ABR $\text{V/I}_{\text{amp ratio}}$ and $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude and area ratios, consistent with the theory of reduced inhibition at the subcortical and cortical levels of the auditory pathway. However, it is well known that other factors such as age and hearing thresholds could influence AEP outcomes as well and, consequently, could contribute to the presence or lack of group differences in these AEP outcomes. The purpose of Specific Aim 3, therefore, was to estimate the extent to which five variables including tinnitus, age, peripheral hearing thresholds ($\text{PTA}_{\text{0.25-20 kHz}}$), noise exposure

history (total NEUs), and SPIN (SNR-50) predicted the objective AEP outcomes hypothesized to reflect reduced subcortical (ABR $\mathrm{V/I_{amp\ ratio}}$) or cortical ($\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratios) inhibition across all participants in the study.

As described in the *Methods* section 2.2.3, multiple linear regression models were used to assess the extent to which each of the five predictor variables influenced the primary measures of inhibition (ABR $\mathrm{V/I_{amp\ ratio}}$ and $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratios). For each predictor variable, the Pearson correlation between that predictor and the AEP outcome measure was determined, along with the best fit simple linear regression model. For the multiple linear regression analysis, comparisons were made between a regression model that included all predictor variables *except* for the predictor of interest (reduced model) with a regression model that included all predictor variables *with the addition of* the predictor of interest (overall model). If the predictor of interest substantially influenced the dependent variable there would be a significant reduction in model error with the overall model, relative to the reduced model. As such, the test statistics associated with each predictor variable included the proportional reduction in error (*PRE*) and the associated *F*-statistic. If the *PRE* or *F* for that variable exceeded associated critical values ($p < 0.05$) then that predictor was considered a significant influence on the dependent outcome measure of inhibition. In addition, the partial correlation ($\sqrt{\mathrm{PRE}}$) represented the extent to which the variable of interest and the outcome correlated after "partialing out" effects of the other predictor variables. Therefore, predictors with significant *PRE* or *F*-statistics were interpreted as significant influencers on the dependent variable and

predictors with larger $\sqrt{\mathrm{PRE}}$ were interpreted having a greater relationship with the dependent variable compared to predictors with smaller $\sqrt{\mathrm{PRE}}$.

For the subcortical outcomes related to inhibition, these analyses were applied to the primary outcome of $\log_{10}\left(\mathrm{V/I}_{\mathrm{amp\ ratio}}\right)$. For the cortical outcomes related to inhibition, analyses were conducted for the primary outcome of $\log_{10}\left(\mathrm{P1\text{-}N1}_{\mathrm{amp\ ratio}}\right)$ and the secondary outcome of $\log_{10}(\mathrm{P1}_{\mathrm{lat\ ratio}})$. These specific dependent variables were selected because previous research (reviewed in *Introduction* section 1.3) has focused on the $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ and for the CAEP measures these outcomes exhibited the largest group differences. Data trends within and across groups may provide information about whether tinnitus in combination with other characteristics, or other characteristics (and not tinnitus), influenced outcomes that reflect inhibition. As previously discussed, the $\log_{10}$ transformation of all dependent variables were assessed due to violations of assumptions of normality.

3.2.3.1: Predictors of Subcortical AEP Outcomes

Scatterplots of the relationships between the primary subcortical outcome measure of interest, $\log_{10}(\mathrm{V/I}_{\text{amp ratio}})$, and the predictor variables of age, $\mathrm{PTA}_{0.25\text{-}20\ \mathrm{kHz}}$, SNR-50, and NEUs are shown in Figure 21 with regression line fits for each group separately and for all participants across both groups. The associated correlation coefficients, *p*-values, and regression equations are in Table 12. Across both groups, as age, $\mathrm{PTA}_{0.25\text{-}20\ \mathrm{kHz}}$, and NEUs increased, the $\log_{10}(\mathrm{V/I}_{\text{amp ratio}})$ also increased. SNR-50 showed the opposite trend and decreased with increases in the $\log_{10}(\mathrm{V/I}_{\text{amp ratio}})$. However, correlations were weak (*r* = 0.11

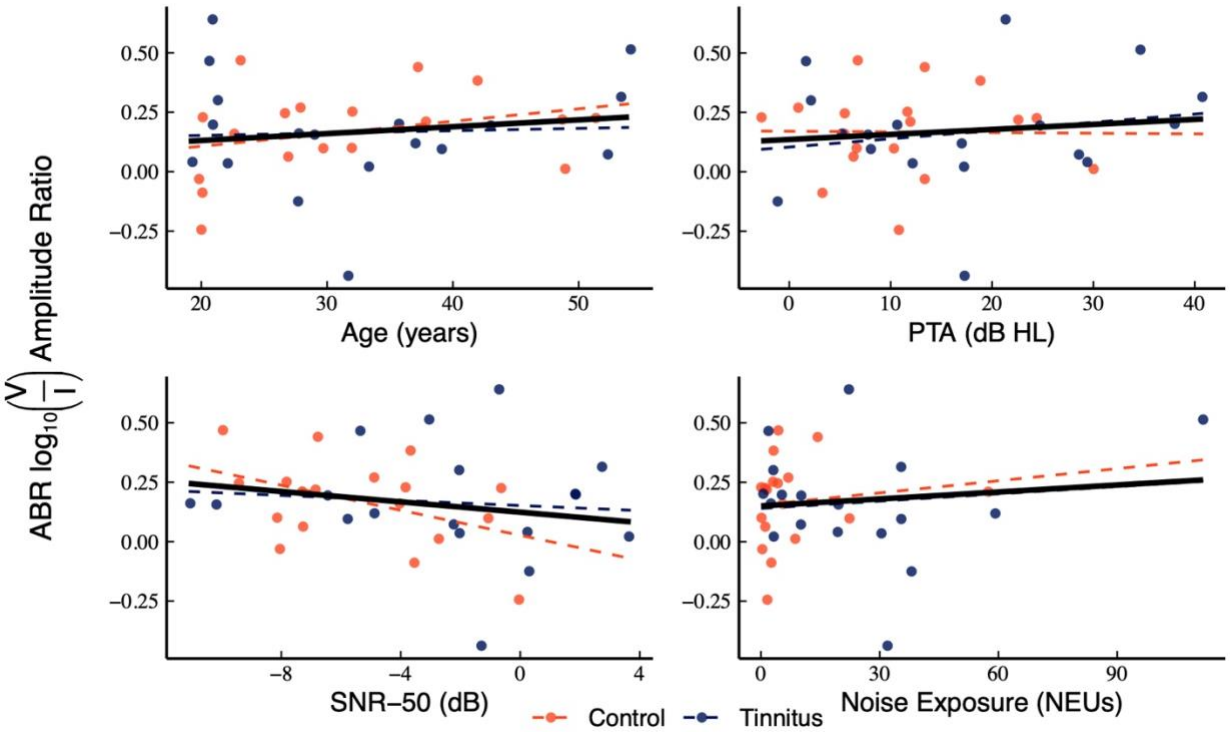


Figure 21. ABR $\log_{10}(\mathrm{V/I}_{\text{amp ratio}})$ distributions for the control (orange) and tinnitus (blue) groups by age, pure tone average (PTA), SNR-50, and noise exposure units (NEUs). Simple linear regression lines shown across all participants (solid black line), and for the control (dotted orange) and tinnitus groups (dotted blue). Associated Pearson correlations and linear regression equations are in Table 12.

to 0.44) and statistically insignificant, suggesting that none of the variables were strongly related to $\log_{10}(\mathrm{V/I_{amp\ ratio}})$.

The overall regression model for the ABR $\log_{10}(\mathrm{V/I_{amp\ ratio}})$, which included all five predictor variables of interest, did not statistically significantly predict $\log_{10}(\mathrm{V/I_{amp\ ratio}})$ outcomes [r^2_{adj} = -0.058, *RMSE* = 0.199, *F*(5,30) = 0.62, *p* = 0.689]. Regression model outcomes for *PRE*, *F*, and $\sqrt{\mathrm{PRE}}$ for the predictive influence of SNR-50, $\mathrm{PTA_{0.25\text{-}20\ kHz}}$, NEUs, age, and tinnitus status on the $\log_{10}(\mathrm{V/I_{amp\ ratio}})$ are reported in Table 13, with predictor variables ordered from largest to smallest $\sqrt{\mathrm{PRE}}$ (largest to smallest partial correlation). None of the *PRE* or associated *F*-statistics exceeded associated critical values and therefore were not significant influencers on the trends observed in the $\log_{10}(\mathrm{V/I_{amp\ ratio}})$. Comparing across variables tested, the two strongest $\sqrt{\mathrm{PRE}}$ were for SNR-50 and $\mathrm{PTA_{0.25\text{-}20\ kHz}}$, suggesting that trends observed in the $\log_{10}(\mathrm{V/I_{amp\ ratio}})$ were best predicted by an individual's SPIN and hearing thresholds relative to the other variables tested. However, the insignificant *PRE* and *F*-statistic

Table 12. For each predictor variable of interest, Pearson correlations and linear regression equations with ABR $\log_{10}(\mathrm{V/I_{amp\ ratio}})$. Statistics correspond to the plots in Figure 20.

Pearson Correlations				
	Age	PTA	SNR-50	NEUs
All Participants	R = 0.15, p = 0.389	R = 0.11, p = 0.510	R = -0.2, p = 0.240	R = 0.11, p = 0.540
Control	R = 0.30, p = 0.220	R = -0.01, p = 0.960	R = -0.44, p = 0.070	R = 0.13, p = 0.620
Tinnitus	R = 0.03, p = 0.850	R = 0.19, p = 0.460	R = -0.09, p = 0.720	R = 0.12, p = 0.650
Linear Regression Equations				
	Age	PTA	SNR-50	NEUs
All Participants	y = 0.07 + 0.003 x	y = 0.14 + 0.002 x	y = 0.42 - 0.011 x	y = 0.15 + 0.001 x
Control	y = 0.002 + 0.005 x	y = 0.17 – 0.0003 x	y = 0.03 - 0.03 x	y = 0.15 + 0.002 x
Tinnitus	y = 0.13 + 0.001 x	y = 0.1 + 0.004 x	y = 0.15 - 0.005 x	y = 0.14 + 0.001 x

for SNR-50 and $\mathrm{PTA}_{0.25\text{-}20\ \mathrm{kHz}}$ highlight the weak relationships. Further, NEUs, tinnitus status, and age were weak predictors of the $\log_{10}(\mathrm{V/I}_{\mathrm{amp\ ratio}})$. Taken together, tinnitus, NEUs, $\mathrm{PTA}_{0.25\text{-}20\ \mathrm{kHz}}$, SNR-50, and age all were poor predictors of the trends observed in the $\log_{10}(\mathrm{V/I}_{\mathrm{amp\ ratio}})$.

Table 13. Proportional reduction in error (*PRE*), associated *F*-statistic, and partial PRE ($\sqrt{\mathrm{PRE}}$) calculated based on the overall model with $\log_{10}(\mathrm{V/I}_{\mathrm{amp\ ratio}})$ as the dependent variable for each predictor variable of interest. Variables are ordered from greatest to lowest $\sqrt{\mathrm{PRE}}$.

	PRE	*F*-statistic	$\sqrt{\mathrm{PRE}}$
SNR-50	0.067	2.24	0.259
PTA	0.019	0.595	0.137
NEUs	0.003	0.100	0.057
Tinnitus	<0.001	0.014	0.021
Age	<0.001	<0.001	0.004

3.2.3.2: Predictors of Cortical AEP Outcomes

Scatterplots of the relationship between the primary outcome measure of sensory gating, the CAEP $\log_{10}(\mathrm{P1\text{-}N1}_{\mathrm{amp\ ratio}})$ with the predictor variables of age, $\mathrm{PTA}_{0.25\text{-}20\ \mathrm{kHz}}$, SNR-50, and NEUs are shown in Figure 22. Again, all predictor variables were weakly correlated with the CAEP outcome measure (r = 0.001 to 0.44). Although in the scatterplot it appears that the control group showed a trend for increasing $\log_{10}(\mathrm{P1\text{-}N1}_{\mathrm{amp\ ratio}})$ with increasing SNR-50 and decreasing $\log_{10}(\mathrm{P1\text{-}N1}_{\mathrm{amp\ ratio}})$ with decreasing NEUs, none of these relationships were significant (Table 14). The weak observable relationships were likely primarily driven by outliers in the data. Overall, age, $\mathrm{PTA}_{0.25\text{-}20\ \mathrm{kHz}}$, SNR-50, and NEUs were not significantly correlated with $\log_{10}(\mathrm{P1\text{-}N1}_{\mathrm{amp\ ratio}})$.

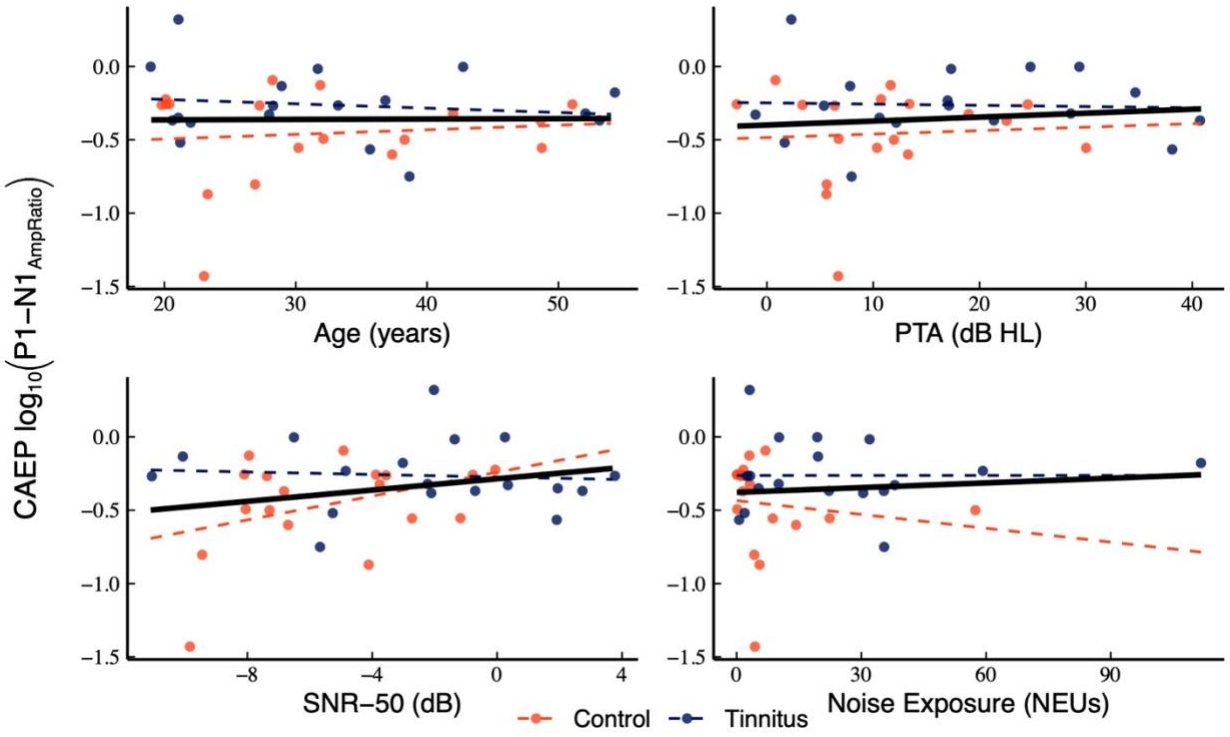


Figure 22. CAEP $\log_{10}(\text{P1-N1}_{\text{amp ratio}})$ distributions for the control (orange) and tinnitus (blue) groups by age, pure tone average (PTA), SNR-50, and noise exposure units (NEUs). Simple linear regression lines shown across all participants (solid black line), and for the control (dotted orange) and tinnitus groups (dotted blue). Associated Pearson correlations and linear regression equations are in Table 14.

Table 14. For each predictor variable of interest, Pearson correlations and linear regression equations with ABR $\log_{10}(\text{P1-N1}_{\text{amp ratio}})$. Statistics correspond to the plots in Figure 21.

Pearson Correlations				
	Age	PTA	SNR-50	NEUs
All Participants	R = 0.001, p = 0.950	R = 0.10, p = 0.560	R = 0.25, p = 0.140	R = 0.08, p = 0.640
Control	R = 0.10, p = 0.690	R = 0.06, p = 0.810	R = 0.38, p = 0.120	R = -0.13, p = 0.600
Tinnitus	R = -0.14, p = 0.570	R = -0.44, p = 0.860	R = -0.07, p = 0.770	R = <0.001, p = 1.00
Linear Regression Equations				
	Age	PTA	SNR-50	NEUs
All Participants	y = -0.37 + 0.0003 x	y = -0.40 + 0.003 x	y = -0.29 + 0.019 x	y = -0.38 + 0.001 x
Control	y = -0.56 + 0.003 x	y = -0.48 + 0.002 x	y = -0.24 + 0.041 x	y = -0.43 - 0.003 x
Tinnitus	y = -0.17 - 0.003 x	y = -0.25 - 0.001 x	y = -0.27 - 0.004 x	y = -0.26 + 0.000 x

The overall regression model for the $\log_{10}(\text{P1-N1}_{\text{amp ratio}})$, which included all five predictor variables, was not statistically significant [r^2_{adj} = -0.013, *RMSE* = 0.276, *F*(5,30) = 0.91, *p* = 0.489]. Regression model outcomes for *PRE*, *F*, and $\sqrt{\text{PRE}}$ for the predictive influence of SNR-50, $\text{PTA}_{\text{0.25-20 kHz}}$, NEUs, age, and tinnitus status on the $\log_{10}(\text{P1-N1}_{\text{amp ratio}})$ are reported in Table 15, with variables ordered in the table from largest to smallest $\sqrt{\text{PRE}}$. Like the ABR $\log_{10}(\text{V/I}_{\text{amp ratio}})$, none of the *PRE* or associated *F*-statistics reached statistical significance for any of the predictor variables suggesting that none of the individual characteristics tested significantly influenced the $\log_{10}(\text{P1-N1}_{\text{amp ratio}})$. However, comparing across variables, the strongest $\sqrt{\text{PRE}}$ was for tinnitus presence, suggesting that trends observed in the $\log_{10}(\text{P1-N1}_{\text{amp ratio}})$ were best (although not significantly) predicted by whether or not an individual has tinnitus. Further, although the *PRE* and *F*-statistics for the tinnitus variable were not significant, a simple linear regression of the predictive influence of tinnitus alone on the $\log_{10}(\text{P1-N1}_{\text{amp ratio}})$, equivalent to a conventional t-test, was statistically significant [r^2_{adj} = 0.109, *RMSE* = 0.279, *F*(1,34) = 4.18, *p* = 0.049]. Therefore, tinnitus presence exhibited a weak relationship with the primary outcome measure of sensory gating such that individuals with tinnitus were more likely to exhibit larger $\log_{10}(\text{P1-N1}_{\text{amp ratio}})$ reflecting poorer sensory gating and poorer cortical inhibition. The β associated with tinnitus was equal to 0.196 (*p* = 0.049) indicating that an individual with tinnitus was predicted to exhibit a $\log_{10}(\text{P1-N1}_{\text{amp ratio}})$ that was 0.196 larger than an individual without tinnitus. The other predictor variables of interest including age, $\text{PTA}_{\text{0.25-20 kHz}}$, SNR-50, and NEUs were unrelated to outcomes observed in the $\log_{10}(\text{P1-N1}_{\text{amp ratio}})$.

Table 15. Proportional reduction in error (*PRE*), associated *F*-statistic, and partial PRE ($\sqrt{\text{PRE}}$) calculated based on the overall model with $\log_{10}(\text{P1-N1}_{\text{amp ratio}})$ as the dependent variable for each predictor variable of interest. Variables are ordered from greatest to lowest $\sqrt{\text{PRE}}$.

	PRE	*F*-statistic	$\sqrt{\text{PRE}}$
Tinnitus	0.070	2.34	0.265
SNR-50	0.022	0.706	0.149
PTA	0.003	0.091	0.054
NEUs	0.002	0.050	0.040
Age	0.001	0.041	0.036

Scatterplots of the relationships between the secondary CAEP outcome, $\log_{10}(\text{P1}_{\text{lat ratio}})$ and age, $\text{PTA}_{\text{0.25-20 kHz}}$, SNR-50, and NEUs are shown in Figure 23. Across all participants, as age, $\text{PTA}_{\text{0.25-20 kHz}}$, SNR-50, and NEUs increased, the $\log_{10}(\text{P1}_{\text{lat ratio}})$ increased. There was a medium strength relationship between age and the $\log_{10}(\text{P1}_{\text{lat ratio}})$ in the control group (r = 0.56, p = 0.017). This significant relationship for the control group indicated that only for participants without tinnitus, as age increased, the relative change in latency between conditioning and test responses decreased. The remaining correlations were weak (r = -0.02 to 0.41) and not statistically significant (Table 16).

The overall regression model for the $\log_{10}(\text{P1}_{\text{lat ratio}})$, which included all five predictor variables, was statistically significant [r^2_{adj} = 0.201, *RMSE* = 0.117, $F(5,30)$ = 2.76, p = 0.036], indicating that SNR-50, $\text{PTA}_{\text{0.25-20 kHz}}$, NEUs, age, and tinnitus status together significantly predicted outcomes in $\log_{10}(\text{P1}_{\text{lat ratio}})$. Regression model outcomes for *PRE*, *F*, and $\sqrt{\text{PRE}}$ for the predictive influence of SNR-50, $\text{PTA}_{\text{0.25-20 kHz}}$, NEUs, age, and tinnitus status on the $\log_{10}(\text{P1}_{\text{lat ratio}})$ are reported in Table 17, ordered from largest to smallest $\sqrt{\text{PRE}}$. The *PRE* for age and tinnitus was statistically significant indicating that an individual's age and tinnitus status exhibited influence on the trends observed in the $\log_{10}(\text{P1}_{\text{lat ratio}})$ such that older individuals and those with tinnitus could be expected to exhibit larger $\log_{10}(\text{P1}_{\text{lat ratio}})$. In the

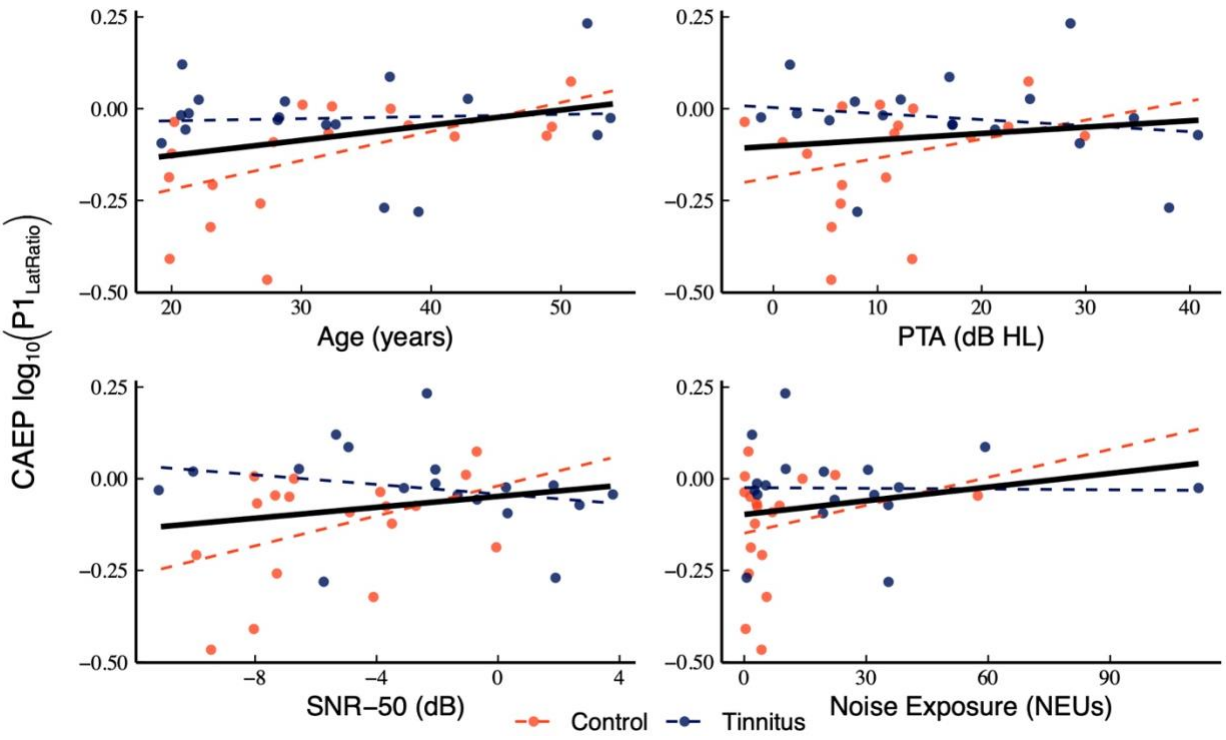


Figure 23. CAEP $\log_{10}(\mathrm{P1}_{\mathrm{lat\ ratio}})$ distributions for the control (orange) and tinnitus (blue) groups by age, pure tone average (PTA), SNR-50, and noise exposure units (NEUs). Simple linear regression lines shown across all participants (solid black line), and for the control (dotted orange) and tinnitus groups (dotted blue). Associated Pearson correlations and linear regression equations are in Table 16.

context of the overall model, the β associated with tinnitus was equal to 0.119 (p = 0.027) and the β associated with age was equal to 0.008 (p = 0.010) indicating that, with all other predictor variables held equal, an individual with tinnitus was predicted to exhibit a $\log_{10}(\mathrm{P1}_{\mathrm{lat\ ratio}})$ that was 0.119 larger than an individual without tinnitus and with each year of increasing age, the $\log_{10}(\mathrm{P1}_{\mathrm{lat\ ratio}})$ was predicted to increase 0.008. None of the other *PRE* nor the *F*-statistics reached statistical significance. Comparing across variables, age exhibited the largest $\sqrt{\mathrm{PRE}}$, which was followed by tinnitus status. The significant *PRE* and relatively large $\sqrt{\mathrm{PRE}}$ indicate that an individual's age best predicted $\log_{10}(\mathrm{P1}_{\mathrm{lat\ ratio}})$ and this was followed by tinnitus status.

However, the similar $\sqrt{\text{PRE}}$ indicated a similar effect size between the two. $\text{PTA}_{0.25\text{-}20\ \text{kHz}}$, SNR-50, and NEUs did not significantly influence $\log_{10}(\text{P1}_{\text{lat ratio}})$.

Table 16. For each predictor variable of interest, Pearson correlations and linear regression equations with ABR $\log_{10}(\text{P1}_{\text{lat ratio}})$. Statistics correspond to the plots in Figure 22. Statistical significance at $\alpha = 0.05$ indicated with cell shading.

Pearson Correlations				
	Age	PTA	SNR-50	NEUs
All Participants	R = 0.32, p = 0.060	R = 0.14, p = 0.430	R = 0.20, p = 0.240	R = 0.20, p = 0.250
Control	R = 0.56, p = 0.017	R = 0.29, p = 0.240	R = 0.41, p = 0.090	R = 0.23, p = 0.360
Tinnitus	R = 0.06, p = 0.820	R = -0.18, p = 0.480	R = -0.23, p = 0.360	R = -0.02, p = 0.950
Linear Regression Equations				
	Age	PTA	SNR-50	NEUs
All Participants	y = -0.21 + 0.004 x	y = -0.1 + 0.002 x	y = -0.05 + 0.007 x	y = -0.10 + 0.001 x
Control	y = -0.38 + 0.008 x	y = -0.19 + 0.005 x	y = -0.02 + 0.020 x	y = -0.15 + 0.003 x
Tinnitus	y = -0.05 + 0.001 x	y = 0.003 – 0.002 x	y = -0.042 - 0.007 x	y = -0.02 – 0.000 x

Table 17. Proportional reduction in error (*PRE*), associated *F*-statistic, and partial PRE ($\sqrt{\text{PRE}}$) calculated based on the overall model with CAEP $\log_{10}(\text{P1}_{\text{lat ratio}})$ as the dependent variable for each predictor variable of interest. Variables are ordered from greatest to lowest $\sqrt{\text{PRE}}$. Statistical significance at $\alpha = 0.05$ indicated with cell shading.

	PRE	*F*-statistic	$\sqrt{\text{PRE}}$
Age	0.201	7.80	0.448
Tinnitus	0.153	5.61	0.391
PTA	0.116	4.05	0.340
SNR-50	0.041	1.32	0.202
NEUs	0.004	0.136	0.066

4.0: Discussion

The aims of the study were to objectively determine and quantify whether individuals with constant tinnitus, relative to non-tinnitus controls, exhibited evidence of reduced inhibition at the subcortical or cortical levels of the auditory pathway, and to estimate the extent to which tinnitus presence and tinnitus-related participant characteristics predicted these objective evoked potential outcomes. For Specific Aims 1 and 2, we hypothesized that individuals with tinnitus would exhibit reduced subcortical and cortical inhibition, represented by a larger ABR $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ and larger sensory gating $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude or area ratios, respectively. For Specific Aim 3, we hypothesized that the presence of constant tinnitus would have the strongest relationship to ABR and CAEP outcomes, but that age, hearing loss, noise exposure history and speech perception in noise (SPIN) performance would contribute to the prediction of these hypothesized measures of reduced subcortical and cortical inhibition.

In summary, contrary to hypotheses there was no evidence of group differences in these objective measures thought to relate to reduced subcortical or cortical inhibition, however, some individuals with tinnitus exhibited a large $\mathrm{P1\text{-}N1}_{\mathrm{amp\ ratio}}$ and $\mathrm{P1}_{\mathrm{T\text{-}P}_{\mathrm{amp\ ratio}}}$ and the tinnitus group overall had a significantly larger $\mathrm{P1}_{\mathrm{lat\ ratio}}$, a secondary outcome of interest which may relate to sensory gating and reduced cortical inhibition. Additionally, at the subcortical level, the $\log_{10}\left(\mathrm{V/I}_{\mathrm{amp\ ratio}}\right)$ was best predicted (although not significantly) by SPIN, not tinnitus. The $\log_{10}\left(\mathrm{V/I}_{\mathrm{amp\ ratio}}\right)$ was also not significantly influenced by age, noise exposure history, or hearing loss. By contrast, at the cortical level, tinnitus significantly predicted the primary outcome measure of sensory gating, the $\log_{10}\left(\mathrm{P1\text{-}N1}_{\mathrm{amp\ ratio}}\right)$ based on a simple linear

regression model including only the tinnitus variable. Further, tinnitus also significantly predicted the secondary CAEP outcome measure which may be related to sensory gating, the $\log_{10}(\mathrm{P1}_{\mathrm{lat\ ratio}})$, however, this secondary outcome measure was best predicted by an individual's age based on the proportional reduction in error (*PRE*). Noise exposure history, hearing loss, nor SPIN significantly influenced the $\log_{10}(\mathrm{P1\text{-}N1}_{\mathrm{amp\ ratio}})$ or the $\log_{10}(\mathrm{P1}_{\mathrm{lat\ ratio}})$.

4.1: Subcortical Inhibition Outcomes: ABR

As reviewed in the *Introduction*, animal models have supported that reduced cochlear output triggers subcortical neural plasticity, which manifests as a decrease in inhibition and subcortical hyperactivity within the cochlear nucleus (CN) of the auditory brainstem. It was therefore hypothesized that reduced ABR wave I amplitudes would be consistent with reduced cochlear output and increased wave V amplitudes would be consistent with subcortical brainstem hyperactivity, leading to larger $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ in individuals with tinnitus. However, contrary to the hypothesis, there were no significant differences in absolute ABR amplitudes, latencies, or the $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ between the group of individuals with constant tinnitus and non-tinnitus controls. These negative results may suggest that at the subcortical level, decreased inhibition is not associated with the perception of tinnitus, at least as reflected in ABR outcomes.

Other studies in the literature have reported larger $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ (sometimes reported as a smaller $\mathrm{I/V}_{\mathrm{amp\ ratio}}$) in tinnitus groups relative to non-tinnitus controls (Bramhall et al., 2018; Gu et al., 2012; Schaette & McAlpine, 2011; Valderrama et al., 2018), but they have varied in whether both wave I and V amplitudes were significantly different between groups. Gu et al. (2012) identified both a significantly smaller wave I amplitude and a significantly larger wave V

amplitude in their tinnitus compared to control group. Schaette and McAlpine (2011) and Bramhall et al. (2018), however, both identified significantly smaller wave I amplitudes but no difference in wave V amplitudes between a tinnitus and control group, still resulting in a larger $\mathrm{V/I_{amp\ ratio}}$. Valderrama et al. (2018) identified no statistically significant tinnitus and control group difference for wave I or wave V, however, the smaller average wave I and larger average wave V in the tinnitus group contributed to a statistically significantly larger $\mathrm{V/I_{amp\ ratio}}$ observed in those with tinnitus relative to controls.

In the current study, while not statistically significant, wave I amplitude was smaller on average for the tinnitus group (*M* = 0.285 μV; *SD* = 0.132) compared to controls (*M* = 0.341 μV; *SD* = 167), consistent with the previous studies finding significant $\mathrm{V/I_{amp\ ratio}}$ differences related to tinnitus. Contrary to these previous studies, however, the tinnitus group had smaller (though not significantly) wave V amplitudes (*M* = 0.409 μV; *SD* = 0.199) compared to controls (*M* = 0.485 μV; *SD* = 0.193). That is, trends in the tinnitus group were consistent with reduced cochlear output, but not with subcortical hyperactivity secondary to reduced inhibition. However, because none of the wave I, wave V or the $\mathrm{V/I_{amp\ ratio}}$ between group comparisons were significant, no differences in either cochlear output or subcortical activity can be attributed to the perception of tinnitus in the current study.

Similar to this outcome, other studies in the literature have also failed to demonstrate a relationship between ABR indices of reduced inhibition ($\mathrm{V/I_{amp\ ratio}}$) and tinnitus. For example, Bramhall et al. (2020) reported that young and normal hearing noise-exposed veterans with and without tinnitus exhibited reduced average wave I amplitudes relative to non-veterans without tinnitus and minimal noise exposure history. However, wave V amplitudes were

significantly smaller for the veterans with tinnitus for most stimulus conditions compared to controls, whereas veterans without tinnitus had wave V amplitudes similar to the non-veteran controls. In other words, the results were consistent with tinnitus-related reduced cochlear output but not with reduced inhibition and subcortical hyperactivity. Likewise, Lemaire and Beutter (1995) reported that among 355 adults with tinnitus, both wave I and wave V amplitudes were reduced relative to 129 adults without tinnitus. It should be noted in their study, the tinnitus group included more women and older subjects than the control group, but the outcomes held true when the participants were split as a function of sex, hearing, and tinnitus laterality.

Further, other studies have shown no relationship between tinnitus and ABR outcomes. In a group of predominantly young, normal-hearing adults, Guest et al. (2017) found that neither wave I nor wave V amplitudes were significantly different between tinnitus and control groups, although average wave V amplitude was smaller for the tinnitus group. Interestingly, in a participant sample of musicians who were primarily young, with normal hearing (similar to the majority of the tinnitus group in the current study), Couth et al. (2020) found results opposite to the hypothesized effect – *increased* wave I amplitudes and *smaller* wave V amplitudes, equivalent to a smaller $\mathrm{V/I}_{\mathrm{amp\ ratio}}$. Although this was not specifically a tinnitus study, musicians were recruited due to greater histories of noise exposure, greater peripheral auditory insult, and therefore hypothesized reduced cochlear output relative to non-musicians (Couth et al., 2020). Although Couth et al. (2020) did not analyze ABR outcomes as a function of tinnitus status, a majority of their participants reported tinnitus (71.5%). However, perception of tinnitus was defined as experiencing it occasionally for a minimum of 5 minutes, which likely

contributed to the large proportion of participants who reported tinnitus. By comparison, the current study and most others that have analyzed the ABR as a function of tinnitus required participant's tinnitus perception to be constant (defined in the current study as daily perception for longer than 6 months).

Overall, the findings of the current study did not conclusively support either reduced cochlear output or compensatory reductions in inhibition and subcortical hyperactivity in individuals who perceive tinnitus relative to those who do not, although trends were at least consistent with reduced auditory peripheral activity in the tinnitus group. In this way, results were more consistent with the studies in the existing literature failing to document a larger $V/I_{amp\ ratio}$ related to tinnitus. Because many participant and methodological factors that possibly contributed to a lack of consensus across previous studies relating ABR $V/I_{amp\ ratio}$ outcomes to tinnitus were controlled and analyzed in the current study, the lack of significant results may suggest that the relationship between subcortical changes in inhibition and tinnitus is weak, or that individual ABR outcomes do not adequately measure the effects of tinnitus. These factors are considered in the following sections.

4.1.1: Participant Characteristics - Relationships to Subcortical Outcomes

Although a tinnitus-related group difference in ABR outcomes was not demonstrated for Specific Aim 1, the goal in Specific Aim 3 was to attempt to account for participant characteristics that frequently co-occur with tinnitus perception and may influence these ABR outcomes (and cortical outcomes as reviewed in *Discussion* section 4.2) either in addition to or instead of the participants' perception of tinnitus. Across studies in the literature examining ABR in tinnitus versus non-tinnitus groups, participant characteristics have varied which may

contribute to the lack of consensus regarding whether ABR outcomes related to tinnitus include changes in wave I amplitude, wave V amplitude, the $\mathrm{V/I_{amp\ ratio}}$, or a combination of these.

In the current study, groups were matched by sex, age, and hearing loss to attempt to control for the confounding effects of these factors for between group comparisons. The effects of age and hearing loss on the ABR are difficult to separate, particularly in the context of tinnitus, and these variables were addressed as part of the multiple regression *PRE* analysis further discussed below. Although not included as a variable in the analysis for Aim 3, sex can also complicate the interpretation of ABR due to physiological differences between males and females. Males have smaller average ABR peak amplitudes and longer latencies than females, primarily thought to be due to larger head sizes, hormonal factors, and possibly longer cochlea contributing to slower cochlear response times and decreased synchrony (as reviewed by Stamper & Johnson, 2015b). Several previous studies reporting an increased $\mathrm{V/I_{amp\ ratio}}$ in individuals with tinnitus consisted of participants primarily of the same sex. Schaette and McAlpine (2011) recruited only females, Gu et al. (2012) recruited only males, and the tinnitus group from Bramhall et al. (2018) was 13 males and 2 females. The groups from the current study were more evenly distributed, with 10 females and 8 males. As a cross-check, it was verified that no tinnitus and control group differences were found in $\mathrm{V/I_{amp\ ratio}}$ when assessed for only female participants [$t(18) = -2.00$, $p = 0.844$] and only male participants [$t(14) = 0.209$, $p = 0.837$]. Therefore, our results suggest that the sex did not significantly influence ABR $\mathrm{V/I_{amp\ ratio}}$ outcomes and this factor may not contribute to variable tinnitus-related ABR outcomes across studies.

The variables included in the analysis for Specific Aim 3 included tinnitus status, age, hearing loss ($PTA_{0.25\text{-}20\ kHz}$), noise exposure history (total NEUs), and SPIN performance (SNR-50). None of these variables on their own or in a multiple regression model significantly predicted ABR $V/I_{amp\ ratio}$, contrary to expectations given the established relationships between these characteristics and the ABR.

Matching of control and tinnitus group counterparts by age to the extent possible reduced the likelihood that this factor significantly influenced ABR comparisons between groups. However, this factor was also included in the regression analysis because age is known to have significant influence on ABR amplitude and latency. In a study controlling for confounding effects of hearing loss with increases in age, Konrad-Martin et al. (2012) found substantially reduced amplitudes of all ABR peaks and that the amplitude decrements for later peaks persisted even after controlling for peripheral changes reflected in wave I amplitude in a sample ranging from 26-71 years. For those with a greater degree of hearing loss ($PTA_{2,3,4\ kHz}$ > 17.5 dB HL), Konrad-Martin et al. (2012) reported that the greatest changes in amplitude and latency occurred between 40-59 years old relative to the participants under 40 years old. Among people with better hearing ($PTA_{2,3,4\ kHz}$ < 17.5 dB HL), ABR amplitude and latency changes occurred at even later ages. Burkard and Sims (2001), however, reported that wave I amplitude was substantially smaller and wave V was "somewhat" smaller in older adults (62-78 years) compared to younger adults (20-27 years). It should be noted that no statistical comparisons were made and that the younger adults had normal hearing, while 5 of the 11 older adults had threshold elevation (>20 dB HL) for at least one frequency. Participants in the current study ranged in age from 19-54 years, with mean ages of approximately 32 years for

each group, primarily younger than the range where significant age-related ABR changes have been observed in these previous studies. Further, the skewed distribution to younger participants between 19 and 23 years old likely led to little influence of advancing age on the ABR in this study, including changes to wave I amplitude, V amplitude, or the $\mathrm{V/I}_{\mathrm{amp\ ratio}}$. This was supported by a lack of an age influence on the $\mathrm{V/I}_{\mathrm{amp\ ratio}}$, represented by an insignificant *PRE* of age on the overall multiple regression model. Relative to other studies that have identified a significantly larger $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ in individuals with tinnitus, the age range of the current study was similar. The participants recruited by Bramhall et al. (2018) were also young (*M* ≈ 26 years, range = 19-35), whereas those recruited by Schaette and McAlpine (2011), Gu et al. (2012), and Valderrama et al. (2018) were slightly older (on average, early to mid 40s). Overall, at least within the predominantly young to middle-aged range of adults recruited across these and the current study, age did not appear to significantly influence ABR outcomes.

The effect of hearing loss on the ABR and the confounding relationship between tinnitus and hearing loss may be the most difficult to assess and control within and between studies. Perhaps one reason for this is that the inclusion of individuals with hearing loss versus normal hearing varies substantially across studies. Across 19 tinnitus-related ABR studies reviewed by Milloy et al. (2017), the number of included observations in the data for individuals with tinnitus were far greater for those who also had hearing loss (n = 919) compared to normal hearing individuals with tinnitus (n = 105). By contrast, for individuals without tinnitus, the number of observations with hearing loss (n = 34) was small compared to the number with normal hearing (n = 248). Definitions for hearing loss slightly differed across reviewed studies, but the least restrictive definition for normal hearing was thresholds ≤ 25 dB HL from 0.25 to 8

kHz. For the meta-analysis results as a whole, wave I amplitudes were smaller and wave V amplitudes were larger (consistent with a larger $\mathrm{V/I}_{\mathrm{amp\ ratio}}$) for tinnitus participants relative to non-tinnitus controls, but only for individuals classified as having normal hearing. Among people classified as having hearing loss in the meta-analysis, participants with tinnitus had smaller wave I amplitudes and smaller wave V amplitudes relative to controls (consistent with no change in the $\mathrm{V/I}_{\mathrm{amp\ ratio}}$). In individual studies specifically examining $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ in tinnitus versus non-tinnitus groups, Valderrama et al. (2018) recruited participants with "near-normal" hearing (although 84% had clinically normal auditory thresholds) and found a significantly larger $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ associated with tinnitus. Guest et al. (2017) on the other hand, found no evidence for a tinnitus-related increase in $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ among normal hearing participants. Results in the literature, although not conclusively, suggest that the larger $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ may be associated with tinnitus more so in studies including normal hearing participants rather than those with both tinnitus and hearing loss.

Despite recruitment for the current study allowing for individuals with up to a moderate hearing loss (≤ 55 dB HL from 0.25-4 kHz), almost 80% of the participants in the current study (n = 30 out of 38) would be classified as having normal hearing based on the previously mentioned criteria (thresholds ≤ 25 dB HL from 0.25-8 kHz). Although each individual with tinnitus was matched to a control by $\mathrm{PTA}_{0.5\text{-}2\ \mathrm{kHz}}$ within 20 dB HL, pure tone thresholds were poorer on average for the tinnitus group for all frequencies above 3 kHz. Group means were roughly 10 dB poorer for individuals with tinnitus at 8 kHz and above, with a maximum of 22 dB greater for the tinnitus group at 12.5 kHz (tinnitus *M* = 34.4 dB HL, *SD* = 31.7; control *M* = 12.4, *SD* = 20.2). The between-group difference was only statistically significant, however, at 8 kHz and none of

the PTA calculations were significantly different between groups. Although it has been reported that up to a $PTA_{2\text{-}4\ kHz}$ of 50-59 dB HL, there is relatively little effect on the high intensity click ABR (Bauch & Olsen, 1988), effects of degree of cochlear hearing loss can't be entirely ruled out. Despite the on-average poorer high frequency hearing in the tinnitus group, the $PTA_{0.25\text{-}20\ kHz}$ was unrelated to the $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ as indicated by the *PRE*. Due to this, it is unlikely that the degree of hearing loss was a primary contributor to a lack of significant group differences in ABR outcomes between tinnitus and control groups in this study, however, the amount of hearing loss may have contributed to the lack of significant relationship between tinnitus and ABR outcomes.

Related to the issue of predominantly normal hearing, participants in the current study may not have had significant enough noise exposure to reduce cochlear output, trigger reductions of subcortical inhibition, and yield an overall larger $\mathrm{V/I}_{\mathrm{amp\ ratio}}$. Many participants reported very little noise exposure history while only a few participants reported high noise exposure histories (n = 8 with 30 or more total NEUs; n = 19 with 5 or fewer total NEUs). Using the same Noise Exposure Structured Interview (NESI) as the current study to quantify the noise exposure of musicians and non-musicians, Couth et al. (2020) found no difference in reported noise exposure as measured by $\log_{10}$ transformed total NEUs between the two groups (musicians *M* = 0.81; *SD* = 0.79 and non-musicians *M* = 0.90; *SD* = 0.70). Further, they found no significant main effects of amount of noise exposure on either ABR wave I amplitude or the $\mathrm{I/V}_{\mathrm{amp\ ratio}}$. By contrast, using a different noise exposure self-report questionnaire [the NEQ (Megerson, 2010)], Stamper and Johnson (2015a) identified a significant relationship between increased noise exposure and decreased wave I amplitudes, but not wave V amplitudes.

Correlational analyses in that study showed that noise exposure explained approximately 15% to 24% of the variance in wave I amplitude across conditions (a medium to large effect size) and less than 5% of the variance in wave V amplitude. Although $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ were not reported, these results suggest that noise exposure potentially enlarged the $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ by decreasing wave I more than wave V. Stamper and Johnson (2015a) did not report whether individuals in their study perceived tinnitus. In the current study, simple correlational analyses showed a significant correlation between increased noise exposure and decreased wave I amplitudes (r = -0.439, p = 0.007), but amount of noise exposure was also associated with decreased wave V amplitudes (r = -0.497, p = 0.002). That is, higher levels of noise exposure reported by participants recruited for the current study was significantly related to both peripheral auditory insult leading to reduced cochlear output (decreased wave I amplitude) and reduced subcortical auditory activity (decreased wave V amplitude). However, in the multiple regression model, the amount of noise exposure did not significantly contribute to the prediction of ABR $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ and explained little of the variance in the model based on the *PRE*.

It is possible that the type of noise exposure reported by the participants in the current study being primarily continuous recreational noise contributed to observed ABR outcomes, or lack of significant outcomes. A common recreational noise reported by the participants in the current study was listening to and playing music, which as a continuous noise, may have different physiological effects on the auditory system compared to impulse noise exposure, such as gun shots, which are more likely to result in acoustic trauma (Clark & Ohlemiller, 2008; Kurabi et al., 2017). Tinnitus populations with impulse noise exposure histories, such as the veterans in the Bramhall et al. (2018) study, may exhibit different physiological outcomes

relative to tinnitus populations with continuous noise exposure histories, such as the musicians in the current study. Bramhall et al. (2018) reported that veterans with tinnitus and impulse noise exposure had smaller wave I amplitudes and larger $\mathrm{V/I_{amp\ ratio}}$ relative to non-veterans without tinnitus nor impulse noise exposure. In a similar follow-up study, reduced wave I amplitudes were again identified in veteran groups with and without tinnitus and histories of impulse noise exposure relative to non-veterans with minimal noise exposure and no tinnitus (Bramhall et al., 2020). Note that although it is reported that wave V amplitudes were similar across all groups in this study, the $\mathrm{V/I_{amp\ ratio}}$ was not reported nor were between group statistical analyses conducted. In contrast with Bramhall et al. (2018, 2020), who related *impulse* noise exposure with reduced wave I amplitudes and possible increased $\mathrm{V/I_{amp\ ratio}}$, Guest et al. (2017) identified no relationship between noise exposure history and wave I amplitude or the $\mathrm{V/I_{amp\ ratio}}$ in a group of young and normal hearing participants with and without tinnitus. Although the specific types of noise exposure the participant's experienced was not reported, the examples provided included bars and concerts, which are both recreational and continuous noise exposures. From the same research group, Couth et al. (2020) and Prendergast et al. (2017) also identified no relationship between noise exposure history with wave I amplitude, wave V amplitude, or the $\mathrm{V/I_{amp\ ratio}}$ among their recruited young and normal hearing participants who presumably exhibited primarily continuous noise exposures (amount of impulse noise exposure was not reported). Overall, it may be that impulse noise exposure has a greater effect on the amplitudes of wave I, V, and the $\mathrm{V/I_{amp\ ratio}}$ relative to continuous noise exposure. However, the prevalence of type of noise exposures reported by the participants in the current study was insufficient to indicate whether

continuous or impulse noise exposure had a greater effect on the ABR. Further, the amount of noise exposure reported by the participants in the current study may not have been great enough to result in the hypothesized reduced cochlear output and associated decrease of subcortical inhibition in the auditory pathway presumed to trigger tinnitus perception leading to the insignificant effect of NEUs on the $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ as indicated by the *PRE*.

The fact that many participants in the current study and in previous studies have tinnitus in the presence of a normal clinical audiogram may suggest that they do not have significant cochlear damage due to noise exposure. However, animal research has demonstrated that noise exposure can lead synaptopathy, the immediate and extensive loss of synapses between cochlear inner hair cells (IHCs) and auditory nerve fibers (ANFs) without damaging IHCs and outer hair cells (OHCs) (Kujawa & Liberman, 2006). As described in *Introduction* section 1.4.2, It has been suggested that tinnitus may specifically relate to the loss of high threshold low- and medium-spontaneous firing rate (SFR) ANFs (Bauer et al., 2007; Bramhall et al., 2018; Paul et al., 2017), which are particularly susceptible to noise damage (Furman et al., 2013). Loss of these fibers, which maximally respond to higher intensity stimuli, means that audibility for lower intensity sounds (near threshold) remains unaffected and individuals present with “normal hearing” based on the audiogram despite the presence of cochlear damage which may trigger neuroplastic changes, including reduced inhibition and tinnitus perception. Although the tinnitus group had poorer high frequency audiometric thresholds and lower DPOAEs, it is possible those with tinnitus also had more extensive synaptic and ANF loss (more extensive synaptopathy) due to the effects of noise exposure that would not be reflected in the audiogram. As reduced ABR wave I amplitudes are highly

correlated with synaptopathy in animal models (Sergeyenko et al., 2013), wave I amplitude has been investigated as a proxy measure for synaptopathy in humans. Research that has identified smaller wave I amplitudes in tinnitus groups with normal hearing as measured by the audiogram may also be consistent with the presence of synaptopathy in the individuals with tinnitus (Bramhall et al., 2018; Gu et al., 2012; Schaette & McAlpine, 2011; Valderrama et al., 2018). These studies have also associated the reduced wave I amplitude with increased $\mathrm{V/I_{amp\ ratio}}$. ABR findings consistent with synaptopathy have also been reported in other noise-exposed groups. For example, Bramhall et al. (2017) identified reduced wave I amplitudes in young (19-35 years) and normal hearing (≤20 dB HL from 0.25 to 8 kHz) veterans and non-veterans with greater histories of noise exposure (including impulse firearm noise) relative to veterans and non-veterans with less noise exposure history. However, wave V amplitudes were similar across all of these groups. Although the $\mathrm{V/I_{amp\ ratio}}$ was not reported, the smaller wave I and similar wave V amplitudes are consistent with a larger $\mathrm{V/I_{amp\ ratio}}$ in the groups with greater noise exposure histories. This finding was supported by a follow-up study conducted by Bramhall et al. (2020) such that groups with greater histories of noise exposure also exhibited reduced wave I amplitudes, yet similar wave V amplitudes relative to groups with less noise exposure history. Across these studies, the results indicate that a potential relationship between noise exposure history and synaptopathy may be present in humans, particularly those with tinnitus. Thus, it is possible that the greater noise exposure history and smaller average wave I amplitudes identified in the tinnitus group for the current study is consistent with greater synaptopathy in that group. This possibility highlights that ABR outcomes are impacted by multiple factors affecting the physiological function of the auditory periphery and

brainstem. That is, while it is possible that ABR amplitudes and latencies may be sensitive to physiological changes in synaptopathy or tinnitus, it may not be specific to distinguishing these pathologies. This consideration may extend to higher levels of the auditory system and associated AEP measures, such as the CAEP and sensory gating as well.

Conflicting data have also been reported such that no associations between noise exposure history and reductions to wave I amplitude or increases to the $V/I_{amp\ ratio}$ were found (Couth et al., 2020; Guest et al., 2017; Johannesen et al., 2019; Prendergast et al., 2017; Spankovich et al., 2017). Reviewed by Bramhall et al. (2019), one distinguishing factor between studies that have and have not found evidence relating noise exposure history to measures of synaptopathy, including the ABR, is the quantification of noise exposure. Studies that have grouped participants by veteran status likely yielded samples with a higher prevalence of impulse noise exposure (such as gunshots during basic training) and perhaps overall greater noise exposure history regardless of noise type relative to other studies that recruited, for example, young and normal-hearing musicians such as the current study or the Couth et al. (2020) study and quantified noise exposure using a self-report questionnaire. While the smaller average wave I amplitude observed in the tinnitus group in the current study may be indicative of synaptopathy due to histories of noise exposure, it is also consistent with cochlear hair cell loss. The latter possibility is supported by the poorer high frequency thresholds and lower DPOAEs identified in the tinnitus group.

A common functional outcome related to both synaptopathy in the presence of a normal audiogram and decreased auditory thresholds, including those in the extended high frequency range such as observed in the tinnitus group, is poorer SPIN (Motlagh Zadeh et al.,

2019; Ryu et al., 2012). In the current study, the tinnitus group had poorer SPIN performance than the controls as reflected by a significantly higher signal-to-noise ratio (SNR) needed to obtain a 50% correct response rate (tinnitus *M* = -2.47 dB, *SD* = 4.18; control *M* = -5.36, *SD* = 3.03). However, SPIN performance as estimated by the SNR-50 was not found to significantly reduce model error for the $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ based on the multiple regression analysis and *PRE*. By contrast, Bramhall et al. (2015) identified a significant association between poorer SPIN [measured using the Quick-SIN (Killion et al., 2004)] and reduced wave I amplitudes (an association with wave V amplitude was not reported). The participants from the Bramhall et al. (2015) study, relative to the current research, were older (19-90 years), had poorer hearing ($\mathrm{PTA}_{0.5,\ 1,\ 2,\ 4\ \mathrm{kHz}}$ ranged from -1.25 to 38.75 dB HL), and poorer SPIN (SNR-50 ranged from -2 to 15 dB). By contrast, in a follow-up study with younger individuals with better hearing, Bramhall et al. (2018) found no association between wave I amplitude and SPIN. It's possible that SPIN perception in the current sample was not poor enough to influence the ABR and this is likely because of a lack of extensive peripheral auditory insult among the recruited participants.

Overall, distinguishing among the effects of age, hearing loss, noise exposure history, and SPIN on the ABR above and beyond the effects of tinnitus remains difficult despite the implementation of the multiple regression analysis used to identify the individual *PRE* associated with each characteristic. Contrary to the hypothesis for Specific Aim 3, even the presence of tinnitus itself was not a significant predictor of the primary outcome of ABR $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ in this study. It may be that tinnitus severity, measured with the TFI, was not enough in the participant sample to be associated with the hypothesized changes in cochlear output and subcortical inhibition as reflected by the ABR. The mean score for the tinnitus group

on the TFI (26.8) was only slightly above 25 (the criterion for a significant self-reported problem with tinnitus) and only half (9 of 18) of the tinnitus participants had scores exceeding this. The three tinnitus participants with the largest $\mathrm{V/I_{amp\ ratio}}$ (4.38, 3.27, and 2.92) had overall TFI scores of 31.6, 36.6, and 26.0, respectively. Although these scores were greater than the mean TFI score, five participants scored higher on the TFI despite having lower $\mathrm{V/I_{amp\ ratio}}$ and the correlation between TFI score and $\log_{10}\left(\mathrm{V/I_{amp\ ratio}}\right)$ was not significant (r = 0.006, p = 0.981). Gu et al. (2012), who reported an overall larger $\mathrm{V/I_{amp\ ratio}}$ in 15 men with tinnitus relative to 21 men without tinnitus, also did not identify a significant relationship between the $\mathrm{V/I_{amp\ ratio}}$ and a subjective measure of tinnitus severity. Other studies who identified larger $\mathrm{V/I_{amp\ ratio}}$ in individuals with tinnitus have not reported outcomes related to tinnitus severity (Bramhall et al., 2018; Schaette & McAlpine, 2011; Valderrama et al., 2018).

The presence of significant hyperacusis may also be related to tinnitus severity and possible changes in subcortical inhibition. In a study examining ABR differences between a tinnitus only and tinnitus with hyperacusis group, Refat et al. (2021) found that, relative to controls, the tinnitus only group exhibited a decreased $\mathrm{V/I_{amp\ ratio}}$ whereas the tinnitus with hyperacusis group exhibited an increased $\mathrm{V/I_{amp\ ratio}}$. That is, reduced cochlear output, decreased inhibition, and subcortical hyperactivity was only identified in the group that experienced *both* tinnitus and hyperacusis, but not tinnitus alone. Further, Refat et al. (2021) found that as the duration an individual experienced tinnitus with no hyperacusis increased, the $\mathrm{V/I_{amp\ ratio}}$ decreased. By contrast, as the duration an individual experienced *both* tinnitus and hyperacusis increased, the $\mathrm{V/I_{amp\ ratio}}$ increased. These group differences may suggest either more severe or different physiological changes may occur over time when both tinnitus and

hyperacusis are present as opposed to tinnitus with no hyperacusis. Zeng (2020) suggested that the primary mechanism contributing to tinnitus may be an increase in auditory "noise" (spontaneous neural activity; auditory SFR and SFR synchrony) whereas the primary mechanism contributing to hyperacusis is an increase in auditory "gain" (sound-evoked auditory neural activity). As the ABR is a sound-evoked response it may be more sensitive to auditory "gain" as opposed to auditory "noise". Therefore, it may be that increased $\mathrm{V/I_{amp\ ratio}}$ are more prevalent in individuals with both tinnitus and hyperacusis (increased "gain" and increased "noise") as opposed to tinnitus alone (only increased "noise"). In support of potentially distinct physiological mechanisms contributing to tinnitus alone versus with hyperacusis, a recent study in noise-exposed animals identified similar results to Refat et al. (2021). Mohrle et al. (2019) also found that the animals with behavioral evidence of tinnitus had decreased $\mathrm{IV/I_{amp\ ratio}}$ (comparable to the $\mathrm{V/I_{amp\ ratio}}$ in humans) following noise-exposure. However, animals with behavioral evidence of hyperacusis had no change to the $\mathrm{IV/I_{amp\ ratio}}$ from pre- to post-noise exposure. In the current study, only two participants (both with tinnitus) were classified as having significant hyperacusis based on the HQ cutoff of 28 reported by Khalfa et al. (2002), with scores of 30 and 31. The $\mathrm{V/I_{amp\ ratio}}$ for these two subjects were 1.32 and 0.365, the latter of which was the smallest $\mathrm{V/I_{amp\ ratio}}$ observed among all participants in the study across the tinnitus and control groups. While the specific pathophysiological changes throughout the auditory system that distinguish tinnitus and hyperacusis remain to be determined, individuals with both tinnitus and hyperacusis may exhibit neuroplastic changes that would have larger effects on ABR outcomes indicating reduced inhibition and hyperactivity relative to individuals with tinnitus and no hyperacusis.

An individual's perceived tinnitus may also influence ABR outcomes in terms of how the tinnitus perception relates to the stimulus frequency. Perceived tinnitus is often frequency-specific and typically high frequency, suggesting frequency-specific changes throughout the auditory system. Although evidence of frequency specific tinnitus-related neuroplastic changes (tonotopic map reorganization) is not perfectly consistent across studies in humans (Langers et al., 2012; Muhlnickel et al., 1998; Wienbruch et al., 2006), animal studies have indicated that auditory neurons exhibit frequency-specific changes following noise-exposure and tinnitus induction such that neurons that were previously most responsive to frequencies within the noise exposure stimulus were re-tuned to be most responsive to adjacent, or "edge", frequencies (Norena & Eggermont, 2003, 2005). Therefore, tinnitus-related pathology may be most evident when responses are evoked by "on-tinnitus" stimuli at frequencies similar to the tinnitus perception and region of greatest hearing loss, or conversely, "off-tinnitus" stimuli at frequencies away from these regions.

The spectral characteristics of the ABR click stimulus is shaped by the resonant properties of the earphone coupling to the ear (Mitchell et al., 1989) and ABR response thresholds correlates best with behavioral thresholds from 2-4 kHz (Jerger & Mauldin, 1978). Bramhall et al. (2018) presented a frequency-specific 4 kHz toneburst rather than a broadband click in their study associating tinnitus with an increased $V/I_{amp\ ratio}$. Although not an on-tinnitus stimulus in the Bramhall et al. (2018) study, it may be that the 4 kHz toneburst more specifically targeted the higher-frequency tonotopic regions of the auditory system most impacted by tinnitus in the participants recruited by Bramhall et al. (2018). However, both the broadband click and 2 to 4 kHz tonebursts still may not maximally stimulate the frequency regions most

impacted by tinnitus. Among the 18 tinnitus participants in the current study, none matched their tinnitus to a 2 kHz pure tone, three matched to 3 kHz, and only one matched to 4 kHz. 13 participants matched their tinnitus to a frequency of 8 kHz or above, ranging as high as 18 kHz. It may be that an on-tinnitus stimulus would produce ABR outcomes that would better distinguish tinnitus and non-tinnitus groups as compared to a click, although this would likely require the use of very high-frequency tonebursts. Such extended high frequency ABRs are poorly studied in humans with tinnitus, but it has been shown that ABRs recorded in 30 normal ears in responses to 8, 10, 12, and 14 kHz tonebursts can be reliably evoked and have similar intra- or inter-session variability as a traditional click stimulus within an individual (Fausti et al., 1991). Other than the Bramhall et al. (2018) study, few ABR studies in tinnitus have used frequency-specific stimuli. Only one of the 19 studies regarding tinnitus and ABR reviewed by Milloy et al. (2017) used toneburst stimuli, from 1 – 8 kHz. This study did not report whether tonebursts were matched to the individual's tinnitus perception and significant differences between groups in ABR amplitudes were not found. However, they identified a prolonged wave VII latency associated with problem tinnitus when the response was averaged across all stimulus frequencies (Gerken et al., 2001).

In general, participants in the current study were predominantly young, with good hearing, good SPIN, and little noise exposure history. Half of the participants had little or mild tinnitus distress and only two had significant hyperacusis. The recruitment strategy for the current study was modified during the COVID-19 pandemic, which impacted the ability to achieve a broader representation across these participant characteristics. Specifically, the majority of recruited participants were college-aged students who participated in the marching

band. It is possible that had participants with and without tinnitus exhibited a more complete range across individual characteristics of interest, including older age, more severe hearing losses, greater noise exposure histories, and poorer SPIN, that a greater influence of these related characteristics on the ABR $V/I_{amp\ ratio}$ would have been identified.

4.1.2: Methodological Factors Influencing ABR Outcomes

There are a few additional methodological factors that may have contributed to ABR outcomes and the lack of consensus across studies. One such factor that could have resulted in smaller $V/I_{amp\ ratio}$ in the current study relative to other studies was the use of an ear canal (tiptrode) reference electrode. Placement of the recording electrode in the ear canal rather than on the mastoid or earlobe is intended to enhance the amplitude of wave I by decreasing the physical distance between the electrode and the neural generators of wave I, the spiral ganglion cell bodies of the VIIIth cranial nerve. Because wave I is generally small, this montage was used to improve the detectability and accuracy of amplitude measures for wave I. However, it also can increase inter-individual variability and decrease the $V/I_{amp\ ratio}$ by enhancing wave I more than wave V amplitude. Schaette and McAlpine (2011), by comparison, who found significantly larger $V/I_{amp\ ratio}$ associated with tinnitus, reported wave I amplitudes using a mastoid reference electrode that were smaller and less variable (tinnitus M = 0.151 µV, SD = 0.015; control M = 0.203 µV, SD = 0.017) than those recorded with a tiptrode in the current study (tinnitus M = 0.285 µV; SD = 0.132; control M = 0.341 µV; SD = 0.167). However, the average wave V amplitudes in the current study (tinnitus M = 0.409 µV; SD = 0.199; control M = 0.485 µV; SD = 0.193) were similar to the Schaette and McAlpine (2011) wave V means of approximately 0.4 µV for each group (estimated from figures). In normal hearing adults,

Stamper and Johnson (2015a) found that wave I amplitude was larger and had greater inter-individual variation when recorded with a tympanic membrane electrode (TM electrode; similar to a tiptrode) compared to a mastoid electrode (TM *M* = 0.870 µV, *SD* = 0.314; mastoid *M* = 0.428 µV, *SD* = 0.153). By contrast, wave V amplitude was more similar or slightly larger with a mastoid electrode (TM *M* = 0.540 µV, *SD* = 0.135; mastoid *M* = 0.661 µV, *SD* = 0.189). Although the $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ was not reported by Stamper and Johnson (2015a), based on this mean data the calculated $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ was substantially larger when recorded using a mastoid, relative to TM electrode (TM *M* = 0.621; mastoid *M* = 1.55) Bramhall et al. (2018), who also found a tinnitus-related group difference in the $\mathrm{V/I}_{\mathrm{amp\ ratio}}$, also used a tiptrode. In response to a 4 kHz toneburst stimulus, they reported wave I amplitudes in the tinnitus (*M* = 0.29 µV, *SD* = 0.10) and control group (*M* = 0.38 µV, *SD* = 0.11) which exhibited similar means and variability relative to the tinnitus and control groups in the current study. Therefore, although the use of the tiptrode in the current study may have improved the detectability of wave I, the larger wave I amplitudes and increased inter-subject variability may have offset the ability to identify tinnitus-related changes on the wave I amplitude or the $\mathrm{V/I}_{\mathrm{amp\ ratio}}$. Although it is possible that variability associated with tiptrode or click stimulus use contributed to the lack of a significant group difference, the mean and distribution of the $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ between the tinnitus and control groups in the current study was similar and any systematic methodological effect, such as due to tiptrode use, would have been present in both groups.

In all, no significant differences in ABR $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ between the tinnitus and control group were identified. Although neither result was significant, on average the tinnitus group had smaller wave I amplitudes as hypothesized, but they also had smaller wave V amplitudes

relative to controls. Further, the results of the multiple regression analyses indicated that tinnitus, age, hearing loss, noise exposure history, and SPIN exhibited an insignificant influence on the ABR $V/I_{amp\ ratio}$ despite previous research relating these characteristics with changes to the ABR. These findings suggest that the mechanism behind tinnitus may not be subcortical changes in inhibition, at least as measured by the ABR $V/I_{amp\ ratio}$. However, the trend for smaller average wave I amplitudes observed in the tinnitus group was likely related to greater peripheral auditory insult and reduced cochlear output in the tinnitus participants. It is also possible that the null findings relating the ABR $V/I_{amp\ ratio}$ to other individual characteristics was due to the predominantly young age, good hearing, little noise exposure history, and good SPIN performance indicative of the participants recruited for the current study. As a group, they may not represent the severity and type of tinnitus that would be most strongly related to the degree of physiological change needed to identify ABR differences related to the perception of tinnitus. Finally, methodological factors including the use of a tiptrode and broadband click stimulus may have also contributed to some of the variability in the ABR amplitude outcomes and led to the lack of significant tinnitus-related findings.

4.2: Cortical Inhibition Outcomes: CAEP Sensory Gating

It is possible that the conscious perception of tinnitus may be more directly related to cortical neuroplastic changes in the CANS beyond subconscious processing in the brainstem. Cortical neuroplastic changes related to reduced inhibition and auditory hyperactivity have been identified in animal models of tinnitus and supported by preliminary human studies utilizing MRI and EEG (e.g., De Ridder et al., 2015; Rauschecker et al., 2015). A common root of several prominent theories of tinnitus generation is that decreased thalamocortical inhibition

fails to prevent irrelevant subcortical auditory hyperactivity from passing through to cortical processing levels and, as a result, the subcortical hyperactivity is consciously perceived as tinnitus (Figure 1). The central nervous system's ability to inhibit irrelevant sensory information, called sensory gating, therefore may be abnormally poor in individuals with tinnitus. Auditory sensory gating has traditionally been objectively measured using a paired stimulus cortical auditory evoked potential (CAEP) paradigm where two identical sounds are successively presented. The second sound in the pair can be considered repetitive or irrelevant auditory information. In an individual with normal sensory gating, a typical CAEP (P1-N1-P2) waveform is elicited to the first "conditioning" stimulus in the pair and a reduced amplitude CAEP is elicited to the second (repetitive and irrelevant) "test" stimulus due to the normal inhibitory sensory gating process. Therefore, normal sensory gating (normal inhibition) is characterized by an amplitude or area reduction of the test CAEP relative to the conditioning CAEP, mathematically equal to a larger $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$. For Specific Aim 2, it was hypothesized that the tinnitus group would exhibit larger $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude or area ratios relative to a control group, representing reduced inhibition of the repetitive and irrelevant test stimulus, indicating impaired sensory gating and decreased cortical inhibition.

The paradigm used in the current study elicited a sensory gating effect in both groups, as evidenced by significant reductions in amplitude and area from the conditioning to test CAEP. Significant amplitude and area reductions were also accompanied by significant decreases in latency from conditioning to test CAEP. While some individuals with tinnitus had large sensory gating ratios, particularly for the $\text{P1-N1}_{\text{amp ratio}}$, contrary to the hypothesis there

were no significant group differences in the these within-individual $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratios for any of the CAEP amplitude or area measurements. However, one significant finding differentiating the tinnitus and control groups in this study was a significantly larger $\mathrm{P1}_{\text{lat ratio}}$ in the tinnitus group compared to the control group. Although latency outcomes have rarely been reported in the sensory gating literature, this finding supports a relationship between tinnitus and neuroplastic changes associated with the inhibition of repetitive and irrelevant auditory stimuli.

Of the primary outcome $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratios (P1-N1, N1-P2, and $\mathrm{P1}_{\text{T-P}}$ amplitude and P1-N1-P2 area), the $\mathrm{P1\text{-}N1}_{\text{amp ratio}}$ was larger on average for the tinnitus group, but with greater variability (*M* = 0.640, *SD* = 0.433) compared to the control group (*M* = 0.420, *SD* = 0.211). While this was not a significant difference, four tinnitus participants, but no controls, had large $\mathrm{P1\text{-}N1}_{\text{amp ratio}}$ greater than the overall mean + 1 *SD* consistent with impaired sensory gating. By contrast, three control participants, but no tinnitus participants, had small $\mathrm{P1\text{-}N1}_{\text{amp ratio}}$ less than the overall mean – 1 *SD* consistent with normal sensory gating. The $\mathrm{P1}_{\text{T-P}_{\text{amp ratio}}}$ and $\mathrm{N1\text{-}P2}_{\text{amp ratio}}$ both did not significantly differentiate groups, despite being slightly larger on average for the tinnitus group ($\mathrm{P1}_{\text{T-P}}$ *M* = 0.695, *SD* = 0.373; N1-P2 *M* = 0.448, *SD* = 0.191) compared to the control group ($\mathrm{P1}_{\text{T-P}}$ *M* = 0.681, *SD* = 0.358; N1-P2 *M* = 0.443, *SD* = 0.180). Finally, the $\mathrm{P1\text{-}N1\text{-}P2}_{\text{area ratio}}$ was also calculated to assess whether a sensory gating measure encompassing the entire waveform might better separate tinnitus and control groups. Because of the distribution of outliers, the mean $\mathrm{P1\text{-}N1\text{-}P2}_{\text{area ratio}}$ was slightly larger for the control group and median slightly larger for the tinnitus group (controls *M* = 0.717, *SD* = 0.445, *Mdn* = 0.548; tinnitus *M* = 0.702, *SD* = 0.396, *Mdn* = 0.613). Three tinnitus and three control

participants exhibited a large $\text{P1-N1-P2}_{\text{area ratio}}$ greater than the mean + 1 *SD*, which might be interpreted as consistent with impaired sensory gating. The most extreme outlier ($\text{P1-N1-P2}_{\text{area ratio}}$ = 2.04), consistent with the most "abnormal" sensory gating, or least inhibition of the response to the test stimulus, was a control subject. Therefore, the $\text{P1-N1-P2}_{\text{area ratio}}$ was not more effective in separating groups based on sensory gating outcomes. Rather, the $\text{P1-N1}_{\text{amp ratio}}$ on average was the most different between the tinnitus and control groups, although not statistically significantly. It is possible that the greater sensory gating effect across groups and the greater sensory gating group difference observed for the $\text{P1-N1}_{\text{amp ratio}}$ relative to the $\text{N1-P2}_{\text{amp ratio}}$ and $\text{P1-N1-P2}_{\text{area ratio}}$ may be due to the different CAEP components measured. As the P1 predominantly reflects earlier pre-attentive thalamocortical activity, it has been suggested that the P1 component is a better reflection of the subconscious sensory gating process (Lijffijt et al., 2009a; Vlcek et al., 2014). The later occurring CAEP components may be more influenced by attention or arousal (Luck, 2005) and thus exhibit a stronger sensory gating effect (smaller $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratios) relative to the earlier P1.

There is not a clear cutoff for normal versus abnormal sensory gating ratios in the literature. As previously noted, the most commonly reported $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude ratio in psychology and psychiatry literature is for the P1 component (sometimes called P50), typically measured from preceding trough-to-peak (denoted $\text{P1}_{\text{T-P}}$ in the current study). In the meta-analysis by Patterson et al. (2008), a significantly larger $\text{P1}_{\text{amp ratio}}$ for groups with schizophrenia, relative to controls, was observed in 45 of 46 comparisons, consistent with

poorer sensory gating due to reduced inhibition of repetitive stimuli. Their reported grand mean $\mathrm{P1}_{\mathrm{amp\ ratio}}$ for controls across studies grouped by research lab and methodology were between 0.25 (*SD* = 0.09) and 0.58 (*SD* = 0.09). In experimental (schizophrenia) groups, the grand average $\mathrm{P1}_{\mathrm{amp\ ratio}}$ was 0.80 (*SD* = 0.24) for data combined across 1445 pathologic individuals. In the current study, $\mathrm{P1}_{\mathrm{T\text{-}P\ amp\ ratio}}$ for the control participants (*M* = 0.68, *SD* = 0.36) was larger than the ratios reported for controls by Patterson et al. (2008). However, the tinnitus group had smaller $\mathrm{P1}_{\mathrm{T\text{-}P\ amp\ ratio}}$ (*M* = 0.70, *SD* = 0.37) compared to the schizophrenic grand mean. It may be that $\mathrm{P1}_{\mathrm{T\text{-}P\ amp\ ratio}}$ is not comparable between these two different populations, or that the underlying changes in inhibition and sensory gating of irrelevant stimuli are not comparable.

In tinnitus samples, Campbell et al. (2018, 2019) reported a preliminary association between reduced sensory gating and tinnitus using a 250 Hz paired toneburst paradigm to evoke the CAEP. In their first study, Campbell et al. (2018) found a significant P1 amplitude reduction from the conditioning to test response for the control group but not for the tinnitus group, indicating a lack of a sensory gating effect in the tinnitus participants (amplitude values were not reported). Neither group exhibited a significant amplitude reduction from conditioning to test CAEP for the N1 or P2 components. By contrast, in their follow-up study, significant P1 amplitude reductions were found from conditioning to test CAEP for both the control and tinnitus groups, but not for N1 or P2 (Campbell et al., 2019). Estimated based on their reported figures, the $\mathrm{P1}_{\mathrm{amp\ ratio}}$ for controls was roughly 0.65 and for the tinnitus group was slightly smaller at roughly 0.59. By comparison, the mean $\mathrm{P1\text{-}N1}_{\mathrm{amp\ ratio}}$ for the current study was smaller for the control group (*M* = 0.420, *SD* = 0.211) and larger for the tinnitus group

(*M* = 0.640, *SD* = 0.433). Although significant tinnitus and control group differences were not identified for any $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude ratios by Campbell et al. (2018, 2019), both studies reported significant correlations such that greater tinnitus severity was associated with poorer sensory gating. It should be noted, however, that this correlation was done using a conditioning minus test middle latency response (MLR) Pa component amplitude difference rather than the amplitude difference or ratio for the later P1, N1, or P2 components. Further, while tinnitus severity was significantly related to sensory gating outcomes, the range of severities included only slight or mild tinnitus among their participants in both studies.

In a more recent sensory gating study from the same research group, no significant conditioning to test CAEP amplitude differences were reported for either normal hearing individuals or those with a mild high frequency hearing loss (Campbell et al., 2020a). While this was not a tinnitus study, and in fact tinnitus was an exclusionary criterion, the lack of amplitude reduction observed from conditioning to test CAEP across *all* participants, whether with normal hearing or mild hearing loss, was an unexpected finding consistent with abnormal sensory gating in both groups. The research did not report amplitude ratios, but in an estimation from figures reporting conditioning and test P2 amplitudes, the $\mathrm{P2}_{\text{amp ratio}}$ was approximately 0.75 for the normal hearing group and approximately 0.90 for the mild hearing loss group. By comparison, in the current study, both the control (*M* = 0.443, *SD* = 0.180) and tinnitus (*M* = 0.448, *SD* = 0.191) groups had smaller $\mathrm{N1\text{-}P2}_{\text{amp ratio}}$, suggesting better (more normal) sensory gating relative to the participants recruited by Campbell et al. (2020a). The lack of a normal sensory gating effect in that study may relate to the use of a paired 250 Hz stimulus paradigm

rather than the more traditional paired click paradigm used in the current study to evoked the sensory gating response (see *Discussion* section 4.2.2).

Auditory sensory gating has also been examined in blast-exposed veteran populations. Papesh et al. (2019) found that a group of blast-exposed veterans had significantly smaller percent changes in conditioning to test P2 amplitudes (but not P1 or N1) relative to controls, consistent with poorer sensory gating. Although they reported their data as a percent change, based on their reported average P2 amplitudes for the conditioning and test CAEP responses, the calculated $\mathrm{P2}_{\mathrm{amp\ ratio}}$ was 0.438 for blast-exposed veterans and 0.346 for the control group of combat veterans with no history of blast exposure or brain injury. Interestingly, the $\mathrm{N1\text{-}P2}_{\mathrm{amp\ ratio}}$ means for both the tinnitus (*M* = 0.448, *SD* = 0.191) and control group (*M* = 0.443, *SD* = 0.180) in the current study were closer to those of the blast-exposed veterans in Papesh et al. (2019), while the veteran control had a smaller ratio than both groups in the current study, indicative of better sensory gating. Papesh et al. (2019) also found that larger $\mathrm{P2}_{\mathrm{amp\ ratio}}$, consistent with poorer sensory gating, was associated with poorer performance on auditory tasks including dichotic listening, SPIN, and perception of rapid speech in this population. The relationship between sensory gating with noise exposure and functional SPIN performance in the current study is further described in *Discussion* section 4.2.1.

While amplitude ratios are the primary reported outcomes for sensory gating studies, delayed latencies for the response to the second (test) stimulus may also be associated with poorer sensory gating in populations with diminished inhibition (Lijffijt et al., 2009b; Smith et al., 2013). These studies have shown that a significantly earlier response latency to the test stimulus relative to the conditioning response latency is indicative of a typical sensory gating

response. However, in clinical populations with abnormal sensory gating, the response to the test stimulus is prolonged relative to controls. That is, the test response latency in impaired sensory gating is more similar to the conditioning response latency yielding a larger $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ latency ratio closer to 1. A larger $\mathrm{P1}_{\text{lat ratio}}$ was the only significant group difference between the tinnitus and control groups in the current study. The average decrease in P1 latency for the control group was 12.4 ms (conditioning *M* = 58.8 ms, *SD* = 15.9; test *M* = 46.4 ms, *SD* = 19.9) compared to 2.4 ms for the tinnitus group (conditioning *M* = 54.1 ms, *SD* = 13.5; test *M* = 51.7 ms, *SD* = 15.6). This led to a significantly larger $\mathrm{P1}_{\text{lat ratio}}$ for the tinnitus (*M* = 0.976, *SD* = 0.266) compared to control group (*M* = 0.782, *SD* = 0.233), indicating a delayed response to the test stimulus in the tinnitus group.

Comparison latency data for normal and impaired sensory gating are limited, but a few studies have reported these outcomes. In a normal control population (no psychiatric pathology, n = 67) Fuerst et al. (2007) reported average P1 latencies of 66.79 ms (*SD* = 10.94) and 60.85 ms (*SD* = 11.45) for the conditioning and test responses respectively, resulting in an average decrease in P1 latency of 5.95 ms and a $\mathrm{P1}_{\text{lat ratio}}$ of 0.911. These values for normal controls, however, were closer to those obtained for the tinnitus group than the controls in the current study (as reported in the previous paragraph). In a group of 16 individuals with schizophrenia compared to 21 age-matched healthy controls, Smith et al. (2013) reported a significant reduction in P1 latency from conditioning to test CAEP for the controls, but not schizophrenic group. The lack of a significant latency change in the schizophrenic group was interpreted as one index of abnormal sensory gating and possible degraded auditory processing in this population. Although the mean values were not reported for the schizophrenia group,

using the average reported latencies for the controls resulted in a calculated $\mathrm{P1}_{\mathrm{lat\ ratio}}$ of 0.897, which falls between the control and tinnitus group in the current study. In a study of individuals with bipolar disorder, Lijffijt et al. (2009b) found a significant P2 latency sensory gating difference in the bipolar group (but not a P1 or N1 group difference). Based on reported means, the calculated $\mathrm{P2}_{\mathrm{lat\ ratio}}$ for the bipolar group was equal to 0.988 and for the controls group was equal to 0.907. The $\mathrm{P2}_{\mathrm{lat\ ratio}}$ in the current study was not significantly different between the control (*M* = 0.933, *SD* = 0.145) and tinnitus groups (*M* = 0.940, *SD* = 0.079), both of which had average ratios between those reported for the experimental and control groups in Lijffijt et al. (2009b).

In auditory sensory gating studies, latency outcomes have not been consistently reported. Only Campbell et al. (2019) and Campbell et al. (2020b) reported latency outcomes that can be compared to the current study. Campbell et al. (2019) identified no significant latency reduction from the conditioning to test CAEP for P1, N1, and P2 among the tinnitus participants whereas controls exhibited a significant latency decrease for both P1 and N1 latencies, but not P2. In that study, latency ratios were not reported directly, and average latency data was only reported for controls and not tinnitus participants. Based on an estimation from their figures, control subjects had a $\mathrm{P1}_{\mathrm{lat\ ratio}}$ of 0.913, similar to the tinnitus group in the current study (0.976). The $\mathrm{N1}_{\mathrm{lat\ ratio}}$ for controls in Campbell et al. (2019) was 0.912, which was smaller than mean ratios for both the tinnitus (*M* = 0.944, *SD* = 0.220) and control group (*M* = 0.952, *SD* = 0.079 in the current study, which were not significantly different between groups. Campbell et al. (2020b) also reported latency outcomes in their study of non-tinnitus participants with normal hearing or mild hearing loss related to SPIN performance

outcomes. They found that those with a “typical” SNR loss had significant reductions in latency from conditioning to test CAEP for the P1 and N1 components, consistent with normal sensory gating outcomes. By contrast, the “mild” SNR loss group had no significant latency reductions for any components, consistent with abnormal sensory gating. The average decrease in P1 latency was 5.03 ms for the typical SNR loss group and 3.06 ms for the mild SNR loss group, equating to a $P1_{\text{lat ratio}}$ of 0.927 and 0.953, respectively. The $P1_{\text{lat ratio}}$ of 0.976 in the tinnitus group in the current study, therefore, exceeded that of the mild SNR loss group, while the $P1_{\text{lat ratio}}$ of 0.782 for controls in the current study was substantially smaller than data reported by Campbell et al. (2020b) for the typical SNR group.

The lack of significant P1 latency reduction from conditioning to test response for participants with tinnitus may be an indicator of abnormal processing, a finding in agreement with sensory gating studies in both the psychiatric and auditory literature. The mechanism behind an abnormal lack of reduction in latency of the response to the second (test) stimulus in a sensory gating paradigm is not entirely clear. Rosburg et al. (2006) suggested that decreased latencies to repetitive stimuli may represent a change in the recovery time of one or more of the generators of the CAEP, which include the auditory cortex (AC) and complex tangential neural generators with temporally overlapping recovery times (Naatanen & Picton, 1987). Whether this change in recovery time is related to reduced inhibition is not clear. However, latency increases are generally interpreted as slower neural processing speed and impairments in temporal processing. For example, age-related changes in the auditory cortex related to reduced inhibition have been associated with greater “neural noise” which may degrade temporal processing, at least in animal studies (Caspary et al., 2008). Although related to visual

rather than auditory processing, an EEG study by Gazzaley et al. (2008) supported a interaction between aging with deficits in neural processing speed and sensory inhibition such that aging was related to a decline in processing speed for tasks that require the inhibition of irrelevant information. While a delayed latency to the repetitive test stimulus may represent slowed temporal processing related to reduced inhibition, it's important to note that due to the broad component peaks of the CAEP representing complex neural activity, differences in absolute peak latency do not necessarily directly correspond with changes in neural generator timing and differences in amplitude do not necessarily strictly correspond with changes in neural generator response magnitude (Luck, 2005). Therefore, while changes in the refractoriness of tangential neural generators may relate to the significantly larger $\mathrm{P1}_{\text{lat ratio}}$ observed in the tinnitus group, the relationship between this result, sensory gating, and reduced cortical inhibition is unclear and requires further research.

In summary, for Specific Aim 2 reduced cortical inhibition was not found for a group of individuals with constant tinnitus compared to non-tinnitus controls, as evidenced by significantly larger sensory gating $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude or area ratios. However, the tinnitus group was found to have a significantly larger $\mathrm{P1}_{\text{lat ratio}}$. This slowed processing of the test stimulus may represent changes in the refractoriness of the CANS, slowed temporal processing, poorer sensory gating, and/or reduced inhibition in individuals with tinnitus. Therefore, the results partially support the hypothesis for Specific Aim 2 that tinnitus may be related to impaired sensory gating, representing reduced cortical inhibition. Similar to the ABR results, factors other than tinnitus such as the characteristics of the participants recruited, or the

methodologies utilized may have contributed to the observed outcomes, as discussed in the following sections.

4.2.1: Participant Characteristics – Relationships to Cortical Outcomes

As with the ABR, accounting for participant characteristics that co-occur with tinnitus perception and may influence sensory gating outcomes was a main goal of this study and this was achieved through participant matching by sex, age, and hearing for between-group comparisons. The number of males and females was identical between groups and sex was not included in the multiple regression analysis. However, when results were cross-checked within males and female subgroups, the only significant finding was a significantly larger $\log_{10}(\text{P1-N1}_{\text{amp ratio}})$ in men with tinnitus relative to men without tinnitus. Across the entire sample (both men and women), of the ten largest $\log_{10}(\text{P1-N1}_{\text{amp ratio}})$, six were from males with tinnitus and only one from a female with tinnitus. Previous data has suggested that in healthy young controls, females have larger sensory gating ratios than males (Hetrick et al., 1996; Patterson et al., 2008). Therefore, the findings in the current study suggest that this relationship in the male subjects may be related to tinnitus-specific mechanisms.

As described throughout the *Introduction*, disentangling the effects of tinnitus from other characteristics on AEP measures thought to relate to tinnitus has been a limitation of previous research. As such, the objective of Specific Aim 3 was to estimate the extent to which individual participant characteristics, including tinnitus, age, noise exposure history (NEUs), hearing loss ($\text{PTA}_{0.25\text{-}20\ \text{kHz}}$), and SPIN (SNR-50) predicted reduced cortical inhibition represented by the $\text{P1-N1}_{\text{amp ratio}}$ and $\text{P1}_{\text{lat ratio}}$ sensory gating outcomes. This was achieved through multiple regression analyses and *PRE* (as previously described in *Methods* section 2.2.3 and *Discussion*

section 4.1.1). Although tinnitus presence alone significantly predicted the P1-$N1_{amp\ ratio}$ based on a simple linear regression model that did not include any other predictor variables, none of the variables, including tinnitus presence, significantly influenced the P1-$N1_{amp\ ratio}$ based on the *PRE*. The $P1_{lat\ ratio}$, which differed significantly between the tinnitus and control groups, however, was significantly predicted by both tinnitus and age based on the *PRE*, although age was the stronger predictor based on $\sqrt{\mathrm{PRE}}$. All together, these results partially supported the hypothesis such that tinnitus itself significantly predicted the $\mathrm{P1\text{-}N1}_{\mathrm{amp\ ratio}}$ but not when other individual characteristics were accounted for by the model. Tinnitus was also a significant predictor of the $\mathrm{P1}_{\mathrm{lat\ ratio}}$, although this outcome measure was best predicted by age.

While not previously studied with respect to tinnitus presence or absence, poorer sensory gating with advancing age has been documented in studies using AEP (Kisley et al., 2005) and magnetoencephalography (MEG) paradigms (Cheng et al., 2015). The older groups in these prior studies were 55 to 85 and 60 to 82 years old respectively, which exceeds the age range of participants in the current study (19-54, *M* = 32.1 years). Kisley et al. (2005) reported a significantly larger $N1_{amp\ ratio}$ in their older group (*M* = 0.659) compared to an 18-23 year old younger group (*M* = 0.301). Interestingly, the $\mathrm{P1\text{-}N1}_{\mathrm{amp\ ratio}}$ for the tinnitus group in the current study (*M* = 0.640, *SD* = 0.433) more closely resembled the $N1_{amp\ ratio}$ of the older group in Kisley et al. (2005) whereas the control group $\mathrm{P1\text{-}N1}_{\mathrm{amp\ ratio}}$ (*M* = 0.420, *SD* = 0.211) was lower. That is, the sensory gating outcome for the tinnitus group in the current study was similar to the older group in the Kisley et al. (2005) study, suggesting that tinnitus may have had a similar effect as aging on sensory gating.

In general, aging has been associated with impaired inhibitory function, as evidenced on a cellular level by selective loss of hippocampal GABAergic interneurons (Barnes et al., 2000; Hernandez et al., 2006) and decline in dopaminergic neurotransmission (Backman et al., 2006), and broadly at the neural level represented by changes in latencies and amplitudes of AEPs (Tremblay et al., 2003; Tremblay et al., 2014). Age-related loss of inhibitory function has also been associated with decreased performance on cognitive tasks such as comprehension of text, word-list learning, and learning factual information (Persad et al., 2002). Age-related neuroplastic changes related to decreased inhibitory processes, such as perceiving temporal cues necessary for speech processing and SPIN, have been associated with N1 and P2 latency prolongations and N1 amplitude increases (Tremblay et al., 2003). In a subsequent study, Tremblay et al. (2004) found significantly larger P1 amplitude, yet smaller N1 amplitude, for 1 kHz tone-evoked CAEPs recorded in normal hearing older adults (63-79 years) compared to normal hearing younger adults (21-33 years). Billings et al. (2015) identified that an older normal hearing group (*M* = 69.4, range = 60 - 78 years) exhibited both poorer SPIN performance and prolonged N1 and P2 latencies relative to a young normal hearing group (*M* = 27.6, range = 23 - 34 years) who were recruited as part of a different study (Billings et al., 2013). Age-related reductions in the ability to inhibit responses to regular repeating information has also been suggested by P300 studies. For example, Stothart and Kazanina (2016) found an increased P3a amplitude and delayed P3a latency in response to irrelevant deviant stimuli inserted randomly in a constant stream of repetitive tonal stimuli in an older group (62–88 years), relative to a young group (18–23 years). Overall, evidence implicates an effect of aging on inhibition that may be reflected by prolongations in CAEP latencies, increases in P1 and P3a amplitude, and

decreases in N1 amplitude (less negative amplitudes). These findings, in combination with the significant effect of age on the $P1_{lat\ ratio}$, suggest that age may confound or moderate the relationship between tinnitus and inhibition in CAEP studies.

Multiple regression analyses in the current study indicated that hearing loss, noise exposure history, and SPIN were not related to sensory gating outcomes (for both the P1-$N1_{amp\ ratio}$ and $P1_{lat\ ratio}$), however previous research has reported conflicting findings. While participant recruitment was limited to individuals with at most a moderate hearing loss (thresholds $\leq$ 55 dB HL from 0.25-4 kHz) to increase the likelihood that the 100 dB ppe SPL sensory gating click stimulus was audible by all participants, there is little research relating hearing threshold and hearing loss to sensory gating CAEP outcomes. The tinnitus group in the current study had slightly poorer hearing in the high frequencies, which was significant for 8 kHz only. However, no measures of sensory gating, including all $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude, area, and latency ratios, significantly correlated with any pure tone average (including $PTA_{0.5\text{-}2\ kHz}$, $PTA_{9\text{-}20\ kHz}$, and $PTA_{0.25\text{-}20\ kHz}$). These results suggest that at least in this study, hearing thresholds did not significantly influence sensory gating. However, the majority of participants met clinical criteria for normal hearing based on $PTA_{0.5\text{-}2\ kHz}$. It is possible that if more hearing-impaired individuals with a wider range of hearing thresholds (with and without tinnitus) were included, a sensory gating effect related to hearing loss may have been observed. In a study of individuals with and without tinnitus, Campbell et al. (2019) identified an association between *better* sensory gating and *worse* extended high-frequency thresholds among 66 participants aged 17-43 years. That is, the extended high frequency PTA for 10, 12.5, and 16 kHz ($PTA_{10\text{-}16\ kHz}$) was positively correlated with better sensory gating (a greater Pa amplitude

difference; r = 0.458, p = 0.032). However, all participants had normal hearing based on clinical frequencies (≤ 20 dB HL from 0.25-8 kHz). Numerical values were not reported, but the $PTA_{10\text{-}16\ kHz}$ estimated from a scatterplot ranged from -5 to 27 dB HL, as compared to the mean $PTA_{10\text{-}16\ kHz}$ of 28.6 dB HL (*SD* = 25.1) and 14.4 dB HL (*SD* = 16.4) for the tinnitus and control group in the current study, respectively. In contrast to their tinnitus research, in their study of non-tinnitus groups with normal hearing and mild hearing loss, Campbell et al. (2020a) identified the more expected relationship. In this study, the 4 and 8 kHz average ($PTA_{4\ \&\ 8\ kHz}$) was significantly correlated with the $P2_{amp\ ratio}$ (r = 0.379, p < 0.05). That is, *greater* hearing loss was associated with *poorer* sensory gating (larger gating ratios). Based on their scatterplot, $PTA_{4\ \&\ 8\ kHz}$ ranged from 1 to 60 dB HL with the average for the majority of participants falling between 10 and 30 dB HL, which was somewhat poorer compared to averages in the current study for the tinnitus (*M* = 12.9 dB HL, *SD* = 12.1) and control group (*M* = 5.97 dB HL, *SD* = 7.53). Overall, the association between *worse* extended high-frequency thresholds with *better* sensory identified by Campbell et al. (2019) was likely a spurious finding as it was not substantiated by Campbell et al. (2020a) or the current study, both of which recruited participants with a greater range of hearing thresholds. However, it may be that, at minimum, a mild-moderate high frequency hearing loss (at 4 and 8 kHz) is necessary to observe the relationship between poorer hearing with poorer sensory gating as indicated by Campbell et al. (2020a).

Similar to hearing loss, the relationship between noise exposure and sensory gating or the CAEP in general has not yet been well studied. Bramhall et al. (2020) compared a high intensity click-evoked CAEP between noise exposed veterans (presumably impulse noise

exposure although quantification by noise exposure type was not reported) and controls with minimal noise exposure. They found that the noise exposed veteran groups, particularly the participants with tinnitus, exhibited an increased P1-N1-P2 response area relative to the control group. However, in response to a higher-frequency 4 kHz and 6 kHz toneburst stimulus, the noise exposed tinnitus group exhibited a decreased P1-N1-P2 response area relative to both the noise exposed veterans without tinnitus and the controls. That is, Bramhall et al. (2020) indicated that neuroplastic changes related to tinnitus were more evident in response to higher frequency stimuli as opposed to broadband clicks and that noise exposure was related to increased CAEP response areas. Regarding the effects of noise exposure on sensory gating specifically, Papesh et al. (2019) reported poorer sensory gating as evidence by significantly smaller percent changes in conditioning to test P2 amplitudes in a group of 16 blast-exposed (24-58 years) compared to 13 non-blast exposed control veterans (19-66 years), all with normal hearing (thresholds ≤ 25 dB HL 0.25-4 kHz). However, noise exposure histories were not quantified, and blast-exposure may yield different effects on the auditory system relative to continuous noises. Histories of noise exposure have not been reported in other sensory gating studies in auditory populations (Campbell et al., 2018; Campbell et al., 2019; Campbell et al., 2020a; Campbell et al., 2020b). Although the current study did not find an association between noise exposure history and sensory gating, like the ABR, future research that recruits a sample with greater noise exposure histories and varied types of noise exposure may better indicate whether or not such a relationship exists.

As with noise exposure history and hearing loss, the multiple regression analysis indicated that SPIN was unrelated to sensory gating outcomes. However, as previously

mentioned, a preliminary association between poorer sensory gating and poorer SPIN has been identified (Campbell et al., 2020b). A group of young, normal hearing adults with a "mild" SNR loss (SNR-50 > 1.5 dB) had a mean $P2_{\text{amp ratio}}$ of 1.00 (*SD* = 0.323), which was significantly larger than the 0.281 $P2_{\text{amp ratio}}$ *(SD* = 2.41) for the young, normal hearing adults with a "typical" SNR loss (SNR-50 ≤ 1.5 dB). Further, the P2 amplitude difference across all participants significantly correlated with the SNR-50 such that poorer sensory gating was related to poorer SPIN (*r* = -0.60, *p* = 0.005). Although specific numerical values were not reported, the estimated average SNR-50 in the typical SNR loss group was equal to roughly 0.75 dB and in the mild SNR loss group SNR-50 was equal to roughly 2.9 dB. By contrast, the average SNR-50 was better at -2.47 dB (*SD* = 4.18) and -5.36 dB (*SD* = 3.03) for the tinnitus and control groups, respectively. When the participants were split up into a group with poorer and better SNR-50 based on the 50th percentile, the better SNR-50 group (*M* = -7.31 dB, *SD* = 2.02) did not significantly differ on any measure of $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude, area, or latency ratios from the worse SNR-50 group (*M* = -0.868 dB, *SD* = 2.24). Further, across all participants the SNR-50 did not significantly correlate with any measure of $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude, area, or latency ratios. It should be noted that across both of these studies, SPIN scores were normal. Even the mild SNR loss group recruited by Campbell et al. (2020b), who had an SNR-50 range of 2 to 5.5 dB, would still be classified as having normal SPIN based on the clinical measure used to determine SNR-50 in that study, the Quick-SIN (Etymotic Research, 2006). It may be that participants with greater SPIN deficits would exhibit a more significant relationship with sensory gating outcomes.

Overall, the multiple regression analysis did provide preliminary evidence relating both tinnitus presence and increased age with poorer sensory gating. However, little evidence was

identified relating noise exposure history, hearing loss, and SPIN to sensory gating outcomes. It may be that other characteristics that were not included in the multiple regression analysis may also explain variation in sensory gating outcomes.

Like the ABR, it is possible that a greater relationship between tinnitus presence and sensory gating outcomes would have been observed had participants exhibited more severe tinnitus. Campbell et al. (2018, 2019) identified a positive correlation between greater tinnitus distress with poorer sensory gating of the Pa component, although the scores indicated mild, if any, tinnitus handicap was present, and some participants were included in both studies. The participants in the current study reported a range of tinnitus handicaps, from none to severe (scores of 2.8–58.8 on the TFI). However, only two participants (out of 18) reported their tinnitus as severely impacting their quality of life based on published cutoffs for the TFI (Meikle et al., 2012). Therefore, tinnitus handicaps of the current research sample were limited in the representation of severe tinnitus. Although the tinnitus handicaps of the participants from the current study represented a greater range of possible scores relative to the Campbell et al. (2018, 2019) studies, there was no significant correlation between tinnitus distress and any amplitude, area, or latency $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratio in the current study.

CAEP responses in individuals with tinnitus may also differ as a function of hyperacusis status. In a recent study, Koops and van Dijk (2021) evaluated fMRI responses to frequency-specific tones from 0.25-8 kHz in two groups of individuals with tinnitus and hearing loss: with and without hyperacusis. They found that, overall, higher subcortical and cortical activity was associated with hyperacusis. However, when stimulated with higher frequency tones more similar to the tinnitus perception (on-tinnitus tones), the group with hyperacusis had smaller

responses relative to the group without hyperacusis. In addition to substantiating the potential importance of relating the stimulus frequency to an individual's perceived tinnitus, Koops and van Dijk (2021) also identified differing results in individuals with tinnitus based on hyperacusis status. As with ABR research (Mohrle et al., 2019; Refat et al., 2021), tinnitus with versus without hyperacusis may represent distinct physiological changes. However, because only two out of 36 participants in this study reported significant hyperacusis, and the lack of significant associations between overall HQ score or loudness sensitivity (UCL and loudness contour slope) with all sensory gating outcomes, further conclusions about the inter-relationships among tinnitus, hyperacusis, and sensory gating can't be made without further study.

Among the tinnitus-related participant characteristics assessed, tinnitus status itself and age had the most significant influence on measures of sensory gating including the P1-$N1_{amp\ ratio}$ and $P1_{lat\ ratio}$. The association between tinnitus with poorer sensory gating supports the hypothesis that decreased thalamocortical inhibition of irrelevant subcortical hyperactivity may be the mechanism by which tinnitus is perceived. The association between aging with poorer sensory gating may also relate to changes in the refractoriness of the neural generators that contribute to the CAEP, slowed temporal processing, poorer sensory gating, and/or poorer cortical inhibition. Overall, these results partially support the hypothesis for Specific Aim 3, that tinnitus had some predictive influence on measures of sensory gating, however, age may negatively impact sensory gating above and beyond the effects of tinnitus. Like the ABR, the predominantly young, little noise exposure history, good hearing, good SPIN, mild tinnitus, and minimal hyperacusis indicative of the research sample may have limited the observation of more significant effects on sensory gating outcomes.

4.2.2: Methodological Factors Influencing CAEP Outcomes

Varying methodological approaches to recording the sensory gating response likely contributed to differences across the literature and between the current study. As described in *Methods* section 2.2.3, two different filter settings were used to process raw EEG data in the current study to yield comparable results to sensory gating research in both auditory and psychiatric populations. While both filter settings removed unwanted recorded electrical activity from the EEG signal, the different filter settings have significant effects on the morphology, amplitude, and latency of measured CAEP components. Therefore, comparisons between sensory gating responses resolved with different EEG filters, both within the current study and across studies, should be made with caution. Other notable differences between the current research and psychiatric sensory gating studies as reviewed by Patterson et al. (2008) include variable stimulus presentation (e.g. sound field, insert, or headphone), stimulus parameters (e.g. click intensity and duration), and amplitude measurement technique (e.g. trough to peak versus baseline to peak). While these methodological differences are an important consideration when comparing the results of the current study to psychiatric literature, the more relevant comparisons are likely to studies in other auditory populations, particularly those with tinnitus rather than schizophrenia or other psychiatric disorders.

While the paired 10 ms click paradigm used in the current study is the most commonly used in sensory gating studies in the literature, other stimuli and parameters have been used. Notably, in their tinnitus and hearing loss related studies, Campbell et al. (2018, 2019, 2020a, 2020b) presented paired 250 Hz toneburst stimuli, reportedly to ensure equal audibility of the stimulus between control groups and groups with auditory impairment (who were also

reported to have sensory gating impairments; tinnitus, hearing loss, SPIN). The effects of various stimulus parameters on sensory gating outcomes has not been extensively studied. Patterson et al. (2008) reported no effect on the $P1_{amp\ ratio}$ between an 80 and 100 dB click intensity or between click durations of 1, 3, and 5 ms. Present sensory gating responses have also been obtained in response to speech stimuli using MEG (Hirano et al., 2010) and CAEPs (Miller et al., 2021). However, the effect of frequency-specific tonebursts on the sensory gating response has not been extensively studied. While Campbell et al. (2018, 2019) found a sensory gating difference related to tinnitus, normal sensory gating was not consistently demonstrated in normal hearing and mild hearing loss groups without tinnitus using this 250 Hz toneburst paradigm (Campbell et al., 2020a). The current study presented a traditional paired click stimulus, demonstrated a measurable sensory gating effect across all participants, and did not identify strong relationships between poorer sensory gating and tinnitus, hearing loss, or SPIN. Due to the poorly described effects of stimulus frequency on sensory gating outcomes, comparison between the current study with studies that presented a 250 Hz paired toneburst stimulus is limited.

As with the ABR, it is possible that “on-tinnitus” stimuli at frequencies similar to the tinnitus perception and region of greatest hearing loss or “off-tinnitus” stimuli at frequencies away from these regions may better differentiate sensory gating outcomes associated with tinnitus. Han et al. (2017) compared the acoustic change complex (ACC; a type of CAEP paradigm) responses in a group of 33 ears (all females) with a tinnitus perception psychoacoustically matched to 8 kHz and 63 ears (39 females) with no history of tinnitus perception (note that it is unclear if individuals with unilateral tinnitus could have participated

in both groups based on the reported number of ears instead of participants). ACC were evoked in response to a 1 kHz tone (off-tinnitus) which changed in the middle to either a 4 kHz tone (off-tinnitus) or an 8 kHz tone (on-tinnitus). They found that response amplitude did not differ for controls between conditions or for the tinnitus group in response to the *off-tinnitus* 4 kHz ACC, however, the tinnitus group exhibited a significantly smaller response to the *on-tinnitus* 8 kHz stimulus. That is, physiological differences associated with tinnitus were most notable when the ACC was evoked by a change from off- to on-tinnitus stimuli, where the on-tinnitus stimulus was psychoacoustically matched to the participant's tinnitus perception. Animal models have also suggested that cortical responses best differentiate between animals with and without tinnitus induced by noise-exposure when on-tinnitus stimuli similar to the behaviorally indicated tinnitus perception are used (Lowe & Walton, 2015). Sensory gating paradigms using on- and off-tinnitus frequency stimuli in identical pairs, and possibly in pairs where the frequency changes, may be more indicative of neuroplastic changes related to tinnitus.

In summary, while sensory gating was observed in the $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ amplitude and area ratios for both groups, the evidence of a greater sensory gating impairment associated with reduced inhibition in individuals with tinnitus based on group differences was only indicated by the secondary sensory gating outcome, the $\mathrm{P1}_{\text{lat ratio}}$. The significantly larger $\mathrm{P1}_{\text{lat ratio}}$ exhibited by the tinnitus group may indicate poorer sensory gating, reduced cortical inhibition, and/or a change in the recovery time, or refractoriness, of neural generators contributing to the CAEP response. Although not supported by group differences, a simple linear regression model indicated that tinnitus presence significantly predicted a larger $\mathrm{P1\text{-}N1}_{\text{amp ratio}}$, indicating poorer

sensory gating and supporting the hypothesis that tinnitus perception may be related to reduced thalamocortical inhibition of subcortical auditory hyperactivity. Further, both tinnitus presence and increased age significantly predicted a larger $P1_{\text{lat ratio}}$, which was best predicted by age. This suggests that inhibitory deficits related to aging may influence sensory gating outcomes in individuals with tinnitus above and beyond the effects of tinnitus itself. Noise exposure history, hearing loss, and SPIN were all unrelated to sensory gating outcomes. Overall, the results of the current study, both for the ABR and CAEP, were impacted by the characteristics of the research sample and methodological variations across studies. Consideration for these and other limitations as well as suggestions to address them for future research are described in the following section.

4.3: Limitations and Future Directions

Possible explanations for the lack of significant between-group findings and limitations to objectively assessing reduced subcortical and/or cortical inhibition in individuals with tinnitus have been previously addressed throughout the *Discussion*. Although recruitment and analyses were designed to account for several participant factors that have varied across previous studies, the tinnitus and demographic characteristics of the sample may not have been adequate to demonstrate the hypothesized neuroplastic reduction of inhibition. Not only may the participants not have had severe enough tinnitus, but there was an overrepresentation of young adults, limited noise exposure history and type, good hearing, and good SPIN performance that may have contributed to the lack of changes in both the ABR and CAEP related to these individual characteristics. The stimulus and recording techniques, while chosen to evoke the most robust responses, may have also contributed to a lack of significant tinnitus-

related findings. Some additional considerations for these limitations and future research are discussed in the following section.

As mentioned, the research sample was not normally distributed by age, with an overrepresentation of young individuals with normal or mild classifications on most outcome measures and underrepresentation of older individuals with more severe classifications on outcome measures. The final research sample was partly the result of recruitment restrictions due to the COVID-19 pandemic. As described in *Results* section 3.1, participants were mainly able to be recruited through the university band whereas older individuals who may be expected to express, for example, greater noise exposure histories, hearing losses, and SPIN deficits were unable to be recruited as easily due to social distancing safety guidelines intended to slow the spread of the COVID-19 virus. As described throughout the *Discussion*, this non-normal distribution likely contributed to the relatively few relationships between tinnitus-related characteristics with ABR $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ and sensory gating $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ outcomes of reduced inhibition. Given that the $\mathrm{P1}_{\mathrm{lat\ ratio}}$ was significantly predicted by age and tinnitus presence, recruitment of participants more equally distributed across a broader age range and possibly including age as a covariate would be valuable in disentangling some of the possible confounding effects of aging on tinnitus and inhibition. Such investigations may help to answer how aging and tinnitus relate to slowed neural processing and inhibitory changes in the CANS.

Greater tinnitus severity or hyperacusis present with tinnitus may be related to distinct, or pronounced, neuroplastic changes including reduced inhibition or auditory hyperactivity (Zeng, 2020). Recruitment of participants with a wider range of quantified hyperacusis and tinnitus severity, with a specific focus on individuals with greater tinnitus severity, would

address whether AEP outcomes may indicate whether the degree of neuroplastic reductions in inhibition may be dependent on tinnitus severity or reaction. Although tinnitus handicap was measured by the TFI in the current study, and basic pitch and loudness estimates were made, these were not significantly related to the AEP outcomes, possibly due to the limited range and overall low tinnitus distress perceived by the sample. As some studies have reported significant correlations, however, between greater tinnitus handicap and AEP outcomes (Campbell et al., 2018; Campbell et al., 2019), this may be a fruitful avenue to pursue. Further, the existence of subgroups of individuals with tinnitus based on, for example, tinnitus handicap has been suggested using statistical cluster analyses (Tyler et al., 2008). Therefore, if AEP outcomes differ by severity, cause of, or reaction to tinnitus, this may prove beneficial in determining individual intervention strategies as well as potentially monitoring effects of intervention.

Further study of the effects of stimulus and recording parameters on ABR and CAEP outcomes in the tinnitus population may also been necessary. Click stimuli were chosen for the ABR and CAEP in order to evoke robust responses and because they are the most common stimuli allowing for comparison to existing literature. However, it is possible that AEP responses evoked by this stimulus were not maximally sensitive to tinnitus-related neuroplastic changes, including reduced inhibition. Due to frequency-specific tonotopic map reorganization associated with tinnitus (Muhlnickel et al., 1998; Norena & Eggermont, 2003, 2005; Wienbruch et al., 2006), group differences between tinnitus and control participants may be more evident when on-tinnitus stimuli composed of frequencies most similar to the tinnitus perception and regions of greatest hearing loss are used to evoked AEPs as opposed to off-tinnitus stimuli composed of frequencies unlike the tinnitus and where hearing is best. The next research steps

would be to examine responses to on- and off-tinnitus stimuli, which may clarify whether and how frequency-specific stimuli influence both ABR and sensory gating responses in normal hearing and hearing impaired individuals. For the ABR, Bramhall et al. (2018) found an association between the ABR $V/I_{amp\ ratio}$ and tinnitus using a 4 kHz stimulus. Although they did not match the stimulus to the participant's tinnitus frequency, this may suggest that investigation of the relationship between frequency-specific tinnitus perception and the $V/I_{amp\ ratio}$ evoked by higher frequency tinnitus-matched toneburst stimuli may be informative. Sensory gating outcomes and their relationship to tinnitus perception may also be stimulus dependent. It may be that the sensory gating response is diminished or exaggerated in response to on- or off-tinnitus stimuli. This avenue would be a logical next step to better investigate how decreased sensory gating and cortical inhibition may relate to psychoacoustic tinnitus perception and may help clarify the lack of consistent sensory gating effects observed across tinnitus and non-tinnitus studies using a 250 Hz paired toneburst paradigm (Campbell et al., 2018; Campbell et al., 2019; Campbell et al., 2020a; Campbell et al., 2020b). If the use of on- and off-tinnitus stimuli improves the validity and reliability of subcortical and/or cortical tinnitus assessments of reduced inhibition, these ABR and CAEP methods may provide a way to objectively and reliably assess a frequency range that is most impacted by tinnitus for an individual. This may advance the current state of tinnitus assessment, which relies on subjective psychoacoustic tinnitus measures which are of poor clinical utility beyond serving as a counseling tool (Tunkel et al., 2014), or provide a tool for comparing the effectiveness of different tinnitus interventions.

In terms of recording AEPs, as previously discussed the use of a tiptrode to record ABR may have limited the observation of a significant $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ group difference due to larger and greater variation of wave I amplitude without significant changes to the wave V amplitude (Stamper & Johnson, 2015a). While this remains a significant limitation in scalp-recorded ABR in human subjects in general, recording responses using both a mastoid electrode and tiptrode, TM electrode, or trans-tympanic electrode (perhaps simultaneously) may help to distinguish if and how the wave I amplitude and $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ within and across individuals with tinnitus is influenced based on the type and location of reference electrode used. For both the ABR and CAEP, a strength of the current study was controlling for within individual variability associated with AEPs by analyzing within-individual ratios. However, factors such as amplitude measurement techniques (baseline to peak, trough to peak, or peak to peak) and the use of absolute versus average amplitude and latency measures may contribute to variability across studies.

Another consideration, particularly as it relates to the sensory gating paradigm, is the limited consideration of the role of attention. Whereas the ABR is a subconscious response that can be recorded while the participant is alert or sleeping, the CAEP (particularly the N1 and P2 components) can be modulated by attention (Picton & Hillyard, 1974). Although sensory gating has traditionally been considered a largely pre-attentive process, active attention to test stimuli has been shown to reduce the sensory gating effect represented by a larger $\frac{\text{test CAEP}}{\text{conditioning CAEP}}$ ratio (Golubic et al., 2019). In the current study, participants were instructed and watched a video (silently) or read a book during the recordings and to ignore the test stimuli. That is, the sensory gating responses were recorded passively. However, it is possible that the attention of tinnitus

participants was focused on their tinnitus perception during the passive listening task. It is possible that an inability to "shut out" this perception of tinnitus plays a part in the gating phenomenon, beyond the gating of the irrelevant repetitive stimuli. Individuals with more problematic tinnitus may particularly have been more focused on their tinnitus during the testing due to greater tinnitus distress and greater value attributed to their tinnitus experience. As a result, this may have reduced the CAEP sensory gating response. However, tinnitus distress in the current study as measured by scores on the TFI were not significantly correlated with sensory gating measures.

Although attention during the task was not directly monitored or measured in the current study, disrupted attention in individuals with tinnitus has been suggested by poor performance on central auditory processing tasks requiring attention, such as binaural separation of dichotic digits (Lima et al., 2020). Further, there is evidence that AEPs may be sensitive to attentional difficulties in individuals who perceive tinnitus compared to controls. For example, Roberts et al. (2012) tested a tinnitus and control group (age and hearing-matched) under active and passive attentional conditions in a CAEP and ASSR (40 Hz cortical response) paradigm. Subjects had to detect (by button press) a target sound embedded within the amplitude modulated AEP stimulus in the active task and ignored the stimuli in the passive task. The participants then underwent training to improve their ability to detect the targets and were retested under the same active and passive conditions. In the control group, N1 and ASSR amplitudes increased in the active relative to passive conditions and the relationship did not change over training sessions. The tinnitus group, by contrast, had no difference in N1 or ASSR amplitude between the active and passive condition at the first test session, suggesting a

possible reduced effect of attention on physiological responses in individuals with tinnitus. With training, however, the tinnitus group also showed increased amplitudes in the active condition yielding a more similar response to the outcomes of the control group. The results of the Roberts et al. (2012) study suggest that, without training, AEP responses from the tinnitus group differed from controls as a function of attention. Although the current study was a passive paradigm with no active conditions, it is possible that attentional differences between the tinnitus and control group impacted the results or contribute to different results across the literature. As better sensory gating outcomes have previously been reported among adults who perform better on attentional tasks (Lijffijt et al., 2009a), it may be that poorer sensory gating identified in individuals with tinnitus is due to disrupted attention, reduced cortical inhibition related to tinnitus generation, or a combination of both. Future research should aim to fill these gaps in knowledge by continuing to study how to reliably manipulate and/or control for attention and how differences in the perception and value placed on perceived tinnitus contributes to AEP measures reflecting sensory gating. Such research may have important clinical implications, for example, if lack of attention during a task is determined to be related to perceptual relevance and distress related to tinnitus, auditory training tasks targeting attentional deficits may help to alleviate problematic tinnitus and potentially improve the ability of a person with tinnitus to function in tasks at work or school.

As a final consideration, it may be that other objective AEP indices of tinnitus-related reduced inhibition are more sensitive to tinnitus presence in humans. For example, we recently identified that 13 individuals with tinnitus (*M* = 52.8, *SD* = 19.3, range = 20 – 73 years) had significantly larger onset-offset CAEP amplitudes in response to long duration white noise

stimuli relative to 13 age, hearing, and sex matched controls (*M* = 54.5, *SD* = 18.0, range = 24 – 76 years) (Morse & Vander Werff, 2021). Typically CAEPs recorded in response to stimulus onset reflect stimulus-evoked synchronous neural excitation, and larger responses reflect greater excitation (Phillips et al., 2002). However, the less frequently studied CAEP response to the offset of a long duration stimulus may reflect a release from inhibition such that a larger response reflects greater inhibition to sustained auditory stimulation (Rajaram et al., 2019). Therefore, a larger amplitude onset response would reflect hyperexcitability and a smaller amplitude offset response would reflect reduced inhibition, mathematically resulting in a larger onset minus offset difference (denoted with a Δ). In that study (Morse & Vander Werff, 2021), larger Δ amplitude/areas were observed in the tinnitus group compared to non-tinnitus controls for all component amplitudes (ΔP1, ΔN1, ΔP2) and area (ΔP1-N1-P2). However, the difference was only statistically significant for ΔP2 amplitude such that the tinnitus group exhibited significantly larger ΔP2 amplitudes (*M* = 1.19 µV, *SD* = 0.962) relative to controls (*M* = 0.472 µV, *SD* = 0.596; $p < 0.001$). This finding may be indicative of cortical hyperactivity and reduced inhibition in the tinnitus group. Further, using a similar multiple regression analysis and *PRE* as used in the current study, it was determined that among participants of all ages (n = 26), only the presence of tinnitus significantly influenced the ΔP2 amplitude (*PRE* = 0.206, $\sqrt{\text{PRE}}$ = 0.453). However, among participants aged 50+ years (n = 19), the influence of tinnitus on the ΔP2 amplitude *increased* in strength (*PRE* = 0.387, $\sqrt{\text{PRE}}$ = 0.622). This finding, coupled with the significant influence of age on the $P1_{\text{lat ratio}}$ identified in the current study suggests that age influences the relationship between tinnitus with reduced inhibition and/or hyperexcitability. As mentioned above, studies that assess whether the interaction between tinnitus and age

significantly influence CAEP measures that reflect reduced inhibition and/or hyperexcitability may indicate if an individual's age modifies the strength of the relationship between tinnitus and reduced inhibition and/or hyperexcitability.

Future research addressing these considerations will contribute to the growing field of objective tinnitus assessment in humans. Specifically, these directions include: (1) more completely reflecting and describing the range and effects of tinnitus-related characteristics on AEP outcomes, (2) identifying and clarifying the relationships among age, tinnitus, and reduced inhibition, (3) determining the extent to which on- versus off-tinnitus stimuli best differentiate between tinnitus and control groups, (4) controlling for and assessing the relationship between attention and tinnitus, and (5) further assessing whether other AEP paradigms such as onset-offset differences are more sensitive indices of tinnitus status.

4.4: Significance and Conclusions

This research was the first to objectively assess reduced inhibition in individuals with tinnitus at both the subcortical and cortical level using ratio outcomes at both levels for assessment of within-individual AEP measurements that reflect inhibition and controlling for sex, age, and hearing differences between tinnitus and control groups. The overarching goals of the study were to contribute to our knowledge regarding tinnitus pathophysiology in humans. Invasive animal studies indicate that tinnitus is caused by peripheral auditory insult, resulting in reduced cochlear output that triggers neuroplastic changes including decreased inhibition yielding subcortical auditory hyperactivity, and decreased thalamocortical inhibition causing a sensory gating failure to prevent the subcortical auditory hyperactivity from being consciously perceived as tinnitus.

Subcortically, the ABR $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ was proposed as a representation of tinnitus-related reduced cochlear output (reduced wave I amplitude) and subcortical auditory hyperactivity (increased wave V amplitude), together leading to a larger $\mathrm{V/I}_{\mathrm{amp\ ratio}}$ (Specific Aim 1). Neither the tinnitus and control group comparison nor the multiple regression analyses indicated a significant relationship between tinnitus with reduced subcortical inhibition. Further, age, noise exposure history, hearing loss, and SPIN all had little effect on the ABR $\mathrm{V/I}_{\mathrm{amp\ ratio}}$. The results suggest that ABR outcomes, at least as measured in the current study using a click stimulus and tiptrode recording electrode, were insensitive to any neuroplastic reductions of subcortical inhibition related to tinnitus that have been documented with invasive studies of animal models. Broader representation of participants with more severe tinnitus and with consideration of age as a moderating factor are needed to better understand the lack of tinnitus-related findings. Consideration of stimulus and recording techniques, particularly the use of on- or off-tinnitus stimuli to evoke responses and comparison of recording electrode sites may result in ABR outcomes that may better relate to tinnitus perception and provide stronger evidence of possible differences in subcortical inhibition in this population.

Cortically, sensory gating was proposed as a representation of tinnitus-related reduced thalamocortical inhibition leading to the perception of irrelevant subcortical auditory hyperactivity. While there was not a significant difference between the tinnitus group and controls on the primary amplitude/area ratio outcomes of sensory gating, the tinnitus group had a significantly larger $\mathrm{P1}_{\mathrm{lat\ ratio}}$. Although not significantly different between groups, a simple linear regression indicated that tinnitus significantly predicted a primary measure of sensory gating, the P1-$\mathrm{N1}_{\mathrm{amp\ ratio}}$. However, when including the effects of age, noise exposure

history, hearing loss, and SPIN performance, the regression was no longer significant. The secondary outcome measure which significantly differed between the tinnitus and control group and may be related to sensory gating, $P1_{\text{lat ratio}}$, was significantly predicted by a multiple regression model including tinnitus, age, noise exposure history, hearing loss, and SPIN. Tinnitus and age were the only two variables to significantly predict $P1_{\text{lat ratio}}$. The lack of a latency reduction for the test response relative to conditioning and the relationship between this outcome tinnitus, and age may be indicative of poorer sensory gating, refractoriness of the neural generators contributing to the CAEP response, slowed neural processing, and/or decreased inhibition. The relationships among sensory gating, tinnitus and aging, is an important area for future study. It may be that there are interactions between processing speed and inhibitory deficits underlying both aging and tinnitus perception.

These results partially support the hypothesized association between tinnitus with reduced cortical inhibition, represented by sensory gating. Namely, the mechanism by which tinnitus is perceived in humans may be related to decreased thalamocortical inhibition of subcortical auditory hyperactivity. Further, the results of this study add to the growing field of sensory gating research in individuals with tinnitus by indicating that age may influence sensory gating above and beyond the effects of tinnitus. Again, recruitment of participants with broader representation and control for age and tinnitus severity is an important next step. Additionally, the use of on- and off-tinnitus stimuli and manipulation and control for attention may better identify tinnitus-related changes in inhibition, the speed of neural processing, and relationships to the perception and handicap associated with tinnitus. In addition, the use of other AEP

paradigms such as onset-offset CAEP differences may be more promising candidates for objective evaluation of tinnitus related cortical plasticity.

In the long term, continued enhancement of objective study of reduced inhibition in humans with tinnitus may lead to substantial advances to tinnitus clinical care including the possible identification of tinnitus subgroups by cause or reaction to tinnitus and indicating specific interventions that may work best for certain individuals within those subgroups. If these next research steps are successful, AEPs may prove to be valid, reliable, non-invasive, low-cost, and clinically feasible objective indices of tinnitus-related reduced inhibition. As such, this field of research has the potential to lead innovations in clinical tinnitus management and, ultimately, improved tinnitus treatment for humans.

Abbreviations

- ABR – Auditory brainstem response
- AC – Auditory cortex
- AEF – Auditory evoked fields
- AEP – Auditory evoked potential
- ANF – Auditory nerve fiber
- CAEP- Cortical auditory evoked potential
- CANS – Central auditory nervous system
- CN - Cochlear nucleus
- CRT – Cognitive Behavioral Therapy
- DCN – Dorsal cochlear nucleus
- DPOAE – Distortion product otoacoustic emissions
- EEG – Electroencephalographic
- EPSP - Excitatory post-synaptic potential
- fMRI BOLD - Functional magnetic resonance imaging blood-oxygen-level
- GPIAS – Gap-prepulse inhibition of the acoustic startle reflex
- HCN - Hyperpolarization-activated cyclic nucleotide-gated channel
- HL – Hearing level
- HQ – Hyperacusis Questionnaire
- IC - Inferior colliculus
- IHC – Inner hair cell

- LTD - Long-term depression
- LTP - Long-term potentiation
- MCL – Most comfortable loudness level
- MEG - Magnetoencephalography
- MGB - Medical geniculate body
- MLR – Middle latency response
- NA - Nucleus accumbens
- NBN – Narrowband noise
- NESI - Noise Exposure Structured Interview
- NEU – Noise exposure unit
- NU-6 - Northwestern University Auditory Test No. 6.4
- OAE – Otoacoustic emission
- OCD – Obsessive compulsive disorder
- OHC – Outer hair cell
- ppe – Peak-to-peak equivalent
- PRE - Proportional reduction in error
- PTA – Pure tone average
- PTSD – Post traumatic stress disorder
- QOL – Quality of life
- SFR – Spontaneous firing rate
- SL – Sensation level
- SNR – Signal to noise ratio
- SOC - Superior olivary complex
- SPIN – Speech perception in noise
- SPL – Sound pressure level
- SVAMC – Syracuse Veterans Affairs Medical Center
- TCD - Thalamocortical dysrhythmia
- TFI - Tinnitus Functional Index
- THI – Tinnitus Handicap Inventory
- TRT – Tinnitus Retraining Therapy
- UCL – Uncomfortable loudness level
- UCL – Uncomfortable loudness level
- VA – Veterans Administration
- VCN – Ventral cochlear nucleus
- vmPFC - Ventromedial prefrontal cortex

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