Altered Neural Gain Following Acute Unilateral Deprivation: Towards a Mechanistic Understanding of Tinnitus

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List of Abbreviations

ABR	Auditory brainstem response
ACC	Accident Compensation Corporation
ANOVA	Analysis of variance
ART	Acoustic reflex threshold
BSA	British Society of Audiology
BPG	Best practice guideline
CAEP	Cortical auditory evoked potential
CHL	Conductive hearing loss
CMS	Common mode sense
dB	Decibel
dB HL	Decibel hearing level
dB SL	Decibel sensation level
dB SPL	Decibel sound pressure level
DRL	Driven right leg
EEG	Electroencephalogram
fMRI	Functional magnetic resonance imaging
fNIR	Functional near-infrared spectroscopy
GABA	Gamma-aminobutyric acid
GSP	Good scientific practice
Hz	Hertz (unit of frequency)
IHC	Inner hair cell
ISO	International Standards Organisation
MEG	Magnetoencephalography

MRI	Magnetic resonance imaging
MTG	Medial temporal gyrus
NZAS	New Zealand Audiological Society
OAE	Otoacoustic emission
OHC	Outer hair cell
OSCE	Objective Structured Clinical Examination
PET	Positron emission tomography
PSD	Power spectral density
PTA	Pure tone audiometry
ROS	Reactive oxygen species
sLORETA	Low resolution brain electromagnetic tomography
SNHL	Sensorineural hearing loss
STG	Superior temporal gyrus
TCD	Thalamocortical dysrhythmia
THI	Tinnitus handicap inventory
VEOG	Vertical electro-oculography

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“It really is a very odd business that all of us, to varying degrees, have music in our heads.”

- (Sacks, 2007)

Chapter 1: Introduction

1.1 Overview

Tinnitus is characterised by the perception of sounds in the absence of any objective physical sound source (Weisz et al., 2005). While some individuals who experience tinnitus are not very troubled by it, others find their tinnitus causes a considerable amount of distress. Various strategies are used in the management of tinnitus including sound therapy, counselling, hearing aid use and cognitive behavioural therapy (Langguth, 2015; Langguth et al., 2019). However, these treatments are primarily aimed at reducing the impact of tinnitus, rather than as a causal intervention for the tinnitus percept (McFerran et al., 2019). This is a treatment approach that is often at odds with the goals of those with tinnitus. This was evident in a study carried out in the United States by Husain et al. (2018), as when asked to define tinnitus treatment success, audiologists defined this as decreased awareness and anxiety relief for their patients. Those with tinnitus on the other hand, defined treatment success as a reduction of tinnitus loudness and elimination of tinnitus. Dissatisfaction with current tinnitus treatment has been reported in several countries, with patients desiring a pharmacological solution over other modalities (McFerran et al., 2018; McFerran et al., 2019; Sanchez & Stephens, 2000; Zarenoe & Ledin, 2014).

A comprehensive understanding of the neurophysiological mechanism of tinnitus remains lacking, which has hampered progress towards a causal intervention such as via pharmacology, auditory training or via an auditory prosthesis. Recurring research challenges have contributed to the absence of a thorough mechanistic understanding and consequently, a potential cure. For instance, control over tinnitus onset is not usually possible; those with tinnitus only present themselves once tinnitus has already set in, which necessitates comparison against non-tinnitus controls. Therefore, there is no within-subjects baseline to

compare anatomical or physiological features in the tinnitus-affected auditory system, without introducing unwanted inter-subject variation.

Heterogeneity amongst tinnitus study participants has also made it difficult to pinpoint the underlying mechanism of tinnitus. Hearing loss, which can be a trigger for tinnitus, is often a further uncontrolled and confounding variable. It is a confound because tinnitus is expected to alter the activity of the auditory system but so is hearing loss, therefore assigning causation of the altered activity can be problematic. One way to address these methodological challenges is via experimentally induced tinnitus. Pre-onset baseline measures are therefore available, enabling a within-subjects comparison and thus eliminating a large source of variability, while hearing status is also controlled across conditions. Therefore, an improved mechanistic understanding of tinnitus may be possible via studying individuals with experimentally induced tinnitus.

The following review will provide introductory information relating to tinnitus. This will first include details on prevalence of the symptom and current methods of assessment. The review will then focus on research which has sought to determine the mechanisms underlying the tinnitus percept, with an analysis of where the gaps in knowledge lie. A rationale regarding the need for an objective assessment of tinnitus will be presented as well as the relevance of investigating a tinnitus biomarker. Finally, the rationale behind the present research will be put forward before outlining the specific aims and hypotheses of this study.

Chapter 2: Literature Review

2.1 Tinnitus

The term tinnitus is derived from the Latin word ‘tinnire’, meaning ‘to ring’. The term tinnitus describes the perception of an auditory sensation in the absence of a corresponding external stimulus (Baguley et al., 2013). Tinnitus is often described as a modern phenomenon. However, while it might be true that widespread awareness of tinnitus has increased in recent years, historical consideration reveals that the symptom was also experienced thousands of years ago. According to Dietrich (2004), the earliest undisputed reference to tinnitus is found in the *Corpus Hippocraticum*, which is ascribed to the Greek physician Hippocrates (460-377 B.C). Tinnitus may be broadly categorised as objective or subjective. The less common of the two categories is objective tinnitus, whereby an observer can also hear the tinnitus. In cases of objective tinnitus, the sound is generated in the body by blood flow, muscular contractions, or acoustical energy caused by spontaneous responses of the active sensory processes of the cochlea, known as spontaneous cochlear emissions (Bauer, 2018). Subjective tinnitus, on the other hand, is the experience of the individual alone. Qualitative descriptions of subjective tinnitus include ringing, hissing, buzzing, clicking, a clear tone, static, roaring and cicada-like sounds, to name but a few (Bauer, 2018; Lentz & Yuan, 2020). The sound or sounds can be experienced as inside or outside the head, or in one or both ears - either intermittently or constantly (Schmidt & Henry, 2018).

This thesis will address the more common category, subjective tinnitus, and this will be referred to as ‘tinnitus’ from this point on.

2.1.1 Tinnitus and the Individual

Most people will experience tinnitus at some point in life. The reader may have, for example, experienced tinnitus for a few minutes or hours upon returning home after an evening of listening to loud music. Such an experience is not uncommon (Zhao et al., 2010).

In their 1953 research, Heller and Bergman found that when normally hearing and healthy participants spent a short time in a quiet room, almost all of them experienced tinnitus. A transient tinnitus that is noticed only when in a quiet environment and/or for a relatively short duration is a normal phenomenon. For others, tinnitus will be experienced as a more regular and sustained presence, and it is these individuals that we typically see in an audiology clinic. The majority of those with tinnitus describe it as a background effect; something that is only noticeable when they think of it, or perhaps only in a quiet environment. For these people, tinnitus is a feature of life, but it is not bothersome. There are others, however, who experience tinnitus as something entirely different. It is estimated that 20% of those who experience tinnitus find their tinnitus severely debilitating, making it a challenge to carry out daily activities (McCormack et al., 2016). Tinnitus is reported to have a wide range of emotional impacts on those who experience it, with some reporting frustration, anxiety, and suicidal thoughts (Aazh & Moore, 2018; Moring et al., 2016; Pryce & Chilvers, 2018). Inability to work and interference with social interaction has also been reported (McCormack et al., 2016). Tyler et al. (2015) recommend determining if patients are curious, concerned or distressed about their tinnitus at the initial interview, as this categorisation will influence their appropriate management plan. Curious patients, for example, typically require basic information about possible causes, mechanisms, and outcomes of their tinnitus. Once the mystery of the tinnitus is explained, their reaction is largely resolved. On the other hand, concerned patients often require more detail and a more formal evaluation, whereas distressed patients may require assistance from psychologists or psychiatrists (Tyler et al., 2015).

2.2 Prevalence

Accurate estimates of tinnitus prevalence are essential for setting priorities of interventions, selection of strategies for interventions and monitoring of programmes at a

national and global level (Pascolini & Smith, 2009). A recent systematic review by Jarach et al. (2022) report a global prevalence of diagnosed tinnitus to be 3.4%. The researchers acknowledged substantial heterogeneity among the studies and used the chi-squared test to control for this. However, in their 2016 systematic review of tinnitus prevalence reporting, McCormack et al. identified widespread inconsistency in the definition and reporting of tinnitus, which was identified as contributing to variability of prevalence estimates across studies. The varying definitions included 'tinnitus lasting more than five minutes at a time', 'ringing in the ears' and 'tinnitus for the past 3 months'. This variability is evident on a review of literature reporting tinnitus prevalence in the past two decades, with Kim et al. (2015) reporting 20.7% prevalence, Nondahl et al. (2002) reporting 8.2%, Kochkin et al. (2011) reporting 10%, Oosterloo et al. (2021) reporting 21.4% and Wu et al. (2015) reporting 6%. Data reported by Wu et al. (2015) is specific to Aotearoa/New Zealand and found that males were more likely to report tinnitus than females, and that tinnitus prevalence increased with age, peaking at 13.5% for adults aged ≥65 years.

In agreement with McCormack et al. (2016), Gallus et al. (2015) found that definitive conclusions regarding tinnitus prevalence are elusive due to the lack of a standardised and validated definition of tinnitus, as well as heterogeneity in terms of the age range in populations studied. These findings indicate that future advancement in understanding the epidemiology of tinnitus will require a standardised definition of tinnitus for research purposes, in addition to a standardised method for measuring and reporting the symptom.

2.3 Tinnitus Risk Factors

Numerous risk factors for tinnitus have been documented in the literature. The most widely accepted risk factor for tinnitus is hearing loss, however there are a range of other risk factors relevant to tinnitus management (Baguley et al., 2013). The following section will detail the biggest risk factors.

2.3.1 Tinnitus and Hearing Loss

Almost anything that results in hearing loss can also result in tinnitus. Sensorineural hearing loss (SNHL) is commonly associated with tinnitus (Sanchez et al., 2005; Savastano, 2008) but this observation may merely reflect SNHL being more common than conductive hearing loss (CHL). In fact, CHL can also trigger tinnitus, suggesting that it is reduced sound input that may be the important factor. Only about 10% of those with tinnitus have hearing thresholds within normative limits (at least when measured by standard audiometry from 250 Hz to 8000 Hz). It is possible that this enigmatic 10% do have some form of hearing loss, but at frequencies above 8000 Hz, thus not normally tested and therefore recorded. It is also important to consider that cochlear structures can be damaged without a corresponding raise in hearing thresholds. This will be discussed in more detail in section 2.3.3.

Many studies have sought to determine the exact relationship between hearing loss and tinnitus. Henry et al. (1999) found that tinnitus sensation and the frequency range of hearing loss appear to be related. In their study, when subjects matched their tinnitus pitch to a pure tone, most of the matches were at frequencies where the listener's hearing was impaired. Work by Noreña et al. (2002) supported that finding, with results from their study also demonstrating that the tinnitus spectrum (i.e. an array of frequency components that comprise a broadband sound matching the tinnitus, and obtained via psychoacoustical tinnitus matching techniques), corresponds to the frequency range of hearing loss. König et al. (2006) found a relationship between the steepness of the audiogram and tinnitus: in their study, maximum steepness of the audiogram was higher in patients with tinnitus, compared to patients without tinnitus. Hearing loss has been shown to lead to reorganisation of the tonotopic map (Noreña & Eggermont, 2005), hyperpolarisation of thalamic cell membranes, increases in neural gain and facilitation of non – auditory inputs (Haider et al., 2018; Shore et al., 2019). These changes can result in altered patterns of neural firing within the central

auditory system, which can produce neural hyperactivity at cortical or subcortical levels, hypersynchrony in the cortex and/or changes in cortical or thalamocortical oscillating activity. These are all mechanisms which have been implicated with the tinnitus percept and will be discussed in Section 2.6. While the link between hearing loss and tinnitus is undoubtedly significant, hearing loss does not always trigger tinnitus. This indicates that hearing loss alone is not responsible for the experience of tinnitus.

2.3.2 Ageing

As hearing loss and tinnitus are closely related, populations with greater levels of hearing loss have a correspondingly greater prevalence of tinnitus (Hoffman & Reed, 2004). Bilateral SNHL is commonly diagnosed as people age, a condition known as presbycusis. It is generally agreed that the prevalence of tinnitus increases monotonically up to about age 70, after which point prevalence either becomes constant or decreases slightly with age (Al-Swiahb & Park, 2016; Møller, 2011; Savastano, 2008). While auditory deprivation may account in some part for the higher prevalence of tinnitus in older adults, other medical factors that become more prevalent with age may be associated with tinnitus and should be considered independently. These factors include vascular disease, diabetes, hypertension, autoimmune disorders, and degenerative neural disorders, all of which can occur with or without hearing loss (Perry & Gantz, 2000). In addition, medical conditions often require the use of medications, some of which can initiate or exacerbate tinnitus (Henry et al., 2005).

2.3.3 Noise Exposure and Tinnitus

A well reported risk factor for both hearing loss and tinnitus is noise exposure (Bhatt et al., 2016; Kim et al., 2015; Ralli et al., 2017a), with certain populations like military service personnel found to be at particular risk (Henry et al., 2020; Theodoroff & Konrad-Martin, 2020). Noise exposure, either over a prolonged period or due to a single impulse noise event, can damage and destroy outer hair cells (OHCs), inner hair cells (IHCs) and

other structures of the sensory epithelia, leading to hearing loss and in a lot of cases, tinnitus (Ralli et al., 2017a). Noise exposure may also account for the wealth of literature reporting the perception of tinnitus in the presence of a 'within normal limits' audiogram (Guest et al., 2017; Hébert et al., 2013; Schaette & McAlpine, 2011; Xiong et al., 2019). Attention has been given to cochlear synaptopathy as a potential explanation for the presentation of tinnitus in the absence of hearing loss. Cochlear synaptopathy occurs when there is a loss of synapses between IHCs and auditory nerve fibres after excessive noise exposure (Chen et al., 2021).

In their 2011 study, Schaette and McAlpine studied 15 females with chronic tinnitus and 18 control participants who did not have tinnitus. All participants had hearing thresholds ≤20dB HL from 125 Hz to 12000 Hz. Auditory brainstem response (ABR) was carried out on all participants and the results showed reduced amplitude of wave I in the tinnitus participants when compared to the controls. Based on this finding, the authors proposed that the perception of tinnitus in audiometrically normal individuals could be due to deafferentation of high threshold auditory nerve fibres. These high-threshold fibres are triggered by sounds heard at high input levels but not at low levels and deafferentation of high-threshold fibres could therefore occur without obvious changes to absolute hearing thresholds on a pure-tone audiogram. An interesting feature of the results by Schaette and McAlpine was that the following waves of the ABR were not reduced in amplitude. The researchers concluded that this finding provided physiologic evidence that "hidden hearing loss" or cochlear synaptopathy manifests as reduced neural output from the cochlea which could lead to pathological increased activity patterns in the auditory brainstem. This in turn could potentially explain the development of tinnitus in those with normal audiograms. Of note in this study is the mean threshold difference of 3.5dB HL at 12000 Hz between the tinnitus and control groups. This disparity could account for group differences between the groups as wave I is dominated by the responses of high frequency auditory nerve fibres (Don &

Eggermont, 1978). Similar findings were reported by Gu et al. (2012), who carried out ABR on males (15 males with tinnitus and 21 males without tinnitus) In this instance, the wave I amplitude was similar in the cohort with tinnitus, but wave V amplitude was also enhanced.

Guest et al. (2017) also sought to investigate changes in ABR wave I amplitude in those with tinnitus when compared to controls but the same ABR finding could not be replicated. Of importance in the Guest et al. (2017) study was the finding that the reported lifetime noise exposure of the participants with tinnitus exceeded that of the control group, despite close matching on the basis of audiometric thresholds, age and sex. This finding provides evidence implicating noise exposure in the experience of tinnitus without hearing threshold elevation.

Given the reports that high levels of tinnitus are experienced by those with greater exposure to noise (Guest et al., 2017; Theodoroff & Konrad-Martin, 2020), tinnitus education would be a worthwhile inclusion to workplace hearing conservation programmes if not already in place.

2.3.4 Medications

Ototoxicity is "an undesirable effect of some drugs that induce reversible and irreversible damage of the inner ear structures, including the cochlea and the vestibule, causing temporary or permanent hearing loss, tinnitus and/or balance alteration" (Altissimi et al., 2020, p. 1). More than 130 drugs are known to be ototoxic, with the major classes of ototoxic drugs including aminoglycoside antibiotics, antimalarials, loop diuretics, antineoplastics and anti-inflammatories (Dille et al., 2010; Salvi et al., 2016). Ototoxic effects are highly variable across individuals, as effects depend on the duration of the therapy, the route of administration, the infusion rate, dosage, individual sensitivity to the drug and genetic pre-disposition (Altissimi et al., 2020; Cianfrone et al., 2011). The generation of reactive oxygen species (ROS) is thought to be the initiating step in some cases of

ototoxicity, as with aminoglycosides and cisplatin (Tabuchi et al., 2011). It is thought that ROS triggers pathways of apoptotic cell death in the cochlea, which can lead to SNHL and tinnitus (Tabuchi et al., 2011). Animal studies have suggested that OHCs comprise one of the main sites of anti-inflammatory ototoxicity, as demonstrated by a reduction in the level of OAEs following administration of high-dose salicylate (Ueda et al., 1996). Ototoxicity related tinnitus is one of the few instances in which the symptom may be reversed upon discontinuation of the medication (Seligmann et al., 1996).

2.3.5 Head Injury

Tinnitus is a symptom known to persist following a traumatic brain or whiplash injury (Folmer & Griest, 2003). Forces generated through head injuries have the potential to cause hearing and labyrinthine dysfunction as a result of damage to the cochlea, auditory nerve, middle ear conducting components, as well as auditory centres in the brain. Tinnitus associated with a head injury may occur instantaneously but, in some cases, neurosensory disorders such as tinnitus appear hours, days or months after the event (Claussen & Constantineau, 1995). Whiplash because of a car accident has a known association with tinnitus onset (Kreuzer et al., 2014) and interestingly, direct contact trauma (a direct knock of the head against a hard surface of the car), is not necessary to cause neurosensory symptoms. Non-contact whiplash can also result in tinnitus. Due to a lack of objective evidence to support the symptom on radiologic and orthopaedic tests following the event, many of these patients can be under suspicion of malingering (Claussen & Constantineau, 1995). Patients who present with tinnitus following a head injury or non-contact whiplash event often present with additional non-acoustical symptoms such as headaches, vertigo, sleep disturbances and depression (Claussen & Constantineau, 1995). It is therefore important to question these patients carefully so all the appropriate medical professionals can be involved in their care.

2.3.6 Tinnitus and Stress

There are many definitions of stress in both scientific and colloquial settings. It is important to differentiate between external or internal stressors and stress responses. Stressors are stimuli that disrupt cellular homeostasis, while a stress response is an individual's biopsychosocial reaction to such triggers (Mazurek et al., 2019). While it has not been proven that stress is a direct risk factor for tinnitus (Pattyn et al., 2016), it appears that there is a relationship between tinnitus and stress. This relationship is frequently reported in tinnitus literature, in web-based tinnitus information and in patient information leaflets. It is thought that the perception of tinnitus is maintained by non-auditory neuronal circuits (Rauschecker et al., 2010). Excessive neuronal activity in frontal and temporal lobes, limbic and para-limbic structures have been reported in those with tinnitus and these areas have also been demonstrated to show stress-related structural and functional changes (Henry et al., 2014; Kreuzer et al., 2013). Cognitive functions that are mainly maintained by limbic structures such as the amygdala and hippocampus can also be affected by stress and tinnitus (Clarke et al., 2020; Mohamad et al., 2016). A recent scoping review by Elarbed et al. (2021) investigated whether exposure to stress plays a role in the pathophysiology of tinnitus and 29% of the patients with tinnitus associated their tinnitus onset with stress. However, no definition of stress was given, and the authors point out that it is not clear if the tinnitus was associated with the occurrence of certain life events, or with emotional distress that occurred when the event was perceived as stressful. Several studies in the scoping review showed that stress increased the loudness and bothersomeness of tinnitus. This is consistent with the suggestion of Baigi et al. (2011), who stated that stress is a key factor in modulating the severity of tinnitus. In the research by Baigi et al. (2011) which comprised questionnaire responses from 12,166 subjects in Sweden, it was demonstrated that the probability of developing tinnitus is almost the same for highly stressed persons as it is for those exposed to

occupational noise and that for those who experience both stress and occupational noise, the risk of tinnitus increases again. Such a finding indicates that in addition to hearing conservation programmes in work environments with high levels of noise, stress management programmes could also be considered.

2.4 Current Methods of Tinnitus Assessment

Best practice guidelines (BPGs) are defined as systematically developed statements which assist clinician and patient decisions about appropriate health care for specific clinical circumstances (Field & Lohr, 1990). In audiological care, comprehensive guidelines exist worldwide with respect to widely used procedures like pure tone audiometry (PTA), hearing aid fitting, paediatric audiological assessment, speech audiometry and auditory brainstem response testing (Audiology Australia, 2022; BSA, 2018; NZAS, 2021). However, there is a dearth of such guidelines for both the assessment and management of tinnitus in many countries, including here in Aotearoa/New Zealand. An online search found that many audiological service providers across this country offer tinnitus assessment and management. However in the absence of BPGs, one may wonder how these appointments are managed and to what extent practice may vary.

As detailed by the New Zealand Audiological Society (NZAS), the assessment of tinnitus as well as the provision of tinnitus treatments including counselling and therapy for persons with tinnitus is listed within the scope of practice for audiologists (NZAS, 2019). However, the same society does not at the time of writing have a published set of BPGs regarding tinnitus assessment and management. An absence of BPGs has previously been shown to lead to lack of standardization in tinnitus care elsewhere. For example, in their 2011 survey of all audiology and hearing therapy staff based in England offering tinnitus care (response rate 39%), Hoare and Hall reported that less than half the respondents used a tinnitus specific questionnaire and fewer than 20% collected psychometric evaluations of

tinnitus. In that same study, respondents were aware of the potential psychological comorbidities in their tinnitus patients but less than 5% screened for anxiety or depression using a validated questionnaire. In 2021, members of the multidisciplinary tinnitus and hyperacusis special interest group of the British Society of Audiology (BSA) produced an evidence-based set of guidelines for tinnitus assessment and management (BSA, 2021). Otoscopy, PTA and tympanometry is the minimum tinnitus test battery recommended. If performed, acoustic reflex testing and uncomfortable loudness levels (ULLs) should be carried out with care as these tests have the potential to exacerbate tinnitus.

The BSA guideline also covers where further investigations are recommended, such as a recommendation of magnetic resonance imaging (MRI) in cases where there is asymmetrical hearing loss and/or unilateral tinnitus, high frequency audiometry in cases where hearing thresholds from 250Hz to 8000Hz are within normative limits and otoacoustic emission (OAE) testing. These guidelines do not recommend psychoacoustic tests such as pitch and loudness matching because the tasks require that patients focus on their tinnitus more and may cause distress.

Importantly, the guidelines also include a section on how to recognise severe distress and steps the clinician can follow in such cases where there is suicidal ideation to ensure safeguarding of those presenting with tinnitus. The authors of the BSA guidelines state that the aim of the guidelines are to “promote uniformity in the evidence-based assessment and management of adult patients with tinnitus” (BSA, 2021, p. 8) and to promote shared decision making between the individual with tinnitus and the clinician. It seems crucial that such a set of guidelines should also exist in Aotearoa/New Zealand. In addition to incorporating high level research evidence into the development of guidelines, BPGs in this country should also include relevant cultural considerations, the importance of which is discussed further in section 5.6. A notable long-standing absence in tinnitus assessment is an

objective measure of tinnitus presence/absence (or severity) which can be used in conjunction with validated questionnaires. Such a combined approach could enable clinicians to determine definitively if treatments have been effective through analysis of before and after measures.

2.5 Does Tinnitus Happen in the Ear or the Brain?

Up until recent decades, tinnitus was thought to be the result of aberrant neural activity which was generated in the periphery of the auditory system (Noreña & Farley, 2013). In a healthy auditory nerve, there is a steady stream of nerve impulses that arise spontaneously, and they increase when a sound is detected by the cochlea. This stream of spontaneous neural activity, known as stochastic noise, contributes to a baseline amount of neural activity in the cochlear nucleus and upwards. When there is hearing loss (deafferentation of the auditory nerve associated with SNHL, or merely attenuation of sound input due to CHL), this neural activity is disrupted. Under this theory, tinnitus was thought to be the perceptual consequence of reduced neural activity generated along the central auditory pathway following damage to the peripheral auditory system, for example by noise (Eggermont & Roberts, 2004).

A cochlear origin of tinnitus was thought plausible, since there is a strong association between the frequency of tinnitus when measured psychoacoustically and the audiometric profile of the hearing thresholds in an individual with tinnitus (Haider et al., 2018; Sereda et al., 2011). However, a series of interventions based on the idea of a peripheral site of generation revealed this is not the case. In 1981, House and Brackman reported that sectioning of the auditory nerve intended to eliminate tinnitus tended to either have no effect or could even exacerbate tinnitus. This finding pointed towards a more central tinnitus generator. Further contradiction to the peripheral origin theory was presented by Heinz and Young (2004), who found that cochlear damage is often accompanied by a large decrease of

spontaneous firing rate in the cochlear nerve. Meanwhile, other studies have found that cochlear lesions are followed by central nervous system hyperactivity (Noreña & Eggermont, 2006; Vogler et al., 2011; Zacharek et al., 2002), which tends to support a central nerve system origin. Despite these distinctions, peripheral and central mechanisms are not completely independent of one another. It is now accepted that many forms of tinnitus reflect a complex interaction involving both peripheral and central mechanisms in the auditory pathway (Noreña & Farley, 2013; Sedley et al., 2016).

2.6 Prominent Tinnitus Mechanism Theories

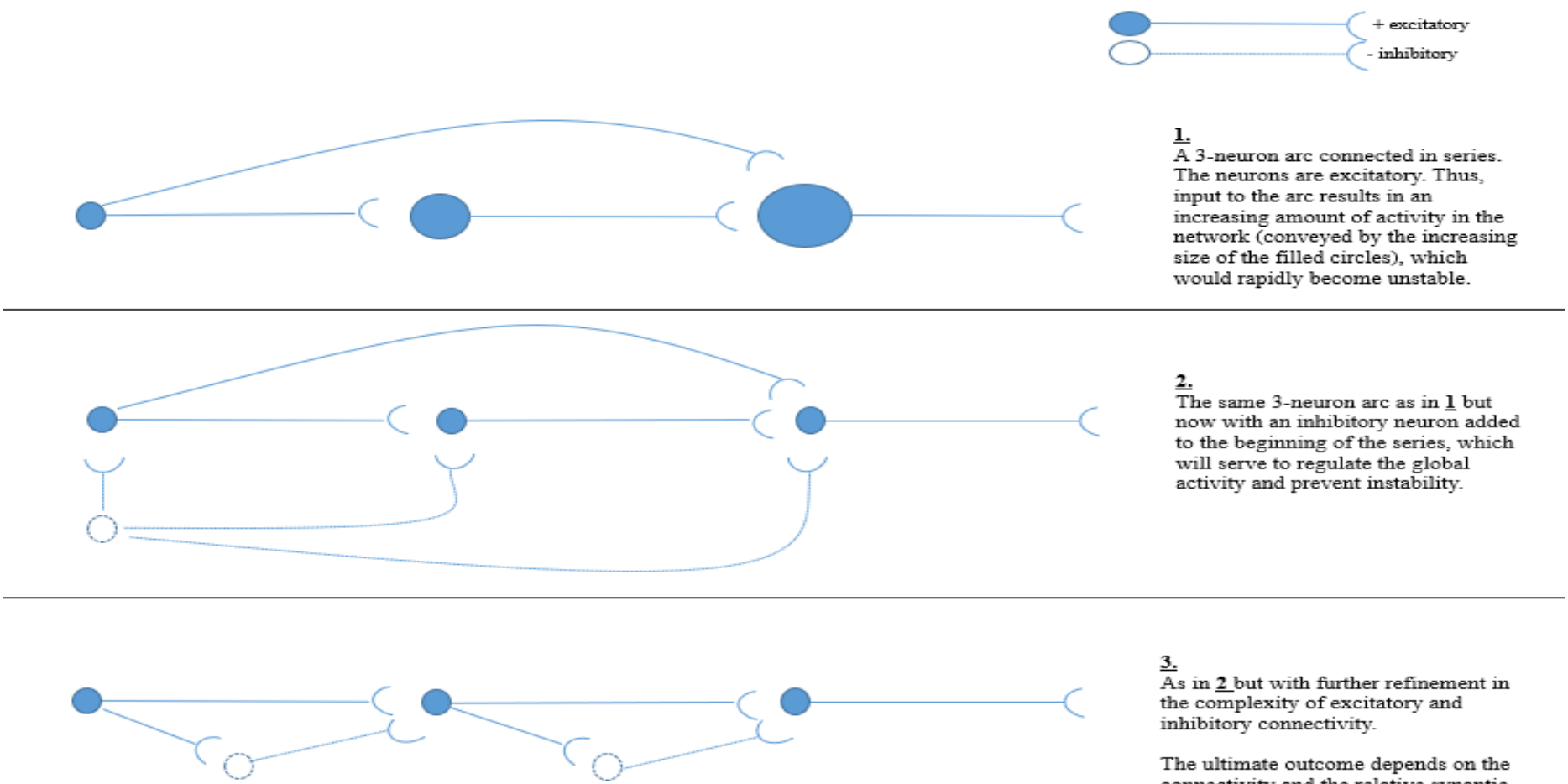
Much research has been conducted to elucidate the pathophysiology of tinnitus from the ear to the cortex, though as of yet, no consensus has been reached. As stated earlier, SNHL is a common presentation alongside tinnitus (Sanchez et al., 2005). However, while cochlear insults may be the triggering event in many cases of tinnitus, we know that cochlear damage is not the only trigger to produce tinnitus-related central changes. This was proven through reports of tinnitus in cases of CHL, where cochlear hair cells and auditory nerve fibres are assumed intact (Ayache et al., 2003). It is important to highlight that auditory deprivation cannot be held singularly accountable for affecting the activity in the central auditory pathways that might then contribute to the generation of tinnitus. Abnormal somatosensory afferent input from the neck and face has also been shown to result in tinnitus (Michiels et al., 2022; Michiels et al., 2018; Ralli et al., 2017b). There is also evidence that changes in the central nervous system related to tinnitus perception are not restricted to auditory pathways; rather they can involve alterations to a network involving both auditory and non-auditory structures (De Ridder et al., 2011; Lanting et al., 2009; Schlee et al., 2008). Details of putative theories underpinning tinnitus will be offered in the following sections.

2.6.1 Peripheral Mechanisms

Usually, two or more triggers (e.g., hearing loss, somatosensory factors, emotional distress) are necessary to elicit a noticeable tinnitus sensation (Shore et al., 2007). Reduced cochlear output through hearing loss likely triggers a cascade of neuromodulatory events which can ultimately lead to hyperactivity in the central auditory circuits (Haider et al., 2018). Reduced cochlear output as a tinnitus trigger could also explain cases in which there is tinnitus without hearing loss, as there can be up to 30% damage to OHCs before hearing loss is detected using standard PTA (Chen & Fechter, 2003). It is thought that a reduction in input to the central auditory system because of hearing loss may result in gain modification in central neurones, resulting in increased spontaneous activity, perhaps from the level of the cochlear nucleus and upwards (Haider et al., 2018). Neural gain is a term which describes the sensitivity of a neuron (its likelihood to fire an action potential) to changes in input and output. Gain modulation allows input sensitivity to be actively regulated while also maintaining a neuron's selectivity for input features (Carandini & Heeger, 2012). Regulation of neural gain provides an integration mechanism where information from multiple sources including those of cognitive, sensory or motor origin, can be non-linearly combined via multiplicative modulation of the cell's response to inputs (Ferguson & Cardin, 2020). A schematic of this concept is detailed in Figure 1.

Figure 1

Activity in Neural Networks



2.6.2 Central Theories

An abundance of central mechanism theories abound. While it is outside the scope of this project to detail and comment on all current theories, commentary will be provided on some of the prevailing theories.

2.6.3 Tonotopic Reorganisation

Rauschecker (1999) proposed expansion of the tonotopic map at the edge of a hearing loss as a mechanism for tinnitus. The underlying thinking in this theory is that neurones representing frequencies at the audiometric edge are over-represented due to map expansion and this increase in activity could generate the tinnitus percept. While some studies have found that tinnitus pitch falls at the edge of steep hearing loss (Henry et al., 2014), others have found that the tinnitus pitch instead occurs in the region of maximal hearing loss (Pan et al., 2009; Sereda et al., 2011). This model would, however, have difficulty accounting for broadband tinnitus perceptions in instances where hearing loss was relatively frequency specific. Additionally, the time course of these physiological changes does not seem to correspond with the tinnitus onset. For example, in their study based on adult cats, Rajan et al. (1993) found that map expansion takes place over days and weeks, but tinnitus can occur almost immediately after sudden SNHL (Michiba et al., 2013). This may also indicate that the mechanisms for acute versus chronic tinnitus generation are different. Acute tinnitus is the term used to describe tinnitus which lasts for approximately three to six months, while chronic tinnitus is the term given to tinnitus which is apparent for more than six months (Esmaili & Renton, 2018). Note that as the present work will be examining the tinnitus percept during short-term treatments (i.e. triggered by a temporary hearing loss lasting a few hours), it may be helpful to place a focus on mechanisms in the acute stage of tinnitus onset.

2.6.4 Network Models

Resting state functional connectivity is a term used to describe interregional correlation of brain activity, and which is typically measured using non-invasive imaging techniques (Husein & Schmidt, 2014). Such measures, which will be detailed in section 2.11, have demonstrated that tinnitus is associated with changes in non-auditory brain structures (Adams et al., 2020). It is thought that tinnitus awareness and distress could be driven by altered connections between several brain networks (Adams et al., 2020), including emotional, attention and memory networks (De Ridder et al., 2014). A recent meta-analysis of whole-brain resting state studies of individuals with chronic tinnitus identified brain regions of increased resting state activity compared to the controls with no tinnitus. These regions included the medial temporal gyrus (MTG), the frontal cortex, the parahippocampus, the insula, the cuneus, and the cerebellum (Chen et al., 2017; Cheng et al., 2020; Geven et al., 2014; Laureano et al., 2014; Leaver et al., 2016).

2.6.5 Theories of Gating and Thalamo-Cortical Dysrhythmia

Rauschecker et al. (2010) proposed the so-called gating mechanism for tinnitus perception. According to this theory, the awareness of tinnitus depends on individual differences in the effectiveness of a ‘noise cancellation’ system (in this context, noise being excessive spontaneous neural activity) that is mediated by structures within non-auditory regions. Some support for this model has come from analysis of structural images of the brain (Leaver et al., 2011) but overall, anatomical studies do not provide overwhelming support for this mechanism (Adjamian et al., 2014b).

Llinás et al. (1999) proposed the thalamo-cortical dysrhythmia (TCD) model to account for tinnitus perception. With TCD, it is thought that tinnitus is due to an interruption of activity between the thalamus and cortex initiated by neural deafferentation, because of hearing loss, which causes inhibition of thalamic neurons (Adjamian, 2014). This inhibition

in turn is thought to lead to changes in oscillatory activity at the cortical level and large-scale slow-wave and gamma activity in the neighbouring cortical regions. However, in keeping with the contradictory nature of tinnitus research in general, findings both in support (Schlee et al., 2014; Vanneste et al., 2011c; Weisz et al., 2007b) and oppositional to this theory (Lorenz et al., 2009; Zobay et al., 2015) have been reported.

2.6.6 Homeostatic Plasticity

The brain can adapt to changes in stimulus intensity involving all sensory systems, an ability termed 'neural adaptation' (Brotherton et al., 2015). Anecdotal reports of increased loudness following occluding earwax and earplug removal are consistent with the notion that neural adaptation occurs following reduced input to the auditory system (Brotherton et al., 2015; Formby et al., 2003). The increased loudness, in this common scenario, would be attributed to the abrupt restoration of normal input to the auditory system after the wax is removed but before the neural response has re-adapted. This neural adaptation can take place over varying time scales, with some mechanisms taking place with a rapid onset (seconds or minutes), while others take place over hours or days. For the purpose of this study and in keeping with the study design and question, adaptation that takes place over a time course of hours will be discussed. Neural adaptation that takes place from hours to days has been termed 'homeostatic plasticity' (Turrigiano, 1999). This plasticity of neural function serves to counterbalance effects of a persistent change in neural activity and is accomplished by scaling the strength of excitatory and inhibitory synapses and by modifying intrinsic neuronal excitability. These actions tend to keep stochastic neuronal firing rates within a functional boundary, therefore, homeostatic plasticity acts as a compensatory gain regulation mechanism (Turrigiano, 1999). Changes in neuronal gain that have been observed after hearing loss (Salvi et al., 1990) or administration of ototoxic drugs (Sun et al., 2009), are consistent with an 'internal volume control' that adjusts neural sensitivity. This enhanced

neural gain can restore neural activity following a cochlear hearing loss by scaling up the strength of excitatory synapses and/or scaling down the strength of inhibitory synapses (Schaette & Kempter, 2006). However, this scaling can also lead to negative consequences and could help explain tinnitus as well as associated abnormalities like hyperacusis (discussed in the next section).

2.7 Hyperacusis and Tinnitus

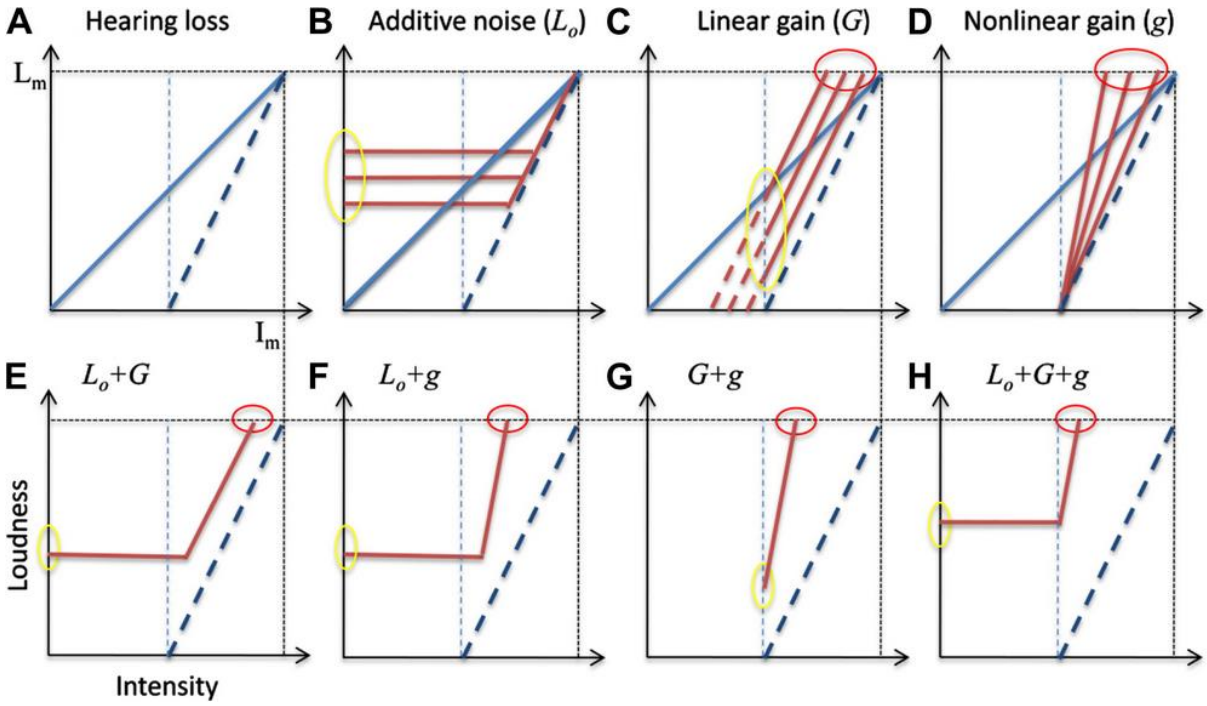
Hyperacusis is a term used to describe the experience of everyday sounds being perceived as intense or overwhelmingly loud and can be conceived as a pathology of loudness (Baguley & Hoare, 2018; Hébert et al., 2013). Tinnitus and hyperacusis commonly occur together (Anari et al., 1999; Dauman & Bouscau-Faure, 2005). Loudness recruitment on the other hand, is the steeper than normal loudness function in the vicinity of elevated hearing thresholds associated with SNHL (Hébert et al., 2013). Due to the high degree of comorbidity between tinnitus and hyperacusis, it has been suggested that there may be a common underlying mechanism for some complaints of tinnitus and hyperacusis (Knipper et al., 2013; Nelson & Chen, 2004). An increase in central gain has been suggested as an underlying mechanism which may account for both, as reduced sensory input through hearing loss would lead to an increase in central gain. Such an increase in gain could amplify spontaneous and stimulus-induced activity, which then could lead to tinnitus and hyperacusis (Hébert et al., 2013).

Zeng (2013) presents an active loudness model developed from a system engineering approach that uses internal noise, and both linear and non-linear gain to account for and predict the relationship between hearing loss, hyperacusis and tinnitus. A key principle in systems engineering theory is to quantify the input-output function of the system. In this case, the input is sound intensity, defined by acoustic pressure level in decibels (dB). The output is loudness, defined by a ratio scale in sones (Stevens, 1936). Figure 2 depicts the possible

relationship between central noise, linear gain and non-linear gain and how these may interact with hearing loss to cause tinnitus and hyperacusis. Briefly, the stochastic noise in the auditory system ('central noise') increases because of increased gain to incoming sound when sound input is reduced due to hearing loss. Therefore, it might be more appropriate to associate gain with hyperacusis, and a sequalae of increased gain is increased central noise, which could underpin the sensation of tinnitus.

Figure 2

A Theoretical Relationship: Central Noise, Linear Gain and Non-Linear Gain



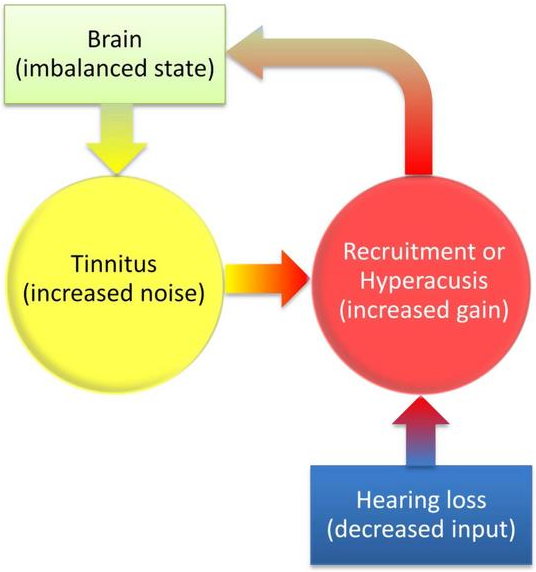
Note. Adapted from Zeng (2013) with permission. Vertical thin dashed line represents elevated hearing threshold. Slanted thick dashed line represents loudness recruitment. The vertical yellow oval represents tinnitus, while the horizontal red oval represents hyperacusis. Figure 2 depicts hearing-impaired loudness growth (steeper dashed line in panel A) and altered loudness growth as a function of central noise (panel B), linear gain (panel C), nonlinear gain (panel D), or a combination of these three factors (bottom panels from E to H).

On consideration of the above model, Zeng (2013) argues against the linear gain mechanism for several reasons. Firstly, it reduces both the input and output dynamic ranges,

which is an unlikely scenario. Next, the linear gain does not improve thresholds and finally, it raises the overall loudness for all intensities within the reduced dynamic range which is a prediction not supported by current data (Zeng, 2013). Removal of the linear gain from the model leaves central noise and non-linear gain as the two parameters that might explain loudness in tinnitus, hyperacusis and hearing loss. Such an active loudness model suggests either peripheral or central origins of tinnitus and hyperacusis as detailed in Figure 3.

Figure 3

Active Loudness Model



Note. Adapted from Zeng (2013) with permission. Peripheral (bottom up) or central (top down) origin of tinnitus and hyperacusis.

Importantly, the model only refers to alterations in the level of the input signal as the trigger for alterations in gain i.e. it does not distinguish between SNHL (which is an injury to the sensory/neural components of the auditory system) and CHL where the sound is merely attenuated. This could help explain a number of previously mentioned phenomena such as the findings of Heller and Bergman (1953), where individuals experienced tinnitus simply from being in a quiet room, anecdotal reports of heightened loudness after earwax removal and reports of altered gain in the auditory system associated with conductive losses (Parry et al.,

2019). These observations also lead to the potential for studying altered gain (and the links to tinnitus and hyperacusis) via temporary conductive hearing loss and this will be explored in section 2.9.

2.8 Limitations and Remaining Questions

It is clear that there are many putative mechanisms underlying the tinnitus percept. No theories to date, either individually or collectively, can account for the varied evidence available regarding tinnitus presentation. The heterogeneous nature of the research carried out, the tinnitus percept, and of the participants themselves, mean that we have many theories yet no definitive mechanism. In an attempt to shed more light on the theory of homeostatic plasticity and its possible relationship with tinnitus, and in an effort to introduce homogeneity to the study design, a research paradigm was designed based on the idea of studying cortical activity brought about by fully reversible tinnitus in a within-subjects design. This idea builds upon previous work that will be discussed in sections 2.9 and 2.11.

2.9 Unilateral Earplug Studies and Tinnitus

One avenue of interest in altered gain within the auditory system and its relevance to tinnitus and hyperacusis stems from incidental observations of loudness perception amongst hearing aid users in the United Kingdom. Up until the mid-2000s, most National Health Service audiology patients received one hearing aid for bilateral hearing loss. This created a prolonged asymmetry in input to the binaural auditory system, which is thought to lead to altered neural gain for sounds heard by the aided and the unaided ear. Evidence of this so-called training induced plasticity was found using cortical auditory evoked potentials (CAEPs) at 2000 Hz, where the hearing aid would have provided most amplification, i.e. the amplitude of evoked potentials was increased in the normally-aided ear and decreased in the normally-unaided ear at these frequencies even though the hearing sensitivity was symmetrical (Gatehouse & Robinson 1996). On the other hand, the researchers found that at

500 Hz where the hearing aid provided minimal gain, there were no differences in the evoked potential amplitude Therefore, the effect occurred at the stimulus frequency where the prolonged asymmetry was greatest. This objective data is supported by a larger sample of behavioural data and electrophysiological data from the brainstem, whereby loudness tolerance and response amplitudes tend to shift in the normally aided ear at frequencies where the hearing aid has the most effect – sometimes referred to as 'acclimatisation' to hearing aid use (Munro et al., 2007; Munro & Merret, 2013). Therefore, simply delivering a sustained imbalance in the input to the binaural auditory system (without injury/SNHL) can drive changes in gain, and this seems to be a predictable phenomenon in the context of homeostatic plasticity.

Schaette et al. (2012) suggest that such a phenomenon may indicate that normal mechanisms of adaption and plasticity in the brain could also play a role in the development of tinnitus. Another means to introduce an imbalance to the binaural system without injury/SNHL is via an earplug worn in one ear. The earplug can produce a fully reversible mild to moderate conductive hearing loss in individuals who usually have thresholds within normative limits, and therefore has the potential to induce fully reversible tinnitus-like phantom sounds as well as hyperacusis. Moreover, using an earplug reduces the potential for confounding variables due to audibility and between-groups comparisons.

There is in fact a fairly extensive history of investigations into the effect of earplug induced changes in physiological and behavioural responses that are related to the phenomenon of altered neural gain (Decker & Howe, 1981; Formby et al, 2003; Munro & Blount, 2009). However, one of the first to characterise tinnitus per se was by Schaette et al (2012). In this study, a cohort of 18 normally hearing participants wore an earplug in one ear for seven days. Of the 18 participants, 14 reported phantom sounds during the seven days and all sounds disappeared upon removal of the earplug. When the sounds were characterised, the

mean tinnitus spectra showed that the sounds were generally high pitched, with the highest similarity ratings obtained at comparison tones of 8000 and 12000 Hz. This finding is similar to the tinnitus spectra of tinnitus patients with mild hearing loss (Roberts et al., 2008) and corresponds to frequencies where the ear plug should give the greatest attenuation. The results from Schaette et al. (2012) indicate that it is not necessarily cochlear damage that is the dominant factor in the development of phantom sounds, but rather a reduction in auditory nerve activity as a result of auditory deprivation. This aligns with reports of individuals who have experienced tinnitus associated with CHL only, such as with occluding wax or otosclerosis (Ayache et al., 2003). However, a limitation of the study was the absence of a control group. Furthermore, the participants were told that they may experience phantom sounds when wearing the earplug, which might in itself have increased the incidence of the sounds through focused attention or participant bias. While homeostatic plasticity may reasonably account for the induction of phantom sounds and their disappearance upon earplug removal, it's not clear why all participants did not experience the phantom sounds.

Building on the findings of Schaette et al. (2012), Brotherton et al. (2019) implemented the unilateral earplug methodology with a view to investigating subcortical changes in neural response gain. Subcortical changes were measured by means of acoustic reflex thresholds (ARTs) in a group of 44 adults with hearing within normative limits. The researchers measured ARTs prior to plugging the ear and participants then wore an earplug for one of two time periods of either four or seven days. Immediately after earplug removal, it was found that ARTs were significantly decreased in the plugged ear compared to the non-plugged ear, consistent with an increased gain in the auditory system. Like the Schaette et al. (2012) study, not all participants who wore an earplug described tinnitus at the end of the earplug period. However, a significant finding was that changes in ARTs were present in all participants following earplug use, even those who did *not* experience tinnitus following

earplug use. This finding indicates that either the subcortical neurophysiological changes underlying the ART are not related to tinnitus or, that these changes might be a necessary component in the generation of tinnitus but require additional changes at higher levels of auditory processing to give rise to tinnitus.

Such findings, while not conclusive, do suggest that using an earplug paradigm could enable further understanding of tinnitus related changes in auditory processing, with Brotherton et al. (2019) suggesting a measure of neuroimaging before and after the earplug period. If conscious perception of tinnitus does indeed require additional changes at a higher level of the auditory pathway, a measure of brain activity could elaborate on such mechanisms. Maslin et al. (2013) had previously attempted to address this question. In their 2013 study, 11 normally hearing adults were recruited, all of whom wore an earplug in one ear for seven days. To obtain a measure of any changes at higher levels of the auditory pathway in response to the inter-aural asymmetry, they analysed CAEPs via fMRI before earplug insertion and seven days later before earplug removal. They also carried out ART measurements. They reported an average decrease of 7 dB HL in the 4000 Hz ART threshold in the plugged ear following earplug removal, thought due to subcortical plasticity following the short term inter-aural asymmetry. This is in keeping with previous earplug studies. There was no evidence of a corresponding CAEP change in the cortex via fMRI. However, the researchers only stimulated the non-plugged ear when carrying out the second fMRI. Therefore, it is not known if a different result would be observed had they stimulated the plugged/deprived ear. Methodological factors may have also influenced the results: fMRI has loud ambient noise from the scanner which may have provided a partial masking effect. In addition, the stimulus level used was 90dB SPL, an intensity level which may have neuronal activity and obscured differences between groups (Parry et al., 2019).

The cortical result reported by Maslin et al. (2013) is different from that of Parry et al. (2019), who did find evidence of gain change in the cortex having stimulated the deprived ear of those with chronic unilateral conductive hearing loss (stimuli presented via bone conduction). In their study, the hearing-impaired group had significantly larger P1-N1-P2 amplitudes when compared with the control group, a finding in support of the hypothesis that unilateral auditory deprivation causes an increase in neural responsiveness at the level of the central auditory system.

Another interesting aspect to studying brain activity using the earplug paradigm is that in the study by Brotherton et al. (2019), participants did not describe their phantom sounds as bothersome. Based on this report, a measure of brain activity before and after earplug use would make it possible to investigate the neural correlates of the phantom sounds without having to contend with neural activity related to tinnitus distress (Song et al., 2015).

Table 1 offers an overview of the literature that focuses on altered auditory gain and hearing loss via earplug use associated with tinnitus research.

Table 1

Summary of Selected Earplug Research: Past to Present

Authors	Brief Methodology	Findings	Conclusion
Decker and Howe (1981)	30 adults* Earplug worn unilaterally for one of 10, 20 or 30 hours. ABR and ART measured before and after earplug use.	Decrease in wave I latency across all groups.	Short term auditory deprivation can result in VIII nerve hyperexcitability upon stimulation directly after deprivation period.
Formby et al. (2003)	10 adults* Bilateral earplugs and a sound enhancing treatment each worn for 2 weeks. Loudness scaling performed before and after each treatment.	Participants needed more intense tones after earplug use and less intense tones after noise enhancement use to achieve same perceived loudness levels.	Results provide evidence in support of adaptive loudness plasticity.
Munro and Blount (2009)	11 adults* Unilateral earplug worn for 7 days. ARTs measured before and after earplug use.	ARTs were measured at a lower sound pressure level in the ear that had been plugged for 7 days.	Effect consistent with central gain mechanism mediated by a process within the brainstem.

Schaette et al. (2012)	18 adults* Unilateral earplug worn for 7 days.	Phantom sounds (tinnitus) reported by 14 of the 18 participants during earplug use which disappeared upon earplug removal.	Homeostatic plasticity as possible mechanism of tinnitus.
Maslin et al. (2013)	11 adults* Unilateral earplug for 7 days. Cortical (fMRI measured during presentation of noise burst stimuli) and subcortical (ART) measured before and after earplug use.	Decrease in high frequency ARTs after earplugging. No change in hemispheric asymmetry.	Change in ART consistent with homeostatic plasticity. Unclear if cortical results due to experimental paradigm.
Brotherton et al. (2019)	44 adults* Unilateral earplug worn for either 4 or 7 days. ARTs and tinnitus questionnaire measured before and after earplug use.	30 of the 44 participants reported experiencing tinnitus. ARTs in the plugged ear significantly decreased compared to pre-plug measure, even in those who did not experience tinnitus.	Subcortical changes underlying ART changes not related to tinnitus or subcortical changes are necessary but in addition to higher level auditory processing.
Dougherty et al. (2021)	Cohort size unknown, participants wore earplug unilaterally for 7 days. EEG measured before and after earplug use.	Central gain ubiquitous in response to reduced peripheral input**	Authors suggest their results may indicate central gain changes do not by themselves account for tinnitus percept.

*All participants had hearing within normative limits

**Full results not available: only an abstract published and attempts to reach authors for further information were unsuccessful.

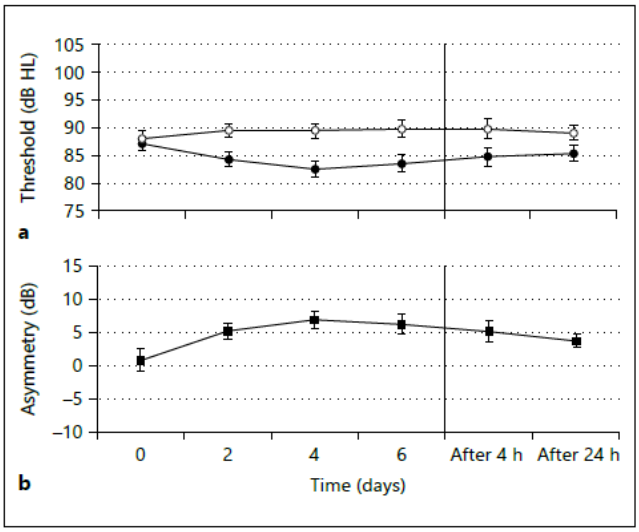
2.9.1 Implementing the Earplug Study Design

As detailed, several previous studies have employed unilateral earplugs to induce temporary auditory deprivation and tinnitus-like phantom sounds (Brotherton et al., 2019; Schaette et al., 2012). Unpublished data by Brotherton et al. (2015) seen in Figure 4, shows evidence of subcortical gain changes four hours following earplug removal. Interestingly, the authors did not report if there was any evidence of gain change four hours after earplug insertion. Instead, they reported gain changes with the earplug in place over a matter of days. It stands to reason that even though not reported, gain changes could reasonably take place four hours after the earplug was inserted, mirroring what was demonstrated four hours after the earplug removal in Figure 4. This would be in line with the sensory adaption timeframe associated with homeostatic plasticity (Turrigiano, 1999).

A pilot study was conducted for this thesis to trial this theory and is discussed in the methodology section.

Figure 4

Changes in ART With Short-Term Earplug use



Note. Adapted from Brotherton et al. (2015) with permission. Showing the mean change in the ART at 2 kHz for days 0, 2, 4 and 6 of earplug use and 4 and 24 h after earplug use. **a** shows mean ipsilateral ART for plugged ear (solid line with filled circles) and not-plugged control ear (dashed line with open circle). **b** shows difference between not plugged control and plugged ear. The vertical line represents earplug removal. The error bars show ± 1 standard error.

2.10 Tinnitus Biomarkers

The acceptance of a reliable objective index for tinnitus presence/absence (or severity) can only be recommended when a reliable biomarker has been discovered. Puntmann (2009) defines a biomarker as "a characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention" (p. 538). Biomarkers can aid in the diagnosis and measurement of diseases and symptoms, as well as assisting in the prediction of prognosis and treatment outcome (Kang et al., 2021). An example of a well-established biomarker in cardiovascular medicine is determining serum cholesterol levels by means of a blood test to determine an individual's cardiovascular risk. Detection of high cholesterol levels means that preventative measures can be implemented in good time.

There are two major types of biomarkers: biomarkers of exposure, which are used in risk prediction, and biomarkers of disease, which are used in screening, diagnosis, and monitoring of a condition. The use of biomarkers in research has grown out of a need to have a more direct measurement of exposures in a causal pathway of a disease or symptom that is free from potential error associated with subjective measures, such as recall bias (Mayeux, 2004). Schulte (1993) recognised that biomarkers have the capability to give insight into potential mechanisms underlying disease pathogenesis and can provide information regarding disease progression and response to therapies.

The hypotheses surrounding tinnitus pathophysiology are diverse and include factors from varying fields such as the nervous system and stress-related neuropsychiatry and correspondingly, studies to identify tinnitus biomarkers have been conducted in various fields. As an example, one line of enquiry focused on a link between tinnitus and dyslipidemia. Dyslipedemia is an imbalance of lipids such as cholesterol in the blood, which can lead to accumulation of lipids in end arteries. This, in turn, can result in reduced blood supply in the cochlea, leading to chronic hypoxia which can impair the cochlear metabolism (Avci, 2021). Avci (2021) and Yüksel et al. (2018) found a significant correlation between high levels of cholesterol detected via blood tests in their groups with chronic tinnitus, compared to control groups without tinnitus. In an animal study, Cai et al. (2009) demonstrated that in cases where inner ear function was reduced because of lipid accumulation, hearing function was preserved by lipid drug treatment. However, contrary findings were reported in a human study by Canis et al. (2011) who reported that tinnitus severity did not decrease with the administration of hyperlipedemia medication in patients with subacute tinnitus; though it is acknowledged that hearing function and tinnitus severity while often related, are not the same thing. As the inner ear can be impaired due to hypoxia caused by microcirculatory disturbance, Kang et al. (2021) concluded that dyslipidemia can

increase the risk of tinnitus, but do not go as far as to describe this finding as a tinnitus biomarker.

Several other methods have also been investigated as potential ways in which to identify a tinnitus biomarker, including pupillometry (Barrett et al., 2022; Juul Jensen et al., 2018), ABR (Milloy et al., 2017; Shim et al., 2017), and analysis of cortisol by means of saliva specimens (Hébert at al., 2004). However, like the dyslipidemia example, while some suggestive links were identified, none offer the necessary specificity and sensitivity to be accepted as a tinnitus biomarker. The absence of a definitive tinnitus biomarker and no objective measure of tinnitus have been a recurring barrier in the advancement of mechanistic tinnitus understanding. This is evident in the fact that despite decades of research, the underlying mechanism of tinnitus is still not agreed upon.

2.11 Resting State Electroencephalography

Neuroimaging is relevant to the understanding of underlying mechanisms of tinnitus because while cochlear damage may be a triggering factor in tinnitus, it is changes in the brain which give rise to the sensation of chronic tinnitus (Henry et al., 2005). Neuroimaging can come in a number of forms such as functional magnetic resonance imaging (fMRI), functional near-infrared spectroscopy (fNIR), magnetoencephalography (MEG) and electroencephalography (EEG). This latter technique is perhaps the most classical approach and is well suited to tinnitus studies, not least because measurements can be obtained in a quiet environment (unlike fMRI), but also because the measurements are relatively resistant to movements (unlike MEG), and data can be obtained from deep and superficial sources (unlike fNIRs).

To visualise and monitor cerebral electrical activity in the microvolt range, it must be of sufficient duration and sustained strength. Synaptic activity meets these criteria and as this activity is thought to be the primary source of EEG, the technique is seen as a suitable

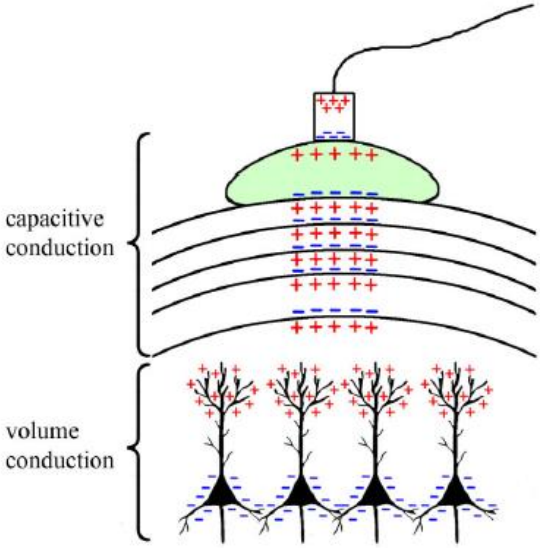
method with which to monitor cerebral activity (da Silva, 2013; Olejniczak, 2006). EEG is a neuroimaging method which produces a graphic representation of the difference in voltage between two scalp locations plotted over time (Olejniczak, 2006). These electrical potentials can be generated spontaneously or evoked through stimulation. Excitation of post synaptic neurons creates an extracellular voltage near neural dendrites that is more negative than elsewhere along the neuron (Jackson & Bolger, 2014). This scenario is called a dipole, where a region of positive charge (the source) is separated by a region of negative charge (the sink) by some distance. Naturally occurring neural activity produces time-varying electrical currents that create local voltages which can be measured by electrodes placed on the scalp (Adams et al., 2020). A single dipole's voltage is too small to be measured as far as the scalp, however, the dipoles from multiple neurons in a region will sum together to produce a measurable voltage (Jackson & Bolger, 2014).

2.11.1 EEG – From Brain to Electrode

Volume conduction is the mechanism which is responsible for the propagation of the EEG signal through the brain and scalp, to be measured by scalp-surface electrodes (Jackson & Bolger, 2014; Olejniczak, 2006). Volume conduction is a process whereby a pool of ions repels nearby ions of the same charge within the electrolytic medium of the brain. Repelled ions in turn repel other adjacent ions, which creates a wave of charge that travels through extracellular space (Jackson & Bolger, 2014). In order to be measured outside the head, the electrical signal must travel from the brain, through the dura layers, through the skull layers, through the scalp and finally to the electrode. As seen in Figure 5, these layers are akin to a stack of capacitors, which become responsible for the signal's propagation.

Figure 5

EEG Neural Signal Propagation



Note. Adapted from Jackson & Bolger (2014) with permission. The neural signal propagating through layers of brain, dura, skull, and electrode gel to reach the electrode. The gel acts as a conductor and ensures that the signal reaches the electrode with less attenuation.

2.11.2 EEG Oscillations

EEG measures can be analysed in the frequency domain, whereby a complex pattern of voltage oscillations is broken down into its frequency components. Analysis of these oscillations dates back to the neurophysiologist Berger, who in 1929 observed oscillations of approximately 10 Hz recorded from the human scalp (Herrmann et al., 2005). Berger coined this oscillation ‘alpha’ frequency. Oscillations in the frequency range of 12-30 Hz were called ‘beta’. Slow oscillations below 4 Hz were labelled ‘delta’. In 1942, oscillations around 40 Hz (though more generally 30-80 Hz) were referred to as ‘gamma’ (Adrian, 1942). Finally, oscillations from 4-8 Hz were named ‘theta’ oscillations (Herrmann et al., 2005). Of particular interest in this study is the relatively high frequency gamma band. These oscillations have been shown to relate to perception of a sensation (Llinás et al., 1998; Weisz et al., 2007a) and are believed to reflect relatively localised cortical activation (Merker,

2013). Note that these oscillations can be observed in the absence of an external sound source. That is, when an individual's EEG is measured while they remain passive, it is referred to as the 'resting state' EEG.

2.11.3 EEG in Tinnitus Research

While analysis of imaging studies confirms that the brain regions associated with tinnitus extend beyond auditory centres (Simonetti & Oiticica, 2015), differing methodologies, participant groups and results among these studies mean that their conclusions as to the mechanisms of tinnitus are suggestive rather than definite. The ultimate goal in tinnitus research using exploratory neuroimaging methods is to identify a concrete biomarker and objective method of assessment for the symptom. Such an assessment should eventually be able to be carried out in an audiology clinic. Therefore, while techniques such as positron emission tomography (PET) and fMRI are incredibly useful neuroimaging tools, their operation is outside the scope of practice of an audiologist and so it seems wise to focus on as assessment method that has the potential to be assimilated into everyday clinic practice. The application of electrodes associated with EEG or MEG is a skill familiar to an audiologist through ABR training and thus, more likely to be readily incorporated into a clinic.

2.11.4 Previous Research Involving Resting State Brain Activity

MEG is a record of brain magnetic fields and like EEG, its signals are described in the same frequency bands. Both measures can play an important role in providing measures of functional and effective connectivity in the brain (da Silva, 2013). Weisz et al. (2005) were the first to describe resting-state oscillatory brain activity amongst people with tinnitus. MEG was used to gather data, which were compared in two groups: 17 adults with tinnitus and a control group of 16 adults without tinnitus. Those with tinnitus were found to have two characteristic differences from the controls - both enhanced delta band power and reduced

alpha band power. Moreover, these differences seemed to localise to the temporal regions, where the auditory cortex is located. Both delta enhancement and alpha reduction were strongly correlated with self-reported tinnitus distress, with correlations for alpha slightly stronger than those for delta. This initial study seems to provide support for the idea of a tinnitus biomarker, although it has several limitations. Firstly, those who experienced tinnitus also suffered from tinnitus, so it isn't clear whether the changes reflect the tinnitus sensation per se, or sequalae like heightened arousal or anxiety. Secondly, there was limited focus on the gamma band, even though this might be expected to more closely reflect a sensation of tinnitus (Llinás et al., 1998). The work has since inspired several follow-on studies.

In 2007, Ashton et al. expanded EEG tinnitus research to include analysis of gamma band resting-state activity. In their study, eight adults with unilateral tinnitus and 21 control subjects without tinnitus underwent EEG. Of the eight participants with tinnitus, six had some degree of high frequency hearing loss in one or both ears. It was not stated if the non-tinnitus controls had any degree of hearing loss. In all eight participants who experienced tinnitus during the EEG recording, the results showed a unilateral left or right localised focus of gamma activity over the temporal lobe auditory cortex. This localised area of high frequency activity was not present in subjects without tinnitus.

In their 2007(b) study of 26 adults with varying causes of tinnitus, Weisz et al. also investigated gamma activity by means of MEG. They hypothesized that changes in gamma activity related to conscious perception may be due to the concerted action of both slow and high frequency oscillations: "Enhanced gamma activity may occur in circumscribed cortical zones between deafferented and normally afferented regions, resulting from a loss of lateral inhibition of the former" (Weisz et al., 2007b., p. 1479). When Weisz et al. purposefully sought out marked enhancement of slow wave activity from five-minute recordings and examined gamma band activity during these periods, they found a significant increase in

gamma band activity which was not observed in the control group without tinnitus. While both Ashton et al. (2007) and Weisz et al. (2007b) report an increase in gamma band activity in tinnitus subjects compared to control groups without tinnitus, due to the variability in sample groups and methodology used, the results are suggestive rather than definitive of an increase in gamma activity being a definite biomarker of tinnitus. Weisz et al. (2007b) also reported gamma results in relation to slow wave activity. They did state that gamma band activity was also "elevated" when the entire data was considered i.e. not just slow wave activity triggered, however no further information was provided in relation to this statement.

A common limitation to all three studies described here was the inability to compare findings to a matched control group with respect to hearing thresholds. Thus, we can expect some degree of variability between participants. As the control groups were not matched for hearing thresholds, the authors cannot come to any unequivocal conclusions as to if the oscillatory activity reported relates to any hearing loss present. Although as Adjamian et al. (2012) point out, finding participants for a control group that are exactly matched by hearing thresholds is a difficult undertaking.

More recently, Zhang et al. (2021) attempted to control for heterogeneity amongst participants through recruitment of a unique participant group. They studied six participants, five of whom exhibited somatoform tinnitus and one who manifested sound evoked tinnitus. Thus, their participants had the ability to turn their tinnitus on and off, enabling a within-subjects' study that was naturally controlled for hearing thresholds. When EEG was measured in the "tinnitus on" state, the onset of tinnitus was associated with new delta, theta, alpha and gamma band sources in the contralateral MTG and inferior temporal gyrus. However even among such a specific set of participants, variability still existed. The pitch, duration, loudness, and side of the tinnitus varied between participants, as did the exact

trigger. For these reasons, the authors concluded that while suggestive of the neural generators involved in tinnitus, their findings may not be generalisable.

Table 2 presents a summary of some prominent research in the area of resting state neuroimaging and tinnitus.

Table 2

Summary of Resting State Tinnitus Research: Mixed Results

Authors	Brief Methodology	Findings	Conclusion
Weisz et al. (2005)	17 adults with chronic tinnitus and hearing loss underwent MEG and completed a tinnitus questionnaire. Control group included*.	Marked reduction in alpha and enhancement in delta power over temporal regions compared to normal hearing controls. Correlations with tinnitus distress associated with this activity pattern.	Spontaneous activity identified could reflect tinnitus-related cortical network.
Ashton et al. (2007)	8 adults** with unilateral tinnitus. Participants underwent EEG, no control group included.	High frequency gamma activity recorded over auditory cortex in all 8 participants with tinnitus compared to no such activity in the 25 normally hearing controls (who were also free from tinnitus).	As high frequency oscillations are believed to be necessary for sensory perception, identification of high frequency "hot spots" may provide a means for monitoring effects of treatments.
Weisz et al. (2007b)	26 adults with varying causes of tinnitus underwent MEG, tinnitus questionnaire and a threshold equalising noise test. Control group included*.	Gamma activity more prominent in tinnitus subjects than in control subjects.	Result suggests that oscillatory activity may be related to conscious perception in the absence of external stimulation.
van der Loo et al. (2009)	15 adults with unilateral tinnitus underwent EEG and completed the visual analogue scale to assess subjective tinnitus loudness. Hearing thresholds not stated. No control group included.	Source analysis of resting state electroencephalographic gamma band oscillations shows a strong positive correlation with visual analogue scale loudness scores in the contralateral auditory cortex.	Suggestion that tinnitus loudness is coded by gamma band activity in the contralateral auditory cortex.
Zeng et al. (2011)	1 adult with debilitating tinnitus in right ear following sudden SNHL. It was found that low-rate stimulus delivered via CI could suppress the tinnitus. EEG and cortical potentials were measured with tinnitus present and in a tinnitus supressed state and compared.	Compared with the results obtained in the tinnitus-present state, the low-rate stimulus reduced cortical potentials while increasing spontaneous alpha power in the auditory cortex.	Suggestion that a decrease in event related N100 cortical potential in front centre region of the brain an increase in alpha power in the temporal regions could be used an objective measure of tinnitus.

Meyer et al. (2014)	24 adults with tinnitus with varying causes of tinnitus completed stress rating tasks and EEG recordings which were compared to 24 control subjects.	Chronic tinnitus with high distress displays increased activity around 25 Hz and tinnitus with high presence displays increased signal strength in lower gamma, delta and alpha bands.	Suggestion that distress and presence should be considered as independent dimensions of chronic subjective tinnitus.
Houdayer et al. (2015)	17 adults with chronic unilateral tinnitus**** underwent EEG, MRI, ABR, psychoacoustic measurements and completed tinnitus questionnaires. Control group included*.	Decreased current density in the left inferior temporal and parietal cortical sources of the alpha, beta and gamma rhythms in tinnitus sufferers. No evidence of increased gamma sources. EEG data did not correlate with tinnitus sufferers' clinical features. Subjects with tinnitus had shorter N1 and P2 latencies. P300 did not differ between groups.	Results may reflect processes of maladaptive cortical plasticity and memory consolidation.
Pierzycki et al. (2016)	42 adults actively seeking intervention to alleviate tinnitus recruited. 20 were fitted with T30 neuromodulator and 22 received a placebo. Participants completed a THI and underwent 2 EEGs, one before treatment and one after.	Test-retest correlation for EEG band powers and self-reported tinnitus measures showed high levels of agreements. EEG band power unrelated to general or tinnitus-specific self-reported measures.	Recommendation not to use whole brain EEG power spectra as an outcome measure for tinnitus.
Meyer et al. (2017)	45 adults with tinnitus with varying tinnitus presentations and hearing sensitivity underwent EEG and completed measures of depression and distress.	Whole brain analysis revealed a cluster of 15 voxels in the beta band correlated with tinnitus-related distress, covering the right posterior intra- and peri-Sylvian regions. No voxels that correlate with measurements of depression were found.	Distress and depression should be conceived as distinct but not completely independent aspects of the tinnitus brain.
Neff et al. (2019)	45 adults with tinnitus. Tinnitus questionnaires and EEG administered in a within-subjects design. In the first condition, participants did not actively listen for their tinnitus and in the second condition they were instructed to actively listen for tinnitus.	Tinnitus questionnaires revealed increased tinnitus distress when participants actively listened for this tinnitus but this did not correspond to any significant neural changes in the EEG data.	The absence of EEG power changes between conditions may support the theory of an invariant resting state brain activity in those with tinnitus which may not be altered by attention.
Zhang et al. (2021)	6 participants with somatoform tinnitus**** underwent EEG and completed THI tinnitus questionnaire in both tinnitus "on" and "off" states.	A global increase in delta and theta band power was observed in tinnitus "on" states, alpha power increased in half of the participants and decreased in the other half in the "on" condition. Gamma band increases were also observed in the "on" state. These power changes were observed in the opposite hemisphere to the side of the tinnitus.	The sudden appearance of new sources of activity in the opposite hemisphere within the inferior temporal gyrus, middle temporal gyrus and perirhinal cortex may initiate the perception of tinnitus perception.

*Control groups had hearing thresholds within normative limits.

**6 participants had some degree of hearing loss.

***16 participants had a measurable degree of hearing loss on audiogram.

****Participants had hearing thresholds within normative limits.

Meyer et al. (2017) point out that the differences in EEG activity across studies may be due to technical and methodological parameters such as recording devices, measurement protocol, signal processing and experimental settings. The word 'heterogenous' comes up often in relation to tinnitus. With such a varied clinical population, tinnitus subtypes have been established in an attempt to classify individuals with tinnitus according to their clinical profiles, aetiologies, response to treatments and neurological markers. Such typologies can however be inflexible; a patient must go into a certain group with no in-betweens (Cederroth et al., 2019). In cases of overlapping subtypes, patients may be deemed borderline, ambiguous, or simply unaccounted for (Mohan et al, 2022). The occurrence of overlapping tinnitus subtypes suggests that tinnitus exists along a continuum, with no apparent boundaries.

Evidence using EEG in support of the continuum idea was put forth by Vanneste et al. (2011b). They measured EEG on 10 individuals with recent onset of tinnitus and on eight individuals with chronic tinnitus. Their data indicated that the generators involved in tinnitus onset appear to change when moving from the acute to the chronic phase of tinnitus, with increased activity apparent in several brain areas indicating changes in generators. These researchers made efforts to keep the control and study groups as homogenous as possible but in doing so excluded a significant population who experience tinnitus, namely those who have experienced head injury, headaches and those being treated for mental health disorders. Such exclusions are common in tinnitus research in an attempt to control heterogeneity.

There is a clear need to identify a reliable and objective method of tinnitus assessment which can account for all patient groups. It is hoped that by establishing a reliable objective method of tinnitus assessment in a homogenous group first, this could later be extended to more diverse patient groups.

2.12 Why is Objectivity Important?

Treatments for tinnitus vary and include hearing aid use, sound and music therapy, counselling, and acupuncture (Hanley et al., 2008). Subjective reports by those with tinnitus, in addition to questionnaires, determine the effectiveness of these treatments. Little attention has been given to the importance of an objective method to evaluate tinnitus treatments (Ibarra-Zarate & Alonso-Valerdi, 2020). Tinnitus is more than a background auditory sensation for some; it also has emotional and cognitive components, making it a complex symptom to manage. In many countries, treatment guidance is not clear and has no specifications. A systematic inspection of tinnitus related clinical processes by Londero and Hall (2017) showed that tinnitus treatment outcome assessment by means of questionnaires follows very unreliable methodology. Meikle et al. (2008) point out that none of the main six tinnitus questionnaires report on responsiveness, which measures the ability to detect a clinically important change over time. Fakrell et al. (2016) also raise the issue that the questionnaire properties that hold for one patient population may not necessarily be relevant for another. In other words, the questionnaires in use to measure treatment outcome may not maintain an equivalence across cultures; a particularly pertinent consideration when considering Aotearoa/New Zealand's status as a bicultural country.

An objective measurement of tinnitus treatment outcome has the potential to fill the gaps left vacant by questionnaires. As neuronal hyperactivity in the auditory nervous system is thought to be the cause of tinnitus, monitoring of neural electrical activity would appear to be a good method of objectively measuring the effects of therapies (Ibarra-Zarate & Alonso-Valerdi, 2020).

Gamma oscillations have been shown to relate to perception of a sensation (Llinás et al., 1998) and as literature has demonstrated changes in gamma activity that appear to be related to those who experience tinnitus when compared to gamma activity in control groups

(Ashton et al., 2007; van der Loo et al., 2009; Weisz et al., 2007b), this frequency band was selected for extensive analysis between conditions in this study.

Changes in alpha activity have previously been correlated with tinnitus distress (Weisz et al. 2005), however Zeng et al. (2011) demonstrated that alpha activity can be modulated in those with tinnitus without any change in distress level. It was not expected that the participants in this study would experience distress with any tinnitus induced by their temporary auditory deprivation. The alpha frequency band was therefore also selected for analysis to determine if there were any significant differences between conditions unrelated to tinnitus distress.

2.13 Summary

Tinnitus is a complex and heterogenous symptom. There has been much research done in the past two decades which has attempted to shed light on the mechanisms underlying the symptom. As of yet, no definite conclusions regarding mechanisms have been reached and so a cure for tinnitus has also eluded the research field.

One postulated mechanism is homeostatic plasticity, a neural gain adaptation that can take place following hearing loss. Earplugs offer a convenient and effective means to investigate underlying tinnitus mechanisms by driving changes in the gain of the central auditory system that mimic hearing loss. We know that even after a relatively short period of plugging one ear, at least some otherwise normally hearing, tinnitus-free individuals will start to experience tinnitus. It will tend to be high frequency in nature, corresponding to where the earplug introduces the biggest hearing loss.

To date, most earplug related studies have focused on characterising the tinnitus sensation as well as altered perception of loudness (hyperacusis) and/or have focussed on physiological measures of gain in subcortical regions of the brain via the ABR and ARTs. Those that have studied cortical activity using the earplug method (Maslin et al., 2013) have

been via sound evoked paradigms. The findings in that study were null but to date there have been no fully reported results characterising resting state activity from the cortex before and after earplug use. Therefore, there is a need to better understand the effect of earplugging in association with tinnitus at these cortical regions.

Resting state EEG appears to be a promising tool for indexing biomarkers of tinnitus based on studies in clinical populations with tinnitus. While promising in this regard, the results have not been consistent. One common thread that affects many of the studies is the possibility that heterogeneity between groups limits the ability to interpret and apply the findings. Earplugging removes much of this heterogeneity as it offers a means to obtain pre-onset baseline measures from the same brain, and because the effect of audibility is controlled between conditions with and without the percept of tinnitus.

Therefore, to expand the earplug related research and to address issues of heterogeneity it may be meaningful to conduct investigations into the resting-state EEG patterns in a group of ear-plugged individuals.

2.14 Aims and Hypothesis

The overarching aim of this study is to characterise brain activity in adult humans with experimentally induced hearing loss and tinnitus associated with earplugging. Specific objectives are to compare oscillatory band power and loci between a baseline condition (no plugging and no tinnitus) and a post-plugging experimental condition (after four hours of unilateral auditory deprivation by means of the earplug).

A secondary aim is to study the relationship between any changes in brain rhythms associated with experimentally induced hearing loss and tinnitus and behavioural characterisations of tinnitus severity associated with that variable.

The study will seek to answer the following hypotheses:

H0: Compared with baseline measures, there will be no changes in spontaneous brain activity that are associated with earplug induced temporary hearing loss and tinnitus.

H1: Compared with baseline measures, there will be changes in spontaneous brain activity that are associated with earplug induced temporary hearing loss and tinnitus.

Chapter 3: Methodology

3.1 Overview

The objective of this project was to characterise the pattern and location of synchronised resting state brain activity (i.e. without sound stimulation) via EEG that is associated with temporary hearing-loss induced tinnitus. An ABA design, also known as a reversal design, was implemented to investigate the research objective.

Study participants were adults with normal audiometric thresholds, who were free from tinnitus and neurological disease. A baseline EEG was conducted and following a period of unilateral earplug use of at least four hours, the participants returned to the lab where they completed a Likert scale of tinnitus loudness and a tinnitus handicap inventory (THI) to determine the tinnitus status. A repeat EEG was then conducted with the earplug in place for comparison with the first EEG. Participants returned to the lab once again, at least 24 hours after and not more than seven days after second EEG. A final EEG was carried out and participants completed the tinnitus Likert scale and THI again.

3.2 Participants and Procedure

Ten adult participants who self-identified as being free from tinnitus, neurological disorder and having hearing thresholds within normative limits were recruited for this study. All participants underwent pure-tone audiometry in a sound treated booth with ambient noise levels meeting the ISO 8253-1 (2010) criteria for testing down to 0 dB HL. Stimuli were presented at octave intervals from 250 Hz to 8000 Hz, including inter-octave intervals using TDH39 supra-aural headphones (NZAS, 2021). All subjects presented with thresholds within normative limits i.e. 15 dB or lower across all frequencies tested. In addition, all participants underwent otoscopic examination and middle ear function testing, and all had type A tympanograms consistent with healthy middle ear function.

3.3 Ethical Considerations

This study received ethical approval from the University of Canterbury Human Research Ethics Committee on the 13th of April 2022 (Appendix A). All procedures in this study were conducted in accordance with the committee's approval. All participants were provided with detailed information about the study upon expressing interest in taking part in the research (Appendix B) and all participants signed informed consent forms prior to taking part in the study.

3.4 Sample size estimation

Ten participants were sought as determined *a priori* by statistical power analysis based on differences between tinnitus and non-tinnitus conditions reported in the seminal study by Weisz et al. (2005). These researchers reported central nervous system activity (scaled power) of 1.15 (SD = 0.23) in relation to tinnitus, and 1.6 (SD = 0.2) in a non-tinnitus control condition. On a two-tailed parametric significance test, these findings indicate the number of participants required in this study to give a statistical power in excess of 80% (at $p < 0.05$) was five. Therefore, a conservative estimate of 10 participants was recruited for the study. Participants were recruited over a six-week period using non-probability volunteer sampling. In this method of sampling, potential participants are told about the research through advertisements or announcements and self-select to become part of the study (Alvi, 2016). Recruitment posters detailing eligibility requirements and study goals were placed around the University of Canterbury campus (Appendix C). Potential participants were instructed to contact the researcher if they were interested in taking part in the study and/or if they wanted more information.

3.5 Earplug Mini Pilot

A pilot study was conducted in the study design phase of this research to ascertain if phantom sounds were likely to be perceived after four hours of earplug use, as surmised from

the work of Brotherton et al. (2015). Four adults who met the inclusion criteria for this study wore a 3M EAR foam earplug unilaterally for four hours. Audiometry was not conducted to ascertain the exact level of attenuation for each individual; however, approximate attenuation was detailed by the earplug manufacturer which can be seen in Figure 6 below. All of those involved in the mini pilot reported the perception of phantom sounds approximately two hours after the commencement of earplug use, which continued until removal of the earplug. Thus, four hours of use was confirmed as sufficient time to drive any gain changes associated with the earplug-induced auditory deprivation.

Figure 6

Approximate Expected Earplug Attenuation

Attenuation

		Frequency (Hz)						
		125	250	500	1000	2000	4000	8000
3M™ E-A-R™ Classic™ Uncorded	Mean Attenuation (dB)	19.8	20.6	27.8	27.4	31.0	38.7	41.2
	Standard Deviation (dB)	9.2	8.6	7.3	8.7	6.3	6.1	9.2

Accessed from 3M website (3M, 2022).

3.6 Procedure Timeline

The data collection sessions were scheduled in the following way:

Session One (A1):

- Otoscopic examination and bilateral tympanometry.
- Tinnitus Likert scale and THI.
- Audiogram.
- Resting state EEG lasting five minutes.
- Insertion of earplug into left ear and remeasurement of PTA via air-conduction, with plug in situ.

- The earplug was a ‘Classic’ model foam plug manufactured by 3M. Each participant was issued with two earplugs in total, one in ear and a single spare earplug with associated instructions for use (see appendix D).

Session Two (B):

- Participants returned to the lab four hours later for the B phase of data collection.
- Repeat of tinnitus Likert scale and THI.
- Abbreviated tinnitus pitch and loudness matching (if applicable). See section 3.10.1.
- Resting state EEG lasting five minutes.
- Earplug removed.

Session Three (A2)

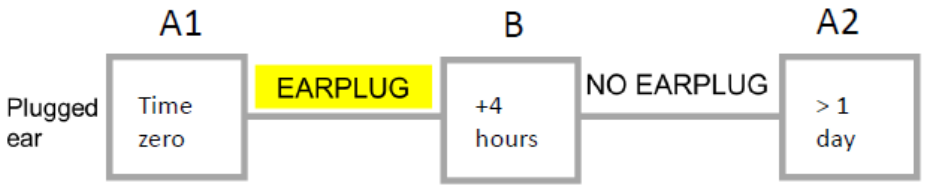
- More than 24 hours but less than seven days after session two, participants returned to the lab for the A2 phase of data collection.
- Tinnitus Likert and THI performed.
- Resting state EEG lasting five minutes.
- In accordance with the tone and loudness reported by the participant in session two as being close to the tinnitus percept, a continuous pure tone or narrowband noise was selected and presented to the participant’s left ear. An additional five-minute EEG was then performed in this condition.

3.7 A-B-A Design

A repeated measures experimental design was chosen for this study. The design allows for a baseline measure to compare the effects of the independent variable (the hearing loss induced by the earplug). The ABA design begins with a baseline phase (A1) and is followed by an intervention phase (B). The independent variable is then withdrawn (A2) which allows additional opportunity to demonstrate the effects of the independent variable (Byiers et al., 2012). The design is depicted in Figure 7.

Figure 7

A1-B-A2 Design



Byiers et al. (2012) highlight the ethical importance of considering the reversibility of the dependant variables (in this case the tinnitus and the objective measured neural activity) before commencing a study of this type. Previous studies using an A-B-A study design with the earplug paradigm demonstrated that the tinnitus and hearing loss (Schaette et al., 2012) induced by use of an earplug is fully reversible upon removal of the earplug. Munro et al. (2014) demonstrated that neural gain changes associated with earplug insertion measured via ART returned to baseline following earplug removal.

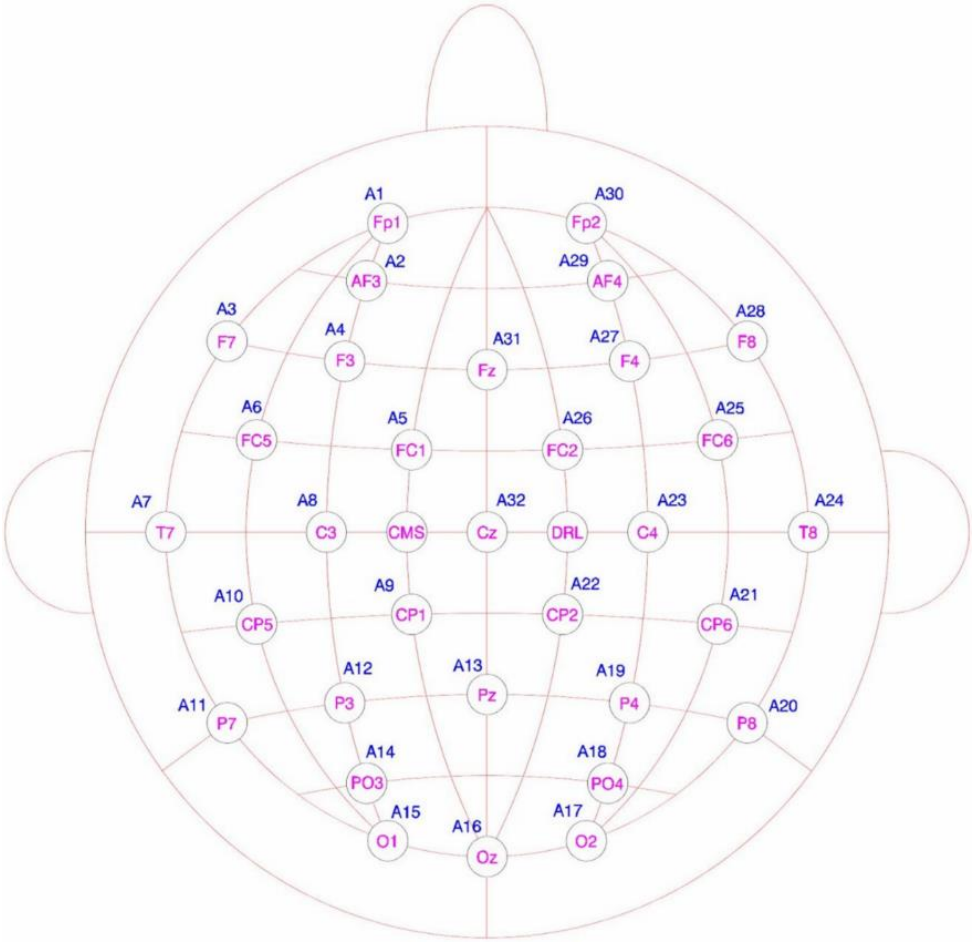
3.8 Resting State EEG Data Acquisition

Resting state EEG was recorded in a sound treated booth at the University of Canterbury. A BioSemi data acquisition system was used to record data from 32 silver/silver chloride active electrodes. The electrodes were arranged in the international 10-20 montage over the scalp, as seen in Figure 8. Participants sat upright on a comfortable chair and were instructed to keep their eyes open and look at an A4 sized rectangular target one meter directly in front of them. Electrode cap size was selected by measuring head circumference. The nasion-inion distance and distance from each pre-auricular point was measured and divided by two to locate the vertex position. Electrode offset reflects the half-cell potential of the electrode/skin/gel interface. Differences in offset are mainly due to the attachment of stray ions at the electrode tips, known as oxidation, or the loss of ions from the tip, known as corrosion. Relatively low and stable electrode offset is a necessary condition for measuring

good quality physiological signals from active electrodes (ActiveTwo, 2016). Signa gel was used to minimise the offset of the active electrodes to no greater than ±40 mV for each channel.

Figure 8

32 Channel EEG Electrode Placement Guide



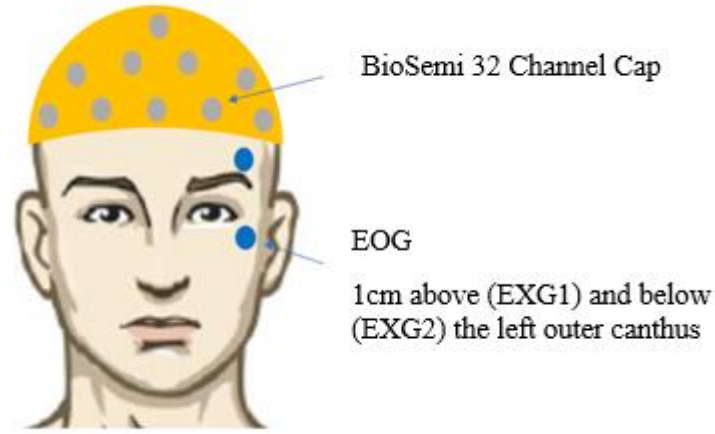
Note. Showing electrode placements of 32 channels according to the international 10-20 system. Adapted from BioSemi website (BioSemi, 2022).

A separate bipolar channel was used to record vertical electro-oculography (VEOG). Electrode placement to record VEOG can be seen in Figure 9. To do this, flat type active electrodes EXG1 and EXG2 electrodes were placed 1cm above and below the left outer canthus. Each EEG was five minutes duration during which time the participants were asked to sit passively and gaze at the target. The EEG was sampled at 16000 Hz, filtered between

0.16 and 100 Hz and referenced to the CMS (common mode sense) active electrode and grounded DRL (driven right leg) passive electrode. Power to the booth was disconnected during EEG measurement to minimise electrical interference; in particular, mains electrical interference (i.e. 50 Hz mains power).

Figure 9

Electrode Placement for EXG1 and EXG2 Electrodes



3.9 Likert Scale and Tinnitus Handicap Inventory

At the beginning of the A1 session, participants were asked to rate the loudness of any tinnitus present on a Likert scale (Appendix E) from 0 – 10, with 0 on the scale indicating no tinnitus, while 10 on the scale indicated tinnitus was extremely strong or loud. Participants had to score 0 on the Likert to continue participation. The THI (Appendix F) was also completed at the start of the A1 session, participants with no tinnitus could mark it N/A if they did not have tinnitus. The THI is a 25-item questionnaire which is used to characterise tinnitus severity as follows: slight (0 - 16), mild (18 - 36), moderate (38 - 56), severe (58 - 76) and catastrophic (78 - 100) (Newman et al., 1998). Both measures were again implemented to assess tinnitus presence and severity in the B and A2 conditions.

3.10 Experimenter and Participant Bias

When a researcher is aware of the experimental conditions in which participants are being tested, they may subtly or inadvertently alter their behaviour and in doing so, communicate the expected outcomes of the study to the participant. This is known as experimenter bias (Brito, 2017). A consequence of experimenter bias is that participants may then alter their behaviour to conform to the researcher's expectations. Participant bias can be broadly defined as a bias that "occurs when the participant's anticipations or thoughts about a study influence their responses and, thus, the study's results" (Brito, 2017, p. 94). In experimental methodologies, participant bias is most often seen in the form of demand characteristics: cues that the participant observes during the study which may lead them to alter their behaviour in ways which they believe either correspond to or contradict, what the researcher expects to find (De Munter, 2005). Demand characteristics can arise from the participant's own motivations, interactions with the researcher, or knowledge of the purpose of the study (Brito, 2017).

Past research has demonstrated that using an earplug can induce temporary hearing loss and tinnitus. As the perception of tinnitus can have negative emotional consequences even when psychoacoustically matched to sensation levels lower than 20dB (Penner, 1986), participants were informed in the information sheet that there was a chance they may experience tinnitus while wearing the earplug as part of ethical considerations. This admission and expectation had the potential to generate a bias and therefore it was necessary to control for this in the study.

3.10.1 Likert Control

An abbreviated form of tinnitus pitch and loudness matching was employed to control for any participant bias on the Likert scale. Participants who reported tinnitus on return to the lab in session two were presented with three pure tones at a comfortable listening level in the

unplugged ear. In pseudorandom order, 250 Hz, 1000 Hz and 8000 Hz (6000Hz was included in cases where earplug attenuation was maximal at that frequency) were presented via an insert earphone and participants were asked which of the three tones sounded most like their tinnitus percept. The selected tone was then reduced to threshold and increased in an ascending manner of 5 dB steps with a presentation time of three seconds. The participants were instructed to press the response button when the tone reached the level of equal loudness to the tinnitus percept.

Previous research has indicated that tinnitus pitch usually occurs in the region of maximal hearing loss (Keppler et al., 2017; Sereda et al., 2015). Since earplug use should induce a mild to moderate hearing loss in the mid to high frequencies, it was predicted that the 6000 or 8000 Hz pure tone would tend to produce the closest match in pitch to the tinnitus because the earplug produced the greatest attenuation in this frequency range. The participants, however, were blinded to this idea. Therefore, if a lower frequency was selected, this could alert to a possible bias effect.

3.10.2 EEG Control

To conduct a control condition into the EEG part of the study, one additional five-minute resting EEG segment was carried out in session three (A2 condition) following earplug removal, during which a continuous pure tone or narrowband noise was presented into the participant's left ear by insert earphone. The frequency of this tone and the loudness was determined by the participant (as described in 3.10.1). It was hypothesised that this sound would simulate any perceived tinnitus experienced by the participant when the earplug was in the ear, and we would expect the resting EEG (gamma) to reflect this. This hypothesis is based on unpublished data by Maslin (2021), whereby increased gamma activity was evident over the contralateral temporal region when an evoked stimulus was presented to control participants monaurally. It was thought that if the resting EEG in session two (B

condition) showed a similar change then the effect was ‘real’ in the auditory system. But if the resting EEG in session two showed a change but it was of a different pattern to this control then we would be alerted to a possible bias effect at play. If no tinnitus was reported by the participant with the earplug in place, an 8000 Hz pure tone at 10dB HL was presented.

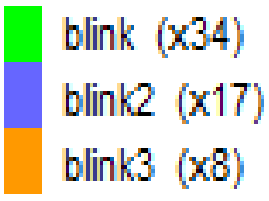
3.11 EEG Processing

Data pre-processing was carried out using the BioSemi system ActiTools v9.01 (ActiveTwo System, 2016). This was used to down-sample the data by a factor of 16, which made the new sampling rate 1024 Hz. Further EEG processing was conducted offline using Brainstorm software (Brainstorm, 2022). Each file was first inspected for rogue channels and any such channels were selected as bad and removed. The resulting file was then moved into the processing box of Brainstorm and was processed using a custom script. EEG electrode positions were added via ICBM152 Biosemi 32 channel default position (BioSemi, 2022), average re-referenced, notch and low pass filtered at 50 Hz (3 dB notch bandwidth of 1 Hz) and 100 Hz respectively, and DC offset corrected.

The resulting files were then manually examined for the presence of eye blink artefacts and these artefacts were then removed from the recordings. This process often detected more than one type of eyeblink, an example of which can be seen in Figure 10.

Figure 10

Three Different Types of Eyeblinks Detected for Participant 7



The different types of blinks are the result of the detection algorithm that not only detects the events of a signal, it also classifies them by morphology. The signals around the event must be sufficiently correlated (> 0.8) to be put in the same category (Brainstorm,

2020). All categories that contain less than five blinks were deleted and the remaining blink categories were manually inspected for artefact removal. On average, humans blink involuntarily once in five seconds and the blink can last from 100-400 milliseconds (Mahajan & Morshed, 2014). The levator muscle potential occurs as a result of an eye blink and is 10 times larger than the EEG amplitude and is the most dominant artefact. Due to the high magnitude of the eye blink and the high resistance of the skull and scalp tissues, the eye blink contaminates the electrode signals (Sreeja et al., 2017). This makes artefact removal a very important part of EEG signal processing so as to avoid contamination of EEG signals. Manual inspection of each file was undertaken, and eye blinks were removed from each file. An example of eye blink artefacts and their removal can be seen in Figures 11 and 12.

Figure 11

Example of eye Blinks Detected on an EEG Recording

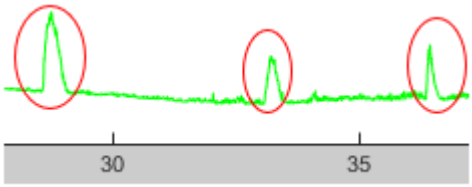
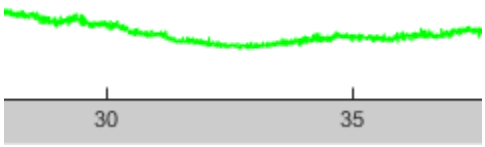


Figure 12

EEG From Figure 11 Following eye Blink Artefact Removal



Following eye blink artefact removal, the power spectral density (PSD; Welch's method) was obtained, with a window length of four seconds and a window overlap ratio of 50% selected as per the guidelines by Niso et al. (2019). Four second windows provide a

frequency resolution of 0.25 Hz. The 50% overlap increases the number of windows, which this maximises the signal to noise ratio.

Spectrum normalisation was carried out by selecting ‘Standardise’, ‘Spectrum Normalisation’ and ‘Relative Power’ (divided by total power). The spectrum normalisation process is done by dividing the PSD by its total power. This process is done to compare and contrast PSD between participants while taking EEG individuality into account. For example, the power could vary from one person to the next due to factors like brain volume differences (some brains are larger than others). The normalisation process allows these variations to be taken into account.

The PSD of the following frequency bands were then obtained: delta (δ; 2 – 4 Hz), theta (θ; 5 – 7 Hz), alpha (α; 8 – 12 Hz), beta (β; 15 – 29 Hz), gamma1 (γ1; 30 – 59 Hz) and gamma2 (γ2; 60 – 90 Hz). The group average of individual PSD sensor data was obtained by dropping each individual result into the process box and averaging the files.

3.12 Source Analysis

Source analysis is the process of estimating the underlying neural sources which generate the EEG. The electrodes used in EEG are relatively large and remote; they only detect summed activities of a large number of neurons that are electrically active in a synchronous manner (Hallez et al., 2007). The activity of trying to find underlying sources which generate the EEG is known as source localisation and consists of solving a forward and inverse problem. The forward problem is solved by starting from a given electrical source and calculating the potentials at the electrodes, while the inverse problem is solved by finding brain sources which are responsible for the measured potentials at the EEG electrodes (Hallez et al., 2007). While highly recommended that individual anatomical information is obtained using an MRI for this process, MRI was not available for this study. Therefore, the head model for each participant was computed in Brainstorm by selecting the 3-shell sphere

and selecting the cortex surface. Empty room recordings to characterise instrument and environmental noise cannot be done with EEG, so a baseline condition was estimated by selecting noise covariants and no noise modelling. Low resolution brain electromagnetic tomography (sLORETA) was then used for source analysis, with Desican-Killiany scouts and right and left superiortemporal regions selected. To obtain numerical figures for statistical analysis, the sLORETA was grouped in frequency bands, spectrum normalised by relative power (method described above) and the corresponding results were exported to Excel for analysis. Individual sLORETAs were averaged together in groups to obtain the source group average. It is important to state that the aim of the present source analysis was not to characterize source locations in each hemisphere, but rather to demonstrate an approximation of these sources such that differences between conditions might shed light on plasticity.

3.13 Statistical Analysis

To test both hypotheses, repeated measures Analysis of Variance (ANOVA) was conducted. A repeated measures ANOVA is a suitable design to utilise when measuring the same variable repeatedly, for example at different time points (Park et al., 2009). Prior to the repeated ANOVA, the assumptions associated with this statistical method were checked: the data was examined for outliers and normality was then examined by conducting a Shapiro-Wilk test. A *p* value of less than 0.05 in this test suggests that the data is not normally distributed. Mauchly's Test of Sphericity was carried out to test whether or not the assumption of sphericity was met in the repeated measures ANOVA. A significance value of less than .05 indicates that the assumption of sphericity has been violated. This is an important step in a repeated measures ANOVA as if sphericity is violated, it causes the ANOVA to become too liberal and therefore increases the likelihood of a type I error. In cases where sphericity was violated, a Greenhouse-Geisser correction was used to obtain

more valid *F*-values. This correction enables a more accurate *p* value when the sphericity assumption is violated (Armstrong, 2017).

Chapter 4: Results

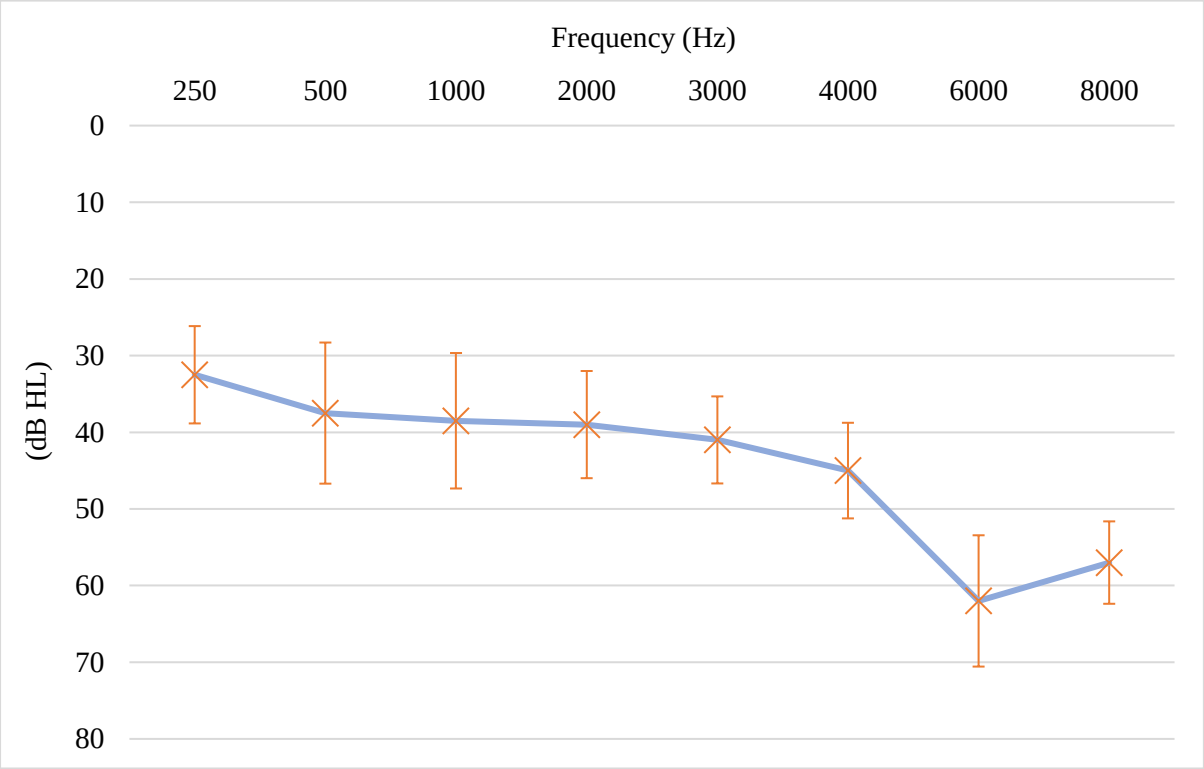
This section outlines the results and statistical analysis of this study.

4.1 Earplug Effect

Based on data available online from the manufacturer of the 3M earplug used with all 10 participants, it was predicted that use of the earplug would attenuate all frequencies from 250 Hz to 8000 Hz, though most attenuation would occur at the high frequencies. All participants had hearing thresholds within normative limits in both ears as defined by NZAS (2021) when measured in session one. The level of attenuation in the left ear induced by the earplug is shown in Figure 13.

Figure 13

Mean Audiogram With Earplug in-situ



Note. N=10. The bars represent +/-1 standard deviation from the mean.

4.2 Participant Characteristics

A summary of the Likert scores, THI, and tinnitus matching results are displayed in Table 1. The age of the participants ranged from 22 to 33 years, of which three participants were male (participants 1, 4 and 8) and seven were female. Of the 10 participants in the study, six reported the experience of tinnitus upon return to the lab for session two, with a mean Likert score of 4.08 (+/-1.53). The THI in session two revealed a mean score of 21.33 (+/- 19.85), indicating mild handicap associated with the temporary tinnitus. The consistent subjective sensation was of a 'high pitched' tinnitus, and this corresponded with the abbreviated pitch matching process, where all participants selected the highest possible frequency (either 6000 or 8000 Hz) as offering the closest match to their sensation.

Table 3

Summary of Self-Reported Tinnitus Characteristics

		Likert							THI		
Participant	Tinnitus	A	B	A	Laterality	Pitch match	Loudness match	Subjective quality	A	B	A
1	N	0	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
2	Y	0	3.5	0	Plugged ear	8kHz	20dB SL	High pitched ringing	N/A	26	N/A
3	N	0	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
4	Y	0	6.5	0	Plugged ear	6kHz	30dB SL	High pitched ringing	N/A	54	N/A
5	Y	0	3.5	0	Pugged ear	8kHz	5dB SL	High pitched static	N/A	30	N/A
6	N	0	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
7	Y	0	2	0	Plugged ear	8kHz	5dB SL	High pitched whooshing	N/A	2	N/A
8	Y	0	4	0	Plugged ear	8kHz	20dB SL	High pitched whooshing	N/A	2	N/A
9	N	0	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
10	Y	0	5	0	Plugged ear	8kHz	10dB SL	High pitched narrowband	N/A	14	N/A

4.3 Behavioural Assessment Results

Since the hypothesis was concerned with EEG features associated with earplug induced tinnitus, only the data of the six participants who reported tinnitus were used in the remaining statistical analysis. Therefore, $n = 6$ in graphs, tables, and images in this chapter.

4.3.1 Likert Scale

Statistical analysis of the Likert results was undertaken. As the data for A1 and A2 conditions equalled zero, only data for the B condition was examined for normality. The B condition data were plotted on a Q-Q plot and visually inspected for extreme outliers with none identified. A Shapiro-Wilk test was performed and did not show evidence of non-normality ($p = .85$). As two of the Likert conditions had a score of 0, there was no significance value in Mauchly's Test of Sphericity and so sphericity was met. A repeated measures ANOVA showed a statistically significant effect of earplug use on the Likert results $F(2,10) = 42.72$, $p = < .001$.

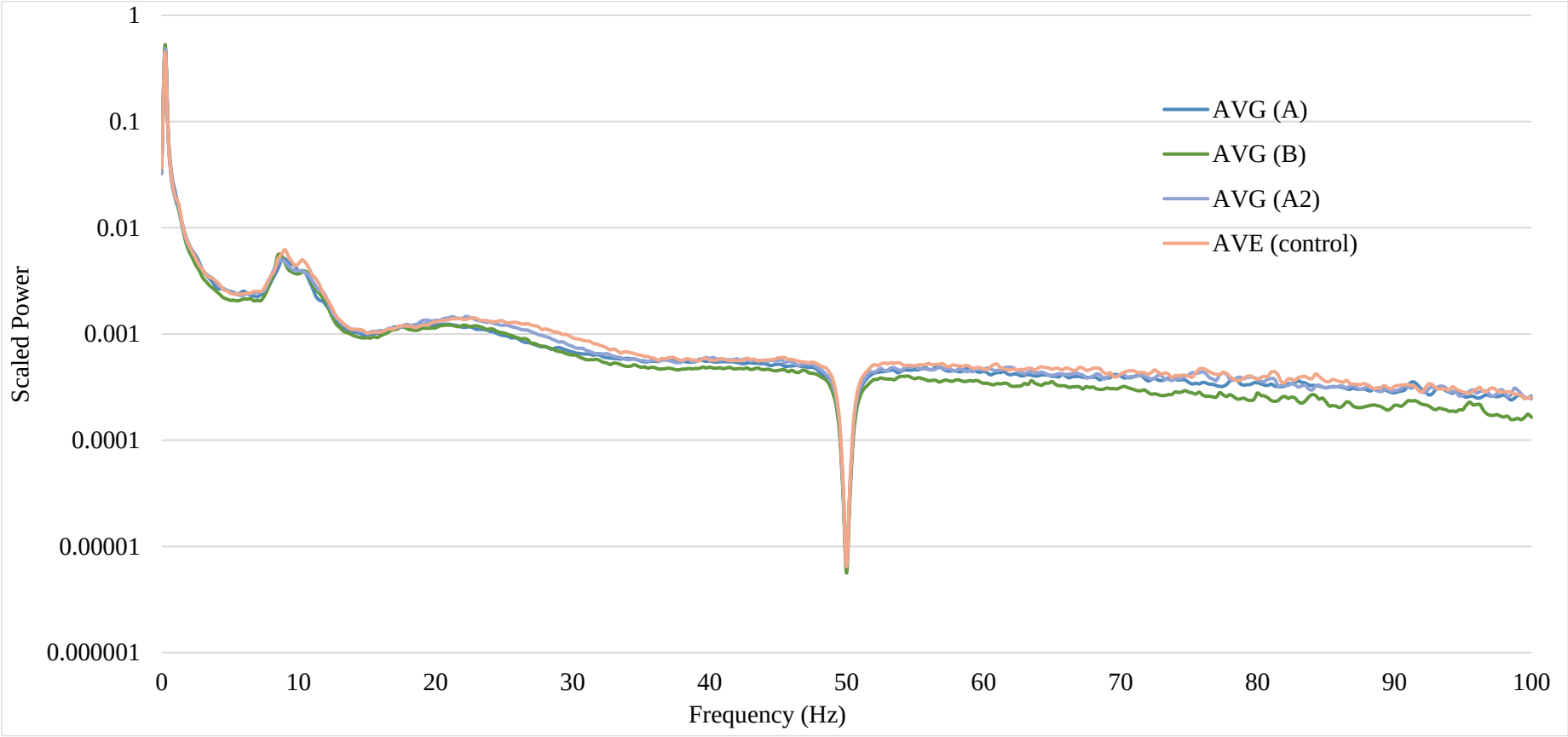
4.4 Grand Averages

The grand average sensor level PSDs of the six participants who experienced tinnitus was exported to Excel and averaged over all sensors in each condition to investigate any trends between conditions. As an initial exploration of the data, the averaged power spectra for each condition (A-B-A and control) are displayed in Figure 14. Each of the traces show the characteristic peak in the delta range (1-4 Hz) and then the power decreases as frequency increases according to the 1/f rule (Demanuele et al., 2007). The data show a peak around 10 Hz, which is the so-called alpha wave. This wave is characteristically present in normal awake EEG recordings. The sharp dip in power at 50 Hz reflects the notch filter used to remove artefacts otherwise caused by energy at the frequency of the alternating mains current. The four PSDs are generally clustered and overlapping across the frequency range,

with no obvious increases in power in any one condition. Thus, an explorative analysis did not reveal any apparent significant differences across conditions in any frequency band.

Figure 14

PSD of Each Condition Averaged Across Sensors

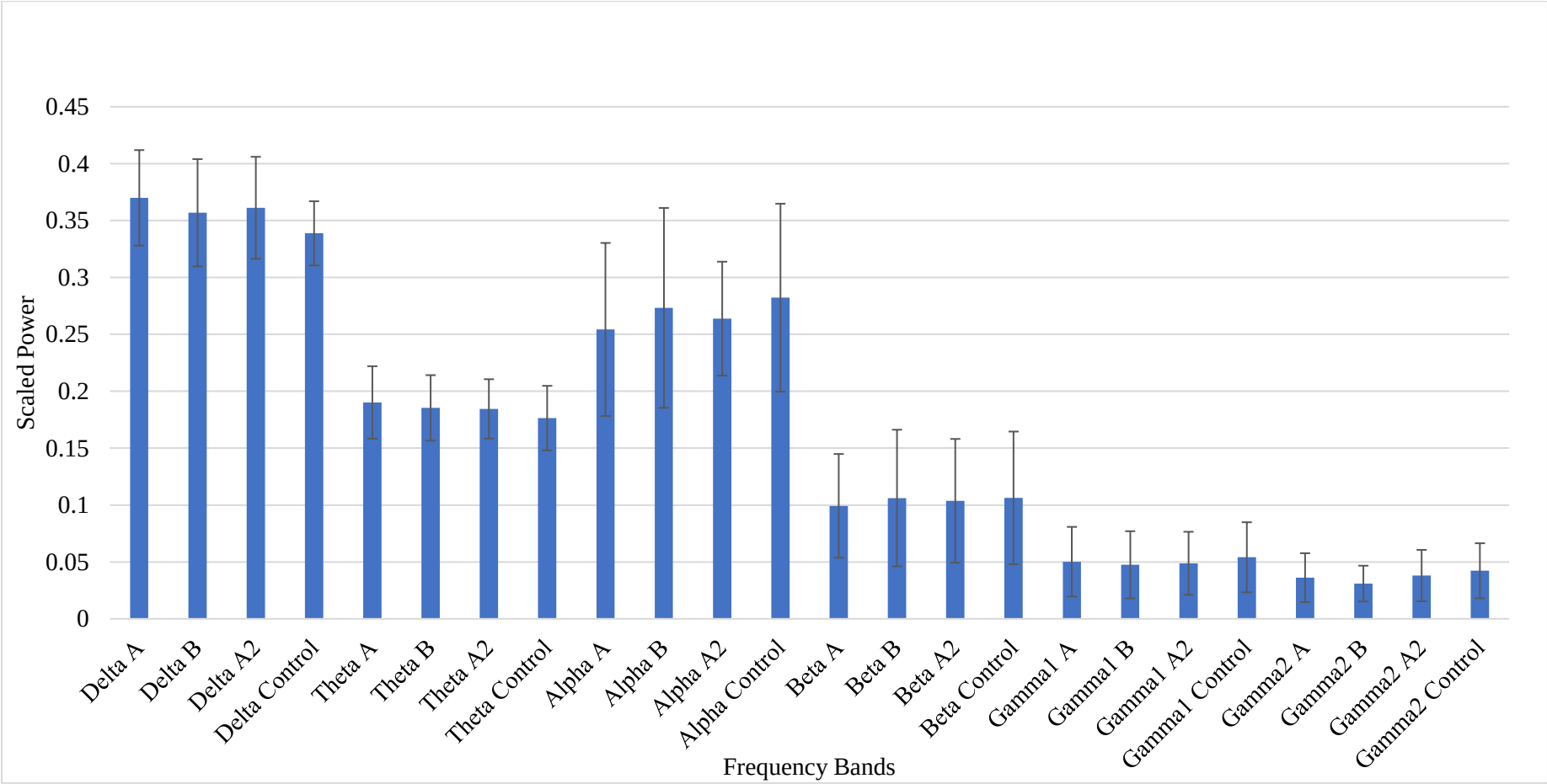


4.4.1 Averaged Power by Frequency Band Across all Electrodes

Figure 15 shows the mean spectral power in each of the frequency bands in each of the conditions, therefore is complementary to Figure 14. The heights of the bars reduce as frequency increases in the same way as Figure 15 (following 1/f) and the bars are of similar amplitude across conditions. Thus, contrary to the hypothesis, this initial exploration of the data did not reveal any clear trends for altered EEG activity when viewed by means of the averaged power spectra across all electrodes. Effects in regions of interest such as temporal regions may be less apparent, therefore a next step was to perform more spatially specific analysis, described in section 4.4.2.

Figure 15

Bar Chart Displaying Averaged Power by EEG Frequency Band



Note. Error bars depict +/-1 SD.

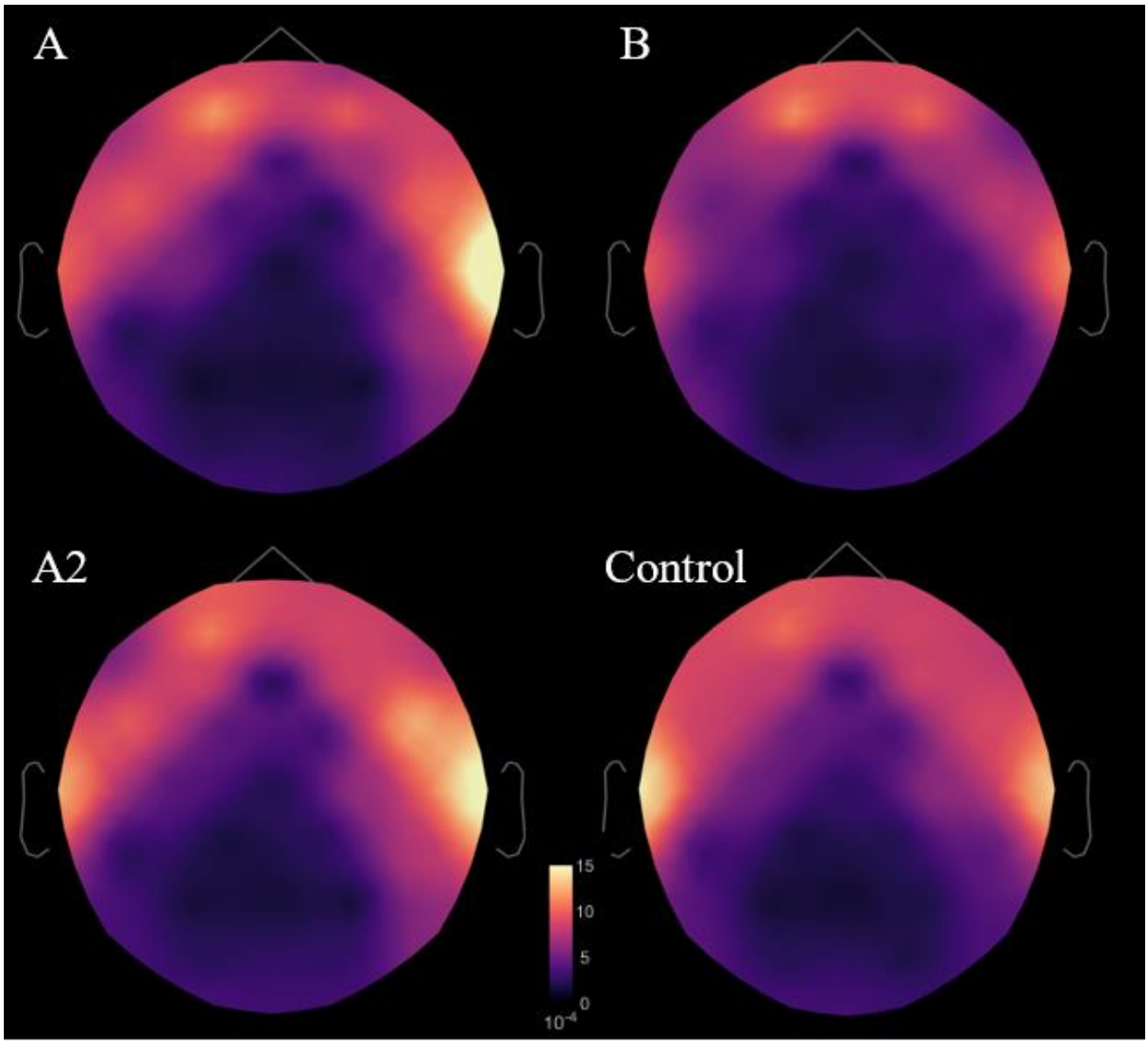
4.4.2 Topographical Analysis of Sensor Level EEG

Figures 16 and 17 show topographical plots of the PSDs described in section 4.4.1 for the gamma and alpha bands, respectively. For gamma (Figure 16), examination of sensor level gamma activity was carried out at 30Hz, 40Hz, 55Hz and 70Hz and similar topographical patterns were noted in all conditions. Therefore, Figure 16 depicts the findings at 40 Hz, which is representative of other gamma frequencies. Visual inspection of sensor level topographical data did not indicate any clear differences across conditions, with power apparently being relatively higher in the bilateral temporal and also frontal regions in each condition compared with the central and posterior regions. In fact, there appeared to be a slight decrease in gamma activity in the B condition.

Similar trends were apparent from Figure 17 depicting alpha oscillations at 10 Hz, which was representative of the alpha band. Again, visual inspection did not indicate any clear differences across conditions, with alpha power relatively higher in occipital regions consistent with the principal generators relating to the visual system. As a final analysis step, inferential statistical analysis was carried out on data at the source level, and these are described in section 4.5.

Figure 16

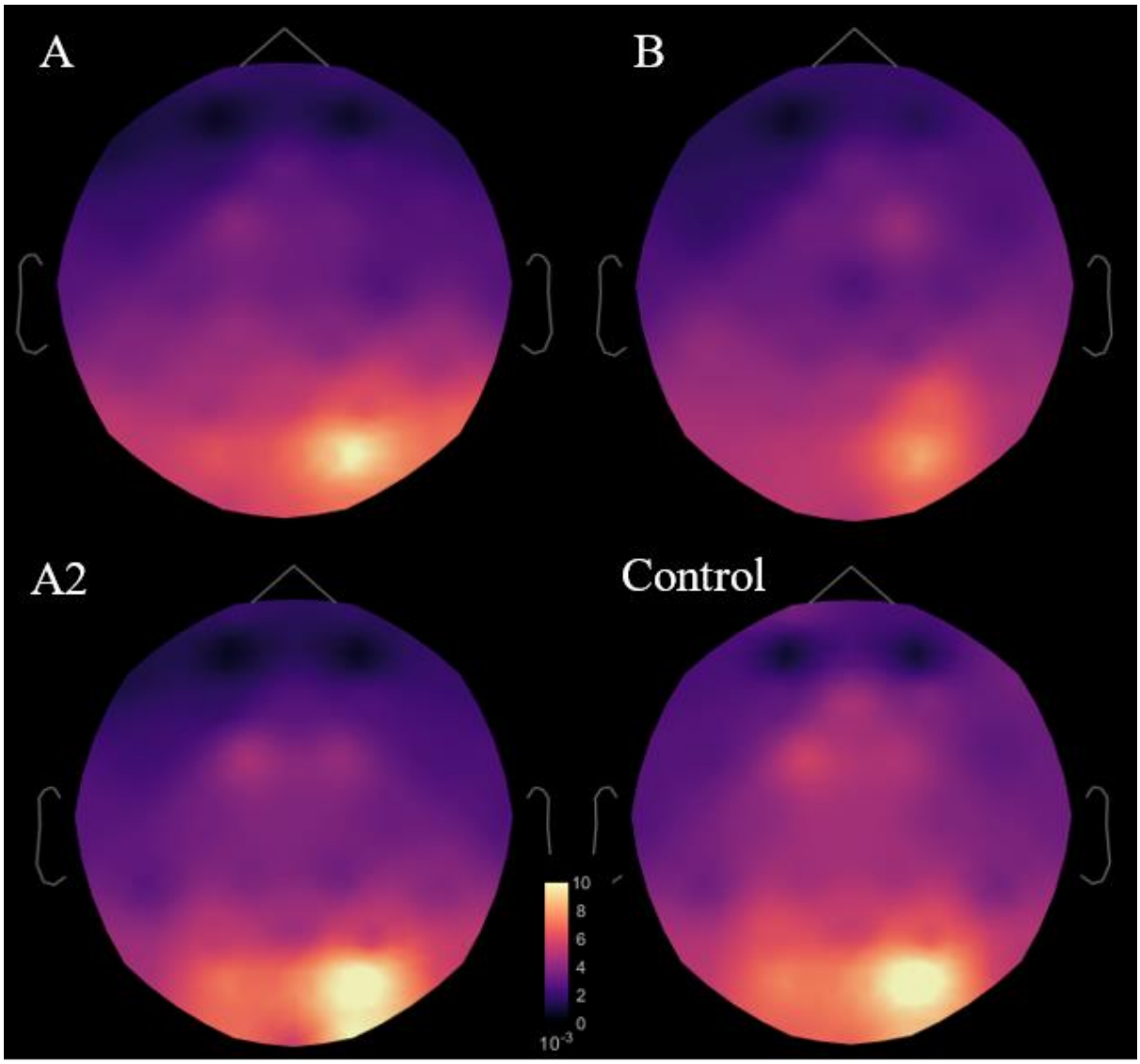
Analysis of Resting State Gamma (40Hz): Grand Average Sensor Level Data



Note. The colour bar indicates gamma signal strength, with brighter colours on the bar indicating greater strength than darker colours.

Figure 17

Analysis of Resting State Alpha (10Hz): Grand Average Sensor Level Data



Note. The colour bar indicates alpha signal strength, with brighter colours on the bar indicating greater strength than darker colours.

4.5 Source Analysis of Right and Left Superior Temporal Gyri

Mean brain images showing source power for the gamma and alpha frequency bands (in left and right hemispheres) are displayed in Figures 18 to 21. Each figure highlights the auditory cortical regions (superior temporal gyri - STG) with a shaded zone.

4.5.1 Gamma Activity in the Right Hemisphere STG

It is clear that the source projections are not restricted to those regions of interest, and consistent with the sensor level topographies, are symmetrical. Source power data for each condition were plotted on a Q-Q plot and visually inspected for extreme outliers with none identified. A Shapiro-Wilk test was performed and did not show evidence of non-normality. Table 4 details descriptive statistics for gamma activity in the right hemisphere STG.

Table 4

Descriptive Statistics: Gamma Activity in Right STG

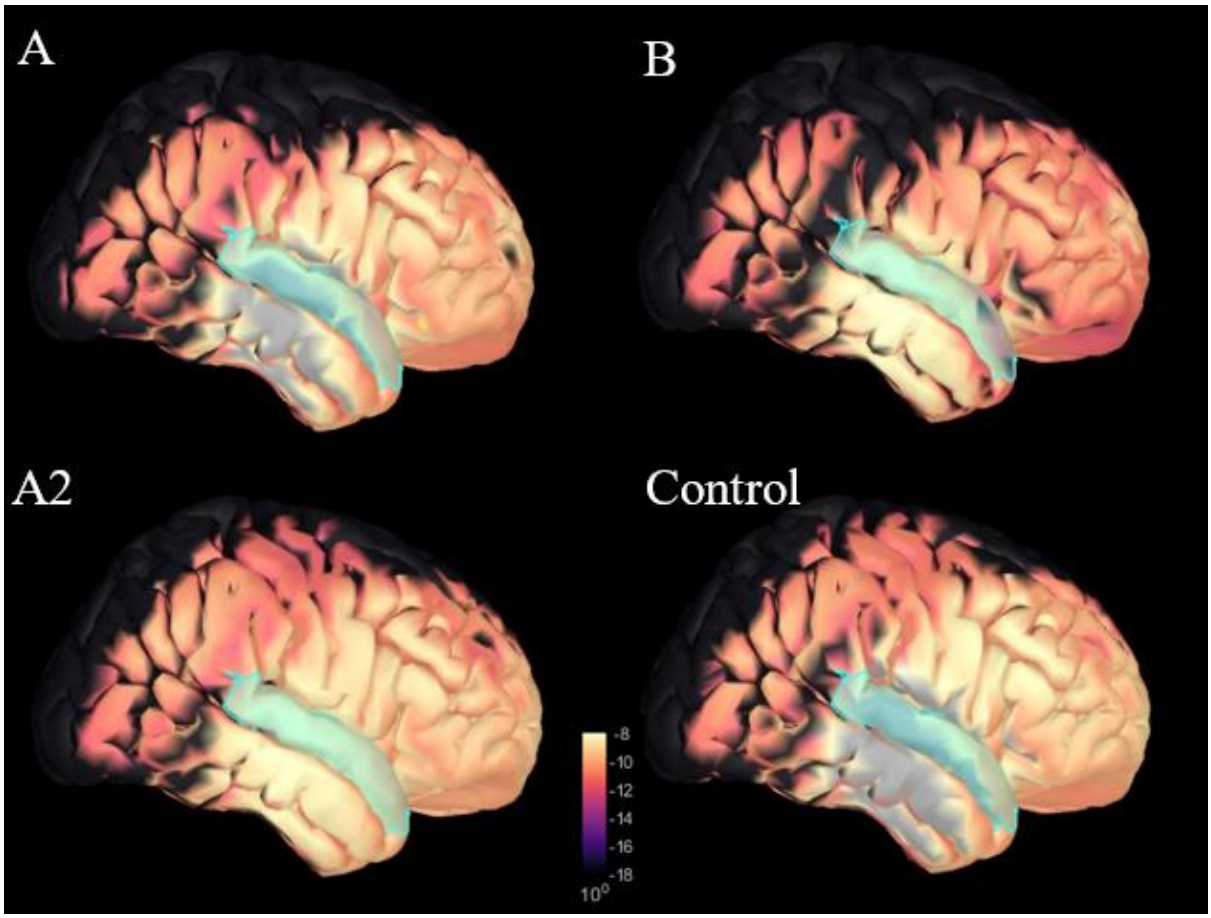
Condition	*M*	*SD*	Shapiro-Wilk p
Gamma A1	0.12	0.05	0.92
Gamma B	0.10	0.05	0.90
Gamma A2	0.12	0.08	0.10
Gamma Control	0.13	0.05	0.76

Mauchly's test indicated that the assumption of sphericity had been violated, $\chi 2(5) = 11.45$, $p = .05$. A Greenhouse-Geisser corrected repeated measures ANOVA showed no statistically significant effect of plugging (or control signal) on gamma power in the right hemisphere STG $F(1.57,7.82) = 0.75$, $p = 0.47$.

Source analysis images depicting gamma and alpha activity in each hemisphere can be seen from Figures 18-21. The amplitude of the source analysis for each image is set to 70%. The source analysis of each condition is displayed in Log(power), with Desikan-Killiany scout right STG illuminated. The colour bar indicates source strength, with brighter colours on the bar indicating greater source strength than darker colours.

Figure 18

Source Analysis of Gamma Oscillations: Right Hemisphere



4.5.2 Gamma Activity in the Left Hemisphere STG

Data for each condition were plotted on a Q-Q plot and visually inspected for extreme outliers with none identified. A Shapiro-Wilk test was performed and did not show evidence of non-normality. Table 5 details descriptive statistics for gamma activity in the left STG.

Table 5

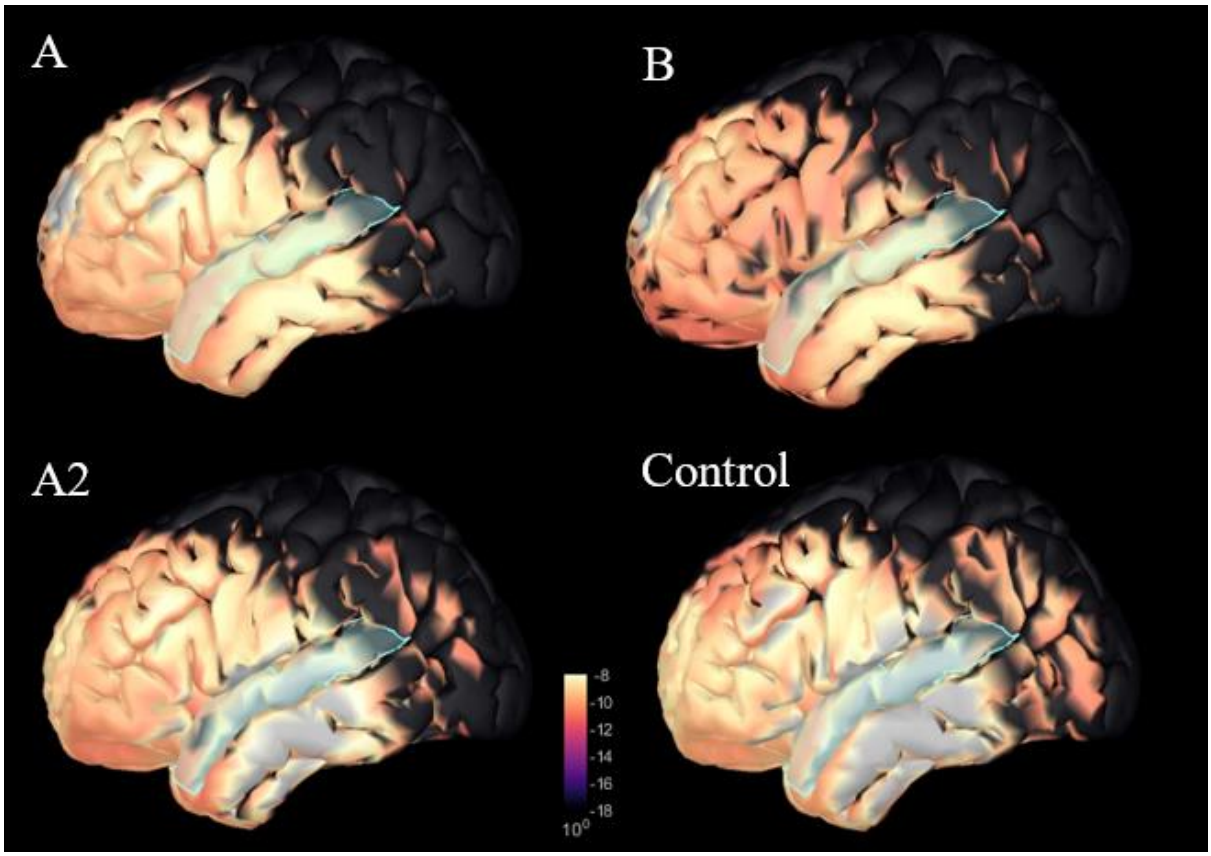
Descriptive Statistics: Gamma Activity in the Left STG

Condition	*M*	*SD*	Shapiro-Wilk p
Gamma A1	0.11	0.04	0.20
Gamma B	0.09	0.06	0.22
Gamma A2	0.13	0.05	0.16
Gamma Control	0.13	0.05	0.60

Mauchly's test indicated that the assumption of sphericity had not been violated, $\chi 2(5) = 5.79$, $p = .34$. A repeated measures ANOVA showed no statistically significant effect of plugging (or control signal) on gamma power in the left hemisphere superior temporal gyrus $F(3,15) = 1.22$, $p = 0.34$.

Figure 19

Source Analysis of Gamma Oscillations: Left Hemisphere



4.5.3 Alpha Activity in the Right Hemisphere STG

Data for each condition were plotted on a Q-Q plot and visually inspected for extreme outliers with none identified. A Shapiro-Wilk test was performed and did not show evidence of non-normality. Table 6 details descriptive statistics for alpha activity in the right STG.

Table 6

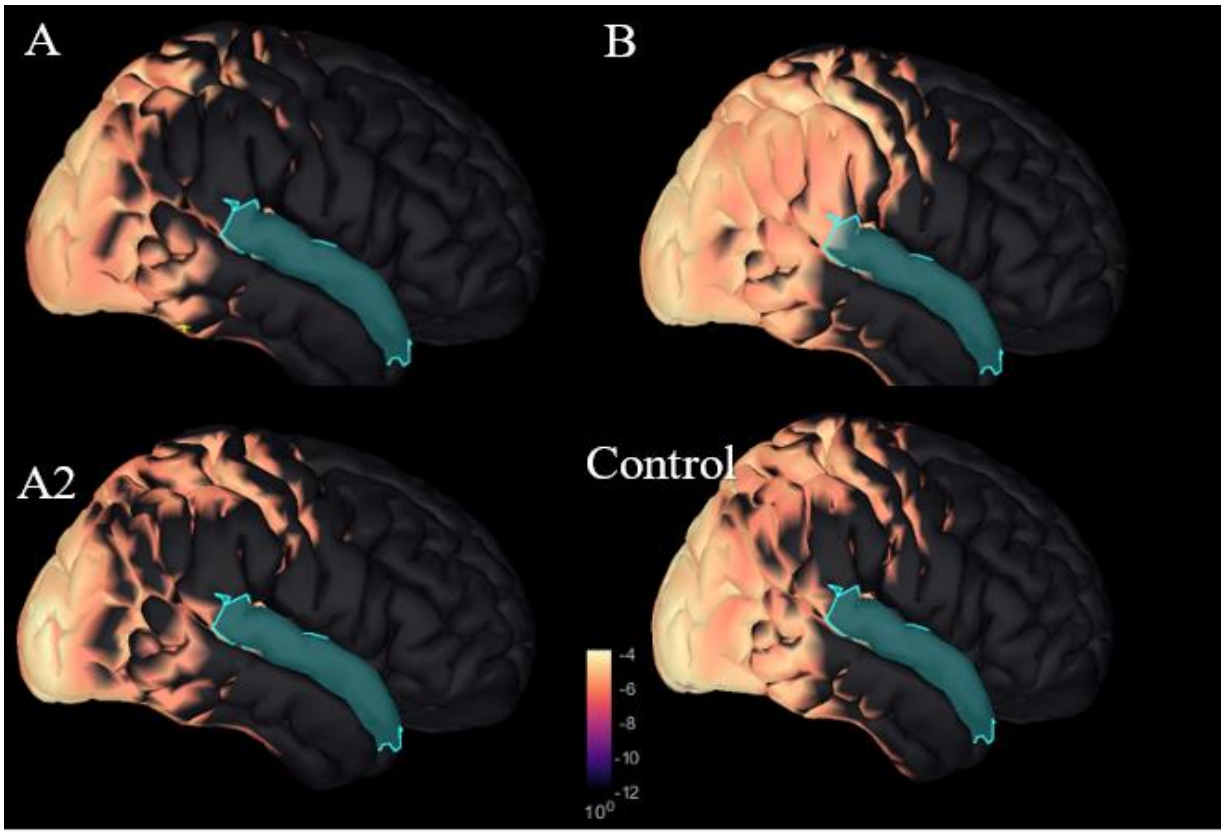
Descriptive Statistics: Alpha Activity in Right STG

Condition	*M*	*SD*	Shapiro-Wilk p
Alpha A1	0.13	0.03	0.39
Alpha B	0.17	0.08	0.31
Alpha A2	0.14	0.08	0.36
Alpha Control	0.16	0.07	0.47

Mauchly's test indicated that the assumption of sphericity had not been violated, $\chi 2(5) = 5.51$, $p = .37$. A repeated measures ANOVA showed no statistically significant effect of plugging (or control signal) on alpha power right hemisphere superior temporal gyrus $F(3,15) = 1.50$, $p = 0.25$.

Figure 20

Source Analysis of Alpha Oscillations: Right Hemisphere



4.5.4 Alpha Activity in the Left Hemisphere STG

Data for each condition were plotted on a Q-Q plot and visually inspected for extreme outliers with none identified. A Shapiro-Wilk test was performed and did not show evidence of non-normality. Table 7 details descriptive statistics for alpha activity in the left STG.

Table 7

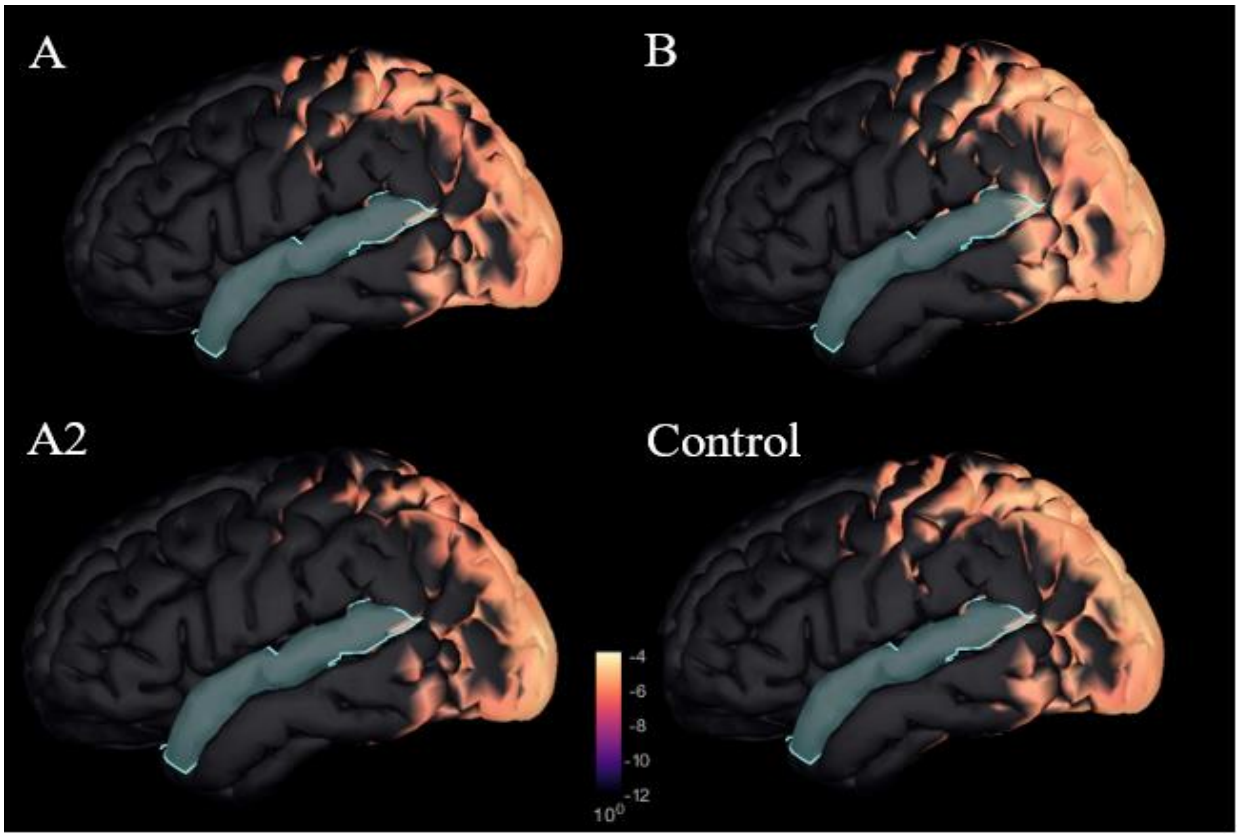
Descriptive Statistics: Alpha Activity in the Left STG

Condition	*M*	*SD*	Shapiro-Wilk p
Alpha A1	0.13	0.02	0.92
Alpha B	0.14	0.04	0.29
Alpha A2	0.14	0.05	0.26
Alpha Control	0.14	0.05	0.28

Mauchly's test indicated that the assumption of sphericity had been violated, $\chi 2(5) = 16.97$, $p = .006$. A Greenhouse-Geisser corrected repeated measures ANOVA showed no statistically significant effect of plugging (or control signal) on left hemisphere alpha power $F(1.87,9.33) = .11$, $p = 0.88$.

Figure 21

Source Analysis of Alpha Oscillations: Left Hemisphere



4.6 Summary of Results

This project aimed to characterise the pattern and location of synchronised resting state neural activity via EEG in participants after tinnitus that is induced temporarily using an earplug in one ear for several hours. A secondary aim was to study the relationship between abnormal brain rhythms and behavioural characterisations of tinnitus severity. This research is novel, since despite a range of reports of altered neural gain following unilateral earplugging and associated perceptual effects related to tinnitus, there are to date no previous reports of associated resting-state EEG data.

The primary hypothesis was, that compared with baseline measures, there would be a change in spontaneous brain activity associated with tinnitus triggered by temporary earplug-induced hearing loss.

The main findings were:

1. Unilateral ear plugging induced a tinnitus sensation of mild to moderate loudness in six out of 10 participants over four hours of use. The tinnitus sensation was subjectively described as high frequency in nature. These same participants also reported mild handicap (mean score) on the THI associated with their tinnitus. In all cases the tinnitus disappeared when the plug was removed.
2. There was no apparent effect of earplugging on the resting-state spectral power. A particular focus on gamma and alpha source power in auditory cortical regions showed no statistically significant differences in power.

These results do not lend support for rejecting the null hypothesis in this study.

Chapter 5: Discussion

5.1 Introduction

The results from Chapter 4 will be discussed in this section, with respect to relevant findings in the literature. In addition, the limitations of the study will be considered as well as recommendations for future research in the field.

5.2 The Earplug Model

The idea of using an earplug to study gain changes associated with tinnitus has been employed on several occasions (Munro et al., 2014; Schaette et al., 2012; Brotherton et al., 2019). In these studies, a decrease in ARTs following the period of time spent wearing the earplug is consistent with subcortical plasticity associated with temporary earplug induced hearing loss. However, as various studies have reported evidence of abnormal connectivity involving both auditory and non-auditory areas of the brain in those with tinnitus (Adams et al., 2020; Chen et al., 2017; Cheng et al., 2020), it was hypothesized that furthering the earplug paradigm to involve neuroimaging could shed light on the additional changes at a higher level of the auditory pathway responsible for conscious perception of tinnitus.

5.2.1 Behavioural Measures and the Earplug Model

The six participants who did report tinnitus described it as “high pitched ringing”, “high pitched static” and “high pitched whooshing” and these descriptions are in keeping with patient reports of tinnitus (Moring et al., 2016). The present work supports the notion that auditory deprivation can trigger temporary and reversible tinnitus. However, it extends the findings by showing that the effect can occur in a matter of hours, where previous studies showing the same effect have plugged the ear for days or a week. Another way in which the present behavioural results extend previous work is that the present study took steps to

mitigate against response bias by blinding the participants in a tinnitus matching task. This lends support to the idea that the experience of the listeners is true tinnitus.

In this study, 60% of participants reported tinnitus on return to the lab after four hours of wearing the foam earplug. This is a lower percentage when compared with previous studies who have used the earplug; 68% of participants in the Brotherton et al. (2019) study reported tinnitus and 78% of participants in the Schaette et al. (2012) study reported tinnitus. It is not immediately clear why a relatively high proportion of participants did not experience tinnitus. One possible reason may be related to the sample size differences of the respective studies; in Brotherton et al. (2019) $N = 44$ and in Schaette et al. (2012) $N = 18$. The smaller sample size in this present study meant that a single participant who did not experience tinnitus had a larger impact on the overall 'no tinnitus' percentage.

Another possibility is that for some individuals, four hours was an insufficient period of time for homeostatic plasticity to occur. Perhaps had the earplugged period been longer, maybe tinnitus would have emerged. Based on the supposed mechanisms driving gain change (Turrigiano, 1999), it is plausible to suggest that the rate of homeostatic plastic change could differ among participants. In addition, the environment the participants were in whilst wearing the earplug was not controlled and some might have been in a higher level of ambient noise than others and thus experienced a greater input asymmetry. Finally, all participants stated that they kept the earplug in place for the duration of the four hours without removing or changing it. However, as will be discussed in section 5.5, participants did comment that they found the earplug uncomfortable, so it is possible that the earplug was adjusted by participants during the four-hour period which could have impacted the effect of the earplug.

In addition to determining tinnitus presence and loudness via the Likert scale, tinnitus severity was measured using the THI. It was not expected that severity would be reported

beyond Grade 1 (0-16 on the scale) based on participant reports from other earplug studies. There were, however, two participants who reported a Grade 2 severity and one participant who reported a Grade 3 severity. This result needs to be considered from an ethical perspective for future research. The THI results also indicate a potential confound in the study design. It was thought that the earplug model was a way to differentiate tinnitus sensation from tinnitus distress; the THI results cast doubt on that argument. Potential confounds are discussed further in section 5.5.2.

5.2.2 EEG Measures and the Earplug Model

On return to the lab for the A2 EEG and the control EEG, some participants commented that the control sound was the same as the sound they had perceived when the earplug was in situ. Despite the significant subjective results demonstrated across the A-B-A conditions, no significant change in spontaneous resting state activity across conditions was found that could account for the conscious perception of tinnitus that the six participants experienced with the earplug.

EEG research by Meyer et al. (2014) offer a potential explanation for this finding. Through analysis of psychometric data and EEG, they offer that the perceived intensity of the sound associated with tinnitus increases with tinnitus duration, with tinnitus presence corresponding to enhanced EEG signal in the lower gamma band. This enhanced activity was evident bilaterally in their study but left dominant over the temporal auditory and left extra-auditory recording sites. Perhaps increased gamma activity would have been evident if the earplug and thus, the temporary induced tinnitus had been in place longer than four hours.

A consideration as to why the control condition did not yield any significant change may be to do with the presentation level of the control signal. As stated in section 3.10.2, the idea for the pure tone control condition came from unpublished data by Maslin (2021). However, Maslin's stimulus was a 70dB SPL 1000 Hz tone. In this study, the stimulus was a

much lower input level, ranging from 5 to 30dB HL as determined by the pitch and loudness matching task completed by each of the six participants who reported tinnitus. The EEG is a physiological measure, akin in ways to the ABR. In the case of ABR, we tend to see physiological response thresholds around 10-20dB above the behavioural threshold (Stapells, 2000). Therefore, it is possible that the control sound was presented at or below the physiological threshold and therefore was not measurable.

5.2.3 Physiological Evidence of Homeostatic Plasticity in Four Hours

In the previously mentioned studies, which have used the earplug paradigm, participants were instructed to wear their earplug for four to seven days. As outlined in the literature review and methodology sections, the rationale for a four-hour earplug time frame came from evidence of homeostatic plasticity in that timeframe by Brotherton et al. (2015) (see Figure 4, p. 29). The results showed no noticeable neural gain change on EEG, which raises the question of whether four hours was in fact enough time to show such a change. There is an ongoing Masters level study by Jeche et al. (2023) at the University of Canterbury that appears to have shed light on this. In that study, the earplug paradigm in an A-B-A study design was used in conjunction with CAEPs. CAEPs provide information concerning the arrival of sound information to the auditory cortex (Durante et al., 2014). When Jeche et al. (2023) delivered stimuli by bone conduction to the plugged ear, a significant increase in amplitude of the P1-N1 wave was reported when measured following four hours of earplug use compared to the baseline result. In addition, the perception of tinnitus was also reported in six out of ten participants during the earplug condition. The amplitude reverted to baseline after removal of the earplug and in keeping with the current study, the perception of tinnitus also disappeared after removal of the earplug. This difference in amplitude lends support to the theory of a neural gain change registered at the level of the auditory cortex following short term auditory deprivation.

It therefore appears that unilateral auditory deprivation for four hours does have the potential to drive a neural gain change. These changes, however, are not apparent at a cortical level when measured by EEG as in the current study. It could be that EEG is simply not an effective method of capturing cortical activity associated with the neural gain changes of short-term auditory deprivation. However, the difference in cortical results between this study and that of the ongoing study by Jeche et al. (2023) could also be due to difference in measurement method. This study employed a resting state EEG method, while Jeche et al. (2023) measured cortical activity via evoked responses. While both EEG and CAEPs measure cortical activity, EEG in this study measured the brain's activity with the auditory system relatively inactive, whereas CAEPs measure electrical potentials following stimulation. Therefore, while they share some similarities, the method of cortical measurement is a key difference which could account for the divergent cortical findings between the two studies.

5.3 EEG – Consideration of Viability as a Tool in Tinnitus Research

5.3.1 Limitations of EEG

In Section 2.11, the potential capabilities of EEG were discussed in relation to tinnitus research. However, the limitations also need to be acknowledged. The main drawback of EEG is regarding the inverse problem; to recap, the inverse problem refers to the problem of estimating the sources of electromagnetic signals from the fields and potentials recorded outside of the head (Adjamian et al., 2014a). Reconstructing precise sources of the signals is not possible from the measured data alone because there are an infinite number of sources which can produce a signal, while there are a limited number of sampling points (Scherg et al., 1991). Furthermore, multiple dipole sources can exist less than .5cm from each other, whereas EEG electrodes on the scalp are approximately 1.5cm from the cortical surface, which can further make the resulting field indistinguishable from the field of a single dipole

(Balish & Muratore, 1990). While source reconstruction techniques have developed over the years to identify and localise the sources of oscillations, research evaluating the accuracy of this technology has shown that there is variability between source localisation algorithms (Bradley et al., 2016). The use of fMRI to supplement EEG findings could be a way to add more clarity to neuroimaging tinnitus research in the future, as fMRI provides an indirect measure of neuronal activity through measuring the effects of the changes in blood flow and blood volume which accompany neuronal activation (Mullinger & Bowtell, 2011). The poor spatial resolution but good temporal resolution of EEG versus the poor temporal resolution but good spatial resolution of fMRI, make the two techniques complementary in measuring brain function.

5.3.2 Limitations of EEG in This Study

This study did not use subject-specific head models built from magnetic resonance head images. Instead, a simple geometric model in Brainstorm was used. While such models allow computationally efficient analytic solutions, they lack precise representation of head shape and as such, may produce relatively poor results (Acar & Makeig, 2013). Head fiducial points were marked on the software, but as individual head shapes were not accounted for, this could have resulted in improper registration of electrode positions which can contribute to localisation errors. Another important consideration is the correct modelling of head tissue conductivities, especially the ratio of the skull relative to the brain and scalp (Acar & Makeig, 2013). Dannhauer et al. (2011) demonstrated that there can be differences in localisation results when they compared results for skulls modelled differently and global models, where the entire skull is assumed to be homogenous. The facilities to obtain individual head information was not available for this study, however, incorporation of this measure into future EEG and tinnitus research could help to remove at least one area of ambiguity in this field of research.

5.3.3 The Issues of Repeatability and Variability

Repeatability of an experiment is the only way to be sure of the reliability and objectivity of the experimental procedure and the results (Mussachia, 1995). Many studies have been conducted on the premise that tinnitus can be evaluated by measuring brain derived oscillations (Eggermont & Tass, 2015). However, there is a great deal of variability in the published results. Let us take just two studied frequency bands, alpha and gamma, as examples of this variability. Several studies have reported reduced alpha oscillations in tinnitus populations compared to controls (Adamchic et al., 2014; Schlee et al., 2014; Weisz et al., 2005), but numerous other studies have failed to replicate this finding (Adjamian et al., 2012; Ashton et al., 2007; Meyer et al., 2014; Vanneste et al., 2011a). Mixed findings have also been reported in relation to gamma band oscillations, will a null effect in this band reported by Weisz et al. (2005), while a tinnitus-related effect was reported by Weisz et al. (2007) and De Ridder et al. (2011). It should also be noted that there is a lack of standardisation regarding what constitutes as an EEG abnormality in these studies, with some authors reporting a decrease in spontaneous activity as indicative of tinnitus, while others report an increase in activity as indicative of that same phenomenon.

Nevertheless, one thing that this study and all of the studies mentioned above have in common is that participants have experienced some degree of tinnitus. If abnormal brain oscillations were a true biomarker of tinnitus, we could reasonably expect common findings across studies. Yet to date, there is no common finding. In fact, Pierzycki et al. (2016) correctly point out that there is a near equal amount of positive and negative findings with regard to each frequency band. On such grounds, there is no definitive EEG biomarker of tinnitus to date. However, there are steps that can be taken which could strengthen the knowledge base between tinnitus and EEG which will be discussed in section 5.4.

5.4 Future EEG Tinnitus Research

5.4.1 Standardisation

If we are to continue investigating the relationship between brain oscillations and the tinnitus percept, a first step in adding viability to the results would be a standardisation of methods across study centres. Remarkably, analysis of EEG literature showed that we do not even have consistency across the definitions of each frequency band. For example, Ashton et al. (2007) defines the gamma frequency band as spanning from 40 to 80Hz, Adjamian et al. (2012) defines it as 25 to 80Hz, while Zhang et al. (2021) defines the same band as 30.5 to 45Hz. Further investigation into these inconsistencies revealed that this variability in EEG band definition is evident in other fields too. Newson (2019) conducted a review of 135 resting-state EEG studies that looked at frequency bands in relation to mental health disorders. Her findings showed wide variability regarding where delta, theta, beta and alpha frequencies began and ended. Such findings underscore that we cannot always take for granted that reports for a particular band are the same from author to author. Standardisation of frequency band definitions would be a helpful addition to all future scientific EEG endeavours.

In addition to standardisation of frequency bands, standardisation of reporting should also be considered. As previously discussed in the literature review, Weisz et al. (2007b) are commonly referenced as evidence that individuals with tinnitus display increased gamma activity on EEG. But Weisz et al. (2077b) purposefully sought out marked enhancement of slow wave activity from five-minute recordings and examined gamma band activity during these periods as opposed to reporting the statistical significance of gamma for the entire recording. Without standardisation of how EEG data is analysed and reported, research in this field runs the risk of being subject to confirmation bias.

Confirmation bias is the tendency of observers to see what they expect to see while conducting scientific research (Marsh & Hanlon, 2007). When new evidence challenges an existing causal belief, that belief is more resistant to change than when a non-causal belief is challenged (Masnick & Zimmerman, 2009). Research from Ahn et al. (1995) and Koslowski (1996) also shows that people are particularly likely to disbelieve new evidence when a theoretical reason or plausible causal mechanism to maintain the current belief is present. Due to the near equal amount of positive and negative findings with regard to each frequency band reported in tinnitus EEG literature (Pierzycki et al., 2016), reporting standards and reporting of null findings are very important to avoid contributing in any way to confirmation bias, and thus type II error, in this field.

5.4.2 Systematic Review of Existing Data

While many attempts have been made to uncover the underlying pathophysiology of tinnitus though the use of EEG, our understanding remains incomplete. Not only that; the results point in many different directions. It would seem prudent at this point, to undertake a systematic review of research undertaken thus far which has incorporated EEG as an investigative means of tinnitus. In doing so, a clearer picture could emerge of what we know to date and could inform future research. Such a review could also be the basis of developing good scientific practice in the realm of EEG and tinnitus research, which will be discussed in section 5.4.3. The availability of a meta-analysis of EEG and tinnitus research could provide the basis for researchers to replicate findings, an important step towards good scientific practice.

5.4.3 EEG: Towards Good Scientific Practice

The generation of scientific knowledge depends upon researchers using appropriate tools, techniques, processes, methods, as well as appropriate ways of thinking and reasoning. Rules, guidelines and principles which define this work are referred to as good scientific

practice (GSP) (Niso et al., 2022). The possibility for cognitive biases and errors to influence research has been recognised and EEG research is not exempt from this, however there are now guidelines on how to mitigate these influences. Niso et al. (2022) recommends careful planning and reasoning by a research team prior to research being carried out, in order to highlight pitfalls and correct mistakes before they are made. Pre-registration, the practice of defining and publicly disclosing experimental plans before data are collected, is a good way to increase transparency and to ensure that valid conclusions can be drawn from the data. In order to address the issues of replication in EEG, the EEGManyLabs project was started and is a large-scale international effort (Pavlov et al., 2021). This project aims to repeat 20 of the most influential psychophysiological EEG findings in at least three laboratories with increased statistical power. The purpose of such open and collaborative research is to increase collective confidence in EEG findings, to inspire new standards for reporting EEG findings and to provide researchers with an open database of raw data and analysis pipelines (Niso et al., 2022). Collaborative working will be the most effective way to reach a coordinated standardisation of EEG.

5.5 General Study Limitations

There were limitations in this study which may have influenced the findings. These limitations are discussed in the proceeding section and should be kept in mind when interpreting the results of this study and when designing future studies.

5.5.1 Repeatability of Study

To draw definitive conclusions about the efficacy of the earplug and EEG paradigm, ideally the method would have been repeated to ascertain if the results remained the same. As there was only a short window in which to complete the testing, which in itself had to be scheduled around the other requirements of the Masters' programme as well as the participant's schedule, this was not possible. Repeating the study on the same group of

participants could provide insight as to if the earplug method repeatably yields the same result as obtained in this study (null) or if there are alternative results.

5.5.2 The Earplug: A Potential Confounding Variable

As detailed in the Chapter 4, the behavioural results in the B (earplug) condition were significantly elevated when compared to the A and A2 (non-earplug) conditions. While participants were asked to answer both the Likert and THI in relation to their tinnitus alone, it is possible that additional factors inflated those results. For example, when participant 4 returned to the lab after wearing the earplug for four hours, they commented that their earplug had felt quite uncomfortable and also reported that they found the attenuation associated with it disorientating. This participant scored 6.5 on the Likert and 54 on the THI following use of the earplug, results which were inflated compared to the other participants. Other participants did also comment that they found the earplug annoying and/or uncomfortable. Participants were asked to complete the Likert and THI in relation to tinnitus alone, however there is a possibility that participants completed these behavioural measures while considering factors such as earplug discomfort and attenuation rather than just the tinnitus sensation alone.

5.5.3 Lack of Previous Research Using Earplug and EEG Method

As previously discussed, subcortical effects of short-term unilateral deprivation through use of an earplug have been studied by analysing changes in ARTs before and after earplug use. Brotherton et al. (2019) suggested implementing a neuroimaging method to assess any evident cortical changes using the same earplug paradigm. When the current study was in its design stages at the end of 2021, a review of the literature did not reveal any published studies which had implemented the earplug as well as the EEG method in an attempt to understand the mechanisms underlying tinnitus. The closest study was by Maslin et al. (2013), who used fMRI rather than EEG. A more recent review since then found that there seems to have been one study carried out in the United States in which participants

wore an earplug for seven days and had an EEG carried out (Dougherty et al. 2021). Unfortunately, the only information available on that study was a meeting abstract. I contacted every author listed on the abstract page to obtain details on their methodology and findings but did not receive any response. Dougherty et al. (2021) stated in their abstract that changes in central gain do not in themselves account for the tinnitus perception however without access to the research, I cannot confidently support or critique that conclusion. Future studies using the earplug paradigm and imaging studies should endeavour to report their findings thoroughly so that researchers may be able to better determine if this method holds relevance in the study of tinnitus mechanisms.

5.5.4 Underpowered for Gamma Activity

When estimating the sample size for this study, there was no study details available that had employed the exact same methodology as I planned to do. As stated above, I have since found evidence that a similar study seems to have been carried out (Dougherty et al., 2021), but I am still not privy to the detail of that research. I referenced the seminal study by Weisz et al. (2005) and conducted statistical power analysis based on differences between tinnitus and non-tinnitus conditions in that study. However, the greatest effect in that study was a reduction in alpha band activity. While I did analyse alpha activity in this study, gamma activity was largely the focus as it was hypothesized that a change in gamma activity across conditions could indicate the presence of tinnitus. It is therefore possible that this study was underpowered to study the effect of the unilateral deprivation on gamma activity. Future research seeking to study the effects of gamma should base statistical power analysis on studies which report gamma effects across the entire EEG recording to determine an effective sample size.

Based on previous research which employed the earplug method, it was anticipated that more than 60% of participants would experience tinnitus. However perhaps owing to the

factors detailed in section 5.2.1, a larger sample size should have been obtained to account for the differing time scale used in this study with the earplug compared to previous research.

5.5.5 Lack of Blinding

This study was a single-blind study, whereby the participants were unaware (as far as was ethically suitable) of key information about what was being assessed but I as the researcher was aware of all aspects of the study method purposes. I was aware of the nature of subconscious bias that can occur when a researcher is not blinded to the research (Day & Altman, 2000). Bias in research, describes a systematic error which leads to the deviation of the measured effect away from the true effect of an intervention (Higgins, 2011). I made efforts to conduct the diagnostic elements of the research free from any language regarding expectations. Similarly, I conducted the behavioural assessments by using exact wording for each participant in order to avoid any leading questions. However, it is possible that subconsciously, some aspect of my behaviour influenced the way in which participants answered the Likert and THI. Ideally, the researcher would also be blinded to the expected outcomes of the research in order to avoid any such subconscious influences. However due to the logistics and timeframe in which the research had to be carried out, this was not possible. Even though the participants were blinded as to the research hypothesis, it is also possible that they had their own expectations as to the research which may have biased the behavioural aspects of the research.

5.6 Future Tinnitus Research in Aotearoa/New Zealand

In my opinion, the most important tinnitus work/research that needs to be conducted in Aotearoa/New Zealand in the immediate future is concerning the development of tinnitus BPGs. Currently, the most comprehensive discussion of tinnitus assessment and management by the NZAS spans less than one page in their document titled ‘Scope of Practice for Audiologists’. In this document it is stated that the scope of practice extends to the

"Measurement and interpretation of sensory and motor evoked potentials…Client groups include persons with…hyperacusis and tinnitus" (NZAS, 2019, p. 5). It is also stated that the scope of practice extends to the "Selection, fitting, evaluation of hearing devices and facilitation of adjustment to hearing devices, including all styles of hearing aids, tinnitus treatment instruments…" (NZAS, 2019, p. 5), as well as the provision of counselling and therapy for persons with tinnitus. Yet despite being in the scope of practice, there are no corresponding guidelines on how an audiologist should go about these duties.

Tinnitus education at the Master of Audiology level can vary across institutions. Tinnitus assessment and management is something that is not assessed in the objective structured clinical examination (OSCE) format used to obtain a clinical competence certificate in Aotearoa/New Zealand. It therefore seems prudent to provide an evidence-based pathway for clinicians to competently provide care to those with tinnitus. As discussed in the literature review section, BPGs for tinnitus assessment and management in adults have recently been published by the BSA (BSA, 2021). A multidisciplinary European guideline for tinnitus diagnostics, assessment and treatment has also been published (Cima et al., 2019). While these guidelines are available for any clinician to view, it is not necessarily straightforward or appropriate to apply guidelines from one country to another.

In an Aotearoa/New Zealand bi-cultural context, this is especially pertinent. Health inequity in Aotearoa/New Zealand between Māori and non-Māori populations is persistent (Hobbs et al., 2019) and this inequity has been found in hearing healthcare. The 2013 census revealed that despite Māori having higher rates of self-reported hearing loss than non-Māori, they had higher unmet needs for assistive equipment compared to non-Māori (Statistics New Zealand, 2015). In their 2021 scoping review, Manuel et al. identified the cost of services and poor patient-clinician relationships within the hearing healthcare space as barriers to effective service provision. It is therefore important to develop health practices which include

consideration of responsiveness to Māori. Responsiveness to Māori reflects the Government's view that health research conducted in Aotearoa/New Zealand should contribute to improving Māori health and eliminating health inequities (Reid et al., 2017). It is my belief that future tinnitus BPGs in this country should include Kaupapa Māori positioning which is interwoven with the existing evidence base on effective tinnitus treatment. In this way, we may hope to provide equitable tinnitus treatment to all members of our society who seek it.

5.7 Conclusion

Tinnitus is a complex and heterogeneous symptom. As audiologists, we will often be the first port of call for those individuals who seek guidance on how to manage the symptom effectively. At present there is no objective method of quantifying the presence and/or severity of tinnitus, nor is there an objective method of measuring how effective a treatment has been. EEG enables non-invasive measurement of oscillatory activity of the brain which has been linked to the tinnitus percept in previous research. Due to a high level of variability among studies to date, no definitive conclusions have been reached regarding if changes in brain oscillations are a biomarker for tinnitus or if EEG is a relevant objective assessment of tinnitus.

This study was not in agreement with previous research which has identified specific brain oscillation frequency bands as indicative of tinnitus. Further tinnitus research using EEG should employ rigorous standardisation of methods and reporting to enable definitive conclusions. It is recommended that in the absence of a tinnitus 'cure', evidence based BPGs should be created in the immediate future to enable a consistent and equitable level of tinnitus management across Aotearoa/New Zealand.

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Appendix A
Ethics Approval

HUMAN RESEARCH ETHICS COMMITTEE

Secretary, Rebecca Robinson
Telephone: +64 03 369 4588, Extn 94588
Email: human-ethics@canterbury.ac.nz

Ref: HREC 2022/10/LR

13 April 2022

Katie Comer
School of Psychology, Speech and Hearing
UNIVERSITY OF CANTERBURY

Dear Katie

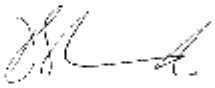
Thank you for submitting your low risk application to the Human Research Ethics Committee for the research proposal titled "Changes in the Brain Following Simulated Hearing Loss in One Ear: Towards an Improved Understanding of Tinnitus".

I am pleased to advise that this application has been reviewed and approved.

Please note that this approval is subject to the incorporation of the amendments you have provided in your email of 11th April 2022.

With best wishes for your project.

Yours sincerely



Dr Dean Sutherland
Chair, Human Research Ethics Committee

Appendix B
Information and Consent Form

School of Psychology, Speech and Hearing

Telephone: NZ +64 336 990 521

Email: kco98@uclive.an.nz

3 March 2022

HREC Ref: HREC 2022/10/LR

Changes in the brain following simulated hearing loss in one ear: towards an improved understanding of tinnitus.

Information Sheet for Participants

My name is Katie Comer and I am a 2nd year student in the Master of Audiology programme at the University of Canterbury. The focus of my research is to investigate what activity can be observed in the brain of adults experiencing experimentally induced hearing loss and tinnitus through use of an earplug. Tinnitus is the perception of sounds coming from the head or ears in the absence of an external sound source.

This research is being conducted for the thesis component of the programme and will be carried out under the supervision of Dr Michal Maslin and MinChul Park. Mike Maslin is a researcher and audiologist based in the University of Canterbury | Te Whare Wānanga o Waitaha (UC) in New Zealand. MinChul Park is an audiologist and PhD Audiology candidate.

What is the purpose of this research?

When an audiologist wants to classify a person's tinnitus, they do this primarily by asking questions. For example, they ask what the tinnitus sounds like, how bothersome it is and is it in one or both ears. These measures are subjective in nature and can be influenced by a person's mood and stress levels on the day of questioning. While we do have a way to measure the pitch and loudness of a person's tinnitus, this is also subjective and does not assist in telling us what the underlying mechanism of the tinnitus is.

To date, there is no definitive understanding of the underlying cause of tinnitus, no widely accepted objective measurement of tinnitus and no known cure for the symptom. This is a challenge because tinnitus can be troubling for many people, causing a range of negative consequences like increased arousal and anxiety or stress, sleep deprivation, impaired concentration. Previous research about tinnitus sufferers using measures of brain activity have sought to identify biological markers of tinnitus, with limited success. This research aims to provide further insight into the identification of a biological tinnitus marker through the use of objective measurement, electroencephalography (EEG).

Identification of a tinnitus biomarker using an objective measurement is important for the following reasons: it would enable us to objectively quantify someone's tinnitus in a clinical setting; it would enable us to objectively track if tinnitus is improving or getting worse and it may enable us to classify different tinnitus subtypes. In addition, identification of a tinnitus biomarker may enable future research to develop a causal intervention for tinnitus.

Why are you a suitable participant?
You have stated that you are 18 years of age or over, have no neurological conditions, no tinnitus and that to the best of your knowledge, your hearing is normal. Previous participants in tinnitus-related research have had widely varying causes of tinnitus and have only been seen by an audiologist, doctor or researcher after their tinnitus has begun. This makes it difficult to know the underlying mechanism of their tinnitus and research has had to be conducted using control participants without tinnitus (ie researching a brain of someone with tinnitus compared to the brain of someone without tinnitus).
By studying brain activity in an adult with experimentally induced hearing loss and tinnitus, we can study the same brain with and without hearing loss and tinnitus in a controlled way. This eliminates a large source of variability that has hampered previous research in this area.

What is involved in participating?
Participation is voluntary. Participation will involve attending room 151a in the Psychology, Speech and Hearing building. On the initial visit, you will have your ears examined (otoscopy), complete a short tinnitus rating, have a hearing test and have a short test done to determine the health of your ear drum. You will then have an electrode cap placed on your head and a measurement taking five minutes will be recorded. You can take a break and then an ear plug will be placed in one ear. Your hearing will then be remeasured to determine how much having the ear plug in your ear has impacted your hearing levels. This initial session will take approximately 1 hour and 15 minutes. You then go about your day and return to the lab four hours later. On return, you will be asked to rate any tinnitus you may be experiencing and then a further measurement of brain activity will be recorded. This session will take approximately 30 minutes. At least 24 hours (but no more than seven days) later you will need to return to the lab to complete another short tinnitus assessment and measurement of brain activity, totalling 30 minutes.

Are there any potential benefits from taking part in this research?
This study will not directly help you, however it may help in the development of a reliable

objective measurement of a tinnitus biomarker thus contribute towards a causal intervention for tinnitus. Therefore, this research has the potential to help many people who suffer from bothersome tinnitus. At the conclusion of the study, we will provide you with a summary of the findings if you wish.

Are there any potential risks involved in this research?
There is a risk of stress for any potential participant for whom a hearing loss is identified in the initial stages of testing. The researcher is a qualified Audiometrist with a certificate of clinical competence from the New Zealand Audiological Society (NZAS). As such, the researcher is qualified to conduct hearing screening and report on the findings of hearing screening under the scope of practice for audiometrists as outlined by the NZAS (2019). If a complex hearing loss or hearing loss requiring medical referral is identified, consultation with an onsite audiologist on level 3 of the Psychology, Speech and Hearing building who is a member of the NZAS can be carried out.

The temporary hearing loss induced by the ear plug and any resulting tinnitus goes away when the earplug is removed from the ear (this has been demonstrated in other previous studies). The brain activity that will be measured is naturally occurring and is measured via an electrode cap routinely in clinical and research settings. As some electrodes (those measuring eye movements) need to be placed very securely on the skin, it is necessary to clean the skin upon which the electrodes will be placed thoroughly using alcohol wipes. Therefore, there is a small risk that the skin will be left a little red following electrode placement.

If you do participate in the study, we will offer you some guidance about what to expect during the time that you would wear an ear plug in one ear. For example, we would expect that wearing the ear plug will mean that the drop in hearing will make it seem more challenging than usual to follow conversations in busy environments such as in a café. However, it should be possible to overcome any such difficulty by sitting or standing with your unplugged ear towards the sound you want to hear. It is also likely that you would find it more difficult than normal to know which direction sounds are coming from. Therefore, we advise extra care when crossing roads and similar activities during the short period that you are wearing a plug. Finally, you may experience some tinnitus after a few hours of wearing an earplug in one ear. It is often a ringing or a whistling sound and if you hear such a sound then it is normal. However, any tinnitus sounds, and any difficulty hearing conversations in busy environments and/or telling the direction of sounds will disappear when the plug is removed. Previous studies that have involved wearing ear plugs continuously and over longer periods such as a week have not reported any negative effects. If you wish to proceed, you will be provided with a detailed information sheet containing further advice about the effects of ear plug use.

What if you change your mind during or after the study?
Participation is voluntary and you have the right to withdraw at any stage without penalty. For the study to work as intended, we ask that you wear the earplug uninterrupted for around 4 hours. However, if you do wish to remove the earplug at any time then this is ok. If you choose to withdraw then you may ask for your data to be destroyed at any point during the data collection session. All data will be anonymous. After the study has finished collecting data from the participants, the anonymised data will no longer be attributable to

any individual, therefore it will become impossible to identify your data among the results at that stage.

What will happen to the information you provide?
We will store all study data in password-protected files on the University of Canterbury computer network. All data will be destroyed five years after completion of the study/publication of study findings.

Will the results of the study be published?
The results of this research may be published in peer-reviewed, academic journals. Results will also be presented during conferences or seminars to wider professional and academic communities. You will not be identifiable in any publication. A summary of results will be sent to all participants who request a copy of these.

Who can you contact if you have any questions or concerns?

Dr Mike Maslin

Lecturer in Audiology

University of Canterbury

Tel: +64 3 369 90521

Email: mike.maslin@canterbury.ac.nz

Katie Comer

Postgraduate research student

University of Canterbury

Tel: +64 3 369 90521

Email: kco98@uclive.ac.nz

This study has been reviewed and approved by the University of Canterbury Human Research Ethics Committee (HREC). If you have concerns or complaints about this research, please contact the Chair of the HREC at human-ethics@canterbury.ac.nz).

What happens next?
Please review the consent form. Ask any questions you wish. If you are happy for your child to participate, please sign and the form will then be collected during the audiology appointment.

Appendix C
Invitation to Apply

HEALTHY EARS NEEDED!

The aim of this research is to further our understanding of tinnitus - that ringing or buzzing sound you've probably heard after being in a loud bar for a while. By studying healthy ears that have a short term simulated hearing loss by means of an ear plug and naturally occurring brain activity, we may further comprehend the neurophysiological mechanisms behind tinnitus. Tinnitus can be severely debilitating for some people and currently, there is no cure. This research aims to contribute to the development of a causal intervention, and you can help!

WHO IS ELIGIBLE?

Adults 18 years or over with:
Normal hearing in both ears
Good neurological health
No tinnitus

DESCRIPTION OF STUDY

Participation will involve:
A basic hearing test
An electroencephalogram (EEG) to measure natural brain activity
Wearing an earplug in one ear to simulate a mild hearing loss for a few hours
Repeat EEG 4 hours after the plug was inserted
Repeat EEG 1-7 days after ear plug removal

INTERESTED?

Please contact Katie Comer at kco98@uclive.ac.nz or Dr Michael Maslin at mike.maslin@canterbury.ac.nz

UC UNIVERSITY OF CANTERBURY
Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

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Appendix D
Participant Earplug Information

Use and Maintenance of Your Earplug

Instructions for Earplug Use

1. We would like you to use your earplug continuously for four hours. This includes wearing it throughout the day and in bed if you are sleeping during this time.

2. We will give you two plugs, one in ear and one spare. This is so you can put a clean earplug in during the four-hour period if you wish. For example, if your earplug should become inadvertently wet through sweating or wearing it in the shower. However, we anticipate that one earplug will probably be sufficient for most people.

3. If you do replace the earplug with a clean one, please ensure that you are in a quiet environment, and wash your hands before replacement.

4. Otherwise, please try not to fiddle with the earplug.

5. If you join the study and then decide not to wear the earplug continuously during the four-hour period, then please feel free to contact me as it may still be possible to complete the intended measurements.

Effects of Wearing an Earplug in One Ear

1. You may find it difficult to tell where sounds are coming from.
    - **Please take extra care when crossing roads** as the traffic may not be coming from where it sounds like it is.

2. You will not be able to hear very well on your plugged side.
    - It might help to make sure that the person you are speaking to is on your 'good' side (the side without an earplug).

3. You may find it more difficult to understand people when there is a lot of other noise.
    - This is what individuals with hearing loss experience every day.
    - Try to make sure the noise is behind you or to the side of your plugged ear.
    - Tell people you are wearing an earplug so they may need to speak more clearly and/or look at you when they are speaking.

Problems?

If you experience any itchiness or hotness in your ear whilst wearing the earplug, or if you experience any other problems, please contact me immediately. My details are given below, and on the main Participant Information Sheet

Contact Details

Email: kco98@uclive.ac.nz
Phone: 02108006820

Appendix E
Likert Scale

Under normal circumstances...

1. How **STRONG** or **LOUD** is your tinnitus?

No tinnitus or

Not at all strong or loud ▶ 0 1 2 3 4 5 6 7 8 9 10 ◀ *Extremely strong or loud*

Appendix F
Tinnitus Handicap Inventory

TINNITUS HANDICAP INVENTORY

Patient Name: _____ Date: _____

INSTRUCTIONS: The purpose of this questionnaire is to identify difficulties that you may be experiencing because of your tinnitus. Please answer every question. Please do not skip any questions.

1. Because of your tinnitus, is it difficult for you to concentrate?	Yes	Sometimes	No
2. Does the loudness of your tinnitus make it difficult for you to hear people?	Yes	Sometimes	No
3. Does your tinnitus make you angry?	Yes	Sometimes	No
4. Does your tinnitus make you feel confused?	Yes	Sometimes	No
5. Because of your tinnitus, do you feel desperate?	Yes	Sometimes	No
6. Do you complain a great deal about your tinnitus?	Yes	Sometimes	No
7. Because of your tinnitus, do you have trouble falling to sleep at night?	Yes	Sometimes	No
8. Do you feel as though you cannot escape your tinnitus?	Yes	Sometimes	No
9. Does your tinnitus interfere with your ability to enjoy your social activities (such as going out to dinner, to the movies)?	Yes	Sometimes	No
10. Because of your tinnitus, do you feel frustrated?	Yes	Sometimes	No
11. Because of your tinnitus, do you feel that you have a terrible disease?	Yes	Sometimes	No
12. Does your tinnitus make it difficult for you to enjoy life?	Yes	Sometimes	No
13. Does your tinnitus interfere with your job or household responsibilities?	Yes	Sometimes	No
14. Because of your tinnitus, do you find that you are often irritable?	Yes	Sometimes	No
15. Because of your tinnitus, is it difficult for you to read?	Yes	Sometimes	No
16. Does your tinnitus make you upset?	Yes	Sometimes	No
17. Do you feel that your tinnitus problem has placed stress on your relationships with members of your family and friends?	Yes	Sometimes	No
18. Do you find it difficult to focus your attention away from your tinnitus and on other things?	Yes	Sometimes	No
19. Do you feel that you have no control over your tinnitus?	Yes	Sometimes	No
20. Because of your tinnitus, do you often feel tired?	Yes	Sometimes	No
21. Because of your tinnitus, do you feel depressed?	Yes	Sometimes	No
22. Does your tinnitus make you feel anxious?	Yes	Sometimes	No
23. Do you feel that you can no longer cope with your tinnitus?	Yes	Sometimes	No
24. Does your tinnitus get worse when you are under stress?	Yes	Sometimes	No
25. Does your tinnitus make you feel insecure?	Yes	Sometimes	No

FOR CLINICIAN USE ONLY

Total Per Column								
	x4		x2		x0			
Total Score		+		+		=		

Newman, C.W., Jacobson, G.P., Spitzer, J.B. (1996). Development of the Tinnitus Handicap Inventory. Arch Otolaryngol Head Neck Surg, 122, 143-8.

To interpret the score please refer to the Tinnitus Handicap Severity Scale shown on the reverse side.