Human Brain Mapping of Tinnitus

Ankit Mathur

Audiology Section, Department of Linguistics

Faculty of Human Sciences

Macquarie University

Sydney, Australia

This thesis is submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD)

June 2018

Contents

Summary

Tinnitus is a phantom auditory perception that occurs in the absence of any external stimulus. Despite a long history of its known existence, few objective methods exist to confirm its presence and better understand the cortical disruptions that are assumed to underpin its perception. However, recent research has demonstrated the existence of an objective measure of tinnitus perception using resting and sound-evoked brain activity measured with magnetoencephalography (MEG). Significant differences have been found in individuals with tinnitus compared to those without. We aim to use similar methods of tinnitus measurement before, during, and after two tinnitus remediation programs to: (i) verify the results of previous studies; and (ii) evaluate whether subjective changes in tinnitus perception during tinnitus remediation correlate with objective measurements. In the first study (Chapter 2) we have discussed the behavioural tests of tinnitus, participant selection criteria, and changes in behavioural reports of tinnitus during remediation. In the second study (Chapter 3) we have compared the spontaneous cortical activity of tinnitus subjects and non-tinnitus controls. The third study (Chapter 4) aimed to evaluate tinnitus treatment-related changes in spontaneous cortical activity and their correlations with changes in objective reports of tinnitus. The fourth study (Chapter 5) looked at the relationship between evoked and spontaneous cortical activity in tinnitus participants and evaluated the effect of treatment on both. There was a significant difference in the spontaneous cortical activity of tinnitus participants and controls, these changes did not completely return to normalcy during the treatment phase. Some indications of treatment-related changes, however, were observed in the evoked responses. From the present experiment, we hypothesise that while spontaneous cortical activity can be used to identify the presence of tinnitus, evoked results could provide a more accurate representation of the benefits of a treatment program.

Declaration

I certify that the work in this thesis entitled "**Human Brain Mapping of Tinnitus**" has not been previously submitted for a degree nor it has been submitted as a part of requirements for a degree to any other university or institution other than Macquarie University.

I also certify that this thesis is an original piece of research and it has been written by me. Any help and assistance that I have received in my research work and the preparation of the thesis itself have been appropriately acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis. The research presented in the thesis was approved by Macquarie University Ethics Review Committee, reference number: HE27FEB2009-R06343.

Signed:

Ankit Mathur (Student Number: 42371694)

15th June 2018

Acknowledgment

Behind every successful project there stand a myriad of people whose help and contribution make it a success. I would like to thank everyone who directly or indirectly helped me in the last few years and encouraged me in their own ways to undertake and complete this thesis.

I would like to express my special appreciation and thanks to my supervisor, Associate Professor Catherine McMahon for her unending patience, untiring support and guidance. I would like to thank you for encouraging my research and for allowing me to grow as a research scientist.

I would also like to thank my co-supervisors, Associate Professor Blake Johnson and Dr. Ronny Ibrahim for their timely help and support.

Special thanks to the staff at MEG lab and Christopher Sewell for helping me with data collection at odd hours and on weekends. I would also like to acknowledge the administrative staff and staff at Macquarie university speech and hearing clinic, especially Lynne Blackford, for their help during data collection.

A special thanks to my family. Words cannot express how grateful I am to my parents, siblings and in-laws for all of the sacrifices that you've made on my behalf. Your prayer for me was what sustained me thus far. I would also like to thank, my uncle, Dr Ashoo Mathur, and aunt, Dr Shilpi Mathur for their guidance, and all of my friends (Chandrakant, Manuj, Amit sir-Minakshi, Yatin-Aakriti and baby Ridit, Sumesh-Anusha and Vijay-Anagha and baby Anvi) who supported and motivated me to strive towards my goal.

I would like to express my appreciation to my beloved wife Aditi who is and will always be my constant source of strength.

Last, but not the least, I would like to acknowledge the participants who volunteered for this study. This research would not have been possible without your selfless support.

List of Abbreviations

ANOVA	Analysis of Variance
ANS	Autonomic Nervous System
AWT	Absence from Work
BBN	Broadband noise
BDI	Beck Depression Inventory
BDI	Beck Depression inventory
BESA	Brain Electrical Source Analysis
BMHS	Blue Mountain Hearing Study
BMI	Body Mass Index
CBT	Cognitive Behaviour Therapy
CL	Central left
CM	Central medial
CNS	Central Nervous System
CO	Control Octave
CR	Central right
dB	deciBel
dBHL	deciBel Hearing Level
DBS	Deep Brain Stimulation
dBSL	deciBel Sensation Level
DPOAE	Distortion-Product Otoacoustic Emissions
DVD	Digital Versatile Disc
EEG	Electroencephalography
FDA	Food and Drug Administration
FL	Frontal left

FM	Fronto-medial
fMRI	Functional Magnetic Resonance Imaging
FpM	Fronto-parietal medial
FR	Frontal right
GABA	Gamma-Aminobutyric Acid
GBA	Gamma Band Activity
H	Help-seeking
ITI	Inter-Stimulus Interval
KIT	Kanazawa Institute of Technology
LC	Locus area of Caudate nucleus
LDL	Loudness Discomfort Level
LE	Lesion Edge
MANOVA	Multivariate Analysis of Variance
MEG	Magnetoencephalography
MML	Minimum Masking Level
MMPI	Minnesota Multiphasic Personality Inventory
MMS	Modified Mini Screen
MOS	Medical Outcome Study
MSR	Magnetically Shielded Room
NBN	Narrow Band Noise
NH	Non Help-seeking
NHP	Nottingham Health Profile
NLME	Non-Linear Mixed Effects
NTT	Neuromonics Tinnitus Treatment
OpM	Occipito-parietal medial

PCA	Principal Component Analysis
PET	Positron Emission Tomography
PL	Parietal left
PM	Parieto-medial
PR	Parietal right
PTA	Pure Tone Average
SF	Short Form
SL	Sensation Level
SPECT	Single-photon emission computerized tomography
SRSL	Symptom Rating Scale List
STAI	State-Trait and Anxiety Inventory
STSS	Subjective Tinnitus Severity Scale
TAL	Temporo-anterior left
TAR	Temporo-anterior right
TCD	Thalamo-cortical Dysrhythmia
TFI	Tinnitus Functional Index
THI	Tinnitus Handicap Inventory
THQ	Tinnitus Handicap Questionnaire
TL	Tinnitus Loudness
TMS	Transcranial Motor Stimulation
TPL	Temporo-parietal left
TPR	Temporo- posterior right.
TQ	Tinnitus Questionnaire
TRQ	Tinnitus Reaction Questionnaire
TRT	Tinnitus Retraining Therapy

TSQ	Tinnitus Severity Questionnaire
VAS	Visual Analog Scale
WHO-ASSIST	World Health Organization-Alcohol, Smoking and Substance Involvement Screening Test

Preamble

Tinnitus is a symptom which has been traditionally defined as any sound generated within the head, regardless of its underlying mechanism(s) or origin. Historically, Joan of Arc, Ludwig Van Beethoven and Michelangelo suffered from tinnitus, while Charles Darwin not only suffered from this but kept daily records of its amplitude and frequency. While historical descriptions of tinnitus have depended highly on cultural factors ("sensitivity to the divine", "bewitched ear") (Stephens, 1984), the most complete and acceptable definition of tinnitus was proposed by Jastreboff (1995). He defined tinnitus as "the perception of sound that results exclusively from activity within the nervous system without any corresponding mechanical, vibratory activity within the cochlea, and non-related to external stimulation of any kind." On the other hand, sounds that are audible to the examiner are termed "somatosounds" (Jastreboff and Hazell, 2004). Somatosounds originate from bodily activities, such as blood flow or the sound of muscular contractions, and are less prevalent than tinnitus (Henry, Dennis, & Schechter, 2005; Jastreboff & Hazell, 2004).

Tinnitus is relatively common in adults; with a reported prevalence of between 10-15% of the general population (Axelsson and Ringdahl, 1989; Davis, 1989; Davis and Raffie, 2000; Fujii et al., 2011; Kvestad et al, 2010). A large part of the variability across studies is assumed to be arising from differences in the wording of the questions used to identify the presence of tinnitus. For example, in the 1999-2004 US National Health and Nutrition Examination Surveys (NHANES), where 14,178 adults aged 20 years and above were assessed using standardised questionnaires, approximately 25.3% reported having *any* tinnitus, whereas 7.9% reported having *frequent* tinnitus (Shargorodsky et al., 2010). In any case, it has a

significantly higher prevalence in clinical populations with hearing loss (85%; Fowler, 1944) and associated disorders, such as otosclerosis (75%; Glasgold & Altmann, 1966) and acoustic neuromas (83%; House & Brackman, 1981). A population-based study of older adults (>55 years) in Australia, the Blue Mountains Hearing Study (BMHS), demonstrated that an 11% increased likelihood of reporting tinnitus existed for each 10 dB increase in four-frequency (500 Hz-4 kHz) pure tone average (Sindhusake et al., 2003b).

Frequent tinnitus is associated with age. Hoffman and Reed (2004) compared six studies that obtained age-specific tinnitus prevalence data in adults; each showed a trend of increasingly greater prevalence at higher age decades, with a plateau in either the 60–69 or 70–79 year decades, and a subsequent decline in older age groups. For example, the 1999-2004 National Health and Nutrition Examination Surveys showed an increase in tinnitus prevalence with age, peaking at 14.3% between 60 and 69 years of age after which it decreased (Shargorodsky et al., 2010). Such changes in prevalence could result from: 1) late symptomatic improvement as a part of the natural history of tinnitus, 2) co-morbidity of tinnitus with other health conditions that reduce the life expectancy of tinnitus sufferers, or 3) a relative reduction in the perception of tinnitus compared with other emerging health conditions (Shargorodsky et al., 2010).

Importantly, however, only approximately 1-2% of the population are severely annoyed by their tinnitus and about 0.5% are prevented from living a normal life (Coles, 1984, 1987). Multiple attempts to determine the severity and / or handicap of tinnitus using the psychoacoustic characteristics of the tinnitus sound itself (e.g., loudness, pitch) have been

undertaken; however, systematic relationships between these do not appear to exist, making it difficult to measure tinnitus other than by self-reporting (Tyler, 2000). For example, contralateral matching of the loudness of an external sound to the tinnitus percept suggests that the sensation level of the tinnitus is usually only within 6-10 decibels of the hearing threshold (Baskill & Coles, 1999) and bears little relation to the degree of subjective complaint, such as severity, loudness and ability to be effectively masked (Baskill & Coles, 1999; Meikle & Taylor-Walsh, 1984; Kuk et al., 1990). However, tinnitus can cause psychological distress in excess of its relatively small sensation level, in some cases, leading to suicidal tendencies (Lewis et al., 1994).

On the other hand, psychological complaints, such as insomnia, anxiety, depression and increased irritability, have been associated with severe tinnitus (Fowler, 1948). Insomnia appears to be a significant problem for between 25-50% of tinnitus patients (Sanchez & Stephens, 1997; Tyler & Baker, 1983) and the level of sleep disturbance appears to be related to tinnitus severity (Folmer & Griest, 2000). Tinnitus patients also often report difficulties with concentration (Hallberg & Erlandsson, 1993), demonstrated by declines in reading performance (Sanchez & Stephens, 1997; Tyler & Baker, 1983). Moreover, tinnitus severity is significantly correlated with anxiety and depression (Halford & Anderson, 1991; Budd & Pugh, 1995).

Despite scientific advances in the field in recent years, tinnitus remains a chronic condition in the majority of cases, as no underlying treatable ear disorder can be identified (Andersson et al., 2005). Given this, various forms of treatments have been developed with the purpose of

providing relief for those with tinnitus by targeting the processes that are suggested to maintain or contribute to tinnitus distress (Andersson, 2002). The purpose of the current thesis is to identify the cortical activity associated with tinnitus using magnetoencephalography (MEG), by studying the changes in cortical activity during a tinnitus remediation program. The current longitudinal study provides a comprehensive pilot study, which now enables a more accurate power calculation to be made for future studies

Thesis Overview:

Chapter 1 provides an introduction to the history of tinnitus, its pathophysiology and models of tinnitus. It also discusses the emergence of measures to objectively record tinnitus-related cortical activity and presents the hypotheses of this thesis' experiments.

Chapter 2 describes the results of the behavioural assessments during the tinnitus treatment program using psychoacoustic tests and questionnaires. It also discusses participant selection criteria and provides an overview of the 30 week Neuromonics Tinnitus Treatment (NTT) program.

Chapter 3 explores the role of spontaneous alpha power in a group of tinnitus participants and changes in alpha power during a 30 week NTT program. This chapter also investigates the eight sub-scales of the tinnitus functional index (TFI) and their relationship with alpha power.

Chapter 4 evaluates the validity of thalamocortical dysrhythmia model of tinnitus by studying alpha (8-13Hz) and gamma (30-100 Hz) spontaneous activity in tinnitus participants in comparison with a young control group, and during remediation program.

Chapter 5 describes the disruption in the tonotopic map in tinnitus patients and explores the plausible reversal in tonotopicity with reduced tinnitus distress during the 30 weeks of tinnitus remediation.

Chapter 6 summarizes the results of the thesis, and discusses future directions in the field of objective measures of tinnitus.

Chapter 1: Introduction

Several general hypotheses describing the origin of tinnitus have been proposed; however, none have yet been proven. It is commonly believed that a tinnitus percept is a result of abnormal neural activity within the higher auditory pathways (Roberts et al., 2010; Mühlnickel et al., 1998; Weisz et al., 2005b), enhanced by abnormal central gain (Norena, 2011; Schaette & McAlpine, 2011), and perceived as an external sound by auditory cortical centres. However, imaging studies support the hypothesis that *chronic* tinnitus occurs when there is involvement of the limbic system (Lockwood et al., 1998; Rauschecker et al., 2010), accompanied by structural changes at the thalamic level (Mühlau et al., 2006).

While multiple models of tinnitus exist, Rauschecker and colleagues (2010) have recently proposed a model whereby they assert that limbic system involvement is a key part of the development of chronic tinnitus, rather than simply a by-product of the emotional distress caused by the tinnitus percept (Jastreboff & Jastreboff, 2000). Specifically, they proposed that chronic tinnitus results when the fronto-striato-thalamic circuits of the brain (involved in signal appraisal and sensory gating) are also disordered (see Leaver et al., 2011), reducing the capacity of these centres to compensate and suppress the enhanced neural activity at the level of the thalamus, prior to tinnitus being perceived. The present study will focus on Rauschecker's model as the basis to understand the tinnitus pathophysiology for the following reasons:

a) This model extends the neurophysiological model of tinnitus (Jastreboff and Jastreboff, 2000); whereby both models illustrate the involvement of auditory and non-auditory brain centres, although the role of non-auditory brain centres is causal in Rauschecker's model. More recently, Leaver et al. (2016) reported that tinnitus pathophysiology involves crosstalk, and perhaps dysregulation, between fronto-striatal and auditory–sensory regions using independent component analysis of fMRI, thereby extending support to the model.

b) This model is the first to explain the involvement of and neuromodulation by multiple brain areas including the cortex, thalamus, and ventral striatum in tinnitus. The involvement of non-auditory central structures in tinnitus has gathered support in the last decade, and is discussed in more details later.

c) It also explains the absence of tinnitus in individuals with hearing loss which was lacking from other models. The model postulates that under normal circumstances, a tinnitus signal is cancelled out, and only becomes chronic if the inhibitory feedback loop fails due to a compromised paralimbic region.

The following section will explain this model of chronic tinnitus development, from disruptions in the cochlea to perception in the cortex, in more detail.

The main role of the cochlea is to transduce sound information into an electrical signal, i.e. to transform mechanical vibrations of the basilar membrane into electrical impulses that are transmitted from the cochlea to the brain via the cochlear nerve and central auditory pathways. Specifically, sound entering the ear canal vibrates the tympanic membrane, and this vibration is transmitted along the ossicular chain to the stapes footplate. This creates a travelling wave, to be generated and propagated along the basilar membrane and ultimately eliciting shearing of the stereocilia on the top of the outer hair cells (OHCs) and inner hair cells (IHCs; sensory cells, responsible for transduction of mechanical to neural stimuli). These receptor cells are located within the organ of Corti, which is situated on the basilar membrane (Figure 1). Deflection of the stereocilia of the hair cells opens gated ion channels, which results in intracellular voltage changes. In response to this change, the lengths of the OHCs are modulated. This change of length causes the tectorial (extracellular connective tissue that covers the stereocilia of the inner and outer hair cells) and the basilar membrane (separating scala media from scala tympani) to move relative to each other. These movements enhance

the response of the IHCs, resulting in better hearing sensitivity and better frequency selectivity (Dallas, 1992).

The perception of tinnitus has been attributed to abnormal neural activity at the cortical level in human and animal studies (Noreña & Eggermont, 2003; Muhlnickel et al., 1998). Acute or immediate increases in spontaneous activity have been observed in the auditory nerve (Evans, Wilson & Borerwe, 1981), the inferior colliculus (Chen & Jastreboff, 1995) and the secondary auditory cortex following salicylate treatment (Eggermont & Kenmochi, 1998) and in the primary auditory cortex following moderate sound exposure (Kimura & Eggermont, 1999). Acute increases in spontaneous activity are also observed in the secondary auditory cortex after quinine treatment, which reduces the spontaneous cochlear activity (Eggermont & Kenmochi, 1998). Chronic increases in spontaneous activity occur in the dorsal cochlear nucleus (Kaltenbach & Afman, 2000), the inferior colliculus (Eggermont & Kenmochi, 1998) and primary auditory cortex following intense noise exposure (Noreña & Eggermont, 2003) and in the dorsal cochlear nucleus and inferior colliculus after cisplatin treatment (Kaltenbach et al., 2002). Hyperpolarisation in thalamic nuclei, when hyperpolarised during deafferentation or overinhibition, have also been reported to cause the enhancement of slow waves of ~4Hz (Jeanmonod et al., 1996) while a possible reduction in the spontaneous firing rate at subcortical levels, namely in the ventral cochlear nucleus (Vogler, Robertson & Mulders, 2011) and inferior colliculus due to acoustic trauma have also been reported (Salvi et al., 1978). Moreover, it is hypothesised that signal recognition and classification circuits, working on neuronal network-like representation, are involved in the perception of tinnitus and are subject to plastic modification (Jastreboff, 1990). A better understanding of the

mechanism of tinnitus generation and neuronal activity related to tinnitus attenuation is required to provide mechanism-specific tinnitus treatment to patients.

Among the earliest and most significant of contributions from psychology researchers to the understanding of tinnitus was Hallam, Rachman, and Hinchcliffe's (1984, cited in McKenna, 2004) psychological model. The authors suggested that a process of habituation (decreased response to a stimulus following repeated presentations) characterises reductions in tinnitus, and that patients' complaints of tinnitus-related distress were due to failure to habituate. The model further proposed that both central nervous system (CNS) and autonomic nervous system (ANS) activity is involved in the manifestation of tinnitus, and that it is necessary to consider attention filters (i.e. the ability to process information from one part of the environment while excluding other parts) in the perception of tinnitus (McKenna, 2004). They pointed out that delayed or failed habituation may arise when there is high level of ANS arousal, sudden or erratic tinnitus, impaired neural pathways or where tinnitus acquires emotional significance through a learning process (Andersson et al., 2005). However, their model does not provide an explicit description of the cognitive behavioural processes which are associated with the detection of tinnitus and the resultant distress.

Simultaneous measurement of electroencephalography (EEG) and electrocardiogram (ECG) in 21 tinnitus participants suggests that tinnitus related distress is associated with high levels of activation of the sympathetic part of the autonomic nervous system and the limbic system (Vanneste & De Ridder, 2013). Under normal physiological conditions, the sympathetic nervous system and limbic system together are responsible for the emotional response of an

individual, and their activation is supported by the fact that people with high levels of tinnitus distress show a strong emotional response to tinnitus, with 60% of the test population (112 adult members of British Tinnitus Association, with long term tinnitus) having elevated anxiety scores, and 23% of sample having seen a psychiatrist with a depressive illness (Halford & Anderson, 1991). The tinnitus signal becomes highly significant, as indicated by difficulty (or even inability) to shift attention away from it, which is hypothesized to be an outcome of the distraction caused by tinnitus (Andersson et al., 2000; Trevis, McLachlan & Wilson, 2016)), causing a specific deficit for the attentional network related to the top-down executive control of attention (Heeren et al., 2014) and also an impairment of cognitive control mechanisms that are involved both in vision and audition (Araneda et al., 2016). This infers the involvement of brain centres involved in attention, and is explained by the neurophysiological model of tinnitus (figure 2, Jastreboff, 1990). This model has been substantiated in light of various observations; such as-modulations in tinnitus percept occur with increases in stress or sleep deprivation (Folmer & Griest, 2000; Hallam, 1996, Jakes et al., 1986), which cannot be explained solely based on constant factors like degrees or configurations of hearing loss. Chen et al. (2015), using animal model, have also supported the involvement of non-auditory centres in tinnitus. They used sodium salycilate to induce tinnitus and hyepracusis, and reported enhanced coupling within the auditory network and segments of the auditory network and cerebellum, reticular formation, amygdala, and hippocampus presumably contributing to the emotional significance, arousal, motor response, gating, and memories associated with tinnitus and hyperacusis. Trevis et al. (2017), conducted cognitively demanding task known to activate the cognitive control network in their functional magnetic resonance imaging study in 15 tinnitus patients and 15 normal controls, and reported altered interactions between non-auditory neurocognitive networks maintaining chronic tinnitus awareness in addition to auditory dysfunction. While Chen et al. (2015)

reported on chemically induced tinnitus in rats, the tinnitus participants in Trevis et al.'s (2017) study had less severe tinnitus than is generally seen in clinical population. But the two studies do provide evidence regarding the involvement of non-auditory centres in the brain in tinnitus. They, however, did not offer an explanation on how neurocognitive network dysfunction develops which could provide an insight into the causes of reduced network integrity and, in turn, causes of chronic tinnitus.

The neurophysiological model suggests that inappropriate activation of the limbic system and the sympathetic part of the autonomic nervous systems by the tinnitus signal is responsible for behavioural reactions such as anxiety, poor concentration, panic attacks and the inability to enjoy activities in life (Jastreboff, 1990). The same types of reactions are observed after overstimulation of the limbic and autonomic nervous systems by many other causes, such as sleep deprivation (Wu et al., 1992), chronic pain (Jänig, 1995), or sensory stimulation over which we do not have control (Jastreboff & Jastreboff, 2006).

Neural network models of tinnitus have gained considerable attention in recent years, although it is not yet known to what extent the auditory and non-auditory cortical systems interact or influence each other, leading to the tinnitus perception and/or tinnitus-related distress (De Ridder et al., 2011, Jastreboff, 1990, Kraus and Canlon, 2012, Rauschecker et al., 2010, Schlee et al., 2012, Vanneste and De Rider, 2012). For example, Møller, Møller and Yokota (1992) report that the perception of loudness of certain forms of tinnitus involves both the classical (lemniscal) auditory pathways and, the extralemniscal auditory system. Further, Lockwood et al. (1998) in a positron emission tomography (PET) study, reported evidence of

development of new neural links between auditory centres and other sensory-motor areas in the central nervous system.

Certainly, limbic and auditory brain areas are thought to interact at the thalamic level (Rauschecker et al. 2010, Leaver et al. 2011). Rauschecker and colleagues (2010) present a "noise-cancellation" model of tinnitus, whereby limbic and pre-frontal areas work synergistically to evaluate a tinnitus signal and may enhance or suppress auditory activity based upon its relevance. They hypothesised that a cochlear lesion induces plastic reorganisation leading to perceptual filling-in of the deafferented frequency range and also generates an initial tinnitus signal (due to generated hyperactivity) in the ascending auditory pathways. This signal is normally identified as noise by the limbic system and eliminated or 'tuned out' by feeding it back to the inhibitory thalamic reticular nucleus (TRN) thus eliminating the signal. This circuit serves as a noise cancellation mechanism (Figure 3A). However, if pertinent limbic regions become dysfunctional, noise cancellation breaks down allowing the tinnitus signal to permeate into the auditory cortex, where it enter consciousness leading to permanent cortical reorganisation (see Figure 3B). This model, unlike Jastreboff's model, assigns a more central role to limbic and paralimbic structures wherein they participate in a self-regulating gating process that may prevent the tinnitus signal from being perceived (via feedback from an inhibitory loop). Recent voxel based MRI techniques that demonstrate reductions in grey matter volume in the subcallosal area of the ventromedial prefrontal cortex in tinnitus patients, supporting this central gating hypothesis (Rauschecker et al. 2015). This is in line with Mühlau and colleagues (2006), who reported a reduction in grey matter volume in the subcallosal area and an increase in grey matter volume in the right posterior thalamus, including medical geniculate nucleus, in people with tinnitus compared to healthy controls.

Using both voxel- and surface-based morphometry, Allan and colleagues (2016) also found significant differences in the grey matter and thickness between tinnitus (n=73) and non-tinnitus (n=55) control participants. However, Melcher et al. (2013) reported no significant difference in grey matter volume between people with tinnitus and healthy controls. Instead, they reported a negative correlation between grey matter volume in the subcallosal area and supra-clinical audiometric thresholds (≥8 kHz), a frequency range which was not measured by Mühlau et al. (2006), which may explain the discrepancy between the two studies. Further, Allan et al. (2016) suggest that the differences between participants across different studies, exaggerated by the lack of meaningful definitions of tinnitus subgroups could explain the diversity in findings.

While the initial "noise cancellation" model does not explain all cases of tinnitus, such as why the feedback inhibitory loop fails in some tinnitus patients and not in other cases where tinnitus is perceived but not reported as a problem (i.e. compensated tinnitus), a revised version of the model was proposed to account for this. Rauschecker et al. (2015) hypothesized that that persons with tinnitus (or chronic pain) have an inherent vulnerability, such as elevated levels of dopamine or serotonin or their interaction which could be related to genetic vulnerability, developmental insults, and environmental stressors, acting as synergistic contributors.

There is some evidence which supports the involvement of extra auditory areas, particularly corticostriatal network (Kable & Glimcher, 2009; Ressler & Mayberg, 2007; Sotres-Bayon & Quirk, 2010), implicating the network in evaluation of reward, emotion, and aversiveness in other domains as well. This network, hence, acts as an appraisal network determining which sensations are important, thus affecting whether those sensations are experienced. An alternate model, proposed by DeRidder and colleagues (2011), suggests that multiple

overlapping brain networks contribute to the generation and persistence of tinnitus, which extends the associations presented by the "noise cancellation" model to those which include networks involved in learning and memory. While the involvement of learning mechanisms brings about the association of the phantom percept to distress, memory mechanisms bring about the persistence of tinnitus awareness while reinforcing the associated distress. This model suggests that any altered activity across the associated brain networks (memory, distress, salience, somatosensory, auditory and perception) could cause a phantom perception of any sensory modality, which could explain the presence of phantom perception in individuals without measurable hearing loss, and fluctuations in tinnitus distress associated with anxiety and depression. However, the model does not explain how the flow of information takes place within these networks involved in phantom perception.

Such network models garner support from recent efforts to treat tinnitus using deep brain stimulation (DBS). Cheung and Larson (2010) reported that neuromodulation of the locus area of the caudate nucleus (LC) can decrease or increase tinnitus loudness perception. This indicates that neuromodulation of area LC, a striatal sensorimotor integration centre that is not part of the classical auditory pathway, may modulate the integration of phantom sensations generated by the central auditory system with brain substrates of perceptual awareness. The change in tinnitus perception as a result of neuromodulation was not accompanied by any changes in hearing thresholds. Also, both frontal cortex transcranial magnetic stimulation (De Ridder et al., 2013) and transcranial direct current stimulation (Vanneste et al., 2011) have been shown to modulate auditory cortex related tinnitus loudness in subjects with functional connectivity between frontal cortex and auditory cortex, either via the anterior cingulate or parahippocampal area (De Ridder et al., 2013; Vanneste et al., 2011).

Further evidence of central involvement in tinnitus comes from functional imaging techniques studies which are discussed later in section 1.2.

1.1 Tinnitus treatments

As tinnitus can be a severely distressing condition that can heavily impair patients' quality of life, its treatment is very important. In previous research, many treatment approaches have been applied and investigated (e.g., tinnitus retraining, cognitive–behavioural treatments, and medications; Andersson & Lyttkens, 1999; Henry et al., 2005; Martinez- Devesa, Waddell, Perera, & Theodoulou, 2007; McFerran & Phillips, 2007; Waddell, 2005). However, studies that investigated the efficacy of pharmacological treatments did not find clear improvements in tinnitus annoyance. Rather, many treatments in the field of conventional and complementary medicine, when subjected to a scientific scrutiny, supplied no benefit beyond a placebo effect (McFerran & Phillips, 2007; Elgoyhen & Langguth, 2010).

Acoustic treatments for tinnitus include hearing aids and masking devices. While masking devices may offer temporary relief, they have no influence on the tinnitus *per se* (Dobie, 1999). Hearing aids have been shown to offer modest reduction in experienced severity of tinnitus by masking the tinnitus percept (Surr, Kolb, Cord, & Garrus, 1999; Surr, Montgomery, & Mueller, 1985) and hearing aids with open fit or with large ventilation have been reported to be more efficient (Sheldrake and Jastreboff, 2004; Searchfield, 2005). In a randomised control trial, Parazzini et al. (2011) showed a similar effect change (measured with the Tinnitus Handicap Inventory) for those with hearing aids and those with sound generators but no significant difference between the two. A recent systematic review

demonstrates the lack of evidence from well controlled studies of the efficacy of reducing tinnitus and its associated symptoms, therefore further research is needed in this field (Hoare et al., 2014).

As discussed earlier, while hearing loss (from slight to profound) is experienced by a great majority of patients with distressing tinnitus, hearing aids are a feasible option only for those with more noticeable levels of hearing impairment, as fitting hearing aids in the absence of, or with minimal hearing loss for the purpose of tinnitus suppression is not a norm, partially due to the cost involved. Two therapies that focus on habituation to the tinnitus percept rather than masking it completely- Neuromonics Tinnitus Treatment (NTT) and cognitive behaviour therapy (CBT), are discussed here.

Habituation (or passive extinction) is traditionally defined as the disappearance of reactions to sensory stimuli due to repeated exposure to it without any associated positive or negative reinforcement (Green, 1987). Habituation (to tinnitus) may occur that that the tinnitus-related neuronal activity is blocked from reaching the auditory cortex and, consequently, there are no negative reactions to the tinnitus (*habituation of reaction;* Hazell, 1985). Moreover, the auditory system is capable of blocking this tinnitus related neuronal activity, preventing it from reaching higher cortical areas and thus being perceived (*habituation of perception*; Stephens, Hallam & Jakes, 1986).

Cognitive behaviour therapy (CBT) is a structured, time-limited psychological therapy. It is usually offered by a registered psychologist in 8-24 weekly sessions (Martinez-Devesa et al., 2010). It involves the patient performing behavioural and cognitive tasks to modify their response to thoughts and situations (Figure 4b). Cognitive behavioural therapy is based on the principle that core beliefs often arise from a specific incident and provide a pattern of assumptions (Rachman, 2014). Mood states or events, similar to the original or critical incident, can cause an emergence of patterns that reinforce the core beliefs, and influence behavioural/emotional responses giving rise to symptoms that may be cognitive, behavioural or somatic. Hence, tinnitus may be conceived as a failure to adapt to a stimulus and be considered as analogous to anxiety states (Jastreboff, 1990). In CBT, the patient and therapist view the patient's fearful thoughts as hypotheses to be critically examined and tested which is achieved by (a) understanding the core beliefs by generating an understanding of the link between the thoughts and feelings arising from an event and (b) modifying these behavioural and cognitive responses by which they are normally maintained (Martinez- Devesa et al., 2010). Education, discussion of evidence for and against the beliefs, imagery modification, attentional manipulations, exposure to feared stimuli and relaxation techniques are used in CBT. Behavioural and cognitive assignments which test beliefs are also used. Potential consequences and hurdles are identified and achievable goals are set so that a successful, and therefore therapeutic, outcome is experienced (Martinez- Devesa et al., 2010). In a Cochrane review of randomised controlled trials of CBT provided to patients with tinnitus, of which 8 trials were included, Martinez- Devesa et al. (2010) reported a signifcant improvement in depression (in six studies) and quality of life scores (in 5 studies) in tinnitus patients. However, in 6 studies, there was no evidence of a significant reduction in the subjective loudness of tinnitus. This suggests that CBT may improve outcomes for patients with tinnitus without altering subjective tinnitus parameters. A meta-analysis of fifteen randomized,

controlled trials that studied CBT (a total of 1091 participants) suggested that these effects were maintained over time but the mechanisms by which the treatment works remain unclear (Hesser et al., 2011).

Overall, though CBT was developed as a psychological tool for treatment of anxiety, pain, depression (Beck, 1970), and other psychological conditions, it has shown some success in management of tinnitus. As with any psychotherapy, the outcome and success of CBT may rely on factors outside of the treatment variables, such as therapist effect (Anderson et al., 2009) making them less predictable. On the other hand, the Neuromonics tinnitus treatment combines the use of acoustic stimulation with a structured program of counselling and support by an audiologist trained in tinnitus rehabilitation. The acoustic component uses spectrally-filtered classical music that aims to broadly stimulate all frequency areas of the cochlea, including auditory areas deprived by hearing loss. Further, classical music is used to stimulate a positive response with the limbic system (Brown et al., 2004) and allow intermittent, momentary tinnitus perception within a relaxing stimulus, thereby facilitating desensitisation to the tinnitus signal (Figure 5; Davis et al., 2007).

The NTT program was developed over a decade and has included three clinical trials. The first clinical trial demonstrated that customised music facilitated relaxation and reduction in tinnitus disturbance (Davis & Wilde, 1996), while the second trial compared NTT with other treatment methods such as counselling and counselling plus masking (Davis, Wilde & Steed, 2003). The second trial demonstrated greater success in tinnitus treatment (40% or greater improvement in more than 86% of participants) than the ‘counselling plus masking’ group

(47% of participants reported improvement) and the ‘counselling only ‘group (23% reported improvement). The third trial compared two variations of NTT; one-stage and two-stage protocols (Davis, Paki & Hanley, 2006). The two-stage protocol was shown to be more consistent, and hence was chosen as the standard protocol to be followed in the clinical setting (Figure 6). Hanley et al. (2008) have also described the most suitable category of patients that derive maximum benefit from NTT. Three main features of a suitable group included, low apparent psychological disturbances, high TRQ score (> 17), and hearing loss not exceeding four frequency average of 50 dBHL in the ear with worse hearing.

The NTT program is delivered using an FDA (Food and Drug Administration, USA) approved class-2 medical device, which is fully programmed to match the client’s hearing profile and includes the following:

i. Pure tone hearing thresholds from 250 Hz to 12.5 kHz
ii. Tinnitus pitch
iii. Tinnitus loudness
iv. Minimum masking level.

Customisation of the device helps standardize the treatment protocol across patients of diverse tinnitus and hearing profile, presenting the customised music at comfortable listening levels (Davis, 2006). Standard procedure involves using the device for approximately six months, during which multiple appointments with an audiologist take place to provide education, support and monitoring of the tinnitus levels. The recommended duration of the first stage, during which a combination of broadband noise (BBN) and music are presented at a specific signal-to-noise ratio (Davis, Paki & Hanley, 2007), is two months, though various studies

have suggested modification of the standard protocol based on individual client's needs (Hanley & Davis, 2008; Davis, 2009). For the entire duration of treatment, the user is instructed to use the device for two-four hours per day, particularly at those times of the day when their tinnitus was most disturbing. An independent clinical study has also demonstrated the long-term benefit of NTT, with 75.7% of participants having a more than 40% reduction in their symptoms up to 94 weeks post-treatment (Vieira et al., 2010), along with a reduction in distress and tinnitus awareness. The distinct advantage of this program is its highly structured nature which makes it a streamlined and standardized procedure for experimental purposes. Also, given the fact that an audiologist can run the entire program, eliminates the need to add more members to the rehabilitation team, making it cost and time effective. Since, the treatment is device based, which is pre-programmed based on patient's audiogram, NTT program also reduces the chances of human error which makes the treatment more controlled between patients, making it ideal for this study. The greatest disadvantage of this program is the cost involved in the cost of the program, which is higher than most tinnitus treatments available presently. While NTT has been appreciated for its structured approach, it was not found to be more effective than sound generators (SG) which, on average, cost less that the NTT program. Further, the magnitude of improvement for both SGs and NTT was dependent on initial perceived tinnitus handicap (Newman & Sandridge, 2012). Also, while SGs provide partial masking using BBN, NTT uses spectrally modified relaxation music which intends to serves a dual objective of reducing the signal-to-noise ratio with the background levels of sound and engaging positively with the limbic system (the involvement of which is assumed to negatively enhance the disturbing effects of tinnitus) while making the habituating stimulus pleasant to listen to, thereby promoting compliance to treatment (Hanley et al., 2008). In the present study, Neuromonics devices were provided to clients at no cost for the duration of the treatment.

While the literature demonstrates that tinnitus remediation programs can be beneficial, their outcomes are variable. There is no established objective test for measuring tinnitus or tinnitus improvement during treatment. Instead, tinnitus is currently evaluated using questionnaire-based surveys including the Tinnitus Reaction Questionnaire (TRQ; Wilson et al., 1991) and the Tinnitus Functional Index (TFI; Meikle et al., 2012). These questionnaires fall into two main categories: non-diagnosis-specific and tinnitus-specific. These are used as both self-report surveys and as structured clinical interviews. Depending on the aspect of tinnitus which is the focus of the questionnaire, different questionnaires may be more or less appropriate. The dimensions of the questionnaires vary and are presented in Table 1 (Holgers et al., 2003).

A lack of objective methods for detecting tinnitus and evaluating its severity has made the selection of proper methods and criteria for assessing the effectiveness of treatment difficult and subject to individual interpretation. However, recent advances in imaging techniques have shown some promise in identifying tinnitus-related neural activity, such as activation of various parts of the brain in tinnitus sufferers (Eggermont & Roberts, 2004; Leaver et al., 2011). Most of the neural activity noticed in the brain of tinnitus patients was on the side contralateral to the affected ear (Weisz et al., 2007). Various imaging techniques that have been employed to study neural correlates of tinnitus include electroencephalography (EEG), functional magnetic resonance imaging (fMRI) and MEG. MEG appears to show focal slow-wave abnormalities more reliably than EEG and has higher spatial resolution, hence shows more promise of providing localising information (Lewine et al., 1999).

1.2 Objective Tests of Tinnitus Measurement

Initial attempts to study changes in the auditory pathway in patients with tinnitus were made using auditory evoked brainstem responses (ABR; Ikner & Hassen, 1990) and spontaneous otoacoustic emissions (Wilson, 1985). While Ikner and Hassen demonstrated statistically insignificant effect of tinnitus on ABR responses, Wilson failed to demonstrate any relationship between those individuals displaying spontaneous otoacoustic emissions and the presence (or absence) of subjective tinnitus. Functional imaging methods have been more successful in studying the neural correlates of tinnitus as they can provide a wide field of view of the brain. Rather than recording information about a single or small number of neuronal cells, an image can capture simultaneous activity across the whole brain. These images also enable us to study dynamic processes in the brain and localise brain areas involved in perception or cognition (Noreña & Eggermont, 2003) and, hence, are the methods of choice for objective measurement of tinnitus. Various methods are available that differ in spatial and temporal resolution and their degree of invasiveness and can measure several important aspects of hypothesised tinnitus-related changes in neural activity. Based on neuroimaging techniques, three underlying mechanisms of tinnitus have been proposed: (1) changes in the level of spontaneous neural activity in the central auditory system, (2) changes in the temporal pattern of neural activity, and (3) reorganisation of tonotopic maps (Lanting, Kleine & Dijk, 2009).

Many functional imaging studies have demonstrated the involvement of emotional and cognitive centres that are separate to the auditory system in tinnitus. Mirz and colleagues (1999), using PET, reported increased neuronal activity caused by tinnitus in the right

hemisphere with significant foci in the middle frontal and middle temporal gyri, in addition to lateral and medial posterior sites revealed by reduced cerebral blood flow, thereby associating the tinnitus percept with activity in cortical regions functionally linked to subserve attention, emotion and memory. This was achieved by suppressing tinnitus by lidocaine treatment or masking. Similar results were presented by Lockwood and colleagues (1998) where the authors hypothesised that "the neural systems involved in tinnitus generation may also mediate the control of emotions and memory functions and that a considerable reorganisation of the auditory cortex may explain the expanded area of activation during processing of external auditory stimuli."

Reorganisation of tonotopic maps has also been hypothesised to be a causal factor of tinnitus, and has mostly been studied following noise exposure or application of ototoxic drugs in animals (using classical conditioning methods). Noreña and Eggermont (2003) reported changes in the primary auditory cortex in cats exposed to a transient pure-tone. In humans, Mühlnickel and colleagues (1998), using MEG, compared the Euclidean distance of tinnitus frequency in response to tones in tinnitus participants (n=10) and comparable frequency in normal hearing non-tinnitus controls (n=15). They reported that a frequency region corresponding to tinnitus pitch is represented abnormally in the auditory cortex of tinnitus participants. Parallels were drawn between the reorganisation of the somatosensory cortex and phantom limb pain after upper extremity amputation with reorganisation of auditory cortex and tinnitus. Although studying stimulus-evoked neural activity is informative, it may not be equivalent to measuring activity corresponding to the tinnitus itself, since presented tone can have variable effects on perceived tinnitus sensations (Tyler et al., 2008). Thus, studying patients with intermittent tinnitus, or using imaging techniques that are able to measure

metabolic activity directly (e.g., PET), may be particularly useful. In another study (Weisz et al., 2005b), the neuromagnetically evoked fields of tinnitus subjects with high-frequency hearing loss were measured, while listening to monaurally-presented lesion edge (LE; normal hearing frequency edging frequency with hearing loss) or control (CO; an octave below LE) tones, and compared with normal hearing controls. The N1m equivalent dipole moments (i.e. the magnetic activity of a group of neurons measured to estimate the locations and activation strength of the neural generator of the signals for LE) were normal in the tinnitus group, whereas tinnitus patients had enlarged responses to the CO tones in the right hemisphere. This effect was positively associated with tinnitus-related distress (Figure 7). Abnormal source locations were found for generators activated by LE tones in the right hemisphere of the tinnitus group. This right-hemispheric map distortion was not associated with subjective variables of tinnitus. A positive correlation with tinnitus distress was reported for the left hemisphere with more anterior sources being associated with enhanced distress as measured by a German version of the Tinnitus Questionnaire.

In the last decade, MEG has been extensively used to detect differences in the auditory responses of tinnitus patients (Weisz et al., 2005a, 2005b, 200; Schlee et al., 2009). Initial attempts at measuring tinnitus using MEG were made by Hoke and colleagues (1989) who reported significant differences between the M100/M200 ratios of the tinnitus and non-tinnitus group. However, the two groups were not hearing-matched, rendering the results questionable as the differences could also be attributed to the hearing loss.

Studies using MEG have also demonstrated altered spontaneous activity in tinnitus sufferers compared with controls, characterised by a reduction in alpha brain waves (8-12 Hz) and a concomitant increase of delta (1.5-4 Hz) activity (Weisz et al., 2005a). In the same study they also reported a correlation between the neurophysiologic data (alpha and delta band power) and distress, suggesting that the right temporal and left frontal cortices might be involved in a tinnitus-related cortical network. A plausible hypothesis is that there is a strong association of the temporal region with perceptual issues (i.e., aspects concerning the character of the sound, e.g., tonal or noise-like, loudness), while the left frontal region is more associated with affective distress and motivational attention of tinnitus (i.e., the tinnitus becoming a signal of high importance that draws the attention of the individual). These findings were further substantiated by Schlee and colleagues (2014), wherein they observed significant differences in alpha power between tinnitus and control groups. They also reported that both the reduction of alpha power and alpha variability were mainly driven by low alpha activity (8–10 Hz). Weisz and his colleagues (2007) also reported enhancement of gamma band Activity (GBA) in a spontaneous MEG recording of auditory cortical activity in tinnitus participants, compared with normal hearing controls. They also suggested that following a long history of deafferentation, GBA could become self-sustained, making tinnitus very therapy-resistant. Adjamian et al. (2012), however, found no correlation between changes in gamma activity and tinnitus. They postulated that gamma activity plays a role in conscious perception of stimuli, and increased slow wave and gamma activity is mediated by deafferentation, implying that an increase in gamma activity is mediated by hearing loss. Thus, it can be expected that enhancement in gamma activity could be present whether or not tinnitus exists, as long as there is some degree of deafferentation.

A consistent drawback of these experiments is a lack of hearing-loss matched control group, which could be partially responsible for the differences between the tinnitus and control groups. Weisz et al (2005a) did acknowledge this shortcoming and reported on the difficulty in finding a group of appropriate size as the two phenomena are closely related. König et al. (2006) are one group that have compared attributes of hearing loss in a tinnitus group and controls with hearing loss but no reports of tinnitus. They reported that the slope of hearing loss appears to be sharper in tinnitus, which could mean that the relevant neuronal reorganizational processes eventually take place at points with steep activational discontinuities. To find such a control group that matches the tinnitus group exactly in slope and severity of hearing loss would be ideal, though it is a very hard group to find.

Another limitation of these experiments is lack of control over laterality of tinnitus in subjects. All the studies included participants with either bilateral or unilateral (left or right sided) tinnitus. Weisz et al. (2005a) suggested that the stronger effect for the right temporal area than for the left in their experiment could be attributed to higher number of participants with left-sided tinnitus, thus hypothesising that this asymmetry could vanish if more individuals with right-sided tinnitus were included in the analysis.

These studies have done much to establish that tinnitus can be measured objectively in humans using MEG, and that tinnitus is a cortical phenomenon with some degree of correlation to the subjective measures of tinnitus such as tinnitus distress. However, recent studies have also raised important questions, pertaining to the validity of literature demonstrating a correlation between spontaneous cortical activity and behavioural attributes of tinnitus. Adjamian et al. (2014) pointed to a careful analysis and interpretation of EEG / MEG data in tinnitus patients and the relevance of comorbidities such as hearing loss,

hyperacusis, stress or depression which could lead to flaws in EEG/MEG research results. On the other hand, Pierzycki et al. (2015) reported no correlation between EEG recordings of spontaneous cortical activity and various psychological and psychosocial tinnitus measures, rejecting the previous reports of such correlations as having Type I error. While the present experiment was conducted prior to the publication of either of these studies, and the premise of the second paper (Pierzycki et al., 2016) has been questioned by De Ridder et al. (2016) in an open letter to the editor, this thesis intends to contribute to the existing literature by identifying the usefulness of MEG as an objective measure of tinnitus, as has been reported over the last two decades.

The present experiment aims to investigate changes in the level of spontaneous and evoked neural activity in the central auditory system by using MEG recordings and their associations with behavioural tests of tinnitus.

1.3 Magnetoencephalography: Advantages and disadvantages

Magnetoencephalography is a relatively new brain imaging technique which non-invasively records and conveys neurophysiological information complementary to that provided by EEG, albeit with higher temporal and spatial resolution (Parra, Kalitzin & da Silva, 2004). The first MEG recordings were performed by David Cohen in 1968, using a one sensor magnetometer. In the last two decades, MEG technology has developed rapidly and devices with 150 or more sensors providing whole-scalp coverage have become available. Surprisingly, despite several advancements in the field and over four decades of use, it is still considered a relatively new neurophysiological technique.

Presently, MEG is the only available neurophysiological technique, besides EEG, which non-invasively measures neuronal activity with temporal resolution in the millisecond range. In comparison, other popular neuroimaging techniques such as PET, single-photon emission computerized tomography (SPECT), and fMRI, measure neuronal activity indirectly and have a rather poor temporal resolution ranging from seconds to several minutes (Parra, Kalitzin & da Silva, 2004). A major limitation of fMRI in auditory research is the acoustic noise produced by the scanner which is typically in excess of 100 dB sound pressure level, thus making it difficult to segregate auditory stimuli to ambient noise, while PET's use of radioactive tracer makes it less suitable for repeated measurements (Lanting, Kleine & Dijk, 2009). Though MEG provides information which in many cases is considered complementary to that provided by EEG, MEG has certain distinct advantages over EEG which makes it a tool of choice for neurophysiological investigations:

1. MEG provides a higher spatial density of recording points than EEG.

2. MEG does not need a reference, so it may provide more accurate estimates than EEG in studies dealing with rhythm synchronisation or coherency that assess phase synchrony or intra-cortical propagation speed (Silberstein, 1995)

3. Electrical fields measured by EEG are prone to distortion effects of the skull, which acts as a low pass filter. Magnetic fields are less distorted, providing better conditions for the recording of fast activity such as gamma band oscillations (Ebersole, 1997).

The most obvious disadvantage of using MEG for research or clinical purposes is the high cost of MEG devices, and the corresponding running cost. It costs around $AUD700 for a single MEG session (approx. GBP 500 GBP or USD 700). In addition, it is very sensitive to movement, which makes a long MEG testing session challenging for young participants.

Also, MEG's inability to record ictal events (a physiologic state or event such as a seizure) is a distinct disadvantage. Long recordings similar to those carried out with EEG are barely feasible, and, moreover, a seizure within the MEG environment may lead to injuries provoked by a collision with the helmet and dewar (Parra, Kalitzin &da Silva, 2004). This, however, is not a deterrent in the current study, which investigates brain changes in non-epileptic, tinnitus patients. Another issue is the extreme sensitivity of MEG to the presence of metal objects (e.g. pacemaker or dental fillings), which can corrupt the results. Participants in the present study were screened for such items.

1.4 Need for the study

Considering the abundant information that is available regarding the neurophysiological generation of tinnitus and its neural basis, and the gap in knowledge regarding the objective measure of tinnitus and its remediation, we identified the following problems that need to be investigated:

i. While an objective test of tinnitus has been identified, the majority of the research at the time that this program of research was developed had come from a single laboratory (Department of Psychology, University of Konstanz, Germany). The present study aims to validate the test by replicating this laboratory's research.

ii. Most studies of the objective measure of tinnitus have had hearing loss as a confounding variable (using normally-hearing people as control). This study aims to compare subjective and objective measures of tinnitus throughout remediation (pre- and post- measure) where hearing loss is expected to remain (relatively) unchanged.

iii. Many studies have different definitions of chronic tinnitus. In this study, chronic tinnitus is defined based on not only its duration, but also its severity in terms of its perception (loudness and pitch), and its psychological correlates such as anxiety, depression and insomnia.

1.5 Hypotheses

In the present study we hypothesise that:

1. The increase in gamma and decrease in alpha band power reported by Weisz et al. (2005) will be reproduced.
2. Subjective reports of tinnitus will be mirrored in the spontaneous cortical measures, recorded by MEG.
3. Two objective measures, i.e. spontaneous and evoked responses in tinnitus patients, will show concomitant changes during tinnitus remediation program giving an insight into the neurophysiological changes associated with tinnitus treatment.

References

Adjamian, P., Sereda, M., Zobay, O., Hall, D. A., & Palmer, A. R. (2012). Neuromagnetic indicators of tinnitus and tinnitus masking in patients with and without hearing loss. *Journal of the Association for Research in Otolaryngology*, *13*(5), 715-731.

Adjamian, P. (2014). The application of electro-and magneto-encephalography in tinnitus research–methods and interpretations. *Frontiers in neurology*, *5*.

Allan, T. W., Besle, J., Langers, D. R., Davies, J., Hall, D. A., Palmer, A. R., & Adjamian, P. (2016). Neuroanatomical alterations in tinnitus assessed with magnetic resonance imaging. *Frontiers in aging neuroscience*, *8*, 221.

Anderson, T., Ogles, B. M., Patterson, C. L., Lambert, M. J., & Vermeersch, D. A. (2009). Therapist effects: Facilitative interpersonal skills as a predictor of therapist success. *Journal of Clinical Psychology*, *65*(7), 755-768.

Andersson, G., Lyttkens, L. (1999). A meta-analytic review of psychological treatments for tinnitus. *British Journal of Audiology*, 33(4), 201–210.

Andersson, G., Eriksson, J., Lundh, L. G., Lyttkens, L. (2000). Tinnitus and Cognitive InterferenceA Stroop Paradigm Study. *Journal of Speech, Language, and Hearing Research*, *43*(5), 1168-1173.

Andersson G. (2002). Psychological aspects of tinnitus and the application of cognitive-behavioral therapy. *Clinical Psychology Review*. 22, 977–90.

Andersson G, Baguley D, MacKenna L, McFerran D. (2005). Tinnitus: A multidisciplinary approach. London: Whurr Publishers.

Araneda, R., De Volder, A. G., Deggouj, N., Philippot, P., Heeren, A., Lacroix, E., Decat, M., Rombaux, P., & Renier, L. (2015). Altered top-down cognitive control and auditory processing in tinnitus: evidences from auditory and visual spatial stroop. *Restorative neurology and neuroscience*, *33*(1), 67-80.

Axelsson, A., Ringdahl, A. (1989). Tinnitus- A study of its prevalence and characteristics. *British Journal of Audiology, 23, 53-62.*

Barnea, G., Attias, J., Gold, S., Shahar, A. (1990). Tinnitus with normal hearing sensitivity: extended high-frequency audiometry and auditory-nerve brain-stem-evoked responses. *International Journal of Audiology*, *29*(1), 36-45.

Baskill, J.L., Coles, R.R.A. (1999). Relationships between tinnitus loudness and severity. In: Hazell J.W.P. (eds). *Proceedings of the Sixth International Tinnitus Seminar.* Cambridge UK: The Tinnitus and Hyperacusis Centre London, 424-428.

Beck, A. T. (1970). Cognitive therapy: Nature and relation to behavior therapy. *Behavior Therapy*, *1*(2), 184-200.

Brown, S., Martinez, M. J., Parsons, L. M. (2004). Passive music listening spontaneously engages limbic and paralimbic systems. *Neuroreport, 15*(13), 2033-2037.

Budd, R. J., Pugh, R. (1995). The relationship between locus of control, tinnitus severity, and emotional distress in a group of tinnitus sufferers. *Journal of Psychosomatic research*. 39, 1015-1018.

Chen, G., & Jastreboff, P. J. (1995). Salicylate-induced abnormal activity in the inferior colliculus of rats. *Hearing research*, *82*(2), 158-178.

Chen, Y. C., Li, X., Liu, L., Wang, J., Lu, C. Q., Yang, M., Jiao, Y., Zang, F., Radziwon, K., Chen, G., Sun, W., Muthaiah, V.P.K., Salvi, R., & Teng, G. (2015). Tinnitus and hyperacusis involve hyperactivity and enhanced connectivity in auditory-limbic-arousal-cerebellar network. *Elife*, *4*.

Cheung, S. W., Larson, P. S. (2010). Tinnitus modulation by deep brain stimulation in locus of caudate neurons (area LC). *Neuroscience*, *169*(4), 1768-1778.

Chung, D.Y., Gannon, R.P., Mason, M.K. (1984) Factors affecting the prevalence of tinnitus. *Audiology, 23, 441-52.*

Cohen, D., Halgren, E. (2003). Magnetoencephalography (Neuromagnetism). *Encyclopedia of Neuroscience*. 3, 1-7.

Coles, R. R. A. (1984). Epidemiology of tinnitus: Prevalence. *Journal of Laryngology and Otology, 98*(Suppl. 9), 7–15.

Coles, R. R. A. (1987). Epidemiology of tinnitus. In J.W.P, Hazell (Ed.), *Tinnitus* (p46-70). Edinburgh: Churchill Livingstone.

Coles, R. R. A. (1996). Epidemiology, aetiology and classification. *In Proceedings of the Fifth International Tinnitus Seminar.* J.A. Vernon & G. Reich (Eds) (p25-30). Portland.

Dallas, P. (1992). The active cochlea. *The Journal of Neuroscience*, *12*, 4575-4585

Davis, A. C. (1989). The prevalence of hearing impairment and reported hearing disability among adults in Great Britain. *International Journal of Epidemiology, 18*(4), 911-917.

Davis, P. B. (2006). Music and the acoustic desensitization protocol for tinnitus. *Tinnitus treatment: Clinical protocols,* 146-160.

Davis, A., & El Refaie, A. (2000). Epidemiology of tinnitus. In R. S. Tyler (Ed.), *Tinnitus handbook* (pp. 1–21). San Diego, CA: Singular Publishing Group.

Davis, P.B. (2009). Effects of severe unilateral hearing loss on tinnitus rehabilitation. Poster presented at the 3rd Tinnitus Research Initiative Meeting, Stressa, Italy.

Davis, P. B., Paki, B., Hanley, P. J. (2007). Neuromonics tinnitus treatment: third clinical trial. *Ear and hearing*, *28*(2), 242-259.

Davis, A., & Wilde, R. A. (1996). Proceedings of the Fifth International Tinnitus Seminar.

Davis, P.B., Wilde, R. A., Steed, L.G. (2003). Trials of desensitization music: Neurophysiology-influenced rehabilitation. In *Proceedings of the seventh international tinnitus seminar*. RB Patuzzi, Ed, Australia: Physiology Dept., University of Western Australia (pp. 74-77).

De Ridder, D., Congedo, M., Song, J. J., & Vanneste, S. (2016). Whole scalp EEG power change is not a prerequisite for further EEG processing. *Hearing research*, *339*, 215-216.

De Ridder, D., Elgoyhen, A. B., Romo, R., & Langguth, B. (2011). Phantom percepts: tinnitus and pain as persisting aversive memory networks. *Proceedings of the National Academy of Sciences*, *108*(20), 8075-8080.

De Ridder, D., Song, J. J., & Vanneste, S. (2013). Frontal cortex TMS for tinnitus. *Brain stimulation*, *6*(3), 355-362.

Dobie, R. A. (1999). A review of randomized clinical trials in tinnitus. *Laryngoscope*, *109*(8), 1202-1211.

Ebersole J. S. (1997). EEG and MEG dipole source modelling. In: J. Engel Jr, T.A. Pedley (Eds.). *Epilepsy: a comprehensive textbook* (pp. 919-935). Philadelphia: Lippincott–Raven.

Eggermont, J. J., & Kenmochi, M. (1998). Salicylate and quinine selectively increase spontaneous firing rates in secondary auditory cortex. *Hearing research*, *117*(1-2), 149-160.

Eggermont, J. J., & Roberts, L. E. (2004). The neuroscience of tinnitus. *Trends in Neurosciences*, *27*(11), 676-682.

Elgoyhen, A. B., & Langguth, B. (2010). Pharmacological approaches to the treatment of tinnitus. *Drug discovery today*, *15*(7-8), 300-305.

Evans, E. F., Wilson, J. P., & Borerwe, T. A. (1981). Animal models of tinnitus. *Tinnitus*, 108-148.

Folmer, R.L., & Griest, S.E. (2000). Tinnitus and Insomnia. *American Journal of Otolaryngology*. 21(5), 287-293

Fowler, E.P. (1944). Head noises in normal and in disordered ears: Significance, measurement, differentiation and treatment. *Archives in Otolaryngology*, 30, 490-503.

Fowler, E. P. (1948). Nonvibratory tinnitus: Factors underlying subaudible and audible irritations. *Archives of otolaryngology*, *47*(1), 29-36.

Fujii, K., Nagata, C., Nakamura, K., Kawachi, T., Takatsuka, N., Oba, S., & Shimizu, H. (2011). Prevalence of tinnitus in community-dwelling Japanese adults. *Journal of Epidemiology*, *21*(4), 299-304.

Glasgold, A., & Altmann, F. (1966). The effect of stapes surgery on tinnitus in otosclerosis. *Laryngoscope*, 76, 1524-1532.

Green, S. (1987). Habituation-attention and memory. In: *Physiological Psychology: An Introduction*. London- Routledge & Kegan Paul, 199-216.

Halford, J. B. S., Anderson, S. D. (1991). Anxiety and Depression in Tinnitus Sufferers. *Journal of Psychosomatic research*. 35 (415), 383-390.

Hallam, R.S. (1996). Correlates of sleep disturbance in chronic distressing tinnitus. *Scandanavian Audiology*, 25, 263–266.

Hallberg, L. R., Erlandsson, S. I. (1993). Tinnitus characteristics in tinnitus complainers and noncomplainers. *British Journal of Audiology, 27*(1), 19-27.

Hanley, P.J., Davis, P.B. (2008). Treatment of tinnitus with a customized, dynamic acoustic neural stimulus: Underlying principles and clinical efficacy. *Trends in Amplification,* 12(3), 210-222.

Hanley, P. J., Davis, P. B., Paki, B., Quinn, S. A., & Bellekom, S. R. (2008). Treatment of tinnitus with a customized, dynamic acoustic neural stimulus: clinical outcomes in general private practice. *Annals of Otology, Rhinology & Laryngology, 117*(11), 791-799.

Hazell, J. W. P., Wood, S. M., Cooper, H. R., Stephens, S. D. G., Corcoran, A. L., Coles, R. R. A., & Sheldrake, J. B. (1985). A clinical study of tinnitus maskers. *British journal of audiology*, *19*(2), 65-146.

Hazell, J. (1991). Tinnitus and disability with ageing: adaptation and management. *Acta Oto-Laryngologica*, *111*(S476), 202-208.

Heeren, A., Maurage, P., Perrot, H., De Volder, A., Renier, L., Araneda, R., Lacroix, E., Decat, M., Deggouj, J., & Philippot, P. (2014). Tinnitus specifically alters the top-down executive control sub-component of attention: evidence from the attention network task. *Behavioural brain research*, *269*, 147-154.

Heller, M.F., & Bergman, M. (1953). Tinnitus aurium in normally hearing persons. *Annals of Otorhinolaryngology, 62*, 73-83.

Henry, J. A., Dennis, K. C., & Schechter, M. A. (2005). General review of tinnitus: Prevalence, mechanisms, effects, and management. *Journal of Speech, Language, and Hearing Research, 48*(5), 1204–1235.

Hesser, H., Weise, C., Westin, V. Z., & Andersson, G. (2011). A systematic review and meta-analysis of randomized controlled trials of cognitive–behavioral therapy for tinnitus distress. Clinical psychology review, 31(4), 545-553

Hoare, D. J., Edmondson-Jones, M., Sereda, M., Akeroyd, M. A., & Hall, D. (2014). Amplification with hearing aids for patients with tinnitus and co-existing hearing loss. *The Cochrane database of systematic reviews*, *1*.

Hoffman, H. J., Reed, & G. W. (2004). Epidemiology of tinnitus. In J. B. Snow, Jr. (Ed.), Tinnitus: Theory and management (pp. 16–41). Lewiston, NY: BC Decker.

Hoke, M., Feldmann, H., Pantev, C., Lütkenhöner, B., & Lehnertz, K. (1989). Objective evidence of tinnitus in auditory evoked magnetic fields. *Hearing research*, *37*(3), 281-286.

Holgers KM, Barrenas ML, Svedlund J, & Zoger S. (2003). Clinical evaluation of tinnitus: A review. *Audiological Medicine.* 2, 101–106

House, J.W., & Brackmann, D.E. (1981) Tinnitus: Surgical treatment. *Tinnitus*. (Ciba Foundation symposium 85): 204-216. London: Pitman Books Ltd.,

Ikner, C. L., & Hassen, A. H. (1990). The effect of tinnitus on ABR latencies. *Ear and hearing*, *11*(1), 16-20.

Jakes, S.C., Hallam, R.S., Rachman, S., & Hinchcliffe, R. (1986). The effects of reassurance, relaxation training and distraction on chronic tinnitus sufferers. *Behavior Research Therapy*, 24(5), 497-507.

Jänig, W. (1995). The sympathetic nervous system in pain. *European journal of anaesthesiology. Supplement*, *10*, 53-60.

Jastreboff, P. J. (1990). Phantom auditory perception (tinnitus): mechanisms of generation and perception. *Neuroscience research*, *8*(4), 221-254.

Jastreboff, P. J. (1995). Tinnitus as a phantom perception: theories and clinical implications, In *Mechanisms of tinnitus*, ed. Vernon, J. & Moller, A.R., p 73-94. Boston, MA: Allyn & Bacon

Jastreboff, P. J., & Hazell, J. W. P. (2004). *Tinnitus retraining therapy: Implementing the neurophysiological model.* Cambridge, England: Cambridge University Press.

Jastreboff, P. J., & Jastreboff M. M (2000). Tinnitus Retraining Therapy (TRT) as a method for treatment of tinnitus and hyperacusis patients. *Journal of the American Academy of Audiology.* 11(3), 162-177.

Jastreboff, P. J., & Jastreboff, M. M. (2006). Tinnitus Retraining Therapy: A Different View on Tinnitus. *Otorhinolaryngology.* 68(1), 23-30.

Kable, J. W., & Glimcher, P. W. (2009). The neurobiology of decision: consensus and controversy. *Neuron*, *63*(6), 733-745.

Kaltenbach, J. A., & Afman, C. E. (2000). Hyperactivity in the dorsal cochlear nucleus after intense sound exposure and its resemblance to tone-evoked activity: a physiological model for tinnitus. *Hearing research*, *140*(1), 165-172.

Kaltenbach, J. A., Rachel, J. D., Mathog, T. A., Zhang, J., Falzarano, P. R., & Lewandowski, M. (2002). Cisplatin-induced hyperactivity in the dorsal cochlear nucleus and its relation to outer hair cell loss: relevance to tinnitus. *Journal of neurophysiology*, *88*(2), 699-714.

Kaltenbach, J. A. (2011). Tinnitus: models and mechanisms. *Hearing research*, *276*(1), 52-60.

Kimura, M., & Eggermont, J. J. (1999). Effects of acute pure tone induced hearing loss on response properties in three auditory cortical fields in cat. *Hearing research*, *135*(1), 146-162.

König, O., Schaette, R., Kempter, R., & Gross, M. (2006). Course of hearing loss and occurrence of tinnitus. *Hearing Research*, *221*(1), 59-64.

Kraus, K. S., & Canlon, B. (2012). Neuronal connectivity and interactions between the auditory and limbic systems. Effects of noise and tinnitus. *Hearing research*, *288*(1), 34-46.

Kuk, F. K., Tyler, R. S., Russell, D., & Jordan, H. (1990). The psychometric properties of a tinnitus handicap questionnaire. *Ear and hearing*, *11*(6), 434-445.

Kvestad, E., Czajkowski, N., Engdahl, B., Hoffman, H.J., & Tambs, K. (2010). Low heritability of tinnitus: Results from the second Nord-Trondelag Health Study. *Archives of Otolaryngology - Head and Neck Surgery, 136 (2),* 178-182.

Lanting, C. P., De Kleine, E., & Van Dijk, P. (2009). Neural activity underlying tinnitus generation: results from PET and fMRI. *Hearing research*, *255*(1), 1-13.

Leaver, A. M., Renier, L., Chevillet, M. A., Morgan, S., Kim, H. J., & Rauschecker, J. P. (2011). Dysregulation of limbic and auditory networks in tinnitus. *Neuron*, *69*(1), 33-43.

Leaver, A. M., Turesky, T. K., Seydell-Greenwald, A., Morgan, S., Kim, H. J., & Rauschecker, J. P. (2016). Intrinsic network activity in tinnitus investigated using functional MRI. *Human brain mapping*, *37*(8), 2717-2735.

Lewine, J. D., Davis, J. T., Sloan, J. H., Kodituwakku, P. W., & Orrison Jr, W. W. (1999). Neuromagnetic assessment of pathophysiologic brain activity induced by minor head trauma. *American Journal of Neuroradiology*, *20*(5), 857-866.

Lewis, J., Stephens, S., & McKenna, L. (1994). Tinnitus and suicide. *Clinical Otolaryngology & Allied Sciences, 19*(1), 50-54

Lockwood, A. H., Salvi, R. J., Coad, M. L., Towsley, M. L., Wack, D. S., & Murphy, B. W. (1998). The functional neuroanatomy of tinnitus Evidence for limbic system links and neural plasticity. *Neurology, 50*(1), 114-120.

Lockwood, A. H., Burkard, R. F., Salvi, R. J., Arnold, S. A., Reyes, S. A., Coad, M. L., Loncoff, N.S., Galatoqicz, P.J., & Wack, D. S. (1999). Positron emission tomographic (PET) studies of gaze-evoked tinnitus. *Journal of the Association for Research in Otolaryngology*, *22*, 119.

Martinez-Devesa, P., Waddell, A., Perera, R., & Theodoulou, M. (2007). *Cognitive behavioural therapy for tinnitus*. Available from Cochrane Reviews, http://www.cochrane.org/reviews/

Martinez-Devesa, P., Perera, R., Theodoulou, M., & Waddell, A. (2010). Cognitive behavioural therapy for tinnitus. Cochrane Database of Systematic Reviews DOI: 10.1002/14651858.CD005233.pub3

McFadden, D. (1982) Tinnitus, facts theories and treatments. Natl. Academy Press, Washington, DC.

McFerran, D. J., & Phillips, J. S. (2007). Tinnitus. *Journal of Laryngology and Otology, 121*(3), 201–208.

McKenna, L., & Andersson, G. (1998). Hearing disorders. In J. B. Snow, Jr. (Ed.), Tinnitus: Theory and management (pp. 16–41). Lewiston, NY: BC Decker.

Mckenna, L. (2004). Models of tinnitus suffering and treatment compared and contrasted. *Audiological Medicine*, *2*(1), 41-53.

Meikle, M., & Taylor-Walsh, E. (1984). Characteristics of tinnitus and related observations in over 1800 tinnitus clinic patients. *The Journal of Laryngology & Otology*, *98*(S9), 17-21.

Meikle, M.B., Vernon, J., & Johnson, R.M. (1984). The perceived severity of tinnitus. *Otolaryngology and Head and Neck Surgery.* 92:689- 696.

Meikle, M. B., Henry, J. A., Griest, S. E., Stewart, B. J., Abrams, H. B., McArdle, R., Myers, P. J., Newman, C. J., Sandridge, S., Turk, D. C., Folmer, R. L., Frederick, E. J., House, J. W., Jacobson, G. P., Kinney, S. E., Martin, W. H., Nagler, S. M., Reich, G. E., Searchfield, G., Sweetow, R., & Vernon, J. A. (2012). The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus. *Ear and hearing*, *33*(2), 153-176.

Melcher, J. R., Knudson, I. M., & Levine, R. A. (2013). Subcallosal brain structure: correlation with hearing threshold at supra-clinical frequencies (> 8 kHz), but not with tinnitus. *Hearing research*, *295*, 79-86.

Mirz, F., Brahe Pedersen, C., Ishizu, K., Johannsen, P., Ovesen, T., Stødkilde-Jørgensen, H., & Gjedde, A. (1999). Positron emission tomography of cortical centers of tinnitus. *Hearing research*, *134*(1), 133-144.

Mirz, F., Gjedde, A., Ishizu, K., & Pedersen, C. B. (2000). Cortical networks subserving the perception of tinnitus: a PET study. *Acta Otolaryngologica Supplement*, 543, 241–243.

Møller, A. R., Møller, M. B., & Yokota, M. (1992). Some forms of tinnitus may involve the extralemniscal auditory pathway. *The Laryngoscope*, *102*(10), 1165-1171.

Mühlau, M., Rauschecker, J., Oestreicher, E., Gaser, C., Röttinger, M., Wohlschläger, A., Simon, F., Etgen, T., Conrad, B., & Sander, D. (2006). Structural brain changes in tinnitus. *Cerebral Cortex*, *16*(9), 1283-1288.

Mühlnickel, W., Elbert, T., Taub, E., & Flor, H. (1998). Reorganization of auditory cortex in tinnitus. *Proceedings of the National Academy of Sciences*, *95*(17), 10340-10343.

Newman, C. W., & Sandridge, S. A. (2012). A comparison of benefit and economic value between two sound therapy tinnitus management options. *Journal of the American Academy of Audiology*, *23*(2), 126-138.

Noreña, A. J., & Eggermont, J. J. (2003). Changes in spontaneous neural activity immediately after an acoustic trauma: implications for neural correlates of tinnitus. *Hearing Research*, *183*(1), 137-153.

Noreña, A. J. (2011). An integrative model of tinnitus based on a central gain controlling neural sensitivity. *Neuroscience & Biobehavioral Reviews*, *35*(5), 1089-1109.

Pan, T., Tyler, R. S., Ji, H., Coelho, C., Gehringer, A. K., & Gogel, S. A. (2009). The relationship between tinnitus pitch and the audiogram. *International journal of audiology*, *48*(5), 277-294.

Parazzini, M., Del Bo, L., Jastreboff, M., Tognola, G., & Ravazzani, P. (2011). Open ear hearing aids in tinnitus therapy: An efficacy comparison with sound generators. *International journal of audiology*, *50*(8), 548-553.

Parra, J., Kalitzin, S.N., & da Silva F. H. (2004). Magnetoencephalography: an investigational tool or a routine clinical technique? *Epilepsy & Behavior*. 5(3). 277–285.

Pierzycki, R. H., McNamara, A. J., Hoare, D. J., & Hall, D. A. (2016). Whole scalp resting state EEG of oscillatory brain activity shows no parametric relationship with psychoacoustic and psychosocial assessment of tinnitus: a repeated measures study. *Hearing Research*, *331*, 101-108.

Pilgramm, M., Rychlick, R., Lebisch, H., Siedentop, H., Goebel, G., & Kirchhoff, D. (1999). Tinnitus in the Federal Republic of Germany: A representative epidemiological study; in Hazell J (ed): *Proceedings of the VIth International Tinnitus Seminar*. Cambridge, The Tinnitus and Hyperacusis Center, 64–67.

Rachman, S. (2014, Nov 14). The Evolution of behaviour therapy and cognitive behaviour therapy. Retrieved from http://www.sciencedirect.com.simsrad.net.ocs.mq.edu.au/science/article/pii/S0005796714001764#

Rauschecker, J.P., Leaver, A.M. & Mühlau, M. (2010). Tuning out the noise: limbic-auditory interactions in tinnitus. *Neuron.* 66, 819–826.

Rauschecker, J. P., May, E. S., Maudoux, A., & Ploner, M. (2015). Frontostriatal gating of tinnitus and chronic pain. *Trends in Cognitive Sciences*, 19(10), 567-578.

Ressler, K. J., & Mayberg, H. S. (2007). Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. *Nature neuroscience*, *10*(9), 1116.

Roberts, L.E., Eggermont, J.J, Caspary, D.M., Shore, S.E., Melcher, J.R., & Kaltenbach, J.A. (2010). Ringing ears: the neuroscience of tinnitus. *Journal of Neuroscience.* 30. 14972–14979.

Salvi, R. J., Hamernik, R. P., & Henderson, D. (1978). Discharge patterns in the cochlear nucleus of the chinchilla following noise induced asymptotic threshold shift. *Experimental Brain Research*, *32*(3), 301-320.

Salvi, R., Lobarinas, E., & Sun, W. (2009). Pharmacological treatments for tinnitus: New and old. *Drugs of the Future*, *34*(5), 381.

Sanchez, L., & Stephens, D. (1997). A tinnitus problem questionnaire in a clinic population. *Ear and Hearing*, *18*(3), 210-217.

Schaette, R., & McAlpine, D. (2011). Tinnitus with a normal audiogram: physiological evidence for hidden hearing loss and computational model. *The Journal of Neuroscience*, *31*(38), 13452-13457.

Schlee, W., Hartmann, T., Langguth, B., & Weisz, N. (2009). Abnormal resting-state cortical coupling in chronic tinnitus. *BMC Neuroscience*, *10*(1), 11.

Schlee, W., Lorenz, I., Hartmann, T., Müller, N., Schulz, H., & Weisz, N. (2011). A global brain model of tinnitus. In *Textbook of tinnitus* (pp. 161-169). Springer New York.

Schlee, W., Mueller, N., Hartmann, T., Keil, J., Lorenz, I., & Weisz, N. (2009). Mapping cortical hubs in tinnitus. *BMC Biology*, *7*(1), 80.

Schlee, W., Schecklmann, M., Lehner, A., Kreuzer, P. M., Vielsmeier, V., Poeppl, T. B., & Langguth, B. (2014). Reduced variability of auditory alpha activity in chronic tinnitus. *Neural Plasticity*, *2014*.

Scott, B., Lindberg, P., Lyttkens, L., & Melin, L. (1985). Psychological treatment of tinnitus. An experimental group study. *Scandinavian Audiology*, *14*(4), 223–230.

Searchfield, G.D. (2005) Hearing aids and tinnitus. In: Tyler R.S. (Ed.), Tinnitus Treatment Clinical Protocols. Thieme Medical Publisher, New York, NY, pp. 161–175.

Sereda, M., Hall, D. A., Bosnyak, D. J., Edmondson-Jones, M., Roberts, L. E., Adjamian, P., & Palmer, A. R. (2011). Re-examining the relationship between audiometric profile and tinnitus pitch. *International journal of audiology*, *50*(5), 303-312.

Shargorodsky, J., Curhan, G.C., & Farwell, .W.R. (2010) Prevalence and characteristics of tinnitus among US adults. *The American Journal of Medicine*, 123, 711-18.

Sheldrake, J. B., & Jastreboff, M. M. (2004). Role of hearing aids in management of tinnitus. *Tinnitus: Theory and management*, 310-313.

Silberstein R.B. (1995) Steady-state visually evoked potentials, brain resonances and cognitive processes. In: Nunez PL, editor. Neocortical dynamics and human EEG rhythms. New York: Oxford Univ. Press. p. 272–303.

Sindhusake D, Golding M, Newall P, Rubin G, Jakobsen K, & Mitchell P. (2003b) Risk Factors for Tinnitus in a Population of Older Adults: The Blue Mountains Hearing Study. *Ear & Hearing*., 24(6), 501-507.

Sindhusake, D., Mitchell. P., Golding. M., Newall. P., Rochtchina. E., & Rubin G. (2003a) Prevalence and Characteristics of Tinnitus in Older Adults: the Blue Mountains Hearing Study. *International Journal of Audiology*. 42(5), 289-294.

Sotres-Bayon, F., & Quirk, G. J. (2010). Prefrontal control of fear: more than just extinction. *Current opinion in neurobiology*, *20*(2), 231-235.

Stephens, S. D. G. (1984). The treatment of tinnitus—a historical perspective. *The Journal of Laryngology & Otology*, *98*(10), 963-972.

Stephens, S. D. G., Hallam, R.S., & Jakes, S. C. (1986). Tinnitus: a management model. *Clinical Otolaryngolology*. 11, 227-238.

Surr, R. K., Kolb, J. A., Cord, M. T., & Garrus, N. P. (1999). Tinnitus Handicap Inventory (THI) as a hearing aid outcome measure. *Journal of the American Academy of Audiology*, *10*, 489-495.

Surr, R. K., Montgomery, A. A., & Mueller, H. G. (1985). Effect of amplification on tinnitus among new hearing aid users. *Ear and Hearing*, *6*(2), 71-75.

Thabet, T.M. (2009). Evaluation of tinnitus patients with normal hearing sensitivity using TEOAEs and TEN test. *Auris Nasus Larynx*, *36*, 633-636.

Trevis, K. J., McLachlan, N. M., & Wilson, S. J. (2016). Cognitive mechanisms in chronic tinnitus: psychological markers of a failure to switch attention. *Frontiers in psychology*, *7*, 1262.

Trevis, K. J., Tailby, C., Grayden, D. B., McLachlan, N. M., Jackson, G. D., & Wilson, S. J. (2017). Identification of a Neurocognitive Mechanism Underpinning Awareness of Chronic Tinnitus. *Scientific Reports*, *7*(1), 15220.

Tyler, R. S., & Baker, L. J. (1983). Difficulties experienced by tinnitus sufferers. *Journal of Speech and Hearing disorders*, *48*(2), 150-154.

Tyler, R. (2000) Psychoacoustic measurement of tinnitus. In Tyler, R. (ed.), *Tinnitus Handbook.* Singular Thomson Learning, 149-179.

Tyler, R., Coelho, C., Tao, P., Ji, H., Noble, W., Gehringer, A., & Gogel, S. (2008). Identifying tinnitus subgroups with cluster analysis. *American journal of audiology*, *17*(2), S176-S184.

Vanneste, S., & De Ridder, D. (2012). The auditory and non-auditory brain areas involved in tinnitus. An emergent property of multiple parallel overlapping subnetworks. *Frontiers in systems neuroscience*, *6*.

Vanneste, S., & De Ridder, D. (2013). Brain areas controlling heart rate variability in tinnitus and tinnitus-related distress. *PloS one*, *8*(3), e59728.

Vanneste, S., Focquaert, F., Van de Heyning, P., & De Ridder, D. (2011). Different resting state brain activity and functional connectivity in patients who respond and not respond to bifrontal tDCS for tinnitus suppression. *Experimental Brain Research*, *210*(2), 217-227.

Vieira, D., Eikelboom, R., Ivey, G., & Miller, S. (2010). A multi-centre study on the long-term benefits of tinnitus management using Neuromonics Tinnitus Treatment. *International Tinnitus Journal*, *16*(2), 111-7.

Vogler, D. P., Robertson, D., & Mulders, W. H. (2011). Hyperactivity in the ventral cochlear nucleus after cochlear trauma. *Journal of Neuroscience*, *31*(18), 6639-6645.

Waddell, A. (2005). Tinnitus. *Clinical Evidence*, *14*(1–2), 1–10.

Weisz, N., Moratti, S., Meinzer, M., Dohrmann, K., Elbert T (2005a). Tinnitus perception and distress is related to abnormal spontaneous brain activity as measured by magnetoencephalography. *PLoS Medicine* 2(6), e153.

Weisz, N., Wienbruch, C., Dohrmann, K., & Elbert, T. (2005b). Neuromagnetic indicators of auditory cortical reorganization of tinnitus. *Brain*. 128, 2722–2731

Weisz, N., Müller, S., Schlee, W., Dohrmann, K., Hartmann, T., & Elbert, T. (2007). The neural code of auditory phantom perception. *Journal of Neuroscience*. 27, 1479-1484

Wilson, J. P. (1985). Otoacoustic emissions and tinnitus. *Scandinavian Audiology. Supplementum*, *25*, 109-119.

Wilson, P. H., Henry, J., Bowen, M., & Haralambous, G. (1991). Tinnitus Reaction Questionnaire: Psychometric properties of a measure of distress associated with tinnitus. *Journal of Speech, Language, and Hearing Research*, *34*(1), 197-201.

Wu, J. C., Gillin, J. C., Buchsbaum, M. S., Hershey, T., Johnson, J. C., & Bunney Jr, W. E. (1992). Effect of sleep deprivation on brain metabolism of depressed patients.

Tables and Figures

Table 1. Tinnitus measurement instruments and their correlations with psychoacoustic and psychological measurements and aspects of general health. (Adapted from Holgers et al., 2003)

Instruments or clinical gradings	**Correlations to Audiometry**	**Correlation to Psychology**	**Correlation to General Health**
TSQ Coles et al., 1991, Baskill et al., 1991 Erlandsson et al., 1992, Holgers & Barrena¨s, 1996, Erlandsson and Holgers, 1999	TSQ vs hearing parameters ns TSQ vs PTA 3; 4; 6 kHz moderate	 TSQ vs perceived attitudes (THSS) low TSQ vs disability/handicap (THSS) moderate TSQ vs emotional disturbances (NHP) high	Frequent headache low dizziness/vertigo low over-sensitivity to sounds low TSQ vs pain and sleep/NHP moderate

THI Newman et al., 1994, 1995, 1998	THI vs pitch and loudness low	THI vs BDI weak vs SRSL high	THI vs MSPQ weak THQ vs general health moderate
THQ Kuk et al., 1990, Newman et al., 1994, 1995, 1998, Meric et al., 1998 loudness match – ns mean heary thresholds – moderate	THQ vs loudness match ns PTA ns – moderate	THQ vs MMPIlow vs perceived loudness moderate vs depression moderate vs life satisfaction moderate	THQ vs general health moderate
TRQ Meric et al., 1998, Wilson et al., 1991		TRQ vs MMPI low	
STSS and clinical ratings (1–3) Halford et al., 1990	STSS vs loudness match at 1 kHz moderate	Clinical ratings vs STSS high	
THSS Erlandsson et al., 1992			
Helpseeking (H) Non	Pure tone thresholds lower in H than NH	More concentration	

Helpseeking (NH) Attias et al., 1995, Hallberg and Erlandsson, 1993		difficulties, irritability and psychiatric symptomatology in the H group	
AWT (+/-) Holgers et al., 2000	AWT vs hearing thresholds moderate speech recognition test ns	AWT vs emotional reactions, social isolation (NHP) high	NHP; physical immobility, sleep, pain Energy (NHP) moderate – high BMT; physical exercise

TSQ- Tinnitus Severity Questionnaire
THI- Tinnitus Handicap Inventory
THQ- Tinnitus Handicap Questionnaire
TRQ- Tinnitus Reaction Questionnaire
STSS- Subjective Tinnitus Severity Scale
H- Help-seeking
NH- Non Help-seeking
AWT- Absence from Work
NHP- Nottingham Health Profile
BDI- Beck Depression Inventory
MMPI- Minnesota Multiphasic Personality Inventory
BMI- Body Mass Index
PTA- Pure Tone Average
SRSL- Symptom Rating Scale List

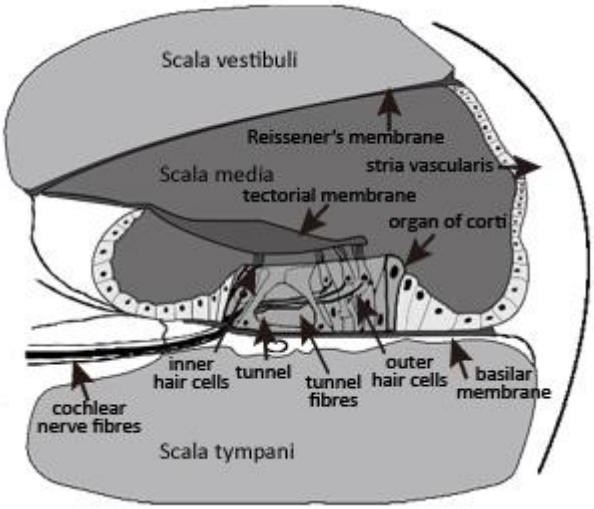


Figure 1. Cross-section of human cochlea

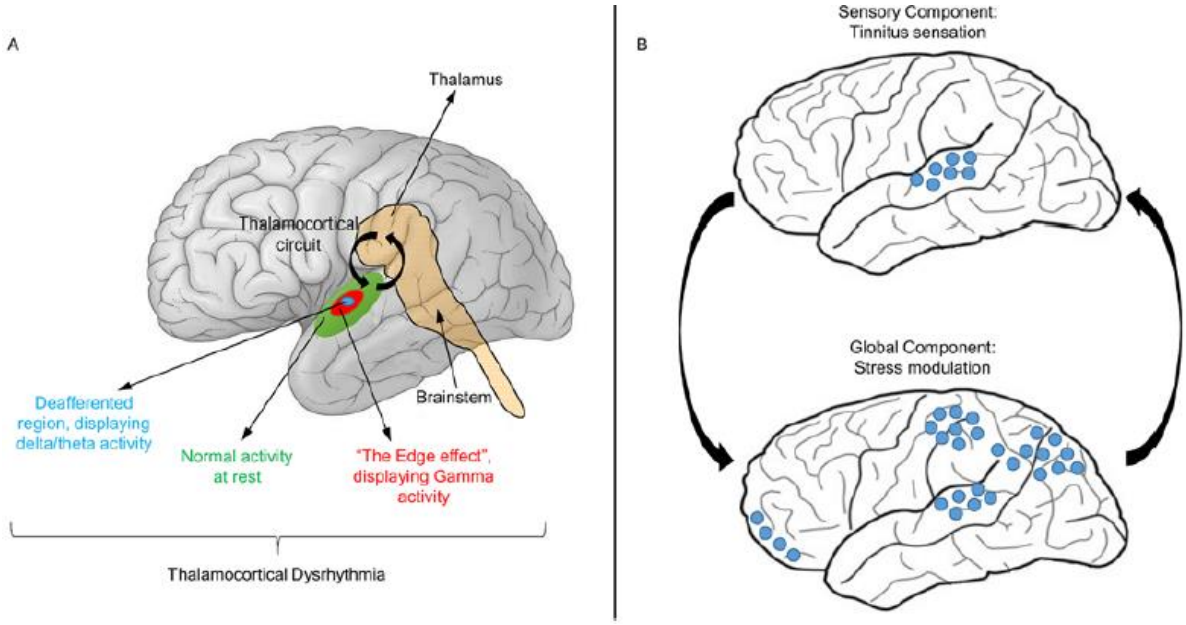


Figure 2. Neurophysiological models of tinnitus include auditory perception of tinnitus, attention and awareness of tinnitus, and emotional response to tinnitus. These are facilitated by various parts of the brain, thus involving a global component, as explained by thalamocortical dysrhythmia.

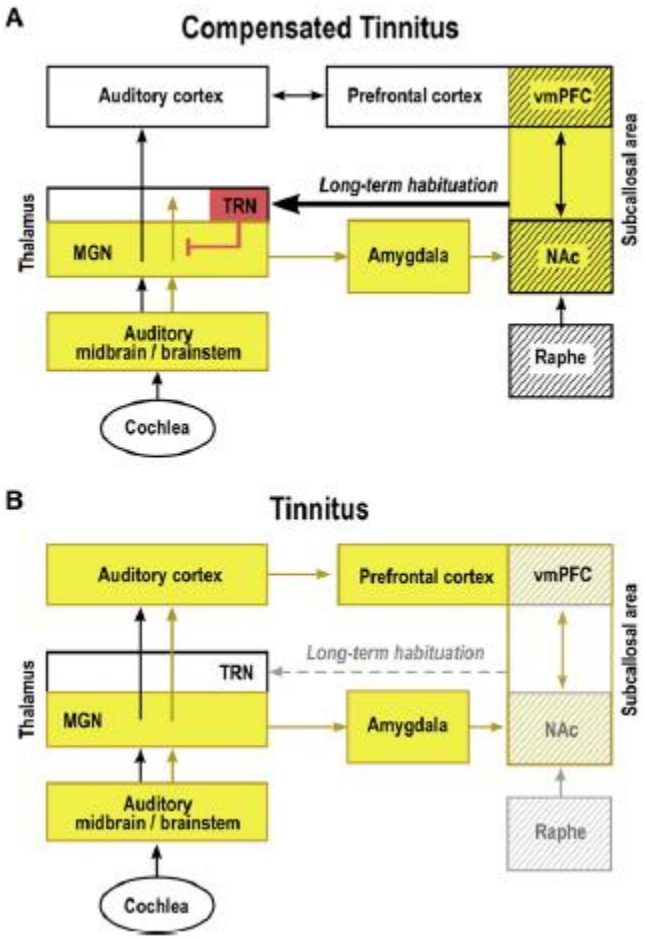


Figure 3. Tinnitus as a result of broken neural 'noise-cancellation" mechanism (Adapted from Rauschecker et al., 2010). NAc-Nucleus Accumbens; vmPFC-ventromedial prefrontal cortex; TRN-thalamo reticular nucleus; MGN-medial geniculate nucleus.

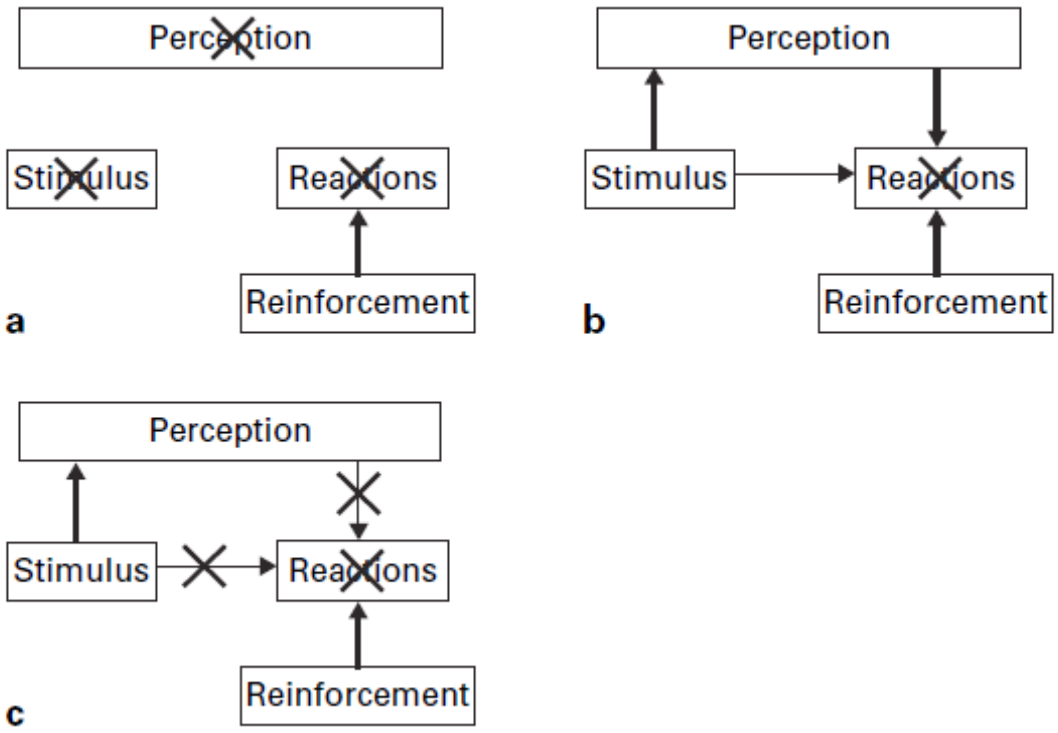


Figure 4. Three possible approaches to tinnitus treatment. **a**. Eliminating tinnitus signal yields removal of both reactions and perception. **b**. Attenuation of tinnitus-induced reactions (e.g., by psychological treatment such as CBT). **c**. Blockage of transmission of the tinnitus-related neuronal activity from auditory system removes reaction (main goal of TRT, habituation of reactions).

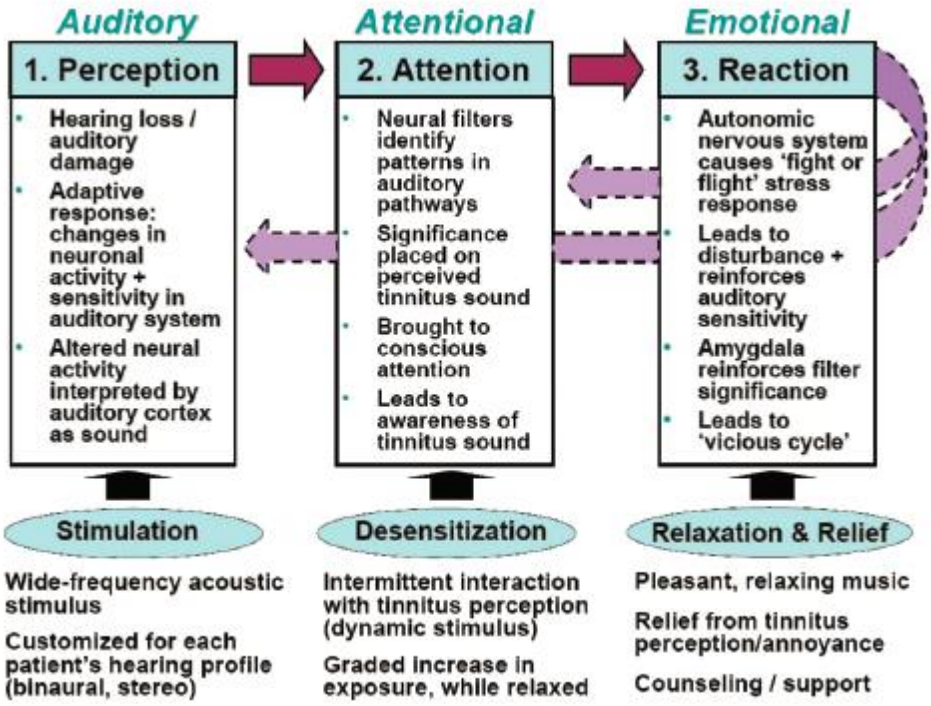


Figure 5. Schematic overview of key processes involved in the development of clinically significant tinnitus and how they are addressed by the NTT (adapted from Hanley & Davis, 2008)

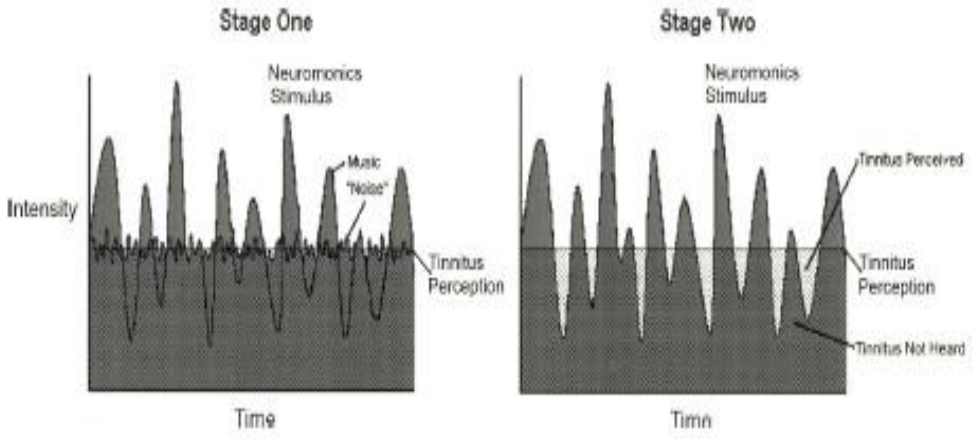


Figure 6. Schematic representation of stage-one and stage-two stimuli in relation to tinnitus perception (adapted from Davis, Paki & Hanley, 2007)

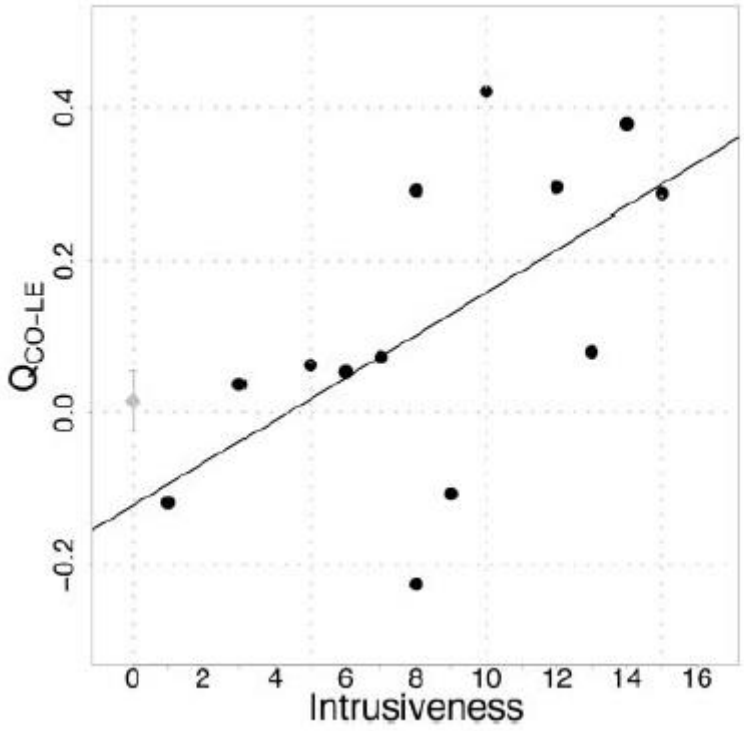


Figure 7. The enhanced activation for CO as compared to LE in the right hemisphere is correlated with tinnitus-related distress, particularly tinnitus intrusiveness. The mean (+- SE) for controls is indicated by the diamond on the y-axis (adapted from Weisz et al., 2005b)

Chapter 2: Changes in behavioural reports of tinnitus during remediation

Ankit Mathur[1, 2], Catherine McMahon[1, 2], Ronny Ibrahim[1, 2]

[1]Department of Linguistics, Faculty of Human Sciences, Macquarie University, Sydney, Australia

[2]The HEARing Cooperative Research Centre, Australia

[3]Department of Statistics, Faculty of Science and Engineering, Macquarie University, Sydney, Australia

2.1 Abstract

Tinnitus research in the past has often been marred by the lack of homogeneity of the group due to the inherent heterogeneous nature of tinnitus population. In the present study, using a restricted selection criteria to address this part, 11 tinnitus participants were selected to undergo a six months Neuromonics tinnitus treatment (NTT) program with the aim to firstly determine the effects of the treatment on behavioural measures of tinnitus and secondly to determine whether associations between the behavioural measures exist. To the authors' knowledge, this study is the first of its kind to use the tinnitus functional index (TFI) and the tinnitus reaction questionnaire (TRQ) to measure the tinnitus distress scores simultaneously (whereby the most typical measure of quantifying tinnitus distress levels using the Neuromonics program is the TRQ). In trying to unpack the relation between tinnitus distress and the behavioural measures, a series of association analyses between these two questionnaires were performed. As it was found that TRQ is highly associated with TFI scores; thereafter only TFI was used in all analyses. Pre-treatment TFI tinnitus distress scores were significantly different from post-treatment scores, showing lower distress levels. An average improvement in tinnitus distress (a reduction of tinnitus distress of more than 40%) was found after the 30 week treatment period. In addition, reductions in the perceived tinnitus loudness measured through the visual analogue scale (VAS) and tinnitus awareness were also seen post-treatment. While there was a strong association between VAS and TFI, there wasn't any association between tinnitus distress and tinnitus loudness, which may suggest that tinnitus loudness does not reflect the degree of severity of tinnitus distress. An increase in loudness discomfort levels (LDL) was also observed at the end of the treatment period, indicating an increase in sound tolerance levels in the participants, which often co-exists with hearing loss and tinnitus. The major TFI's sub-components which influence the

changes in the tinnitus distress score were *intrusiveness, sleep, relaxation and quality of life*. These results demonstrate a significant improvement in complaints of tinnitus distress and tinnitus perception in the participant group, measured using questionnaires and behavioural tests, and the sub-components of tinnitus that show maximum improvement. It is recommended that future research focus on specialised tests of these sub-components to identify the effect of these on tinnitus distress during remediation, and also evaluated the impact of other tinnitus treatment programs such as cognitive behavioural therapy on these sub-components.

2.2 Introduction

Chronic tinnitus is characterised by phantom perception of a pure tone or noise in the absence of a real sound, often associated with stress, depression, and inability to sleep (Sanchez & Stephens, 1997; Budd & Pugh, 1995). People suffering from tinnitus often form a very heterogeneous group since tinnitus could be associated with other ear and health related disorders such as otosclerosis (75%; Glasgold & Altmann, 1966), acoustic neuromas (83%; House & Brackman, 1981), prescribed medication, past/current history of coronary heart disease, and knee joint pain requiring medical consultation (Michikawa et al., 2010). Initial studies of tinnitus were mainly focused on identifying the type (objective or subjective tinnitus), quality (tonal or non-tonal), or duration (acute or chronic) tinnitus. Furthermore, tinnitus studies focussed on the behavioural measures of tinnitus in an attempt to measure the severity of tinnitus distress using questionnaires such as tinnitus handicap index (THI; Newman, Jacobson & Spitzer, 1996), tinnitus reaction questionnaire (TRQ; Wilson et al., 1991), and others. An attempt has always been made to understand the source of tinnitus, and the plausible explanations have ranged from superstitions ("witch ear") to various models of tinnitus, as discussed in chapter 1.

While various methods exist to identify the severity of tinnitus, the two that appear most relevant from the patient's perspective are tinnitus distress and tinnitus loudness. Tinnitus distress usually is a sum total of various problems experienced by tinnitus sufferers such as anxiety, depression, insomnia and concentration difficulties (Andersson, 2002; Tyler & Baker, 1983). The TRQ was developed by Wilson et al. (1991), and was reported to provide a useful index of distress related to tinnitus for subject selection and clinical assessment with good test-retest reliability. Since the TRQ was developed to identify tinnitus distress in

patients, such a questionnaire was also utilised to evaluate the improvement in tinnitus distress during treatment, more specifically to identify the efficacy of treatment, and also to compare the outcome of various treatment programs. TFI was developed over a period seven years by Meikle et al. (2011) with a documented validity both for scaling the severity and negative impact of tinnitus for use in intake assessment and for measuring treatment-related changes in tinnitus. The TFI appears to be gradually gaining importance due to its sensitivity and usefulness in identifying well-defined 8 components of tinnitus distress or disturbance (i.e. *intrusiveness, sense of control, cognitive, sleep, auditory, relaxation, quality of life*, and *emotional* effects of tinnitus). In a recently published study, Henry et al. (2016) have the confirmed sensitivity of the TFI along with its subscales, and because of its demonstrated responsiveness to treatment-related change, comprehensive coverage of the domains of tinnitus impact, and other psychometric properties the TFI is showing promise as a standard instrument for both clinical and research settings. TFI has been demonstrated to have a high internal consistency and reliability, and shows high correlations with THQ, THI, and moderate correlations with VAS and BDI, although its efficacy as a measure of change has been questioned due to a floor effect in some items (Fackrell et al., 2016), and warrants further independent replication.

Alternatively, tinnitus loudness can be recorded to quantify the tinnitus distress. This is either measured as self-perceived loudness levels on a visual analogue scale (VAS) or by tinnitus loudness (TL) balance by presenting an external, pitch matched sound. TL measurement have been found to be an ineffective method of measuring tinnitus distress, as TL has been observed to underestimate the perceived loudness, and hence undermine the distress associated with tinnitus e.g. Graham (1960) in his PhD thesis reported that 75.3% of 73

tinnitus patients had TL < 10 dB SL, while Vernon and Schleuning (1978) reported that in 513 tinnitus patients with severe tinnitus, the loudness of tinnitus was usually measured at 5-10 dB SL. This has been attributed to recruitment, the abnormal rise of loudness levels, which is often associated with hearing loss (Tyler & Corad-Armes, 1983). On the contrary, VAS was reported to significantly correlate with instruments measuring tinnitus handicap and distress (Figueiredo, Azevedo, & Oliveira, 2009). Other measures of tinnitus that are frequently used include masking levels (broadband and narrowband masking levels), although these have not been identified as a measure of tinnitus distress, and are rather used to determine the masking levels required for masking treatments such as tinnitus maskers (Smith et al., 1991).

With the advent of various imaging techniques, currently, the aim of tinnitus researchers is to identify the precise location of brain areas that are associated with tinnitus, and relationship between these areas (Weisz et al., 2005a, 2005b, 2007; Schlee et al., 2009). Studies aiming to identify the cortical changes in tinnitus patients have highlighted the variability in the participant characteristics employed in tinnitus research. For example, Weisz and colleagues (2005a) included participants with unilateral or bilateral tinnitus of any degree with symmetrical or asymmetrical hearing loss, while Llinas and colleagues (1999) included a heterogeneous group that consisted of subjects suffering from various neuropsychiatric disorders that included only one tinnitus patient. Similarly, Mühlnickel and colleagues (1998) included a group of participants that had either unilateral or bilateral tinnitus, which could have influenced the degree of cortical changes and also the cortical areas involved in unilateral versus bilateral tinnitus patients as reported by Smits et al. (2007).

Cortical reorganisation as a result of cochlear hearing loss has been reported (Dietrich et al., 2001, McDermott et al., 1998); hence, it is ideal to segregate tinnitus patients from individuals with hearing loss to study tinnitus-related cortical activity. However, it is rare to find tinnitus sufferers without any hearing loss – such subjects comprised 8% of the tinnitus subjects of Barnea et al. (1990) over a period of 3 years, and 55 of 744 (~7.5%) tinnitus subjects according to Sanchez et al. (2005). The presence of hidden hearing loss (i.e. reduced amplitude of wave I of auditory brainstem response in response to supra-threshold stimuli) has been reported in tinnitus patients without measurable hearing loss (Schaette & McAlpine, 2011). Elevated activation of the primary auditory cortex in tinnitus patients with normal hearing (observed by fMRI) has also been reported (Gu et al., 2010), thereby demonstrating changes at the cortical level even in normal hearing individuals with tinnitus. Since most tinnitus patients only undergo routine audiometry, and are generally not tested for auditory brainstem response or fMRI, it is not difficult to imagine that the actual percentage of tinnitus sufferers with normal hearing could be lesser than that reported by Barnea et al. (1990) and Sanchez et al. (2005).

Although the reported prevalence of tinnitus is between 10-15% in general population (Fujii et al., 2011; Kvestad et al, 2010), a significantly higher prevalence has been reported in clinical populations with hearing loss (85%; Fowler, 1944) with an 11% increased likelihood of reporting tinnitus for each 10 dB increase in four-frequency (500 Hz-4 kHz) pure tone average (Sindhusake et al., 2003). Hearing loss has been reported to be the single greatest risk factor for the prevalence of tinnitus (Nondahl et al., 2002). The present study is a part of a larger study with the primary aim to identify cortical changes in tinnitus patients during a 30 week NTT program (chapters 3-5). In this chapter, we will discuss the behavioural measures and treatment related changes in them.

2.3 Method

Participant recruitment

Participants for the study were recruited by publishing advertisements in local newspapers, and interested candidates contacted the main experimenter via phone or e-mail. An informal screening was conducted on phone and participants were excluded based on the presence or absence of tinnitus and duration of tinnitus. An initial information consent form for tinnitus research and another one for brain imaging using Magnetoencephalography (MEG) was sent out to perspective participants, along with questionnaires including Iowa tinnitus history inventory, MEG candidacy questionnaire, past tinnitus treatment and tinnitus reaction questionnaire (TRQ).

Participants were initially selected based on two main criteria:

1. Neuromonics' minimum criteria for acceptance to their treatment program, i.e., a minimum TRQ score of 17 at the time of screening, and
2. MEG acceptability criteria i.e., no metal implants in the head and neck region.

Selected participants had a complaint of tinnitus for at least 12 months and had not undergone any treatment prior to this study. Also, applicants with unilateral tinnitus were excluded to avoid the laterality effects it may have on cortical activity.

Participants were then screened at Macquarie Speech and Hearing Clinic. Tests included a hearing evaluation (air conduction and bone conduction thresholds at 250Hz to 8 kHz), Modified Mini Screen (MMS) designed to identify persons in need of assessment for mood disorders, anxiety disorders and psychotic disorders (developed by New York State Office of

Alcoholism and Substance Abuse Services), the Beck Depression Inventory (BDI; Beck and Steer, 1984) and the World Health Organization-Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST; Humeniuk et al., 2008). Subjects with a four frequency pure tone average of ≥ 50 dBHL, or with middle ear pathology (conductive component) were ruled out. None of the participants that applied for participation had high MMS, BDI or WHO-ASSIST scores, which were criteria for rejection. Subjects thus selected were invited for a complete hearing and tinnitus evaluation and MEG imaging of their brains. A copy of the questionnaires is attached in the appendix.

Objective and subjective tests were conducted at five time points related to the commencement of the tinnitus remediation program: pre-treatment (week zero), week 5, week 10, week 20 and week 30. Week 30 marked the end of the NTT. Participants also completed two questionnaires at each time point to measure the severity of tinnitus distress, i.e. TRQ and TFI.

A complete hearing evaluation was also conducted. This involved a hearing test conducted within a sound proof room using the standard Hughson-Westlake procedure (air conduction thresholds at octave frequencies between 250 -12,000 Hz and bone conduction thresholds between 500 – 4,000 Hz; Carhart & Jerger, 1959), tympanometry and reflexometry, which helped to rule out conductive component. Lastly, tinnitus evaluation was conducted which included tinnitus pitch matching, tinnitus loudness balancing, broadband noise and narrowband noise minimum masking level (MML), and loudness discomfort levels. The procedures for these tests are discussed below.

Tinnitus pitch match: In general, the test ear was the ear contralateral to the predominant or

louder tinnitus ear, if a difference existed between the two sides. If the tinnitus was equally loud on both sides or was localised in the head, the test ear was the one with the better hearing threshold (based on pure tone average for 500 Hz, 1 kHz and 2 kHz). A two-alternative forced-choice (2AFC) method was used, in which pairs of tones were presented and subjects were asked to identify which one best matched the pitch of their tinnitus. Test frequencies were typically multiples of 1 kHz. Before each tone pair was presented, each tone was adjusted to a loudness level equivalent to that of the tinnitus (see details of loudness-matching). After establishing the loudness settings (in dB) for a given pair of tonesthe two tones were presented alternately until the subject indicated which one was closest to the pitch of the tinnitus.

Tinnitus loudness balance: The test ear was normally the contralateral ear, as described in the procedure for tinnitus pitch matching. As indicated there, a loudness match for the subject's tinnitus was obtained at the frequency obtained as tinnitus pitch match. The loudness-matching technique involved the following steps at the frequency of interest:

i. Subject's thresholds were determined at that frequency in 1 dB steps.
ii. The sound level was then increased in small steps (typically 1 dB) until the subject reported that the external tone was just equal in loudness to their tinnitus. It is important to start with a test tone that is below the subject's threshold and use only an ascending series of intensity levels, in order to minimise residual inhibition.
iii. The dB level of the loudness match was recorded in dB SL (sensation level, i.e. dB above threshold).
iv. Steps i-iii were repeated as necessary to confirm the reliability of the measure at that frequency.

Broadband noise and narrowband noise minimum masking level (MML): This test attempted to determine the lowest level at which a standard band of noise "covered" the tinnitus (i.e. rendered it inaudible). The test ear was typically on the side with the louder or predominant tinnitus; if there was no difference between the sides, then the ear with the lower hearing threshold was considered as the dominant ear. The test stimulus consisted of a standardised band of noise. The participant's threshold for the noise band was measured in dB SL, and the level of the noise band was then increased in 1 dB increments until the participant reported that the tinnitus was no longer audible (up to the limits of the equipment or the participant's tolerance level, whichever was reached first). The level at which the tinnitus was just rendered inaudible was recorded in dB SL and was referred to as the minimum masking level (MML). This process was carried out for both broad band noise (BBN) and narrow band noise (NBN; at tinnitus pitch).

Loudness Discomfort Level (LDL): LDL testing was done at 500 Hz, 1 kHz and 4 kHz using an intermittent tone. The specific instructions were “we want to go past ‘too loud’ to where it would actually be uncomfortable;” “This is not an endurance test;” “I will stop immediately when you tell me that it is enough;” “Try to hold on as long as possible;” “This test cannot do any permanent damage to your hearing or permanently make your hearing worse” (Jastreboff & Hazell, 2004). The Neuromonics tinnitus treatment loudness measurement protocol has response options on paper, reflecting a 9-point ascending scale. The printed options are: Very soft, soft, comfortable but slightly soft, comfortable, comfortable but slightly loud, loud but OK, uncomfortably loud, extremely uncomfortable, and painfully loud. The continuously presented intermittent ones were slowly and consistently increased in 5-dB steps until the participant indicated that the tone was uncomfortably loud. At that point, the level was

reduced by 10 dB, and then increased again in 2 dB steps until the uncomfortably loud level was confirmed. The procedure was then repeated for other frequencies.

Participants were also asked to rate three other aspects of tinnitus:

1. Loudness of tinnitus as perceived by the participants on a scale of zero to ten.
2. The percent of time they were aware of their tinnitus on a scale of zero to 100 percent in steps of 10%.
3. The percent of time their tinnitus was disturbing. This data was stored as tinnitus awareness and tinnitus disturbance score.

Pre-treatment hearing test results and results of tinnitus evaluation were used by Neuromonics to customize the broadband signal using a proprietary sound modulation formula. Details of NTT program are discussed in Chapter 1.

2.4 Results

The assessment of psychoacoustic characteristics of tinnitus, which demonstrates perceived or self-reported changes in tinnitus characteristics during treatment, was important since the present study intended to identify treatment-related changes in tinnitus characteristics and cortical activity. Various behavioural measures were employed to determine the effect of treatment, which included tinnitus-related distress, as measured by TRQ and TFI, subjective loudness perception, as measured by VAS, and objective tinnitus loudness balance (TL).

Firstly, the most important factor was the changes in tinnitus distress with treatment, demonstrated in Figure 2 showing a constant reduction in tinnitus distress over treatment

duration. This reduction in distress from pre-treatment to post-treatment was demonstrated by both TFI and TRQ (see Figure 3). There was a strong association between the TFI and TRQ measures ($R^2 = 0.6763$; $p<0.01$) demonstrating that TRQ, though not designed to measure changes in tinnitus score during treatment, can be used with some degree of confidence to evaluate the efficacy of a treatment program (Figure 4). In the present study, both TRQ and TFI scores indicated an overall improvement in tinnitus distress during the 30 weeks of treatment (Figure 3).

VAS, which was used to identify the perceived tinnitus loudness on a scale of zero to ten, also demonstrated a constant reduction in perceived tinnitus loudness (Figure 5) and also strongly associates with TFI scores (Figure 6a). This was in contrast with tinnitus loudness balance which showed a weak association with tinnitus distress (Figure 6b).

Participants were also asked to report on the percentage of time they were aware of tinnitus, and were disturbed by tinnitus. Trends show a reduction in both awareness and disturbance pre- and post-treatment though the reduction was not linear (Figure 7a). Both, tinnitus awareness scores and tinnitus distress scores were strongly associated with TFI scores (Figure 7b). Furthermore, out of the eight sub-components of TFI described above, *intrusive, sleep, relaxation,* and *quality of life* components demonstrated a strong association with tinnitus distress (Figure 8).

Finally, the results also demonstrated increased tolerance to loud sound as measured using LDLs during the treatment, with the final LDL scores being significantly higher than pre-treatment values (mean change: 7.2 dB; Figure 9).

MML results did not show significant changes or pattern throughout the treatment and are not presented in this study.

Coefficient of determination (R^2) was calculated to identify the association between various measures, and are reported in the figures, and paired t-test was used to identify if the changes pre- and post- treatment are significant. Regression analysis was conducted to study the relationship between various behavioural measures.

2.5 Discussion

Tinnitus can affect people at various ages, co-occurring with different pathologies, and by itself, is a very heterogeneous group in nature. An attempt was made to select a less heterogeneous group of participants that are controlled in hearing levels with 4 frequency PTA < 50 dB HL (consistent with the selection criteria for Neuromonics treatment) thereby limiting the likelihood of hearing loss induced cortical changes, tinnitus duration (chronic tinnitus), tinnitus laterality (bilateral tinnitus), tinnitus severity (> 17 on TRQ scale at the time of screening), as well as suitability for MEG testing (no metal implants in the head and neck region). Apart from these, subjects with significant psychosis, depression, and cognitive incapacity were also excluded. Claustrophobia and inability to remain still for long durations due to physical conditions (both of which were imperative for MEG testing), also acted as a deterrent to subject selection, while commitment to treatment for six months also reduced the number of potential subjects. The small participant group available in the end was as homogenous as was possible considering the restraints of the selection criteria.

The apparent outcome of a tinnitus treatment can be influenced by the specificity of the tool measuring those outcomes, hence they are heavily dependent on the method used to measure tinnitus and tinnitus-related distress. The importance of the issue can be gauged by the fact that Tyler (1999) recommended the use of three handicap measurement tools when validating any clinical trial of intervention for tinnitus. However, the time taken and the necessary effort

from the patient that would need to go into such a process, as well as the overlap in concepts assessed, renders it unnecessarily prohibitive. This process can be simplified by the use of standardised and universally accepted tinnitus questionnaires. The principal reason for using measures of tinnitus distress, (i.e. TRQ and TFI), was to measure the outcome of Neuromonics treatment (Figure 4). While there are many tinnitus remediation programs and pharmaceutical options available, only some of them are regularly prescribed in clinical settings. The most popular and successful of these include Tinnitus Retraining Therapy (TRT), cognitive behavioral therapy (CBT, modified for tinnitus) and Neuromonics treatment. Jastreboff and Jastreboff (2000), the main proponents of TRT, have reported a 75% success rate using TRT alone, and a 64- 84% effectiveness, reported in McKinney's PhD thesis, which used TRT with sound generators. No significant differences in subjective tinnitus loudness were found between tinnitus participants undergoing CBT and a control group (tinnitus subjects not undergoing CBT). The success rate of Neuromonics treatment (as measured using TRQ) is reported to be at least 40%, with a mean improvement of 65% in at least 80% of the participants (i.e. > 40% reduction in reported tinnitus distress in over 80% of participants). In the present study, 7 out of 11 participants (63.6%) that completed the treatment showed over 40% improvement (i.e. > 40% reduction in self-reported tinnitus distress) with a mean improvement of 54.6% according to TRQ scores. The TFI results were also similar, with 6 out of 10 participants (60%) having > 40% reduction in distress with a mean improvement of 46.7%. The results of the present study demonstrate that Neuromonics treatment can substantially decrease tinnitus distress. The improvements were somewhat lower than reported by Davis, Paki and Hanley (2007), and emphasize on the need of independent review on the success rate of the NTT. Once again, these results highlight the similarity in outcomes of TFI and TRQ which has not been reported elsewhere. The present study is first of its kind which has employed both TFI and TRQ to evaluate tinnitus distress

and documented changes in tinnitus distress score throughout a treatment program. The TFI was developed to overcome the limitations of existing tinnitus questionnaires, and mainly focuses on the identification of treatment-induced changes in tinnitus distress (Meikle et al. 2012).

Also, it is worth noting that TFI scores in Figure 2 appear to demonstrate a steeper improvement during the first 10 weeks of the treatment. This coincides with the first stage of the Neuromonics treatment whereby a masking noise is embedded in the spectrally modified music. The purpose of stage 1 is to reduce tinnitus related distress by fully masking the tinnitus percept, thereby aiming to improve relaxation and reduce the negative emotional reaction towards the tinnitus to a neutral reaction by targeting the limbic system mediated secondary reaction that is believed to be a major contributor to tinnitus disturbance (Davis et al., 2007). Improvements in tinnitus distress is less prominent in stage 2, the purpose of which is to desensitize the individual to the tinnitus percept through a process of habituation (Davis et al., 2007). It is not surprising that more improvement is seen during the masking stage, as it provides more sense of control when using the device, thereby improving relaxation while using the device. However, previous studies have demonstrated that complete masking provides only temporary relief from the percept (Vernon, Griest & Press, 1990). On the other hand, the main aim of the NTT is to maintain the levels of relief from the distress produced by tinnitus, therefore this therapy uses a model of partial masking to maximise opportunities for habituation. It will be interesting in a future study to evaluate the NTT using two different methods, one using the standard protocol and the other using the masking noise throughout the treatment provides greater relief to the patients, and if this relief is lasting due to the dependency on masking noise throughout the treatment.

While the validity of TFI in Australian population has not yet been tested, TFI results did strongly correlate with TRQ scores, as discussed above, which was developed in Australia by Wilson et al. (1991) and was reported to have very good test-retest reliability (r= .88) and internal consistency (Cronbach's alpha= .96). It is recommended that a study dedicated to find the validity of TFI in Australian population be conducted since we found it to be a useful tool in studying the improvements in tinnitus distress during treatment.

Baskill and Coles (1999) have reported a weak correlation between various methods of measuring tinnitus loudness, which can be attributed to recruitment (which causes an abnormal level of loudness perception) thus rendering TL an unhelpful method of measuring tinnitus-related stress. On the other hand, VAS is a direct representation of subject's perception of tinnitus loudness. In the past, studies have used the term TL while reporting results of a self-reported analogue scale of tinnitus loudness perception, e.g. Van der Loo et al. (2009) reported a relationship between tinnitus loudness and cortical resting state gamma power. Here, TL was used to denote subjective tinnitus loudness as reported using VAS, and was not objective tinnitus loudness measured using a comparative method. In the present study, it was observed that TL and VAS, which were both measures of tinnitus loudness, did not associate with each other thus indicating that the two were indeed not measuring the same attribute of tinnitus. Further, strong association were observed between VAS and tinnitus distress, while these were absent between TL and tinnitus demonstrating that participant's perception of loudness was a better representation of the distress it caused rather than an externally loudness matched sound. Adamchic et al. (2012) have reported similar findings, with a strong correlation between VAS (loudness) and tinnitus distress, and also a strong

correlation between VAS (tinnitus awareness) and tinnitus distress. These results may help to explain the low correlation between subjectively perceived tinnitus loudness and tinnitus balance. While TL procedures mainly rely on sensory judgments, the rating of subjectively perceived tinnitus loudness presumably depend on emotional and cognitive connotations so it is likely that different phenomena are being measured (Adamchic et al., 2012).

As discussed earlier, the TFI focuses on the eight factors to measure changes in the various components of tinnitus that cause distress, with an effort to be sensitive to the changes in each component during various treatments. These factors were *intrusiveness, sense of control, cognitive, sleep, auditory, relaxation, quality of life*, and *emotional* effects of tinnitus. Of these 8 factors, only 4 factors, viz. intrusiveness, sleep, relaxation and quality of life showed significant correlations with tinnitus distress scores measured using TFI (Figure 8), indicating that these factors contribute towards tinnitus distress. Results also indicated a strong association between tinnitus awareness and tinnitus distress scores, as is evident from Figure 7b. Based on De Ridder's modification of the TCD model (De Ridder et al., 2011), phantom percept results from sensory de-afferentation and reach awareness only when increased neuronal activity in the primary sensory cortex is connected to a larger co-activated awareness or global workspace brain network, involving frontal and parietal areas. Thus reduced awareness, associated with decreased tinnitus distress, indicates a reduction in neural activity, as well as improved inhibitory network resulting in decreased awareness of the phantom perception.

Finally, an increase in LDLs was observed in across all participants between pre- and post-treatment measures. LDLs are an index of the patient's tolerance of louder sounds and are frequently quite reduced in tinnitus patients. LDLs are considered to reflect how much 'central auditory gain' is present in an individual (Hazell, Sheldrake & Graham, 2002). Improvements in sound tolerance levels in tinnitus patients using sound based tinnitus treatment has been reported by Gold et al. (2002) using tinnitus retraining therapy, and Davis, Paki & Hanley (2007) using NTT. The improvement in LDL possibly reflects a gradual process of neuro-plastic change (Davis, Paki & Hanley, 2007) due to sound enrichment, by providing acoustic signals that are tailored to correct for hearing loss, so that stimulation is provided across the broadest possible range of neurons (Eggermont, 2006).

The results from the present study demonstrate that NTT can be used to successfully alleviate complaints of tinnitus distress. Though the improvement was observed in fewer participants than what is predicted by the makers, the small number of participants in the study make it an unfair assessment of the NTT program. Based on the present results, it can be suggested that TFI is a robust measure of tinnitus distress and sensitive to changes in distress, but further validation in Australian population is highly recommended.

Author contributions

Conceived and designed the experiments: CMM, AM. Performed the experiments: AM. Analysed the data: AM RKI. Wrote the paper: AM CMM RKI. Delivered the tinnitus treatment program: AM.

References

Adamchic, I., Langguth, B., Hauptmann, C., & Tass, P. A. (2012). Psychometric evaluation of visual analog scale for the assessment of chronic tinnitus. *American Journal of Audiology*, *21*(2), 215-225.

Andersson G. (2002). Psychological aspects of tinnitus and the application of cognitive-behavioral therapy. *Clinical Psychology Review*. 22, 977–90.

Barnea, G., Attias, J., Gold, S., & Shahar, A. (1990). Tinnitus with normal hearing sensitivity: extended high-frequency audiometry and auditory-nerve brain-stem-evoked responses. *Audiology*, *29*(1), 36-45.

Baskill, J.L., Coles, R.R.A. (1999). Relationships between tinnitus loudness and severity. In: J.W.P. Hazell. (Eds). *Proceedings of the Sixth International Tinnitus Seminar.* Cambridge UK: The Tinnitus and Hyperacusis Centre London, 424-428.

Budd, R. J., Pugh, R. (1995). The relationship between locus of control, tinnitus severity, and emotional distress in a group of tinnitus sufferers. *Journal of Psychosomatic research*. 39, 1015-1018.

Carhart, R., & Jerger, J. (1959). Preferred method for clinical determination of pure-tone thresholds. *Journal of Speech & Hearing Disorders*.

Davis, P. B., Paki, B., & Hanley, P. J. (2007). Neuromonics tinnitus treatment: third clinical trial. *Ear and hearing*, *28*(2), 242-259.

Dietrich, V., Nieschalk, M., Stoll, W., Rajan, R., & Pantev, C. (2001). Cortical reorganization in patients with high frequency cochlear hearing loss. *Hearing research*, *158*(1), 95-101.

Eggermont, J. J. (2006). Cortical tonotopic map reorganization and its implications for treatment of tinnitus. *Acta Oto-Laryngologica*, *126*(sup556), 9-12.

Fackrell, K., Hall, D. A., Barry, J. G., & Hoare, D. J. (2016). Psychometric properties of the Tinnitus Functional Index (TFI): Assessment in a UK research volunteer population. *Hearing research*, *335*, 220-235.

Figueiredo, R. R., Azevedo, A. A. D., & Oliveira, P. D. M. (2009). Correlation analysis of the visual-analogue scale and the Tinnitus Handicap Inventory in tinnitus patients. *Revista Brasileira de Otorrinolaringologia*, *75*(1), 76-79.

Fowler, E. P. (1948). Nonvibratory tinnitus: Factors underlying subaudible and audible irritations. *Archives of otolaryngology*, *47*(1), 29-36.

Fujii, K., Nagata, C., Nakamura, K., Kawachi, T., Takatsuka, N., Oba, S., & Shimizu, H. (2011). Prevalence of tinnitus in community-dwelling Japanese adults. *Journal of Epidemiology*, *21*(4), 299-304.

Gold, S., Formby, C., Frederick, E. A., Suter, C., & Patuzzi, R. (2002). Shifts in loudness discomfort level in tinnitus patients with and without hyperacusis. In *Proceedings of the Seventh International Tinnitus Seminar* (pp. 170-2).

Graham, J. T. (1960). *An Analysis of Certain Psychophysical Parameters of Tinnitus Aurium*. Division of Speech Pathology and Audiology, Stanford University.

Hanley, P. J., & Davis, P. B. (2008). Treatment of tinnitus with a customized, dynamic acoustic neural stimulus: underlying principles and clinical efficacy. *Trends in amplification, 12*(3), 210-222.

Hazell, J. W. P. (2002). Decreased sound tolerance: predisposing factors, triggers and outcomes after TRT. In *Proceedings of the Seventh International Tinnitus Seminar 2002. University of Western Australia, Perth* (pp. 255-261).
Henry, J. A., Griest, S., Thielman, E., McMillan, G., Kaelin, C., & Carlson, K. F. (2016). Tinnitus Functional Index: Development, validation, outcomes research, and clinical application. *Hearing Research*, *334*, 58-64.

Humeniuk, R., Ali, R., Babor, T. F., Farrell, M., Formigoni, M. L., Jittiwutikarn, J., De Lacerda, R.B., Ling, W., Marsden, J., Monteiro, M. & Nhiwatiwa, S. (2008). Validation of the alcohol, smoking and substance involvement screening test (ASSIST). *Addiction, 103*(6), 1039-1047.

Jastreboff, P. J. &. Jastreboff M. M (2000). Tinnitus Retraining Therapy (TRT) as a method for treatment of tinnitus and hyperacusis patients. *Journal of the American Academy of Audiology.* 11(3), 162-177.

Kado, H., Higuchi, M., Shimogawara, M., Haruta, Y., Adachi, Y., Kawai, J., Ogata, H., & Uehara, G. (1999). Magnetoencephalogram systems developed at KIT. *Applied Superconductivity, IEEE Transactions on, 9*(2), 4057-4062.

Kvestad, E., Czajkowski, N., Engdahl, B., Hoffman, H.J., & Tambs, K. (2010). Low heritability of tinnitus: Results from the second Nord-Trondelag Health Study. *Archives of Otolaryngology - Head and Neck Surgery, 136 (2),* 178-182.

Llinás, R. R., Ribary, U., Jeanmonod, D., Kronberg, E., & Mitra, P. P. (1999). Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proceedings of the National Academy of Sciences, 96*(26), 15222-15227.

McDermott, H. J., Lech, M., Kornblum, M. S., & Irvine, D. R. (1998). Loudness perception and frequency discrimination in subjects with steeply sloping hearing loss: Possible correlates of neural plasticity. *Journal of the Acoustical Society of America, 104*(4), 2314-2325.

McKinney, C.J., Hazell, J.W.P., Graham, R.L. (1999). An evaluation of the TRT method. In J. Hazell (Ed.). *Proceedings of the 6th International Tinnitus Seminar*, Cambridge, UK, THC, London (pp. 99-105).

Meikle, M. B., Henry, J. A., Griest, S. E., Stewart, B. J., Abrams, H. B., McArdle, R., Myers, P. J., Newman, C. J., Sandridge, S., Turk, D. C., Folmer, R. L., Frederick, E. J., House, J. W.,

Jacobson, G. P., Kinney, S. E., Martin, W. H., Nagler, S. M., Reich, G. E., Searchfield, G., Sweetow, R. & Vernon, J. A. (2012). The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus. *Ear and hearing*, *33*(2), 153-176.

Michikawa, T., Nishiwaki, Y., Kikuchi, Y., Saito, H., Mizutari, K., Okamoto, M., & Takebayashi, T. (2010). Prevalence and factors associated with tinnitus: a community-based study of Japanese elders. *Journal of Epidemiology*, *20*(4), 271-276.

Mühlnickel, W., Elbert, T., Taub, E., & Flor, H. (1998). Reorganization of auditory cortex in tinnitus. *Proceedings of the National Academy of Sciences*, *95*(17), 10340-10343.

Newman, C. W., Jacobson, G. P., & Spitzer, J. B. (1996). Development of the tinnitus handicap inventory. *Archives of Otolaryngology–Head & Neck Surgery*, *122*(2), 143-148.
Nondahl, D. M., Cruickshanks, K. J., Wiley, T. L., Klein, R., Klein, B. E., & Tweed, T. S. (2002). Prevalence and 5-year incidence of tinnitus among older adults: the epidemiology of hearing loss study. *Journal of the American Academy of Audiology*, *13*(6), 323-331.

Sanchez, T. G., Medeiros, Í. R. T. D., Levy, C. P. D., Ramalho, J. D. R. O., & Bento, R. F. (2005). Tinnitus in normally hearing patients: clinical aspects and repercussions. *Revista Brasileira de Otorrinolaringologia*, *71*(4), 427-431.

Sanchez, L., & Stephens, D. (1997). A tinnitus problem questionnaire in a clinic population. *Ear and Hearing*, *18*(3), 210-217.

Schlee, W., Hartmann, T., Langguth, B., & Weisz, N. (2009). Abnormal resting-state cortical coupling in chronic tinnitus. *BMC Neuroscience*, *10*(1), 11.

Smith, P. A., Parr, V. M., Lutman, M. E., & Coles, R. R. A. (1991). Comparative study of four noise spectra as potential tinnitus maskers. *British Journal of Audiology*, *25*(1), 25-34.

Smits, M., Kovacs, S., De Ridder, D., Peeters, R. R., Van Hecke, P., & Sunaert, S. (2007). Lateralization of functional magnetic resonance imaging (fMRI) activation in the auditory pathway of patients with lateralized tinnitus. *Neuroradiology*, *49*(8), 669-679.

Sindhusake D, Golding M, Newall P, Rubin G, Jakobsen K, & Mitchell P. (2003) Risk Factors for Tinnitus in a Population of Older Adults: The Blue Mountains Hearing Study. *Ear & Hearing*., 24(6), 501-507.

Tyler RS. The use of science to find successful tinnitus treatments. . In J. Hazell (Ed.). *Proceedings of the 6th International Tinnitus Seminar*, Cambridge, UK, THC, London (pp. 3-9).

Tyler, R. S., & Baker, L. J. (1983). Difficulties experienced by tinnitus sufferers. *Journal of Speech and Hearing disorders*, *48*(2), 150-154.

Tyler, R.S., & Gonrad-Armes, D. (1983). The determination of tinnitus loudness considering the effects of recruitment. *Journal of Speech and Hearing. Research,* 26 (1983) 59-72.

Uehara, G., Adachi, Y., Kawai, J., Shimogawara, M., Higuchi, M., Haruta, Y., Ogata, H., & Hisashi, K. (2003). Multi-channel SQUID systems for biomagnetic measurement. *IEICE Transactions on Electronics, 86*(1), 43-54.

Van Der Loo, E., Gais, S., Congedo, M., Vanneste, S., Plazier, M., Menovsky, T., Heyning, P. V., & De Ridder, D. (2009). Tinnitus intensity dependent gamma oscillations of the contralateral auditory cortex. *PLoS One, 4*(10), e7396

Vernon, J., Griest, S., & Press, L. (1990). Attributes of tinnitus and the acceptance of masking. *American journal of otolaryngology*, *11*(1), 44-50.

Vernon, J., & Schleuning, A. (1978). Tinnitus: a new management. *The Laryngoscope*, *88*(3), 413-419.

Weisz, N., Hartmann, T., Dohrmann, K., Schlee, W., & Norena, A. (2006). High-frequency tinnitus without hearing loss does not mean absence of deafferentation. *Hearing Research*, *222*(1), 108-114.

Weisz, N., Moratti, S., Meinzer, M., Dohrmann, K., Elbert T (2005a). Tinnitus perception and distress is related to abnormal spontaneous brain activity as measured by magnetoencephalography. *PLoS Medicine* 2(6), e153.

Weisz, N., Wienbruch, C., Dohrmann, K., & Elbert, T. (2005b). Neuromagnetic indicators of auditory cortical reorganization of tinnitus. *Brain*. 128, 2722–2731

Weisz, N., Müller, S., Schlee, W., Dohrmann, K., Hartmann, T., & Elbert, T. (2007). The neural code of auditory phantom perception. *Journal of Neuroscience*. 27, 1479-1484

Wilson, P.H., Henry, J., Bowen, M., & Haralambous, G. (1991). Tinnitus reaction questionnaire: psychometric properties of a measure of distress associated with tinnitus. *Journal of Speech, Language, and Hearing Research*, *34*(1), 197-201.

Tables and Figures

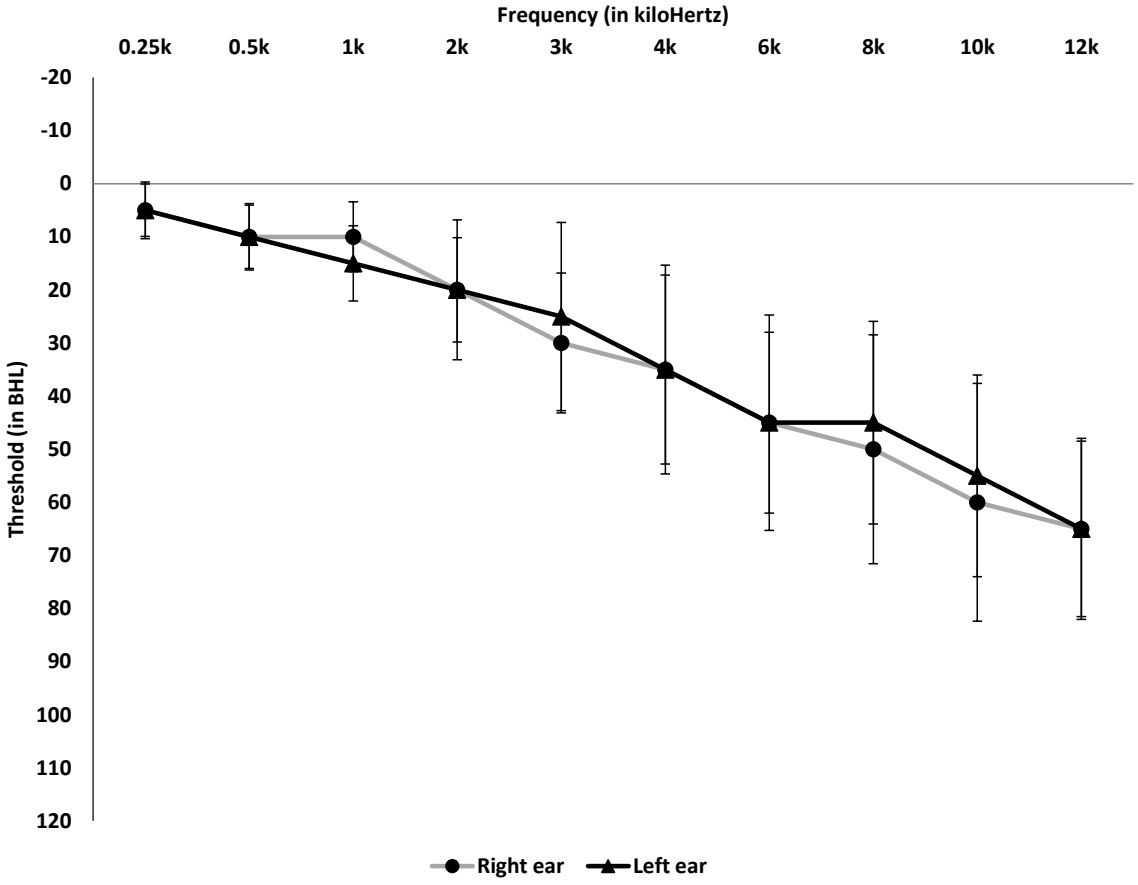


Figure 1. Mean (±SE) audiogram of tinnitus participants.

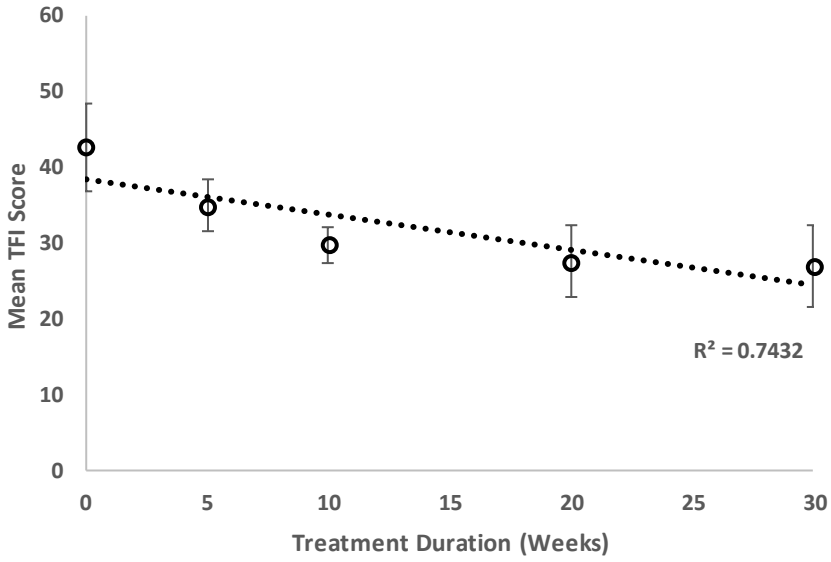


Figure 2. TFI scores show reduced mean distress scores (±SE) measured at fixed time points during the treatment (R^2= 0.7432; p<0.005)**.**

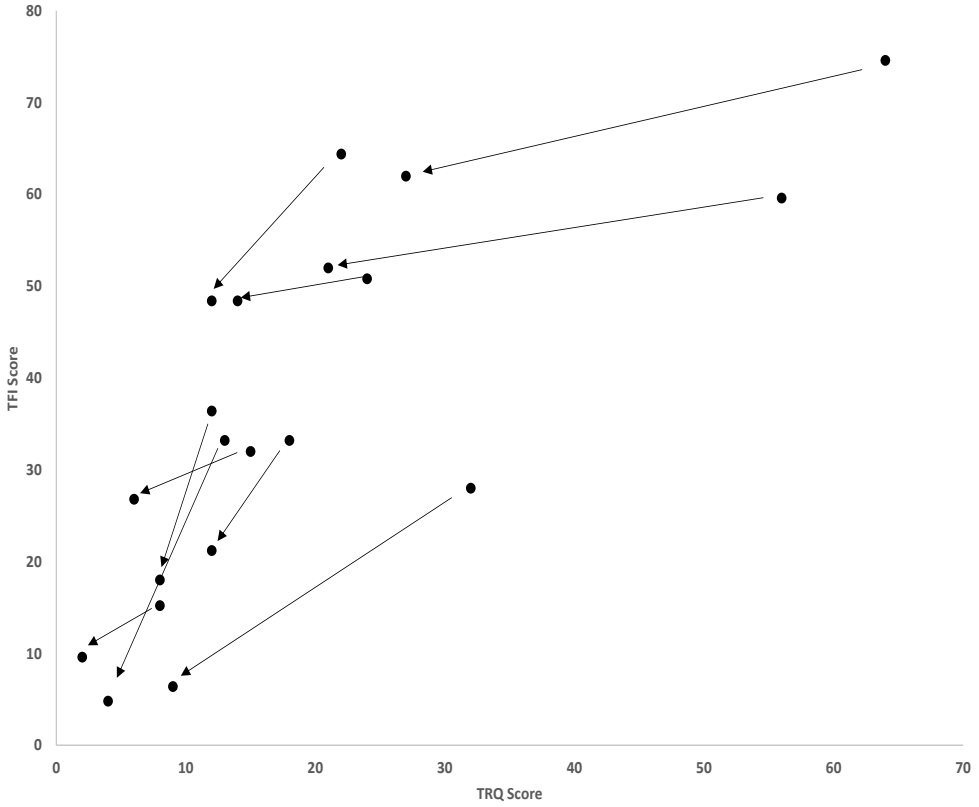


Figure 3. Pre and post treatment TFI and TRQ scores showed reduced distress scores in each participant. Ten participants are shown as pre-treatment TFI was not tested for one participant.

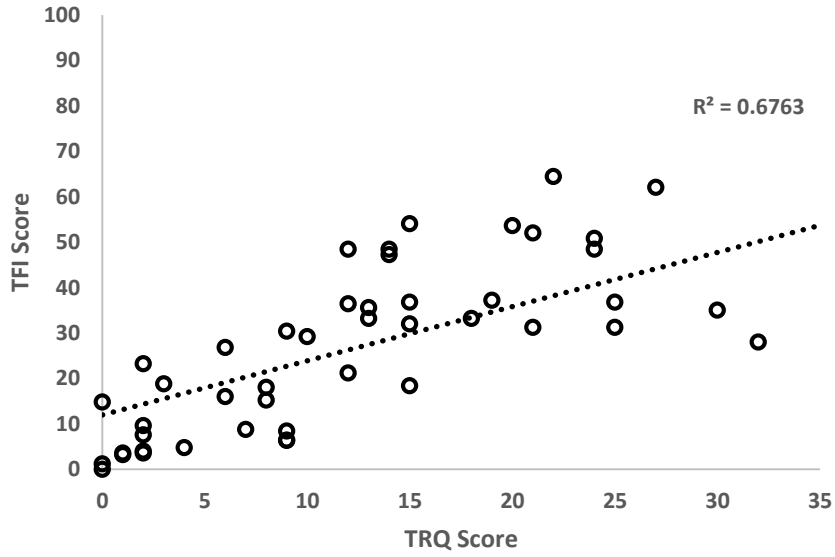


Figure 4. Correlation between TFI and TRQ ($R^2 = 0.6763$;$p<0.01$) scores of 11 participants at during treatment.

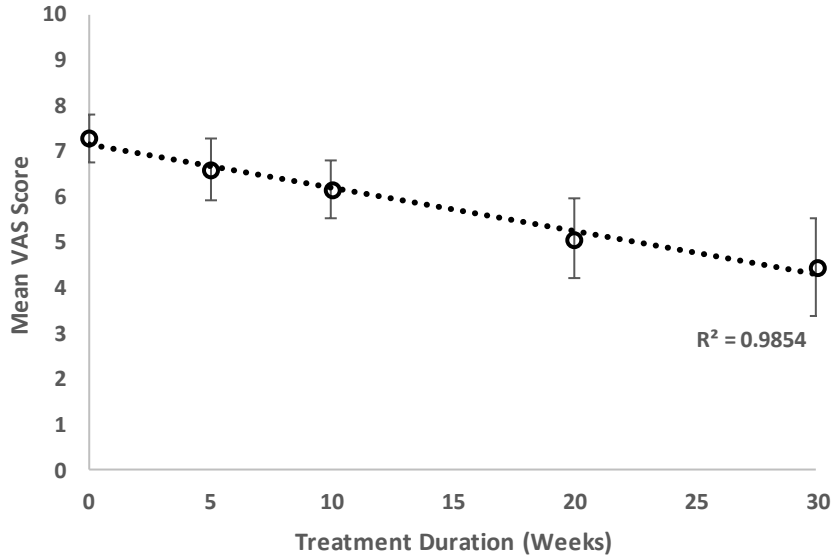
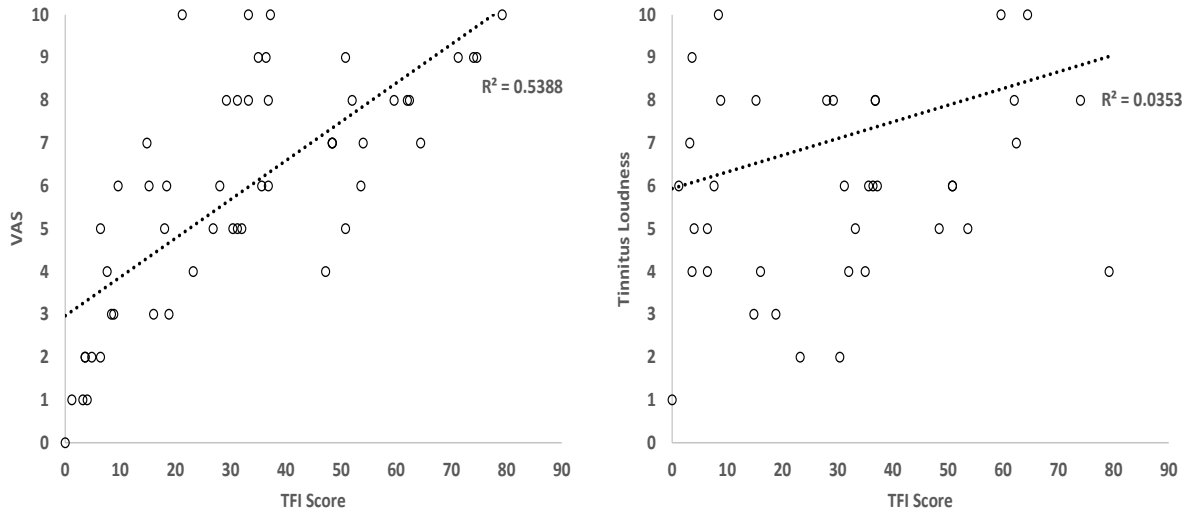
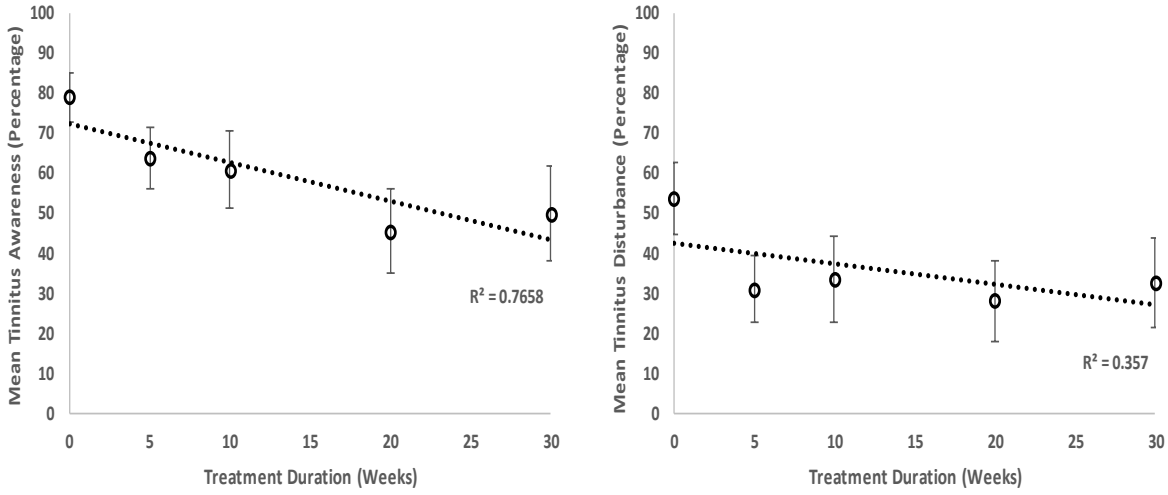


Figure 5. Mean self-reported score of tinnitus loudness on Visual Analog Scale (±SE) during the 30-week treatment program demonstrated a consistent reduction in tinnitus loudness over time (R^2 =0.9854; $p<0.05$).

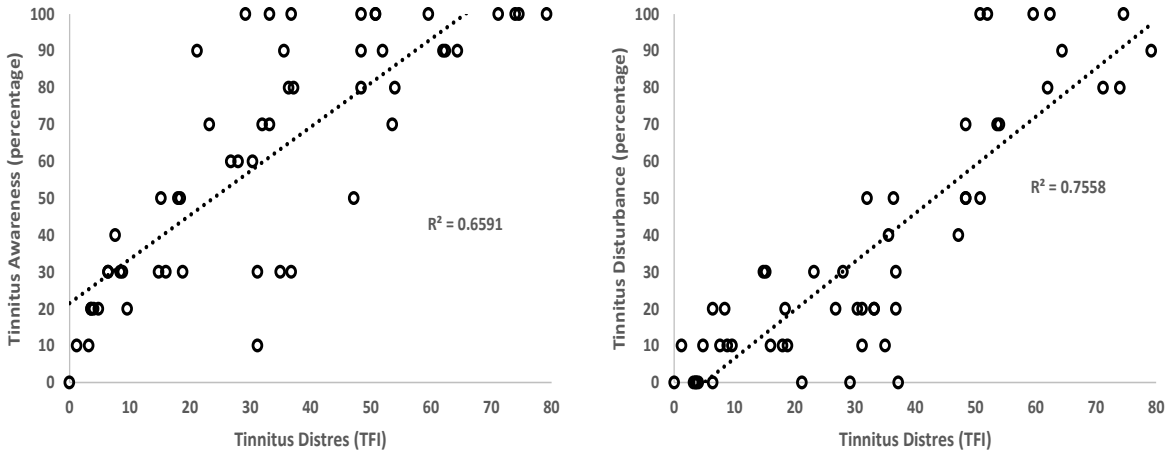


(a) **(b)**

Figure 6. Associations between subjective report of tinnitus loudness (VAS) and tinnitus distress (TFI Score; R^2=0.5388; $p<0.05$) vs tinnitus loudness match and tinnitus distress (TFI Score; R^2=0.353; $p<0.001$).



(a)



(b)

Figure 7. (a) Changes in mean self-reported tinnitus awareness (R^2=0.7658; p<0.05) and mean self-reported tinnitus disturbance (R^2=0.357; p<0.05) recorded at 5 time points during 30 weeks treatment program. **(b)** Associations between self-reported scores of tinnitus awareness-TFI (R^2=0.6591; p<0.05) and self-reported tinnitus disturbance-TFI (R^2=0.7558; p<0.001).

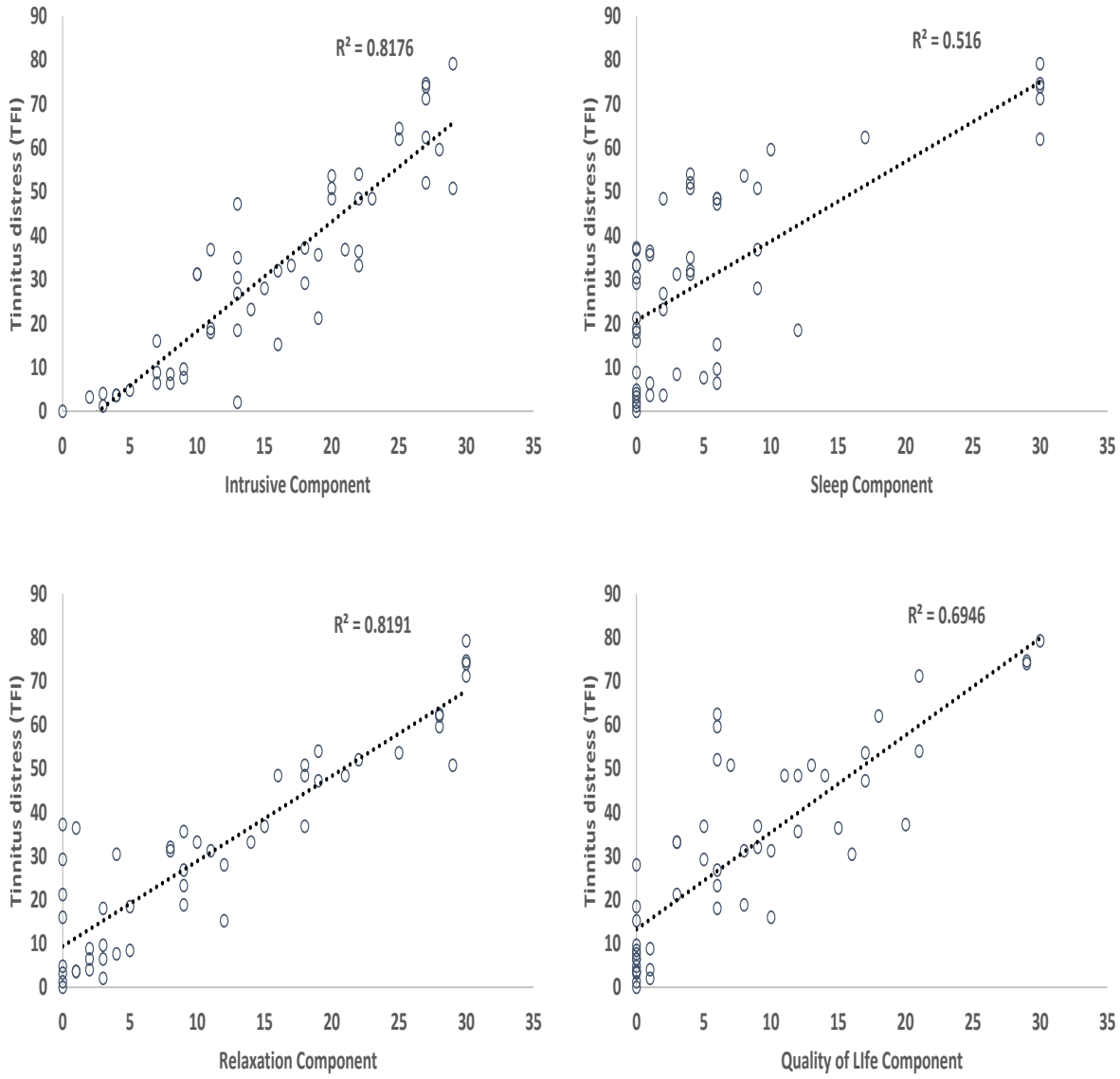


Figure 8. Strong associations were found between Intrusive (R^2=0.8176; p<0.05), Sleep (R^2=0.516; p<0.001), Relaxation (R^2=0.8191; p<0.001) and Quality of life (R^2=0.6946; p<0.001) component with tinnitus distress scores measured using TFI.

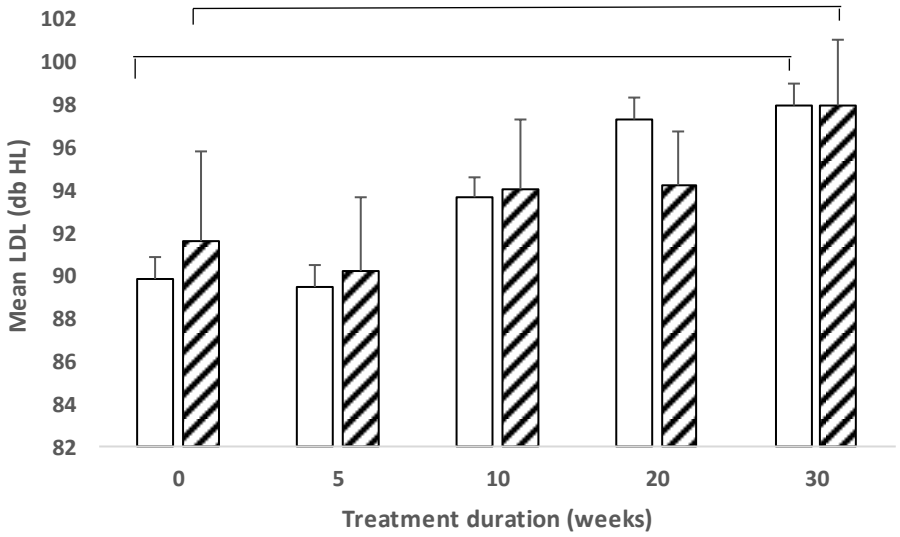


Figure 9. Change in loudness discomfort levels (LDL) average for 500 Hz, 1000 Hz and 4000 Hz for left and right ears (±SE) recorded at five time points during tinnitus treatment. An increase in sound tolerance is observed, with significant increase in LDLs for right and left ears pre- to post-treatment ($p<0.05$) only

Chapter 3: Alpha power as a predictor of tinnitus

Ankit Mathur[1, 2], Catherine McMahon[1, 2], Ronny Ibrahim[1, 2], Petra Graham[3]

[1]Department of Linguistics, Faculty of Human Sciences, Macquarie University, Sydney, Australia

[2]The HEARing Cooperative Research Centre, Australia

[3]Department of Statistics, Faculty of Science and Engineering, Macquarie University, Sydney, Australia

3.1 Abstract

Chronic tinnitus is assumed to result from abnormal cortical activity within the auditory system and has been associated with a reduction in alpha power, particularly in the left temporal region. The present study was conducted to evaluate associations between alpha power and the behavioural measure of tinnitus distress, during a 6-month Neuromonics tinnitus treatment program. Eleven subjects with bilateral chronic tinnitus (>12 months in duration) but without clinical depression or anxiety, and 10 non-tinnitus subjects participated in this study. Spontaneous cortical activity was measured over a 5 minute period using 160 channel whole head MEG recordings before, during and after tinnitus treatment. Tinnitus distress was evaluated using the Tinnitus Functional Index (TFI), a self-report questionnaire. They were significantly lower mean spontaneous alpha power measurements in the left temporo-parietal, left temporo-anterior, right temporo-anterior (TAR) and right parietal (PR) brain regions of tinnitus subjects compared with controls. A weak but significant correlation was found between tinnitus distress and left temporal spontaneous cortical activity and significant changes were found in the cognitive sub-component of TFI associated with TAR alpha during treatment. These results support previous findings that alpha power may be a biomarker of tinnitus distress, however, post-treatment reduction in alpha power did not correlate with self-reported distress in the current study. Such reductions in alpha power observed at baseline might indicate an inability to inhibit unwanted stimuli or elevated auditory attention towards the tinnitus percept. Further research is needed to better understand the associations between abnormal spontaneous oscillations and tinnitus.

Keywords: Tinnitus, magnetoencephalography, spontaneous cortical activity, alpha power.

3.2 Introduction

Tinnitus is the continuous or intermittent perception of ringing or buzzing noises despite the absence of any external sound. This phantom perception is known to cause significant distress in many individuals, often leading to sleeplessness and anxiety (Budd & Pugh, 1995; McKenna & Andersson, 1998). A relatively high percentage of adults report suffer from tinnitus in western society (10 - 15%; Davis & Raffie, 2000), with higher rates occurring in older age classes (67% in ≥ 55 years; Sindhusake et al., 2003) and clinical populations with ear disorders (Fowler, 1944; Glasgold & Altman, 1966; House & Brackman, 1981). Despite this, only a small proportion of those affected (5%) report persistent, severe tinnitus that affects their lifestyle (Scott & Lindberg, 2000; Vernon & Sanders, 2001).

Despite its long history and high prevalence, research investigating a neural basis of subjective chronic tinnitus in humans has gathered momentum only in the last decade (Weisz et al., 2005, Schlee et al., 2009, Leske et al., 2014). Few treatment options exist that provide lasting relief (Dobie, 1999; Fuller et al, 2017; Henry et al., 2005; Thomspon et al, 2017), focusing predominantly on the auditory percept (such as tinnitus retraining therapy and masking) or reducing the emotional distress using counselling techniques (e.g. cognitive behavioural therapy). Such limited knowledge on the neurophysiological correlates of tinnitus has hampered the development of standardised objective measurement tools for tinnitus and a targeted approach to treatment. Early objective evidence for tinnitus was reported by Hoke and colleagues (1989) using magnetoencephalography (MEG). They suggested that a reduction in the ratio of the 1 kHz sound-evoked magnetic waves (M200/M100) could be used to differentiate tinnitus from non-tinnitus populations below the age of 50 years. More recently, Weisz and colleagues (2005, 2007) have shown that tinnitus is associated with

differences in spontaneous oscillatory cortical activity. Spontaneous cortical activity has been a subject of research in humans over the last decade owing to improvements in technology, which has provided non-invasive methods for measuring neural activity at high temporal resolutions. Reduced spontaneous cortical alpha power (typically between 8 - 12Hz) has been reported in individuals with tinnitus compared with normal-hearing controls (Weisz et al., 2005, 2007; Schlee et al., 2014). Oscillatory alpha activity has been proposed to play role in attention by gating information flow to the relevant sensory regions through the inhibition of irrelevant regions (see Klimesch, 2012 for a review). Extensive research in the visual modality has demonstrated that anticipatory alpha activity reflects the orienting of attention (Foxe et al., 1998; Sauseng et al., 2005) and influences detection performance (Handel, Haarmeier & Jensen, 2011). As such, abnormal alpha power in individuals with tinnitus could be related to the detection of and attention towards a tinnitus percept. Certainly, Weisz et al. (2005) reported that the lower alpha power of a tinnitus group, compared to normal hearing, non-tinnitus controls, correlated with tinnitus distress, as measured by the German Tinnitus Questionnaire, though such a correlation was not found in their later studies (Schlee et al., 2009; Dohrmann et al., 2007a). This difference across studies may, in part, be due to heterogeneity among the sampled tinnitus sufferers and / or variability in the way that individual's rate and self-report the severity and distress of their tinnitus.

Therefore, the aim of the present study was to evaluate associations between spontaneous alpha power and subjective tinnitus characteristics with a highly controlled and homogenous tinnitus cohort undergoing a prescriptive tinnitus treatment program. Specifically, the current study attempts to evaluate the reports of reduced alpha power in tinnitus patients and its correlation with tinnitus distress throughout a long duration remediation program.

3.3 Methods

Participants

This study used eleven participants (mean ± SD age: 56.3 years ± 12.3; 3 females) who had significant tinnitus (Tinnitus Reaction Questionnaire, TRQ, scores ≥17 at the time of recruitment) for at least12 months and four frequency (500, 1000, 2000 and 4000 Hz) pure tone average thresholds of < 50 dB HL (measured using standard pure tone audiometry within a sound proof room; Table 1). All tinnitus participants had bilateral tinnitus. Five reported central tinnitus (equally loud in both ears), four had left-dominant and two had right-dominant tinnitus. Exclusion criteria included unilateral tinnitus, mood disorders, anxiety disorders, or psychotic disorders (mini-modified screen, MMS, scores ≥ 6 in any section), depression (Beck Depression Inventory, BDI scores ≥ 29), excessive substance use (World Health Organization Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST) scores < 27) and conductive hearing loss (difference between air and bone conduction thresholds >10dB at octave frequencies between 250 - 4,000 Hz). Participants completed questionnaires on the same day as behavioural and objective tests (discussed below) which were conducted pre-treatment and at 5, 10, 20 and 30 weeks during treatment. Ten participants with normal hearing and no complaint of tinnitus (mean ± 27.6 years ± 5.6 years; 4 females) were recruited as a control group.

Behavioural measures

The present study was a part of a larger study evaluating dynamic changes in sound-evoked and spontaneous cortical activity during a tinnitus treatment program (see McMahon et al.

2015; Chapter 5). All participants completed a hearing test within a sound proof room using the standard Hughson-Westlake procedure (Carhart & Jerger, 1959; air conduction thresholds at octave frequencies between 250 - 8,000 Hz and inter-octave frequencies of 3,000, 6,000, 10,000 and 12,000 Hz, and bone conduction thresholds at octave frequencies between 500 - 4,000 Hz). While two of the tinnitus participants had hearing within normal limits (≤ 20 dBHL) across all tested frequencies, most tinnitus participants showed mild to moderately-severe sensorineural hearing loss for frequencies >1000 Hz. Tinnitus loudness matching and pitch matching was conducted by matching the tinnitus sound level and pitch to an external sound presented to the less dominant tinnitus ear or the ear with the better hearing thresholds. TRQ (Wilson et al., 1991) scores were used to assess tinnitus distress at six time points; at the time of participant recruitment, at the time of first MEG testing (week zero), three times during the treatment at week five, ten and twenty and at the end of treatment (week 30). The Tinnitus Functional Index (TFI; Meikle et al., 2012) was also used to measure tinnitus-related distress and the relationship between TRQ and TFI scores was explored (Figure 1). As expected, substantial variability in TRQ scores was measured between and within participants across the two pre-treatment baseline measures assessed. The time between recruitment and MEG testing ranged from 10—38 weeks, over which time there was a mean reduction of 12 points in TRQ scores (30.8%, compared with 3—8% reductions observed in studies with 6—12 week waiting periods; Hesser et al., 2006).

Data Acquisition

A whole-head MEG system (Model PQ1160R-N2, KIT, Kanazawa, Japan) was used to acquire MEG data. It consisted of 160 coaxial first-order gradiometers with a 50 mm baseline (Kado et al., 1999; Uehara et al., 2003) installed in a magnetically shielded room (MSR). A

sampling rate of 1000 Hz with a band pass filter of 0.03 – 200 Hz was used. The MEG data was spatially co-registered using five marker coils placed on the participants' heads. Head shape was measured using a pen digitiser and head position was measured by energizing the marker coils in the MEG dewar immediately before and after the recording session. Five minutes of spontaneous cortical activity was measured in a state of relaxed wakefulness and the participants were instructed to look at a fixation cross, displayed on a screen on the ceiling, while they lay in a supine position.

Treatment protocol

Participants completed a Neuromonics tinnitus treatment program over a period of 30 weeks. The Neuromonics program was developed to address the emotional, auditory and attentional processes underlying tinnitus using spectrally-modified classical music for relaxation, auditory stimulation and systematic desensitization (see Hanley et al., 2008 and Davis et al., 2008 for further details of the treatment program).

Data analysis

Analyses of MEG were performed using Brain Electrical Source Analysis (BESA) Research 5.3 (GHbH, Germany). Using adaptive artefact correction with principal component analysis (PCA), artefacts from eye blinks and heartbeats were removed from the raw MEG data. Channels identified as too noisy (≥3200 femto-Tesla) during recording due to dental implants or other unknown factors were removed. Fifteen dipoles were placed (derived from the Talairach head model; Talairach & Tournoux, 1988) to observe brain activity at various locations. Four-second epochs of each brain region signal were averaged across the five

minutes of spontaneous cortical activity and the fast Fourier transform (FFT) was used to obtain the amplitude spectrum of the signal. Normalised power was calculated for each brain region by dividing the power of frequency sample points by the total power spectrum of the corresponding brain region. Normalised alpha band power (8 - 13 Hz) was extracted from the normalised power spectrum and compared between participants and groups (tinnitus & controls).

Statistical Analysis

A linear mixed-effects model was used to assess whether there was an association between normalised alpha power in the four specified brain regions with TFI whole score, the sub-components of TFI, and change across sessions. The data was analysed in the NLME package (Pinheiro et al., 2015) within R (R Core Team, 2015). Figures showing the interaction between alpha power and, TFI (whole score or sub-component) with time were constructed using ggplot 2 (Wickham, 2009).

3.4 Results

To identify which brain regions showed significant differences in normalised alpha power between tinnitus (pre-treatment) and non-tinnitus groups, multivariate analysis of variance (MANOVA) was used. Results demonstrated significantly lower normalised alpha power in the temporal posterior left (TPL), temporal anterior left (TAL), temporal anterior right (TAR) and parietal right (PR) brain regions of tinnitus participants compared with non-tinnitus controls ($p < 0.05$; Table 2). Therefore, further analyses were conducted using these brain

regions only, assuming that these differences in alpha power resulted from the differences in the tinnitus percept or physiological mechanisms underpinning this.

Tinnitus distress was measured using two clinically-validated questionnaires. Figure 1 shows that the reductions in distress were significant between pre-treatment and during treatment at session 3 (week 10), and session 4 (week 20) for both TFI and TRQ and also at session 5 (week 30) for TRQ ($p < 0.05$). Furthermore, regression analyses for the pre-treatment values suggests that TFI is highly correlated with TRQ (adjusted $R^2 = 0.670$, $p < 0.001$). As such, TFI was used for further analyses.

Figure 2 shows mean (±SE) normalised alpha power in TPL, TAL, TAR and PR at pre- and 5, 10, 20 and 30 weeks post-treatment time points, to illustrate the effect of tinnitus treatment on alpha power. There were no significant increases in alpha power from pre- to post-treatment as anticipated, despite a significant reduction in self-reported tinnitus-related distress (shown in Figure 1).

A linear mixed-effects model was used to assess whether associations existed between normalised alpha power with TFI whole score, the sub-components of TFI, and change across sessions. There were no significant correlations between TFI scores and normalised alpha power for right and left anterior temporal regions (TAR; $p = 0.191$, TAL; $p = 0.114$). A significant interaction over time was seen for TAR ($p = 0.0439$) but not for TAL ($p = 0.308$). That is, as time and TFI increases, alpha power in TAR decreases. A weak but significant correlation, Bonferroni corrected, was found between TFI and alpha power for the left temporo-parietal (TPL; $p = 0.042$), and was trending towards significance in the right parietal

region (PR; p = 0.052). No significant interaction with time was found for either PR (p = 0.949) or TPL (p = 0.173).

The correlations between TFI and alpha power in these four brain regions (TPL, TAL, TAR and PR) were influenced by one or more of the eight subscales of TFI (i.e. intrusiveness, sense of control, cognitive, sleep, auditory, relaxation, quality of life and emotional; Table 3). All subscales, except *sense of control*, *auditory* and *quality of life*, showed a moderate correlation with TPL alpha power, whereas none were correlated with that of the TAL, and TAR alpha power was only correlated with cognitive subscale. Alpha power in the PR was significantly correlated with *intrusiveness*, *sense of control*, *cognitive* and *relaxation* (Table 3).

There was a highly significant interaction effect between alpha power at the TAR and the *cognitive* TFI sub-scale with time (p = 0.009). That is, over time or during subsequent treatment sessions, alpha power decreased more rapidly with increasing *cognitive* scores, where higher scores indicate poorer ability to concentrate, attend and focus attention on any task due to tinnitus. No other significant interactions were observed between alpha power, the TFI subscales and time.

3.5 Discussion and Conclusion

Using alpha power to map the human brain and identify a biomarker of tinnitus severity has been hampered by difficulties in integrating outcomes across studies. This is partly due to differences in the brain areas over which alpha power has been averaged, the methods used to normalise alpha power, and the heterogeneity of individuals with tinnitus (i.e. confounding

effects of hearing loss, age and aetiology). Few studies have assessed changes in tinnitus subjects during a tinnitus treatment program (see Dohrmann et al., 2007), where hearing loss and age remain unchanged but tinnitus severity decreases significantly. The present experiment used a carefully selected cohort to minimise the heterogeneity known to occur across tinnitus populations, and assessed changes at multiple time points across a well-established prescriptive tinnitus treatment program. The results suggest that the left and right temporal and right parietal regions of the brains of tinnitus subjects have significantly lower alpha power compared with non-tinnitus controls. However, the only significant correlation between alpha power and tinnitus distress during treatment was observed in theTAR ($p = 0.0439$). Before treatment, significant relationships were found between alpha power in the TPL and PR regions of the brain and the sub-categories of TFI which characterise tinnitus severity and impacts (such as *intrusiveness, ability to relax* and *cognitive* abilities). Interestingly, no significant associations were observed for the auditory subcomponent, i.e. ability to hear clearly, understand people talking or follow conversations, or quality of life (enjoyment of social activities, enjoyment of life, relationships with others, and performing work or other tasks). The *cognitive, intrusive* and *relaxation* sub-categories of TFI were correlated with alpha power in both cortical areas. However, only the *cognitive* component had a strong interaction with time in the TAR brain region. That is, over time, TAR alpha power decreases more rapidly with increasing cognitive scores (i.e. ability to concentrate, think clearly and focus attention on things other than tinnitus). This is an interesting finding, since these three abilities include the major complaints of tinnitus patients, and a concomitant change in alpha power and problems affecting cognitive scores demonstrate an effect of alpha power on cognition.

Reduced mean normalised alpha power in the left and right temporal and right parietal regions of the tinnitus group compared with the non-tinnitus group were observed, which are consistent with the results reported by Weisz et al. (2005). They found an inverse relationship between global (whole head) alpha power and tinnitus distress (measured using the German version of the Tinnitus Questionnaire; TQ), which predominantly arose from the temporal regions of the brain. Interestingly, these findings could not be replicated in a similar study measuring long-range coupling between alpha and gamma powers and using TQ to measure tinnitus distress severity (Schlee et al., 2009). However, they were able to discriminate between tinnitus perception and no tinnitus perception. The authors suggested that the inability to find correlations between tinnitus distress and alpha power could mean that different neural mechanisms were at play, one relating to tinnitus perception and another to distress. Demonstrating a strong, consistent and replicable relationship between alpha power and tinnitus distress is important. A direct, objective correlate such as this could be an objective measurement of tinnitus distress.

The results of the current study support the importance of cognitive factors on tinnitus-related distress. These results are consistent with reports of reduced reading span (used as a measure of ability to concentrate) and reduced auditory attention in tinnitus participants during tinnitus remediation programs (Cuny et al., 2004, Rossiter et al., 2006). Rossiter and colleagues (2006) further reported that, compared with controls, tinnitus subjects had slower reaction times and lower accuracy in tasks demanding divided attention, which could not be attributed to tinnitus-related anxiety. Their results indicate that tinnitus can reduce cognitive capacity, affecting the ability to perform tasks requiring voluntary and strategic control.

That alpha power in two brain regions was significantly related to cognition and relaxation is supported by studies investigating the role of alpha power in normal hearing young adults. Spontaneous alpha power has been related to a gating function in attention to stimuli (Jensen & Mazehari, 2010). Oscillations in alpha range are suppressed in brain regions processing attended information, and an inability to shift attention from unwanted stimuli is reported with reduced alpha states (Mazehari et al., 2014). Anticipation of a target stimulus leads to a de-synchronization of alpha oscillations, as demonstrated in the visual (Thut et al., 2006), somatosensory (Babiloni et al., 2004) and auditory (Mazehari et al., 2014) areas involved in processing a distractor. Reduced alpha power in tinnitus participants could therefore be an indicator of the difficulty that individuals with distressing tinnitus have in shifting attention from the tinnitus percept, which could further enhance its loudness or severity, as per the neurophysiological model of tinnitus (Jastreboff, 1990). This hypothesis is also supported by reports of reduced reaction times in tinnitus subjects (compared to controls) in a Stroop task, suggesting a degenerative effect of tinnitus on selective attention performance (Stevens et al., 2007). Mirz et al. (2000) reported in their positron emission tomography (PET) study of tinnitus patients, that there was activation of the cortical centres subserving attention. This was proposed to be a cause of the continuous irritability that is associated with severe tinnitus. Interestingly, the *cognitive* sub-category of TFI, that was found to be inversely related to treatment related changes in alpha power, comprises questions on the ability to concentrate (question 7), think clearly (question 8) and focus attention on things other than tinnitus (question 9). While this does not provide us with definite evidence of a relationship between spontaneous alpha power and attention in all individuals with tinnitus, it does lead us to believe that the present results could lend support to the results of Cuny et al (2004) who reported increased attention focus on the tinnitus ear, and poorer detection of deviant sound in

the non-tinnitus ear. This reduced ability to focus attention may exist in tinnitus patients and contribute to the correlation between alpha power and tinnitus distress during treatment.

Jastreboff (1990) also proposed that the involvement of the limbic and sympathetic parts of the autonomic nervous systems in the tinnitus signal could lead to increased anxiety, a common complaint in tinnitus sufferers (Stephens & Hallam, 1985). Although alpha changes appear to be associated with anxiety changes, a biofeedback study using alpha power measured via EEG found that, anxiety was inversely related to alpha power only in high trait anxiety subjects (Hardt & Kamiya, 1978). Anxiety is the autonomic response of the body to a threatening or unknown stimulus that triggers the "fight or flight" response and readies the individual to respond to danger or a change in the environment. Meanwhile, relaxation is the voluntary release of muscle or psychological tension (Andrews, 2003). Subclinical scores on the STAI were a pre-requisite for participation in the present study. Therefore, only a negative but weak correlation between trait anxiety and alpha power (PR) was found (results not shown) which may account for the lack of a relationship between alpha power and state and trait anxiety scores. Furthermore, the relaxation TFI sub-category was correlated with alpha power in the TPL and PR regions of the cortex, demonstrating a relationship between the ability to relax and alpha power. These results demonstrate that tinnitus-induced anxiety may be related to spontaneous alpha power which would again help explain the inconsistent reports of relationship between alpha power and tinnitus distress, as proposed earlier. These results add to the increasing evidence that reductions in alpha power could be related to the neurophysiological correlate of tinnitus. However, a lack of strong correlations between alpha power and the key tinnitus factors such as tinnitus distress and anxiety could mean that alpha power is indirectly related to tinnitus, i.e. it is a measure of an unknown factor which affects tinnitus distress and loudness. This argument gains is supported by the fact that a

reduction in tinnitus distress is not reflected in changes in alpha power, which remains below that of non-tinnitus controls. These results also suggest there is an unknown factor that causes alpha power reductions in tinnitus participants, which remains low even with reductions in tinnitus distress.

The present study used a relatively small number of participants. A larger sample of people, with various durations of tinnitus history and various degrees of stress and anxiety, is needed to further understand the relationship between tinnitus and alpha power. A lack of strong correlation between tinnitus distress and alpha power, especially during treatment when reductions in tinnitus distress were reported, could mean that a direct correlation between the two either does not exist, or that neurophysiological changes occur after treatment (and hence were not measured by the current study).

Apart from a small participant group, another limitation of the current study is that the control and tinnitus groups were not age- and hearing-loss matched. Such matching could have addressed the potential effects of age and hearing loss on spontaneous cortical activity. However, finding such a group is a challenge as has been reported by Weisz et al. (2005), since it is difficult to find a large sample of non-tinnitus subjects with hearing loss. While studying the influence of tinnitus on cortical reorganisation using MEG, Dietrich et al (2001) reported tinnitus complaints in almost all participants with high frequency hearing loss. Although it is rare to find individuals with cochlear hearing loss and no complaints of tinnitus, such individuals hold the key to better understanding the causes of tinnitus perception in individuals with hearing loss.

Author contributions

Conceived and designed the experiments: CMM, AM. Performed the experiments: RKI AM. Analysed the data: AM RKI CMM PG. Wrote the paper: AM CMM RKI. Delivered the tinnitus treatment program: AM.

References

Andrews, G. (2003). *The treatment of anxiety disorders: Clinician guides and patient manuals*: Cambridge University Press.

Babiloni, C., Brancucci, A., Vecchio, F., Arendt-Nielsen, L., Chen, A. C., & Rossini, P. M. (2006). Anticipation of somatosensory and motor events increases centro-parietal functional coupling: an EEG coherence study. *Clinical Neurophysiology, 117*(5), 1000-1008.

Budd, R. J., & Pugh, R. (1995). The relationship between locus of control, tinnitus severity, and emotional distress in a group of tinnitus sufferers. *Journal of psychosomatic research, 39*(8), 1015-1018.

Carhart, R., & Jerger, J. (1959). Preferred method for clinical determination of pure-tone thresholds. *Journal of Speech & Hearing Disorders*.

Cuny, C., Norena, A., El Massioui, F., & Chéry-Croze, S. (2004). Reduced attention shift in response to auditory changes in subjects with tinnitus. *Audiology and Neurotology, 9*(5), 294-302.

Davis, A., & Rafaie, E. A. (2000). Epidemiology of tinnitus. *Tinnitus handbook*, 1-23.

Davis, P. B., Wilde, R. A., Steed, L. G., & Hanley, P. J. (2008). Treatment of tinnitus with a customized acoustic neural stimulus: a controlled clinical study. *Ear, Nose, & Throat Journal, 87*(6), 330-339.

Dietrich, V., Nieschalk, M., Stoll, W., Rajan, R., & Pantev, C. (2001). Cortical reorganization in patients with high frequency cochlear hearing loss. *Hearing Research, 158*(1), 95-101.

Dobie, R. A. (1999). A review of randomized clinical trials in tinnitus. *Laryngoscope, 109*(8), 1202-1211.

Dohrmann, K., Elbert, T., Schlee, W., & Weisz, N. (2007). Tuning the tinnitus percept by modification of synchronous brain activity. *Restorative Neurology and Neuroscience, 25*(3), 371-378.

Fowler, E. P. (1944). Head noises in normal and in disordered ears: significance, measurement, differentiation and treatment. *Archives of Otolaryngology—Head & Neck Surgery, 39*(6), 498.

Foxe, J. J., Simpson, G. V., & Ahlfors, S. P. (1998). Parieto-occipital~ 10 Hz activity reflects anticipatory state of visual attention mechanisms. *Neuroreport, 9*(17), 3929-3933.

Fuller, T., Cima, R., Langguth, B., Mazurek, B., Waddell, A., Hoare, D. J., & Vlaeyen, J. W. (2017). Cognitive behavioural therapy for tinnitus. *The Cochrane Library*.

Glasgold, A., & Altmann, F. (1966). The effect of stapes surgery on tinnitus in otosclerosis. *The Laryngoscope, 76*(9), 1524-1532.

Wickham, H. (2009). ggplot2: elegant graphics for data analysis. New York: Springer.

Händel, B. F., Haarmeier, T., & Jensen, O. (2011). Alpha oscillations correlate with the successful inhibition of unattended stimuli. *Journal of Cognitive Neuroscience, 23*(9), 2494-2502.

Hanley, P. J., Davis, P. B., Paki, B., Quinn, S. A., & Bellekom, S. R. (2008). Treatment of tinnitus with a customized, dynamic acoustic neural stimulus: Clinical outcomes in general private practice. *Annals of Otology, Rhinology & Laryngology, 117*(11), 791.

Hardt, J. V., & Kamiya, J. (1978). Anxiety change through electroencephalographic alpha feedback seen only in high anxiety subjects. *Science, 201*(4350), 79-81.

Henry, J. A., Dennis, K. C., & Schechter, M. A. (2005). General review of tinnitus: prevalence, mechanisms, effects, and management. *Journal of Speech, Language, and Hearing Research, 48*(5), 1204-1235.

Hesser, H., Weise, C., Rief, W., & Andersson, G. (2011). The effect of waiting: a meta-analysis of wait-list control groups in trials for tinnitus distress. *Journal of Psychosomatic Research, 70*(4), 378-384.

Hoke, M., Feldmann, H., Pantev, C., Lütkenhöner, B., & Lehnertz, K. (1989). Objective evidence of tinnitus in auditory evoked magnetic fields. *Hearing Research, 37*(3), 281-286.

House, J. W., & Brackman, D. (1981). *Tinnitus: Surgical treatment.* Paper presented at the Ciba Foundation Symposium.

Jastreboff, P. J. (1990). Phantom auditory perception (tinnitus): Mechanisms of generation and perception. *Neuroscience research, 8*(4), 221-254.

Jensen, O., & Mazaheri, A. (2010). Shaping functional architecture by oscillatory alpha activity: gating by inhibition. *Frontiers in human neuroscience, 4*.

Kado, H., Higuchi, M., Shimogawara, M., Haruta, Y., Adachi, Y., Kawai, J., Ogata, H., & Uehara, G. (1999). Magnetoencephalogram systems developed at KIT. *Applied Superconductivity, IEEE Transactions on, 9*(2), 4057-4062.

Klimesch, W. (2012). Alpha-band oscillations, attention, and controlled access to stored information. *Trends in Cognitive Sciences, 16*(12), 606-617.

Lehtelä, L., Salmelin, R., & Hari, R. (1997). Evidence for reactive magnetic 10-Hz rhythm in the human auditory cortex. *Neuroscience Letters, 222*(2), 111-114.

Leske, S., Tse, A., Oosterhof, N. N., Hartmann, T., Müller, N., Keil, J., & Weisz, N. (2014). The strength of alpha and beta oscillations parametrically scale with the strength of an illusory auditory percept. *Neuroimage, 88*, 69-78.

Mazaheri, A., van Schouwenburg, M. R., Dimitrijevic, A., Denys, D., Cools, R., & Jensen, O. (2014). Region-specific modulations in oscillatory alpha activity serve to facilitate processing in the visual and auditory modalities. *Neuroimage, 87*, 356-362.

McKenna, L., & Andersson, G. (1998). *Hearing disorders*. Lewiston, NY: BC Decker.

Meikle, M. B., Henry, J. A., Griest, S. E., Stewart, B. J., Abrams, H. B., McArdle, R., Myers, P. J., Newman, C. J., Sandridge, S., Turk, D. C., Folmer, R. L., Frederick, E. J., House, J. W., Jacobson, G. P., Kinney, S. E., Martin, W. H., Nagler, S. M., Reich, G. E., Searchfield, G., Sweetow, R. & Vernon, J. A. (2012). The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus. *Ear and hearing, 33*(2), 153-176.

Mirz, F. (2000). Cortical networks subserving the perception of tinnitus-a PET study. *Acta Oto-Laryngologica, 120*(543), 241-243.

Müller, N., & Weisz, N. (2012). Lateralized auditory cortical alpha band activity and interregional connectivity pattern reflect anticipation of target sounds. *Cerebral Cortex, 22*(7), 1604-1613.

Pinheiro, J., Bates, D., DebRoy, S., & Sarkar, D. (2015). R Core Team. nlme: Linear and Nonlinear mixed effects models. R package version 3.1–117; 2014. <URL: http://CRAN.R-project.org/package=nlme>.

R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

Ray, W. J., & Cole, H. W. (1985). EEG alpha activity reflects attentional demands, and beta activity reflects emotional and cognitive processes. *Science, 228*(4700), 750-752.

Rossiter, S., Stevens, C., & Walker, G. (2006). Tinnitus and its effect on working memory and attention. *Journal of Speech, Language, and Hearing Research, 49*(1), 150-160.

Sauseng, P., Klimesch, W., Stadler, W., Schabus, M., Doppelmayr, M., Hanslmayr, S., Gruber, W. R., & Birbaumer, N. (2005). A shift of visual spatial attention is selectively associated with human EEG alpha activity. *European Journal of Neuroscience, 22*(11), 2917-2926.

Schlee, W., Hartmann, T., Langguth, B., & Weisz, N. (2009). Abnormal resting-state cortical coupling in chronic tinnitus. *BMC Neuroscience, 10*(1), 11.

Schlee, W., Schecklmann, M., Lehner, A., Kreuzer, P. M., Vielsmeier, V., Poeppl, T. B., & Langguth, B. (2014). Reduced variability of auditory alpha activity in chronic tinnitus. *Neural Plasticity, 2014*.

Scott, B., & Lindberg, P. (2000). Psychological profile and somatic complaints between help-seeking and non-help-seeking tinnitus subjects. *Psychosomatics, 41*(4), 347-352.

Sindhusake, D., Mitchell, P., Newall, P., Golding, M., Rochtchina, E., & Rubin, G. (2003). Prevalence and characteristics of tinnitus in older adults: the Blue Mountains Hearing Study: Prevalencia y características del acúfeno en adultos mayores: el Estudio de Audición Blue Mountains. *International Journal of Audiology, 42*(5), 289-294.

Stephens, S., & Hallam, R. (1985). The Crown-Crisp Experiential Index in patients complaining of tinnitus. *British Journal of Audiology, 19*(2), 151-158.

Stevens, C., Walker, G., Boyer, M., & Gallagher, M. (2007). Severe tinnitus and its effect on selective and divided attention: acufeno severo y sus efectos sobre la atención selectiva y dividida. *International Journal of Audiology, 46*(5), 208-216.

Talairach, J., & Tournoux, P. (1988). Co-planar stereotaxic atlas of the human brain. 3-Dimensional proportional system: An approach to cerebral imaging. Stuttgart: Thieme.

Thompson, D. M., Hall, D. A., Walker, D. M., & Hoare, D. J. (2017). Psychological therapy for people with tinnitus: a scoping review of treatment components. *Ear and Hearing, 38*(2), 149.

Thut, G., Nietzel, A., Brandt, S. A., & Pascual-Leone, A. (2006). α-Band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *Journal of Neuroscience, 26*(37), 9494-9502.

Uehara, G., Adachi, Y., Kawai, J., Shimogawara, M., Higuchi, M., Haruta, Y., Ogata, H., & Hisashi, K. (2003). Multi-channel SQUID systems for biomagnetic measurement. *IEICE Transactions on Electronics, 86*(1), 43-54.

Vernon, J. A., & Sanders, B. T. (2001). *Tinnitus: Questions and answers*: Allyn and Bacon.

Weisz, N., Moratti, S., Meinzer, M., Dohrmann, K., & Elbert, T. (2005). Tinnitus perception and distress is related to abnormal spontaneous brain activity as measured by magnetoencephalography. *PLoS medicine, 2*(6), e153.

Weisz, N., Müller, S., Schlee, W., Dohrmann, K., Hartmann, T., & Elbert, T. (2007). The neural code of auditory phantom perception. *The Journal of Neuroscience, 27*(6), 1479-1484.

Wilson, P. H., Henry, J., Bowen, M., & Haralambous, G. (1991). Tinnitus Reaction Questionnaire: Psychometric Properties of a measure of distress associated with tinnitus. *Journal of Speech, Language, and Hearing Research, 34*(1), 197-201.

Tables and Figures

Table 1 Participant information

Subject	**Age (yrs)**	**Sex**	**Hearing Loss**	**3FA - Better ear**	**Duration (years)**	**TRQ Score**	**Dominant Tinnitus**
1	58	M	Mild-moderate	30	1	46	Left
2	51	F	Mild-moderate	18.3	4	64	Left
3	53	F	Mild-severe	15	20	56	Right
4	59	M	Mild-severe	30	20	18	Central
5	63	M	Mild-severe	26.7	10	15	Left
6	69	M	Mild-moderate	30	15	24	Central
7	64	M	Mild-severe	25	12	13	Central
8	56	M	Normal	1.7	4	32	Central
9	68	F	Normal	1.7	2	8	Left
10	24	M	Mild-severe	16.7	8	22	Right
11	54	M	Mild-severe	30	2	12	Central

Table 2 Comparison of the normalised alpha powers of 15 brain regions using a Bonferroni corrected multivariate analysis of variance model. Significant differences were observed in the temporal (TAL, TPL, TAR) and parietal (PR) brain regions only.

Source	Dependent Variable	F	P	Partial Eta Squared
Corrected Model	TAL	**4.832**	**0.041**	0.203
	TPL	**7.116**	**0.015**	0.272
	FL	2.727	0.115	0.126
	CL	2.896	0.105	0.132
	PL	2.278	0.148	0.107
	FpM	1.044	0.320	0.052
	FM	.473	0.500	0.024
	CM	2.904	0.105	0.133
	PM	.658	0.427	0.033
	OpM	1.997	0.174	0.095
	FR	3.987	0.060	0.173
	CR	1.849	0.190	0.089
	PR	**12.892**	**0.002**	0.404
	TAR	**16.653**	**0.001**	0.467
	TPR	.939	0.345	0.047

Table 3. Interaction between alpha power in TAL, TPL, PR and TAR, and the eight sub-components of TFI using a linear mixed-effects model. Significant associations are indicated in bold.

TFI Sub-Component	TAL			TPL			PR			TAR		
	α-value	Std. Error	p-value	α-value	Std. Error	p-value	α-value	Std. Error	p-value	α-value	Std. Error	p-value
Intrusive	-0.41 e-03	0.25e-03	0.11	**-1.57e-03**	**0.65e-03**	**0.02**	**-1.37e-03**	**0.51e-03**	**0.01**	-0.40e-03	0.30e-03	0.19
Sense of Control	-0.19e-03	0.20e-03	0.35	-0.86e-03	0.53e-03	0.11	**-1.07e-03**	**0.42e-03**	**0.01**	-0.32e-03	0.23e-03	0.17
Cognitive	-0.43e-03	0.24e-03	0.08	**-1.45e-03**	**0.63e-03**	**0.03**	**-1.18e-03**	**0.53e-03**	**0.03**	-0.44e-03	0.29e-03	0.14
Sleep	-0.32e-03	0.25e-03	0.21	**-1.63e-03**	**0.67e-03**	**0.02**	-0.57e-03	0.54e-03	0.30	-0.30e-03	0.33e-03	0.37
Auditory	-0.24e-03	0.25e-03	0.34	-0.22e-03	0.66e-03	0.74	-0.46e-03	0.55e-03	0.40	-0.18e-03	0.28e-03	0.53

Relaxation	-0.27e-03	0.20e-03	0.18	**-1.37e-03**	**0.48e-03**	**0.01**	**-0.96e-03**	**0.38e-03**	**0.02**	-0.21e-03	0.25e-03	0.40
Quality of Life	-0.39e-03	0.25e-03	0.12	-0.80e-03	0.65e-03	0.23	-0.67e-03	0.51e-03	0.20	-0.23e-03	0.29e-03	0.43
Emotional	-0.33e-03	0.30e-03	0.26	**-1.84e-03**	**0.73e-03**	**0.02**	-0.73e-03	0.63e-03	0.26	-0.16e-03	0.35e-03	0.65

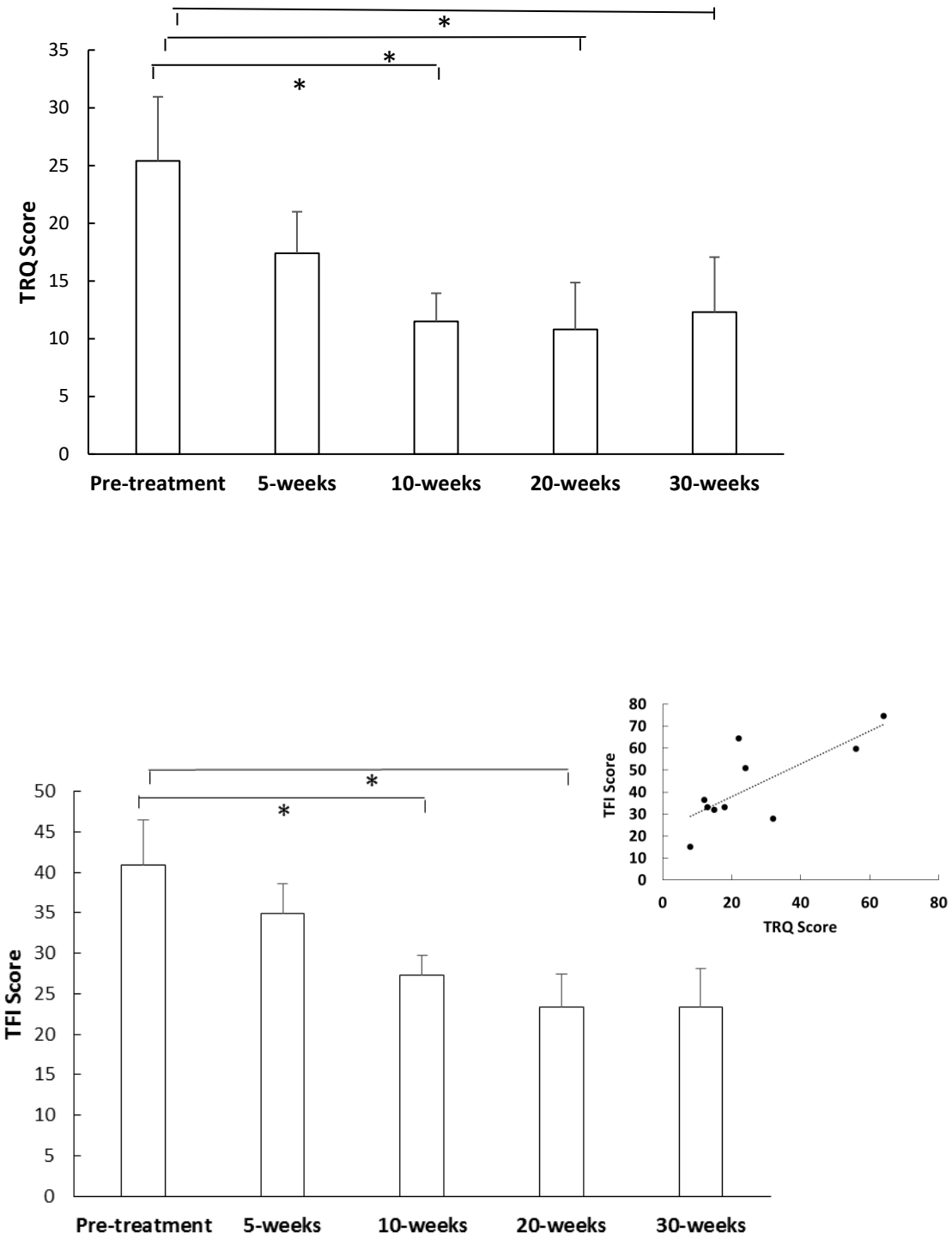


Figure 1 Changes in tinnitus distress over the tinnitus treatment period measured using two scales of tinnitus distress; TRQ (upper graph) and the TFI (lower graph). Significant differences between each time-point were only observed in comparison to pre-treatment scores, suggesting that the largest reduction in distress occurred within the first 5 weeks of treatment. The correlation between the two scales is shown in the inset ($R^2 = 0.670$, $p < 0.001$).

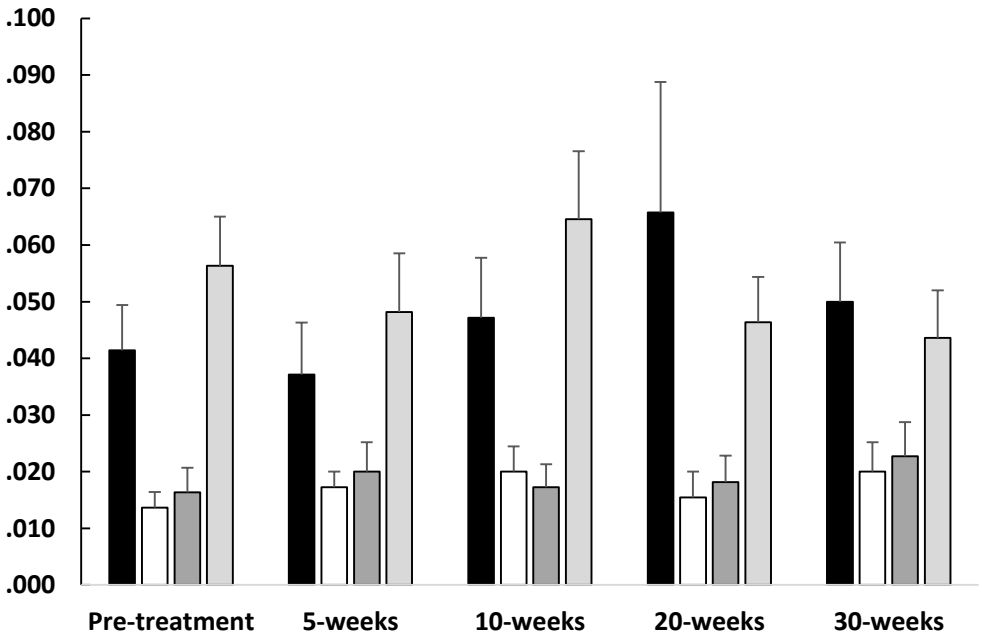


Figure 2 Mean changes in alpha power (+SE) during the 30-week tinnitus treatment program for the brain regions TPL (black bars), TAL (white bars), TAR (dark grey bars), and PR (light grey bars). No significant changes in the mean alpha power amplitude were observed at the end of the treatment program.

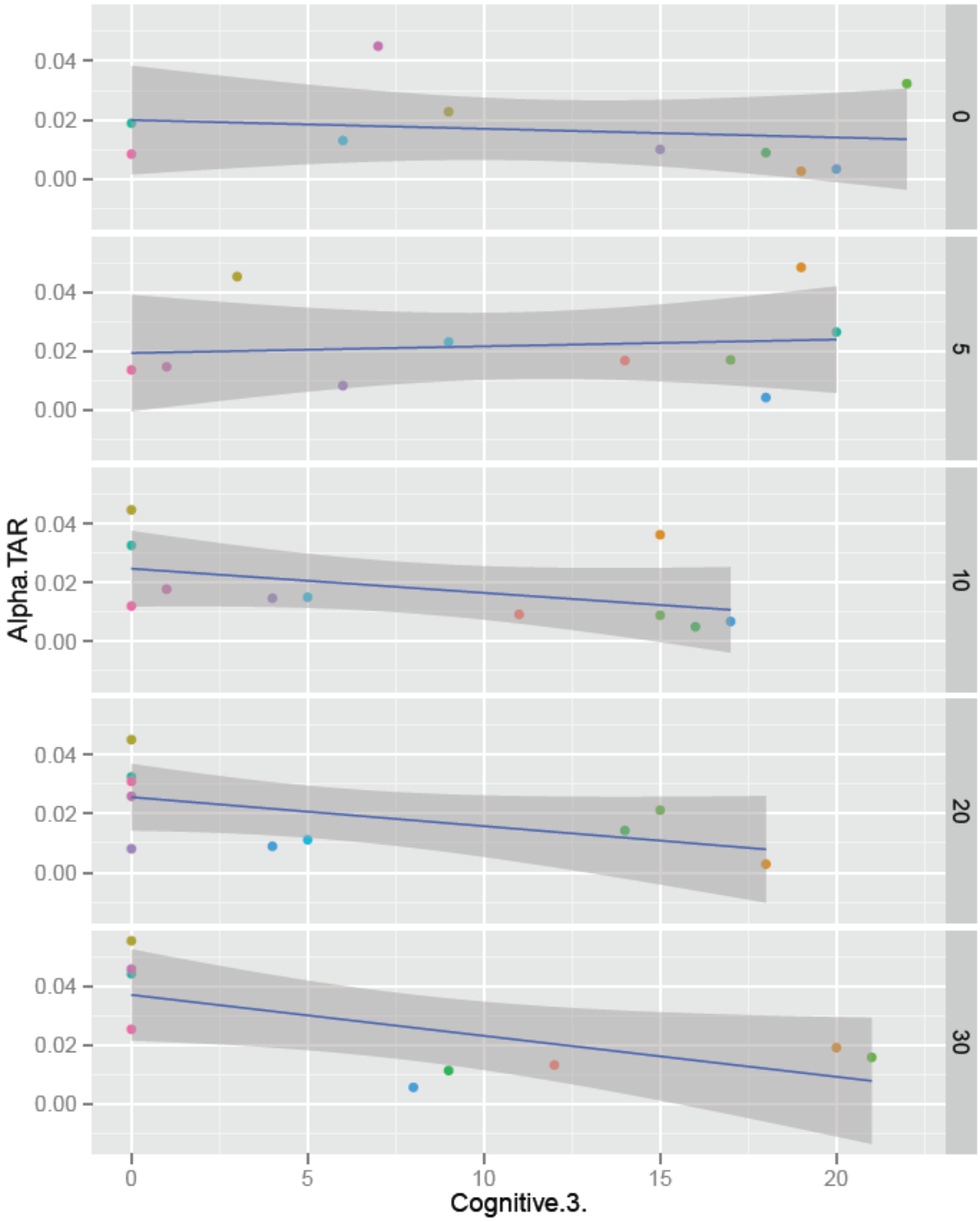


Figure 3. Interaction between alpha power, and cognitive TFI sub-component at the five sampling time points (from top: week 0, 5, 10, 20 and 30). TAR alpha power decreases with increasing *cognitive* scores, with the relationship becoming stronger at successive time points.

Chapter 4: Thalamocortical dysrhythmia and tinnitus remediation

Ankit Mathur[1, 2], Catherine McMahon[1, 2], Ronny Ibrahim[1, 2], Petra Graham[3]

[1]Department of Linguistics, Faculty of Human Sciences, Macquarie University, Sydney, Australia

[2]The HEARing Cooperative Research Centre, Australia

[3]Department of Statistics, Faculty of Science and Engineering, Macquarie University, Sydney, Australia

4.1 Abstract

Thalamocortical dysrhythmia (TCD), a disruption of the neural circuitry or resonances between cortical and thalamic neurones, has been suggested to underpin many neurological and psychiatric disorders, including chronic tinnitus. It is characterised by disruptions to resting state brain oscillations, specifically alpha waves (8 - 13Hz), which moves towards lower frequencies, and gamma waves (30 - 100 Hz), which can be measured objectively in humans using magnetoencephalography (MEG). While this represents a plausible model of the physiological disruptions causing a tinnitus percept, it is not yet clear whether tinnitus remediation programs, which significantly reduce tinnitus distress, are associated with changes in these brain oscillations changing towards a restorative outcome. In this study, alpha and gamma power was measured in 15 discrete brain regions across the head and averaged in a tinnitus (n = 11) and non-tinnitus (n = 10) group. Furthermore, changes in the whole head alpha/gamma ratios over time were assessed during a long duration Neuromonics tinnitus treatment program. Results demonstrated lower alpha and higher gamma power in tinnitus participants compared with non-tinnitus controls. While this pattern is consistent with the TCD model, the differences were not significant. While a significant difference existed between the whole head alpha/gamma ratios between the groups, changes in the alpha/gamma ratio over time (during the treatment program) were not significant. This suggests that although tinnitus remediation program significantly reduced tinnitus-related distress, it either did not restore thalamo-cortical disruptions, or the rate of psychological change was more rapid than that of neurophysiological change and, therefore, could not be observed by this study.

4.2 Introduction

Chronic tinnitus is associated with increased cortical metabolic or neural activity, enhanced cortical gain, abnormal cortical network coupling, and maladaptive cortical reorganisation (see Adjamian et al., 2014 and Auerbach et al., 2014 for reviews). Several brain network models of tinnitus have been proposed, including thalamocortical dysrhythmia (TCD; Llinas et al., 1999), which has been suggested to encompass multiple proposed pathophysiological models of tinnitus (see DeRidder et al., 2015). It has been proposed that TCD can account for both chronic tinnitus and chronic pain (specifically phantom limb pain), and parallels have been drawn between tinnitus perception and phantom limb pain since 1987 (De Ridder et al., 2011; Moller, 2000; Tonndorf, 1987). Phantom limb pain afflicts individuals who perceive pain in a non-existent, perhaps recently-amputated, limb. In contrast, tinnitus often emerges after loud noise exposure and is commonly associated with hearing loss (Phoon et al., 1993). Support for an association between chronic tinnitus and pain comes from magnetoencephalography (MEG) studies of cortical reorganisation and abnormal resting state cortical oscillatory activity. Flor and colleagues (1995) demonstrated the presence of a strong, direct relationship between the magnitude of phantom limb pain (measured using standardised questionnaires and scales after arm amputation in 13 subjects) and cortical somatosensory map reorganisation measured using MEG. Similarly, there is a significant relationship between the subjective strength of tinnitus (measured using a standardised tinnitus scale) and the amount of disruption to the cortical tonotopic map in the primary auditory cortex (Mühlnickel et al., 1998). Abnormal resting state gamma band (30 - 80 Hz) neural activity has also been reported in both chronic tinnitus and chronic pain. As seen in phantom limb pain, while a signal-locked focal gamma activity is normal, a persistent gamma activity localised in a brain region can be considered pathological (Llinas et al., 1999). Increased gamma activity

has more recently been associated with tinnitus lateralisation (Weisz et al., 2007) and tinnitus loudness (Van Der Loo et al., 2009). This knowledge, along with the reports of theta-gamma coupling in auditory sensory processing (Canolty et al., 2006, Doesburg et al., 2012) lend support to the TCD model of tinnitus.

Developmental studies of resting-state brain oscillations in the visual cortex of cats suggest that gamma band activity is associated with myelination of cortico-cortical connections and the development of inhibitory gamma-aminobutyric acid (GABA) synapses (see Uhlhaas et al., 2009 for a review). GABAergic interneurons play a key role in establishing highly coherent oscillations in large neural ensembles in the gamma band range (Bartos et al., 2007). Animal models of tinnitus and pain support the hypothesis that downregulation or suppression of GABAergic inhibition contribute to the underlying pathophysiology of each (Middleton et al., 2011; Fukuoka et al., 1998). Certainly, human studies have shown some relief from phantom pain, neuropathic pain or chronic tinnitus with GABA-enhancing drugs (Johnson et al., 1993; Woolf & Mannion, 1999). Furthermore, successful alleviation of chronic tinnitus symptoms has been demonstrated in rats by elevating their central GABA levels (Brozoski et al., 2007). These results suggest that GABA-induced alterations in gamma power could be a common denominator in both chronic pain and tinnitus.

The model of TCD is based on the global workspace model (proposed by Baars, 1993) which proposes that pain and tinnitus are expressions of global workspace hyperactivity where different sources of information are integrated into a single percept, and are not limited to a single system. Specifically, this model posits that an increase in global gamma power, concomitant with reduced alpha (which is hypothesised to be shifted towards the theta band), causes excessive inhibition. This leads to high frequency, phase-locked coherent activation of

neighbouring cortical modules (cortical gamma activity), forcing certain brain structures to generate gamma frequencies in an ongoing stereotyped manner, eventually generating cognitive behaviour in the absence of context with the external world and without the intentionality that normally characterises human function. An edge effect is therefore proposed, wherein deafferentation at the thalamic level causes $GABA_A$-mediated lateral-inhibition-inducing gamma waves (>30Hz) and generation of positive symptoms. This model also explains that peripheral hearing loss (a negative symptom) is reflected by theta activity while gamma power leads to the conscious perception of positive symptoms such as tinnitus. This explains how peripheral hearing loss, whether measurable or non-measurable by a traditional audiogram, can lead to tinnitus perception. Despite the plausibility of the TCD model, it has not yet been extensively evaluated in humans during a tinnitus treatment program. Lanting et al. (2014) reported that tinnitus involves the interplay between multiple brain regions in participants with unilateral tinnitus, both along and beyond classical auditory pathway. Recently, Vanneste and De Ridder (2018) have demonstrated, using support vector machine learning for analysing resting-state electroencephalography oscillatory patterns in patients with tinnitus. They demonstrated that the theta, beta, and gamma-frequency bands are important in differentiating between neuropsychiatric disorders and healthy control subjects as proposed by and in confirmation of the TCD model. If the TCD model holds, it might be associated with the severity of tinnitus (based on reduced alpha power or increased gamma power), as well as the degree of improvement in subjective reports of tinnitus during treatment.

In this study, we assessed spontaneous oscillatory brain activity in 11 participants before, during and after a well-characterised long duration tinnitus treatment program using magnetoencephalography (MEG). In particular we aimed to determine 1) whether alpha and

gamma band activity (compared to a non-tinnitus group) are consistent with the TCD model and 2) whether improvements in tinnitus distress during tinnitus treatment are associated with expected changes in alpha and gamma band activity.

4.3 Method

Participants

Eleven participants with normal to moderately-severe sensorineural hearing loss and significant chronic bilateral tinnitus (Tinnitus Reaction Questionnaire, TRQ, scores ≥ 17 at the time of recruitment and for at least 12 months), mean age of 56.3 years (SD: 12.3; 3 females), and ten participants with normal hearing and no complaint of tinnitus (mean ± SD age: 27.6 years ± 5.6; 4 females) participated in this study. Participants completed questionnaires on the same day as behavioural and objective tests which were conducted pre-treatment and at 5, 10, 20 and 30 weeks during treatment.

Behavioural measures

Hearing tests were conducted for all participants within a sound proof room using the standard Hughson-Westlake procedure (Carhart & Jerger, 1959; air conduction thresholds at octave frequencies between 250 - 8,000 Hz and inter-octave frequencies 3,000, 6,000, 10,000 and 12,000Hz, and bone conduction thresholds at octave frequencies between 500 - 4,000 Hz). Only two of the tinnitus participants had clinically normal hearing (four frequency average ≤ 20 dBHL) across all tested frequencies, while other tinnitus participants showed mild to moderately-severe sensorineural hearing loss at frequencies > 1000 Hz. Tinnitus

loudness and pitch were matched to an external sound presented to the less dominant tinnitus ear or the ear with the better hearing thresholds. Lastly, TRQ (Wilson et al., 1991) and TFI (Meikle et al., 2012) scores were used to assess tinnitus distress.

Data acquisition

MEG data was acquired using a whole-head MEG system (Model PQ1160R-N2, KIT, Kanazawa, Japan) consisting of 160 coaxial first-order gradiometers with a 50 mm baseline (Kado et al., 1999; Uehara et al., 2003), installed in a magnetically shielded room (MSR). A sampling rate of 1000 Hz with a band pass filter of 0.03–200 Hz was used. The MEG data was spatially co-registered using five marker coils placed on the participants' heads. Head shape was measured using a pen digitiser and head position was measured by energising the marker coils in the MEG dewar immediately before and after the recording session. Five minutes of spontaneous cortical activity was measured in a state of relaxed wakefulness and the participants were instructed to look at a fixation cross displayed on a screen on the ceiling, while they lay in a supine position.

Treatment protocol

Participants completed a Neuromonics tinnitus treatment program over a period of 30 weeks, using the device for 2 – 4 hours every day, as is recommended by the NTT protocol. The Neuromonics program was developed to address the emotional, auditory and attentional processes underlying tinnitus (see Hanley & Davis, 2008; Davis et al., 2008 for details of the

treatment program) using spectrally-modified classical music for relaxation, auditory stimulation and systematic desensitisation.

Data Analysis

Analyses of MEG data were performed using Brain Electrical Source Analysis (BESA) Research 5.3 (GHbH, Germany). Using adaptive artefact correction with principal component analysis, artefacts from eye blinks and heartbeats were removed from the raw MEG data. Noisy channels (≥3200 femto-Tesla) due to dental implants or other unknown factors were removed to maintain noise-free data. Fifteen dipoles were placed (derived from the Talairach head model; Talairach & Tournoux, 1988) to observe brain activity at various locations. Four second epochs of each brain region signal were averaged across the five minutes of spontaneous cortical activity and the fast Fourier transform (FFT) was used to obtain the amplitude spectrum of the signal. To be consistent with previous research on TCD by Llinas et al. (1999), non-normalised alpha band power (8 - 13 Hz) and gamma band power (30 - 100 Hz) were extracted from this spectrum, allowing comparisons between participants and between the non-tinnitus and tinnitus groups.

Statistical analysis

A linear mixed-effects model was used to assess whether there was an association between normalised alpha power, gamma power and alpha/gamma ratio over time. The data was analysed in the NLME package (Pinheiro et al., 2015) within R software (R Core Team,

2015). Wilcoxon rank-sum tests were used to compare tinnitus and non-tinnitus groups in terms of alpha power, gamma power and alpha/gamma whole head ratio.

4.4 Results

Whole head average spectra of tinnitus and non-tinnitus groups was compared (Figure 1). There was lower spontaneous power in the low frequencies centred around 10 Hz (alpha frequencies) and higher power in gamma range frequencies between 35 - 100 Hz in tinnitus group. Because of the non-normality of the outcomes, a Wilcoxon rank-sum test was used to compare the alpha power, gamma power and alpha/gamma power ratio of the two groups to determine whether differences existed. In the control group, alpha power was higher than gamma power (Figure 2), as evident from the ratios > 1, while this was not always the case for the tinnitus group. The alpha/gamma ratios were significantly different between groups ($p=0.013$); however, there were no differences in the alpha ($p = 0.152$) and gamma ($p = 0.349$) power bands.

A linear mixed-effects model was used to evaluate changes in whole head alpha power, gamma power and alpha/gamma ratio over the course of the treatment. The results demonstrated that alpha and gamma power both declined slightly, but the change was not significant (alpha- $p=0.61$; gamma- $p=0.23$). The alpha/gamma ratio, on the other hand, remained constant over time.

It is possible that alpha and gamma differences between groups are greater in specific brain regions, which may dilute the results that are obtained. Therefore, multivariate analysis of variance (MANOVA) was conducted to identify brain regions with significant differences in

alpha and gamma power between the two groups (Figure 3). The tinnitus group had lower spontaneous alpha power in the fronto-polar (FpM; $p = 0.005$) and right anterior temporal (TAR; $p = 0.046$), but higher gamma power in the mid-occipital (OpM; $p = 0.020$), right posterior temporal (TPR; $p = 0.025$) and left posterior temporal (TPL; $p = 0.014$). While it appeared that the temporal region showed significant differences between alpha and gamma powers between the two groups, because these did not fall within the same brain regions, further analyses were not undertaken.

4.5 Discussion

The present study aimed to investigate whether tinnitus subjects displayed cortical oscillatory patterns consistent with the TCD model (i.e. reduced alpha power and enhanced gamma power), and whether these became more like patterns observed in non-tinnitus subjects over the course of a sound based tinnitus treatment program. As the data analyses of this chapter is based on the TCD model of tinnitus (Llineas et al., 1999), thus non-normalised data was used to keep results relevant to the TCD model (unlike previous chapter where data was normalised). Hence, a direct comparison between the results of the two chapters is not advisable.

The pre-treatment tinnitus and non-tinnitus groups demonstrated different alpha/gamma ratios, although there were no differences in individual frequency bands. In terms of independent brain regions, the tinnitus group had lower alpha power lateralised to the right temporal region, and higher gamma power in both the left and right temporal regions.

Thalamocortical dysrhytmia is characterised by an increase in gamma power associated with a reduction in alpha or increase in theta power, which could be attributed to either a bottom-up deafferentation and/or top-down noise cancelling deficit (Ridder et al., 2015). Enhanced gamma and reduced alpha (or a shift in the alpha peak towards lower frequencies - theta) in the present study is consistent with a TCD model and results found in multiple neurological and psychiatric disorders (including those found in neuropsychiatric patients, Parkinson's disease, neurogenic pain and tinnitus patients; see Jeanmonod et al., 2003). However, a complete shift of the alpha peak towards theta band frequencies was not found in the current study (there were no significant differences in the mean theta powers of tinnitus and non-tinnitus participants) nor was it observed within patients in Jeanmonod et al.'s (2003) study. As the oscillatory frequency bands (theta, alpha, delta, gamma etc.) are arbitrary representations, it is likely that a relative shift of the peak towards lower frequencies is associated with TCD, rather than a shift into the theta band *per se*. It is also possible that the magnitude of the shift is related to the magnitude of the disruption; however, this was not assessed within the current study. Similarly, the lack of significant differences in mean alpha and gamma power between the tinnitus and non-tinnitus groups could be associated with the milder levels of tinnitus distress (i.e. none were categorised as severely distressed) measured in the tinnitus population in the pre-treatment session.

An interesting observation that emerges from these results is that while alpha power appeared to be significantly reduced in the right temporal region of the tinnitus group, there were no between-group differences in the left temporal regions. Gamma frequency, on the other hand, was most significantly different in the TPL. Recent research has suggested lateralisation of low frequencies to the right hemisphere (Tang et al., 2016) and lateralization of high frequencies to left, which is also related to better speech perception amidst background noise

(Thompson et al., 2016). Since the perception of speech in noise involves cognitive mechanisms such as memory and attention (Anderson et al., 2013), enhanced gamma power in the left auditory cortex in tinnitus participants could also indicate an increased attention to specific sounds, in this case, tinnitus. Present results, though, cannot justify these reports completely since alpha and gamma were not lateralised to right and left temporal regions exclusively, but were spread across various regions, with greater presence in the right (alpha) and left (gamma) temporal regions.

Llinas et al. (2005) in a review of TCD, reported that the power spectra of TCD patients differed from those of control in four important respects: i) power in the low frequency band was increased, ii) the low frequency band was shifted to the left (towards the theta band), iii) alpha band activity was reduced or absent, and iv) localisation of the theta rhythm was related to the type of dysrhythmia generated. In the absence of altered theta activity, the present results satisfy some of these conditions and thus indicate that a TCD model could be applicable to tinnitus patients. Reduced alpha power, with a left-shifted peak could lead to cross-frequency coupling with a high frequency gamma band, causing its disinhibition in the cortex, leading to tinnitus perception in the absence of external sound. It is also noteworthy that while present study only investigated tinnitus subjects, Llinas et al. (1999) tested a group with various neurological and neuropsychiatric disorders, making it more heterogeneous sample. This could contribute to the differences in our findings. Also, the gamma frequency band by the present study (30 - 100Hz) is higher than that defined by Llinas et al. (25 - 50 Hz), whose range has been often considered “higher beta” (12-30 Hz; Ray et al., 2009) or “lower gamma” by other studies (< 46Hz; Schlee et al., 2009). These factors could be a source of inconsistency between the present study and that of Llinas et al.

The lack of an age- and hearing-loss matched control group is a shortcoming of the current experiment. While this is similar to the original TCD experiment of Llinas et al. (1999) where the control group was healthy, and in the age range of 24-45 years while patients ranged between 28 and 73 years old and the patient population was also significantly heterogeneous, which included four patients with Parkinson's disease, one patient with tinnitus, two with neurogenic pain and two with major depression. It is recommended that future research in the field reduce the heterogeneity while testing the TCD model in tinnitus group.

While these results do lend support to the TCD model, i.e. the role of co-modulated low and high frequency activity that gives rise to tinnitus sensation. However, it is proposed that reduced alpha power could also be a candidate for the focal low-frequency activity that causes disinhibition of the high frequency gamma band in the auditory cortex giving rise to tinnitus perception. Interestingly, the aggregated results of the current study did not demonstrate a significant change in cortical oscillatory activity during treatment, as has been shown in phantom limb pain (Nandi et al., 2003, Ray et al., 2009). Thus, it was demonstrated that while sound-based tinnitus treatment can improve tinnitus perception and distress (i.e. reduced self-reported tinnitus distress scores), the neurophysiology underlying the tinnitus percept does not significantly change, as shown by the lack of change in alpha and gamma power, or the alpha/gamma ratio over time. This, in the long term, could indicate that thalamo-cortical disruptions remain even after "successful" remediation, but could leave those with tinnitus susceptible to relapse of chronic tinnitus. It is possible that such neurophysiological changes could either be hard-wired into the brains of patients with chronic tinnitus, or that they occur after the improvements in tinnitus loudness and distress have occurred. This is further evaluated in Chapter 5, which investigates sound-evoked neurophysiological responses in tinnitus patients.

The limitations of the current study include the small numbers of participants, which was due to our strict inclusion criteria and attrition during the long treatment program. The present results, hence, may act as a pilot to future studies involving different types of treatment programs, preferably involving higher numbers of well-matched participants in each group.

Author contributions

Conceived and designed the experiments: CMM, AM. Performed the experiments: RKI AM. Analysed the data: AM RKI CMM PG. Wrote the paper: AM CMM RKI. Delivered the tinnitus treatment program: AM.

References

Adjamian, P., Hall, D. A., Palmer, A. R., Allan, T. W., & Langers, D. R. (2014). Neuroanatomical abnormalities in chronic tinnitus in the human brain. *Neuroscience & Biobehavioral Reviews, 45*, 119-133.

Ahissar, E., & Vaadia, E. (1990). Oscillatory activity of single units in a somatosensory cortex of an awake monkey and their possible role in texture analysis. *Proceedings of the National Academy of Sciences, 87*(22), 8935-8939.

Auerbach, B. D., Rodrigues, P. V., & Salvi, R. J. (2014). Central gain control in tinnitus and hyperacusis. *Frontiers in Neurology, 5*(206.10), 3389.

Baars, B. J. (1993). A cognitive theory of consciousness. Cambridge University Press.

Bartos, M., Vida, I., & Jonas, P. (2007). Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nature Reviews Neuroscience, 8*(1), 45-56.

Brozoski, T. J., Spires, T. J. D., & Bauer, C. A. (2007). Vigabatrin, a GABA transaminase inhibitor, reversibly eliminates tinnitus in an animal model. *Journal of the Association for Research in Otolaryngology, 8*(1), 105-118.

Canolty, R. T., Edwards, E., Dalal, S. S., Soltani, M., Nagarajan, S. S., Kirsch, H. E Berger, M.S., Barbaro, N.M., & Knight, R. T. (2006). High gamma power is phase-locked to theta oscillations in human neocortex. *Science, 313*(5793), 1626-1628.

Carhart, R., & Jerger, J. (1959). Preferred method for clinical determination of pure-tone thresholds. *Journal of Speech & Hearing Disorders*.

Crone, N. E., Boatman, D., Gordon, B., & Hao, L. (2001). Induced electrocorticographic gamma activity during auditory perception. *Clinical Neurophysiology, 112*(4), 565-582.

De Ridder, D., Elgoyhen, A. B., Romo, R., & Langguth, B. (2011). Phantom percepts: Tinnitus and pain as persisting aversive memory networks. *Proceedings of the National Academy of Sciences, 108*(20), 8075-8080.

De Ridder, D., Vanneste, S., Langguth, B., & Llinas, R. (2015). Thalamocortical dysrhythmia: a theoretical update in tinnitus. *Frontiers in Neurology, 6*.

Doesburg, S. M., Green, J. J., McDonald, J. J., & Ward, L. M. (2012). Theta modulation of inter-regional gamma synchronization during auditory attention control. *Brain Research, 1431*, 77-85.

Flor, H., Elbert, T., Knecht, S., Wienbruch, C., Pantev, C., Birbaumers, N., Larbig, W., & Taub, E. (1995). Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature, 375*(6531), 482-484.

Fukuoka, T., Tokunaga, A., Kondo, E., Miki, K., Tachibana, T., & Noguchi, K. (1998). Change in mRNAs for neuropeptides and the GABA A receptor in dorsal root ganglion neurons in a rat experimental neuropathic pain model. *Pain, 78*(1), 13-26.

Hanley, P. J., Davis, P. B., Paki, B., Quinn, S. A., & Bellekom, S. R. (2008). Treatment of tinnitus with a customized, dynamic acoustic neural stimulus: Clinical outcomes in general private practice. *Annals of Otology, Rhinology & Laryngology, 117*(11), 791.

Jeanmonod, D., Schulman, J., Ramirez, R., Cancro, R., Lanz, M., Morel, A., Magnin, M., Siegemund, M., Kronberg, E., & Llinas, M. (2003). Neuropsychiatric thalamocortical dysrhythmia: Surgical implications. *Thalamus & Related Systems, 2*(02), 103-113.

Johnson, R. M., Brummett, R., & Schleuning, A. (1993). Use of alprazolam for relief of tinnitus: a double-blind study. *Archives of Otolaryngology–Head & Neck Surgery, 119*(8), 842-845.

Kado, H., Higuchi, M., Shimogawara, M., Haruta, Y., Adachi, Y., Kawai, J., Ogata, H., & Uehara, G. (1999). Magnetoencephalogram systems developed at KIT. *Applied Superconductivity, IEEE Transactions on, 9*(2), 4057-4062.

Lanting, C. P., de Kleine, E., Langers, D. R., & van Dijk, P. (2014). Unilateral tinnitus: changes in connectivity and response lateralization measured with fMRI. *PloS one, 9*(10), e110704.

Lisman, J. E., & Jensen, O. (2013). The theta-gamma neural code. *Neuron, 77*(6), 1002-1016.

Llinas, R., Ribary, U., Contreras, D., & Pedroarena, C. (1998). The neuronal basis for consciousness. *Philosophical Transactions of the Royal Society of London B: Biological Sciences, 353*(1377), 1841-1849.

Llinás, R., Urbano, F. J., Leznik, E., Ramírez, R. R., & van Marle, H. J. (2005). Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. *Trends in neurosciences, 28*(6), 325-333.

Llinás, R. R., & Paré, D. (1991). Of dreaming and wakefulness. *Neuroscience, 44*(3), 521-535.

Llinás, R. R., Ribary, U., Jeanmonod, D., Kronberg, E., & Mitra, P. P. (1999). Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proceedings of the National Academy of Sciences, 96*(26), 15222-15227.

Meikle, M. B., Henry, J. A., Griest, S. E., Stewart, B. J., Abrams, H. B., McArdle, R., Myers, P. J., Newman, C. J., Sandridge, S., Turk, D. C., Folmer, R. L., Frederick, E. J., House, J. W., Jacobson, G. P., Kinney, S. E., Martin, W. H., Nagler, S. M., Reich, G. E., Searchfield, G., Sweetow, R. & Vernon, J. A. (2012). The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus. *Ear and hearing, 33*(2), 153-176.

Middleton, J. W., Kiritani, T., Pedersen, C., Turner, J. G., Shepherd, G. M., & Tzounopoulos, T. (2011). Mice with behavioral evidence of tinnitus exhibit dorsal cochlear nucleus

hyperactivity because of decreased GABAergic inhibition. *Proceedings of the National Academy of Sciences, 108*(18), 7601-7606.

Moller, A. R. (2000). Similarities between severe tinnitus and chronic pain. *Journal of the American Academy of Audiology, 11*(3), 115-124.

Mühlnickel, W., Elbert, T., Taub, E., & Flor, H. (1998). Reorganization of auditory cortex in tinnitus. *Proceedings of the National Academy of Sciences, 95*(17), 10340-10343.

Nandi, D., Aziz, T., Carter, H., & Stein, J. (2003). Thalamic field potentials in chronic central pain treated by periventricular gray stimulation–a series of eight cases. *Pain, 101*(1), 97-107.

Phoon, W., Lee, H., & Chia, S. (1993). Tinnitus in noise-exposed workers. *Occupational Medicine, 43*(1), 35-38.

Ray, N., Jenkinson, N., Kringelbach, M., Hansen, P., Pereira, E., Brittain, J., Holland, P., Holliday, I.E., Owen, S., Stein, J., & Aziz, T. (2009). Abnormal thalamocortical dynamics may be altered by deep brain stimulation: using magnetoencephalography to study phantom limb pain. *Journal of Clinical Neuroscience, 16*(1), 32-36.

Sasaki, K., Nambu, A., Tsujimoto, T., Matsuzaki, R., Kyuhou, S., & Gemba, H. (1996). Studies on integrative functions of the human frontal association cortex with MEG. *Cognitive Brain Research, 5*(1), 165-174.

Steriade, M., McCormick, D. A., & Sejnowski, T. J. (1993). Thalamocortical oscillations in the sleeping and aroused brain. *Science, 262*(5134), 679-685.

Talairach, J., & Tournoux, P. (1988). Co-planar stereotaxic atlas of the human brain. 3-Dimensional proportional system: An approach to cerebral imaging. Stuttgart: Thieme.

Tonndorf, J. (1987). The analogy between tinnitus and pain: a suggestion for a physiological basis of chronic tinnitus. *Hearing Research, 28*(2-3), 271-275.

Uehara, G., Adachi, Y., Kawai, J., Shimogawara, M., Higuchi, M., Haruta, Y., Ogata, H., & Hisashi, K. (2003). Multi-channel SQUID systems for biomagnetic measurement. *IEICE transactions on electronics, 86*(1), 43-54

Uhlhaas, P., Pipa, G., Lima, B., Melloni, L., Neuenschwander, S., Nikolić, D., & Singer, W. (2009). Neural synchrony in cortical networks: History, concept and current status. *Frontiers in integrative neuroscience, 3*, 17.

Van Der Loo, E., Gais, S., Congedo, M., Vanneste, S., Plazier, M., Menovsky, T., Van de Heyning, P., & De Ridder, D. (2009). Tinnitus intensity dependent gamma oscillations of the contralateral auditory cortex. *PLoS One, 4*(10), e7396.

Vanneste, S., Song, J. J., & De Ridder, D. (2018). Thalamocortical dysrhythmia detected by machine learning. *Nature communications, 9*(1), 1103.

Weisz, N., Müller, S., Schlee, W., Dohrmann, K., Hartmann, T., & Elbert, T. (2007). The neural code of auditory phantom perception. *Journal of Neuroscience, 27*(6), 1479-1484.

Welker, E., Soriano, E., & Van der Loo, H. (1989). Plasticity in the barrel cortex of the adult mouse: Effects of peripheral deprivation on GAD-immunoreactivity. *Experimental Brain Research, 74*(3), 441-452.

Woolf, C. J., & Mannion, R. J. (1999). Neuropathic pain: Aetiology, symptoms, mechanisms, and management. *Lancet, 353*(9168), 1959-1964.

Tables and Figures

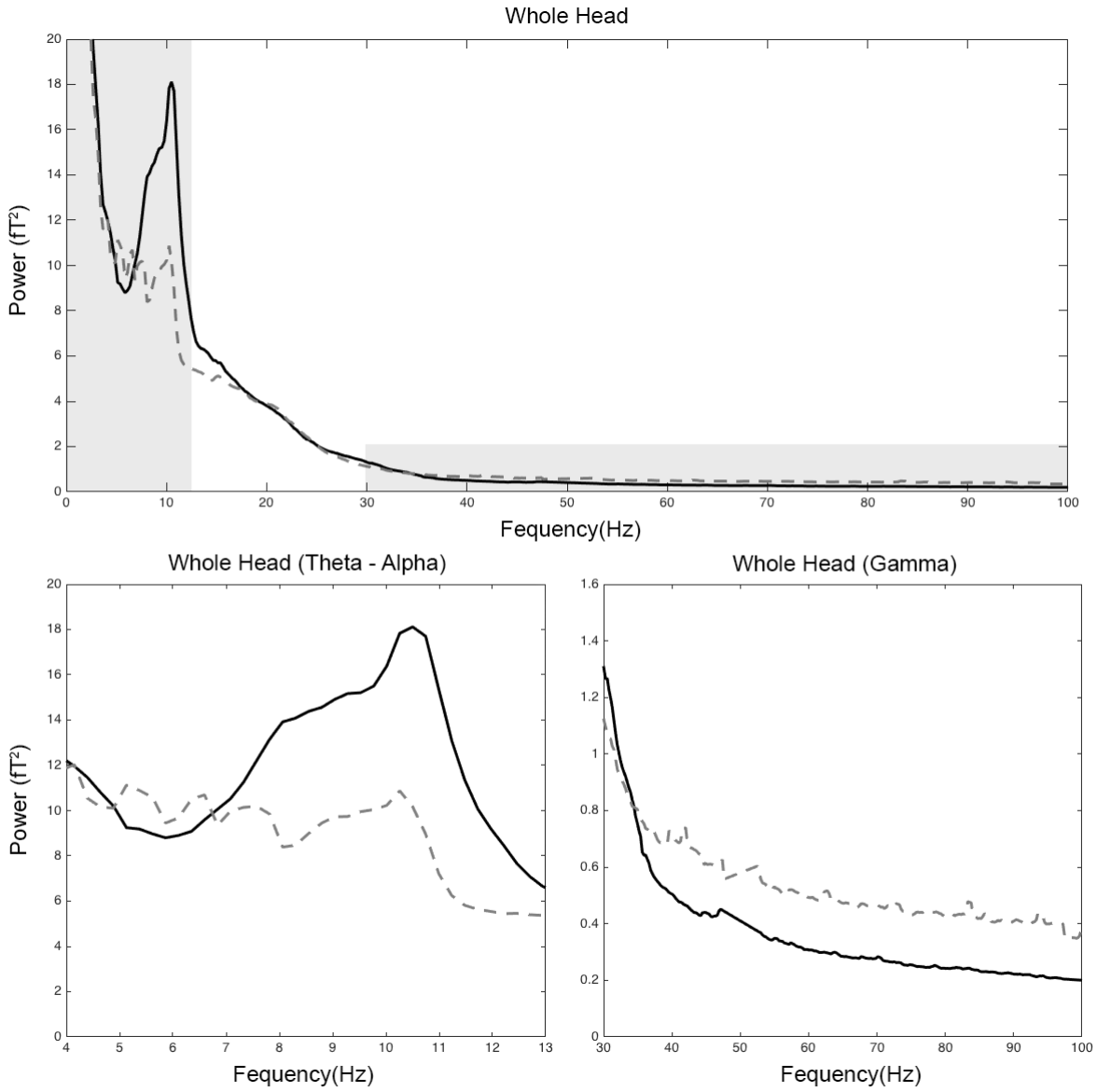


Figure 1. Top: Overlapping power spectra of non-tinnitus controls (solid line) and tinnitus subjects (broken line) from 0 - 100 Hz. Graph shows distinct differences between the two groups in alpha and gamma power. Bottom right: Tinnitus group has increased gamma power (30 - 100 Hz) and (bottom left) reduced alpha power compared to control group.

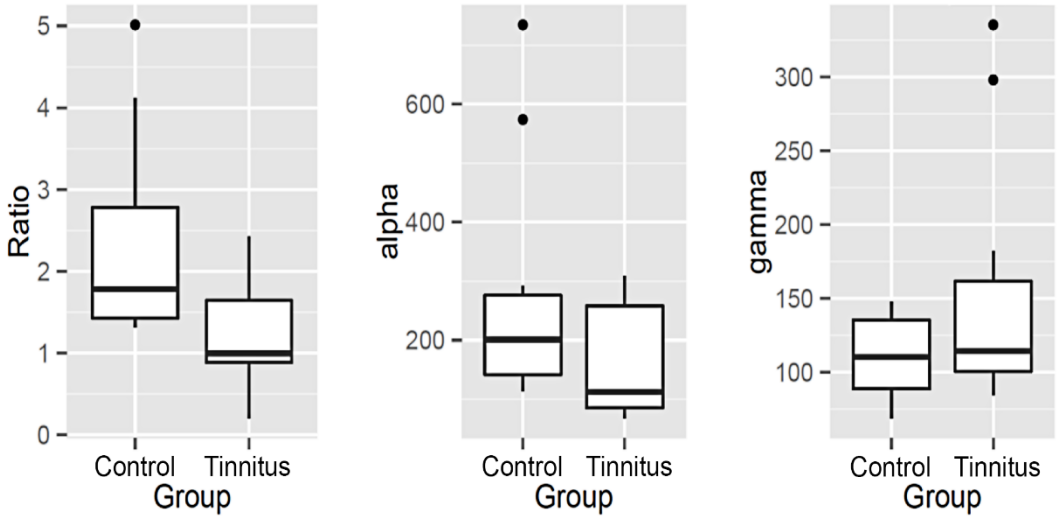


Figure 2. Comparisons between control (non-tinnitus) and tinnitus (pre-treatment) groups for alpha-gamma ratio (left box plot; p=0.013), whole head alpha (middle box plot; p = 0.152) and whole head gamma (right box plot; p = 0.349) power.

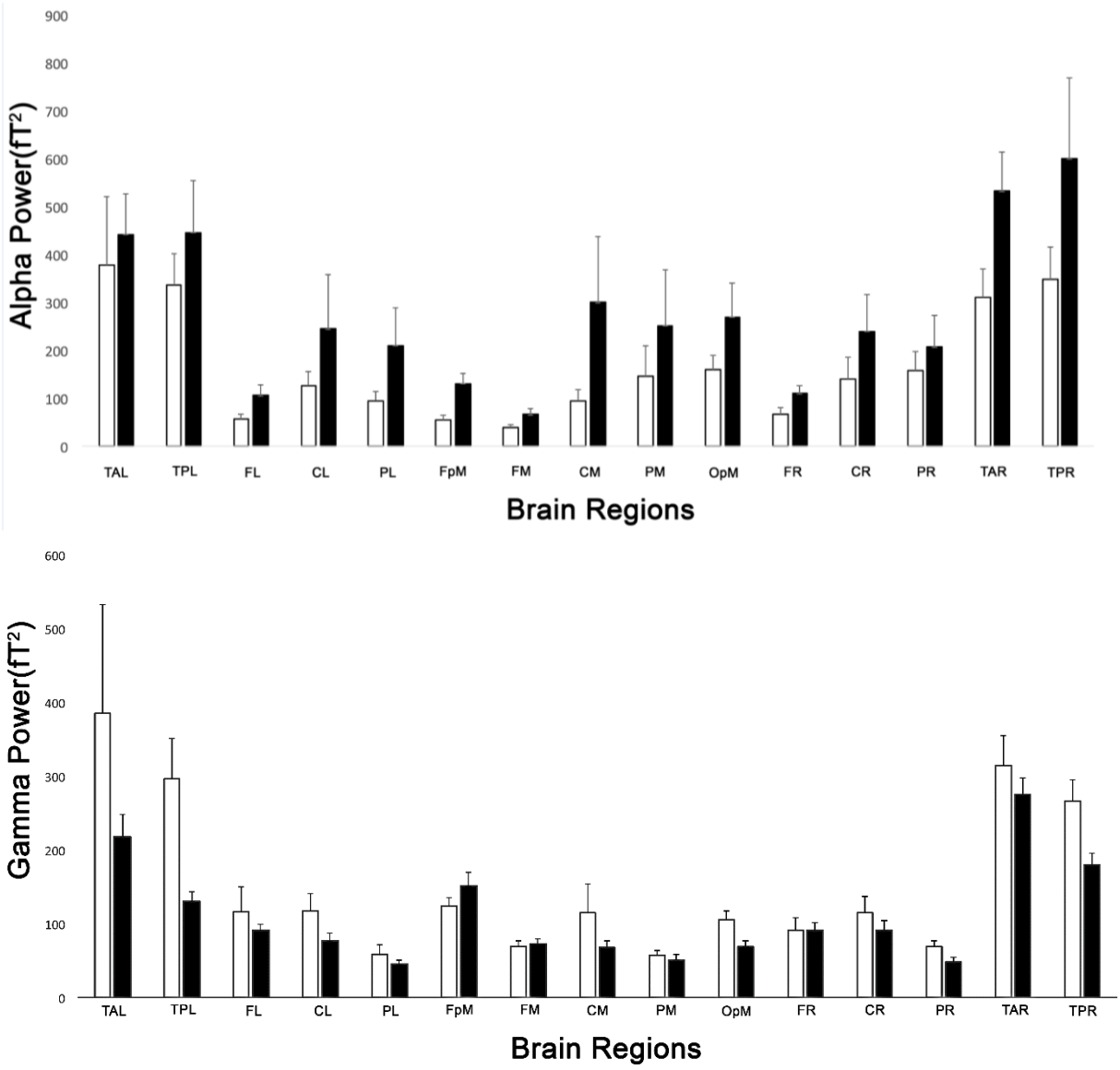


Figure 3. Mean +SE alpha and gamma power in various brain regions in controls (black) and tinnitus subjects (white) pre-treatment. Between group differences were observed for alpha power in the fronto-polar (FpM; $p = 0.005$) and right anterior temporal (TAR; $p = 0.046$), and for gamma power in the mid-occipital (OpM; $p = 0.020$), right posterior temporal (TPR; $p = 0.025$) and left posterior temporal (TPL; $p = 0.014$).

Chapter 5: Cortical reorganisation during a 30-week tinnitus treatment program

Catherine McMahon[1,2], Ronny K Ibrahim[1,2], Ankit Mathur[1,2]

[1]Department of Linguistics, Faculty of Human Sciences, Macquarie University, Sydney, New South Wales, Australia

[2]The HEARing Cooperative Research Centre, Australia

A version of this chapter has been published as:

McMahon, M.C., Ibrahim, R.K., & Mathur, A. (2016). Cortical reorganisation during a 30-week tinnitus treatment program. PLoS One, 11(2): e0148828

5.1 Abstract

Subjective tinnitus is characterised by the conscious perception of a phantom sound. Previous studies have shown that individuals with chronic tinnitus have disrupted sound-evoked cortical tonotopic maps, time-shifted evoked auditory responses, and altered oscillatory cortical activity. The main objectives of this study were to: (i) compare sound-evoked brain responses and cortical tonotopic maps in individuals with bilateral tinnitus and those without tinnitus; and (ii) investigate whether changes in these sound-evoked responses occur with amelioration of the tinnitus percept during a 30-week tinnitus treatment program. Magnetoencephalography (MEG) recordings of 12 bilateral tinnitus participants and 10 control normal-hearing subjects reporting no tinnitus were recorded at baseline, using 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz tones presented monaurally at 70 dBSPL through insert tube phones. For the tinnitus participants, MEG recordings were obtained at 5-, 10-, 20- and 30-eek time points during Neuromonics tinnitus treatment. Results for the 500 Hz and 1000 Hz sources (where hearing thresholds were within normal limits for all participants) showed that the tinnitus participants had a significantly larger and more anteriorly-located source strengths compared to non-tinnitus participants. During the 30-week tinnitus treatment, the tinnitus participants' 500 Hz and 1000 Hz source strengths remained higher than the non-tinnitus participants'; however, the source locations shifted towards the direction recorded from the non-tinnitus control group. Furthermore, in the left hemisphere, there was a time-shifted association between the trajectory of change of the individual's objective (source strength and anterior-posterior source location) and subjective measures (using the tinnitus reaction questionnaire, TRQ). The differences in source strength between the two groups suggest that individuals with tinnitus have enhanced central gain which is not significantly influenced by tinnitus treatment, and may result from hearing loss itself. On the other hand, the shifts in the

tonotopic map towards the non-tinnitus participants' source location suggests that tinnitus treatment might reduce the disruptions in the map, presumably produced by the tinnitus percept directly or indirectly. Furthermore, the similarity in the trajectory of change across the objective and subjective parameters after time-shifting the perceptual changes by five weeks suggests that during or following treatment, perceptual changes in the tinnitus percept may precede neurophysiological changes. Subgroup analyses conducted by magnitude of hearing loss suggest that there were no differences in the 500 Hz and 1000 Hz source strength amplitudes for the mild-moderate compared with the mild-severe hearing loss subgroup, although the mean source strength was consistently higher for the mild-severe subgroup. The mild-severe subgroup had 500 Hz and 1000 Hz source locations located more anteriorly (i.e., more disrupted compared to the control group) compared to the mild-moderate group, although this was trending towards significance only for the 500 Hz left hemisphere source. While the small numbers of participants within the subgroup analyses reduce the statistical power, this study suggests that those with greater magnitudes of hearing loss show greater cortical disruptions with tinnitus and that tinnitus treatment appears to reduce tonotopic map disruptions but not the source strength (or central gain).

5.2 Introduction

Subjective tinnitus is the perception of sound which does not arise from a detectable external physical source. For some individuals, tinnitus may severely affect quality of life, concentration, attention, and working memory (Rossiter, Stevens & Walker, 2006; Nondahl et al., 2007). In spite of growing neurophysiological research in humans and animals, the pathophysiological mechanisms that cause tinnitus remain unclear (Baguley, 2002; Kaltenbach, 2011; Møller, 2007). Tinnitus is commonly accompanied by measurable hearing loss (Sindhusake et al., 2003; Davis & Rafaie, 2000) or more subtle cochlear pathology without concomitant loss of hearing thresholds, such as outer hair cell dysfunction or disruption of high threshold neural activity (Shiomi et al., 1997; Schaette & McAlpine, 2011). In the undamaged auditory system, spontaneous activity is normally present, but it tends to be relatively weak, incoherent, and masked by background noise (Heller & Bergman, 1953; Rodieck Kian & Gerstein, 1962). On the other hand, peripheral damage which causes reduced input from the auditory periphery appears to trigger adaptive compensatory shifts in the balance of neural excitation and inhibition that may preserve neural firing rates within a prescribed range. However, an unwanted side effect may be localised hyperactivity or temporal synchrony, resulting in a tinnitus percept (see (Schaette & Kempter, 2012) for a review). Animal models of tinnitus have shown that increases in spontaneous and sound-evoked responses occur in the cochlear nucleus (Kaltenbach et al., 2002; Kaltenbach et al, 2004), inferior colliculus (Salvi, Wang & Ding (2000), and auditory cortex (Sun et al., 2009; Yang et al., 2007; Chen et al., 2013), despite reductions in spontaneous and evoked activity in the primary afferent neurons of the cochlea (Salvi et al., 2000). Furthermore, in hamsters exposed to loud noise, Kaltenbach and colleagues (2004) showed that moderate correlations exist between the peak level of dorsal cochlear nucleus hyperactivity and behavioural

correlates of tinnitus, further supporting a more central mechanism of tinnitus. In humans, N1-P2 waves of late auditory evoked responses demonstrated a difference between the non-tinnitus and tinnitus groups, with the ability to objectively identify affected ear in unilateral tinnitus (Norena, Cransac & Chery-Croze, 1999).

In addition to central changes in neural activity, tonotopic map reorganisation is widely believed to be associated with tinnitus (see (Eggermont, 2006; Weisz et al., 2005)). Map reorganisation, as assessed by neuromagnetic imaging, has been reported in tinnitus patients in whom a measurable hearing loss was present (Mühlnickel et al., 1998; Wienbruch et al., (2006). However, cortical tonotopic map changes have been observed in animals with hearing loss caused by age, loud noise and mechanical disruptions (Robertson & Irvine, 1989; Wang, Ding & Salvi, 2002). Therefore, it is unclear whether the association exists between the map disruption and the tinnitus percept or the sensory deprivation (or hearing loss).

Multiple studies in humans show the adaptability of the adult brain to auditory training and rehabilitation (Kraus et al., 1995; Tremblay et al., 1997; Tremblay et al., 2001; Menning, Roberts & Pantey, 2000), but few have been conducted in the case of tinnitus. Therefore, to better understand the association between tinnitus and disruptions in cortical tonotopic maps and sound-evoked responses, we used MEG to measure sound-evoked responses during a six month tinnitus treatment. As hearing thresholds did not significantly change throughout the six month rehabilitation process, we assumed that any changes in the source-evoked waveforms and the cortical tonotopic maps, resulted from the tinnitus treatment. We also compared these responses with a non-tinnitus control group. Specifically, the current study aimed to: (i) identify whether disruptions in the tonotopic cortical maps and source waveform

amplitudes occur in adults with tinnitus as compared to those without tinnitus; (ii) evaluate the brain changes of tinnitus sufferers before, during and after a tinnitus sound therapy; and (iii) investigate whether these changes are associated with perceptual measures of loudness and distress.

5.3 Materials and Methods

Participants

In this study, 12 bilateral tinnitus sufferers (mean = 54.5 years old, SD = 12.7 years) and 10 normal- hearing non-tinnitus control subjects (mean = 27.6 years old, SD = 5.7) participated. At the time of recruitment, all of the tinnitus group participants reported a history of tinnitus of > 6 months duration, showed high levels of tinnitus distress as measured on the Tinnitus Reaction Questionnaire (TRQ scores >17; (Wilson et al., 1991)), had no self-reported clinical depression as measured using the Beck Depression Inventory (BDI scores <29 (Beck, Steer & Carbin, 1998)) or addictive tendencies (WHO-ASSIST scores < 27 (Group, 2002)), and had a pure tone average four-frequency hearing threshold PTA (500-4000Hz; <40 dBHL. The mean audiogram of the tinnitus and non-tinnitus control groups are presented in Figure 1 and demographic information on the tinnitus participants is provided in Table 1.

Clinical testing, including pure tone audiometry, tympanometry, acoustic reflex testing, and distortion-product otoacoustic emissions (DPOAEs), magnetoencephalography testing, psychoacoustic evaluation of the tinnitus percept (discussed below), and questionnaires (TRQ; Tinnitus Functional Index, TFI (Meikle et al., 2012)[32]; BDI; State-Trait Anxiety

Inventory, STAI (Speilberger & Gorsuch, 1983); Medical Outcomes Study, MOS, sleep scale (Hays et al., 2005); SF-36 quality of life measure (Ware, Kosinski & Gandel, 2000); and modified self-efficacy scale) were completed at baseline (pre-treatment) and at 5-, 10-, 20- and 30-week time points after commencement of the tinnitus treatment program. Psychoacoustic testing included pitch-matching, tinnitus loudness balance, broadband noise (BBN) and narrowband noise (NBN) threshold measurements, BBN and NBN minimum masking levels, and loudness discomfort levels. Psychoacoustic and self-reported data is discussed in Chapter 2.

At the baseline evaluation, pure tone audiometry (using air and bone conduction; Madsen OB 822 diagnostic audiometer) was measured for octave frequencies between 250–8000 Hz and at 3000, 6000, 10000 and 12000 Hz using a modified Hughson and Westlake technique (Carhart & Jerger, 1959). All testing was conducted in a sound proof room. In addition, acoustic reflex testing and tympanometry was performed.

Tinnitus treatment

Each of the tinnitus participants completed a 30-week standard Neuromonics tinnitus treatment program delivered by an experienced clinical audiologist (see (Davis & Rafaie, 2000; Távora-Vieira, Eikelboom, & Miller, 2011; Davis, Paki & Hanley, 2007)for further information about the remediation program). Briefly, Neuromonics provides a structured program of audiological counselling and clinical support alongside the fitting of an acoustic stimulation device (delivering spectrally-enhanced classical music) that is customised to the individuals hearing thresholds. This program was selected because it was highly structured

and provided an auditory approach to remediation (rather than a cognitively-based approach). Further, device was used for 2-4 hours per day as recommended, and its use was monitored using device logging to evaluate program compliance.

MEG testing Procedure

MEG recordings were obtained in a magnetically shielded room using a KIT-Macquarie MEG160 system (KIT, Kanazawa, Japan), which consists of 160 coaxial first-order gradiometers with a 50 mm baseline. Prior to MEG measurements, MEG marker coils were placed on the participant's head and marker coil positions and head shape were measured with a pen digitiser (Polhemus Fastrack, Cochester, VT). Participants were positioned in a supine position in the MEG environment and pure tone stimuli of 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz (70 dB SPL; 300 ms; 10ms rise/fall) were presented mono-aurally via plastic tubes, with an interstimulus interval (ITI) between 900 and 1200 ms. A silent DVD was shown on a projection screen and the participants were told to watch the DVD and ignore the sound stimuli. Block conditions (222 pure tones per condition) were presented for each ear separately in a random order, resulting in a total of 888 pure tones per subject.

Data acquisition and processing

Brain Electrical Source Analysis [BESA] Research 5.3 was used to analyse the neuromagnetic data which were acquired at a sampling rate of 1000 Hz and bandpass filtered from 0.03 to 200 Hz. Adaptive artefact correction which utilised principle component analysis

was used to remove eye blinks and heart beat artefacts (Ille, Berg & Scherg, 2002). Noisy channels (channels which had more than 75% rejected trials) were omitted from further analysis and 1000 ms epochs were extracted (including a 400 ms pre-stimulus interval). Noisy epochs were rejected (signal channels with amplitudes exceeding 1200fT - this is a stricter epoch rejection criterion compared to that used by (Nenonen et al., 2010) to ensure better source modelling) and accepted epochs were averaged to perform source analysis. The aim of performing source analysis was to: (i) determine the neuronal response strengths for each condition; and (ii) detect any disruptions on the tonotopic representation. A montage consisting of eight regional sources was created, consisting of six fixed sources and two non-fixed sources, placed symmetrically and bilaterally in the auditory cortex. The aim of using the six additional fixed sources was to ensure that the two sources of interest (that were placed on the auditory cortex region) did not get disrupted from surrounding brain activations, acting as a spatial filter. A time window of 30 ms around the prominent peak was used for the discrete source search. Source strengths were determined by obtaining the maximum orientation from the source waveform since no substantial activation could be found for orientation 2. The Talairach coordinate was used to quantify the source location. Subject (T-08) data were omitted from the analysis due to noise. Furthermore, to better understand the relationships between hearing loss and source strength or source location, the tinnitus group was divided into a mild-moderate hearing loss subgroup, which included normal hearing subjects (n = 6) and mild-severe (n = 5) hearing loss subgroups based on their pure tone audiogram results.

This study was approved by and conducted under the ethical oversight of the Macquarie University Human Research Ethics Committee (ref: 5200900061). Written informed consent was obtained from all participants prior to commencement of the study.

5.4 Results

Ten tinnitus participants showed high frequency sensorineural hearing loss [ranging from mild-severe], with thresholds between 250–1000 Hz within normal limits (20 dBHL), whereas two had hearing thresholds within normal limits across all tested frequencies. All of the tinnitus participants had normal tympanograms and middle ear reflexes expected for the degree of measured hearing loss. The tinnitus pitch was predominantly matched to a 6000 Hz pure tone and ranged between 4000 – 12,000 Hz. Tinnitus loudness was matched between 4 - 12 dB, using contralateral loudness balance matching.

N1m source strengths and location comparison between tinnitus and non-tinnitus groups

Figure 2A compares the two groups' left hemisphere mean source waveforms. The mean N1m peaks for 500 Hz tone were 26.8 ± 3.6 nAm SE for the tinnitus group and 15.2 ± 2.6 nAm SE for the non-tinnitus group. N1m peak amplitudes are shown for the left (Figure 2B) and right (Figure 2C) hemispheres at 500, 1000, 2000 and 4000 Hz. Results of a one-way multivariate analysis of variance (MANOVA) with Bonferroni correction showed significantly larger peak amplitudes for tinnitus participants than non-tinnitus participants ([$F_{[4, 14]} = 4.137$, $p = 0.02$; Wilks' $\Lambda = 0.458$; partial $\eta 2 = 0.542$). There were significant increases in the left but not right hemispheres of the tinnitus participants at the 500 Hz and 1000 Hz frequencies, which were tested using a post-hoc univariate ANOVA (p - 0.006 and 0.003, respectively). This difference was not evident at higher frequencies, presumably due to

high-frequency hearing loss in most tinnitus participants causing a reduction of the peak amplitude of the N1m.

To minimise the confounding effects of hearing loss on the N1m amplitude, and for comparison between tinnitus and non-tinnitus groups, in following analyses, only 500 Hz and 1000 Hz source strength responses were used. Figure 3A shows a comparison of brain dipole modelling for a single tinnitus and non-tinnitus participants. Disruptions of the cortical tonotopic maps for the 500 Hz source location were investigated by measuring the source location in the medio-lateral (Figure 3B), anterior-posterior (Figure 3C) and inferior-superior (Figure 3D) directions. Similarly, the cortical maps for 1000 Hz were measured and presented in medio-lateral (Figure 3E), anterior-posterior (Figure 3F), and inferior-superior directions (Figure 3G). The mean values of the 500 Hz source locations of the tinnitus group (meanML mm 51.0±3.3 SE; meanAP -3.7mm ±1.8 SE; meanIS 50.9±1.76 SE) and non-tinnitus group (meanML mm 49.9±2.2 SE; meanAP -11.1mm ±1 SE; meanIS 50.0±2.2 SE) show that the tinnitus group's source was located more anteriorly than the non-tinnitus group's, for both hemispheres (Figure 3B), although this was significant for the left hemisphere only ($p < 0.05$). There were no significant differences in source locations in medio-lateral or inferior-superior directions.

N1m Source Strengths and Source Location during tinnitus treatment

The mean source strengths for the left and right hemispheres of each group at 500 Hz and 1000 Hz throughout the 30 weeks of tinnitus treatment are shown in Figure 4. At baseline, the source strength in the left hemisphere was greater in tinnitus participants than non-tinnitus

participants and remained so throughout the treatment program. On the other hand, the right hemisphere source strength amplitude was not significantly higher in tinnitus subjects at baseline. Although it increased throughout the treatment period, it did not become significantly higher than that of non-tinnitus subjects. While the source strength for both hemispheres in the tinnitus participants increased between the baseline and first treatment testing sessions (5 weeks after treatment commencement), it then decreased at the 10-week test session. A repeated measures ANOVA shows that these changes were not significant throughout the remediation period.

To determine whether changes in source location occurred during tinnitus remediation, we evaluated the 500 Hz and 1000 Hz sources (in the anterior-posterior and lateral medial direction) pre-treatment and at 5, 10, 20, and 30 weeks during treatment. Figure 5A shows a scatterplot of tinnitus source locations for all tinnitus participants, measured at week 5, 10, 20 and 30 in the left hemisphere. Each data point was re-referenced to each subject's pre-treatment source location. In general, there was a trend for the source location to initially move slightly more anteriorly (week 5), then more posteriorly (weeks 10–30) over time. The right hemisphere source locations displayed considerably less movement, and are therefore not shown here (see Figure 6 for more detail). In the two participants with normal hearing, similar disruptions and changes to source strength were observed, supporting Mühnickel et al. (1998) suggesting that cortical tonotopic map disruptions are related to the tinnitus percept itself, though the presence of hidden hearing loss (Schaette & McAlpine, 2011) cannot be ruled out. However, unlike their study, we only evaluated changes in non-disrupted frequency regions (500 and 1000 Hz), rather than at the tinnitus frequency, and no correlations were found between the participants' 500 and 1000 Hz source locations in any direction (inferior-superior, anterior-posterior, or medial-lateral) and their TRQ scores (data not shown).

To illustrate the movement in source location more clearly, a single participant's source location (subject T-11) is shown in Figure 5B from pre-treatment to week 30 post-treatment. This shows that the tinnitus source moved towards the control (non-tinnitus) source location (closed square, meanAP -11.06mm ± 1 SE; meanML -50.6mm ± 2.3 SE).

To determine whether cortical changes measured objectively (source strength and source location) were associated with subjective changes in tinnitus distress (measured using the TRQ), each of these measures were plotted over the treatment time-course (see Figure 7A, where 0 represents pre-treatment). Figure 7A shows that TRQ scores decreased exponentially over the progression of the tinnitus treatment, with the greatest magnitude of change occurring within the first 10 weeks (similar to (Davis, Paki & Hanley, 2007; Davis et al., 2008)). On the other hand, the source strength increases, initially, before decreasing, while the source location initially shifted in the anterior direction, before moving posteriorly. Based upon this, to identify whether the trajectories of change for subjective and objective measures were similar for each participant, we shifted the objective measure results by 5 weeks and aligned and replotted these with the TRQ scores (Figure 6B). It can be seen that the source strength and the source location data largely followed the TRQ score trend except for participant T-04, which suggests that the psychological effects of tinnitus treatment may precede neurophysiological changes.

To better understand how hearing loss affected the source strength and location, the tinnitus group were sub-categorised into mild-moderate and mild-severe sub-groups. Figures (6A–6D) show the source strengths from 500 Hz and 1000 Hz tones. These appeared to be greater

in the left and right hemispheres of the mild-severe group than in the mild-moderate group, however, a one-way MANOVA showed this to be insignificant ($F_{[4, 5]} = 4.395$, $p = 0.68$; Wilks' $\Lambda = .221$; partial $\eta 2 = .779$). Figures (6E–6H) compare the source location over the 30-week treatment program. Posterior source movement (comparing the pre-treatment with the 20-week during-treatment session, where we had data for all participants) for the mild-moderate group was observed in both hemispheres and at both frequencies, while posterior movement in the mild-severe group was only seen in the left hemisphere (Figures 6E and 6G). Using a one-way repeated ANOVA, this was trending towards significance at 500 Hz (uncorrected $p = 0.017$, corrected $p > 0.05$) but not at 1000 Hz ($p = 0.243$). However, the right hemisphere sources (Figures 6F and 6H) do not shift significantly (500 Hz, $p = 0.065$; 1000 Hz, $p = 0.113$) over the 20 week time period.

5.5 Discussion

In the current study, we examined sound-evoked MEG source amplitudes recorded in response to pure tones at octave-intervals between 500–4000 Hz, and 500 Hz cortical source locations (where hearing loss was not present).These were compared between a non-tinnitus control group, and a group with significant tinnitus before, during, and after a 30-week tinnitus treatment program. The results demonstrated differences in the mean source strengths of 500 Hz and 1000 Hz sound-evoked responses in the left hemispheres of tinnitus subjects and controls, which did not change significantly throughout treatment. Furthermore, the mean source locations of both frequencies were more anterior in the left hemispheres of tinnitus subjects at baseline compared to the controls. No differences were observed along the medio-lateral or inferior-superior axes, or anywhere in the right hemisphere. Importantly, for the first time, we have demonstrated that during tinnitus treatment (from 10-weeks post treatment),

tinnitus subjects had shifts in the left hemisphere cortical tonotopic map towards the source location of control subjects. This may provide further support for an association between the tinnitus percept and disruptions to tonotopic maps; alternatively, it could have resulted from sound enrichment (through the Neuromonics device) of areas that have been deprived of sensory input. Finally, we showed that the trajectory of change for self-reported tinnitus distress was similar to that of the 5-week time-shifted objective measures. This may suggest that perceptual changes precede neurophysiological plasticity, or that it is the dynamic nature of the change which is more important than the time-course of change.

The difference in left hemisphere 500 Hz and 1000 Hz source-evoked responses, which were larger in tinnitus subjects thank in controls, is consistent with a model of enhanced central gain (Noreña, 2011; Salinas & Sejnowski, 2001). Central gain control has been suggested to play a role in multiple systems, including the enhancement of sensory activity during selective attention (Hillyard, Vogel & Luck, 1998) and pathological pain (Sarkar et al., 2001, Woolf & Salter, 2000; Kuner, 2010). Flor and colleagues (1997) demonstrated enhanced RMS peak amplitudes of MEG waveforms elicited by electrical bipolar pulses delivered to the backs of patients with chronic back pain that were significantly related to chronicity and showed greater activation for painful stimuli compared with non-painful stimuli, presumably mediated by increases in central gain. In tinnitus research, considerable support for central gain has been shown in animal and computational models of tinnitus as well as by human studies (see (Schaette & Kemper, 2012; Auerbach, Rodrigues & Salvi, 2014; Zeng, 2013)). It could also explain the phenomenon of hyperacusis, which is often associated with tinnitus (Noreña & Chery-Croze, 2007). Using chronically implanted electrodes in chinchillas, Salvi and colleagues (2000) reported that increased sound-evoked responses in the inferior colliculus were measured at high sound intensities after loud-noise exposure, despite reduced responses

occurring in the more peripheral cochlea and cochlear nucleus. Brain imaging techniques have also shown cortical hyperactivity in the posterior superior temporal cortex of humans with tinnitus (Lockwood et al., 1998; Leaver et al., 2011), which is not affected by age or hearing loss. Weisz et al. (2005) found significantly enhanced source strength amplitudes at frequencies an octave below the lesion-edge (the audiometrically normal edge of the hearing loss slope) in the right hemisphere in 14 tinnitus subjects compared to 11 normal hearing controls, which was correlated with self-reported tinnitus intrusiveness. Within the current study, there were no significant reductions in source strength amplitudes during tinnitus treatment, despite a significant reduction in self-reported tinnitus severity. There appeared to be a small, but non-significant increase in the source strength amplitudes for both hemispheres at 5 weeks after treatment. This may have resulted from the Neuromonics tinnitus treatment program, which promotes the use of daily sound enrichment within the first 5–10 weeks of rehabilitation. Certainly, if central gain is driven by reductions in neural activity from the periphery, then it is reasonable that gain modulations could occur when the neural input is restored or enhanced [i.e. during listening to spectrally-enhanced music], with the steady state being restored once the sound enrichment was removed or significantly reduced. Interestingly, in eight adults with hyperacusis, Noreña and Chery-Croze (2007) showed significant reductions in loudness discomfort levels (LDLs) and self-report measures (using the multiple activity scale of hyperacusis) that were retained at least one month post-treatment after daily listening to low-level spectrally-shaped pure tones, suggesting a desensitisation of central gain. It is not clear whether the differences in central gain modulation observed in these two studies resulted from differences in their treatment paradigms, the pathophysiological problem being treated (i.e. tinnitus versus hyperacusis), the measures used to assess central gain, or were simply the result of their relatively small sample size.

In the current study, between-group differences in source strength amplitude were found at low frequencies in the left hemisphere only. The lack of difference at higher frequencies was likely due to differences in the stimuli's perceptual loudness (which were presented at a fixed level rather than a fixed sensation level), rather than lack of changes in central gain. Interestingly, the laterality of tinnitus hyperactivity has been demonstrated across multiple studies, although the hemisphere which is hyperactive is not consistent. For example, positron emission tomography [PET] studies using [18F] deoxyglucose (FDG-PET) measures in participants suffering from tinnitus demonstrated asymmetric metabolic hyperactivity. This predominated in the left hemisphere and was independent of tinnitus laterality and handedness, factors which are correlated with tinnitus improvements (Langguth et al., 2006; Wang et al., 2001).

It is possible that subjective changes in tinnitus severity and loudness perception precede neurophysiological changes that are measured objectively. Certainly in the current study, during tinnitus treatment, tinnitus participants' subjective tinnitus distress measure (i.e. TRQ scores) decreased rapidly during the first 10 weeks and then showed no further significant change. On the other hand, objective measurements of the 500 Hz evoked responses showed that the source strength amplitude increased and the source location moved anteriorly before moving posteriorly towards the location recorded for the non-tinnitus control group. Similarities between the trajectories of change were observed using a time-shifted comparison between the neurophysiological changes (which occur at a later stage) and perceptual changes (see Figure 4B) where the source moved posterior after the second treatment session (week 10), though the magnitude of the shift was not significant. A correlation between source-

evoked responses and tinnitus distress might not be a simple relationship, as it may involve other aspects such as attention, stress and emotion (Jastreboff, Hazell & Graham, 1994). Alternatively, the source-evoked responses could be associated with other features of tinnitus, such as perceptual characteristics, rather than distress itself. Leaver and colleagues (Leaver et al., 2012) demonstrated that cortical morphological markers of tinnitus distress and perceptual characteristics are not the same. Further, studies in perceptual learning suggest that neurophysiological changes might precede perceptual changes; therefore, differences in the time course of neurophysiological and behavioural changes are likely to exist across different sensory modalities, although it remains unclear how these interact (Dietrich et al., 2001; Pienkowski & Eggermont, 2012).

Disruptions to the cortical tonotopic map have been observed in humans with hearing loss and tinnitus (Mühlnickel et al., 1998; Eggermont, 2007). Such cortical disruptions typically correspond to the frequencies close to the lesion edge [more clearly observed for steeply sloping hearing losses], where there is an expansion or over-representation of audiometrically normal frequencies adjacent to disrupted frequencies [see Noreña & Eggermont (2005) for a review]. In the current study, however, the majority of subjects showed only a mild audiometric slope in the higher frequencies, so that a clearly defined lesion edge did not exist. Therefore we used a control octave of 500 and 1000 Hz, where hearing was within normal limits [<20dBHL], to evaluate differences between tinnitus and non-tinnitus groups. Consistent with the current study pre-treatment condition, Mühlnickel et al. (1998) and Weisz et al. (2005) showed that the disrupted frequencies in tinnitus participants were shifted anteriorly, relative to non-tinnitus controls. Specifically, Mühlnickel et al. (1998) showed, in ten adults with tinnitus and only mild hearing loss that a strong correlation existed between tinnitus strength and tinnitus frequency deviation from the expected tonotopic map in the

contralateral hemisphere [$r = 0.82$, $p < 0.01$]. The mechanisms underpinning cortical tonotopic map disruptions in tinnitus subjects are unclear, but may arise from unmasking of intra-cortical or thalamo-cortical connections in the affected frequency region (Robertson & Murre, 1999). Interestingly, Noreña and Eggermont (2005) have shown that disruptions to the tonotopic map in adult cats exposed to loud traumatic noise can be reduced by sound-enriched environments. Of fourteen adult cats which were acoustically traumatised, seven were placed in a continuously-sound enriched environment using a high frequency complex tone for at least 35 days. These cats showed significantly reduced peripheral hearing loss in the higher frequencies and normal cortical tonotopic maps compared to those without sound enrichment, suggesting that the presence of non-traumatic sound can compensate for the reduced neural activity caused by hearing loss. In the current study, during the 30 week tinnitus treatment program which used spectrally-shaped classical music, tinnitus subjects' 500 Hz and 1000 Hz source locations moved posteriorly after week 5, towards the source locations of non-tinnitus participants. Presumably, the changes in source location are a direct result of the sound therapy in combination with associated increases in arousal and attention (Rossini et al., 1998), rather than reductions in tinnitus impact. Furthermore, subjects with mild-moderate hearing loss demonstrated trends of source movements towards the locations of non-tinnitus controls, which might suggest that they were remediated more effectively over the 30 week program than were the mild-severe subjects. However, further studies are needed to determine the relative contributions of the counselling and the sound therapy components of the tinnitus treatment program to tonotopic map changes.

Brain plasticity in adults during rehabilitation from injury has been observed in other areas of healthcare. Studies in mono-hemispheric stroke rehabilitation using transcranial motor stimulation [TMS] and MEG, show associations between reorganisation of the motor and

sensory cortices and functional recovery of limb and hand movements (for a review see Kopp et al., 1999). Shifts in the hand motor maps along the mediolateral and anteroposterior axes have been observed (Liepert, Hamzei & Weiller, 2000; Traversa et al., 1997), as well as hyper-excitability of the unaffected hemisphere, assumed to result from disinhibition (Platz et al., 2005) and partial restoration of excitability in the affected hemisphere with gains in motor function (Hummel et al., 2005). For example, Platz and colleagues (2005) assessed changes in the motor cortex of stroke patients with severe arm paresis during a 4-week rehabilitation program, and compared these to functional changes measured using Fugl-Meyer improvement scores. Using multiple step-wise regression, they showed that a medial shift in the centre of gravity coordinates of the affected hemisphere was the only statistically significant predictor of motor improvement. Understanding brain plasticity might enable new tools for intervention to be designed or better targeted to the individual.

The current longitudinal study is limited by a relatively small numbers of participants which reduced the statistical power measures of the longitudinal study, and might limit its generalisability across individuals with chronic tinnitus. Furthermore, the control group was not age- or hearing-matched due to the difficulty in recruiting age matched individuals with similar levels of hearing loss and no tinnitus. However, similar results have been demonstrated by other studies with similar numbers of participants (Weisz et al., 2005; Mühlnickel et al., 1998), and many of the findings are consistent with animal models of tinnitus. Therefore, it is likely that the differences in sound-evoked cortical responses observed between the two groups were associated with the tinnitus percept rather than with confounders. As hearing thresholds did not significantly change throughout the 30 week treatment program, we assume that the changes in sound-evoked waveforms resulted either

from perceptual changes in tinnitus or its impact, or were a direct result of elements of the treatment program [e.g. sound enrichment].

In summary, the results of our study suggest that tinnitus is associated with increased central gain and disruptions to the cortical tonotopic map. Subjects with mild-moderate hearing loss may gain greater benefit from the sound therapy treatment than those with more severe losses. However, while a combined counselling and sound therapy-based tinnitus treatment program might reduce the negative effects of the tinnitus percept and mitigate the disruptions to the tonotopic map, enhanced central gain appears to be maintained, which suggests that it is more related to the reduced sound input associated with hearing loss rather than the tinnitus percept itself.

Author Contributions

Conceived and designed the experiments: CMM. Performed the experiments: RKI AM. Analysed the data: RKI CMM AM. Contributed reagents/materials/analysis tools: RKI. Wrote the paper: CMM RKI AM. Delivered the tinnitus treatment program: AM.

References

Auerbach, B. D., Rodrigues, P. V., & Salvi, R. J. (2014). Central gain control in tinnitus and hyperacusis. *Frontiers in neurology*, *5*, 206.

Baguley, D. M. (2002). Mechanisms of tinnitus. *British medical bulletin*, *63*(1), 195-212.

Beck, A. T., Steer, R. A., & Carbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical psychology review*, *8*(1), 77-100.

Carhart, R., & Jerger, J. (1959). Preferred method for clinical determination of pure-tone thresholds. *Journal of Speech & Hearing Disorders*.

Chen, G. D., Stolzberg, D., Lobarinas, E., Sun, W., Ding, D., & Salvi, R. (2013). Salicylate-induced cochlear impairments, cortical hyperactivity and re-tuning, and tinnitus. *Hearing research*, *295*, 100-113.

Davis, A., & Rafaie, E. A. (2000). Epidemiology of tinnitus. *Tinnitus handbook*, 1-23.

Davis, P. B., Paki, B., & Hanley, P. J. (2007). Neuromonics tinnitus treatment: third clinical trial. *Ear and hearing*, *28*(2), 242-259.

Davis, P. B., Wilde, R. A., Steed, L. G., & Hanley, P. J. (2008). Treatment of tinnitus with a customized acoustic neural stimulus: a controlled clinical study. *Ear, Nose & Throat Journal*, *87*(6), 330.

Dietrich, V., Nieschalk, M., Stoll, W., Rajan, R., & Pantev, C. (2001). Cortical reorganization in patients with high frequency cochlear hearing loss. *Hearing research*, *158*(1-2), 95-101.

Eggermont, J. J. (2006). Cortical tonotopic map reorganization and its implications for treatment of tinnitus. *Acta Oto-Laryngologica*, *126*(sup556), 9-12.

Eggermont, J. J. (2007). Correlated neural activity as the driving force for functional changes in auditory cortex. *Hearing research*, *229*(1-2), 69-80.

Flor, H., Braun, C., Elbert, T., & Birbaumer, N. (1997). Extensive reorganization of primary somatosensory cortex in chronic back pain patients. *Neuroscience letters*, *224*(1), 5-8.

Group, W. H. O. (2002). The alcohol, smoking and substance involvement screening test (ASSIST): development, reliability and feasibility. *Addiction*, *97*(9), 1183-1194.

Hays, R. D., Martin, S. A., Sesti, A. M., & Spritzer, K. L. (2005). Psychometric properties of the medical outcomes study sleep measure. *Sleep medicine*, *6*(1), 41-44.

Heller, M. F., & Bergman, M. (1953). VII Tinnitus Aurium in Normally Hearing Persons. *Annals of Otology, Rhinology & Laryngology*, *62*(1), 73-83.

Hillyard, S. A., Vogel, E. K., & Luck, S. J. (1998). Sensory gain control (amplification) as a mechanism of selective attention: electrophysiological and neuroimaging evidence. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *353*(1373), 1257-1270.

Hummel, F., Celnik, P., Giraux, P., Floel, A., Wu, W. H., Gerloff, C., & Cohen, L. G. (2005). Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain*, *128*(3), 490-499.

Ille, N., Berg, P., & Scherg, M. (2002). Artifact correction of the ongoing EEG using spatial filters based on artifact and brain signal topographies. *Journal of clinical neurophysiology*, *19*(2), 113-124.

Jastreboff, P. J., Hazell, J. W., & Graham, R. L. (1994). Neurophysiological model of tinnitus: dependence of the minimal masking level on treatment outcome. *Hearing Research*, *80*(2), 216-232.

Kaltenbach, J. A. (2011). Tinnitus: models and mechanisms. *Hearing research*, *276*(1-2), 52-60.

Kaltenbach, J. A., Rachel, J. D., Mathog, T. A., Zhang, J., Falzarano, P. R., & Lewandowski, M. (2002). Cisplatin-induced hyperactivity in the dorsal cochlear nucleus and its relation to outer hair cell loss: relevance to tinnitus. *Journal of neurophysiology*, *88*(2), 699-714.

Kaltenbach, J. A., Zacharek, M. A., Zhang, J., & Frederick, S. (2004). Activity in the dorsal cochlear nucleus of hamsters previously tested for tinnitus following intense tone exposure. *Neuroscience letters*, *355*(1-2), 121-125.

Kopp, B., Kunkel, A., Münickel, W., Villringer, K., Taub, E., & Flor, H. (1999). Plasticity in the motor system related to therapy-induced improvement of movement after stroke. *Neuroreport*, *10*(4), 807-810.

Kraus, N., McGee, T., Carrell, T. D., King, C., Tremblay, K., & Nicol, T. (1995). Central auditory system plasticity associated with speech discrimination training. *Journal of cognitive neuroscience*, *7*(1), 25-32.

Kuner, R. (2010). Central mechanisms of pathological pain. *Nature medicine*, *16*(11), 1258.

Langguth, B., Eichhammer, P., Kreutzer, A., Maenner, P., Marienhagen, J., Kleinjung, T., Sand, P., & Hajak, G. (2006). The impact of auditory cortex activity on characterizing and treating patients with chronic tinnitus–first results from a PET study. *Acta Oto-Laryngologica*, *126*(sup556), 84-88.

Leaver, A. M., Renier, L., Chevillet, M. A., Morgan, S., Kim, H. J., & Rauschecker, J. P. (2011). Dysregulation of limbic and auditory networks in tinnitus. *Neuron*, *69*(1), 33-43.

Leaver, A. M., Seydell-Greenwald, A., Turesky, T., Morgan, S., Kim, H. J., & Rauschecker, J. P. (2012). Cortico-limbic morphology separates tinnitus from tinnitus distress. *Frontiers in systems neuroscience*, *6*, 21.

Liepert, J., Hamzei, F., & Weiller, C. (2000). Motor cortex disinhibition of the unaffected hemisphere after acute stroke. *Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine*, *23*(11), 1761-1763.

Lockwood, A. H., Salvi, R. J., Coad, M. L., Towsley, M. L., Wack, D. S., & Murphy, B. W. (1998). The functional neuroanatomy of tinnitus Evidence for limbic system links and neural plasticity. *Neurology*, *50*(1), 114-120.

Meikle, M. B., Henry, J. A., Griest, S. E., Stewart, B. J., Abrams, H. B., McArdle, R., ... & Folmer, R. L. (2012). The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus. *Ear and hearing*, *33*(2), 153-176.

Menning, H., Roberts, L. E., & Pantev, C. (2000). Plastic changes in the auditory cortex induced by intensive frequency discrimination training. *Neuroreport*, *11*(4), 817-822.

Møller, A. R. (2007). Tinnitus: presence and future. *Progress in brain research*, *166*, 3-16.

Mühlnickel, W., Elbert, T., Taub, E., & Flor, H. (1998). Reorganization of auditory cortex in tinnitus. *Proceedings of the National Academy of Sciences*, *95*(17), 10340-10343.

Nenonen, J., Nurminen, J., Kičić, D., Bikmullina, R., Lioumis, P., Jousmäki, V., Taulu, S., Parkkonen, L., Putaala, M., & Kähkönen, S. (2010). Correction of disturbances caused by temporary and continuous head movements. In *17th International Conference on Biomagnetism Advances in Biomagnetism–Biomag2010* (pp. 43-46). Springer, Berlin, Heidelberg.

Nondahl, D. M., Cruickshanks, K. J., Dalton, D. S., Klein, B. E., Klein, R., Schubert, C. R., Tweed, T. S., & Wiley, T. L. (2007). The impact of tinnitus on quality of life in older adults. *Journal of the American Academy of Audiology*, *18*(3), 257-266.

Noreña, A. J. (2011). An integrative model of tinnitus based on a central gain controlling neural sensitivity. *Neuroscience & Biobehavioral Reviews*, *35*(5), 1089-1109.

Noreña, A. J., & Chery-Croze, S. (2007). Enriched acoustic environment rescales auditory sensitivity. *Neuroreport*, *18*(12), 1251-1255.

Noreña, A. J., & Eggermont, J. J. (2005). Enriched acoustic environment after noise trauma reduces hearing loss and prevents cortical map reorganization. *Journal of Neuroscience*, *25*(3), 699-705.

Pienkowski, M., & Eggermont, J. J. (2012). Reversible long-term changes in auditory processing in mature auditory cortex in the absence of hearing loss induced by passive, moderate-level sound exposure. *Ear and hearing*, *33*(3), 305-314.

Platz, T., Van Kaick, S., Möller, L., Freund, S., Winter, T., & Kim, I. H. (2005). Impairment–oriented training and adaptive motor cortex reorganisation after stroke: a fTMS study. *Journal of neurology*, *252*(11), 1363-1371.

Robertson, D., & Irvine, D. R. (1989). Plasticity of frequency organization in auditory cortex of guinea pigs with partial unilateral deafness. *Journal of Comparative Neurology*, *282*(3), 456-471.

Robertson, I. H., & Murre, J. M. (1999). Rehabilitation of brain damage: Brain plasticity and principles of guided recovery. *Psychological bulletin*, *125*(5), 544.

Rodieck, R., Kiang, N.S., & Gerstein, G. (1962). Some quantitative methods for the study of spontaneous activity of single neurons. *Biophysical Journal*, 2(4):351.

Rossini, P. M., Calautti, C., Pauri, F., & Baron, J. C. (2003). Post-stroke plastic reorganisation in the adult brain. *The Lancet Neurology*, *2*(8), 493-502.

Rossini, P. M., Caltagirone, C., Castriota-Scanderbeg, A., Cicinelli, P., Del Gratta, C., Demartin, M., Pizzella, V., Travera, R., & Romani, G. L. (1998). Hand motor cortical area reorganization in stroke: a study with fMRI, MEG and TCS maps. *Neuroreport*, *9*(9), 2141-2146.

Rossiter, S., Stevens, C., & Walker, G. (2006). Tinnitus and its effect on working memory and attention. *Journal of speech, language, and hearing research*, *49*(1), 150-160.

Salinas, E., & Sejnowski, T. J. (2001). Book review: gain modulation in the central nervous system: where behavior, neurophysiology, and computation meet. *The Neuroscientist*, *7*(5), 430-440.

Salvi, R. J., Wang, J., & Ding, D. (2000). Auditory plasticity and hyperactivity following cochlear damage. *Hearing research*, *147*(1-2), 261-274.

Sarkar, S., Hobson, A. R., Furlong, P. L., Woolf, C. J., Thompson, D. G., & Aziz, Q. (2001). Central neural mechanisms mediating human visceral hypersensitivity. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, *281*(5), G1196-G1202.

Schaette, R., & Kempter, R. (2012). Computational models of neurophysiological correlates of tinnitus. *Frontiers in systems neuroscience*, *6*, 34.

Schaette, R., & McAlpine, D. (2011). Tinnitus with a normal audiogram: physiological evidence for hidden hearing loss and computational model. *Journal of Neuroscience*, *31*(38), 13452-13457.

Shiomi, Y., Tsuji, J., Naito, Y., Fujiki, N., & Yamamoto, N. (1997). Characteristics of DPOAE audiogram in tinnitus patients. *Hearing research*, *108*(1-2), 83-88.

Sindhusake, D., Golding, M., Newall, P., Rubin, G., Jakobsen, K., & Mitchell, P. (2003). Risk factors for tinnitus in a population of older adults: the Blue Mountains hearing study. *Ear and hearing*, *24*(6), 501-507.

Spielberger, C. D., & Gorsuch, R. L. (1983). *State-trait anxiety inventory for adults: Manual, instrument, and scoring guide*. Mind Garden, Incorporated.

Sun, W., Lu, J., Stolzberg, D., Gray, L., Deng, A., Lobarinas, E., & Salvi, R. J. (2009). Salicylate increases the gain of the central auditory system. *Neuroscience*, *159*(1), 325-334.

Távora-Vieira, D., Eikelboom, R. H., & Miller, S. (2011). Neuromonics tinnitus treatment for patients with significant level of hearing loss: an adaptation of the protocol. *International journal of audiology*, *50*(12), 881-886.

Traversa, R., Cicinelli, P., Bassi, A., Rossini, P. M., & Bernardi, G. (1997). Mapping of motor cortical reorganization after stroke: a brain stimulation study with focal magnetic pulses. *Stroke*, *28*(1), 110-117.

Tremblay, K., Kraus, N., Carrell, T. D., & McGee, T. (1997). Central auditory system plasticity: generalization to novel stimuli following listening training. *The Journal of the Acoustical Society of America*, *102*(6), 3762-3773.

Tremblay, K., Kraus, N., McGee, T., Ponton, C., & Otis, B. (2001). Central auditory plasticity: changes in the N1-P2 complex after speech-sound training. *Ear and hearing*, *22*(2), 79-90.

Wang, H. T., Tian, J. H., Yin, D. Y., Jiang, S., Yang, W., Han, D., Yao, S., & Shao, M. (2001). Regional glucose metabolic increases in left auditory cortex in tinnitus patients: a preliminary study with positron emission tomography. *Chinese medical journal*, *114*(8), 848-851.

Wang, J., Ding, D., & Salvi, R. J. (2002). Functional reorganization in chinchilla inferior colliculus associated with chronic and acute cochlear damage. *Hearing research*, *168*(1-2), 238-249.

Ware, J. E., Kosinski, M., & Gandel, B. (2000). SF–36® health survey: Manual and interpretation guide (QualityMetric, Lincoln, RI).

Weisz, N., Wienbruch, C., Dohrmann, K., & Elbert, T. (2005). Neuromagnetic indicators of auditory cortical reorganization of tinnitus. *Brain*, *128*(11), 2722-2731.

Wienbruch, C., Paul, I., Weisz, N., Elbert, T., & Roberts, L. E. (2006). Frequency organization of the 40-Hz auditory steady-state response in normal hearing and in tinnitus. *Neuroimage*, *33*(1), 180-194.

Wilson, P. H., Henry, J., Bowen, M., & Haralambous, G. (1991). Tinnitus reaction questionnaire: psychometric properties of a measure of distress associated with tinnitus. *Journal of Speech, Language, and Hearing Research*, *34*(1), 197-201.

Woolf, C. J., & Salter, M. W. (2000). Neuronal plasticity: increasing the gain in pain. *Science*, *288*(5472), 1765-1768.

Yang, G., Lobarinas, E., Zhang, L., Turner, J., Stolzberg, D., Salvi, R., & Sun, W. (2007). Salicylate induced tinnitus: behavioral measures and neural activity in auditory cortex of awake rats. *Hearing research*, *226*(1-2), 244-253.

Zeng, F. G. (2013). An active loudness model suggesting tinnitus as increased central noise and hyperacusis as increased nonlinear gain. *Hearing research*, *295*, 172-179.

Tables and Figures

Table 1. Subject characteristics

Participant	Age (years)	Gender	Tinnitus Side	Tinnitus Loudness (dB)	Tinnitus Pitch (kHz)	Tinnitus Duration (years)	Hearing Loss
T-01	**59**	M	Equal	12	12	20	M-S
T-02	**56**	M	Equal	9	6	2	M-S
T-03	64	M	Central	5	8	12	M-S
T-04	**58**	M	Left	4	6	1	M-M
T-05	**63**	M	Left	4	6	6	M-S
T-06	**56**	M	Central	8	6	4	N/A
T-07	**24**	M	Right	10	8	8	M-S
T-08	**53**	F	Right	10	4	20	M-S
T-09	**51**	F	Left	8	6	4	M-M
T-10	**42**	M	Central	4	4	3	M-M
T-11	**68**	F	Left	8	6	2	N/A
T-12	**69**	M	Central	6	6	15	M-M

* M-S = Mild – Severe; M-M = Mild - Moderate

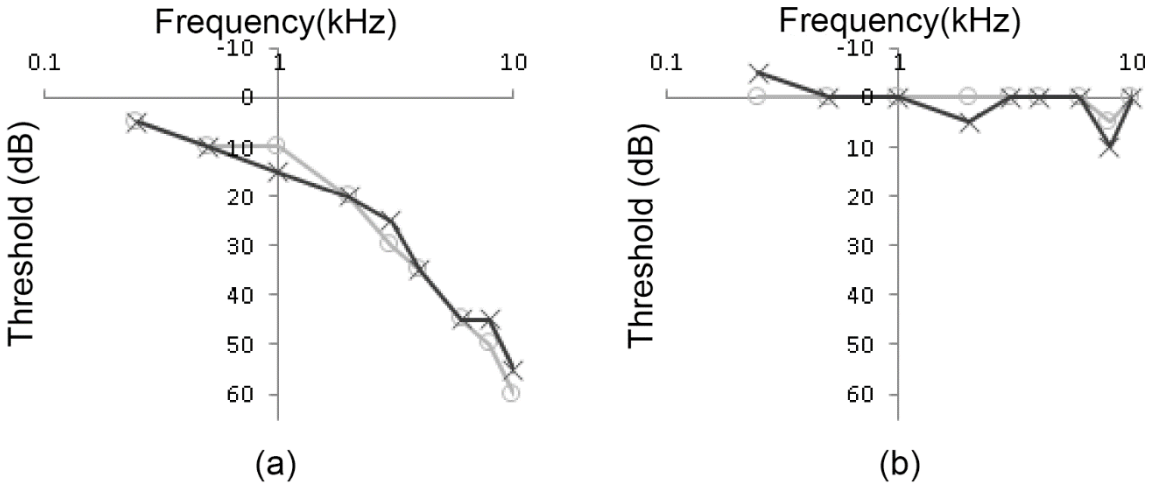


Figure 1. Mean audiograms for the (a) tinnitus group and (b) non-tinnitus group, where the black line represents the left ear and the light grey line represents the right ear.

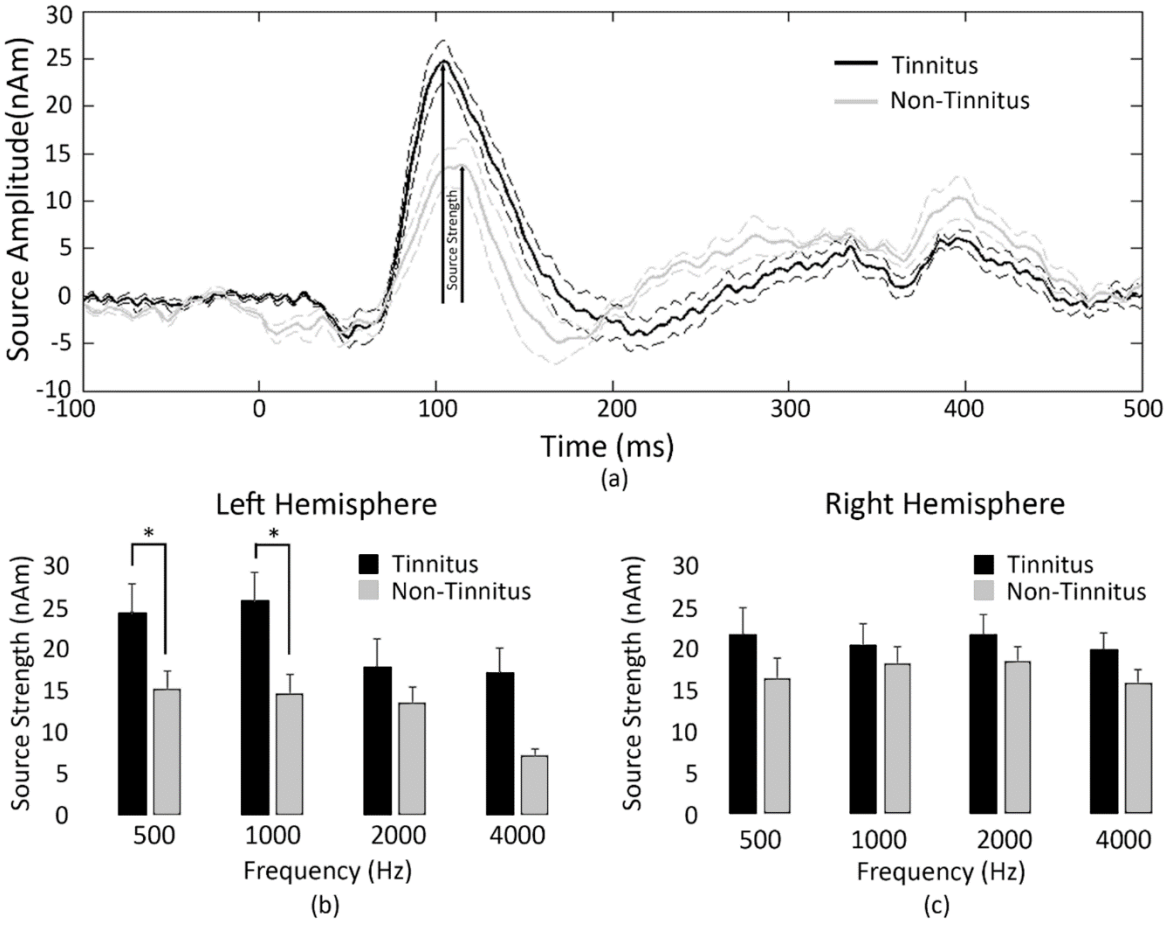


Figure 2. (a) Mean 500 Hz source waveforms for tinnitus (black, solid curve) and non-tinnitus (grey, solid curve) groups with standard errors shown in dotted lines for the left hemisphere source. (b) Mean (±SE) source strength measured in the left hemisphere in tinnitus (grey) and non-tinnitus (black) groups for octave frequencies between 250-4000Hz. (c) Mean (±SE) source strength measured in the right hemisphere in tinnitus (grey bars) and non-tinnitus (black bars) groups for octave frequencies between 250 - 4000Hz. Note that asterisks show statistical significance ($p<0.005$).

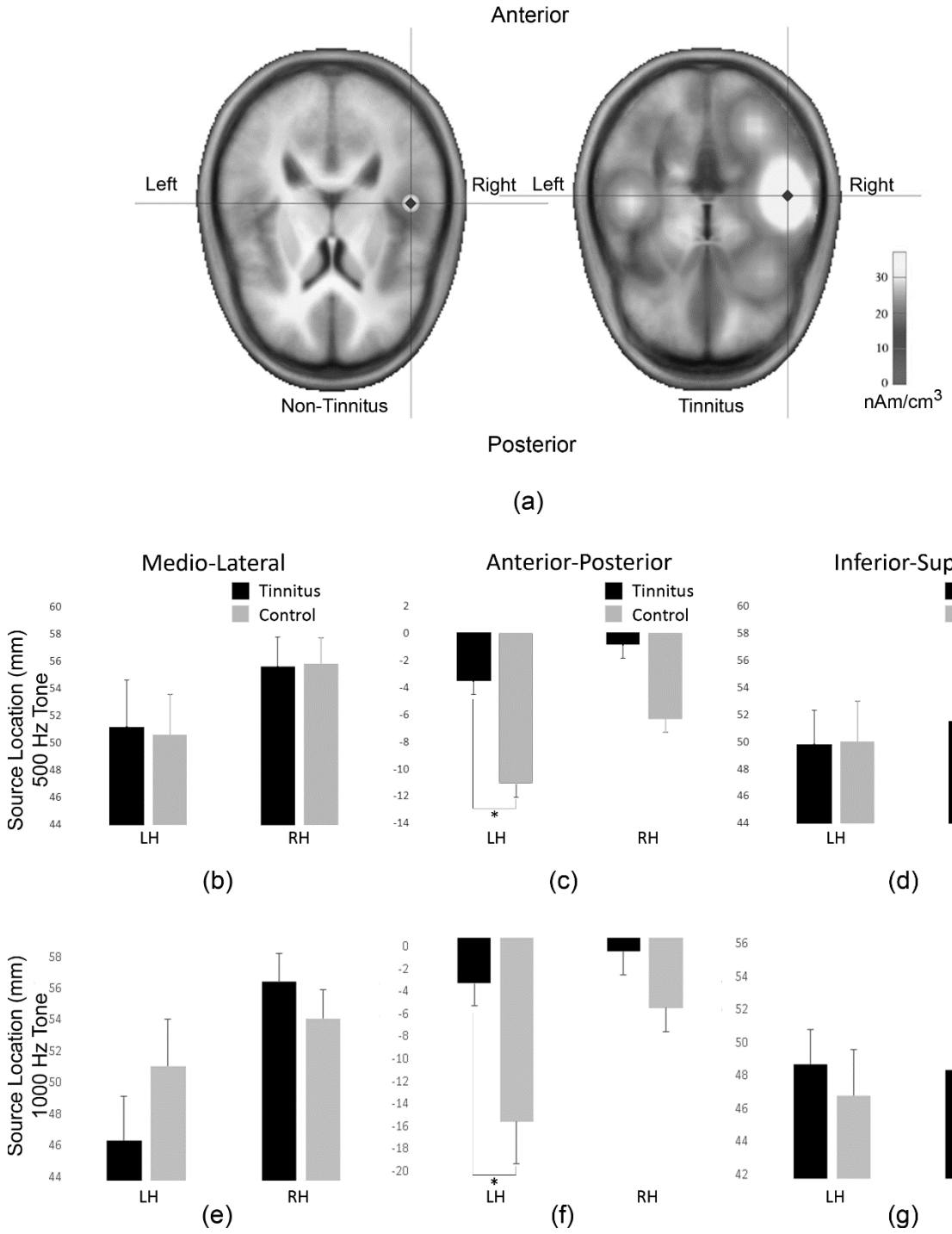


Figure 3. (a) Source location comparison between a non-tinnitus and tinnitus subject on the transverse place from a 500 Hz tone (subject T-11). Mean source location comparisons for tinnitus (black bars) compared with non-tinnitus (grey bars) subjects in the (b) medio-lateral (c) anterior-posterior (d) inferior-superior plane from the 500 Hz stimuli. Mean source location comparisons for tinnitus (black bars) compared with non-tinnitus (grey bars) subjects in the (e) medio-lateral (f) anterior-posterior and (g) inferior-superior plane from the 1000 Hz stimulus.

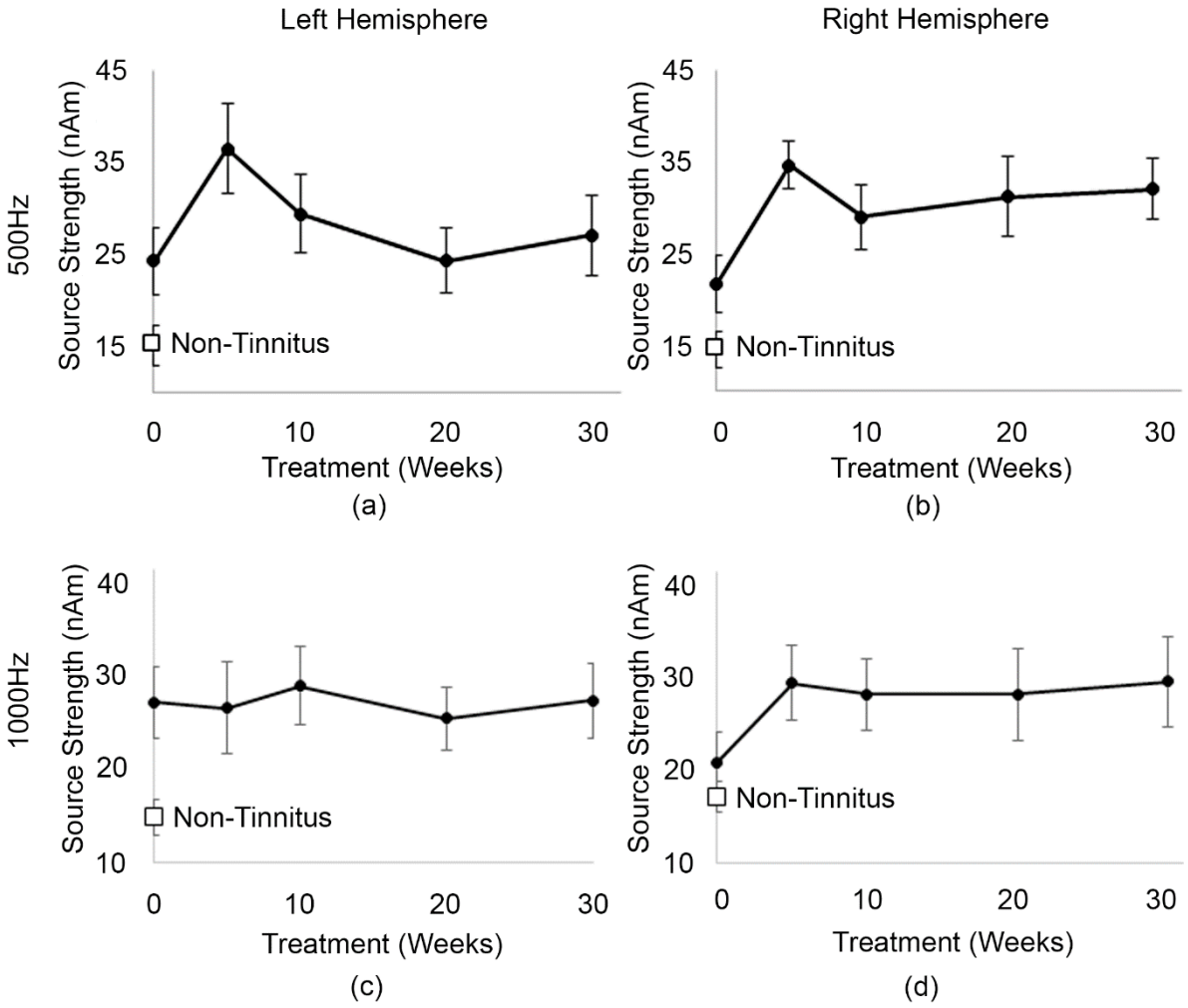


Figure 4. Mean source strength for tinnitus group throughout the 30 weeks tinnitus treatment program±SE for (a) 500Hz tone at the left hemisphere (b) 500Hz tone at right hemisphere (c) 1000Hz tone at left hemisphere (d) 1000Hz tone at right hemisphere. For comparison, the mean ± SE source strength for the non-tinnitus group is displayed (white box).

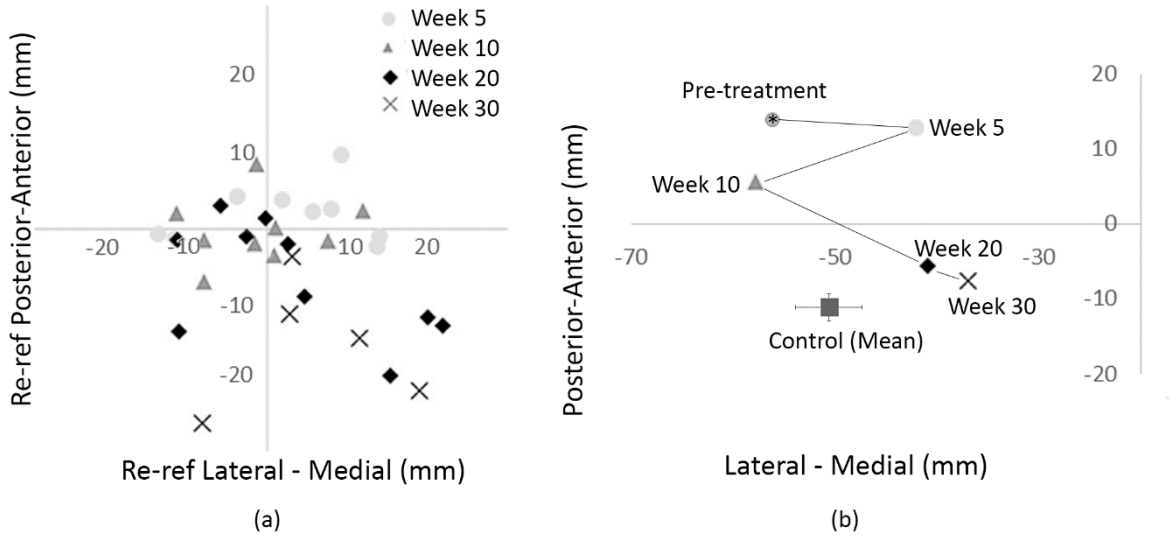


Figure 5. (a) Scatter plot of the left hemisphere 500 Hz source locations for tinnitus subjects referenced to pre-treatment values from week 5–30. (b) Changes in subject T-11's left hemisphere 500 Hz source location throughout treatment, compared to the mean (±SE) non-tinnitus group 500 Hz source location.

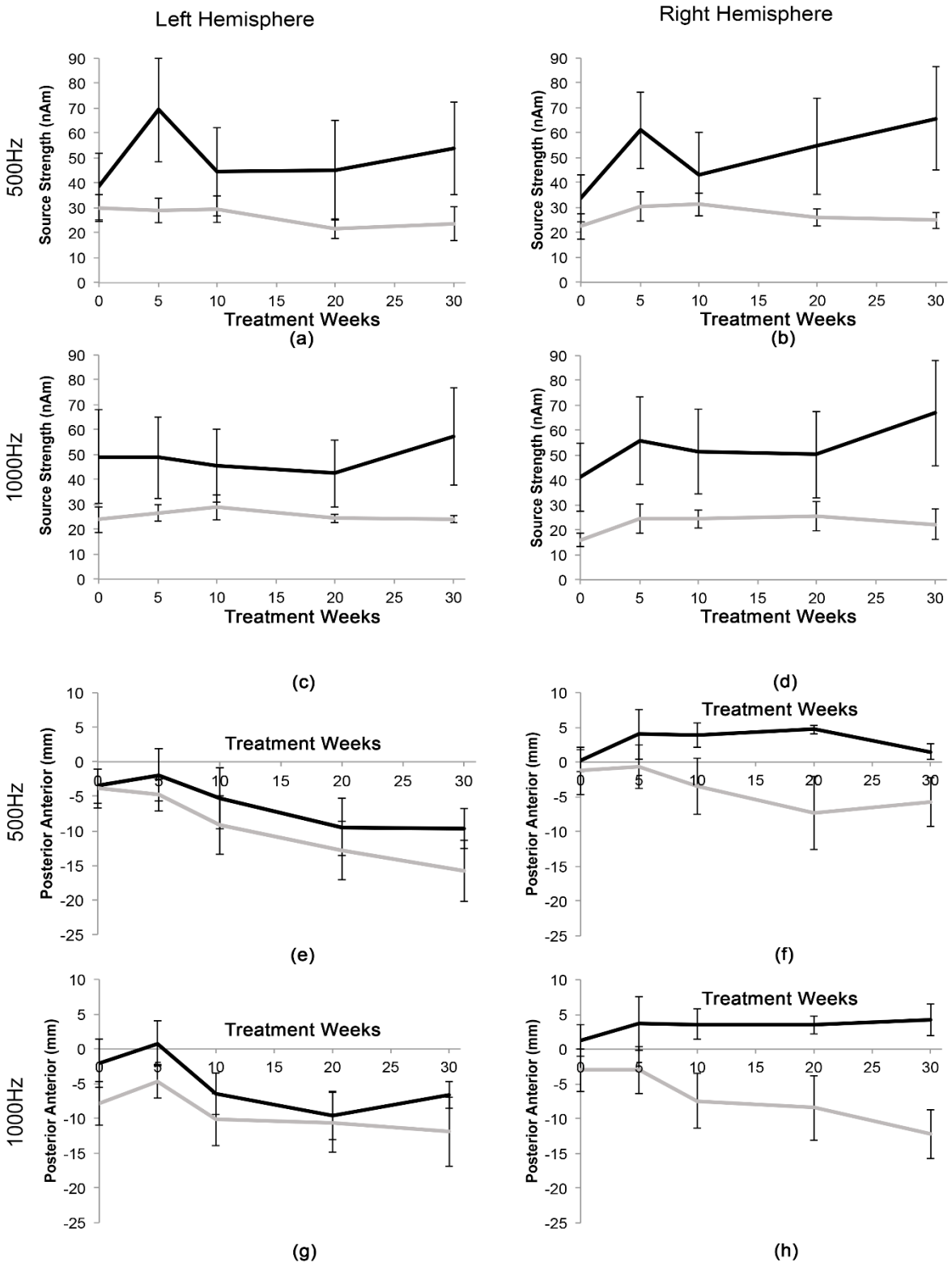


Figure 6. Comparisons between mild-moderate (grey lines) and mild-severe (black line) subjects' mean (±SE) source strengths for: (a) 500 Hz tone, left hemisphere; (b) 500 Hz tone, right hemisphere; (c) 1000 Hz tone, left hemisphere; and (d) 1000 Hz tone, right hemisphere. Mean anterior-posterior source locations for: (e) 500 Hz tone, left hemisphere; (f) 500 Hz tone, right hemisphere; (g) 1000 Hz tone, left hemisphere; and (h) 1000 Hz tone, right hemisphere.

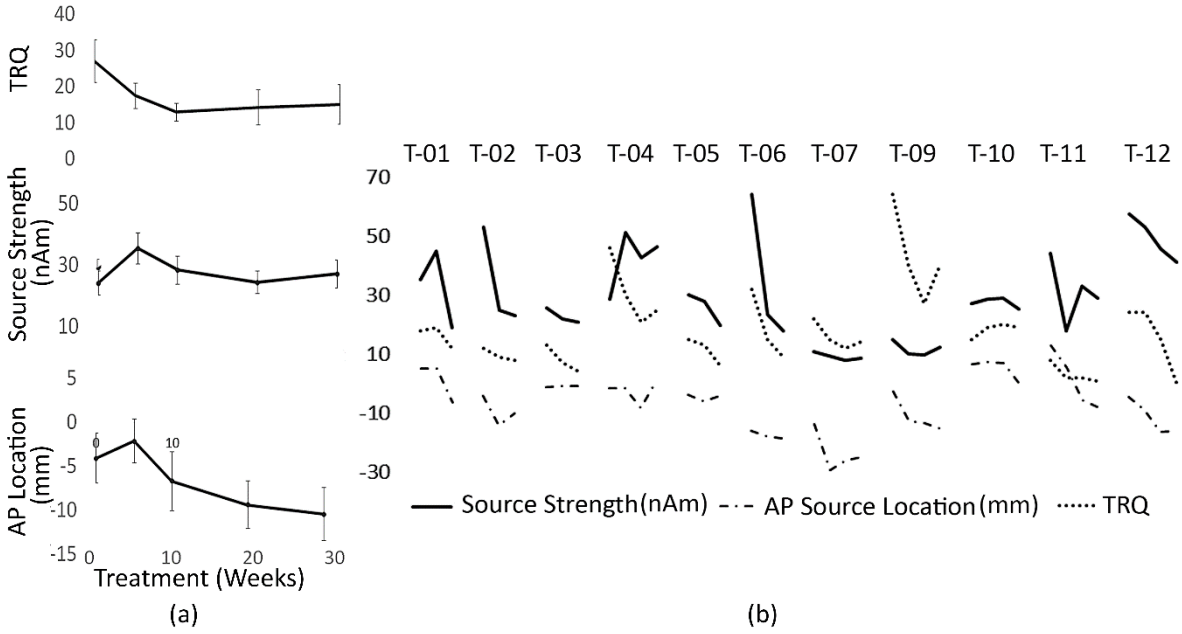


Figure 7. (a) Group mean (± SE) TRQ, source strength and anterior-posterior (AP) location during treatment. (b) Five week time-shifted source strength and anterior-posterior (AP) location and TRQ plotted for all tinnitus subjects.

Chapter 6: Discussion and conclusion

Ankit Mathur[1, 2], Catherine McMahon[1, 2], Ronny Ibrahim[1, 2]

[1]Department of Linguistics, Faculty of Human Sciences, Macquarie University, Sydney, Australia

[2]The HEARing Cooperative Research Centre, Australia

[3]Department of Statistics, Faculty of Science and Engineering, Macquarie University, Sydney, Australia

The present study was undertaken to better understand the pathophysiological factors that underpin tinnitus, their changes during a treatment program, and to identify whether cortical oscillations could be reliably used as a biomarker of tinnitus. Previous research has demonstrated that reduced alpha power and increased gamma power are consistently associated with tinnitus severity (Weisz et al., 2005, 2007, Schlee et al., 2014). Tonotopic map reorganisation in tinnitus patients has also been associated with tinnitus severity (Mühlnickel et al., 1998). Tinnitus is a complex phenomenon, and is typically accompanied by various comorbidities including hearing loss, varying degrees of anxiety and stress, and often depression (Fowler, 1944, 1948, Budd & Pugh, 1995). Therefore, it remains a challenge to exclusively associate the neurophysiological changes to the tinnitus percept or its severity. Pierzycki et al. (2016), using resting state whole scalp EEG, tested 42 tinnitus patients for test-retest variability and correlations between subjective (psychoacoustic and psychosocial) and objective measures of tinnitus. Despite a high test-retest correlations between EEG band power and tinnitus variables, they found no correlation between the objective and subjective measures, thus concluding that resting state whole scalp EEG cannot be used as a biomarker of tinnitus. Given the extensive literature reporting the usefulness of resting state cortical activity in identifying tinnitus objectively (see Chapter 1), and the contradictory nature of results reported by Pierzycki and colleagues (2016), the present study comes at a very crucial juncture. It uses a method that has not been attempted before - long term recording and comparison of resting state cortical activity based on MEG imaging and changes in resting state cortical activity during remediation. The present study attempted to isolate the distress associated with tinnitus (measured using two clinically-validated questionnaires) and associate this with neurophysiological changes, using repeated MEG testing of tinnitus patients during a six month tinnitus treatment program (concurrent with behavioural assessments), with the aim of identifying changes in the aforementioned biomarkers. It is

noteworthy that presently, to the best of our knowledge, no literature exists that describes long-term changes in cortical activity due to treatment, which could substantiate the identified biomarkers or help understand how psychological changes (tinnitus distress) are associated with the neurophysiological changes.

The first study was conducted to investigate the role of spontaneous alpha power in 11 tinnitus participants, and the changes in alpha power during the treatment program. Results suggested significantly reduced alpha power in temporal and parietal areas in tinnitus participants (before treatment), compared with normal hearing controls (*n=10*), and significant interactions were seen between TFI and alpha power in the TAR region over time. Furthermore, changes in distress were not correlated to alpha power, but there were moderate correlations between TPL alpha power and the *cognition* sub-component of TFI. This highlights the roles of focussed attention and the ability to concentrate in tinnitus patients, and the association of these factors with the neurophysiological changes. This experiment highlights that alpha power is a strong candidate to be a biological marker of tinnitus, though its ability to measure tinnitus distress needs further research.

In the second study, we critically evaluated the thalamocortical dysrhythmia (TCD) model of tinnitus, which classifies tinnitus with other neurological and neuropsychiatric disorders such as Parkinson's disease and neurogenic pain. The TCD model works on the principle of global workspace, wherein abnormal coupling of low (theta-alpha complex) and high (gamma) frequencies leads to perception in absence of external stimuli, e.g. tinnitus and phantom limb pain. In the present study, tinnitus patients did demonstrate reduced alpha power and increased gamma power but the differences were not statistically significant. However, the

alpha-gamma ratio was found to be significantly different between the tinnitus and non-tinnitus participants which, even in the absence of independent frequency band differences between groups, supports the model of TCD. No significant changes were found in the alpha/gamma ratio during treatment, despite a significant reduction in self-reported tinnitus distress. It is possible that neurophysiological disruptions are "hard-wired" in tinnitus patients and, despite relief from symptoms during therapy, chronic tinnitus sufferers are susceptible to tinnitus in future; or that neurophysiological changes occur at a later stage following reductions in tinnitus symptoms. It will be interesting to see if the neurophysiological changes are delayed or hard-wired, since the latter could explain relapses of tinnitus after successful intervention. Of course, the relatively low numbers of participants and the likely variability in neurophysiological changes occurring over a tinnitus treatment program could cause the present study to have insufficient statistical power to identify neurophysiological changes over time.

Chapter 5 aimed to investigate the disruptions to cortical gain (assessed using source strength) and the tonotopical map of tinnitus sufferers by studying cortical activity evoked by 500 Hz and 1000 Hz tones, where hearing was normal at test frequencies across both the tinnitus and non-tinnitus populations. There were more anterior source locations in the tinnitus group, with higher source strengths, compared to controls. A shift in the source location of the tinnitus group towards the non-tinnitus group's source location was recorded and an association between tinnitus distress and source location and strength was found, albeit with a time lag. These results highlight two important points:

i. Tinnitus and/or its comorbidities are either an outcome of tonotopic changes in the cortex, or cause the tonotopic changes in the cortex,

ii. The delay in neurophysiological changes, in relation to the psychological changes observed during tinnitus remediation, postulated in the previous experiment, gains support from this experiment. It also supports our hypothesis that treatment related neurophysiological changes may occur later than changes in reported distress. This calls for a change in methodology in future tinnitus studies, especially those involving objective evaluation of tinnitus remedial programs.

The neurophysiological changes identified in the experiment here describe two types of cortical changes co-occurring with tinnitus: 1) a change in alpha/gamma rhythms, and 2) change in the tonotopical map. We believe that the significance of these results was hampered by the small number of participants. It is therefore recommended to study larger groups in similar fashion, and also to identify whether a correlation exists between these two changes in the brain i.e. is the cortical reorganization associated with the changes in the alpha-gamma rhythm, and correlate with the same pathology, or are they distinct entities related to different comorbidities. Despite this study's other limitations, i.e. the absence of hearing- and age-matched control, which has been a handicap in most studies to date, the outcomes of the present study are mainly based on the longitudinal changes within tinnitus subjects during treatment, which overcomes the limitations of the control group to some extent.

With increasing evidence relates tinnitus perception to neurophysiological changes, it is highly recommended that a successful treatment program should address both top-down and bottom-up mechanisms i.e. cognitive and auditory components of the tinnitus percept and tinnitus-related distress. Methodology from present study can be adopted to evaluate the changes occurring in the brainwaves and tonotopicity during and after treatment to compare

the efficacy and methods of delivery of bottom-up treatment approaches (sound-based remedy) versus top-down methods (cognitive approaches such as CBT). It is recommended that such studies should continue after the treatment program since cortical changes may continue to occur post-treatment (as demonstrated by the lagged correlations between tonotopic changes and tinnitus distress in Chapter 5) which may be the key to identifying a more effective treatment.

An interesting avenue of research would be to study changes in cortical activity and tonotopic maps while administering GABA-enhancing drugs to tinnitus patients. Significant improvement in neuropathic pain using gabapentin, a GABA agonist, were demonstrated by Rosenberg et al. (1997), and some success in reversing tinnitus in rats has also been demonstrated by Bauer and Brozoski (2001). Identifying the changes that occur in the brain during the recession of tinnitus symptoms would do much to improve our understanding of tinnitus and other neurophysiological disorders.

Given the role of attention (auditory; Cuny et al., 2004; selective and divided; Stevens et al., 2007) in tinnitus patients and from the relationship discovered between alpha power and cognition (Chapter 3), it is regretful that no direct measure of attention was used in the present experiment. Measuring the attentional abilities of tinnitus patients, and changes in these abilities during the tinnitus remediation program would have helped understand the role, importance and presence or absence of a causal relationship between attention and tinnitus.

There are also other factors that can trigger or affect tinnitus, e.g. in the present study, two participants (one male, one female) reported stressful work environment. The male participant

retired from work during the course of treatment program, and reported improvement in self-reported tinnitus (initial TFI score: 43.40, final TFI score: 28.43) while the female participant continued working in the stressful environment and demonstrated minimal improvement (initial TFI score: 59.6, final TFI score: 50.8). It would be ideal to control stress, amongst other factors related to tinnitus, though it is not possible in real world situations, posing challenge to such psychological research.

Tinnitus participants in the present study had hearing levels ranging from clinically normal hearing (n=2) to moderately-severe high frequency hearing loss (n=9). Though a hearing level based comparison was not made in all the experiments (owing to the small number of participants, especially ones with normal hearing), such an experiment could reveal the role of hearing loss in tinnitus-related cortical changes and warrants future research.

Another interesting observation made in the present study was the effect of tinnitus duration on the spontaneous alpha power. To determine whether tinnitus duration influenced the magnitude of alpha power, tinnitus participants were divided into two groups, using a median split: (i) those with shorter ($\leq$ 8 years; n = 6) or (ii) longer (> 8 years; n = 5) durations of tinnitus. The longer duration tinnitus group tended to have lower alpha power compared with shorter group (Figure 1). These differences, however, were not significant for any brain region. Despite the small number of participants in the study and insignificant differences based on duration, the difference between the two groups is still an interesting trend.

Future directions

Based on the results of the present study, following recommendations for future research are made:

a) Similar long-term treatment studies with objective recordings conducted beyond the treatment duration to confirm if the neurophysiological changes are delayed, and follow psychological changes, or are hard wired in tinnitus patients.
b) Since the present results have, to some extent, demonstrated the role of cognitive mechanisms associated with neurophysiological changes, it is recommended that future research should expand the selection criteria for tinnitus participants and classify patients into groups based on the degree of severity of associated symptoms such as attention, anxiety and degree of hearing loss, not just tinnitus severity.
c) It is also recommended that future research focus on correlations between other frequency bands such as delta and beta, along with theta, alpha and gamma, and identify their roles in the global workspace model.
d) It is recommended to consider duration of tinnitus as an additional factor for classifying tinnitus groups as it may have a significant effect on the neurophysiological changes measured during treatment. It is possible that a longer tinnitus duration can hard-wire cortical changes which are hard to reverse with the current traditional treatment methods, and requiring different treatment protocols for long-duration subjects.

Conclusion

The present study succeeded in using MEG to differentiate between the tinnitus and control group, however we are still a long way from using MEG as an objective measure of tinnitus

distress. Certainly, the current study can be considered a pilot study for further research in to the development of improved methodologies for the objective measures of tinnitus and identification of improved remedial techniques targeting both top-down and bottom-up mechanisms. Such developments may lead to causal therapeutic interventions which provide tinnitus sufferers with lasting relief.

References

Bauer, C. A., & Brozoski, T. J. (2001). Assessing tinnitus and prospective tinnitus therapeutics using a psychophysical animal model. *JARO-Journal of the Association for Research in Otolaryngology*, *2*(1), 54-64.

Budd, R.J. & Pugh, R. (1995). The relationship between locus of control, tinnitus severity, and emotional distress in a group of tinnitus sufferers. *Journal of Psychosomatic research*. 39, 1015-1018.

Fowler, E.P. (1944). Head noises in normal and in disordered ears: Significance, measurement, differentiation and treatment. *Archives in Otolaryngology*, 30, 490-503.

Fowler, E. P. (1948). Nonvibratory tinnitus: Factors underlying subaudible and audible irritations. *Archives of Otolaryngology*, *47*(1), 29-36.

Mühlnickel, W., Elbert, T., Taub, E., & Flor, H. (1998). Reorganization of auditory cortex in tinnitus. *Proceedings of the National Academy of Sciences*, *95*(17), 10340-10343.

Pierzycki, R. H., McNamara, A. J., Hoare, D. J., & Hall, D. A. (2016). Whole scalp resting state EEG of oscillatory brain activity shows no parametric relationship with psychoacoustic and psychosocial assessment of tinnitus: a repeated measures study. *Hearing Research*, *331*, 101-108.

Rosenberg, J. M., Harrell, C., Ristic, H., Werner, R. A., & de Rosayro, A. M. (1997). The effect of gabapentin on neuropathic pain. *Clinical Journal of Pain*, *13*(3), 251-255.

Schlee, W., Schecklmann, M., Lehner, A., Kreuzer, P. M., Vielsmeier, V., Poeppl, T. B., & Langguth, B. (2014). Reduced variability of auditory alpha activity in chronic tinnitus. *Neural Plasticity*, *2014*.

Weisz, N., Moratti, S., Meinzer, M., Dohrmann, K., & Elbert, T. (2005). Tinnitus perception and distress is related to abnormal spontaneous brain activity as measured by magnetoencephalography. *PLoS Med*, *2*(6), e153.

Weisz, N., Müller, S., Schlee, W., Dohrmann, K., Hartmann, T., & Elbert, T. (2007). The neural code of auditory phantom perception. *Journal of Neuroscience*, *27*(6), 1479-1484.

Tables and Figures

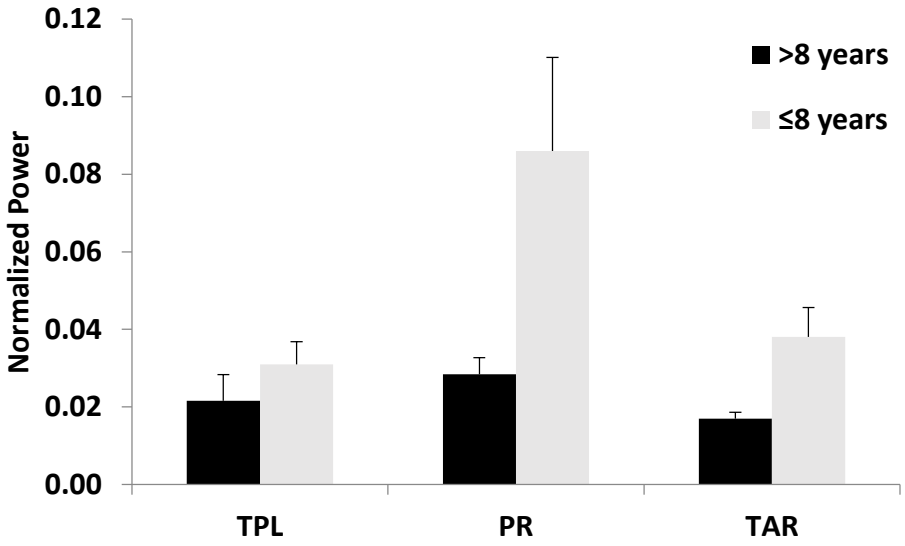


Figure 1. Effect of tinnitus duration on alpha power in several brain regions (mean+SE). Higher alpha power was recorded for participants with shorter histories of tinnitus. Participants were grouped based on the median duration of reported tinnitus.

Appendix

For Patient

Tinnitus Reaction Questionnaire (TRQ)

Name Date Completed:

This questionnaire is designed to find out what sort of effects tinnitus has had on your lifestyle, general well-being, etc. Some of the effects below may apply to you, some may not. Please answer all questions by circling the number that best reflects how your tinnitus has affected you **over the past week**.

	Not at all	A little of the time	Some of the time	A good deal of the time	Almost all of the time
1. My tinnitus has made me unhappy.	0	1	2	3	4
2. My tinnitus has made me feel tense.	0	1	2	3	4
3. My tinnitus has made me feel irritable.	0	1	2	3	4
4. My tinnitus has made me feel angry.	0	1	2	3	4
5. My tinnitus has led me to cry.	0	1	2	3	4
6. My tinnitus has led me to avoid quiet situations.	0	1	2	3	4
7. My tinnitus has made me feel less interested in going out.	0	1	2	3	4
8. My tinnitus has made me feel depressed.	0	1	2	3	4
9. My tinnitus has made me feel annoyed.	0	1	2	3	4
10. My tinnitus has made me feel confused.	0	1	2	3	4
11. My tinnitus has "driven me crazy".	0	1	2	3	4
12. My tinnitus has interfered with my enjoyment of life.	0	1	2	3	4
13. My tinnitus has made it hard for me to concentrate.	0	1	2	3	4
14. My tinnitus has made it hard for me to relax.	0	1	2	3	4
15. My tinnitus has made me feel distressed.	0	1	2	3	4
16. My tinnitus has made me feel helpless.	0	1	2	3	4
17. My tinnitus has made me feel frustrated with things.	0	1	2	3	4
18. My tinnitus has interfered with my ability to work.	0	1	2	3	4
19. My tinnitus has led me to despair.	0	1	2	3	4
20. My tinnitus has led me to avoid noisy situations.	0	1	2	3	4
21. My tinnitus has led me to avoid social situations.	0	1	2	3	4
22. My tinnitus has made me feel hopeless about the future.	0	1	2	3	4
23. My tinnitus has interfered with my sleep.	0	1	2	3	4
24. My tinnitus has led me to think about suicide.	0	1	2	3	4
25. My tinnitus has made me feel panicky.	0	1	2	3	4
26. My tinnitus has made me feel tormented.	0	1	2	3	4
Total					

Wilson et al. 1991

TINNITUS FUNCTIONAL INDEX

Today's Date _____ (Month / Day / Year) Your Name _____ (Please Print)

Please read each question below carefully. To answer a question, select *ONE* of the numbers that is listed for that question, and draw a *CIRCLE* around it like this: (10%) or (1).

I — Over the PAST WEEK...

1. What percentage of your time awake were you consciously **AWARE OF** your tinnitus?

Never aware ► 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% ◄ *Always aware*

2. How **STRONG** or **LOUD** was your tinnitus?

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

3. What percentage of your time awake were you **ANNOYED** by your tinnitus?

None of the time ► 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% ◄ *All of the time*

SC — Over the PAST WEEK...

4. Did you feel **IN CONTROL** in regard to your tinnitus?

Very much in control ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Never in control*

5. How easy was it for you to **COPE** with your tinnitus?

Very easy to cope ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Impossible to cope*

6. How easy was it for you to **IGNORE** your tinnitus?

Very easy to ignore ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Impossible to ignore*

C — Over the PAST WEEK how much did your tinnitus interfere with...

7. Your ability to **CONCENTRATE**?

Did not interfere ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Completely interfered*

8. Your ability to **THINK CLEARLY?**

Did not interfere ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Completely interfered*

9. Your ability to **FOCUS ATTENTION** on other things besides your tinnitus?

Did not interfere ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Completely interfered*

SL — Over the PAST WEEK...

10. How often did your tinnitus make it difficult to **FALL ASLEEP** or **STAY ASLEEP**?

Never had difficulty ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Always had difficulty*

11. How often did your tinnitus cause you difficulty in getting **AS MUCH SLEEP** as you needed?

Never had difficulty ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Always had difficulty*

12. How much of the time did your tinnitus keep you from **SLEEPING** as **DEEPLY** or as **PEACEFULLY** as you would have liked?

None of the time ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *All of the time*

08.15.08

Please read each question below carefully. To answer a question, select *ONE* of the numbers that is listed for that question, and draw a *CIRCLE* around it like this: (10%) or (1).

A	**Over the PAST WEEK, how much has your tinnitus interfered with...**	*Did not interfere*										*Completely interfered*
13.	Your ability to **HEAR CLEARLY**?	0	1	2	3	4	5	6	7	8	9	10
14.	Your ability to **UNDERSTAND PEOPLE** who are talking?	0	1	2	3	4	5	6	7	8	9	10
15.	Your ability to **FOLLOW CONVERSATIONS** in a group or at meetings?	0	1	2	3	4	5	6	7	8	9	10

R	**Over the PAST WEEK, how much has your tinnitus interfered with...**	*Did not interfere*										*Completely interfered*
16.	Your **QUIET RESTING ACTIVITIES**?	0	1	2	3	4	5	6	7	8	9	10
17.	Your ability to **RELAX**?	0	1	2	3	4	5	6	7	8	9	10
18.	Your ability to enjoy "**PEACE AND QUIET**?"	0	1	2	3	4	5	6	7	8	9	10

Q	**Over the PAST WEEK, how much has your tinnitus interfered with...**	*Did not interfere*										*Completely interfered*
19.	Your enjoyment of **SOCIAL ACTIVITIES**?	0	1	2	3	4	5	6	7	8	9	10
20.	Your **ENJOYMENT OF LIFE**?	0	1	2	3	4	5	6	7	8	9	10
21.	Your **RELATIONSHIPS** with family, friends and other people?	0	1	2	3	4	5	6	7	8	9	10

22. How often did your tinnitus cause you to have difficulty performing your **WORK OR OTHER TASKS**, such as home maintenance, school work, or caring for children or others?

Never had difficulty ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Always had difficulty*

E	**Over the PAST WEEK....**

23. How **ANXIOUS** or **WORRIED** has your tinnitus made you feel?

Not at all anxious or worried ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely anxious or worried*

24. How **BOTHERED or UPSET** have you been because of your tinnitus?

Not at all bothered or upset ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely bothered or upset*

25. How **DEPRESSED** were you because of your tinnitus?

Not at all depressed ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely depressed*

 08.15.08

INSTRUCTIONS FOR SCORING THE TINNITUS FUNCTIONAL INDEX (TFI)

1. PREPARATION FOR SCORING:

A. Two items to be transformed: Items #1 and #3 require a simple transformation from a percentage scale to a 0-10 scale, achieved by dividing the values circled by the respondent by 10. The examiner should write the transformed value in the margin beside the relevant item, preferably using ink of a different color than that used by the respondent.

B. Ambiguous items: Because respondents differ in regard to how clearly they circle or mark their answers on the 0-10 scale for each item, the examiner should review every item to resolve any ambiguities. It is helpful if examiners note their decision about each answer in the margin beside the given item, using the differently-colored ink. Some commonly-occurring ambiguities and how to handle them are as follows:

(1) **More than one value marked on the 0-10 scale for a given item**—Typically done by respondents whose tinnitus undergoes large variations over time. The clinic or the examiner should settle on a consistent procedure for all such responses, such as (a) averaging the multiple values indicated for a given item, or (b) marking the item "cannot code", thus removing that item from consideration in the overall TFI score. (The latter choice reduces the information available for calculating the respondent's overall score, and may be desirable only in extremely variable cases where the respondent's reliability is questionable.)

(2) **Respondent marks a value *between* the 0-10 values on the item scale**— Again, the clinic or the examiner should settle on a consistent procedure for handling all such ambiguous responses in the same way, such as (a) noting a value of 3.5 in the margin, for a respondent who marked the scale between 3 and 4, or (b) collapsing the intermediate value either to the right (to 4) or to the left (to 3).

(3) **Respondent does not make any response to a given item**—The clinic or examiner should decide beforehand how they will indicate missing values, and that notation (e.g. "NA" for "No Answer") should be entered in the margin. If the data will be entered into a computer database, a standard missing value such as"99" can be entered in the margin beside the relevant item. Of course, care must be taken to exclude "99" values if the examiner performs a manual calculation of the overall TFI score.

C. Unambiguous items: To facilitate rapid scanning and summing of *all* valid answers to obtain the respondent's overall TFI score, all of the unambiguous values indicated by the respondent should also be noted in the margin, each such value beside its corresponding item. The examiner can then quickly generate a valid score for the overall TFI.

2. CALCULATION OF OVERALL TFI SCORE:

1) Sum all valid answers from both TFI pages (maximum possible score = 250 if the respondent were to rate all 25 TFI items at the maximum value of 10).

2) Divide by the number of questions for which that respondent provided valid answers (yields the respondent's mean item score for all items having valid answers).

3) Multiply by 10 (provides that respondent's overall TFI score within 0-100 range).

CAUTION—Overall TFI score is **not valid** if respondent **omits more** than 7 answers. To be valid as a measure of tinnitus severity, the respondent must answer **at least 18 items** (72% of items).

3. CALCULATION OF SUBSCALE SCORES

The 8 subscales address 8 important domains of negative tinnitus impact as indicated below. Each subscale has a brief title (in capital letters) and a 1- or 2-letter abbreviation (e.g. **I** for Intrusive , Sc for Sense of Control):

SUBSCALE NAME (and conceptual content)	ITEMS IN SUBSCALE
I: INTRUSIVE (unpleasantness, intrusiveness, persistence)	#1, #2, #3
Sc: SENSE OF CONTROL (reduced sense of control)	#4, #5, #6
C: COGNITIVE Cognitive interference	#7, #8, #9
Sl: SLEEP Sleep disturbance	#10, #11, #12
A: AUDITORY Auditory difficulties attributed to tinnitus	#13, #14, #15
R: RELAXATION Interference with relaxation	#16, #17, #18
Q: QUALITY OF LIFE (QOL) Quality of life reduced	#19, #20, #21, #22
E: EMOTIONAL Emotional distress	#23, #24, #25

Each of the 8 subscales consists of 3 items except for the Quality of life subscale, which consists of 4 items *(SEE ITEMS LIST ABOVE)*. **For valid subscale scores**, no more than 1 item should be omitted from the 3-item subscales, and no more than 2 items omitted from the QOL scale. Computation of subscale scores is as follows:

1) Sum all of that respondent's valid answers for a given subscale.

2) Divide by the number of valid answers that were provided by that respondent for that subscale.

3) Multiply by 10. For the respondent in question, this procedure generates a subscale score in the range 0-100 for each valid subscale.

CAUTION—Do not attempt to compute a respondent's overall TFI score by combining that respondent's valid subscale scores, as the valid subscales may encompass a total number of items that is different from the number of items accepted as valid for the overall TFI score.

Modified Mini Screen (MMS)

Client Name: _____ OASAS ID _____

Weeks since admission _____ Interviewer _____

Today's Date_____ Supervisor Initials (Optional)_____

SECTION A

1. Have you been consistently depressed or down, most of the day, nearly every day, for the past 2 weeks?	YES	NO
2. In the past 2 weeks, have you been less interested in most things or less able to enjoy the things you used to enjoy most of the time?	YES	NO
3. Have you felt sad, low or depressed most of the time for the last two years?	YES	NO
4. In the past month, did you think that you would be better off dead or wish you were dead?	YES	NO
5. Have you ever had a period of time when you were feeling up, hyper or so full of energy or full of yourself that you got into trouble or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.)	YES	NO
6. Have you ever been so irritable, grouchy or annoyed for several days, that you had arguments, verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or overreacted, compared to other people, even when you thought you were right to act this way?	YES	NO
PLEASE TOTAL THE NUMBER OF "YES" RESPONSES TO QUESTIONS 1-6		

BDI

Name:
No:

Choose one statement from among the group of four statements in each question that best describes how you have been feeling during the **past few days**. Circle the number beside your choice.

1	**0** I do not feel sad. **1** I feel sad. **2** I am sad all the time and I can't snap out of it. **3** I am so sad or unhappy that I can't stand it.	8	**0** I don't feel I am any worse than anybody else. **1** I am critical of myself for my weaknesses or mistakes. **2** I blame myself all the time for my faults. **3** I blame myself for everything bad that happens.
2	**0** I am not particularly discouraged about the future. **1** I feel discouraged about the future. **2** I feel I have nothing to look forward to. **3** I feel that the future is hopeless and that things cannot improve.	9	**0** I don't have any thoughts of killing myself. **1** I have thoughts of killing myself, but I would not carry them out. **2** I would like to kill myself. **3** I would kill myself if I had the chance.
3	**0** I do not feel like a failure. **1** I feel I have failed more than the average person. **2** As I look back on my life, all I can see is a lot of failure. **3** I feel I am a complete failure as a person.	10	**0** I don't cry any more than usual. **1** I cry more now than I used to. **2** I cry all the time now. **3** I used to be able to cry, but now I can't cry even though I want to.
4	**0** I get as much satisfaction out of things as I used to. **1** I don't enjoy things the way I used to. **2** I don't get any real satisfaction out of anything anymore. **3** I am dissatisfied or bored with everything.	11	**0** I am no more irritated by things than I ever am. **1** I am slightly more irritated now than usual. **2** I am quite annoyed or irritated a good deal of the time. **3** I feel irritated all the time now.
5	**0** I don't feel particularly guilty. **1** I feel guilty a good part of the time. **2** I feel quite guilty most of the time. **3** I feel guilty all of the time.	12	**0** I have not lost interest in other people. **1** I am less interested in other people than I used to be. **2** I have lost most of my interest in other people. **3** I have lost all of my interest in other people.
6	**0** I don't feel I am being punished. **1** I feel I may be punished. **2** I expect to be punished. **3** I feel I am being punished.	13	**0** I make decisions about as well as I ever could. **1** I put off making decisions more than I used to. **2** I have greater difficulty in making decisions than before. **3** I can't make decisions at all anymore.
7	**0** I don't feel disappointed in myself. **1** I am disappointed in myself. **2** I am disgusted with myself. **3** I hate myself.	14	**0** I don't feel that I look any worse than I used to. **1** I am worried that I am looking old or unattractive. **2** I feel that there are permanent changes in my appearance that make me look unattractive. **3** I believe that I look ugly.

15	**0** I can work about as well as before. **1** It takes an extra effort to get started at doing something. **2** I have to push myself very hard to do anything. **3** I can't do any work at all.	19	**0** I haven't lost much weight, if any, lately. **1** I have lost more than five pounds. **2** I have lost more than ten pounds. **3** I have lost more than fifteen pounds. (Score 0 if you have been purposely trying to lose weight.)
16	**0** I can sleep as well as usual. **1** I don't sleep as well as I used to. **2** I wake up 1-2 hours earlier than usual and find it hard to get back to sleep. **3** I wake up several hours earlier than I used to and cannot get back to sleep.	20	**0** I am no more worried about my health than usual. **1** I am owrried about physical problems such as aches and pains, or upset stomach, or constipation. **2** I am very worried about physical problems, and it's hard to think of much else. **3** I am so worried about my physical problems that I cannot think about anything else.
17	**0** I don't get more tired than usual. **1** I get tired more easily than I used to. **2** I get tired from doing almost anything. **3** I am too tired to do anything.	21	**0** I have not noticed any recent change in my interest in sex. **1** I am less interested in sex than I used to be. **2** I am much less interested in sex now. **3** I have lost interested in sex completely.
18	**0** My appetite is no worse than usual. **1** My appetite is not as good as it used to be. **2** My appetite is much worse now. **3** I have no appetite at all anymore.		

A. WHO - ASSIST V3.0

INTERVIEWER ID		COUNTRY		CLINIC	
PATIENT ID		DATE			

INTRODUCTION *(Please read to patient)*

Thank you for agreeing to take part in this brief interview about alcohol, tobacco products and other drugs. I am going to ask you some questions about your experience of using these substances across your lifetime and in the past three months. These substances can be smoked, swallowed, snorted, inhaled, injected or taken in the form of pills (show drug card).

Some of the substances listed may be prescribed by a doctor (like amphetamines, sedatives, pain medications). For this interview, we will not record medications that are used as prescribed by your doctor. However, if you have taken such medications for reasons other than prescription, or taken them more frequently or at higher doses than prescribed, please let me know. While we are also interested in knowing about your use of various illicit drugs, please be assured that information on such use will be treated as strictly confidential.

NOTE: BEFORE ASKING QUESTIONS, GIVE ASSIST RESPONSE CARD TO PATIENT

Question 1

(if completing follow-up please cross check the patient's answers with the answers given for Q1 at baseline. Any differences on this question should be queried)

In your life, which of the following substances have you ever used? *(NON-MEDICAL USE ONLY)*	No	Yes
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	3
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	3
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	3
d. Cocaine (coke, crack, etc.)	0	3
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	3
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	3
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	3
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	3
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	3
j. Other - specify:	0	3

Probe if all answers are negative:
"Not even when you were in school?"

If "No" to all items, stop interview.

If "Yes" to any of these items, ask Question 2 for each substance ever used.

Question 2

In the past three months, how often have you used the substances you mentioned *(FIRST DRUG, SECOND DRUG, ETC)*?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	2	3	4	6
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	2	3	4	6
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	2	3	4	6
d. Cocaine (coke, crack, etc.)	0	2	3	4	6
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	2	3	4	6
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	2	3	4	6
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	2	3	4	6
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	2	3	4	6
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	2	3	4	6
j. Other - specify:	0	2	3	4	6

If "Never" to all items in Question 2, skip to Question 6.

If any substances in Question 2 were used in the previous three months, continue with Questions 3, 4 & 5 for each substance used.

Question 3

During the past three months, how often have you had a strong desire or urge to use *(FIRST DRUG, SECOND DRUG, ETC)*?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	3	4	5	6
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	3	4	5	6
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	3	4	5	6
d. Cocaine (coke, crack, etc.)	0	3	4	5	6
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	3	4	5	6
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	3	4	5	6
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	3	4	5	6
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	3	4	5	6
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	3	4	5	6
j. Other - specify:	0	3	4	5	6

Question 4

During the past three months, how often has your use of *(FIRST DRUG, SECOND DRUG, ETC)* led to health, social, legal or financial problems?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	4	5	6	7
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	4	5	6	7
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	4	5	6	7
d. Cocaine (coke, crack, etc.)	0	4	5	6	7
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	4	5	6	7
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	4	5	6	7
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	4	5	6	7
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	4	5	6	7
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	4	5	6	7
j. Other - specify:	0	4	5	6	7

Question 5

During the past three months, how often have you failed to do what was normally expected of you because of your use of *(FIRST DRUG, SECOND DRUG, ETC)*?	Never	Once or Twice	Monthly	Weekly	Daily or Almost Daily
a. Tobacco products					
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	5	6	7	8
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	5	6	7	8
d. Cocaine (coke, crack, etc.)	0	5	6	7	8
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	5	6	7	8
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	5	6	7	8
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	5	6	7	8
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	5	6	7	8
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	5	6	7	8
j. Other - specify:	0	5	6	7	8

Ask Questions 6 & 7 for all substances ever used (i.e. those endorsed in Question 1)

Question 6

Has a friend or relative or anyone else ever expressed concern about your use of *(FIRST DRUG, SECOND DRUG, ETC.)*?	No, Never	Yes, in the past 3 months	Yes, but not in the past 3 months
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	6	3
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	6	3
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	6	3
d. Cocaine (coke, crack, etc.)	0	6	3
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	6	3
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	6	3
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	6	3
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	6	3
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	6	3
j. Other – specify	0	6	3

Question 7

Have you ever tried and failed to control, cut down or stop using *(FIRST DRUG, SECOND DRUG, ETC.)*?	No, Never	Yes, in the past 3 months	Yes, but not in the past 3 months
a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)	0	6	3
b. Alcoholic beverages (beer, wine, spirits, etc.)	0	6	3
c. Cannabis (marijuana, pot, grass, hash, etc.)	0	6	3
d. Cocaine (coke, crack, etc.)	0	6	3
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)	0	6	3
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)	0	6	3
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)	0	6	3
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)	0	6	3
i. Opioids (heroin, morphine, methadone, codeine, etc.)	0	6	3
j. Other – specify	0	6	3

Question 8

	No, Never	Yes, in the past 3 months	Yes, but not in the past 3 months
Have you ever used any drug by injection? *(NON-MEDICAL USE ONLY)*	0	2	1

IMPORTANT NOTE

Patients who have injected drugs in the last 3 months should be asked about their pattern of injecting during this period, to determine their risk levels and the best course of intervention.

PATTERN OF INJECTING	INTERVENTION GUIDELINES
Once weekly or less or Fewer than 3 days in a row	→ Brief intervention including "risks associated with injecting" card
More than once per week or 3 or more days in a row	→ Further assessment and more intensive treatment*

HOW TO CALCULATE A SPECIFIC SUBSTANCE INVOLVEMENT SCORE

For each substance (labelled a. to j.) add up the scores received for questions 2 through 7 inclusive. Do not include the results from either Q1 or Q8 in this score. For example, a score for cannabis would be calculated as: **Q2c + Q3c + Q4c + Q5c + Q6c + Q7c**

Note that Q5 for tobacco is not coded, and is calculated as: **Q2a + Q3a + Q4a + Q6a + Q7a**

THE TYPE OF INTERVENTION IS DETERMINED BY THE PATIENT'S SPECIFIC SUBSTANCE INVOLVEMENT SCORE

	Record specific substance score	no intervention	receive brief intervention	more intensive treatment *
a. tobacco		0 - 3	4 - 26	27+
b. alcohol		0 - 10	11 - 26	27+
c. cannabis		0 - 3	4 - 26	27+
d. cocaine		0 - 3	4 - 26	27+
e. amphetamine		0 - 3	4 - 26	27+
f. inhalants		0 - 3	4 - 26	27+
g. sedatives		0 - 3	4 - 26	27+
h. hallucinogens		0 - 3	4 - 26	27+
i. opioids		0 - 3	4 - 26	27+
j. other drugs		0 - 3	4 - 26	27+

NOTE: *FURTHER ASSESSMENT AND MORE INTENSIVE TREATMENT may be provided by the health professional(s) within your primary care setting, or, by a specialist drug and alcohol treatment service when available.

B. WHO ASSIST V3.0 RESPONSE CARD FOR PATIENTS

Response Card - substances

a. Tobacco products (cigarettes, chewing tobacco, cigars, etc.)
b. Alcoholic beverages (beer, wine, spirits, etc.)
c. Cannabis (marijuana, pot, grass, hash, etc.)
d. Cocaine (coke, crack, etc.)
e. Amphetamine type stimulants (speed, diet pills, ecstasy, etc.)
f. Inhalants (nitrous, glue, petrol, paint thinner, etc.)
g. Sedatives or Sleeping Pills (Valium, Serepax, Rohypnol, etc.)
h. Hallucinogens (LSD, acid, mushrooms, PCP, Special K, etc.)
i. Opioids (heroin, morphine, methadone, codeine, etc.)
j. Other - specify:

Response Card (ASSIST Questions 2 – 5)

Never: not used in the last 3 months

Once or twice: 1 to 2 times in the last 3 months.

Monthly: 1 to 3 times in one month.

Weekly: 1 to 4 times per week.

Daily or almost daily: 5 to 7 days per week.

Response Card (ASSIST Questions 6 to 8)

No, Never

Yes, but not in the past 3 months

Yes, in the past 3 months

C. ALCOHOL, SMOKING AND SUBSTANCE INVOLVEMENT SCREENING TEST (WHO ASSIST V3.0) FEEDBACK REPORT CARD FOR PATIENTS

Name_____ Test Date _____

Specific Substance Involvement Scores

Substance	Score	Risk Level
a. Tobacco products		0-3 Low 4-26 Moderate 27+ High
b. Alcoholic Beverages		0-10 Low 11-26 Moderate 27+ High
c. Cannabis		0-3 Low 4-26 Moderate 27+ High
d. Cocaine		0-3 Low 4-26 Moderate 27+ High
e. Amphetamine type stimulants		0-3 Low 4-26 Moderate 27+ High
f. Inhalants		0-3 Low 4-26 Moderate 27+ High
g. Sedatives or Sleeping Pills		0-3 Low 4-26 Moderate 27+ High
h. Hallucinogens		0-3 Low 4-26 Moderate 27+ High
i. Opioids		0-3 Low 4-26 Moderate 27+ High
j. Other - specify		0-3 Low 4-26 Moderate 27+ High

What do your scores mean?

Low:	You are at low risk of health and other problems from your current pattern of use.
Moderate:	You are at risk of health and other problems from your current pattern of substance use.
High:	You are at high risk of experiencing severe problems (health, social, financial, legal, relationship) as a result of your current pattern of use and are likely to be dependent

Are you concerned about your substance use?

a. tobacco	Your risk of experiencing these harms is:..... Low ☐ Moderate ☐ High ☐ (tick one) Regular tobacco smoking is associated with:
	Premature aging, wrinkling of the skin
	Respiratory infections and asthma
	High blood pressure, diabetes
	Respiratory infections, allergies and asthma in children of smokers
	Miscarriage, premature labour and low birth weight babies for pregnant women
	Kidney disease
	Chronic obstructive airways disease
	Heart disease, stroke, vascular disease
	Cancers

b. alcohol	Your risk of experiencing these harms is:..... Low ☐ Moderate ☐ High ☐ (tick one) Regular excessive alcohol use is associated with:
	Hangovers, aggressive and violent behaviour, accidents and injury
	Reduced sexual performance, premature ageing
	Digestive problems, ulcers, inflammation of the pancreas, high blood pressure
	Anxiety and depression, relationship difficulties, financial and work problems
	Difficulty remembering things and solving problems
	Deformities and brain damage in babies of pregnant women
	Stroke, permanent brain injury, muscle and nerve damage
	Liver disease, pancreas disease
	Cancers, suicide

c. cannabis	Your risk of experiencing these harms is:..... Low ☐ Moderate ☐ High ☐ (tick one) Regular use of cannabis is associated with:
	Problems with attention and motivation
	Anxiety, paranoia, panic, depression
	Decreased memory and problem solving ability
	High blood pressure
	Asthma, bronchitis
	Psychosis in those with a personal or family history of schizophrenia
	Heart disease and chronic obstructive airways disease
	Cancers

d. cocaine	Your risk of experiencing these harms is:.... Low ☐ Moderate ☐ High ☐ (tick one) **Regular use of cocaine is associated with:**
	Difficulty sleeping, heart racing, headaches, weight loss
	Numbness, tingling, clammy skin, skin scratching or picking
	Accidents and injury, financial problems
	Irrational thoughts
	Mood swings - anxiety, depression, mania
	Aggression and paranoia
	Intense craving, stress from the lifestyle
	Psychosis after repeated use of high doses
	Sudden death from heart problems

e. amphetamine type stimulants	Your risk of experiencing these harms is:..... Low ☐ Moderate ☐ High ☐ (tick one) **Regular use of amphetamine type stimulants is associated with:**
	Difficulty sleeping, loss of appetite and weight loss, dehydration
	Jaw clenching, headaches, muscle pain
	Mood swings –anxiety, depression, agitation, mania, panic, paranoia
	Tremors, irregular heartbeat, shortness of breath
	Aggressive and violent behaviour
	Psychosis after repeated use of high doses
	Permanent damage to brain cells
	Liver damage, brain haemorrhage, sudden death (ecstasy) in rare situations

f. inhalants	Your risk of experiencing these harms is:..... Low ☐ Moderate ☐ High ☐ (tick one) **Regular use of inhalants is associated with:**
	Dizziness and hallucinations, drowsiness, disorientation, blurred vision
	Flu like symptoms, sinusitis, nosebleeds
	Indigestion, stomach ulcers
	Accidents and injury
	Memory loss, confusion, depression, aggression
	Coordination difficulties, slowed reactions, hypoxia
	Delirium, seizures, coma, organ damage (heart, lungs, liver, kidneys)
	Death from heart failure

g. sedatives	Your risk of experiencing these harms is: Low ☐ Moderate ☐ High ☐ (tick one) Regular use of sedatives is associated with:
	Drowsiness, dizziness and confusion
	Difficulty concentrating and remembering things
	Nausea, headaches, unsteady gait
	Sleeping problems
	Anxiety and depression
	Tolerance and dependence after a short period of use.
	Severe withdrawal symptoms
	Overdose and death if used with alcohol, opioids or other depressant drugs.

h. hallucinogens	Your risk of experiencing these harms is:..... Low ☐ Moderate ☐ High ☐ (tick one) Regular use of hallucinogens is associated with:
	Hallucinations (pleasant or unpleasant) – visual, auditory, tactile, olfactory
	Difficulty sleeping
	Nausea and vomiting
	Increased heart rate and blood pressure
	Mood swings
	Anxiety, panic, paranoia
	Flash-backs
	Increase the effects of mental illnesses such as schizophrenia

i. opioids	Your risk of experiencing these harms is: Low ☐ Moderate ☐ High ☐ (tick one) Regular use of opioids is associated with:
	Itching, nausea and vomiting
	Drowsiness
	Constipation, tooth decay
	Difficulty concentrating and remembering things
	Reduced sexual desire and sexual performance
	Relationship difficulties
	Financial and work problems, violations of law
	Tolerance and dependence, withdrawal symptoms
	Overdose and death from respiratory failure

E. TRANSLATION AND ADAPTATION TO LOCAL LANGUAGES AND CULTURE: A RESOURCE FOR CLINICIANS AND RESEARCHERS

The ASSIST instrument, instructions, drug cards, response scales and resource manuals may need to be translated into local languages for use in particular countries or regions. Translation from English should be as direct as possible to maintain the integrity of the tools and documents. However, in some cultural settings and linguistic groups, aspects of the ASSIST and it's companion documents may not be able to be translated literally and there may be socio-cultural factors that will need to be taken into account in addition to semantic meaning. In particular, substance names may require adaptation to conform to local conditions, and it is also worth noting that the definition of a standard drink may vary from country to country.

Translation should be undertaken by a bi-lingual translator, preferably a health professional with experience in interviewing. For the ASSIST instrument itself, translations should be reviewed by a bi-lingual expert panel to ensure that the instrument is not ambiguous. Back translation into English should then be carried out by another independent translator whose main language is English to ensure that no meaning has been lost in the translation. This strict translation procedure is critical for the ASSIST instrument to ensure that comparable information is obtained wherever the ASSIST is used across the world.

Translation of this manual and companion documents may also be undertaken if required. These do not need to undergo the full procedure described above, but should include an expert bi-lingual panel.

Before attempting to translate the ASSIST and related documents into other languages, interested individuals should consult with the WHO about the procedures to be followed and the availability of other translations. Write to the Department of Mental Health and Substance Dependence, World Health Organisation, 1211 Geneva 27, Switzerland.

SELF-EVALUATION QUESTIONNAIRE STAI Form Y-1

Please provide the following information:

Name_____Date_____S_____

Age_____ Gender (*Circle*) **M** **F** T_____

DIRECTIONS:

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel *right* now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	NOT AT ALL	SOMEWHAT	MODERATELY SO	VERY MUCH SO
1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I am tense	1	2	3	4
4. I feel strained	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes	1	2	3	4
8. I feel satisfied	1	2	3	4
9. I feel frightened	1	2	3	4
10. I feel comfortable	1	2	3	4
11. I feel self-confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I am jittery	1	2	3	4
14. I feel indecisive	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel confused	1	2	3	4
19. I feel steady	1	2	3	4
20. I feel pleasant	1	2	3	4

STAIP-AD Test Form Y
www.mindgarden.com

SELF-EVALUATION QUESTIONNAIRE

STAI Form Y-2

Name_____ Date_____

DIRECTIONS

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you *generally* feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

	ALMOST NEVER	SOMETIMES	OFTEN	ALMOST ALWAYS
21. I feel pleasant	1	2	3	4
22. I feel nervous and restless	1	2	3	4
23. I feel satisfied with myself	1	2	3	4
24. I wish I could be as happy as others seem to be	1	2	3	4
25. I feel like a failure	1	2	3	4
26. I feel rested	1	2	3	4
27. I am "calm, cool, and collected"	1	2	3	4
28. I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4
29. I worry too much over something that really doesn't matter	1	2	3	4
30. I am happy	1	2	3	4
31. I have disturbing thoughts	1	2	3	4
32. I lack self-confidence	1	2	3	4
33. I feel secure	1	2	3	4
34. I make decisions easily	1	2	3	4
35. I feel inadequate	1	2	3	4
36. I am content	1	2	3	4
37. Some unimportant thought runs through my mind and bothers me	1	2	3	4
38. I take disappointments so keenly that I can't put them out of my mind	1	2	3	4
39. I am a steady person	1	2	3	4
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	1	2	3	4

STAIP-AD Test Form Y
www.mindgarden.com

Human Research Ethics Committee

MACQUARIE UNIVERSITY

FINAL REPORT FORM
FOR TEACHING OR RESEARCH INVOLVING HUMAN PARTICIPANTS

***** Submission Instructions ******

- If you are a student, this form must be either signed or submitted via email by your supervisor
- If your application was reviewed by a Human Ethics Faculty Sub-Committee or you have received an email reminder from a faculty sub-committee, then you can submit your completed final report form to the relevant faculty sub-Committee.
- For all other Final Reports please submit your completed form to ethics.secretariat@mq.edu.au or to the Ethics Secretariat, Research Office, Level 3, Research HUB, Building C5C.

Handwritten forms will not be accepted.

Once your report has been submitted it will be noted by the Committee. ***Please note that you will NOT receive any correspondence from the HREC regarding your report.*** *However, the HREC may undertake an audit at any time without notification.*

Please answer all questions. Please do not delete questions or any part of a question.
Use lay terms wherever possible.

1. **TITLE of research project or unit code and name:**

Objective measures of tinnitus and its remediation

2. **REFERENCE NO.:** **HE27FEB2009-R06343**

3. **CHIEF INVESTIGATOR:**
(If you are submitting a Final Report for an ethics application submitted after 1 January 2010 then the CI must be a staff member/supervisor)

Name:	**Catherine McMahon**
Title:	
Staff No.:	
Student No.:	
Position held:	

Department & Faculty	
Tel. No.: (work)	
Email address:	

4. **SUPERVISOR: (For Honours, Post-Graduate and HDR Students:** If you are submitting a Final Report for an application submitted **prior to 2010** please complete supervisor's details)

** FOR APPLICATIONS SUBMITTED PRIOR TO 2010 where Student is CI **

Name:	
Title:	
Staff No.:	
Department & Faculty	
Tel. No.: (work)	
Email address:	

5. Please indicate the current status of the project:

(a) *Completed on* [ ] (dd/mm/yyyy)

(b) *Not completed but the project has run for 5 years from the original approval therefore this is a Final Report for the current ethical approval.*

I will be submitting a new application for approval to enable the project to continue. ☐ Yes ☒ No

(c) *Not commenced or discontinued on* [ ] (dd/mm/yyyy)

Give a brief report below explaining why the project was not commenced or was discontinued:

6. During the course of the project, have you complied with the conditions of approval (i.e. any conditions imposed by the Committee and the standard conditions of approval outlined on your letter of final approval)?

☒ Yes ☐ No

If you have answered NO, explain what conditions have not been met and why:

7. Have any ethical concerns or difficulties arisen during the course of the project? ☐ Yes ☒ No

If you answered **YES**, describe the ethical concerns or difficulties and any adverse effects on participants, and steps taken to deal with these:

8. The following questions relate to the current and future storage arrangements of the research data and the maintenance of its confidentiality and security:

(a) Will the data be securely stored as listed in the initial Application (Item 6.9)? ☒ Yes ☐ No

If NO, please provide details.

(b) Will anyone else have access to the data besides those listed in the application (Item 6.10) or in any approved amendments? ☐ Yes ☒ No

If YES, please provide details

(c) Will you be keeping the data for the minimum 5 year period from the date the research was completed or 5 years from the date of the last publication? ☒ Yes ☐ No

If NO, please provide details.

(c) Are there plans to destroy the data which were not mentioned in the initial application?

☐ Yes ☒ No

If YES, please provide details,

9. **CERTIFICATION:**

NB. If you are Honours, Postgraduate or HDR student and you submitted an ethics application prior to 2010, then your report needs to be signed by yourself and your supervisor. (Submission by your supervisor's email will be accepted in lieu of a signature).

I confirm that this project has been conducted in a manner that conforms in all respects with the *National Statement on Ethical Conduct in Human Research* (2007), all other relevant pieces of legislation, codes and guidelines and the procedures set out in the original protocol.

(Guidelines and National Statement available via http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/policy)

Supervisor:	*Student Investigator (If applicable):*
Signed:	*Signed:* **Ankit Mathur**
Name: Catherine McMahon	*Name:* **ANKIT MATHUR**
Date: 4-11-2014	*Date:* **4/11/2014**

Please note that you will NOT receive any correspondence from the HREC regarding your report.

NB. Students: Form must be signed by your supervisor (or submitted via email from your supervisor)