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The Use of Hearing Aids and Transcranial Direct Current Stimulation (tDCS) for Tinnitus Management

Giriraj Singh Shekhawat

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Audiology, The University of Auckland, 2013.

Abstract

Background/Aim: Tinnitus is a perception of sound in the absence of an external sound source. Millions of people world-wide experience some form of tinnitus and for approximately 5% of them, tinnitus can have catastrophic effects on their quality of life. There are currently no effective pharmacological cures, but many therapies that attempt to reduce tinnitus perception or reaction through a combination of counselling and sound therapy or neuromodulation exists. The primary objective of this doctoral thesis was to explore a novel approach for tinnitus management combining hearing aids (sound therapy) and transcranial direct current stimulation (tDCS).

Methods: Five studies were undertaken as a part of this doctoral thesis. 1. A retrospective analysis, of the audiometric and tinnitus test records of 192 participants suffering from chronic tinnitus was undertaken to investigate the best audiometric predictor of tinnitus pitch. 2. A scoping literature review, investigating the role of hearing aids in tinnitus management was undertaken. Out of 277 shortlisted studies, data was charted for 29 studies (18 research studies and 11 reviews) based on their relevance to the topic of investigation. 3. An exploratory pilot study was completed by 25 participants with chronic tinnitus and aidable hearing loss to study the impact of variation of the desired sensation level input/output [DSL(I/0) v5.0] hearing aid prescription procedure of hearing aid output on tinnitus. 4. A dose-response tDCS trial aimed to optimise the intensity and duration of anodal tDCS of the left temporoparietal area (LTA) for suppressing tinnitus in 25 participants with chronic tinnitus. 5. A double-blind sham controlled randomised clinical trial (seven month duration) of tinnitus treatment in which multi-session tDCS of the LTA was used along with hearing aids in 40 participants with chronic tinnitus and aidable hearing loss.

Results and Discussion: The best predictor of tinnitus pitch was found to be the frequency at which the hearing threshold was approximately 50 dBHL. This was proposed to be the point of transition from predominantly outer hair cell damage to the threshold of inner hair cell damage resulting in deafferentation triggered tinnitus. The scoping review supported the use of hearing aids for tinnitus management; however more quality evidence and randomised control trials documenting the effectiveness of hearing aids for tinnitus management was recommended. The exploratory study of hearing aid prescription

revealed DSL(I/0) v5.0 as a good starting point for prescribing hearing aid gain for tinnitus management. The most effective tDCS settings for transient tinnitus suppression were 2mA current intensity and 20 minutes duration. Hearing aids can significantly improving tinnitus related quality of life irrespective of tDCS. tDCS lead to positive effects on the minimum masking levels however no effect on tinnitus questionnaires.

Conclusions: High frequency audiometry should be an integral part of tinnitus assessment. Hearing aids (sound therapy) are effective in managing tinnitus. Further research is needed to explore whether sound therapy may be improved by methods priming the auditory system.

DEDICATION

My Spiritual Mentor Satguru Baba Hardev Singh Ji

For shaping my spiritual life

Mom, Dad, Anita, Khushi, & Muskaan

For their unconditional love and support

All my Teachers especially Dr. Grant D Searchfield

For nurturing & mentoring my academic life

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Glossary

ABR – Auditory Brainstem Response

ANOVA – Analysis of Variance

ANS – Autonomic Nervous System

ATM – Audiological Tinnitus Management

BA – Brodmann Area

BDI – Beck Depression Inventory

CBT – Cognitive Behaviour Therapy

CGI – Clinical Global Impression

cm – Centimetre

cm^2 – Centimetre square

CR – Co-ordinated Reset

dB – DeciBel

DCN – Dorsal Cochlear Nucleus

DLPFC – Dorsolateral Prefrontal Cortex

DPOAE – Distortion Product Otoacoustic Emission

DSL (I/O) v5.0 – Desired Sensation Level (Input/Output) version 5.0

ECT – Electro Convulsive Therapy

EEG – Electroencephalography

fMRI – Functional Magnetic Resonance Imaging

GABA – γ-(Gamma) Aminobutyric Acid

HADS – Hospital Anxiety Depression Scale

HHI – Hearing Handicap Inventory

HL – Hearing Level

Hz – Hertz

ICF – Intracortical Facilitation

IHC – Inner Hair Cell

kHz – Kilo Hertz

LTA – Left Temporoparietal Area

LTD – Long-Term Depression

LTP – Long-Term Potentiation

LVAS – Loudness Visual Analogue Scale

M – Molar

mA – milliAmpere

MEP – Motor Evoked Potential

mM – milliMolar

MML – Minimum Masking Level

MRI – Magnetic Resonance Imaging

MT – Motor Threshold

NAL – National Acoustic Lab

NAL-NL1 – National Acoustic Lab-Non Linear 1

NMDA – N-Methyl-D-aspartate

OHC – Outer Hair Cell

PATM – Progressive Audiological Tinnitus Management

PET – Positron Emission Tomography

QOL – Quality of Life

RCT – Randomised Control Trial

REAR – Real Ear Aided Response

RI – Residual Inhibition

rTMS – Repetitive Transcranial Magnetic Stimulation

SAS – Statistical Analysis System

SD – Standard Deviation

SFR – Spontaneous Firing Rate

SL – Sensation Level

SPL – Sound Pressure Level

SPSS – Statistical Package for the Social Sciences

TAT – Tinnitus Activities Treatment

TBS – Theta Burst Stimulation

TCHQ – Tinnitus Case History Questionnaire

tDCS – Transcranial Direct Current Stimulation

TEN - Threshold Equalising Noise

TENS – Transcutaneous Electrical Nerve Stimulation

THI – Tinnitus Handicap Inventory

THQ – Tinnitus Handicap Questionnaire

TQ – Tinnitus Questionnaire

TRQ - Tinnitus Reaction Questionnaire

TRT – Tinnitus Retraining Therapy

TSI - Tinnitus Severity Index

TSNS – Tinnitus Severity Numeric Scale

V – Volts

VAS – Visual Analogue Scale

VCN – Ventral Cochlear Nucleus

2 AFC – 2-Alternative-Forced-Choice

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Cathy M Stinear	Feedback on the draft of manuscript before submission

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Grant D Searchfield	Provided editorial support and advice concerning tinnitus

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Chapter 1. Introduction

Tinnitus is a phantom perception of sound (1), commonly described as a ringing, buzzing, hissing, whistling and humming sound in the head or ears (2). It can have a profoundly negative effect on attention, sleep, and overall quality of life (3, 4). Its effects include anger, frustration, depression, anxiety and potentially, suicidal thoughts (5-8). Tinnitus is a very common, yet poorly understood condition (5, 9). Tinnitus affects 400,000 New Zealanders and, it is conservatively estimated, approximately 5% of these suffer from annoying tinnitus (10).

Tinnitus sufferers usually have some degree of hearing loss (11, 12). This hearing loss is believed to result in maladaptive changes in the way the brain analyses and interprets signals from the ear (1, 13, 14). This auditory plasticity may result in a central gain adaptation process, resulting in normally unheard auditory activity becoming audible (15).

Many treatments for tinnitus attempt to reverse this central gain, usually by directly or indirectly stimulating the auditory brain. Transcranial direct current stimulation (tDCS) attempts to noninvasively stimulate the brain areas thought to be responsible for tinnitus. tDCS is a neuromodulatory intervention technique, which is well tolerated and safe (16). tDCS has been used extensively for modulation of motor cortex (17-19), enhancing cognitive/behavioural tasks (20-23) and management of various clinical conditions such as stroke (24-27), depression (28-30), pain (31, 32), craving (33-35), Parkinson's disease (36) and migraine (37, 38). Its use in the area of tinnitus is relatively new. The first published study regarding the effectiveness of tDCS for transient tinnitus suppression came in 2006 (39). Since then there have been some attempts in the use of tDCS for neuromodulation of tinnitus (40-44).

Hearing aids indirectly try to modify brain function by compensating for hearing loss and, in so doing, potentially removing the driving force for gain adaptation (45). Since hearing aids have been used for tinnitus management for the past 60 years (46), there is a weight of evidence supporting the use of hearing aids for management of tinnitus. However, most of this past research had methodological limitations, because most hearing aids were programmed for correction of hearing loss and optimum communication instead of for tinnitus perception (47). Research regarding the prescription of hearing aids to specifically target tinnitus is in its infancy.

Indirect stimulation through hearing aid use can lead to long lasting tinnitus reduction, but full effectiveness is often only achieved after 6 - 12 months of use (48-51). tDCS on the

other hand, has been demonstrated to give immediate but short lasting tinnitus relief. This dichotomy in effect between direct and indirect stimulation allows the probing of the process responsible for tinnitus and its management. The design of the present doctoral thesis permits the investigation of the combined use of tDCS with hearing aids as an enhanced method for tinnitus management. We hypothesise that the use of multi-session tDCS, followed by hearing aid fitting and use will accelerate the process of tinnitus management.

The central theme of this thesis is to explore a novel approach to tinnitus management by combining hearing aids use with multi-session tDCS. A brief overview of this thesis is as follows: Chapter 2 reviews the tinnitus literature, its prevalence, psycho-social impact and underlying mechanisms. Various popular tinnitus intervention options will be discussed along with non-invasive neuromodulation techniques. tDCS and existing research for tinnitus management will be presented along with the safety protocol and guidelines used in the present study.

Five studies were planned as part of this PhD and these are presented in Chapters 3 - 7 in this thesis. Chapter 3 is a retrospective study investigating the relationship between tinnitus pitch and hearing sensitivity. The goal was to find the most effective tinnitus pitch predictor based on the audiogram. We hypothesised that the frequency of audiometry equating to a threshold of 50 dBHL (edge of inner hair cell loss) would be more strongly correlated to tinnitus pitch than the “edge” frequency of hearing loss or frequency of maximum hearing loss. Chapter 4 is a scoping review aimed at investigating the role of hearing aids in tinnitus management. Unlike a systematic review or meta-analysis, scoping reviews include research studies irrespective of their quality as long as they are relevant. It provides coverage of key literature available in the area of hearing aids as tinnitus management tools. The paucity of research regarding optimisation of prescription procedures for hearing aids motivated a study examining prescription of hearing aid output for tinnitus relief (Chapter 5). Based on early research undertaken in this area by Wise 2003 (52) and Searchfield 2006 (53), changes in desired sensation level input/output (DSL [I/O] v5.0) prescription in the high frequencies was simulated to study its effect on tinnitus relief. There is no uniformity among the existing research studies about the most effective stimulation parameters (current intensity and duration) of tDCS for transient tinnitus suppression. Chapter 6 is a dose-response study with the goal of optimisation of tDCS intensity and duration. The findings of Chapter 5 and Chapter 6 were incorporated in

planning a seven month long clinical trial. Chapter 7 describes this double-blind, sham controlled, randomised study where multi-session tDCS was used along with hearing aids to investigate the potential for combined beneficial effect of direct and indirect stimulation of the auditory brain.

A combined treatment using hearing aids and tDCS has yet to be published. Modelling of the auditory system suggests that altered peripheral input to the central auditory system can lead to tinnitus perception (54) and this is maintained by thalamocortical loops. Independently, the use of hearing aids (51) and anodal tDCS modulation of activity in the left temporoparietal area (LTA) (39), have been demonstrated to provide tinnitus sufferers with some relief. It was proposed that hearing aids should normalise bottom-up sensory driven activity (55) while the tDCS might prime the auditory system, enabling plastic modifications based on new peripheral activity.

The effects of hearing aids and tDCS are potentially complementary; the hearing aids being considered a long-term intervention while tDCS provides an immediate but short-term benefit. A template for such a prime (tDCS) and train (hearing aids) method comes from investigations into the use of repetitive transcranial magnetic stimulation (rTMS) and exercise following stroke (56). Facilitating ipsilesional motor cortex excitability prior to motor practice with the paretic upper limb leads to greater functional improvements than motor practice alone (57).

1.1. Objectives

In exploring a novel approach for tinnitus management, this doctoral thesis was undertaken with the following objectives:

- To investigate the relationship between hearing sensitivity (0.25 - 16 kHz) and tinnitus pitch (Chapter 3).
- To conduct a scoping review regarding the role of hearing aids in tinnitus management (Chapter 4).
- To ascertain prescription of hearing aid output that results in the greatest tinnitus relief (Chapter 5).
- To study dose-response relationship between tDCS parameters (intensity and duration of stimulation) that results in the greatest tinnitus relief (Chapter 6).
- To compare tinnitus outcomes between combined amplification and tDCS with amplification alone (Chapter 7).

Chapter 2. Literature Review

2.1. Tinnitus

Tinnitus is derived from the Latin word '*tinnire'* which means '*to ring'* or '*a ringing'* (58). It is a symptom rather than a disease (59). Documentation of tinnitus dates back to the 13th century (58). Research and clinical studies in the past few decades have enhanced the understanding of tinnitus and it is now commonly defined as perceived sound that cannot be attributed to an external source (60). Tinnitus is an auditory phantom sensation (ringing of the ears) experienced when no external sound is present (1). Tinnitus sounds are commonly described as ringing, buzzing, cricket-like, hissing, whistling, and humming (2). Tinnitus can occur due to any form of malfunction occurring along the auditory pathways (1, 5, 11, 59, 61, 62).

Tinnitus can be acute or chronic, based on the duration it lasts for (63). Acute tinnitus lasts for days or weeks, however, chronic tinnitus lasts for more than six months. The causes of acute tinnitus (e.g., ear infections, ear wax, head or neck injury, medications, change in blood pressure, or metabolism) can sometimes be identified and treated resulting in the resolution of tinnitus (64). Chronic tinnitus possibly occurs from a cascade of changes occurring at various cortical (1) and subcortical centres (14) potentially starting with: dysfunction of cochlear receptors or reduced spontaneous firing rate (SFR) of the auditory nerve fibers (13) leading to compensate for this reduction, with an increase in central gain potentially through a reduction in cortical inhibition (15).

Tinnitus can be classified as subjective and objective (65) or true and somatosound (64). Subjective tinnitus is perceived by the sufferer only in the absence of external sound. Objective (or somatosound) tinnitus is created by an acoustical source within the body and can be heard by people in proximity through a stethoscope placed over head and neck structures near the patient's ear (5, 61). Objective tinnitus or somatosounds are rare and accounts for <1% of all cases (64).

2.1.1. Prevalence of Tinnitus

Several research studies have been conducted around the world aimed to determine tinnitus prevalence. However, there has been a wide variations in prevalence due to various reasons such as: methods of data collection, distribution of age, and hearing loss in the sample (66), the definition of tinnitus, and demographic differences between

populations and methodologies (67, 68). Table 2:1 is a summary of a few selected tinnitus prevalence studies.

Table 2:1. Tinnitus prevalence in various parts of the world.

Location	Sample Size	Definition of Tinnitus	Prevalence	Key Findings
USA (69)	14,178 participants from National Health and Nutrition Examination Survey. Participants were interviewed and examined.	Two questions were asked Q.1: "In the past 12 months, have you ever had ringing, roaring, or buzzing in your ears?" Q.2: "How often did this happen?" Participants answering 'Yes' to Q.1 were included as experiencing any tinnitus and answering "Almost always" or "at least once a day" to Q.2 were included as experiencing frequent tinnitus.	25.3% (50 million) - experiencing any tinnitus. 7.9% (16 million) experiencing frequent tinnitus.	Tinnitus prevalence increased with age until 69 years after which it decreased with age. Higher tinnitus prevalence in male, non-Hispanic whites (race), smokers, hypertension, diabetes mellitus, dyslipidemia, occupational noise exposure, loud leisure time, firearm noise, hearing loss and generalized anxiety disorder.
Japan (68)	Community-based cross sectional study. 1,320 participants (584 men and 736 women) aged 65 years and above were interviewed.	Two questions were asked Q.1: "In the past year have you experienced any ringing, buzzing or other sounds (tinnitus) in your ears?" Those who answered "Yes" were asked Q.2: "Have these sounds interfered with your concentration or ability to sleep?" Those who answered "Yes" were classified as having "Severe Tinnitus" and those who answered "No" were classified as having "Mild Tinnitus".	18.6% (men = 18% and women = 19%)	Tinnitus is not related to age and gender. Hearing difficulty, depressed feeling, and prescribed medication, past/current history of coronary heart disease and knee joint pain requiring medical consultation were associated with tinnitus.
Australia (67)	Blue Mountain Hearing Study, population-based survey of 2,015 participants (1,156 women and 859 men) mean age 69.8 years.	One question was asked: "Have you experienced any prolonged ringing, buzzing or other sounds in your ears or head within the past year that is, lasting for five minutes or longer?" with three options "Yes", "No" and "Missing response".	30.3%	Tinnitus prevalence did not vary with gender and age. Higher rates of hearing loss were found in persons reporting tinnitus.
British Columbia, Canada (66)	30,000 workers with noise exposure.	One question was asked: "Do you have ringing in your ears?" with two options "Yes" and "No". If the answer is yes then left and/or right ear has to be indicated.	6.6%	Tinnitus prevalence positively correlated with hearing loss (most important factor), history of smoking and shooting. Unilateral tinnitus usually occurred in the ear with worse hearing.

				Age, gender, lateral differences were not related with tinnitus prevalence.
Wisconsin (USA) (70)	3,753 participants with mean age of 65.8 years.	Three questions were asked: Q.1:"In the past year have you had buzzing, ringing, or noise in your ears?" (No/Yes/Unknown) Q.2: "How severe is this noise in its worst form?" (Mild/Moderate/Severe/Unknown) Q.3: "Does this noise cause you to have problems getting to sleep?" (No/Yes/Unknown) Significant Tinnitus – having buzzing, ringing or noise of at least moderate severity and difficulty in falling asleep due to tinnitus or both.	8.2% (had significant tinnitus)	Age and gender did not affect tinnitus prevalence. Hearing loss, cardiovascular disease, and history of head injury were positively associated with tinnitus.
Sweden (71)	2,378 (male = 1135, female = 1,243) falling in the age range of 20 to 80 years.	Used a questionnaire which was mailed to the participants and it defined tinnitus as "The Latin name of the ear noises is "tinnitus", which is a fairly common symptom. Tinnitus differs and may sound as a peep, chirping, roaring, wind blowing in the trees, etc." Subjects who suffer from tinnitus "often" or "always" were asked to complete the further questions probing the further detail characteristics about tinnitus.	14.2% (suffered from tinnitus 'often' or 'always')	Tinnitus was more common in males than females. Localisation of tinnitus was more common on left ear than right ear. Tinnitus more commonly coexisted with hearing loss. Severity of tinnitus was directly proportional to the "difficulties in falling asleep".
Sweden (72)	Gerontology and geriatric population Longitudinal study of 674 persons aged 70 years.	Two questions were asked Q.1: "Do you hear buzzing sounds?" with three options a) Presence of tinnitus, b) Occasional tinnitus, c) No tinnitus. Q.2: Was asked by those who had tinnitus to know if they had continuous tinnitus or occasional tinnitus.	27–34% (combination of continuous and occasional tinnitus)	No difference was found between men and women in tinnitus prevalence. The prevalence of occasional tinnitus increased with age. Positive correlation between tinnitus and exposure to occupational noise. Hearing loss contributes to tinnitus prevalence.
Poland (73)	10,349 (52.7% men and 47.3% women) aged 17 years and above.	A questionnaire composed of 13 questions was used. Questions regarding tinnitus were directed towards the following aspects: the presence of tinnitus lasting over 5 minutes, the presence of constant tinnitus, its annoyance, causes, etc.	20.1% reported tinnitus. 4.8% reported constant tinnitus.	Prevalence of tinnitus increased with age. Prevalence of tinnitus more in men than women (men more susceptible to various diseases and noise exposure than women).

Lublin District, Poland (74)	16,614 (9,113 = women, 7502 = men).	Questionnaire (details of the questions not given).	51.1% (rarely = 37.7% and frequent = 13.3%)	Tinnitus prevalence increased with age. No significant correlation between tinnitus and laterality (left or right ear). More prevalent in women than men.
Florida, (USA) (75)	267 participants falling in the age range of 57 to 91.5 years.	One question: "Do you have noises in your ears? If yes, for how long? Please describe the noises you hear.	24%	All the participants had normal otoscopic examination, no history of: noise exposure, disequilibrium and systemic disease associated with tinnitus.
Toronto, (Canada) (76)	Retrospective study of 3,466 participants claiming compensation for occupational hearing loss from 1980 to 1985 falling in the age range of 16 to 81 years with a mean age of 60.5 years.	Questionnaire with 15-items regarding tinnitus, its description and degree of subjective problem was used.	49.8% (29.2% tinnitus was major problem, 61.5% minor problem & 9.3% not bothersome)	Prevalence of tinnitus does not increase with age and hearing loss. Prevalence of tinnitus was more in people with history of noise exposure for more than 10 years than less than 10 years. Localisation of tinnitus was more common in left ear than right ear.

2.1.2. Psychosocial Impact of Tinnitus

Tinnitus adversely affects the overall quality of life (QOL) of sufferers (3, 4). It can lead to anger, frustration, tension, poor communication, and lack of sleep (5, 6) and the suffer may become trapped in a vicious cycle between a constant state of anxiety and attention towards tinnitus (77) (see Figure 2:1).

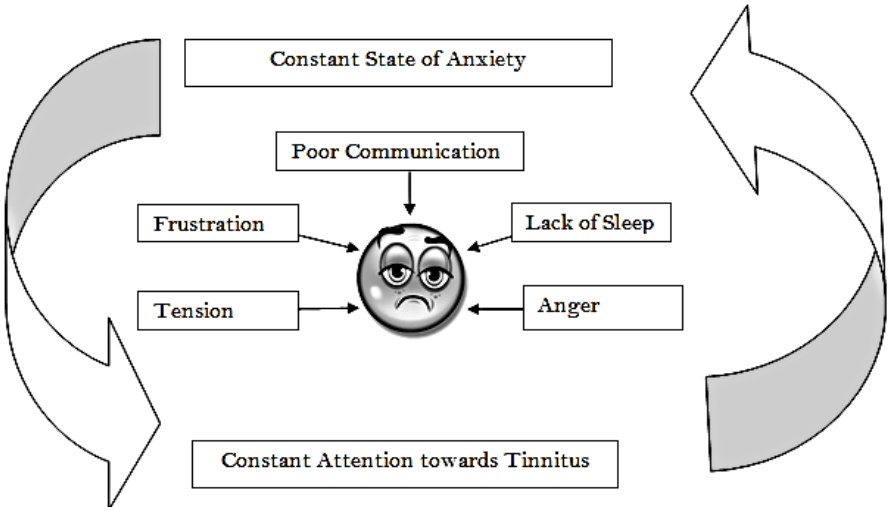


Figure 2:1. Psychosocial impact of tinnitus.

Fifty-two percent of the geriatric population with tinnitus suffer from insomnia which negatively influences their QOL (78). Commonly encountered insomnia symptoms by tinnitus sufferers are difficulty in falling asleep, maintaining sleep, early morning wakefulness, non-restorative sleep, daytime sleepiness, and increased frequency of sleep deterioration (79). People with tinnitus often find it difficult to relax and are overburdened with the stress of daily events (80).

As the severity of tinnitus increases, it has a more profound impact on people's QOL (81). People with hearing loss (along with tinnitus) have an overall poorer QOL than those with tinnitus alone (82). Acceptance of tinnitus also plays a significant role in the perception of tinnitus related distress. Schutte et al. (83) found an inverse relationship between tinnitus related distress and acceptance of tinnitus. Higher tinnitus related distress was found in people with lesser acceptance and vice-versa.

Stuerz et al. (84) studied body image and body concepts in patients with chronic tinnitus, and found that people with tinnitus attained significantly lower scores on dimensions such as "attractiveness/self-confidence", "emphasis on physical appearance", and "vitality and

body dynamics" reflecting low self-confidence, a negative perception towards their own body, and less pleasure in physically experiencing their own body compared to their healthy controls. When people with severe to very severe tinnitus were compared with those with mild to moderate tinnitus, the former had a significantly higher degree of insecurity and concerns about their own body than the later.

People with tinnitus tend to have higher scores on anxiety and depression and lower scores on self-esteem and well-being (85). Tinnitus patients have significantly higher prevalence of major depression and psychosocial problems compared to controls, 62% of patients with tinnitus have lifetime prevalence of major depression, and 48% have current depression (86). Severity of tinnitus is also significantly correlated with the severity of anxiety and depression (87). Patients suffering from depression rate their tinnitus more severe than those who are not suffering from depression (88). When depression was treated, it also had a positive influence in reducing the severity of tinnitus (89). It is debatable whether tinnitus leads to depression, or depression leads to tinnitus, tinnitus is multidimensional and it is likely that many common factors predispose a person to tinnitus as well as depression.

There is no direct relationship between tinnitus and suicide (90). However, tinnitus sufferers constitute a high risk group due to associated factors such as depression, mental illness, social isolation, and old age (7). Long-standing intractable tinnitus is one risk factor for suicide along with feelings of helplessness, inability to communicate, depression, and socio-cultural isolation (8). In a study by Lewis et al. (7), within the span of two years 40% of tinnitus patients from a sample of 28 committed suicide. However, it is important to note that this sample was not representative of the tinnitus population, as all of the patients had major psychiatric disturbances. Sanchez et al. (91) carried out a study to find difficulties associated with tinnitus, and identified five major categories: psychological problems (30.1%), hearing difficulties (23.5%), health problems (20.7%), sleep problems (14.6%), and situational difficulties (11.1%). Zoger et al. (92) revealed that 45% of the patient population showed anxiety disorder, 39% suffered from a depressive disorder at the time of survey, and 62% had a history of lifetime depressive disorder during the course of their tinnitus. Due to this high prevalence of depression and anxiety disorders in patients with tinnitus, this could be used as a clinical marker for depressive disorders. Tinnitus acts as a stressor, and people who have higher vulnerability to stress find tinnitus more annoying and this annoyance leads to depression (93). A higher degree of

psychosocial stress and anxiety disorder was found in patients with severe tinnitus (92). Severity of tinnitus could be predicted by anxiety disorder and poor well-being (94). Relaxation therapy results in reduction of tinnitus-related stress (95).

McKenna et al. (96) conducted a study to find the prevalence of psychological disturbance in neurotology patients, and found that 45% of patients with tinnitus had psychological disturbances and were offered psychological help. Blunted cortisol response to acute psychosocial stress was elicited in people with tinnitus, reflecting reduced glucocorticoid efficacy which was similar to other patients with stress related disorders-this study demonstrated physiological relationship between tinnitus and stress (97).

2.2. Mechanism of Tinnitus

No single theory explaining the cause of tinnitus is universally accepted. Tinnitus can occur due to any form of malfunction occurring along the entire auditory pathway (59, 61) or central nervous system (5). There are different models proposed by various researchers explaining the mechanism of tinnitus, and the mechanisms are related and not mutually exclusive. Some of the popular models are outlined below:

1. Psychological Models
2. Jastreboff's Neurophysiological Model
3. Neural Synchrony Models
4. Sensitisation Models
5. Gain Models
6. Network Models

2.2.1. Psychological Models

According to psychological models, cognition (98, 99), attention (100, 101), learning (100, 102), and habituation (100, 101) are significant psychological factors underlying tinnitus. These models are based on the neurophysiological disturbances in the auditory system (103). In these models, psychological processes play a significant role in tinnitus perception. Tinnitus is a psychosomatic and somatopsychic disorder (103). Hallam, Rachman, and Hinchcliffe (100) proposed that attention regulates tinnitus perception,

therefore constant perception of tinnitus may not be possible as it may not receive constant attention. Factors such as masking, distractions, and changes in arousal level may affect tinnitus perception. These models are supported by the notion that many people that experience tinnitus do not find it bothersome (6), and there is no direct relationship between the psycho-acoustic features of tinnitus and perceived distress (100). Orientation to tinnitus is influenced by signal-to-noise ratio in a quiet environment tinnitus is more evident. According to a model proposed by Hallam et al. persistent tinnitus undergoes habituation as the tinnitus signal loses its novelty. Habituation is delayed if the sufferer is experiencing high arousal of the autonomic nervous system (ANS). In these cases, tinnitus is more intense and unpredictable and is conditioned with emotional responses also.

Therapeutic approaches based on the psychological model include relaxation therapy to reduce the arousal of ANS and cognitive behaviour therapy (CBT). The fundamental assumption of CBT is that changing thoughts facilitate a change in behaviour (104).

2.2.2. Jastreboff's Neurophysiological Model

This model was proposed by Jastreboff (105), and is often called "The Neurophysiological Model". It is one of several models underpinned by neurophysiological concepts, and has had a significant impact on clinical practice. According to this model, tinnitus is a by-product of roles played by auditory and non-auditory systems of the brain. Auditory pathway (cochlear damage) is responsible for the emergence of tinnitus and non-auditory systems (especially the limbic system which plays an important role in emotion, memory, and learning), and the ANS is blamed for the association of annoyance with tinnitus as shown in Figure 2:2.

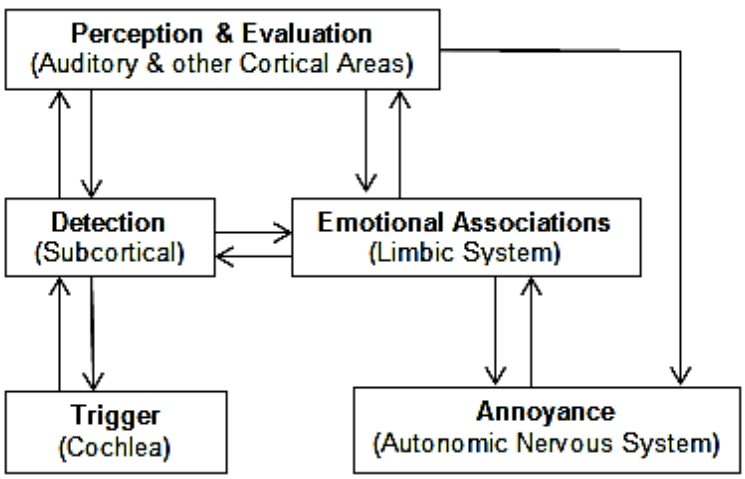


Figure 2:2. Involvement of central nervous system in the development of tinnitus. Cochlear damage triggers tinnitus detection at the subcortical level and the involvement of limbic system and ANS is responsible for the association of annoyance with tinnitus. Redrawn from Jastreboff et al. (1996, p. 237) (106).

In this model, tinnitus is triggered by a discordant damage to inner hair cells (IHC) and outer hair cells (OHC) (105, 107) or any other damage to the auditory system (106). This leads to initial orientation towards the signal due to its novelty. If there are no negative emotions such as fear, anxiety, and threat associated with this signal it gradually habituates, and for these people tinnitus is not a problem and does not affect their day-to-day life. When this initial detection gets paired with the activation of the limbic system (negative emotions) and ANS (which prepares the body for 'fight or flight'), the tinnitus signal is conditioned with annoyance (103). The activation of the limbic system and ANS further facilitates the detection and enhancement of tinnitus (106) and the psychoacoustical characteristics of tinnitus become insignificant to its overall perception.

Based on this model, Jastreboff (108) proposed tinnitus retraining therapy (TRT) (109-111). Jastreboff described TRT as a two-stage process involving directive counselling (to decrease negative emotions associated with tinnitus) and sound therapy (to decrease the contrast between tinnitus and background neuronal activity).

2.2.3. Neural Synchrony Models

Changes in neural synchrony may contribute to tinnitus perception. Animal studies have shown evidence of tinnitus following hearing loss induced by noise exposure (112) and ototoxic drugs (113, 114). Tinnitus is usually associated with hearing loss (11, 12). Often cochlear damage is found even in the presence of normal auditory thresholds in tinnitus sufferers (115). Hearing loss disconnects the brain from the ear, leading to cortical reorganisation of the tonotopic map in the primary auditory cortex (1, 116). Neurons in the region of hearing loss do not respond to their characteristic frequency, instead they reflect the frequency of their unaffected neighbours (1, 117, 118). These changes in the neural response properties lead to over-representation of edge frequencies which are hypothesised to be related to tinnitus (1). Figure 2:3 depicts the cortical reorganisation followed by noise exposure in a cat, and how the neurons in the region of hearing loss start responding to the unaffected neurons' characteristic frequency.

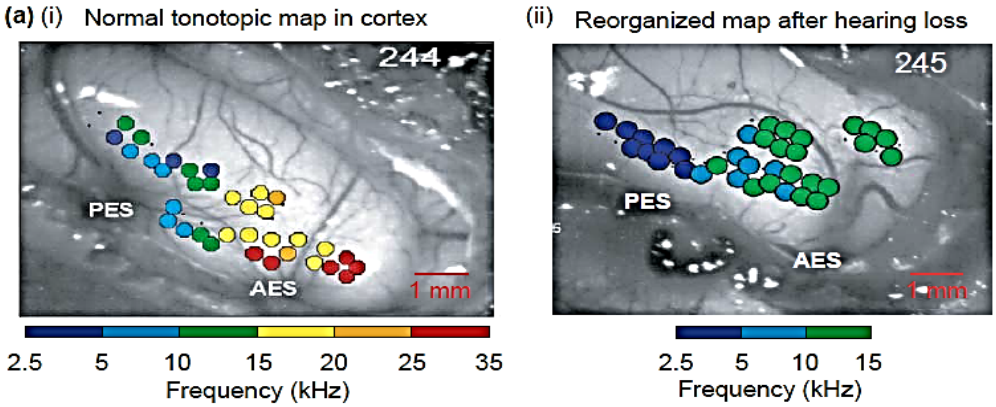


Figure 2:3. Normal tonotopic map (i) and reorganised map (ii) of the primary auditory cortex in a cat after noise exposure. Characteristics frequency of each recording site is colour coded. Hearing loss was limited to frequencies above 10 kHz and neurons in this region of hearing loss depict the characteristic frequency of lower frequencies (ii). 244 and 245 are cat identification numbers. Printed with permission from Elsevier, p. 678 (1).

Neural synchrony is described as the simultaneous firing of individual neurons and synchronised oscillations of membrane potentials in a network of neurons connected with electrical synapses (119). Some researchers believe synchrony to be the neural correlate of consciousness (120, 121). Increased SFR (122, 123) and changes in neural synchrony (124, 125) may be important factors underlying tinnitus perception. Weisz et al. (126) investigated the differences between the spontaneous neuronal activity in individuals with and without tinnitus as measured by magnetoencephalography. Tinnitus patients were characterized with a significant reduction in alpha power (8–12 Hz) and enhancement in delta (1.5–4 Hz) frequency bands as compared to normal-hearing participants. Tinnitus related distress was strongly correlated with abnormal spontaneous brain activity in right temporal and left frontal areas. Weisz et al. (127) found increased gamma-band activity in tinnitus patients compared to the control group, which also correlated with the lateralisation of tinnitus. Kahlbrock and Weisz (128) studied the relationship between the spontaneous brain activity and change in tinnitus intensity in tinnitus patients experiencing residual inhibition (RI). This study revealed a significant reduction in the delta frequency band (1.3–4.0 Hz) and in temporal lobe regions of tinnitus patients experiencing RI. Kahlbrock and Weisz (128) proposed that RI might reflect the transient re-establishment of balance between excitatory and inhibitory neuronal assemblies via reafferentation, which was perturbed in the majority of tinnitus patients due to associated hearing damage. Tinnitus could be a result of alteration in neural synchrony especially pronounced during silence (119).

2.2.4. Sensitisation Models

According to the sensitisation model (62), tinnitus signals originate in the cochlea, followed by conditioning and sensitisation pathways: conditioning pathway: which is similar to Jastreboff's neurophysiological model (105) where the tinnitus signal is conditioned with negative emotions and activates the limbic system and ANS. However, this is secondary, as the primary focus of this model is the sensitisation pathways. Sensitisation pathways are based on non-conditioned learning procedures (129, 130). Sensitisation involves enhanced neuronal activity within a system in response to unconditioned tinnitus stimuli (62). Simultaneously to sensitisation, the tinnitus signal leads to unconditioned defensive startle responses.

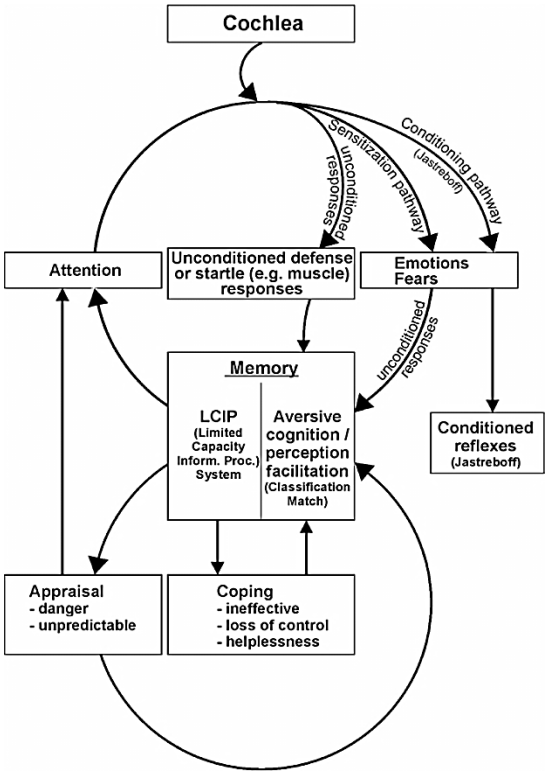


Figure 2:4. Sensitisation model explaining tinnitus double cycle which is continuously repeated. The pathological cochlear signal simultaneously causes sensitisation (increased attention and secondary appraisal of tinnitus signal, labelling it as noxious-aversive and unpredictable, which is associated with ineffective coping, loss of control, and helplessness) and long-term facilitation (significant reduction in the central threshold for tinnitus perception and cognition) making it a debilitating condition. Reprinted with permission from Wolters Kluwer Health, p. 1057 (62).

Sensitisation leads to increased attention and secondary appraisal to tinnitus, which associates the tinnitus to be aversive and unpredictable and results in ineffective coping strategies such as feeling of helplessness and loss of control. The ability of the brain to process information is limited, and as it is based on the priority of stimuli, it then decides

about amplification of some stimuli and attenuation of others (131, 132). This limited capacity information processing is responsible for the dominance of tinnitus over the other stimuli. Sensitisation leads to long-term synaptic facilitation which lowers the perceptual and cognitive threshold for the cochlear signal (tinnitus) resulting in hyperactive cortical responses of the brain to tinnitus. This entire process is cyclic, and eventually results in permanent interconnections. As a result, tinnitus is not perceived as an isolated sound but as a complex pattern (Figure 2:4).

2.2.5. Gain Models

Proponents of gain models believe that damage to hair cells leads to reduced sensory input to the auditory nerve, and to compensate for this reduction in input, homeostatic mechanisms come into play which increase central gain and reduce cortical inhibition, leading to amplification of neural noises which in turn results in tinnitus (15, 133). According to these models, the tinnitus pitch should fall in the region of hearing loss and there have been a number of studies supporting this notion (134-138).

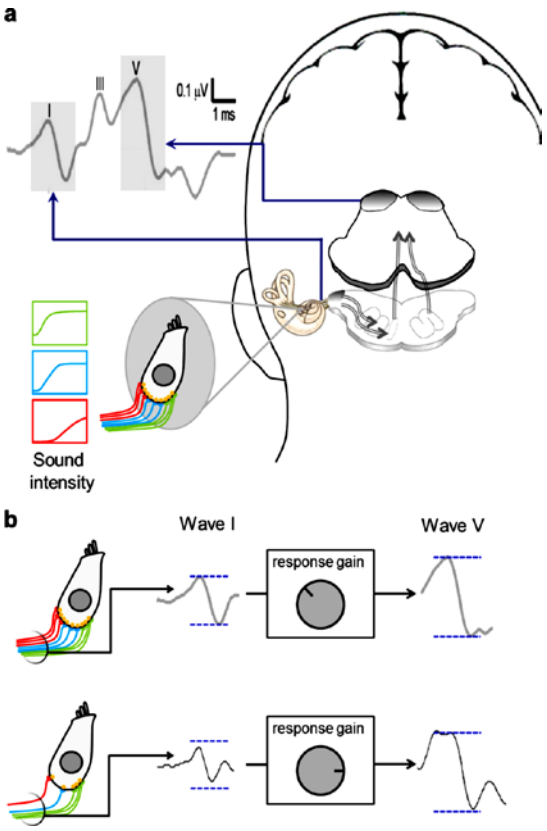


Figure 2:5. A) Generation site for wave I (auditory nerve) and wave V (mid brain), B) Increase in the homeostatic gain control normalizing the amplitude of wave V in spite of having lower amplitude of wave I as depicted in the lower panel of the figure. Reprinted with permission from the Journal of Neuroscience Permission Policy, p. 13454 (139).

Schaette and McAlpine (139) measured auditory brainstem response in 33 females (15 with chronic tinnitus, mean age of 36.3 years and 18 controls with a mean age of 33.2 years, no significant age difference) with normal-hearing until 8 kHz and no significant difference in thresholds beyond that. The mean amplitude of wave I was significantly smaller in the tinnitus group compared to the non-tinnitus group, however the mean amplitude of wave V did not differ significantly for the two groups. The site of generation of wave I is the auditory nerve and wave V is mid brain (140) (Figure 2:5 A). It was proposed that the increase in response gain (homeostatic gain control) assisted in restoring the amplitude of wave V (Figure 2:5 B).

Norena 2011 (15) also proposed a tinnitus model based on the increase in central gain (Figure 2:6)

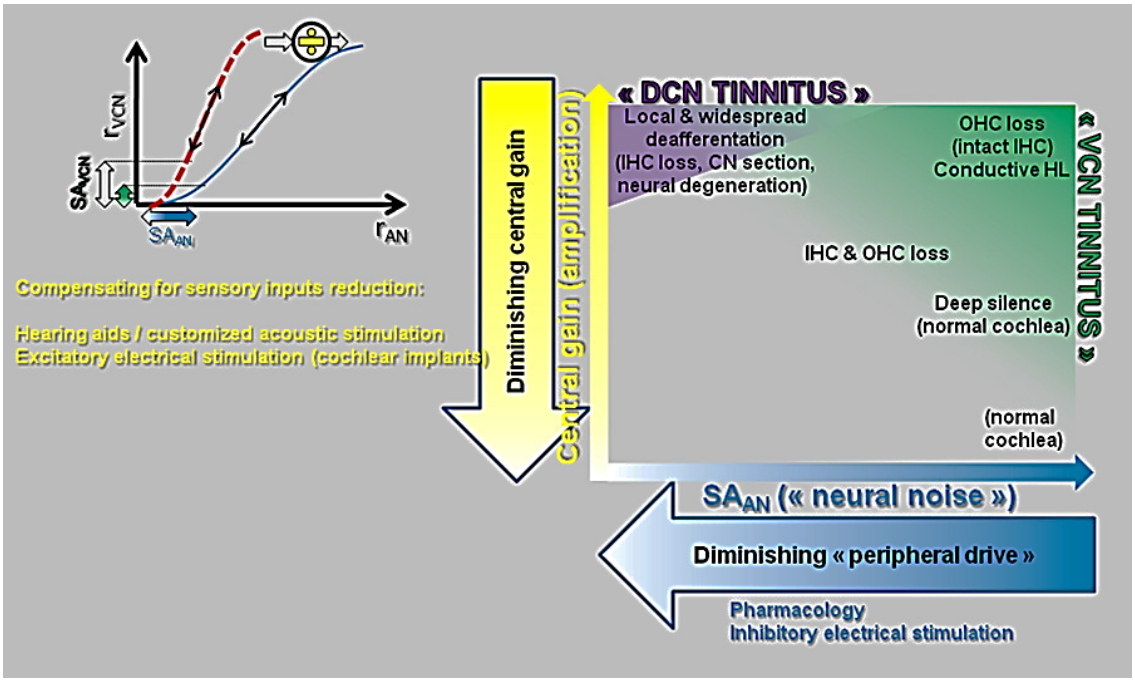


Figure 2:6. Integrative tinnitus model based on the central gain controlling neural sensitivity. The right panel of the figure depicts the two factors on which tinnitus depends (x-axis is the spontaneous firing of the auditory nerve and y-axis is central gain). The green gradient represents the ventral cochlear nucleus (VCN) tinnitus and violet gradient represents the dorsal cochlear nucleus (DCN) tinnitus. VCN tinnitus is caused by increased firing in the VCN and presence of tinnitus in patients with profound hearing loss and sectioning of cochlear nerve is explained by the DCN tinnitus (after cochlear destruction the DCN receives the non-auditory inputs and supplement VCN in maintaining stable neural activity in auditory centres and is called DCN tinnitus). Based on this model, two therapeutic strategies are recommended (large yellow arrow representing strategies to reduce the central gain such as hearing aids, cochlear implants and blue large arrow represents the strategies to reduce spontaneous activity of cochlear nerve such as pharmacology interventions and inhibitory electrical stimulation). The top left panel illustrates the reduction in input–output function of the central neurons. Reprinted with permission from Elsevier, p. 1100 (15).

Norena's model highlights the putative relationship between tinnitus and hearing loss (71, 141). Any form of damage to the cochlea is likely to result into sensory deprivation, leading to central hyperactivity in various parts of auditory cortex (125, 142-144), which triggers the homeostatic mechanism (increase in central gain) (49, 139, 145) and in the process of maintaining the stability of neural activity and neural coding efficiency, amplification of neural noise occurs which could lead to tinnitus (15). Two therapeutic strategies are proposed based on this model. The first is aimed at reducing the central gain (acoustic stimulation, hearing aids, and cochlear implants) and the second is targeted towards diminishing the peripheral drive (pharmacological or inhibitory electrical stimulation) (15).

2.2.6. Network Models

According to network models, phantom perception is a result of various overlapping and parallel brain networks (146). As shown in Figure 2:7, the major networks proposed to be involved in the perception of tinnitus are: a perception network, salience network, distress network, and memory network. Sensory deafferentation of hair cells in the cochlea leads to hyperactivity in the auditory cortex. This is perceived as stimuli by the activation of perception network which involves the prefrontal cortex, parietal cortex, precuneus, posterior cingulate cortex, subgenual, and dorsal anterior cingulate cortex. Activation of the dorsal anterior cingulate cortex and anterior insula which forms the salience network is responsible for this perception to reach consciousness, which gets associated with distress due to anterior cingulate cortex, anterior insula and amygdala (distress network), and the memory network (parahippocampal area, amygdala, and hippocampus) facilitates the persistence of this percept. This model has been supported by functional magnetic resonance imaging (fMRI) studies confirming increased connection between the auditory cortex and attention, and memory and limbic systems (11, 147-149). These studies are discussed below.

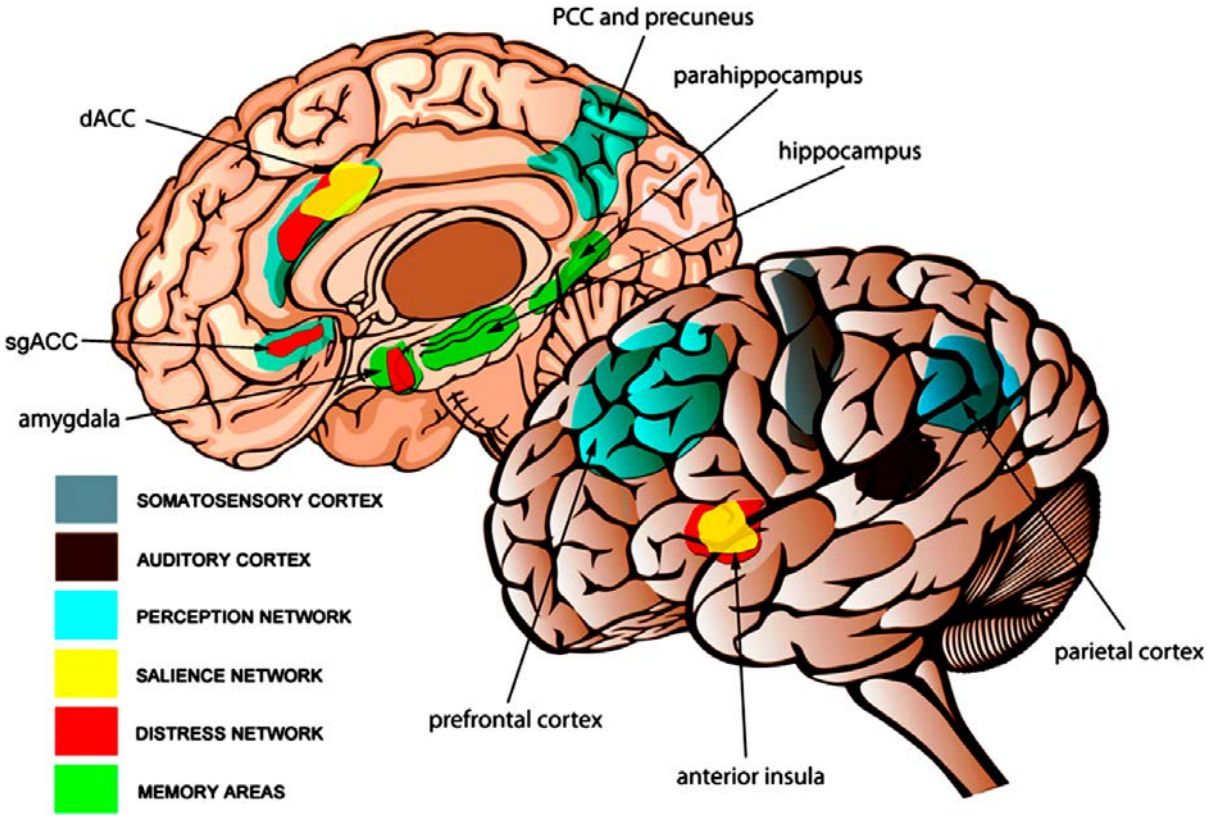


Figure 2:7. Brain networks involved in phantom perception of pain and tinnitus. In the case of tinnitus, the cochlear deafferentation leads to the activation of auditory cortex (brown colour). The four major networks involved in the perception and distress associated with tinnitus are: perception network [depicted in blue colour and it includes subgenual anterior cingulate cortex, dorsal anterior cingulate cortex, posterior cingulate cortex , precuneus, parietal cortex, and frontal cortex], salience network (shown in yellow colour involving dorsal anterior cingulate cortex and anterior insula), distress network [represented in red colour and comprised of anterior cingulate cortex (subgenual anterior cingulate cortex and dorsal anterior cingulate cortex), anterior insula, and amygdala] and memory areas shown in green colour involving amygdala, hippocampus and parahippocampus. Reprinted with permission from PNAS, p. 8077 (146).

Kim et al. (147) investigated the alterations of functional connectivity in four patients with chronic tinnitus lateralised towards the left ear using fMRI and six age-matched controls. Increased connectivity between the auditory cortex and the limbic system (including amygdala) was found in tinnitus patients compared to controls. This supports the result of an earlier imaging study done by Lockwood et al. (11) pointing to the involvement of the limbic system in tinnitus processing. Another interesting finding of this study was the significantly lower functional connectivity scores between the left and right auditory cortical regions in tinnitus patients than in controls. This lack of coherence in spontaneous resting-state neural activity between the left and right auditory cortex in tinnitus patients has been linked to the altered excitatory–inhibitory balance reflecting the down-regulation of inhibition in the auditory cortex (150). There was also an increased connectivity between the auditory network and dorso-medial prefrontal cortex in tinnitus patients. dorso-medial prefrontal cortex has been associated with attention processing (148) which

may reflect the increased auditory perception with changes in attention and top–down control of auditory signals.

In another recent study by Maudoux et al. (149), auditory resting-state network connectivity was investigated in 13 patients suffering from chronic tinnitus and 15 age-matched healthy controls using fMRI. They found an overall alteration in the cortical and sub-cortical functional connectivity in tinnitus patients involving attention, memory, and emotional networks (increased connectivity in extra-auditory regions such as the brainstem, basal ganglia, cerebellum, parahippocampal, right prefrontal, parietal and sensorimotor areas and decreased connectivity in right primary auditory cortex, left prefrontal, left fusiform gyrus, and bilateral occipital regions) supporting the findings of De Ridder et al. (146) who proposed the involvement of various parallel and overlapping brain networks in tinnitus perception.

Schlee et al. (151) found an alteration of long-range coupling (functional interaction between the distant neuronal cell assemblies) in 83% tinnitus patients. They reported a decrease in long-range coupling in the alpha (9–12 Hz) frequency band and increase in gamma (48–54 Hz) coupling in tinnitus patients as compared to the controls. For patients with less than four years of tinnitus history, the gamma network was limited to the left temporal cortex and for those with a duration of more than four years. The gamma network was widely distributed including the frontal and parietal regions. This possibly indicates a sequel for the development of tinnitus from primarily auditory perception through to the involvement of non-auditory regions in chronic tinnitus perception and associated distress.

Burton et al. (152) found a dissociation between the functional connectivity between auditory cortex and visual, attention and control networks in patients with bothersome tinnitus. Recently De Ridder et al. (153) proposed a theoretical pathophysiological framework according to which tinnitus perception involves several, parallel, dynamically changing and overlapping sub-networks (minimal set of brain areas which are needed to jointly activated for tinnitus perception). Each sub-network encodes a specific aspect of tinnitus perception and communication between them occurs at brain areas/hub (which are involved in multiple sub-networks simultaneously) at discrete oscillatory frequencies.

Rauschecker et al 2010 (154), proposed a model focusing on limbic-auditory interactions in tinnitus. According to this model although in majority of cases tinnitus is triggered by peripheral damage to auditory system (damage to hair cells, aging, noise exposure etc.), it

can be tuned out by feedback from limbic regions. The nucleus accumbens and its associated paralimbic network (ventromedial prefrontal cortex and raphe) plays a noise cancellation role that may contribute to long-term habituation of tinnitus. If these paralimbic regions are compromised, the tinnitus signal is not inhibited at the thalamic level (failure of the noise cancellation mechanism) and it reaches the auditory cortex, leading to cortical reorganisation, and chronic tinnitus. This model is a relatively new view and needs confirmatory evidence. It would be interesting to study the relevant networks in animal models.

Network models have certainly enhanced our understanding about tinnitus and have broadened the focus of tinnitus to the entire brain and various parallel networks, rather than limiting it to be a disorder of the auditory system. This model should be kept in mind when planning the neuromodulation designs for tinnitus intervention.

2.3. Tinnitus Management

Diverse approaches have been used for tinnitus management (155) such as neurophysiological, psychological, pharmacological, and surgical (119). The majority of patients usually find some degree relief from these approaches (156). It would be wonderful to have a drug which could cure tinnitus; however, the search for that silver bullet is on-going. As far as pharmacological research in the area of tinnitus management is concerned, there have been several prescriptions and off label drugs tried for tinnitus relief, however until this time there is not a single drug approved by the food and drug administration or the European medicines agency for tinnitus treatment (156). Surgical approaches may be useful for tinnitus management especially if tinnitus is associated with certain conditions which can be treated surgically, such as conductive hearing loss or severe temporomandibular joint disorder. Surgeries for pathologies of the auditory nerve (e.g.,vestibular schwannoma) have been shown to offer some relief from tinnitus (157). Relatively recent research by De Ridder and Vanneste (158) has shown some success with fMRI guided neuronavigated electrode implantation in tinnitus suppression. Three different locations have been used for auditory cortex stimulation: extradurally on the area overlying secondary auditory cortex (159), intradurally, on the surface of the brain (groove or sulcus of primary auditory cortex), and intradurally (160) deep inside the brain stimulating the intraparenchymatous white matter (161). More research is underway in optimising this technique for better results.

In the following section, I discuss audiological/neuropsychological and psychological based therapies. Pharmacological and surgical tinnitus management options are beyond the scope of this review.

2.3.1. Counselling and Psycho-Education

Counselling plays a significant role in the majority of tinnitus management options (162) including hearing aids (53), TRT (163), and other sound therapies (164), to different extents and in different forms (165). Counselling is a broad term and for its relevance in the area of tinnitus Searchfield et al. (166) define counselling as a "*process of facilitating change by informing, advising, and empowering individuals who need support*".

Tinnitus can result in negative effects on lifestyle (167) and result in emotional problems, sleep disturbance, poor general heath, and difficulties in hearing (168). Studies have shown the association between chronic tinnitus and anxiety (169), depression (88), and suicidal tendencies (7, 170). Psychoacoustical features of tinnitus are not directly related to the degree of distress encountered by the sufferer (171-173), instead neurophysiology suggests that activation of the limbic system and ANS leads to annoyance and negative emotions in response to tinnitus (102, 106). The main purpose of counselling is to assist the patient understand tinnitus, and in doing so minimise the negative thoughts and emotions associated with it (162). It is important to be supportive and provide needed information to patients with tinnitus while counselling them (174). Tyler (174) documented three significant components of most successful counselling programmes:1) changing thoughts, 2) behaviour, and 3) understanding an individual patient's needs. Listening can be the first step towards understanding what the patient is going through, and how tinnitus is influencing their overall life. Providing information can be important in changing a patient's thoughts and actions.

There are various counselling approaches for tinnitus management e.g., psycho-education, directive counselling, and group and individual counselling. After reviewing these approaches, an example of a particular psycho-educational approach (tinnitus activities treatment [TAT]) will be described.

For some patients, sharing information is enough (101, 175), however for others, counselling can require multiple-sessions addressing many different factors. Tinnitus counselling can potentially be one-to-one or group-based. Group counselling can be more

time and cost effective for the dissemination of information and the patients in the group can offer support and encouragement to each other. However, it has shortcomings in that it may not be appropriate for patients needing personal attention and who need to discuss more specific, intimate, problems related to their tinnitus. Both of these counselling types have been effective in tinnitus management (176). In the audiological tinnitus management (ATM) programme (177, 178), described later, Level 3 involves group sessions for participants, however, for patients with advance level of difficulties, personal intervention is offered.

Directive counselling is an integral part of TRT proposed by Jastreboff and Hazel (1993) (102). According to the developers, directive counselling involves physiological explanations/education about the causes of tinnitus, identifying specific anxieties related to tinnitus, and retraining the thinking associated with tinnitus. Directive counselling involves explaining the results of all audiological and medical tests of patients about their tinnitus, its benign nature, origin, mechanisms, and addressing misconceptions regarding tinnitus (106). It is based on the psychological principle that the fear of unknown is greater than known unpleasant phenomenon (179). Directive counselling assists patients in making tinnitus a more understandable concept instead of a mystery. Once the patient understands tinnitus and its mechanism and the misconceptions are cleared, it is possible to bring down the level of annoyance and negative thoughts associated with it (106). There are several concerns/controversies about directive counselling (180). It has been criticised as being a ‘teaching approach’ towards the counselling, instead of being an interactive approach (180). Many researchers in the past have acknowledged the significance of an educational approach (181, 182), suggesting nothing is new about TRT directive counselling, and it has been strongly criticised for also neglecting procedures to assist patients to modify their behaviours (183). Counselling in TRT is intended to be provided one-to-one. Henry et al. (184), randomised 269 patients with chronic tinnitus into three groups: 1) educational counselling based on TRT (four weekly 1.5 hour sessions, conducted by audiologists, who participated in educational presentations covering various aspects of tinnitus and TRT); 2) traditional support (four weekly 1.5 hour discussion-type group sessions, moderated by the project coordinator, no education was provided in the support group); and 3) no treatment. Tinnitus evaluations were undertaken at baseline, one, six and twelve months following counselling. Educational counselling based on TRT proved to be significantly better than either traditional support or the no treatment group.

The psycho-educational approach is a client-centred approach based on the belief that the more information the patient has about their condition, the better treatment outcomes will be (185). Providing education about a condition is the first step towards effective management (183) and it helps the patient in clearing various doubts, misconceptions, and false beliefs about their tinnitus (165). The key elements in psycho-education as enlisted by Searchfield et al. (166) are the following: needs and goal setting, understanding anatomy/neurophysiology of the ear, results of audiological assessment, perception of sound and tinnitus, habituation, attention, treatment approaches, self-management/coping strategies, referral, relapse prevention, hyperacusis, and homework. The homework consists of goal setting, practising sleep hygiene, relaxation techniques, and attention control, and communication strategies when hearing loss is accompanied with tinnitus (186). Clinicians should be flexible in their approach to giving and receiving feedback and encourage open communication with patients.

TAT is a picture-based psycho-educational approach (168, 187-189), using the psychological framework of Hallam (101) and Henry and Wilson (175, 190). The counselling has two main components: 1) informational counselling, and 2) activities therapy (four broad categories of problems encountered by tinnitus sufferers: emotional well-being, hearing, sleep, and concentration) (188). Although there are four activities treatment areas, based on an initial assessment the areas requiring focus for a particular patient are determined. This comprehensive treatment plan is usually provided over several sessions to avoid information overload, however, some patients might not need as much of an intensive approach as others, and this can be determined based on the initial assessment of the condition (188). Emotional well-being is addressed by listening to the patient; providing information regarding tinnitus, attention, hearing and hearing loss; discussing ways to make tinnitus less important, and changing lifestyle to effectively deal with tinnitus. If at any point the clinician feels the condition is beyond their expertise, then appropriate referrals are made to a psychologist or psychiatrist (188). Sleep problems are usually associated with chronic tinnitus (79, 191). The goal of tinnitus activities treatment is to understand normal sleep patterns, find the factors significant in affecting sleep i.e., stress room temperature and environmental noise, making changes in the patient's diet, physical activities, bedroom arrangement, and sleep environment to promote better sleep. The goal of tinnitus activities treatment for hearing related problems is to empower them with strategies to improve hearing and reduce communication related stress associated

with hearing loss (188) such as amplification, modification in environment (good lighting, positioning, minimising noise, and visual distractions), and to facilitate better communication (192). Discussion regarding difficulties due to hearing loss and tinnitus is carried out for better understanding and management of the condition. Concentration difficulties are addressed by discussing how environmental factors and physical and mental state can affect concentration. Patients are trained to reduce the prominence of tinnitus by using partial masking and background music, and focus more on the task-at-hand by practising to control their attention (193).

Open research trials on the effectiveness of TAT are yet to be published. However, Tyler (personal communication, 2013) conducted two parallel studies with and without hearing aids, and in each study the participants were randomised into three groups: counselling alone, counselling and binaural noise generators/hearing aids to completely mask the tinnitus, and counselling and binaural noise generators/hearing aids to partially mask tinnitus. TAT was used in all three groups. In the study without hearing aid use (where sound generators were used), the average decrease in tinnitus handicap was 15% (counselling group), 25% (counselling and binaural noise generators to completely mask tinnitus), and 14% (counselling and binaural noise generators to partially mask tinnitus). The three groups did not differ from each other significantly. In the group where participants used hearing aids, the average reduction in tinnitus handicap for the three groups was 12%, 13%, and 16% respectively, and they did not differ from each other significantly. These results are contrary to the findings of Searchfield et al. (51), who found a significant difference between counselling alone and the combination of hearing aids and a counselling group. More research is needed to confirm the effectiveness of TAT.

2.3.2. Cognitive Behaviour Therapy

Cognitive behaviour therapy for tinnitus has largely evolved from the psychological model of tinnitus proposed by Hallam et al. (100). Along with an emphasis on the patient's cognitive thoughts towards tinnitus, behavioural change is considered in this approach hence it is called Cognitive Behavioural Therapy (103). This behavioural approach is usually used by trained psychologists (119) and is aimed at assisting patients to cope effectively with tinnitus rather than abolishing it (194). Some people believe that CBT should be provided by audiologists (195), and others think that it should involve a trained

psychologist (183). At a minimum, the provider should have competency in understanding the patient's problem, and should be able to plan accordingly (165). In CBT, the psychologist and patient collaborate as a team (183). CBT targets ANS arousal, negative emotional association with tinnitus, and other stressors (103). The primary techniques used in CBT are: relaxation therapy, cognitive restructuring, attention control, imagery, and behavioural techniques (194). These techniques are used in combination towards the treatment plan instead of using them as the sole treatment method (196).

Relaxation therapy involves several forms of relaxation training such as: progressive muscle relaxation, short progressive relaxation, and cue-controlled relaxation (controlled breathing). In progressive muscle relaxation, the patient is taught to sequentially tense and relax various parts of their body (197). This is initially practised in a comfortable setting under supervision, and is then gradually moved into real-life situations. Short progressive relaxation is a slightly advanced version of progressive muscle relaxation. It involves relaxing without tensing of the muscles and requires less time. Some imagery techniques are introduced in this relaxation technique. Cue-controlled relaxation (controlled breathing) involves linking a cue word to a calm, smooth, breathing pattern. More deep and controlled breathing can lead to quicker relaxation. The main aim of relaxation therapy is to reduce the arousal of the ANS (194).

Cognitive restructuring is based on the fundamental belief that modification of behaviour can be achieved by modification of thoughts (cognition) and cognition can be monitored (104). CBT practitioners believe it is not tinnitus per se that leads to distress, but the interpretation of tinnitus which is significant in determining how some people react to tinnitus with very strong emotional reaction, while others do not (103). Cognitive restructuring aims to identify dysfunctional thoughts, patient monitoring, and discussion with the therapist to then substitute them with more positive thoughts with the help of attention control, imagery, and behavioural techniques (194).

Attention control techniques involve taking control over attention and directing it towards external or internal environment to minimise tinnitus. Other sensory modalities such as taste, touch, and olfactory sensation can be used to also assist this process. Imagery techniques involve masking tinnitus through imagination without using any real sound e.g., the patient is asked to imagine that tinnitus is masked by the sound of a waterfall or rain, or to incorporate it with pleasant images such as walking in an enjoyable landscape

and listening to various sounds masking tinnitus such as birds chirping. It can be helpful in maintaining a relaxed state and increased general well-being (198). Behavioural techniques are prepared by the therapist and involve encouraging the patient to face situations where they feel distressed by tinnitus, such as attending a noisy situation or social gathering. The goal is to make the patient realise that they can cope with these threatening situations without major negative outcomes.

Research has shown that psychological treatments are effective in the reduction of tinnitus related stress (196). In a Cochrane review meta-analysis of six randomised control trials (RCT), Martinez et al. (199, 200) found that CBT was effective in tinnitus management. It did not change the subjective tinnitus loudness or associated depression, but it did lead to a significant reduction in global tinnitus severity therefore improving QOL.

2.3.3. Mindfulness and Tinnitus

Kabat-Zinn (201) defines mindfulness as “paying attention in a particular way, on purpose, in the present moment, and non-judgmentally”. Mindfulness based tinnitus treatment is aimed at encouraging patients to pay attention on the present, and observe their feelings, sensations, thoughts with openness, curiosity, and acceptance, and therefore tinnitus is neither actively ignored nor avoided (202). It differs from CBT in two aspects: no judgement or effort is taken to modify thoughts, feelings, or sensations related to tinnitus irrespective of how irrational, unrealistic, or illogical they are and the change in perception towards tinnitus facilitates reduction of stress (202). Sadlier et al. (203) used mindfulness meditation along with CBT for tinnitus management in 25 patients with chronic tinnitus. One group received CBT/mindfulness meditation in four one-hour sessions while another group waited for three months for the same treatment and acted as their own control group. Four to six months following treatment, 80% of participants reported to be better (much better based on their feedback), and this was correlated with their response on the Hallam tinnitus questionnaire (204) (29% reported 0–20% improvement, 33% reported 20–40% improvement, and 21% reported > 40% improvement). However, it was not possible to distinguish the effectiveness of CBT vs. mindfulness in this study. Participants were not randomised before commencing this study, and this study had limited external validity. Recently, Philippot et al. (205) conducted a randomised controlled trial investigating the effectiveness of mindfulness based therapy for tinnitus management in 25 tinnitus patients. All participants were offered a single session of psycho-education and after a period of

two months they were divided into two groups receiving six weekly sessions of either mindfulness or relaxation training. Results revealed the effectiveness of psycho-education in tinnitus management, and the benefits of psycho-education were maintained or enhanced by mindfulness training. These effects eroded in the relaxation training group. In another randomised controlled trial by Kreuzer et al. (206), the effectiveness of the mindfulness based group treatment for 32 chronic tinnitus patients were compared to a waiting list control. A significant reduction in scores on the German version of the tinnitus questionnaire (TQ) was observed for the treatment group compared to the waiting list. These results differ from that of Philippot et al. (205), who failed to show an immediate impact of mindfulness based therapy, which could be attributed to the fact that participants received large treatment effects from the psycho-education alone. Another difference was the stagnation (significant difference between the control group and intervention group on the tinnitus questionnaire at Week 7 and 9, but no difference at the Week 24 follow up) of results in the Kreuzer et al. (206) study compared to Philippot et al. (205). This could have been due to the lack of training maintenance in the Kreuzer et al. (206) study, and this highlights the significance of boosting sessions for maintaining treatment effects.

In this thesis, specifically the RCTs of tDCS and hearing aids (Chapter 7) I have deliberately not included counselling. While counselling has undoubted benefits, and should be used in clinical practice, it was avoided so as to try to isolate hearing aid and tDCS benefits from any other contaminating effects.

2.4. Sound Therapy

2.4.1. Introduction

Sound therapy is one of the most widely used therapeutic options for tinnitus (207, 208). Sound therapy is a broad term and the literature shows differences in interpretation of its meaning. Some reviewers have included masking (209, 210) and habituation (102, 211) as forms of sound therapy and others have not (164). Reavis et al. (207) defined sound therapy as the use of external sounds to provide short and long-term relief from tinnitus via acoustical or electrical stimulation. Different types of sounds have been used effectively in tinnitus management such as: environmental sounds, music, broadband noise and nature sounds (177, 212, 213). The goal is to use sounds which stimulate the neural pathways of the auditory system reducing tinnitus audibility, and when appropriate, compensating for

hearing loss (214), providing relaxation (215) or facilitating positive emotional response (209). Tinnitus is usually associated with hearing loss (216) which may lead to a reduction in afferent activity which possibly leads to an increase in central gain, amplification of spontaneous activity, and tinnitus perception (145). Although there is limited evidence for the benefit of sound therapy on its own (164), masking (217), habituation (102), relaxation (215), and reversing abnormal cortical reorganisation (45, 218) are proposed as potential mechanisms underlying sound therapies benefit on tinnitus.

2.4.2. Sound Therapy Mechanisms

The most popular proposed potential mechanisms underpinning the benefits of sound therapies on tinnitus are: masking (217), habituation (102), relaxation (215), gain adaptation, and neuromodulation (45, 119, 218). Turner et al. (219) provided some preliminary evidence of changes occurring in the peripheral and central properties of the auditory system of aged CBA/Caj mice exposed to sound. They exposed the mice to either an augmented acoustic environment (six weeks of low-level, 70 dBSPL, broadband noise, 12 hours per night) or normal vivarium conditions. Male mice exposed to augmented acoustic environment showed improvements in both the auditory brainstem response (ABR) thresholds and hair cell counts, however females had the opposite effect, which could possibility be due to the differences in the hormonal systems (female mice were beyond menopause and hence likely to have much lower estrogen levels than males). It would be premature to generalise these findings to hearing aid use to a geriatric human population with tinnitus, but it does provide some preliminary evidence regarding the changes that might occur in the auditory system as a result of hearing aid use which may provide relief to patients with tinnitus.

2.4.2.1. Masking

Normally hearing individuals with no previous tinnitus history experience tinnitus when they are in a sound-proof room for a few minutes (220, 221). This strengthens the argument that if environmental masking can inhibit the perception of tinnitus in normal-hearing non-tinnitus sufferers, it should be possible to assist tinnitus sufferers as well (119). Kidd et al. (222) defined masking of sound as the process where one sound is presented to reduce the audibility of another sound through the reduction in probability of detection or interference with different identifying features such as pitch, loudness,

location, or meaning. Tinnitus masking can be divided into two types: total masking and partial masking (207). Total masking involves sufficiently loud presentation of external sound to make the tinnitus inaudible. Partial masking involves sound presentation in which both the tinnitus and masking sound are heard, but tinnitus is less audible than without the sound present. Tinnitus masking differs from masking of sound (223). Feldmann (1971) (223) proposed five different masking patterns for tinnitus: 1) convergence type, usually observed with high pitch tinnitus associated with high frequency hearing loss—tinnitus could be masked at low sensation levels at high frequencies and high sensation levels at low frequencies; 2) divergence type, where tinnitus could be masked at low sensation levels at low frequencies and high sensation levels at high frequencies with mild to moderate hearing loss; 3) congruence type, where tinnitus could be masked just above the threshold throughout the frequency range; 4) distance type, where tinnitus could be masked at high levels throughout the frequency range; and 5) persistence type where tinnitus could not be masked. Penner et al. (224) explored the temporal course of masking of tinnitus and external tone, and revealed that the intensity of broadband noise required to mask tinnitus increased by 45 dB during a 30-minute timeframe where the participant was exposed to noise. Contrary to this, the intensity required to mask an external tone remains constant. They propose the likely reason for this to be the central origin of tinnitus. It has been suggested that masking of tinnitus is a combination of both an energetic (bottom-up) process and informational (central top-down) process (225).

Vernon (1977) (217) demonstrated the potential of tinnitus maskers in tinnitus management. He presented two cases where patients suffering from chronic tinnitus received relief from tinnitus (one patient experienced complete relief from tinnitus and another experienced benefit in going to sleep). Hazell et al. (226) conducted a study to investigate the effectiveness of tinnitus maskers, combination instruments (masker and hearing aid), and hearing aids for tinnitus management in 472 patients with tinnitus across three different centres. There were two control groups who received counselling only. They concluded that maskers are more effective than counselling or hearing aids. However, hearing aids should be the first intervention option for patients with hearing loss as well as tinnitus. This study had certain limitations in the methodology due to the three different sites of study, and there were differences in the implementation of protocol. The details of the differences were not documented in the paper, but different maskers and hearing aids were used in different sites of the study, which makes it difficult to compare

and generalise the overall outcome of this study. Henry et al. (227) hypothesised that the effectiveness of tinnitus maskers can be enhanced by expanding auditory stimulus options to patients. Twenty-one participants compared the effectiveness of white noise and custom sounds for tinnitus relief while sitting in a sound booth. They found specially designed dynamic sounds to be more effective than white noise in tinnitus suppression. 'Dynamic' acoustic technology is proprietary to Petroff Audio Technologies Inc. Dynamic sounds have variations in amplitude over time induced by the use of computer-generated algorithms, sounds with natural dynamics of peaks and troughs were preferred. Tinnitus maskers can be used for patients with normal-hearing thresholds who do not need hearing aids for tinnitus management (226). In the presence of hearing loss, combination devices are more likely to be used (228). Most of the devices used for sound therapy (intended or not) result in some form of masking.

2.4.2.2. Habituation

Habituation is the gradual reduction in response to a stimulus or to the environment (106). The goal of tinnitus habituation therapy in tinnitus management is to convert tinnitus to an uninteresting background sound, and the fundamental condition to induce habituation of tinnitus is to interrupt the association between the limbic system activation and the tinnitus signal (106). If habituation therapy is followed it may reduce the associated distress caused by tinnitus in approximately 6 to 18 months' time. One of the popular habituation based sound therapy approaches is TRT. TRT is based on Jastreboff's (105) (1990) neurophysiological model of tinnitus. According to TRT, habituation can be achieved by a two stage process involving directive counselling and sound therapy (103). TRT combines directive counselling with a specific form of sound therapy at the mixing point of sound and tinnitus. According to Jastreboff's model, there are two neural loops which participate in tinnitus processing. The 'upper loop' involves cognitive processing of tinnitus which is dominant in the initial stage of tinnitus, and the 'lower loop' is the subconscious loop and becomes dominant in chronic tinnitus sufferers. The primary goal of TRT is tinnitus habituation through passive extinction of conditioned responses (119). Habituation is thought to be achieved when although the tinnitus signal is unchanged, patients are unaware of tinnitus until they focus on it. In TRT, directive counselling targets the 'upper loop' by providing explanations of patients tinnitus based on Jastreboff's neurophysiological model—to reduce the tinnitus-evoked negative reactions and lowering

the activation of limbic system and ANS (103). TRT sound therapy is based on the principle that the brain uses the contrast between the neuronal signal and background neuronal activity to determine the strength of the signal (179). In psychoacoustics, this contrast effect can be explained by Helson's (1964) adaptation level theory (229). Sound therapy is used to reduce tinnitus perception by increasing the background neuronal activity in the auditory pathways to reduce the contrast between tinnitus and background, which in-turn facilitates habituation (106). According to Jastreboff (2010), two fundamental principles to remember are: 1) any sound which creates annoyance or discomfort for any reason should not be used for sound therapy as it will activate the limbic system and ANS, making the process of habituation more difficult (179); and 2) the process of sound enrichment should be used all the time because it is likely to reduce the contrast between tinnitus and background sounds by enhancing the background neuronal activity.

2.4.2.3. Gain and Adaptation

The literal meaning of the term 'gain' is the increase in the volume or signal, and the term 'adaptation' in the context of tinnitus means the change in the perception of tinnitus due to experience. Gain adaptation is the likely phenomenon to underlie sound therapy for tinnitus management by reducing the brains gain control for tinnitus (15). According to Norena's model (15), due to the cochlear damage there is a reduction in the sensory information reaching the brain and to maintain neural homeostasis the central gain is thought to increase, which results in the perception of neural noise as tinnitus. Two therapeutic strategies proposed based on this model are: to reduce the central gain (acoustic stimulation, hearing aids, and cochlear implants) and diminish the peripheral drive (pharmacological or inhibitory electrical stimulation) (15). Formby et al. (230) plugged the ears of some individuals continuously for two weeks and found the loudness rating of sounds to be higher compared to before ear plugging, and similarly, some people were continuously exposed to low level noise for two weeks and reflected lower ratings of loudness compared to the pre-exposed condition. Munro et al. (231) investigated 16 elderly people with age related hearing loss, who used monaural hearing aids (median hearing aid use of 3 years) and showed asymmetry of + 2 to + 9 dB between ears in the sound level for loudness discomfort and acoustic reflex thresholds. This provided evidence for adaptive plasticity in elderly monaural hearing aid users, which could be measured at

the level of auditory brainstem. Munro and Merrett (231) studied the impact of short term monaural hearing aid (five days) use on the brainstem plasticity of the normal-hearing adult listeners. They found acoustic reflexes at a higher sound pressure level in the aided ear after five days of hearing aid use, providing evidence for plasticity in brainstem of adult listeners. These findings are in agreement to those of sensory deprivation by ear plugging done by Formby et al. (230) and also support the existence of a gain control mechanism, since the ear with hearing aid fitting had enhanced inputs, the gain was reduced and it was reflected in the higher acoustic reflect thresholds. These findings support the potential for changes in auditory plasticity induced by hearing aid use to manage tinnitus.

There has been electrophysiological evidence based on animal studies (45, 142) supporting the prevention of tinnitus following noise trauma by constant acoustic stimulation in the region of potential hearing loss. Studies have shown that acoustic stimulation in the region of hearing loss is more effective than overall broadband noise (232, 233). In a recent study by Searchfield et al. (229), perceptual adaptation to tinnitus has also been linked to factors such as memory and personality of the sufferer.

2.4.2.4. Relaxation

Tinnitus is closely related to stress. It can either cause stress or be a consequence of stress related event (3, 4). Relaxation is an integral part of tinnitus counselling, psycho-education, and some sound therapies which help the patient cope better with tinnitus. There are several ways to induce relaxation such as by using applied relaxation techniques (progressive relaxation, short progressive relaxation, and controlled breathing) and using several cognitive techniques such as positive imagery and cognitive restructuring of thoughts and beliefs associated with tinnitus. Music has also been a popular therapeutic option for several physical and psychological conditions (234) and has been used for tinnitus management also (235). In a study conducted by Sweetow and Sabes, (2010) (215), 86% of participants with hearing loss and a primary complaint of tinnitus, reported less annoyance and more relaxation while listening to fractal tones.

2.4.2.5. Neuromodulation

Most sound therapies have a positive impact on the neural activity of the brain. Tinnitus is likely to be a by-product of altered neuronal activity in the central nervous system (236-

239). Modification of this pathological neuronal activity is referred to as neuromodulation for tinnitus relief (240, 241). Neuromodulation techniques are likely to induce neural plastic changes and modulate the pathological neural networks responsible for tinnitus (240). Hwang et al. (242) investigated the changes in the activation pattern of the auditory cortex following long-term monaural amplification using fMRI. They found that speech-elicited activation decreased after monaural amplification bilaterally during unaided or aided ear stimulation, but recovered at the contralateral hemisphere during aided ear stimulation, suggesting the neuroplasticity of auditory cortex after hearing aid use. In a review study by Eggermont (243) concerning the role of sound in the auditory cortical plasticity of humans and cats, he concluded that long-term exposure to spectrally enhanced acoustic environments of moderate sound can result in pronounced changes in the cortical tonotopic maps. These studies provide early evidence for the plastic changes that hearing aids may induce after use, which might be helpful in reversing tinnitus related cortical reorganisation, explaining the potential mechanism of hearing aids' effect on tinnitus suppression.

Techniques such as Acoustic Co-ordinated Rest (CR) neuromodulation, hearing aids, combination devices, and several other devices' effect on tinnitus management are mediated by the indirect modulation of brains plasticity. These therapeutic interventions will be discussed in the next section.

2.4.3. Sound Therapy Devices and Methods

When using sound therapy for tinnitus management there are some important aspects which should be considered such as: hearing status of patient, willingness and motivation for its use, assisting patients in choosing the most appropriate sound therapy device based on their needs and expectations, and follow-ups should also be encouraged to address patients concerns and compliance with recommendations (244). There are various device options for sound therapy such as: hearing aids, cochlear implants, custom sound generators, combination devices, table top sound generators, acoustic CR neuromodulation, the Sound cure (Serenade device), Tipa tinnitus devices, the Phase-shift/ Phase-out, music, and the Neuromonics Oasis^{TM} device. Most of these devices have multiple mechanisms of effect (masking, habituation, relaxation, gain adaptation, and neuromodulation). In the following section, I describe devices and studies specific to

devices, before discussing therapies that use a range of devices and the outcomes of these therapies.

2.4.3.1. Hearing Aids

Tinnitus is usually associated with hearing loss (216), which may lead to a reduction in afferent activity which possibly leads to an increase in central gain, amplification of spontaneous activity, and tinnitus perception (145). Hearing aids are devices that fit in or on the ear to amplify sounds. Open-ear hearing aids are amongst the most commonly used tools for sound therapy (245, 246). Hearing aids provide compensation for the degree of hearing loss, may turn down central gain, mask tinnitus, assist the brain to suppress tinnitus and reduce the communication stress associated with hearing loss (214). Hearing aids possibly enact all the proposed sound therapy mechanism of effect, such as masking, habituation, relaxation, gain adaptation, and neuromodulation to assist in tinnitus management. Clinical outcomes of fitting hearing aids are reviewed in Chapter 4.

2.4.3.2. Cochlear Implants

Hearing aids and tinnitus maskers are ineffective for sound therapy in people with severe to profound hearing loss (244). Cochlear implants are surgically implanted electronic devices that provide a sense of sound for patients with severe to profound hearing loss; cochlear implantation may be a viable option for not only correcting hearing loss but also providing tinnitus relief. Several studies have shown the effectiveness of cochlear implants in managing tinnitus (247-250). Similar to hearing aids, cochlear implants also may affect tinnitus by many different mechanisms (masking, habituation, relaxation, gain adaptation, and neuromodulation). Ito (248) investigated 60 patients who underwent cochlear implantation and reported reduction in tinnitus loudness in 93% of patients and duration in 61% of patients after two months of its use. Similar findings were reported by Souliere et al. (250), when they used a closed-ended questionnaire to evaluate the effectiveness of cochlear implantation in 33 post-lingually deafened patients. Fifty-four percent of patients demonstrated a loudness reduction of 30% or more, 43% demonstrated a reduction in tinnitus annoyance by 30% or more, and 48% demonstrated a reduction of 30% or more in daily tinnitus duration. These studies support the use of cochlear implants for tinnitus management; however, it is more suitable for people with a severe to profound degree of

hearing loss and along with the cost of cochlear implantation, results in a much more restricted target population than other tinnitus management options.

2.4.3.3. Custom Sound Generators

Custom sound generators are used for both total and partial masking (209). They are usually used for people having tinnitus with normal/near-normal hearing sensitivity. They look like regular hearing aids and are worn in or behind the ear and typically produce a hissing sound (wide band noise). Proposed mechanisms of effect of custom sound generators are masking, habituation, relaxation, and gain adaptation. Trials with these devices will be discussed in a section on clinical trials with TRT.

2.4.3.4. Combination Devices

Combination devices or tinnitus “instruments” are devices which combine two circuits (hearing aids and sound generator) in one wearable unit (244). Many hearing aid companies have developed combination instruments for tinnitus management. Typically, they use broad band noise along with hearing aids, but lately other sounds have been used including fractal tones (215). Schleuning and Johnson (1997) (228) studied the use of hearing aids, tinnitus maskers, and combination devices for tinnitus management in 100 patients with chronic tinnitus. All three options were helpful in effectively masking tinnitus. However, 37.1% patients experienced residual inhibition with combination devices, 33.3% experienced it with hearing aids, and 27.8% experienced it with tinnitus maskers.

Fractal tones sound somewhat like wind chimes; they are pleasant and non-repeatable, utilise harmonics but are not predictable (251, 252). The mechanisms of effects are believed to be the same as hearing aids and custom sound generators. Kuk et al. (253) and Sweetow and Sabes (215) have documented the effectiveness of fractal tone combination devices in tinnitus management. The study conducted by Kuk et al. (253) had some methodological limitations, being that it was a survey design based on the feedback from clinicians about their tinnitus patients, which might not be a true representation of the actual condition of tinnitus patients; the results can be biased based on the competency of the clinicians and the protocol used for the management of their patients. Although the details of the survey were not given in the paper, it was documented to be a very short survey taking approximately five minutes, which again raises questions about the depth of

clinicians' perception regarding their patient's condition. In the research done by Sweetow and Sabes (215), 14 tinnitus patients with hearing loss were prescribed amplification only, fractal tones only, and a combination of amplification, noise, and/or fractal tones. Thirteen out of 14 tinnitus patients reported improvement with one of the conditions, but in this study it was difficult to ascertain the effect of hearing aids vs. fractal tones. Piskosz and Kulkarni (254) documented the effectiveness of the ReSound Live TS combination instruments for tinnitus management. They reported the findings of two studies. In the first study, 30 chronic tinnitus patients were fitted with ReSound Live TS combination instrument using broad band noise, and were followed up after three and six months of device use. There was a significant reduction in the scores of tinnitus handicap inventory (THI) and structured interview, visual analogue scale (VAS) scores for "annoyance", "intensity", and "tinnitus effects on patient's life". In the second study, 24 tinnitus patients were fitted with a ReSound Live TS combination instrument to evaluate personal preferences for certain features of combination instruments such as amplitude modulation, automatic volume control vs. manual volume control, and filter settings (to allow broad band noise or narrow band noise) and were then followed for six months. Overall, there was a significant reduction in the tinnitus handicap as measured by THI and tinnitus handicap questionnaire (THQ). The majority of the patients (68%) preferred a manual volume control over the automatic volume control feature, continuous noise over the modulated noise (73%), and filter settings allowing broad band noise instead of narrow band noise (82%). These two studies were multi-site trials (participants were not from one location rather from tinnitus clinics worldwide [exact details about location were not provided in the paper]). However, Piskosz and Kulkarni (254) used some form of counselling and TRT treatment along with the use of combination devices, making it difficult to determine the exclusive impact of the combination devices on tinnitus perception. More trials are needed to confirm these findings.

2.4.3.5. Table-top Sound Generators

Table-top sound generators are desktop sound generating devices with volume control, speakers, and power supply (208). Different environmental sounds such as sea waves, rain, white noise, and waterfall can be chosen. Various table-top sound generator devices (244) are available and sold as consumer products (e.g., http://www.marpac.com). The predominant mechanism of effect is to induce relaxation, but masking and habituation

could also be underlying their effectiveness to manage tinnitus. Handscomb (2006) (255) documented the effectiveness of bedside sound generators in significantly reducing sleeping difficulties in 35 tinnitus patients and the preference of sound was linked to its pleasant emotional effects.

2.4.3.6. Acoustic Co-ordinated Reset (CR) Neuromodulation

The Acoustic Co-ordinated Reset (218) method is a technique which attempts to counteract pathological neural synchrony as the basis of tinnitus (256). It is based on the principle of self-organisation (257). This technique involves listening to sequential tones for a few hours per day. Based on computational models, it can facilitate the shifting of synchronised neuronal networks with strong synaptic connectivity to a desynchronised state with weak connectivity (258, 259). As a result of this, the pathological synchrony and connectivity associated with a disorder (tinnitus) is unlearnt (258). The predominant mechanism of effect of Acoustic CR is neuromodulation. Tass et al. (218) investigated the impact of Acoustic CR Neuromodulation on tinnitus in a randomised, placebo-controlled prospective study design with 63 patients suffering from chronic tinnitus. Results revealed a significant reduction in scores of a tinnitus questionnaire, tinnitus pitch, and reversal in tinnitus related electroencephalography (EEG) alternations. The positive effects were long lasting (up to 10 months). This study was limited to patients with tonal tinnitus, so the findings cannot be generalised to patients with other forms of tinnitus. Although it was a randomised trial, the placebo group differed significantly from the control group on baseline measures. Hence, more research investigating the impact of this technique is required with a stronger methodology and appropriate randomisation. Recently Silchenko et al. (260) conducted a study to explore if CR neuromodulation can alter the connectivity in participants with tinnitus who responded well to this therapy. They reported a significant reduction in the delta and gamma power along with increase in alpha power in the primary auditory cortex, dorsolateral prefrontal cortex (DLPFC). The posterior cingulate cortex of tinnitus participants who responded positively to CR therapy was indistinguishable from the healthy normal participants supporting the use of this technique for tinnitus management.

2.4.3.7. SoundCure Serenade Device

The SoundCure Serenade device is a computer programmed hand-held device. It delivers 'cortically interesting' sounds (modulated pulse rate signals which produces highly synchronised and robust cortical response) to affect the synchrony of the cortical responses (261) and is based on the work undertaken by Zeng et al. (262). Zeng et al. (262) presented a novel case study where a unilaterally-deafened cochlear implant subject experienced complete tinnitus suppression by a low-rate (< 100 Hz) stimulus delivered at a level softer than tinnitus to the apical part of the cochlea. The neurophysiological evidence revealed a reduction in cortical N100 potentials (which was abnormally high in the patient before this treatment) leading to the restoration of a normal cortical state and increase in spontaneous alphas power (7–9 Hz) in the temporal region of the auditory cortex. The SoundCure Serenade device is an acoustic version of a similar stimulation pattern. It offers three customizable tones (two S-tones and one narrow band sound). The uniqueness of S-tones is that they are comprised of 'cortically interesting sounds' which can be heard at a very low volume level, yet can reduce the sound burden and provide relief. This technique is used to provide relief from tinnitus and is combined with counselling to address negative thoughts associated with tinnitus. The predominant mechanism of effect of SoundCure Serenade device is likely to be neuromodulation. There is a lack of research about the effectiveness and neurophysiological effect of this technique, and it is unclear what a 'cortically interesting' sound is and why it should be important.

2.4.3.8. Tipa Tinnitus Devices

The Tipa tinnitus device is a hand-held battery powered player, which uses insert ear phones to deliver Tipa sound signals with the aim of prolonging residual inhibition in tinnitus sufferers. The Tipa signals are a series of non-sinusoidal, very low frequency complex tones. There are three different signals each lasting for three minutes and presented in 1, 2, 1, 3 sequence. In addition to residual inhibition, the proposed mechanism of effect of Tipa devices could be masking, habituation, or neuromodulation. Winkler (263) presented case studies describing the success of using the Tipa tinnitus device in three patients where residual inhibition lasted for up to two weeks. Winkler claimed to have developed Tipa signals by trial and error based on five years of his work, however, neither the details of the Tipa signal nor the measure used to assess the three tinnitus patients have been explained in detail, raising questions about the validity of this study,

and further evidence is awaited for this technique. The basis for the signals used and the presentation order, and why this should be important is not clear from current publications.

2.4.3.9. Phase-shift/ Phase-out

Both the Phase shift (264) and Phase out (265) techniques appear to be inspired by work on noise cancellation. In active noise cancellation, presenting a stimulus with the same amplitude and frequency as noise (but with inverted phase) cancels the target sound. This can't occur for tinnitus as it exists as a neural, not acoustic signal. Phase shift involves a signal pitch matched to tinnitus, but phase-shifted sequentially by six degrees at intervals of 30 seconds. Choy et al. (265) documented the worldwide (six centres from New York, London, Pennsylvania, Antwerp, Italy, and Kuala Lumpur) experience of 493 tinnitus patients with sequential phase-shift sound cancellation for the treatment of predominant tonal tinnitus from 2000 to 2009. A reduction of tinnitus volume (defined as $\geq$ 6 dB) was seen in 49% to 72% of patients across the six centres. This study did not use any psychometric measures to ascertain QOL effects and ignored the associated distress and annoyance experienced by tinnitus sufferers. Although there was a change in the psycho-acoustical properties of tinnitus (loudness in this study), handicap is usually independent of psycho-acoustical properties of tinnitus (106). It would have been interesting to see if the reduction in tinnitus loudness also resulted in improved QOL and reduction in tinnitus handicap. Choy et al. (265) failed to provide any satisfactory explanation about the proposed mechanism of effect of this technique in their paper. Heijneman et al. (266), conducted a double-blind, crossover, randomised controlled trial comparing the efficacy of phase-shifting pure tones and tones without phase-shifting in 22 patients with tonal tinnitus and failed to see any significant effect of either approach.

2.4.3.10. Music

Music assists in inducing relaxation and can help people with tinnitus to cope with it effectively (267). Recent research (235, 268) has shown the effectiveness of using music for tinnitus management. The primary mechanism of the effect of music is masking, habituation, relaxation, and neuromodulation possibly though lateral inhibition. Okamoto et al. (235) conducted a double-blind study with patients suffering from chronic tinnitus. Patients in the experimental group (n = 8) were exposed to self-chosen, enjoyable music which was notched in the tinnitus frequency range, based on the individual patients'

tinnitus frequency (one octave frequency band centred at the tinnitus patients' tinnitus frequency was removed via a digital notch filter). Control group (n = 8) patients were exposed to analogous placebo-notched music (the energy in the 1-octave frequency band surrounding the individual tinnitus frequency remained strictly unchanged and 1-octave width energy in the remaining frequency range was filtered). After one year of regular listening through the supplied closed headphones with convenient loudness (the exact duration of use was not mentioned in the study), the experimental group showed a significant reduction in perceived tinnitus loudness as compared to the control group. Auditory evoked measurement also revealed a reduction in the activity in auditory cortex areas (corresponding to tinnitus frequency) in the experimental group as compared to the control group. More trials are required to ascertain the efficacy of notched music for tinnitus management, however, it is one of the few tinnitus sound therapies with objective measure (auditory evoked) supporting findings. One concern for any treatment based around tinnitus pitch, is that pitch matches are inherently variable and can change with treatment (269). Contrary to the results of Okamoto et al. (235), Vanneste et al. (268) concluded that music therapy was not beneficial for tinnitus. He conducted a double-blind, placebo controlled study, where the control group participants listened to unmodified music and the compensated treatment group listened to spectrally tailored music to compensate for their hearing loss (selectively increasing the gain at the frequencies of hearing loss) and the overcompensated treatment group listened to music tailored to overcompensate their hearing loss (a notch is created at the edge of the hearing loss and gap is overcompensated). Participants were given MP3 players to listen to the music for a minimum of three hours per day for one month. No significant difference was seen between the control group and compensated treatment group. Participants in the overcompensated group revealed a worsening of tinnitus loudness, annoyance, and depressive feelings also associated with increased gamma band activity in the primary auditory cortex which is correlated with perceived tinnitus loudness (270). The lack of positive results of music therapy in the Vanneste et al. (268) study (contrary to the Okamoto et al. (235) study) could be attributed to the fact that this trial was only one month long, and the listening of music for three hours per day for only one month was not sufficient enough to bring in necessary positive changes unlike Okamoto and colleagues study which lasted for one year. The presence of dead regions (271) in the participants was not ruled out in the Vanneste et al. (268) study, which possibly could prevent the

participants in getting enough stimulation in the frequencies of severe hearing loss and be a cause for negative results.

2.4.3.11. Neuromonics

The acoustic desensitisation approach, "neuromonics" was proposed by Davis et al. (272). This approach is a combination of counselling with modified music to compensate for hearing loss delivered though the Oasis^{TM} device with high-fidelity head phones. The therapeutic basis is similar to TRT, but also considers systematic desensitisation as an explanation for improvement. Systematic desensitisation is a technique based on the principles of phobic reaction and uses relaxation techniques to gradually become less sensitive to an anxiety provoking situation or stimulus (273). Users are advised to listen to modified music passively for about two to four hours per day. Mechanisms contributing to the effect of neuromonics could also include masking, habituation, relaxation, and neuromodulation. Studies have shown the effectiveness of neuromonics in managing tinnitus (274-280). The general criticism about many of these trials is a lack of methodological transparency (281) and potential bias from manufacturer sponsorship. A study by Newman and Sandridge (282) suggests that while the neuromonics approach may be beneficial, it is less cost effective than ear level sound generators.

2.4.4. Clinical Trials

There have been mixed opinions as to the effectiveness of sound therapy for tinnitus management. There are some studies which support the use of sound therapy such as Jastreboff (283) who investigated tinnitus patients who were either treated with one session of directive counselling (n = 22), or directive counselling along with sound therapy (n = 102). Based on patients' self-perception, a significant improvement was found for those using sound therapy along with directive counselling, as compared to counselling alone, however this study had some limitations such as a lack of control group and lack of details about the methodology and analysis. Folmer et al. (48) studied the long-term effectiveness of sound therapy in 150 tinnitus patients who were divided into three groups: hearing aid users, sound generator users, and a third group which did not use any devices. All three groups received counselling and reported improvement in their tinnitus severity, however those who used ear level devices for sound therapy showed comparatively higher improvement. Although this study supports sound therapy for tinnitus management, it was

difficult to extract the improvement contributed by sound therapy on its own. Searchfield et al. (51) conducted a study investigating 58 patients with chronic tinnitus, randomised into two groups: receiving counselling alone (n = 29) and hearing aids with counselling (n = 29). On the primary outcome measure of the THQ, patients using hearing aids alongside counselling reported twice the reduction in tinnitus handicap compared to counselling alone supporting the use of sound therapy for tinnitus management.

The effect of TRT on tinnitus loudness and annoyance was investigated by Bauer et al. (211) in a controlled trial. Participants with chronic tinnitus and near-normal-hearing sensitivity (pure tone average at 0.5, 1, 2, and 4 kHz ≤ 30 dBHL) were assigned to a TRT group (directive counselling and sound therapy) or control group (general counselling and a sham sound therapy). Participants were followed from three to eighteen months following intervention. Participants in both groups revealed a significant reduction in their tinnitus, however the larger effect size was documented for the TRT group (1.13) compared to the control group (0.78). This study was restricted to participants with near-normal-hearing in speech frequencies and hence any generalisation of the results should be done with caution. Fukuda et al. (284) compared the efficacy of TRT using portable music players, tinnitus control instruments, and hearing aids. Twenty-three participants with chronic tinnitus were divided into three groups based on the type of device they were fitted with: portable music player (7 participants), tinnitus control instruments (6 participants), and hearing aids (10 participants). The sound pressure output from the portable music device was kept lower than participants' tinnitus level and recorded environmental sound (murmur of a stream) was used. The sound pressure output from tinnitus control instruments was also set lower than the tinnitus level. Hearing aids were fitted according to the standard procedure (details of prescriptive approach not given) and gain was 5 to 10 dB higher in the tinnitus frequency region and 5 to 10 dB lower under 500 Hz. Participants were followed up for one year using the THI as a primary outcome measure. Results revealed that TRT using a portable music player had equal efficacy (efficacy ratio of 71%) as opposed to the use of tinnitus control instruments (efficacy ratio of 67%), or hearing aids (efficacy ratio of 70%) supporting the use of portable music players as a cost effective option for TRT.

Henry et al. (285) conducted an 18-month controlled clinical trial to evaluate the efficacy of tinnitus masking and TRT in 123 patients with chronic tinnitus. Patients were assigned to receive either tinnitus masking or TRT. Results revealed the effectiveness of both

techniques for ameliorating tinnitus. Tinnitus masking provided immediate relief (maximum at the third month) but TRT provided the most improvement with continued treatment (12 to 18 months). The aim of sound therapy in TRT is to recondition the connections in subcortical areas masking tinnitus awareness, hence when using sound therapy in TRT it has been considered important not to mask the tinnitus signal completely as completely masked tinnitus signal cannot be habituated (106). However, this view has been recently been challenged (286). Tyler et al. (286), challenged the traditional concept of avoiding complete masking to achieve habituation. Forty-eight patients with chronic tinnitus were randomised into three groups (counselling alone, counselling along with total masking, and counselling along with partial masking). After 12 months, the average reduction of tinnitus handicap as measured by the THQ was 16.7% for the counselling group, 31.6% for the partial masking group, and 36.4% for the total masking group. The three groups did not differ significantly on the average score, reflecting that partial masking was not superior to total masking.

Studies have documented the effectiveness of TRT for tinnitus management, however, they had methodological limitations such as: lack of control group, absence of RCT, were unable to follow the exactly proposed TRT model by Jastreboff, and were unable to use psychometrically validated tests as outcome measures (183). More empirical evidence and research is needed before accepting it to be the best available tinnitus management option as proposed by Jastreboff (287).

Henry et al. (288, 289) began ATM in an attempt to use existing audiological based tinnitus treatments or management in a staged manner in which persons with tinnitus receive the most appropriate level of treatment based on their need. This approach has been adapted by veterans' affairs in the USA, as a method of efficiently providing tinnitus treatment when faced with increased patients and financial burden. The updated and expanded version of ATM is called progressive audiological tinnitus management (PATM) (177, 178). This programme is adaptive and flexible to accommodate the individual needs of tinnitus suffers. PATM consists of five levels. Level 1 is triage stage and it provides basic guidelines for the appropriate referrals. This is mainly for non-audiologists (primary care workers, psychologists, psychiatrists, neurologists, oncologists, and otolaryngologists) who need help in providing appropriate referrals for the tinnitus sufferers. Level 2 to 5 are for audiologists and the services provided by them. Level 2 is audiological evaluation and its primary objective is to determine if the patient needs audiological intervention for

hearing loss, tinnitus, or both. Level 3 is group education and is comprised of two sessions. The first session is used to explain the significance of sound management and planning for the patient based on their needs. The second session is usually planned after two weeks of follow up, where patients are supposed to implement the programme planned for them. The primary focus of this session is to ensure that patient understands the plan and its effective use in tinnitus management along with new information. Level 4 is tinnitus evaluation and is for those patients who still need more support after successfully competing Level 3. This level includes an interview and psychoacoustic tinnitus assessment and other necessary evaluations such as mental health evaluation and screening for sleep problems to help manage tinnitus. Level 5 is called individualised management, which involves individual counselling and deeper interaction with the tinnitus patient. PATM is a flexible approach for tinnitus management and caters to the individual needs of the patient. Controlled trials documenting the effectiveness of PATM are yet to be published. The value of a staged approach to tinnitus management is potentially cost effective in finding the appropriate level and depth of intervention for any given patient. Although PATM was designed with veteran affairs in the USA in mind, other funding bodies such as the accident compensation corporation in New Zealand has adopted a similar strategy for tinnitus patients.

There have been some studies not supporting sound therapy as a standalone tinnitus management approach. Eysel-Gosepath et al. (290) conducted a prospective study where 40 patients suffering from chronic tinnitus were randomised into two groups (Group A and B). All participants were provided with counselling and relaxation training. In Group A, participants were fitted with hearing aids or white noise generators and learned to distract their attention away from tinnitus using sound or music. In Group B, participants were directed to use imagination facilitated by light or thermal stimuli to direct attention away from tinnitus. The two groups did not differ from each other immediately after and after six months of therapy. Both groups had significantly less annoyance and disability from their tinnitus. The researchers concluded the effectiveness of attention diversion for reducing tinnitus related distress and proposed that other methods can be equally effective as sound. Goebel et al. (291) studied the effectiveness of sound therapy alone (broad band noise generators), counselling alone (four sessions of cognitive behaviourally based coping therapy), a combination of sound therapy with counselling (broad band noise generators and four sessions of cognitive behaviourally based coping therapy), and a control group

with no therapy. Participants with counselling alone and a combination of sound therapy with counselling showed significant improvement on tinnitus annoyance, tinnitus control, and depressiveness measures. Although the two groups did not differ from each other significantly, they showed the improvement of counselling in tinnitus management while raising questions about the need for sound therapy. McKenna and Irwin (164) conducted a review investigating evidence of sound therapy for tinnitus management. They reviewed 11 papers which detailed sound therapy as a distinct component of tinnitus management. The majority (7 out of 11) of the studies did not offer support for the effectiveness of sound therapy for tinnitus treatment. They concluded counselling to be effective and significant for tinnitus management, however, sound therapy on its own was of limited benefit. They did not refute the use of sound therapy for tinnitus management, but reported too little evidence for its support in their review.

Although there have been mixed reviews about the effectiveness of sound therapy on its own, it does appear to be a promising management option for patients with tinnitus and more RCTs are needed specifically targeting the effectiveness of sound therapy on its own (without counselling).

2.5. Neuromodulation Techniques for Tinnitus

Tinnitus processing and perception is the by-product of altered neuronal activity in the central nervous system (236-239). Modification of this pathological neuronal activity for tinnitus management is referred as neuromodulation for tinnitus relief (240, 241). Neuromodulation techniques are hypothesised to work based on modulating neuronal excitability and/or synaptic strength and disturbing the pathological neural networks responsible for tinnitus (240). These techniques have shown initial positive trends in tinnitus management but none of them have been promising enough yet to use as regular clinical intervention option. Neuromodulation techniques can be divided in to two categories: non-invasive (neurofeedback, TMS, transcutaneous electrical nerve stimulation [TENS], transcutaneous vagus nerve stimulation , and tDCS) and invasive (involves auditory cortex stimulation, DLPFC stimulation, sub-cutaneous occipital nerve stimulation, and deep brain stimulation). Invasive stimulation is beyond the scope of this review.

2.5.1. Neurofeedback

Neurofeedback involves acquiring signals from the patient's brain (using EEG, fMRI, and near infrared spectroscopy) (292) and then delivering it back to the individual, in real-time after extracting relevant aspects of the signal so they can monitor their neuronal activity (293). It is based on the principle of operant conditioning (294). The patient is rewarded immediately after the feedback signal reaches a predefined target. Studies have shown improvement in epilepsy (295-297) and attention deficit hyperactive disorder (298) using neurofeedback. There have been few studies addressing neurofeedback in tinnitus patients (293, 299-302).

Haller et al. (302) studied six patients with chronic tinnitus to see if they could voluntarily reduce the activation of auditory system with the help of real-time fMRI neurofeedback and its impact on tinnitus symptoms. The location of the auditory cortex was identified using a standard fMRI auditory block-design localiser and training was provided to use visual biofeedback to reduce the activation of auditory system. Five out of six patients successfully learned to down-regulate the activation of the auditory system, and two felt the subjective reduction in tinnitus giving a positive sign regarding use of fMRI biofeedback for tinnitus suppression. Dohrmann et al. (301) found that tinnitus patients have enhanced delta- and reduced tau-power in temporal brain regions and hypothesised that by normalising the aberrant rhythms in the on-going synchronous brain activity tinnitus could be reduced. Twenty-one patients with chronic tinnitus were studied. Neurofeedback training was provided for 10 sessions each lasting for 30 minutes over four weeks. There was a significant change in tinnitus intensity before (25 dB) and after (16.9 dB) intervention by simultaneous alternation of both frequency bands. For two patients with the greatest training success, tinnitus disappeared completely over the course of training. Hartmann et al. (293) trained 16 patients to modulate alpha power and delta power using EEG feedback. Post training there was a significant increment in alpha power and reduction in delta power, and significant reduction in the average tinnitus questionnaire scores from 22 points to 17 points. Tinnitus intensity was reduced from 26 dB average to 23 dB post training.

Using a similar technique to Hartman et al., Schenk et al. (300) studied the impact of EEG-alpha (23 participants) and EEG-Beta (13 participants) training in 36 patients with chronic tinnitus, and after 12 sessions found both the groups showed a significant reduction in

tinnitus annoyance. Gosepath et al. (299) trained forty patients to up-regulate the amplitude of alpha activity and down-regulate the amplitude of beta activity during muscle relaxation and acoustic orientation with the help of neurofeedback to study its impact on tinnitus. After 15 training sessions, a significant reduction in tinnitus-related distress was associated with a significant increase in alpha amplitudes and decrease in beta amplitudes.

Neurofeedback has existed for 40 years, but its use in managing tinnitus has been relatively recent (293). Research has shown a difference in the spontaneous brain activity of tinnitus patients (higher delta, theta bands, and lower alpha power associated with increased gamma band activity) compared to healthy subjects (126). The overall mechanism of how neurofeedback leads to tinnitus relief is still not understood well. However, with the advancement of techniques in neurofeedback and better understanding of tinnitus, it would be interesting to see the development of neurofeedback for tinnitus management.

2.5.2. Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation is a non-invasive neuromodulation method that creates a brief high intensity magnetic field (up to 2 Tesla , depending on the stimulus intensity used, which lasts for approximately 100 microseconds) to the cortical area underneath a coiled electromagnet (303, 304). Magnetic coils used for TMS have different shapes such as round coils and figure-eight-shaped coils. Round coils provide relatively powerful magnetic field, but figure-eight coils are more focal at the intersection of two round components (305). More recently, double-cone coils (306) with larger angled windings have also been used for TMS. Double-cone coil stimulation is more effective than other coil configurations (round coils and figure-eight coils) in modulating distal cortical areas (307).

A repeated train of TMS is referred as rTMS. As compared to single pulse TMS, rTMS appears to have a longer lasting impact on the brain (308). rTMS can have either excitatory or inhibitory effect on the underlying cortex which can outlast the stimulation period (309). When a frequency of 1 Hz or lower is used for rTMS, it’s referred as low frequency rTMS and leads to transient suppression in cortical excitability (310). When a frequency between 5 to 20 Hz is used for rTMS it’s referred as high frequency rTMS and it results in a transient increase in cortical excitability (311). These changes in cortical excitability are

mediated by processes similar to long-term potentiation (LTP) and long-term depression (LTD) which are significant in memory and learning physiology (312).

Along with modulating the stimulated area, TMS also affects other areas which are functionally connected to the target area (305, 313). Pathological neuronal activities occurring in the auditory cortex (314, 315) and temporoparietal regions (11, 316, 317) are speculated to be one of the underlying causes of tinnitus. TMS has the ability to focally modulate the cortical activity and it is hypothesised that TMS interferes with the abnormal neural activity associated with tinnitus to provide tinnitus relief (308). TMS is a well-tolerated and safe technique (318). Mild scalp discomfort or transient headache have been reported by about 10% of treated patients (308). There have been some reported incidences of epileptic seizures induced by rTMS (319, 320) hence, safety guidelines proposed for TMS should be used (321). These recommend that TMS should not be undertaken with people with epilepsy, metal implants in their body, heart conditions, and pregnant women.

Some studies use neuronavigational approaches for coil positioning and others depend upon anatomic landmarks (probabilistic approach) using the international 10–20 EEG system. A recent study has shown that results obtained with the probabilistic approach are consistent with the neuronavigational approach (322). Some important limitations of TMS are: its stimulation is not very focal and the magnetic field induced by TMS falls off rapidly with the distance from the coil surface (119) and it is also difficult to plan effective blinding of patients while using TMS due to the auditory and somatosensory stimulation that is concurrent with the magnetic stimulation (308).

There have been many studies using single session and multiple sessions of TMS for tinnitus management. I will discuss a representative selection of these, starting with the single session TMS research. Plewnia et al. (323) applied 10 Hz rTMS in 14 patients with chronic tinnitus at eight scalp and four control positions according to the international 10–20 EEG system to study the impact of rTMS on tinnitus and identify which location leads to best tinnitus suppression. Stimulation was applied at an intensity of 120% of the individual resting motor threshold (MT) with 30 pulses per train, delivered at 10 Hz, for 5 trains. MT is defined as the minimum intensity required to produce motor evoked potentials of 50 micro volts in 5 out of 10 consecutive trials (324). Stimulation of the left temporoparietal cortex resulted in tinnitus suppression in 53% (n = 8) of patients and emerged as the winning location for tinnitus relief. De Ridder et al. (325) conducted a

retrospective analysis of 114 patients (106 unilateral tinnitus and 8 bilateral tinnitus) as selection criteria for surgical implantation of electrodes in auditory cortex. One, 3, 5, 10 and 20 Hz rTMS were performed at 90% MT and 200 pulses delivered in a single continuous train at each frequency. TMS had good effect in 28 patients (25%), partial effect in 32 patients (28%), and no effect in 54 patients (47%). Unfortunately, 63% patients (n = 38) had a positive placebo effect, which was higher than actual TMS response.

Fregni et al. (39) studied the impact of rTMS of left temporoparietal areas in seven patients with chronic tinnitus. Ten Hz rTMS was delivered at 20% MT; each participant received 9 trains of 30 stimuli (3 second durations) and 5 minute intervals between trains. Transient tinnitus suppression was observed in 3 out of 7 (42%) patients. Folmer et al. (326) found partial tinnitus suppression in 6 out of 15 patients lasting from 20 minutes to 4 days. Two patients responded positively to sham stimulation. The bilateral temporal cortex was stimulated by 10 Hz rTMS at 150 pluses/session (326). Plewnia et al. (316) stimulated 9 patients with chronic tinnitus with 1 Hz rTMS at 120% MT, 300, 900 and 1200 pulses/session. The site of stimulation was determined by the maximum tinnitus related positron emission tomography (PET) activation (temporoparietal cortex). Six patients reported tinnitus relief lasting up to 30-minutes and better results were seen with higher pulses. Poreisz et al. (327) conducted a study where 20 patients with chronic tinnitus received 600 pulses of continuous, intermittent, and immediate theta burst stimulation (TBS) over the left inferior temporal cortex at 80% MT. TBS is a low-intensity burst of rTMS where three stimuli delivered at 50 Hz repeated every 200 ms, capable of targeting a specific neuronal population (cortico-spinal fibers) in the motor cortex (328). Transient improvement of tinnitus symptoms were observed only with continuous theta burst stimulation (40 second train of uninterrupted TBS is given for [600 pulses] which suppresses motor evoked potentials [MEP]). Intermittent TBS is a two second train of TBS repeated every 10 seconds for a total of 190 seconds (600 pulses) and it facilitates MEPs. When tonic stimulation was compared with the burst stimulation in effectiveness of tinnitus suppression, it was the burst stimulation which had a transient suppressing effect on both pure tone as well as narrow band tinnitus, unlike tonic stimulation which was effective only for suppressing pure tone tinnitus (329, 330). The effectiveness of burst neuromodulation in suppressing both the pure tone and narrow band tinnitus could possibly be due to its effectiveness in modulating both the extralemniscal system as well as

lemniscal system; however tonic neuromodulation might only modulates the lemniscal system (330).

Multi-session rTMS results in long-term improvement of tinnitus symptoms when compared to single sessions (331). Studies using multiple session (5 to 10) low frequency rTMS with 1200 to 2000 pulses per session have shown significant improvement of tinnitus (332-334). Long-term effects lasting up to one year have been observed by some researchers (331, 335, 336). A case study has shown that maintenance of rTMS can inhibit the return of tinnitus (337). Recently increased numbers of multi-session rTMS studies have been conducted with low-frequency rTMS in 1200–2000 pulses over five to ten sessions. All these studies with control design show a significant improvement of tinnitus symptoms, however, there are variations in the degree and duration of improvement, which could be attributed to the difference in the research design, inclusion–exclusion criteria of participants and stimulation parameters used in the studies (308). Some of the multi-session rTMS studies are discussed below.

Kleinjung et al. (335) conducted a placebo-controlled cross-over study involving 14 patients with chronic tinnitus who underwent five sessions of rTMS (110% MT, 1 Hz, 2000 stimuli/day). A neuronavigational system was used to localise the TMS coil on the identified areas of increased metabolic activity in the auditory cortex (fusing of the individual PET-scan with the structural magnetic resonance imaging (MRI) scan [T1, MPRAGE]) for stimulation. Significant improvement of tinnitus symptoms lasting for six months was found after active rTMS compared to sham rTMS. Langguth et al. (338) conducted an open treatment trial with 28 patients suffering from chronic tinnitus. Ten sessions of rTMS (110 MT, 1 Hz and 2000 stimuli/day) were carried out targeting the left auditory cortex. Nineteen patients showed a significant tinnitus reduction and two experienced tinnitus worsening. Improvement in tinnitus symptoms lasted for three months. Plewnia et al. (339) stimulated six patients with chronic tinnitus by 10 sessions of rTMS (120 MT, 1 Hz and 1800 stimuli/day) in a sham-controlled cross-over design. The area of maximum tinnitus related PET activation was selected as stimulation site. Participants showed significant tinnitus reduction with active rTMS compared to sham rTMS, however these changes were not lasting unlike other studies (335, 338). Forty-five patients with chronic tinnitus underwent 10 sessions of rTMS (110% MT, 1 Hz and 2000 stimuli/day) of left auditory cortex in a study by Kleinjung et al. (340). Significant improvement of tinnitus symptoms were seen after rTMS. Short tinnitus duration and less

hearing impairment correlated positively with the responsiveness to rTMS, tinnitus related neuroplastic changes may be less profound and easier to modulate in such patients hence the better response to rTMS. A similar finding regarding less hearing impairment and responsiveness to rTMS was also reported by Fregni et al. (39). In a study by Rossi et al. (332) 16 patients with chronic tinnitus underwent rTMS (120% MT, 1 Hz and 1200 stimuli/day) of left temporoparietal region in a double-blind, sham-controlled cross-over design. Eight patients experienced significant tinnitus reduction after active rTMS compared to sham and the results were not lasting, similar to the findings of Plewnia et al. (339).

Khedr et al. (341) compared the effect of different frequencies of rTMS (1 Hz, 10 Hz and 25 Hz) in 66 patients with chronic tinnitus. The left temporoparietal cortex was stimulated in 10 sessions over the period of two weeks. Greater tinnitus reduction was observed with active rTMS than sham; however there was no difference between the different frequencies of rTMS. Longer tinnitus duration was negatively linked to the responsiveness to rTMS, similar to the findings of Kleinjung et al. (340). In a one-year follow up study by Khedr et al. (336), lasting tinnitus relief was reported by 10 patients. Marcondes et al. (334) conducted a sham-controlled parallel group design study in which 20 patients with chronic tinnitus underwent rTMS (1 Hz, 110% MT and 1020 pulses/session) of left temporoparietal cortex over five sessions. Active rTMS lead to significant tinnitus relief lasting up to six months as compared to sham rTMS.

Unlike most of the studies discussed above, Lee et al. (342) did not find significant reduction of tinnitus by rTMS in pilot study involving eight veterans with chronic tinnitus; a possible reason for this could be the different parameters used in this study (0.5 Hz, 100% MT and 600 pulses/session) over the left temporoparietal cortex in five sessions. Four patients with chronic tinnitus underwent rTMS (110% MT, 1 Hz and 1800 stimuli/day) in sham-controlled, cross-over design conducted by Smith et al. (333). Three patients gave a modest non-statistically significant response to active rTMS. Langguth et al. (343) investigated if the high-frequency priming could improve the therapeutic efficacy of low-frequency rTMS in clinical applications. Thirty-two patients with chronic tinnitus were randomly divided into two groups and underwent two different protocols. The standard protocol involved low-frequency rTMS (110% MT, 1 Hz and 2000 stimuli/day) and the stimulation protocol involved priming with a 6 Hz rTMS (90% MT, 960 stimuli) followed by low-frequency rTMS (110% MT, 1 Hz and 1040 stimuli/day). The left

auditory cortex was stimulated over 10 sessions. Results revealed no significant difference with the two protocols; both protocols resulted in no significant improvement of tinnitus symptoms.

Kleinjung et al. (344) proposed another new treatment strategy for chronic tinnitus sufferers by providing a combination of high-frequency pre-frontal and low-frequency temporal rTMS. Since tinnitus is not only limited to the neuronal changes in the classical auditory pathways but electrophysiological studies have indicated the involvement of top-down inhibitory processes from the pre-frontal lobe also (345). Hence, targeting pre-frontal lobe along with temporal lobe might enhance tinnitus management. Thirty-two patients with chronic tinnitus were divided into two groups, one group underwent a standard protocol with 2000 stimuli, 1 Hz left temporal rTMS and another group was stimulated with combined protocol (1000 stimuli, 20 Hz left dorsolateral prefrontal combined with 1000 stimuli, 1 Hz, left temporal cortex). Immediately after the stimulation, both groups showed improvement with no significant difference between the two groups, however after three months, the group which received the combined protocol showed greater improvement than the other group. In a follow up study Kleinjung et al. (346) researched whether administration of levodopa (a dopamine precursor) before low-frequency rTMS would increase its efficiency in managing tinnitus. A controlled study of 32 patients with chronic tinnitus was carried out. One group (n = 16) received 100mg of levodopa before each session of rTMS (1 Hz, 110% MT and 2000 pulses/session) and another group (n = 16) received only rTMS with the same parameters. After 10 sessions of stimulation of left auditory cortex in both groups, there was a significant reduction in tinnitus symptoms, however no difference was observed between the groups.

TMS does appear to be a potential tool for tinnitus management, however further research and controlled trials are needed for the replication of results. Recently, researchers have started exploring a combination of low and high frequency rTMS for stimulating the temporal and prefrontal lobe. Similarly combining rTMS with other neuromodulation techniques or other tinnitus management options need to be explored to see if they provide better management options for tinnitus patients than rTMS alone.

2.5.3. Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation is a non-invasive, safe technique and has been used to provide relief from acute and chronic pain (347-349). TENS can be broadly defined as a technique involving delivery of electricity across the intact surface of the skin to activate the underlying nerves (350). TENS can generate biphasic pulsed currents in a repetitive manner using pulse rates of 1–200 Hz, pulse duration 50–250 μs and an intensity of 0–100 mA (44, 350). It can be self-administered and differs from tDCS as the latter is a transcranial technique and the proposed mechanism of effect is different for the two techniques. In the management of tinnitus, TENS is applied to electrically stimulate the skin around the ear (351). Although it has been used since the1960s (352), its use in the area of tinnitus is relatively new. Various researchers have used different forms of electrical stimulation in TENS with the help of electrodes placed around the ears (353). These methods will be described below.

TENS has predominantly been used for the management of somatic tinnitus. In some tinnitus sufferers, modulation of tinnitus is possible by: neck and orofacial movements, tactile stimulation and upper extremities movement (354), change in gaze (355), and temporomandibular joint movement (356). Somatic tinnitus is defined as tinnitus which is temporally associated to a somatic disorder involving the head and neck (357). The underlying mechanisms of tinnitus relief by TENS are complex and incompletely understood (351), however one hypothesised mechanism is shown in Figure 2:8. TENS of areas around the pinna may lead to activation of the DCN though the somatosensory pathway. This involves the stimulation of C2 nerve and activation of the inhibitory role of DCN (358, 359) on the central auditory nervous system and results in tinnitus relief (360). Studies considering TENS in relation to the mechanism of somatosensory tinnitus have been conducted by Vanneste et al. (357), Herraiz et al. (360), Steenerson & Cronin (361) and Moller et al. (362), and are discussed below.

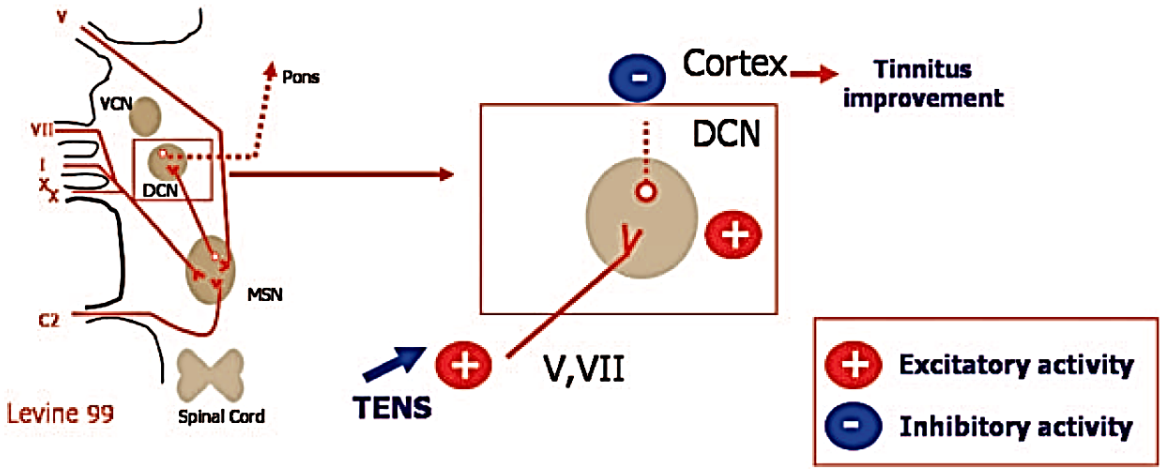


Figure 2:8. Pathways involved in somatic tinnitus modulation. It is hypothesized that TENS enhances the activation of DCN through the somatosensory pathways, which in turn facilitates the inhibitory role of DCN on the central nervous system leading to tinnitus suppression. Reprinted with permission from Elsevier, p. 390 (360).

Vanneste et al. (357) investigated 240 patients with somatic tinnitus. Real and sham TENS treatment was applied for 30 minutes (10 minutes, 6 Hz stimulus, followed by 10 minutes of 40 Hz stimulation and 10 min of sham). The intensity of TENS stimulation was gradually increased until patients felt clear sensation of paresthesia (for most patients it was 30 mA) and the current level was decreased gradually to sub-threshold level. For sham stimulation, the stimulator was turned on for 30 seconds and then turned off. Significant tinnitus relief was observed by 17.9% of patients (n = 43) with mean improvement of 42.9% on a VAS of tinnitus loudness. Six participants felt total tinnitus suppression. Only 2.5% participants (n = 6) in the sham group also experienced transient tinnitus relief. Herraiz et al. (360) found that 46% of patients obtained tinnitus relief (23% did not hear tinnitus and 23% experienced a reduction in tinnitus intensity) with TENS use. They studied 26 patients who had experienced somatic tinnitus suffering for more than six months. Patients had TENs explained and demonstrated and they then used a stimulator at home. The positive electrode was placed on the TMJ or sternocleidomastoid muscle and the negative electrode was placed on the skin of mastoid. Patients were instructed to adjust the stimulation intensity to highest level without discomfort. The average TENS intensity used was 27 mA. The mean VAS ratings dropped significantly post treatment from 6.47 to 6.0. This decrease was statistically significant, but clinically small.

Steenerson and Cronin (361) conducted a large scale study with 500 patients. Twenty different points were arbitrarily selected on the pinna and tragus and were stimulated for

30 seconds at each point, and repeated twice. The average time for stimulation was 25 to 30 minutes for each ear. The current intensity used in the treatment varied from 0.3 mA to 0.6 mA and a total of 6 to 10 visits were undertaken. Tinnitus improvement was defined as a minimum 2 point reduction in the subjective rating of tinnitus on intensity rating scale of 1 to 10, where 1 being barely noticeable and 10 being intolerable. Of the 500 patients, 265 (53%) received significant benefit. Average tinnitus intensity rating dropped from 7 to 4 post treatment on a subjective tinnitus intensity rating scale. A worsening in tinnitus was reported by 2.6% patients (n = 13), 7% (n = 36) reported total tinnitus suppression following treatment and 72% (n = 360) had continuous benefit up to 3-months post treatment. This was not a sham control design. Moller et al. (362) demonstrated that TENS of the median nerve could lead to tinnitus suppression. The electrical stimulation was initially applied at 2 Hz at the level below the threshold and then the strength was gradually increased till a strong tingling sensation but no pain was felt by patients. The stimulation was applied for 10 to 15 seconds and it was repeated three to five times. Six out of 26 patients reported reduction in tinnitus, four felt worsening and the remaining 16 patients did not feel any change in their tinnitus.

Based on the above studies, TENS is considered as a safe, potential technique for tinnitus management; however it has been limited to somatic tinnitus management.

2.5.4. Transcutaneous Vagus Nerve Stimulation

Animal research has shown some preliminary evidence in eliminating physiological and behavioural correlates of tinnitus by pairing tones with brief pulses of vagus nerve stimulation (363). Reversal in the pathological plasticity was observed in rats with noise-induced tinnitus and the benefits persisted for few weeks (363). Lehtimaki et al. (364) used the combination of transcutaneous vagus nerve stimulation (left auricular branch of the vagus nerve was stimulated at 25 Hz, to patients left tragus) along with tailored sound therapy (classical music with 1 octave representing patients tinnitus pitch was deleted) and found improvement in mood as measured on world health organisation 5-point questionnaire (365) along with reduction in subjective loudness and annoyance of tinnitus. This study was limited to participants with only tonal tinnitus, and it’s difficult to estimate the exclusive impact of vagus nerve stimulation as it was used along with sound therapy. This study also gave some evidence of reduction in amplitude of auditory N1m responses

in both hemispheres (similar to the invasive vagus nerve stimulation) which are linked to be beneficial in tinnitus (364). These findings need to be replicated in other studies.

2.6. Transcranial Direct Current Stimulation

The history of non-invasive electrical brain stimulation dates back to 43AD where Scribonious Largus, physician to a Roman emperor documented the use of electric torpedo fish for the treatment of headaches and gout (366). It was not until the 1960s, when formal experiments started that researchers used mild direct current on the animal cortex to study its impact on neuronal activity. tDCS should not be confused with electroconvulsive therapy (ECT) or electroshock. ECT is a psychiatric treatment in which seizures are induced electrically in anesthetised patients for therapeutic effects (367). There is a significant risk of memory loss and rarely death with ECT (368). Unlike ECT, tDCS uses a weak electric current; it is a safe neuromodulation technique with no documented significant adverse side-effects and has been used extensively for various clinical conditions. In early studies, Creutzfeldt et al. (369) studied the influence of transcortical direct current stimulation on neuronal activity in cats and showed that motor and visual cortex neurons up to the depth of 6mm were activated by the inward (surface positive) transcortical current and the degree of activation was directly proportional to the current strength. Bindman et al. (370) explored the impact of polarising current on the cortex of rats and found that neuronal firing was increased by surface-positive current and it was decreased by the surface-negative current. Similar results have been seen in humans also (371).

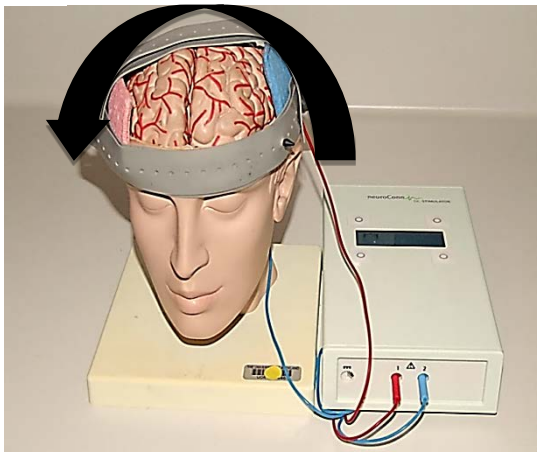


Figure 2:9. tDCS unit (NeuroConn DC stimulator) and the electrode placement on the head model depicts the direction of current flow during tDCS; from anode to cathode (as represented by the black arrow).

A tDCS device is usually comprised of a 9 volt battery as the current source and two electrodes attached to it: anode and cathode. Depending upon the polarity of the stimulation, tDCS can increase or decrease the cortical excitability in the brain region to which it is applied. Anodal stimulation leads to an excitatory effect due to neuronal depolarisation and cathodal stimulation leads to inhibitory effect on the cerebral cortex due to neuronal hyperpolarisation (372-374). The direction of current flow is form anode to cathode (375) (Figure 2:9). The amount of current applied at the scalp does not reach the cortex, some of it is shunted through the scalp tissue, skull, and cerebrospinal fluid, only the remaining current reaches the brain (374, 376) .

Miranda et al. (377) studied current distribution during tDCS via modelling and found that based on the location, size, and number of electrodes used, only a fraction (39% to 59%) of current reaches the brain. The distance between the electrodes is directly proportional to the current density and intensity reaching the brain. By increasing the distance between the electrodes, the amount of current shunted through the scalp can be reduced; hence a higher amount of current reaches the brain and in turn increases the current density in depth.

Nitsche et al. (378) revealed that the modification of the size of electrode can lead to a more focal treatment effect. Decreasing the size of the stimulating electrode leads to spatial restriction of the stimulation area and increasing the size of the reference electrode makes it functionally inert which helps in increasing the selectivity of tDCS.

According to Gandiga et al. (379), tDCS can be used as an effective tool for double-blind, sham-controlled clinical studies. In their study, none of the participants (healthy volunteers and chronic stroke patients) or the investigators were able to distinguish between the tDCS and sham condition (in both real and sham condition the current ramped up for 10 seconds until reaching 1 mA and then during sham stimulation it was stopped after 30 seconds and for real condition it was maintained for 20 minutes). A relatively recent study has raised questions about the effectiveness of blinding with 2 mA current intensity (380). However, this study had certain limitations, 59 out of 98 participants had noticeable redness under the actual stimulation, which is unusual, suggesting the possibility that the methods used were not representative of the majority of studies (as described in the next section). The study was also a cross-over design which increases the possibility of guessing real vs. sham conditions. Contrary to this, Palm et al. (381) investigated the sham tDCS for

randomised, placebo-controlled clinical trials and with current intensity of 2 mA, duration = 20 minutes, and research participants were not able to distinguish between the active and sham tDCS stimulation and they recommended it to be suitable for placebo-controlled trials in keeping subjects blind to the treatment condition.

2.6.1. Safety Considerations During tDCS

The current intensity, duration and location of electrodes are important parameters in determining the impact of tDCS (372, 382). tDCS has been applied safely without any significant adverse effect to more than 3,000 individuals with the following standard protocol: current intensity 1 to 2 mA, electrode size of 25 to 35 cm^2 and stimulation duration between 20 to 30 minutes per session (374, 382, 383). tDCS is a well-tolerated and comfortable technique (16). However it's not uncommon to observe mild tingling and light itching sensations under the electrodes, during the stimulation (379, 384).

Poreisz et al. (384) investigated the adverse effects of tDCS. They studied 102 people which comprised of healthy participants (75.5%), tinnitus patients (9.8%), migraine patients (8.8%), and post-stroke patients (5.9%). During tDCS, 70.6% of the participants reported mild tingling sensation as the most common adverse effect, followed by moderate fatigue and a light itching sensation reported by 35.3% and 30.4% of participants respectively. The incidence of these adverse sensations declined significantly post tDCS suggesting the association of these sensations with the onset of the tDCS. Similar findings were reported by Gandiga et al. (379) where 73.7% of young patients [age = 26.6 ± 1.77, n = 9 for Gandiga et al. (379) and age = 25.9 ± 4.95, n = 77 for Poreisz et al. (384)] felt mild tingling sensation and 15.8% reported transient mild burning sensations. There was a difference in these adverse effects as a function of age. In older patients, 46.4% experienced a tingling sensation and 33.9% experienced mild burning sensation (379); Poreisz et al. (384), 64% experienced tingling and 20% experienced mild burning sensation. Headache, nausea, and insomnia were also reported by some patients post tDCS, however they were very rare and resolved within a few hours to two days (379, 384).

There have been four published studies of tDCS showing evidence of skin lesions (380, 385-387). Frank et al. (387) were the first to publish a report about anodal skin lesions induced by tDCS in three patients who underwent tDCS with the following parameters (current intensity = 1.5 mA, duration = 30 minutes, 8 second ramp in and ramp out, two

days per week for three weeks). These three patients were the last in the group of 15, and the first 12 patients did not report any skin irritation or lesion. Tap water was used to soak the electrodes and the authors speculated that toxic substances in the tap water accumulated over the period of time in the sponge that led to the skin damage. Frank et al. (387) recommended the use of sodium chloride solution instead of tap water and regular replacement of sponges and electrodes to avoid skin lesions.

Palm et al. (386) reported skin lesions at the right supraorbital region under the cathode in five patients after the fourth or fifth tDCS session with the following parameters (current intensity = 2mA, duration = 20 minutes, 15 second ramp in and ramp out, five days per week session for two weeks). The size of the lesion was directly proportional to the skin impedance measured before the testing. The lesion size ranged from 2–3 mm to 2 cm and the skin impedance for the small lesions was in the range from 30 to 35 kΩ and for the 2cm lesion it was 50-55 kΩ. The possible explanation for the lesion could be a combination of various factors such as the use of higher current intensities for longer durations, higher skin impedance due to the use of tap water to soak electrodes, and reduced surface area of contact between the skin and electrode due to drying of electrodes. The possibility of a small skin lesion due to the thermal properties of cathodal direct current could not be ruled out, as this may further compound the other factors mentioned. Palm et al. (386) gave the following recommendations for the prevention of skin lesions: improving the contact between the sponge electrodes and skin by regularity wetting the electrodes, regular disinfecting of the sponges, and applying gel on the skin to avoid sensitisation after a few sessions.

Lagopoulos et al. (385) highlighted a single case with a dark circular burn under the anode following a tDCS session with the following parameters (current intensity = 1mA, duration = 20 minutes, 10 second ramp in and ramp out). Lagopoulos et al. used 0.05 M NaCl gel on the electrodes (impedance is directly proportional to the amount of heat generated at the electrode skin interface (388)). The researchers found that after the completion of the test session, the NaCl gel was missing from certain underside parts of the anode which resulted in the reduction of the surface area of contact between the anode and the skin, which in turn increased the impedance it resulted in excessive heat generation leading to a skin lesion. Lagopoulos et al. also used alcohol swabs to clean the site of electrode placement, and there is a possibility that abrasion of skin might have happened during the cleaning which resulted in the lesion (389). Loo et al. (389) recommend intact electrode-skin

interface and regular replacement of the conductive medium between the electrode and the skin to avoid adverse effects and skin lesions. Dundas et al. (16) suggested the usage of NaCl solution with a concentration between 15 to 140 millimolar (mM). This concentration was perceived as comfortable during the tDCS and it allows good conduction of current.

O'Connell et al. (380) reported noticeable redness under the stimulation electrode for 59 out of 98 participants, however, in this study the electrodes were not damped regularity, which could be a possible cause of noticed redness.

2.6.2. Distribution of Electric Field and Current Density during tDCS

Parazzini et al. (390) conducted a study to explore the distribution of current density and electric field in a human head model during tDCS for tinnitus management. Two popular montages were compared (anodal tDCS of LTA and DLPFC) with 1 mA current stimulation (Figure 2:10).

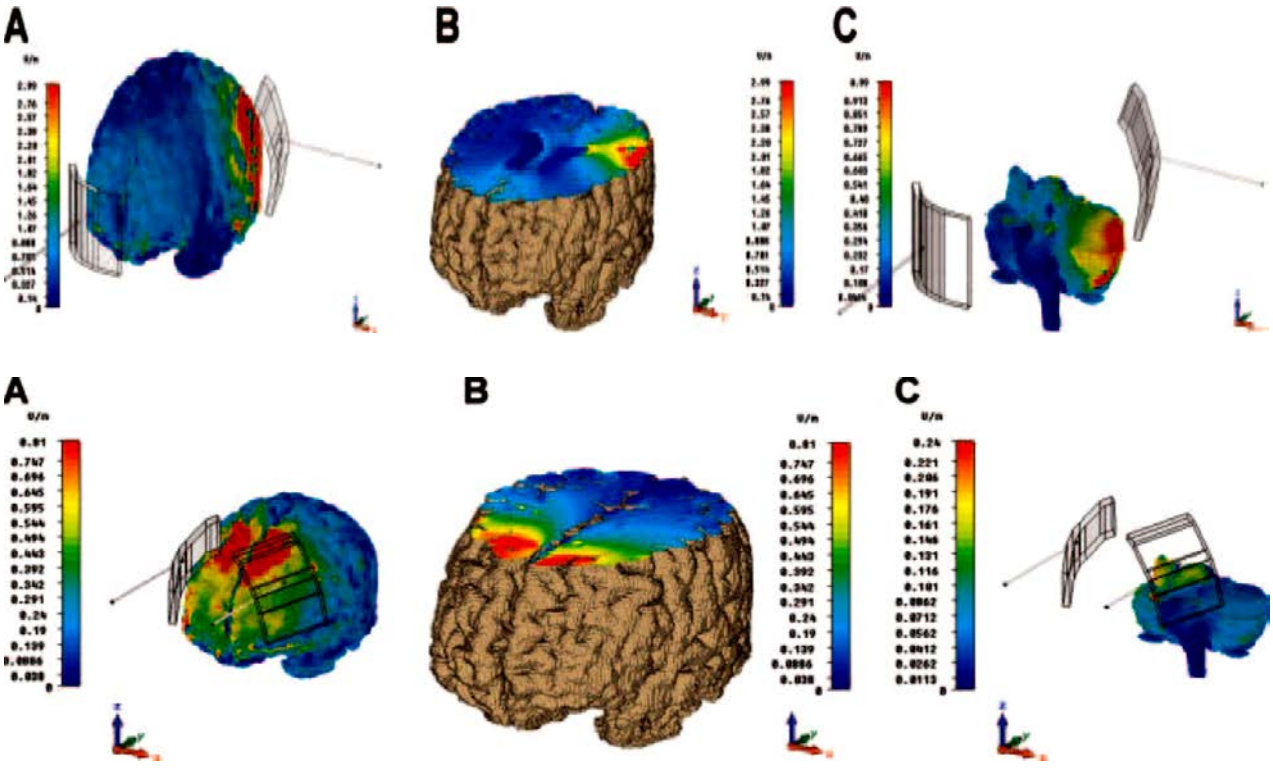


Figure 2:10. Magnitude of electric field distribution during tDCS of LTA (upper panel) and DLPFC (lower panel). A: Over the cortex surface. B: On an axial plane passing through the cortex and white matter C: Over the thalamus, hypothalamus, midbrain, pons, medulla oblongata, and cerebellum surfaces. The maximum

value of the colour scale was set to the 99th percentile of the magnitude field distribution over the different brain structures. Reprinted with permission from John Wiley and Sons, p. 479–480, (390).

Human head and electrode models based on the high resolution MRI of healthy volunteers were used to study the distribution of electric field during tDCS of LTA and DLPFC. It was found that during tDCS of LTA, the distribution of electric field was more widespread and generalised leading to stimulation of various other cortical and subcortical areas along with the target LTA. On the contrary, the distribution of electric field during tDCS of DLPFC was more localised and concentrated on the target area itself. The proposed reason for these patterns of electric field distribution is the location of electrodes in the two montages (the distance between anode and cathode is greater with the LTA montage, leading to more widespread distribution, unlike the DLPFC montage where the two electrodes are close to each other leading to a focal stimulation). This distribution pattern supports the two hypotheses given by Fregni et al. (39), that tDCS of LTA results in stimulation of various cortical and subcortical areas which by competition or inhibitory connections result in the reduction of tinnitus related pathological activity and Vanneste et al. (41): that DLPFC's inhibitory modulation of the auditory cortex results in tinnitus relief.

Another interesting finding by Parazzini et al. (390) was that the magnitude of electric field and current density reaching DLPFC areas during tDCS of LTA and DLPFC was comparable with the same amount of current intensity used. The only difference was in the mean vector which could be explained by electrode positioning for the two montages. As shown in Figure 2:10, during stimulation using the DLPFC montage, the two electrodes were positioned sideways across the brain (anode and cathode on right and left DLPFC respectively), however during tDCS of LTA the electrodes were positioned front (cathode) and back (anode) relative to each other, leading to the possible difference in mean vector during the stimulation.

2.6.3. Physiological Mechanisms Underlying Effects of Anodal tDCS

Understanding of the physiological mechanism underlying tDCS is based on the work undertaken in motor cortex stimulation, but it is likely that similar explanations apply to stimulation of auditory cortex also (371). The after-effects of anodal tDCS can be explained based on changes happening during and after stimulation. During stimulation, anodal tDCS leads to depolarisation of the resting membrane potentials in neurons; after

stimulation there are three possible mechanisms for associated effects: activation of NMDA receptors (*N*-methyl-D-aspartate), reduction in GABAergic tone (γ-amino butyric acid) and role of certain neuromodulators (catecholamines acetylcholine and serotonin) (371). During anodal tDCS, the resting membrane potential is influenced and it causes neuronal depolarisation which in turn increases excitability (373); there is no change in the synaptic strength during stimulation (371). The after-effects of anodal tDCS are modulated by the following factors: increase in intracortical facilitation (ICF) (391) and activation of the NMDA receptor (d-cycloserine) facilitates the duration of after-effects but has no effect on the magnitude of after-effect (392). A reduction in GABA concentration may have an important role in facilitating LTP and has a significant role in increasing the magnitude of effect after tDCS (393). Stagg et al. (393) found a reduction in GABA concentration in the area of stimulation after 10 minutes of anodal tDCS. Two important neuromodulators facilitating after-effects of anodal tDCS appear to be catecholamines acetylcholine (enhances NMDA dependent LTA like plasticity), and serotonin (increase the magnitude and duration of after effects) (371). Understanding of the physiological mechanism underlying the after-effects of tDCS is still limited, and with more research in future, hopefully their will be better understanding of the exact mechanisms of effect.

2.6.4. tDCS and Tinnitus Research

Research in the area of tinnitus and tDCS is limited to few studies. These studies have used different polarities of tDCS, stimulation site, current intensity, duration, sample size, inter-session intervals, and electrode sizes. However, none of the studies aimed to modify different stimulation parameters (intensity and duration) to study their effectiveness. Hence, the study documented in Chapter 6 was undertaken. In this section, I have documented studies published so far about the effectiveness of tDCS in tinnitus management.

The first published evidence of tinnitus suppression by tDCS came in 2006 by Fregni et al. (39). Seven patients with chronic tinnitus underwent anodal, cathodal, and sham tDCS (two sessions each condition, 1mA current intensity, 3 minutes stimulation duration, anode and cathode size = 35cm^2, anode placed on LTA and cathode on contralateral supra orbital area) of LTA with a six minute interval between sessions. Three participants (42%) experienced transient tinnitus suppression following anodal tDCS of LTA. There were no positive responders after cathodal and sham tDCS. Responders had less hearing loss

compared to non-responders, and the hypothesis for the negative effects of hearing loss was that a higher degree of hearing loss was associated with more profound plastic changes and may require higher intensity and duration stimulation for noticeable tinnitus relief. Although this study was limited to a small sample size (seven participants) and used a short stimulation duration (three minutes), it was a landmark study and drew more attention towards use of tDCS for tinnitus management.

Vanneste et al. (41) conducted an open label study (not sham-controlled) which supported the role of the DLPFC in the pathophysiology of tinnitus. Four hundred and seventy-eight patients with chronic tinnitus underwent one session of tDCS (anodal and cathodal stimulation, stimulating electrode at DLPFC and reference electrode at contra DLPFC, 20 minutes stimulation duration, current intensity 1.5 mA, anode and cathode size = $35cm^2$). A significant reduction in tinnitus intensity and distress was observed for 29.9% (n = 134) of patients (anode right and cathode left DLPFC). The amount of improvement was not related to factors such as age, gender, tinnitus type, tinnitus laterality, and duration of tinnitus. Compared to the Fregni et al. (39) study, Vanneste et al. (41) used a much larger sample size (478 participants compared to 7), higher intensity (1.5 mA), and duration (20 minutes) but was an open label study compared to the sham-controlled trial by Fregni et al. This was the first trial documenting the effectiveness of DLPFC (stimulation site) in transient tinnitus suppression.

Vanneste and De Ridder (394) tried to explore the underlying mechanisms behind the effect of bifrontal tDCS. Twelve patients with chronic tinnitus and positive response to bifrontal tDCS (a minimum 25% suppression on tinnitus perception and tinnitus distress) were included in the study. Patients underwent one session of anodal tDCS (stimulating electrode at right DLPFC and reference electrode at left DLPFC, 20 minutes stimulation duration, current intensity 1.5 mA, anode and cathode size = $35cm^2$) and sham tDCS (same electrode placement, ramped up and down for 5 seconds each, to mimic transient sensation on the skin during the beginning of the stimulation). There was a gap of one week between the real and sham tDCS session. EEG was sampled with 19 electrodes and recorded for five minutes before and after stimulation (real and sham tDCS). Significant suppression of tinnitus perception (41.67%) and tinnitus related distress (43.20%) was observed after real tDCS and no significant results were seen for the sham condition. A visual analogue scale for tinnitus perception (how loud is your tinnitus? 0 – no tinnitus and 10 – as loud as imaginable) and tinnitus distress (how stressful is your tinnitus? 0 – no distress and 10 –

suicidal distress) was used before and after tDCS sessions. Responders were defined as (VAS pre – VAS post > 0). Other studies such as Fregni et al (39) and Garin et al (40) have defined the minimum change as a 1 point reduction in the VAS as significant suppression. EEG analysis revealed significant increase of alpha 1 activity in the pregenual anterior cingulate cortex, significant decrease of activity for beta3 and gamma in the right primary auditory cortex, and inferior primary somatosensory cortex post tDCS as compared to pre tDCS. However, no such changes were seen after sham tDCS. This study revealed that bifrontal tDCS not only modulate the area under DLPFC, but also indirectly affects the functionally connected brain areas related to perception of tinnitus and its distress.

A double-blind, placebo-controlled, randomised clinical trial was undertaken by Garin et al. (40) with 20 patients suffering from chronic tinnitus. Patients underwent three sessions of tDCS (anodal, cathodal and sham, one session each condition) targeting LTA with the following parameters: current intensity 1 mA, duration = 20 minutes, interval between each session = two weeks. They used a relatively large cathode ($55cm^2$) electrode on contralateral frontal scalp compared to anode ($35cm^2$) on LTA. Seven out of 20 patients (35%) responded positively to anodal tDCS of LTA. The primary outcome measure used in this study was a VAS. The scale ranged from “full relief” (+4) to “very strong deterioration” (-4) with 0 being “unchanged”. A global analysis revealed a significant reduction ($p = 0.013$) for tinnitus intensity immediately after tDCS. A significant difference between sham and anodal tDCS ($p =0.020$) was observed, however failed to obtain a significant difference between sham and cathodal tDCS ($p = 0.414$) or anodal and cathodal tDCS ($p = 0.132$).

Along with transient tinnitus suppression, some patients reported tinnitus benefits lasting for up to 15 days. Garin et al. (40), suggested a need for the optimisation of tDCS parameters for tinnitus relief. This was the first study documenting after effects, lasing for two weeks, and reflected the possibility of tDCS to be having long lasting impact on tinnitus, unlike the study by Fregni et al. (39) and Vanneste et al. (41) who reported transient benefit lasting for just a few hours.

Bifrontal tDCS may modulate tinnitus distress but not necessarily tinnitus loudness. Faber et al. (43) conducted a double-blind, placebo-controlled, cross-over study with 15 patients with chronic tinnitus by using the following tDCS parameters: 1.5 mA current intensity, 20 minutes duration, six sessions of tDCS, anode and cathode size = $35cm^2$, eight weeks

washout between actual and sham tDCS. For eight patients, the anode was on the left DLPFC and cathode on contralateral DLPFC, and for seven patients the anode was on the right DLPFC and cathode on the contralateral DLPFC. Irrespective of anodal position, tDCS lead to a reduction in tinnitus annoyance but no change was observed with tinnitus loudness as measured with VAS. These results were different from the findings of Vanneste et al. (41) who documented transient reduction in tinnitus loudness using DLPFC as the site of stimulation. Recently, Vanneste et al. (395) compared the tDCS of DLPFC with transcranial alternating current stimulation of DLPFC and found transcranial alternating current stimulation to have no effect on tinnitus loudness or annoyance unlike tDCS of DLPFC which lead to suppression of tinnitus annoyance as well as loudness which was contrary to the findings of Faber et al. (43).

In a study by Frank et al. (42), 32 patients with chronic tinnitus underwent six sessions of bifrontal tDCS (1.5 mA current intensity, 30 minutes = duration, anode on right DLPFC and cathode on left DLPFC). Scores on the THI, TQ, and Beck depression inventory (BDI) remained unchanged; however positive results were seen in numeric rating scores for tinnitus loudness, discomfort, and unpleasantness. This was one of the first studies to report the effect of gender on the treatment response. Females reported more positive results than males on the THI. The reason proposed for this was the difference between males and females in the neural activity of orbitofrontal and anterior cingulate cortex (396) and neural responses (397) during emotional processing.

There has been disparity in the results of studies investigating tDCS and tinnitus which can be attributed to the differences in the research design, sample size, washout period, and stimulation parameters used. Based on the site of stimulation, the studies can be broadly grouped into two categories: using LTA and DLPFC. Interestingly, studies using LTA have shown the effectiveness of single session of anodal tDCS for modulating tinnitus intensity but not tinnitus annoyance (39, 40). Contrary to this Faber et al. (43) documented the effectiveness of bifrontal tDCS in modulating tinnitus annoyance but not loudness, however this was questioned by other studies conducted by Vanneste et al. (41, 395). Another interesting aspect of existing studies has been the duration of after-effects of tDCS. The majority of the studies have reported transient benefits lasting for less than a day, however Garin et al. (40) reported longer-lasting effects (improvement/worsening and change in tinnitus features) of real tDCS for up to two weeks compared to sham. Garin and colleagues study (40) differed from previous studies in its research design (double-blind,

sham-controlled, cross-over design with long washout period of two weeks) and use of relatively large cathode (55cm^2) compared to anode size (35 cm^2).

Despite utilisation of different methods in the above studies; one finding which was common across studies was the potential tDCS can have as a technique for tinnitus management (398). It would appear that LTA stimulation can be effective in modulating tinnitus intensity; however optimisation of tDCS parameters and randomised clinical trials to study the effectiveness of those parameters for tinnitus management is needed before making tDCS a clinical tool. Research is required to explore the possibility of converting the transient impact of tDCS into lasting relief.

2.6.5. Responsiveness towards Neuromodulation

There has been a preliminary evidence based on animal studies that different genotypes may respond differently towards DCS (399). Vanneste et al. (400) investigated the difference between resting-state brain activity and functional connectivity in responders and non-responders to bifrontal tDCS for tinnitus suppression. They found that responders differed from non-responders in the resting-state brain activity in the right auditory cortex and the parahippocampal area (increased gamma band activity in right primary Brodmann area [BA] 41, BA42, and secondary auditory cortex BA21, BA22, and parahippocampal areas BA19, BA20 and BA37) and functional connectivity between DLPFC, sgACC, and parahippocampal area (increased gamma band activity between right DLPFC BA9, BA46 and right parahippocampal area BA37, between right DLPFC and subgenual angular cingulate cortex sgACC;BA25, and between right secondary auditory cortex BA21, BA22 and left parahippocampal area BA37). There is some early research speculating roles for brain-derived neurotrophic factor gene in tinnitus-related plasticity changes (401). A nucleotide polymorphism (BDNF Val66Met) is linked with differences in hippocampal volume and memory (402) and tinnitus has been linked with altered structural volume as well (403). It would be interesting to explore the biomarkers or endophenotypes which may predict the responsiveness towards neuromodulation for tinnitus management in future research (241) and based on the findings the candidacy for neuromodulation might predict better results.

2.6.6. Comparison between tDCS and rTMS

tDCS and rTMS are two popular neuromodulation techniques for tinnitus research. The differences between these two techniques are outlined in Table 2:2.

Table 2:2. Comparison between tDCS and rTMS from Gandiga et al. (379) and Vanneste et al. (382).

Mode	**Electrical**	**Magnetic**
Parameter	**tDCS**	**rTMS**
How it works	It modifies the membrane potential of the neurons (anodal tDCS leads to depolarisation of neurons and cathodal tDCS leads to hyperpolarisation).	It induces action potentials in the cortical neurons.
Quality of sensations	No sound, mild transient tingling sensations and no twitches.	Sound, light tap on the scalp, muscle twitch under the coil if suprathreshold.
Duration of sensations	Only in the initial few seconds of application, then fades.	Throughout application.
Discomfort of sensations	Transient and mild.	Mild if sub threshold, higher if suprathreshold.
Up-regulation/down-regulation of cortical excitability	Well documented.	Well documented.
Focality of stimulation	Less focal.	More focal.
Duration of modulatory effects	From seconds to hours.	From seconds to hours.
Time resolution	Poor: Seconds.	Excellent: Milliseconds.
Capacity to elicit a virtual lesion	Less tested, but promising.	Well documented.
Ease of design sham-controlled double-blind studies	Less difficult.	More difficult.
Safety of intervention	Safe so far but further studies needed.	Well documented.
Simplicity of application	Easily applied.	Easily applied, but requires additional holder to keep coil in constant position.
Artefacts	Lower.	Higher.
Equipment	Compact, portable and low cost.	Bulky and higher in cost.

Vanneste et al. (44) explored if responsiveness to one neuromodulation technique can predict the responsiveness to others. They carried out one session of TMS, TENS, and tDCS on 152 patients with chronic tinnitus. The stimulation parameters for tDCS were: stimulating electrode at right DLPFC and reference electrode at left DLPFC, 20 minutes stimulation duration, current intensity of 1.5 mA, and an anode and cathode size of 35cm^2. The positive response rate observed with tDCS was 27% (11% and 38% with TENS and TMS respectively), and the mean suppression rate for responders was 30.13% (38.45% and 49.13% with TENS and TMS respectively). Results showed that tDCS predicts TMS response and vice-versa. TENS predicts tDCS and TMS better than the opposite. A dual working mechanism underlying tDCS and TMS was proposed (direct brain modulating mechanism and TENS like mechanisms), however more research and functional imaging evidence are required to support this.

Chapter 3. The Relationship Between Tinnitus Pitch and Hearing Sensitivity

3.1. Preface

Publication

This chapter includes content from the article “The relationship between tinnitus pitch and hearing sensitivity” published ahead of print in the Journal of European Archives of Oto-Rhino-Laryngology and Head & Neck, 2013, doi: 10.1007/s00405-013-2375-6. The latest available impact factor of the journal was 1.214 (2010).

What was undertaken?

This was a retrospective study which aimed to define the relationship between tinnitus pitch and hearing sensitivity. A positive correlation between tinnitus pitch and frequency at which hearing threshold was 50 dBHL was found. This could be due to a change from primarily OHC damage to lesions including IHC at these levels of hearing loss as an ignition point for upstream neuroplastic changes which are perceived as tinnitus.

Why it was needed?

Tinnitus pitch is a significant measure for tinnitus assessment and management. Research has shown the effectiveness of hearing aids when tinnitus pitch falls within the stimulated frequency range. There have been few attempts to explore the relationship between tinnitus pitch and edge frequency or frequency with worst hearing with mixed results; however none of these studies have considered looking at the relationship between tinnitus pitch and T50 or have considered extended high frequency assessment. Hence this study was planned to find the strongest predictor for tinnitus pitch which could be helpful in its effective management as well.

How does it contribute to the objectives of the PhD?

This study reflects the significance of extended high frequency testing in tinnitus assessment and also provides the information regarding the strongest predictor for tinnitus pitch. This chapter served to familiarise the author to the topic and methodology used through the thesis.

3.2. Abstract

Objectives - Tinnitus is the phantom perception of sounds. No single theory explaining the cause of tinnitus enjoys universal acceptance, however it is usually associated with hearing loss. The aim of this study was to investigate the relationship between tinnitus pitch and audiometry, Minimum Masking Levels (MML), tinnitus loudness, and Distortion Product Otoacoustic Emissions (DPOAE).

Study Design - This was a retrospective analysis of participant's records from the University of Auckland Hearing and Tinnitus Clinic database. The sample consisted of 192 participants with chronic tinnitus (more than 18 months) who had comprehensive tinnitus assessment from March 2008 to January 2011. There were 116 males (mean = 56.5 years, SD = 12.96) and 76 females (mean = 58.7 years, SD = 13.88).

Results – Seventy-six percent of participants had a tinnitus pitch ≥ 8 kHz. Tinnitus pitch was most often matched to frequencies at which hearing threshold was 40 - 60 (T50) dBHL. There was a weak but statistically significant positive correlation between tinnitus pitch and T50 ($r = 0.150$ at $p < 0.043$). No correlation was found between tinnitus pitch and DPOAEs, MML, audiometric edge and worst threshold.

Conclusions – The strongest audiometric predictor for tinnitus pitch was the frequency at which threshold was approximately 50 dBHL. We postulate that this may be due to a change from primarily OHCs damage to lesions including IHCs at these levels of hearing loss.

3.3. Introduction

Tinnitus is a perceived sound that cannot be attributed to an external source (60). Tinnitus can be constant or intermittent, and is commonly described as ringing, buzzing, cricket-like, hissing, whistling, and humming (2). No single theory explaining the cause of tinnitus is universally accepted. Tinnitus can occur due to any form of malfunction occurring along the auditory pathways (1, 5, 11, 59, 61, 62). Chronic tinnitus possibly occurs from a cascade of changes occurring at various cortical (1) and subcortical centres (14) including: dysfunction of cochlear receptors and reduced spontaneous firing rate of the auditory nerve fibers (13) and to compensate for this reduction, there is an increase in central gain by reduction in cortical inhibition leading to tinnitus perception (15).

Tinnitus is usually associated with hearing loss (11, 12). The range for human hearing is between 20 Hz to 20 kHz (404). For routine clinical measurement conventional audiometry assesses frequencies from 250 Hz to 8 kHz (405). However for disorders which initially affect high frequencies such as noise induced hearing loss, presbycusis, and ototoxicity, it may be useful to measure the auditory thresholds at extended high frequencies as it gives in depth and early information about the underlying pathology (405, 406).

High frequency audiometry is also useful for assessment of tinnitus (407). Roberts, Moffat, & Bosnyak (2006) showed that 25% of tinnitus research participants had normal hearing up to 8 kHz yet all revealed hearing loss with extended high frequency audiometry, and experienced residual inhibition to sounds in this high frequency range (134). Hyun et al. (2009) reported similar findings; in their study 66.7% of tinnitus participants had normal hearing below 8 kHz but when extended high frequency audiometry was conducted all of them had hearing loss at 10, 12, 14 or 16 kHz (408). The pitch of tinnitus most often corresponded to frequencies above the audiogram edge (409).

Tinnitus pitch is usually associated with frequencies showing hearing loss i.e. high pitch tinnitus is usually associated with high frequency hearing loss and low pitch tinnitus with low frequency hearing loss (15, 135). However, there is large inter- and intra-session variability associated with pitch matching (410). Above 3 kHz the tinnitus pitch usually corresponds to the frequency at which the hearing loss becomes clinically significant (136,

409, 411, 412). In addition the shape of the audiogram can also indicate tinnitus, as the steepness of hearing loss is positively correlated with the incidence of tinnitus (409).

Hearing loss can lead to cortical reorganisation in animals due to a reduction in the spontaneous outflow of the cochlea (117). Damage to the IHCs, OHCs, and cochlear neurons give rise to elevated hearing thresholds (271, 413). Spontaneous activity recorded from the reorganised tonotopic maps is generally higher than that of the normal/un-reorganised map (143). It has been speculated that spontaneous activity could be the possible neural correlate of tinnitus and the characteristic frequency dominating the reorganised map may constitute the pitch of tinnitus (414).The maximum amount of cortical reorganisation occurs at the transition from good hearing to impaired hearing (415).

OHCs are more vulnerable to damage than the IHCs (416, 417). However IHC damage may be a significant contributor or prerequisite for changes in spontaneous afferent output of the cochlea (418) and for tonotopic reorganisation (419, 420). The region in the cochlea where there are no functioning IHCs and/or neurons is referred as the dead region (413). Using the Threshold Equalizing Noise (TEN) test Weisz et al. (2006) demonstrated that 72.7% of tinnitus suffers had dead regions (115). Dead regions are often associated with high frequency sloping hearing loss, but it is considered difficult to identify them with just pure tone audiometry (271). Cochleae of cadavers with cochlear hearing loss have been examined to explore the relationship between audiogram and loss of IHCs (421). No IHC damage was noticed with thresholds at and below 40 dBHL in any cochlea examined, damage to IHC started appearing after that (421). Hence 50 dBHL was taken as the cut-off point for suggesting damage of the IHC in the current study.

Robertson (2003) used a linear regression model to assess if the audiometric edge of OHC function could predict tinnitus pitch and found a strong positive correlation between audiometric edges and tinnitus pitch in 71% of participants (422). The audiogram is generally considered a poor indicator of the degree of cochlear damage (115). The “edge” of hearing defining a reduction in spontaneous activity (and hence potential plasticity) is not the edge between a normal audiometric threshold and an elevated audiometric threshold it is actually the frequency at which IHC or neural loss begins. From human cadavers IHC loss beings to occur after 50 dBHL. We hypothesised that, if spontaneous output from the cochlea contributes to the so-called edge effect the frequency at which

audiometric threshold is approximately 50 dBHL would be more strongly correlated with tinnitus pitch than the frequency at which hearing loss beings according to the audiogram (thresholds at 20 dBHL [T20]) (which may not have any change in spontaneous outflow of the cochlea due to OHC loss not IHC loss). Maximum hearing loss (TW) may (depending on extent of hearing loss) be at frequencies removed from the lowest frequency of IHC damage. The psychoacoustical illusion equivalent to the edge effect (i.e. the perception of sound after a band of noise is, the "Zwicker" tone) (423) . The Zwicker tone is most strongly elicited at the low frequency edge of a gap in sound. This has been considered to be the equivalent of the edge of a hearing loss in some models of tinnitus (54).

The aim of this study was to investigate the relationship between tinnitus pitch and audiometry, MMLs, tinnitus loudness, and DPOAEs. It was hypothesised that the frequency of audiometry equating to a threshold of 50 dBHL would be more strongly correlated to tinnitus pitch than the "edge" frequency of hearing loss or frequency of maximum

3.4. Methods

This study was approved by the University of Auckland human participants' ethics committee.

Participants

This was a retrospective analysis of client records from the University of Auckland Hearing and Tinnitus Clinic database. From the database 300 participants were randomly chosen from March 2008 to January 2011 and those with incomplete assessment (e.g., unable to match tinnitus pitch, alternative assessment undertaken) were excluded. The sample consisted of 192 participants with chronic tinnitus (more than 18 months) who completed a comprehensive tinnitus evaluation. There were 116 males (mean = 56.5 years, SD = 12.96) and 76 females (mean = 58.7 years, SD = 13.88). For 103 participants the predominant tinnitus was towards the right ear, for 83 it was towards left ear and 6 people found it equally loud in both ears (both ears were included for them in analysis). Participants were excluded if any of the clinical measurements described below were not undertaken.

Procedure

Client records were examined and then pure tone audiometry (250 Hz to 16000 Hz), DPOAE, MML, and tinnitus loudness were compared to tinnitus pitch. All tinnitus assessments had been undertaken in audiometric test booths (ISO 82531 - 2009) using two-channel audiometers (either GSI - 61 audiometer [Grason Stadler] or AC40 [Interacoustics]). While assessing hearing thresholds at extended high frequencies where the audiometer limit was reached, the maximum levels at those frequencies were recorded as the response. Measurements used standard ear phones (TDH - 50P Telephonics) or insert headphones (E.A.RTONE 3A, 0.25 – 8 kHz) and high frequency headphones (Sennheiser HDA 200, 8 -16 kHz). Audiometry was obtained using the modified Hughson-Westlake procedure (Carhart & Jerger) (424). GSI (Grason Stadler) Tymp star v.2 Immittance audiometers were used and DPOAE were measured using an ILOv 6 (Otodynamics, Ltd.) OAE analyser. Tinnitus pitch, loudness and MML were obtained using the audiometer in the following manner.

Pitch Matching

A two-alternative forced-choice (2AFC) method was used, in which pairs of tones were presented based on the audiogram and perceptual feedback from participants regarding tinnitus pitch and participants were asked to identify which one best matched the pitch of their tinnitus. Each tone was presented at a sensation level of 10 dBSL. Once the settings for a given pair of tones were established, the two tones were presented in alternating manner until the participant indicated which one was closest to the pitch of their tinnitus. Pitch match was then compared to tones 1 octave above and below to rule out octave confusion.

The instructions given to participants were *"we want you to compare two sounds to your tinnitus. Indicate whether the first or second sound is closest to your tinnitus. Both sounds may not exactly match your tinnitus that is okay, we want to know which is most similar"*. This was repeated with the following instruction, *"we are now going to repeat this comparison, again indicate whether sound 1 or 2 is closest to your tinnitus"*. If there was a perceived difference in tinnitus loudness between sides of the head, the test ear was chosen to be the ear contralateral to the predominant or louder tinnitus. If the tinnitus was equally loud on both sides or localised in the head, the test ear was the one with the better hearing

(if there was no difference between the acuity of the two ears the ear was chosen randomly).

Exceptions to the contralateral rule were:

1. Contralateral ear had hearing loss in the severe to profound range and it was impossible to present at tinnitus loudness due to the degree of loss and limits of equipment.

2. Cases of known diplacusis.

3. Cochlear dead regions in contralateral ear (identified using TEN test or psychoacoustic tuning curves). These tests were not routinely undertaken.

Sensation Level Matching

Sensation level matching ("loudness" matching) was conducted contralateral to the tinnitus ear as outlined for pitch matching. Air conduction threshold was obtained for the frequency closest to their tinnitus using 1 or 2 dB steps. At the test frequency, the starting level was below threshold and ascended continuously in 1 or 2 dB steps until the participant indicated that it was just as loud as their tinnitus. This measurement was undertaken 3 times and then the average of the 2nd and 3rd response was taken as the loudness match. The sensation level of tinnitus was determined by subtracting the dial dB at threshold from the dial dB at loudness match.

Instructions given were

For threshold: *"You will hear a series of tones; we want you to indicate every time you hear the sound, even if it is very quiet."*

For sensation level: *"You will now hear a series of tones indicate when the sound is equally loud to your tinnitus."*

MML

The MML was the minimum sound that "covered" the individual's tinnitus (i.e. rendered the tinnitus inaudible). The participant's threshold for noise (dB dial) was measured and recorded. The level of the noise was then raised in 5 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. MML in sensation level was the difference between the masked level and threshold for that noise. The MML was tested using narrow band noise at 500 Hz, 1kHz, 2kHz, 4kHz and where possible at tinnitus pitch.

Instructions given were as follow, *"You will hear a hissing sound. Indicate each time you hear it, even if it is very quiet. The level of sound will gradually increase. Indicate when it covers your tinnitus. If the sound becomes uncomfortable indicate and it will be stopped."*

The test ear was the side with the louder or predominant tinnitus; if there was no difference between the sides, each ear was tested separately. When the masking sound was able to render the tinnitus inaudible, that result was recorded as "complete masking". In some cases, the masking stimulus was only able to make the tinnitus somewhat less audible, and was recorded as "partial masking". In a small percentage of cases, the masking stimulus had no effect on the audibility of tinnitus and was recorded as "not masked".

Analysis

Statistical package for the social sciences (SPSS) software (IMB Version 19) was used for statistical analysis. T-tests and correlation analyses were carried out to explore the relationships between tinnitus pitch and other measures (hearing thresholds, MML and DPOAE). Auditory thresholds were divided into three cut off frequencies, T20, T50 and TW. T20 was the first frequency at which the hearing threshold crossed 20 dBHL and its consecutive frequency hearing threshold was worse than 20 dBHL. TW was the highest frequency at which auditory threshold was at its highest (poorest hearing) and T50 was the frequency between T20 and TW at which the threshold was equal to or close to 50 dBHL (Figure 3:1). It represents the approximate degree of hearing loss required for transition from OHC to IHC loss (421). This classification was undertaken to study the relationships between the tinnitus pitch and the points at which the hearing is normal (T20), most affected (TW) and the theoretical border between OHC and IHC impairment (T50). Participants were excluded if it was not possible to calculate T20, T50 or TW for any reason.

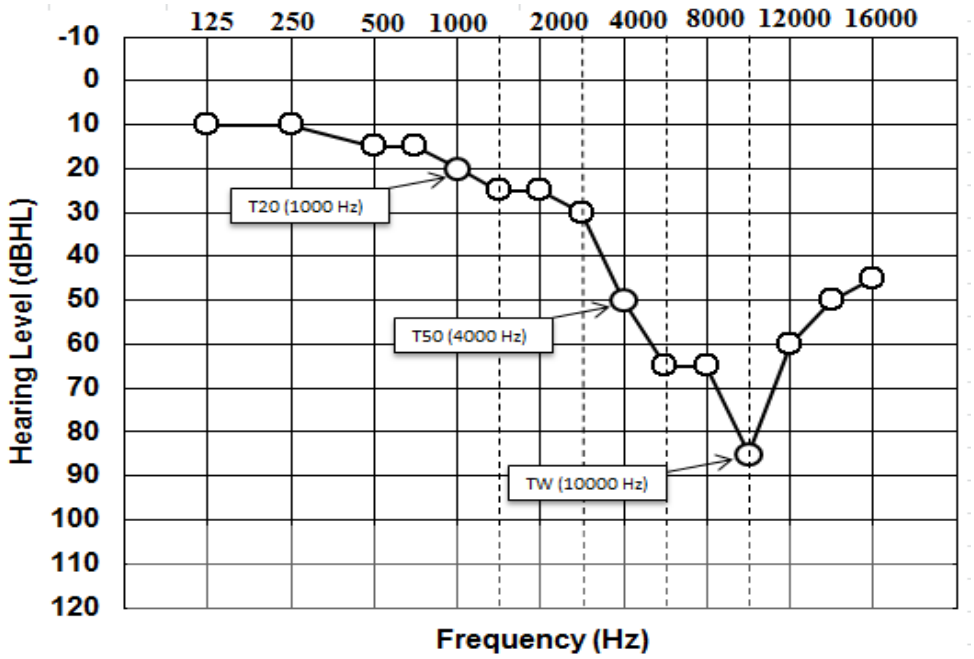


Figure 3:1. An example of how T20, T50 and TW were calculated. T20 was the first frequency where threshold crossed 20 dBHL and its consecutive frequency threshold was worse than 20 dBHL; in this case it is 1000 Hz. TW was the highest frequency at which auditory threshold was at its highest (poorest hearing, 10000 Hz) and T50 was the frequency between T20 and TW where the threshold was equal to or close to 50 dBHL (4000 Hz in this case). Although, the threshold is 50 dBHL at 14000 Hz the lowest frequency between T20 and TW, is at 4000 Hz.

3.5. Results

All participants with tinnitus had some degree of hearing loss and the severity of hearing loss was greater in the extended high frequencies. Overall hearing levels were fairly symmetrical between right ears and left ears. Hearing thresholds were below 25 dBHL until 2 kHz, beyond which a sloping deterioration was observed (except at 13 kHz, where thresholds were better compared to adjacent frequencies). No significant difference was seen between the right and left ears' mean threshold up to 12 kHz. Right ear thresholds were worse than those of the left ear at 14 kHz, 15 kHz and 16 kHz; however this difference was not more than 10 dBHL (Figure 3:2).

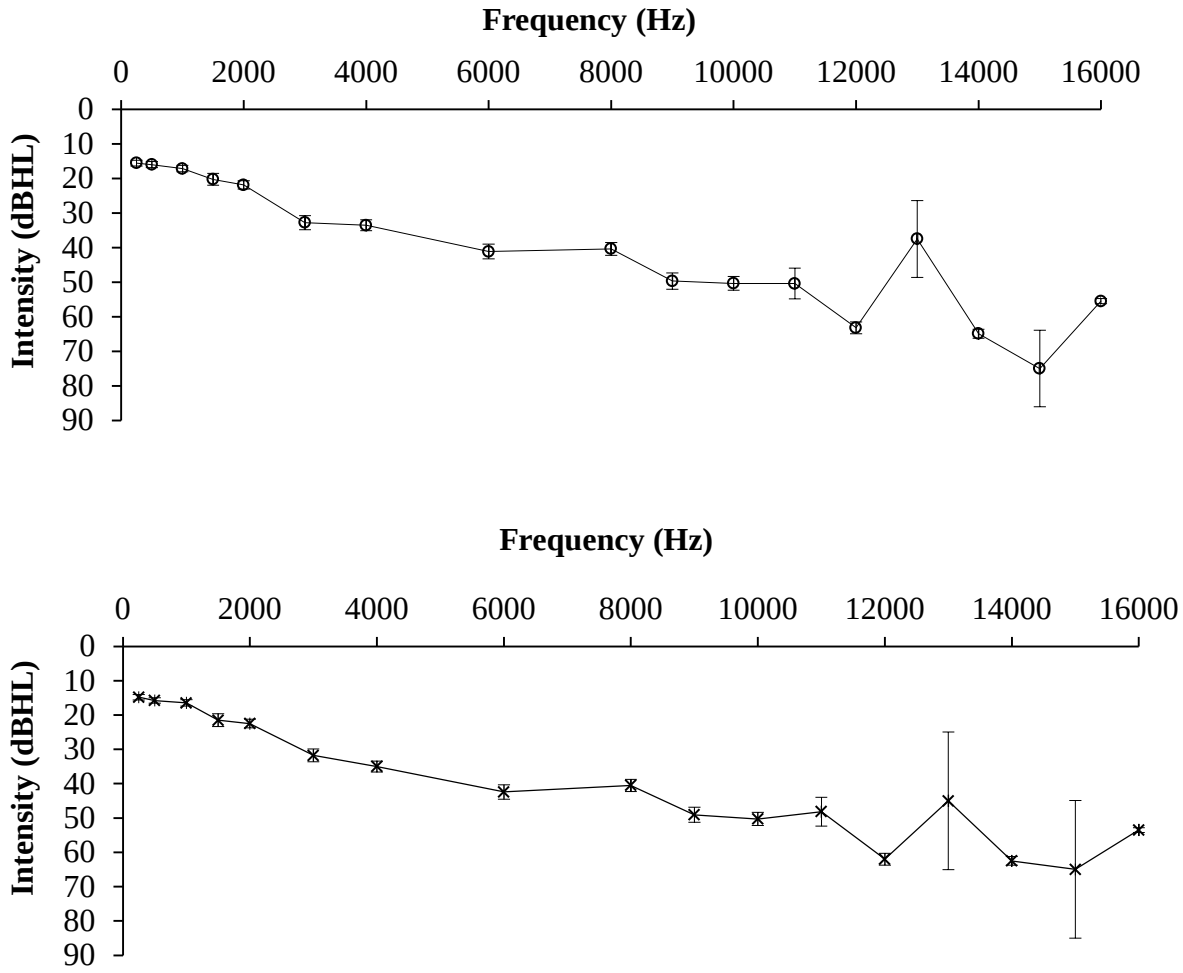


Figure 3:2. The mean hearing thresholds for right (circles) and left ear (crosses) for participants across the frequency range of 250 Hz to 16 kHz (N = 192). The error bars represent ± 1 standard error of the mean.

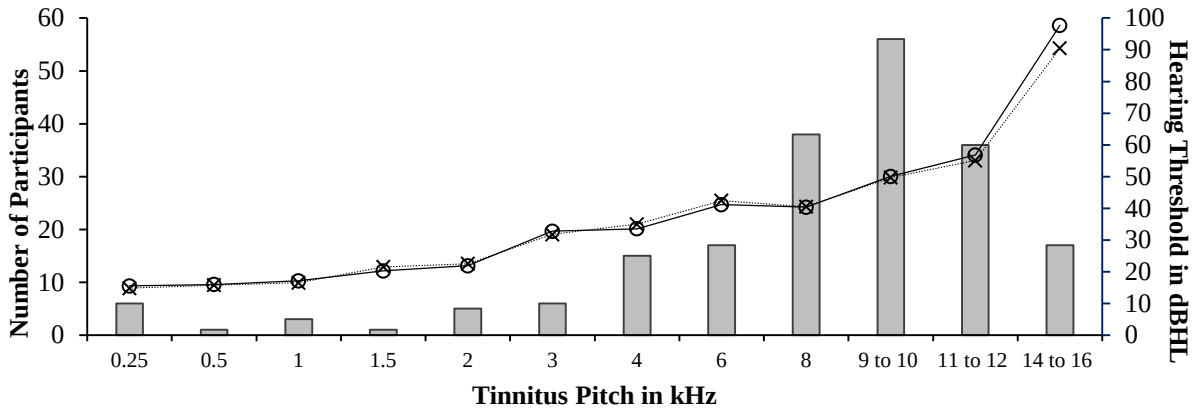


Figure 3:3. The numbers of participants reporting tinnitus pitch matches as a function of frequency (bars) and mean hearing thresholds corresponding to these frequencies (symbols).

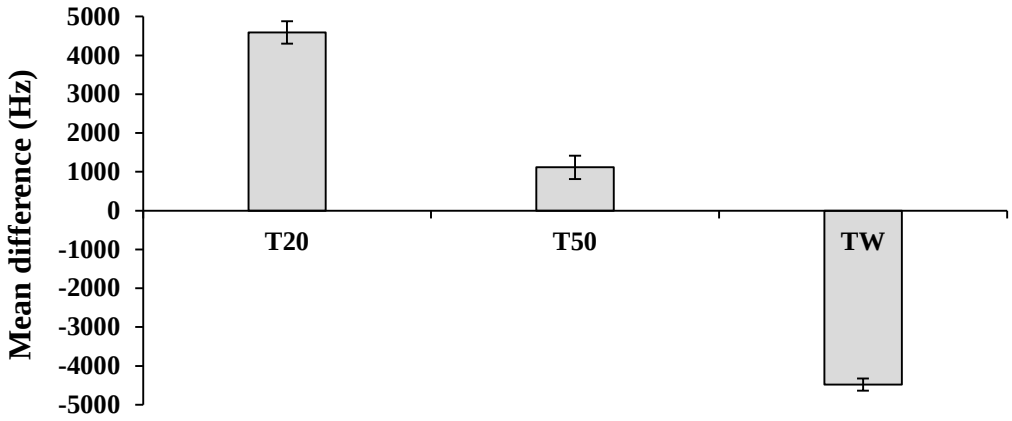


Figure 3:4. Mean differences between TP and T20, T50 and TW. The error bars represent ± 1 standard error of the mean.

The majority of participant's tinnitus was characterised as being high pitched. A bell shape curve skewed towards the high frequencies can be observed across the frequency range for tinnitus pitch with tinnitus most frequent at 9 to 10 kHz, followed by 8 kHz and 11 to 12 kHz (Figure 3:3). Tinnitus pitch fell between 8 kHz to 10 kHz for 49% of participants. Tinnitus pitch was most often matched to frequencies at which hearing threshold was 40 - 60 dBHL (T50). The difference between TP and the estimated pitch at T20, T50 and TW was calculated (Figure 3:4). TW resulted in a higher estimate of tinnitus pitch than measured (mean difference = - 4479.65), T20 resulted in a lower estimate (mean difference = 4595.49), T50 (mean difference = 1115.98) provided the closest estimate to measured tinnitus pitch. Paired t-tests were undertaken to explore the mean difference between T20, T50, TW and TP (TW-TP, TP-T20 and TP-T50), there was a significant difference between TP-T20 and TP-T50 [$t(182) = 18.56$, $p < 0.001$] and TW-TP and TP-T50 [$t(182) = -5.38$, $p < 0.001$], but TW-TP and TP-T20 were not statistically different. Although T50 resulted in the closest estimate of tinnitus pitch there was still considerable variation (SD = 5011.05).

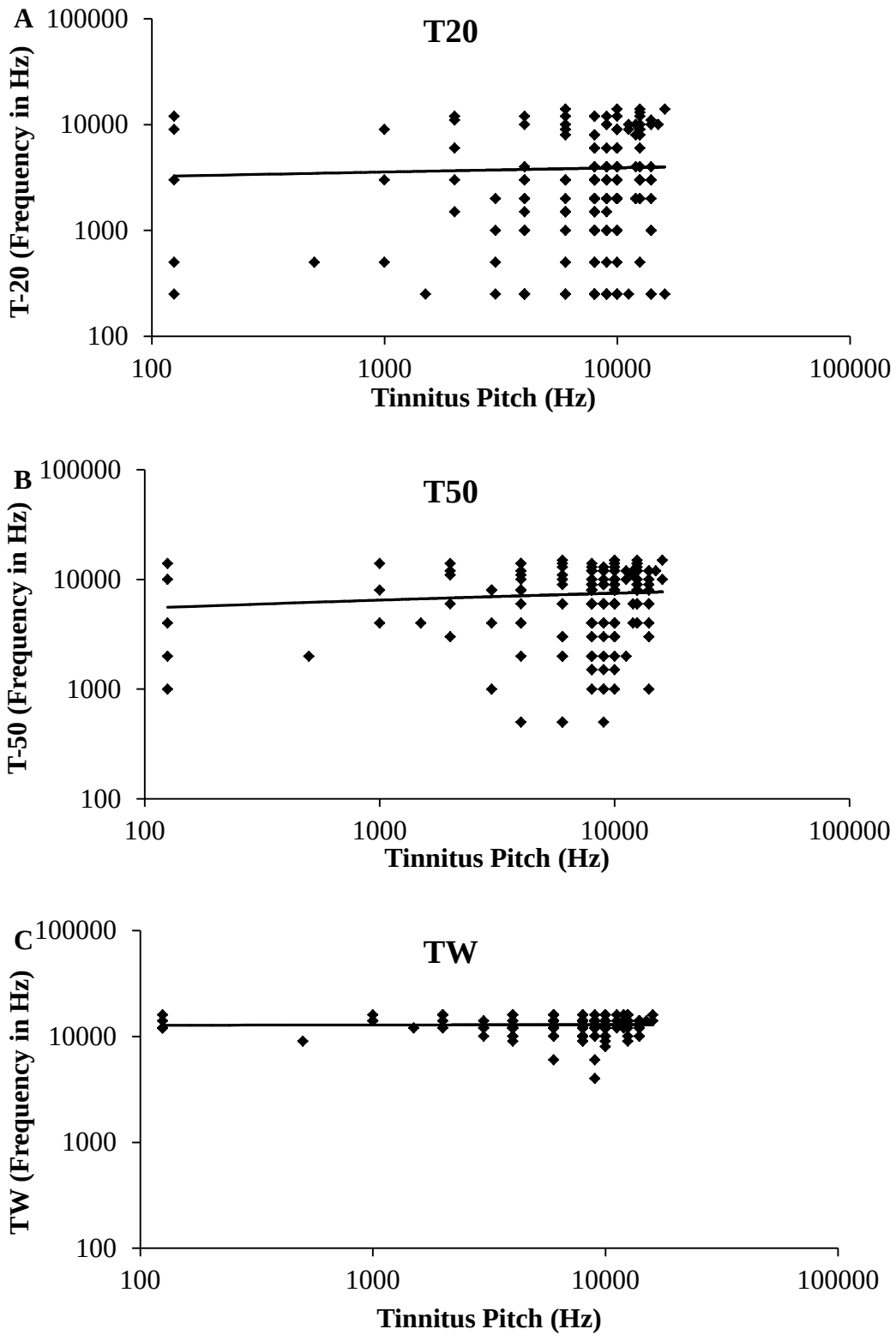


Figure 3:5. Correlation between T20 (r = 0.130), T50 (r = 0.150), TW (r = 0.089) and tinnitus pitch.

There was a small but statistically significant positive correlation between tinnitus pitch and T50 ($r = 0.150$, $p < 0.043$). Tinnitus pitch increased with higher T50 frequency. A

similar positive trend was observed at T20 and TW however their correlations did not meet the adopted level of statistical significance ($p < 0.05$, Figure 3:5).

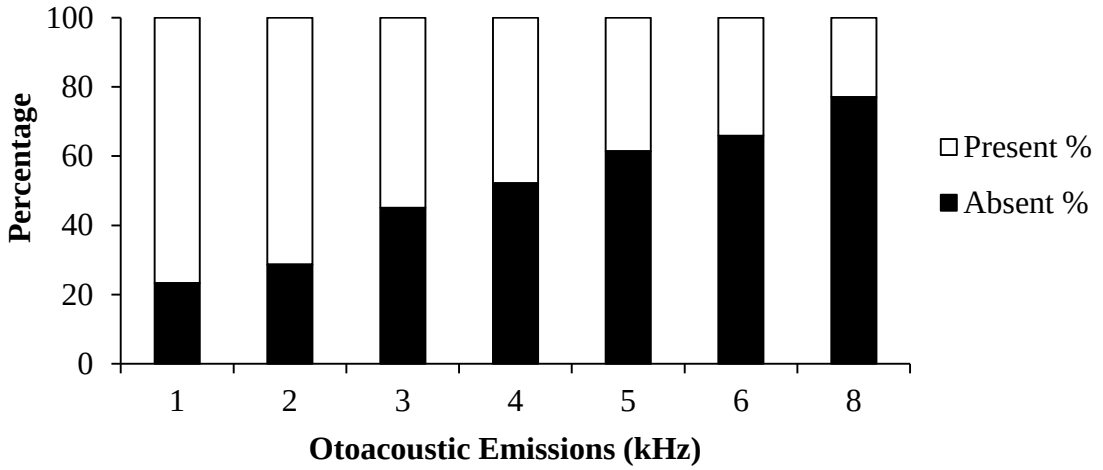


Figure 3:6. DPOAEs present and absent as a function of stimulus frequency.

As the stimulus frequency increased the presence of DPOAE reduced. For the majority of participants the emissions were present at 1 kHz (247 ears) however at 8 kHz only 11 ears had DPOAEs present (Figure 3:6).

3.6. Discussion

This study reports the audiological profile of 192 participants with tinnitus from the University of Auckland Hearing and Tinnitus Clinic database. The average hearing loss was normal in the low frequencies sloping to mild at 8 kHz, but moderate to severe hearing loss above 8 kHz (up to 16 kHz). We believe this indicates the importance of high frequency testing in the tinnitus assessment battery (134, 408).

Seventy three percent of participants matched their tinnitus pitch between 8 kHz to 16 kHz. The strongest audiometric predictor for tinnitus pitch was the frequency at which threshold was 50 dBHL (T50). This threshold intensity is hypothesized to be important in tinnitus generation as it represents the approximate degree of hearing loss required for transition from OHC to IHC loss (421). Cochlear deafferentation is believed to be the peripheral driver for central adaptation mechanisms creating tinnitus (115). The IHCs provide the bulk of afferent input to the central pathways; IHC damage (beginning at approximately hearing thresholds of 50 dBHL) may contribute to tinnitus pitch as a consequence of central plastic changes at the frequency of initial deafferentation.

There have been several efforts to explore the relationship between tinnitus pitch and audiometry. The majority of the work in this area can be divided into two important phenomena – so called “edge effect” and “homeostatic mechanisms”. Some studies have demonstrated a positive correlation between tinnitus pitch and edge frequency (409, 425) while others have failed to do so (426, 427). Proponents of the homeostatic mechanism hypothesis believe that damage to hair cells leads to reduction in sensory input to the auditory nerve. To compensate for this reduced input, homeostatic mechanisms may come in to play which increase central gain and reduce cortical inhibition, leading to amplification of neural noises which in turn results in tinnitus (15, 133). According to this model the tinnitus pitch should fall in the region of hearing loss. There have been a number of studies supporting this notion (134-138).

There have been a few studies looking at the relationship between tinnitus pitch and the frequency with maximum hearing loss, with some showing a positive correlation (138) and others not (135, 426). However none of the studies have looked at the relationship between tinnitus pitch and T50. The majority of studies attempting to explore the relationship between tinnitus pitch and audiogram have failed to incorporate the high frequency hearing thresholds beyond 8 kHz (135, 138, 139, 409, 425, 426). The present data indicate that high frequency testing is important for tinnitus assessment, and can provide new insights regarding its mechanisms.

Elsaeid (2009) reported that 85% of tinnitus ears had abnormal TEOAEs, especially at 2, 4 and 8 kHz (428). Granjeiro et al. (2008) found 70.2% and 68.4% of tinnitus participants showed abnormal TEOAEs and DPOAEs respectively (429). In the present study the percentage of abnormal DPOAEs increased with frequency, 23.29% had abnormal DPOAEs at 1 kHz, which doubled at 4 kHz (52.16%) and tripled at 8 kHz (77.08%) reflecting the dysfunctioning of OHCs especially at high frequencies. The majority of participants in the present study (73%) matched their tinnitus pitch to 8 kHz and above, that is beyond frequencies associated with OHCs. This suggests that the damage to IHCs accompanying OHC dysfunction may be an important underlying factor or precursor for tinnitus generation. Confirmation of this result would require the use of tests to identify dead regions in tinnitus sufferers, such as use of the TEN test (115) and/or psychophysical tuning curves (430).

Assessment of tinnitus pitch is significant not only for systematic documentation of patients' symptoms, but also for monitoring the impact of interventions and planning tinnitus treatment involving acoustic stimulation such as tinnitus maskers (137). Although psychoacoustical characteristics of tinnitus (such as tinnitus pitch, loudness etc.) do not appear to determine tinnitus annoyance or severity of complaint (106) they may be useful as markers for neural plasticity if the tonotopic representation in the central auditory system is modified after treatment.

Feldmann 1971 showed that tinnitus can be masked by narrow band noise and other noises (broad band noise, pure tones) in a frequency specific manner similar to masking of external sounds in only 34% of cases (223). In the present study the MML required to mask tinnitus decreased as the frequency increased, with the lowest level occurring at tinnitus pitch. However no correlation was found between tinnitus pitch and MML.

Undertaking extended high frequency audiometry might also have ramifications for predicting the usefulness of high frequency amplification. Hearing aids may be more effective in treating tinnitus if the tinnitus pitch falls within the stimulated frequency range (49, 431). A technical limitation of current hearing aids is that they don't produce sufficient output beyond 5 - 6 kHz to overcome high frequency hearing loss (432), limiting the beneficial effects for participants with tinnitus pitch falling beyond the range of acoustic stimulation (49). Further technical advancements in this area could be of significant advantage, especially for people suffering from high pitched tinnitus (433).

In the present study the edge frequency was defined differently to previous studies (409, 425). Moore et al. (425) calculated Δn (differences in threshold between successive audiometric frequencies). The lower of the two frequencies for which Δn was largest was assigned as the edge frequency. If there were two equal values of Δn and they were adjacent to one another in frequency, then the lower one was used for calculating edge frequency and if they were not adjacent, two edge frequencies were assumed for those participants. König et al. (409) calculated edge frequency based on the steepest slope in the normal hearing range or if not possible a similar criteria used in our study ([T20] the first frequency at which the hearing threshold crossed 20 dBHL). Our method was simpler than previous studies (409, 425), but we believe would result in similar estimates to König et al. (409). The Moore et al. (425) method was applied to mild-moderate high frequency

sloping hearing loss in a small sample. Their method for edge calculation would likely result in a relatively higher, or multiple frequencies, of edge compared to our study.

All these methods are limited by the sensitivity of the audiogram to hearing damage, true edges of damage (such as loss of neuronal populations) are not going to be detected using the audiogram (434). This may account for the variations in study outcomes and variability with in the studies. Potential differences in calculation of edge frequency and the interpretations of results (if any) are open for further discussion and research.

Limitations

Only sloping audiograms were included in present study hence, this analysis may not be transferable to patients with other audiogram configurations. The audiogram is a crude measure of mechanisms that may contribute to tinnitus pitch; future research should consider alternative methods which may enhance sensitivity.

3.7. Conclusions

The present study highlights the significance of high frequency audiometry and recommends it as a useful test in the tinnitus assessment battery. The most important audiometric predictor for tinnitus pitch was the frequency at which threshold was approximately 50 dBHL. We postulate that this may reflect a transition from primarily OHC damage to lesions including IHCs at these levels of hearing loss. Further research is needed in this area to confirm these findings.

Chapter 4. Role of Hearing Aids in Tinnitus Intervention: Scoping Review

4.1. Preface

Publication

This chapter includes content from the article “Role of hearing aids in tinnitus intervention: A scoping review” published in the Journal of American Academy of Audiology, volume 24, page no 747-762, 2013. The latest available impact factor of the journal was 1.296 (2011).

What was undertaken?

This scoping review was conducted to study the role of hearing aids in tinnitus management. After an intensive search of the existing literature, 29 studies were included and majority of them (27 studies) supported the use of hearing aids for tinnitus management.

Why it was needed?

Scoping reviews are emerging as a popular literature review method in several disciplines. Unlike systematic reviews, scoping reviews do not exclude research based on its quality. As long as the study is relevant, it is included in the review. The majority of systematic review studies undertaken in the area of tinnitus and hearing aids have only been able to consider a limited number of studies due to strict inclusion-exclusion criteria. This scoping review was undertaken in an attempt to get an overall picture of the existing literature on the role of hearing aids in tinnitus management and to guide future directions needed in research.

How does it contribute to the objectives of the PhD?

This study appears to be the first scoping review of the role of hearing aids in tinnitus management. Although the quantity of evidence supports the use of hearing aids for tinnitus management, there is a need for stronger methodology and RCTs, for example more research is needed in the area of hearing aid prescription for tinnitus relief. I addressed this issue by conducting a pilot study considering the prescription of hearing aid output for tinnitus intervention (Chapter 5).

4.2. Abstract

Background: Tinnitus can have devastating impact on the quality of life of the sufferer. Although the mechanisms underpinning tinnitus remain uncertain, hearing loss is often associated with its onset and hearing aids are amongst the most commonly used tools for its management.

Purpose: To conduct a scoping review to explore the role of hearing aids in tinnitus management.

Research Design: Scoping review based on the 6 stage framework of Arksey & O'Malley (2005) (435).

Study Sample: Relevant studies were identified using various databases (Scopus, Google Scholar, Springer link and Pub Med) and hand searching of journals and a reference list of articles. Out of 277 shortlisted articles 29 studies (18 research studies and 11 reviews) were chosen for charting of data based on their abstracts.

Data Collection and Analysis: Tinnitus assessment measures used in studies were recorded along with change in their scores. Measures used in studies included the THI, THQ, tinnitus severity index (TSI), tinnitus reaction questionnaire (TRQ), German version TQ, BDI and VAS of tinnitus intensity. Where possible Cohen's (d) effect size statistic was calculated.

Results: Although the quality of evidence for hearing aids' effect on tinnitus is not strong, the weight of evidence (17 research studies for, 1 against) suggests merit in using hearing aids for tinnitus management.

Conclusions: The majority of studies reviewed support the use of hearing aids for tinnitus management. Clinicians should feel reassured that some evidence shows support for the use of hearing aids for treating tinnitus, but there is still a need for stronger methodology and randomised control trials.

4.3. Introduction

Tinnitus is the perception of sound in the absence of an external sound source. Tinnitus is usually associated with hearing loss (12) and hearing aids have been used for management of tinnitus for at least the last 60 years (46). In a narrative review Beck (2011) (436) speculated that, based upon the evidence provided by others, hearing aids were effective in assisting clients with tinnitus by: helping the brain to distinguish between true sounds vs. pseudo sound (tinnitus), increasing neural activity and assisting the brain in correcting for the potential negative effects of disinhibition, partial masking of tinnitus, and improving the ability to cope with tinnitus by reducing communication stress.

Hearing aids' may act as maskers, reducing awareness of tinnitus, they may facilitate better communication, reducing stress (437, 438) and may directly act against tinnitus generation by reducing drivers of central gain adaptation or inhibition (439). Appropriate compensation for peripheral deficits may reduce central gain (54) or central homeostatic hyperactivity (440) leading to a reduction in tinnitus. Animal based physiological evidence suggests that stimulation of frequency regions of hearing loss (and tinnitus) are important in preventing or reversing tinnitus related cortical reorganisation and homeostatic plasticity (45, 440). Similar reorganisation effects in humans might be achieved with the use of hearing aids (439). Improved frequency discrimination performance at the edge of steeply sloping hearing loss is associated with cortical reorganisation (441), after hearing aid use discrimination performance begins to approach normal, suggestive of cortical map plasticity (442, 443). An analogous effect has been observed in phantom pain (444). Weiss et al. (1999) (444) demonstrated that somatosensory feedback from a prosthetic hand could decrease phantom limb pain presumed to be a process of use-dependent, cortical reorganisation. This concept is similar to Schechter and Henry, (2002) (445) reported that the key purpose of providing amplification or combination devices (amplification and masking) is to create a rich auditory environment. In their introduction of the ATM protocol Henry et al. (288) recommended use of combination instruments (amplification and noise generator in same device) for a combined benefit of amplification and constant broad band noise to achieve this enhanced soundscape. Hearing aids' are widely used in TRT. TRT is a therapy which combines directive counselling with sound therapy (sound generators or hearing aids) to promotion habituation to tinnitus (163).

Although hearing aids have been widely used in tinnitus management (446), clinicians' use of hearing aids is not built on what would normally be considered a strong evidence base, as there have been few randomised control studies for management of tinnitus using device generated sound or hearing aids (164, 447). There is currently no Cochrane or other systematic review addressing tinnitus management with amplification, although there are some studies using hearing aids reported in a Cochrane review of masking (447).

Review of literature is an integral part of research in any discipline (448). It involves systematic identification, location, and analysis of documents containing information related to the research problem (449). The basic purpose of the literature review is to: provide context for research and justify it, identify what is already done in the area and identify research gaps, justify significance of the research undertaken and gain new perspectives on the existing literature (450). The most common approaches for review of literature are narrative (448), empirical (451), meta-analysis (452-456), systematic (448, 457-460) and scoping reviews (435, 461-463).

There has been a recent trend for the use of systematic reviews and meta-analysis to define the level of evidence for treatments. A systematic review is based on rigorous methodology and is replicable if necessary (460) an example of which is the Cochrane data base (447) (http://www.thecochranelibrary.com 2010, Issue-3). Systematic reviews for sound based therapies are able to include very few studies which match search criteria (464). An example of systematic reviews in tinnitus includes those of Ernst & Stevinson (1999) (465) and Park et al. (2000) (466). However, systematic reviews are only as good as the evidence available and the question asked, in the case of tinnitus there are few RTC as we are still in a discovery phase of treatment research (467). The paucity of RCT for hearing aid effects on tinnitus may be due to the high cost of such trials (e.g. cost per hearing aid), that tinnitus benefits are secondary to the prime purpose of aids (hearing assistance) and that there may not be the same regulations or commercial drivers as for pharmaceutical trials. In addition research that has been undertaken may be limited by the assessment and criteria for determining success. Studies have used various assessment tools which have questionable validity e.g. tinnitus loudness (49).

Due to the lack of RCTs, the existing systematic reviews of the topic cannot definitively confirm the strength of current evidence (468). Given the absence of large RCT, but a plethora of small, often open trials, an alternative approach to a systematic review is to use

a scoping review. Scoping reviews have been used in various disciplines in health care (462), including nursing (463, 469-471), education (470, 471), business (472), and public services (473).

According to Mays et al. (2001) (474) scoping reviews:

"aim to map rapidly the key concepts underpinning a research area and the main sources and types of evidence available, and can be undertaken as standalone projects in their own right, especially where an area is complex or has not been reviewed comprehensively before". (Mays et al. 2001; Page 194) (474)

The four reasons for which a scoping review might be undertaken are:

1. To examine the extent, range and nature of research activity.
2. To determine the value of undertaking a full systematic review.
3. To summarize and disseminate research findings.
4. To identify research gaps in the existing literature

(Arksey & O'Malley. 2005; Page 21) (435).

Scoping reviews do not exclude research based on research quality; instead they identify areas which lack research (475). Poth & Ross (2009) (460) highlighted the three major methodological differences between scoping reviews and others (systematic review and meta-analysis): In scoping reviews all studies irrespective of quality are included as long as they are relevant. So the scoping review doesn't have a strict inclusion, exclusion criteria as long as the study is addressing the topic. From the included studies, the entire data is charted; themes and key issues are identified and the methodology of a scoping review includes an optional "consultation process" which involves discussion with key stakeholders to add value and insights. The research question for the current scoping review was: how effective are hearing aids as tinnitus management tools?

4.4. Methods

A scoping review of the literature was undertaken using the methods of Arksey & O'Malley (2005) (435) (Table 4:1)

Table 4:1. Scoping review framework

Stage No	Stage Name	Description
Stage 1	Identifying the research question.	For appropriate search, determine which aspects or 'facets' of research question are most significant.
Stage 2	Identifying relevant studies.	Identify primary studies (published and unpublished) and reviews to answer the central research question via different sources such as electronic databases, reference lists, hand-searching of key journals, existing networks, relevant organisations and conferences.
Stage 3	Study selection.	From the outset adopt greater flexibility with inclusion and exclusion criteria, as familiarity with data progress redefinition of search term may be needed.
Stage 4	Charting the data.	From the primary research reports being reviewed. This stage is equivalent to 'data extraction' in systematic review. It uses narrative review framework with a broader view.
Stage 5	Collating, summarizing and reporting the results.	Present the overview of materials reviewed.
Stage 6	Consultation exercise.	This is optional stage. It involves discussion with key stakeholders to add value and insights.

To identify relevant studies an intensive search was carried out using the following databases (Scopus, Google Scholar, Springer link and Pub Med) with the combination of following key words "hearing aids", "tinnitus", "tinnitus intervention", "tinnitus treatment". Reference lists of the articles were reviewed and hand searching of key journals about the topic was undertaken. After initial consideration of title relevance to the study 277 articles were shortlisted and after reading the abstracts 29 studies were chosen for charting of data. Six studies were identified that were published before 2000, since 2000 there have been 23 studies illustrating an increase in interest in the field.

In studies where multiple devices (e.g. hearing aids and sound generators), were used (48, 49) raw data for hearing aids alone were, where possible, used for calculation of success rates. The tinnitus assessment measures used in studies were recorded along with change in their scores. Measures used in studies included the THI (476), THQ (477), TSI (478), TRQ (479), German version of TQ (480), BDI (481), and various VAS (482) of tinnitus intensity. Where possible Cohen's (d) was calculated.

4.5. Results

Of the 29 studies that met the search criteria 18 were research studies (Table 4:2) and 11 were review studies. The type of study, conditions (research arms within the studies), number of participants and the outcomes are provided in the tables.

Table 4:2. Charting the data of scoping review for research studies.

Authors/ Year	Title	Participants	Measures	Results
Parazzini et al. (50), 2011	Open ear hearing aids in tinnitus therapy: an efficacy comparison with sound generators.	91 participants mean age of 38.8 years randomly divided in to two groups, 49 fitted with open ear hearing aids, 42 with sound generators.	Structured interviews along with Questionnaires VAS & THI.	TRT was equally effective with sound generators as open ear hearing aids in tinnitus intervention.
Searchfield et al. (51), 2010	Hearing aids as an adjunct to counselling: tinnitus patients who choose amplification do better than those that don't.	58 participants mean age of 64.17 years self-selected into two groups of 29 each, one group receiving only counselling and other receiving hearing aids along with counselling.	THQ was used.	Hearing aids were effective in tinnitus management. Participants using hearing aids along with counselling showed twice the reduction in tinnitus handicap than counselling alone.
Schaette et al. (49), 2010	Acoustic stimulation treatments against tinnitus could be most effective when tinnitus pitch is within the stimulated frequency range.	15 participants mean age of 51.7 years. 11 of them had hearing loss fitted hearing aids and 4 with minimal or no hearing losses fitted with sound generators.	VAS & TQ German version.	Reduction in perceived loudness of tinnitus was observed in client's with tinnitus pitch < 6 kHz. Tinnitus pitch was considered an important factor when fitting hearing aids.
Sweetow, & Sabes (215), 2010	Effects of acoustical stimuli delivered through hearing aids on tinnitus.	14 adults with hearing impairment and subjective tinnitus. Participants were fitted with hearing aids with the following options, amplification only, fractal tones only, and combination of amplification, noise and/or fractal tones.	THQ, TRQ and Tinnitus Annoyance Scale .	13 out of 14 participants showed improvement on tinnitus annoyance with one of the amplified conditions. Difficult to ascertain effects of hearing aid versus fractal tones.
Moffat et al. (439), 2009	Effects of hearing aid fitting on the perceptual characteristics of tinnitus.	Control Group (I) (n = 8, mean age 61.9 years, not fitted with hearing aids). Two experimental groups Group (II) (n = 11, mean age 63.7 years, fitted with standard amplification regime) and Group (III) (n = 9, mean age 65.7 years, fitted with high bandwidth	Psychoacoustic measures of tinnitus were recorded in all groups.	No significant difference was observed in group I and III Group II showed significant change in tinnitus spectrum within one month of treatment period.

		amplification regime).		
Trotter & Donaldson (483) , 2008	Hearing aids and tinnitus therapy: a 25-year experience.	Prospective data from 2153 participants from 1980 to 2004. 1440 participants fitted with hearing aids (826-unilateral and 614 with binaural hearing aids).	Pre and post fitting tinnitus perception was measured using VAS.	554 (67%) and 424 (69%) participants with unilateral and binaural hearing aids respectively showed improvement in tinnitus perception following hearing aid fitting. Statistically significant improvement was observed in tinnitus perception with digital hearing aids as compared to analogue hearing aids. Digital hearing aids play significant role in tinnitus intervention when hearing loss is associated with tinnitus.
Kochkin & Tyler (446), 2008	Tinnitus treatment and effectiveness of hearing aids: hearing care professional perceptions.	Online survey of tinnitus management, 230 hearing care professionals responded.		60% of hearing care professionals reported that hearing aid usage results in some relief of tinnitus. 22% of hearing care professionals reported that it results in major relief.
Ferrari et al. (484), 2007	The efficacy of open molds in controlling tinnitus.	50 participants mean age of 64.4 years were divided into two groups: (1) Behind the ear (BTE) and open mould (2) BTE and pressure vent moulds. After 30 days and wash out period the ear molds were changed.	Quantitative assessment using Numeric Scale. Qualitative assessment using a closed question "what happened to your tinnitus?" options were "improved", "unaltered", "and worsened".	82% participants felt improvement of tinnitus with any type of mould. Suppression of tinnitus by hearing aids did not depend upon the type of ear molds used.
Zagólski (485), 2006	Management of tinnitus in patients with presbycusis.	33 participants mean age of 71 years suffering from very annoying tinnitus and hearing loss.	Comprehensive audiological evaluation and subjective self-assessment survey of tinnitus characteristics.	28 out of 33 participants reported significant reduction in tinnitus after being fitted with hearing aids. Participants with binaural hearing loss required binaural fitting and those with unilateral hearing loss, fitting the impaired ear was sufficient.
Del Bo et al. (245), 2006	Using Open-ear Hearing aids in tinnitus therapy.	22 participants (8 fitted with binaural hearing aids, 14 with one hearing aid	THI	Sound stimulation with OHI along with TRT was effective in tinnitus suppression.

		in the ear with tinnitus and hearing loss) underwent TRT using open-fitting hearing instruments.		
Herráiz, et al. (482), 2006	Tinnitus retraining therapy in Meniere's disease.	25 participants with Meniere's disease underwent TRT. 22 wore hearing aids. 3 rejected hearing aids.	THI (Spanish version), VAS subjective assessment with closed question "Do you believe that your tinnitus is "better/the same/worse" than before starting the treatment?"	TRT is effective in Tinnitus intervention in participants with Meniere's disease. All the participants who rejected hearing aids showed no improvement in tinnitus.
Folmer & Carroll (48), 2006	Long-term effectiveness of ear-level devices for tinnitus.	150 divided into 3 groups, Group I (50 participants, mean age 55.8 years, used hearing aids), Group II (50 participants, mean age 49.8 years, used sound generators), Group III (50 participants, mean age 52.8 years, did not use any device).	TSI, BDI, self-rated loudness of tinnitus and subjective assessment with closed question "Did the (device) help your tinnitus?" options "Not at all/ a little/ a moderate amount/ quite a bit/ very much".	Group I and II showed significant tinnitus reduction (23 % and 17 % respectively on TSI). There was a reduction in self-rated loudness of tinnitus for all the three groups however the magnitude of reduction was smaller for group III (8%) than Group I (16%) and Group II (18%). Amplification facilitated better communication and improved hearing.
Sanchez & Stephens (486), 2000	Survey of the perceived benefits and shortcomings of a specialist tinnitus clinic.	Open ended questionnaire mailed to tinnitus patients who attended a specialist tinnitus clinic 148 responded.		34.9% of patients mentioned fitting of hearing aids was the major benefit of attending the clinic.
Melin et al. (487), 1987	Hearing aids and tinnitus - an experimental group study.	39 participants (13 men and 26 women) mean age of 72.7 years. Randomly divided in to control (not fitted with hearing aids, n=19) and experimental group (fitted with hearing aids for hearing purpose, n=20).	Scaling with VAS and interviews.	Hearing aids assisted hearing but they had no impact on patient's tinnitus. -Hearing aids alone are not effective for reduction of tinnitus.
Surr et al. (488), 1985	Effect of amplification on tinnitus among new hearing aid users.	Survey of 200 new hearing aid users.	TQ	62% had tinnitus and half of them reported a total or partial relief from tinnitus, facilitated by the use of hearing aids.

Brooks & Bulmer (489), 1981	Survey of binaural hearing aid users.	Survey 204 adults who had binaural hearing aids for a minimum of 3 months.	Questionnaire used comprised of 20 items answered in yes/no, forced choice and open ended formats.	71 participants reported to have tinnitus, 56 believed hearing aids were effective in tinnitus suppression. Binaural hearing aids were significantly better than monaural in tinnitus suppression.
Stacey St (490), 1980	Apparent total control of severe bilateral tinnitus by masking, using hearing aids.	Case study of a 61 year old client with severe bilateral sensorineural hearing loss and severe bilateral tinnitus.		Complete disappearance of tinnitus with the help of binaural hearing aids.
Saltzman & Ersner (46), 1947	A hearing aid for the relief of tinnitus aurium.	Case studies tinnitus and hearing aids.		Patients with tinnitus benefit from hearing aids.

The 18 research studies included case studies, surveys and clinical trials. Seventeen of the studies suggested positive effects of hearing aids on tinnitus. There were 4 survey based studies and all of them indicated benefits of hearing aids for tinnitus suppression. Three studies (486, 488, 489) included the tinnitus sufferer's perspective and 1 study (446) asked hearing care professionals' opinions. The Brooks and Bulmer (489) (1981) study focused on the use of binaural hearing aids; 71 of 155 participants reported tinnitus and 47 of them reported the effectiveness of binaural hearing aids, only 9 participants mentioned monaural hearing aid to be effective in suppressing tinnitus.

Surveys

The survey by Surr et al. (488), focused on the impact of amplification on tinnitus using tinnitus questionnaires. The questionnaire consisted of 10 items focusing on tinnitus perception, severity, onset etc. One item questioned the effect of hearing aid performance on tinnitus. Of 58 participants in a group suffering from frequent tinnitus, 41.4% reported disappearance of tinnitus, 24.1% said it became softer and 34.5% reported no benefit. In a second group (117 participants, suffering from continuous tinnitus) 14.5 % reported disappearance of tinnitus, 23.9% felt it became softer and 61.6% reported no change. Participants with continuous tinnitus responded that the aids abolished tinnitus less often than those with intermittent tinnitus (488).

Sanchez and Stephens (486), asked participants to make an ordered list of all benefits and shortcomings they experienced as a result of visiting a specialized tinnitus clinic. The fitting of hearing aids was the largest benefit reported, by 34.9% of participants, and 13.8% reported reduction in the perceived tinnitus loudness, less intrusiveness and diminished general awareness of tinnitus. Kochkin & Tyler (446), surveyed 230 hearing health care professionals (audiologists, hearing instrument specialists and Ear Nose Throat physicians) who reported that 1 in 5 (22%) of their patients experienced major tinnitus relief from hearing aid fitting and 6 out of 10 (60%) reported minor to major relief.

Case Studies

The literature search identified two case studies: Stacey (490) and Saltzman & Ersner (46) that reported benefits of hearing aids in tinnitus suppression. Stacey (1980) documented complete suppression of tinnitus by binaural amplification in a 61 year old female with

bilateral tinnitus while Saltzman & Ersner (1947) reported five clients with tinnitus and all of them achieved some relief in tinnitus with the use of hearing aids.

Investigational Studies

Eleven research and clinical trials undertaken in the past decade documented the positive influence of hearing aids in tinnitus treatment. Parazzini et al. (50) compared the use of sound generators and open-ear hearing aids in tinnitus retaining therapy. Despite the absence of significant hearing loss in the speech range, identical results were obtained for both sound generators and hearing aids. Folmer & Carroll (48) found similar results; participants using hearing aids and sound generators achieved significant reductions in TSI scores (23% and 17% respectively) however a control group, not using any device, did not show the significant reduction. Del Bo et al. (245) documented the success of open fit hearing aids in managing tinnitus during TRT and reported a 51.41% change in THI scores after 6.91 months of open ear hearing aid usage. Herraiz et al. (482) studied TRT in participants with Meniere's disease and tinnitus. THI scores dropped from 47% to 20.5% after one year of hearing aid use; however those participants who rejected hearing aids did not show any significant change in their THI score (Herraiz et al. 2006). Similarly, Searchfield et al. (51) found that when counselling was used in conjunction with hearing aids a 36.82% change in THQ score was obtained, but this improvement dropped to 14.17% for a group who chose not to have hearing aids.

Schaette et al. (49) (2010) revealed significant reductions in self-rated tinnitus loudness for participants with tinnitus pitch falling in the range of acoustic stimulation, while no significant changes were obtained for participants with tinnitus pitch beyond the range of acoustic stimulation. Moffat et al. (439) studied the effect of hearing aid fitting on the perceptual characteristics of tinnitus in 3 groups; one with 8 participants not fitted with hearing aids, another group with 11 participants fitted with standard amplification, and a third group of 9 participants were fitted with high-bandwidth amplification. Significant change occurred in the tinnitus spectrum [a psychoacoustic measure of the similarity of a range of sounds to the tinnitus (411)] of persons fitted with standard amplification, but no change was seen in the control group and extended bandwidth group.

Trotter & Donaldson (483) collected data from 2153 patients over 25 years (1980 to 2004) and concluded that digital hearing aids were superior to analogue hearing aids in tinnitus treatment. Ferrari et al. (484) explored the efficacy of different ear mould styles (open and closed) in tinnitus intervention and found that the benefit offered by hearing aids were independent of the type of ear moulds. Zagolski (485) supported the use of binaural hearing aids in participants with binaural hearing loss and tinnitus, but they also concluded that participants with unilateral hearing loss and tinnitus received benefit from monaural hearing aid fitting.

Only one research study (487) indicated that hearing aids were not effective for tinnitus treatment; this study was methodologically different form the other studies; it used interviews and scaling techniques unlike the majority of other studies described in which questionnaires were used. Melin et al. (487) recommended controlled trials to study the impact of counselling and hearing aids fitting separately on tinnitus.

The various experimental studies reviewed were compared (Table 4:3) and the difference between the pre and post score of the measures used (THI, THQ, TSI, TRQ, TQ, BDI, and VAS) were calculated in an attempt to clarify the effectiveness of hearing aids in treating tinnitus.

Table 4:3. A comparison of the results of various studies and the measures used.

Measures	Treatment	Before	After	Change in score	% change	Study
THI	Open ear hearing aids	57.9	27.9 [12 months]	30	51.81	Parazzini et al. (50), 2011
	Hearing aids + Fractal tones	58.71	42 [6 months]	16.71	28.46	Sweetow and Sabes (215), 2010
	TRT (open ear hearing aids)	51.82	25.18 [6.91 months]	26.64	51.41	Del Bo et al. (245), 2006
	TRT (Hearing aid)	47%	20.5% [12 months]	N/A	26.5	Herraiz et al. (482), 2006
THQ	Hearing aid + Counselling	59.2	37.4 [12 months]	21.8	36.82	Searchfield et al. (51), 2010
	Counselling alone	50.8	43.6 [12 months]	7.2	14.17	
TRQ	Hearing aids + Fractal tones	52.57	40.86 [6 months]	11.71	22.28	Sweetow and Sabes (215), 2010
TSI	Hearing aids	38.2	29.6 [6 months]	8.6	22.51	Folmer and Carroll (48), 2006
TQ	Hearing aids	29.73	24 [6 months]	5.73	19.27	Schaette et al. (49), 2010
BDI	Hearing aids	5.2	5.2 [6 months]	0	0	Folmer and Carroll (48), 2006
VAS	Hearing aids	71.18	60.09 [6 months]	11.09	15.58	Schaette et al. (49), 2010
	TRT (Hearing aid)	6.6	6.4 [12 months]	0.2	3.03	Herraiz et al. (482), 2006
	Hearing aids	7.5	6.3 [6 months]	1.2	16	Folmer and Carroll (48), 2006

The THI was the most popular assessment tool, used in 4 of the 7 research studies, followed by VAS for rating tinnitus loudness (3 studies), other tools (THQ, TRQ, TSI, TQ and BDI) were used in the remaining studies. All of the questionnaire and VAS tools used for pre and post assessment showed significant reduction following the fitting of hearing

aids except the BDI used by Folmer and Carroll (48). However, since the pre assessment BDI score of 5.2 is considered normal, reflecting no depression, the observation that the score remained unchanged post 6 months of hearing aid use was not unexpected (48).

Parazzini et al. (50) and Del Bo et al. (245) reported large improvements in the THI of 51.81% and 51.41% respectively. Sweetow and Sabes (215) and Herraiz et al. (482) reported 28.46% and 26.5% improvement respectively. Searchfield et al. (51), documented an improvement of 36.82% in THQ scores following a combination of hearing aids and counselling, which dropped to 12.17% when only counselling was used. Sweetow and Sabes (215), used the TRQ and found 22.28% improvement in the scores of TRQ when a combination of hearing aids and fractal tones were used. Folmer and Carroll (48) used hearing aids and found a 22.51 % improvement in the TSI score and Schaette et al. (49) reported a 19.27% improvement in TQ scores with the use of hearing aids for 6 months.

It was possible to calculate effect size for four studies (Table 4:4). To interpret the effect size, guidelines developed by Cohen (491) were used. Medium to large effect size (effect size 0.32 to 0.73) were reported for the use of hearing aids. However the effect size values need to be interpreted with caution and in context as the studies vary significantly in quality and sample size.

Table 4:4. Cohen's (d) for 4 studies

Study	**Cohen's (d)**		**Interpretation**
Schaette et al. (49), 2010	2.14		Large effect
Searchfield et al. (51), 2010	Counselling alone	0.33	Small effect
	Hearing aid + Counselling	1.13	Large effect
Sweetow & Sabes (215), 2010	0.67		Medium effect
Folmer & Carroll (48), 2006	1.03		Large effect

Review Studies

Ten review studies which were all narrative reviews concluded that hearing aids had a positive role to play in tinnitus intervention (Table 4:5).

Table 4:5. Charting the data of scoping review for review studies

Authors/Year	Title	Methods	Results
Beck (436), 2011	Hearing aid amplification and tinnitus: 2011 overview.	Literature review.	Hearing aids are the primary treatment option for tinnitus. Have positive impact on tinnitus and are reversible (can be removed if do not lead to positive impact on tinnitus).
Hobson et al. (447), 2010	Sound therapy (masking) in the management of tinnitus in adults.	Literature review.	Sound therapy on its own is of unproven benefit in the treatment of tinnitus. Use of hearing aid improves the hearing handicap and quality of life however it's very difficult to determine how much it affects the tinnitus handicap.
Henry et al. (177), 2008	Using therapeutic sound with progressive audiologic tinnitus management.	Literature review.	Hearing aids can benefit participants with tinnitus by masking tinnitus. Reducing stress associated with hearing loss. Stimulate regions of auditory system which are deprived of auditory stimulation.
Del Bo & Ambrosetti (438), 2007	Hearing aids for the treatment of tinnitus.	Literature review.	Hearing aids improve communication and reduce tinnitus awareness. Binaural open ear hearing aids with widest amplification band and disabled noise reduction control can be beneficial for tinnitus intervention along with counselling.
Jastreboff (212), 2007	Sound therapies for tinnitus management.	Literature review.	Sound therapy can be effective in tinnitus intervention and hearing aids are important tool for offering sound therapy.
Searchfield (53), 2006	Hearing aids and tinnitus.	Book chapter focused on the practical aspects of digital hearing aid fitting for tinnitus suppression.	Hearing aids are effective in tinnitus intervention when used along with counselling. The most effective settings of hearing aid for tinnitus suppression may not be same as for enhancing communication.
Henry et al. (288), 2005	Clinical guide for audiologic tinnitus management II: treatment.	Describes audiologic tinnitus management.	Hearing aid fitting and use of noise generator forms an integral part of this treatment approach.
Henry et al. (492), 2005	General review of tinnitus: prevalence, mechanisms, effects, and management.	Literature review.	Hearing aids lead to tinnitus relief. They can be fitted with the primary purpose of providing tinnitus relief or to offer tinnitus relief as a secondary benefit.

Gold (493), 2003	Clinical management of tinnitus and hyperacusis.	Review of efficacy of sound therapy in tinnitus intervention.	For patients with tinnitus and hearing loss but no hypercusis, hearing aids can lead to habituation of tinnitus.
Schechter & Henry (445), 2002	Assessment and treatment of tinnitus patients using a "masking approach".	Informal review regarding the assessment and treatment for tinnitus.	Hearing aids usually offer tinnitus relief. If these fail to offer benefit then other instruments with combination of amplification and masking should be tried.
Newman (437), 1999	Audiologic management of tinnitus: issues and options.	Review of tinnitus.	Hearing aids are used for tinnitus intervention and help in the following ways: masking effect on tinnitus, improvement of communication, and reduction of stress.

Similarly Henry et al. (177) described the beneficial impact of amplification on reducing the stress associated with tinnitus by enhancing the ability to hear soothing sounds. They suggested that hearing aids lead to attention diversion (active and passive) from tinnitus by providing more accessibility to interesting sounds (active attention diversion) and by overall enhancement of background sounds (passive attention diversion). Henry et al. (492) and Newman (437) proposed a similar explanation, that reduction in stress associated with hearing loss and amplification of ambient sounds are the plausible ways hearing aids are effective in tinnitus management.

Only one review (447) concluded that hearing aids were not effective for tinnitus management. They reviewed 6 randomised controlled studies, most of which used a combined treatment approach (counselling/masking/noise generators/sound enrichment/hearing aids) complicating the process of effectively evaluating the role of each of those approaches separately. They reported that hearing aids' had a positive impact on hearing handicap and quality of life, however, it was difficult to support the use of hearing aids' for reducing tinnitus handicap; the absence of evidence makes refuting the use of hearing aids' equally difficult.

4.6. Discussion

Hearing aids' have been a popular choice for tinnitus intervention (446). This scoping review demonstrates evidence to support the practice of fitting hearing aids' for tinnitus management. The studies differed with respect to reported benefit of hearing aids, the methods used to study effect, counselling accompanying the hearing aids, prescription of gain and rationales used, as well as the technology employed. In this discussion we will consider the differences between studies in an attempt to explain why some studies showed strong effects, while others weaker or no benefits of hearing aids. We will then propose potential mechanisms of effect and avenues for future research.

Scoping reviews such as this report, unlike systematic reviews, do not reject studies on the basis of research methodology; however it is worth discussing areas of weakness of the research studies, and areas for improvement. Appropriate control groups for comparison of interventions used were missing in 9 studies (e.g. Herraiz et al. (482), Del Bo et al. (245), Zagolski (485), Ferrari et al. (484), Kochkin & Tyler (446), Trotter & Donaldson (483), Sweetow & Sabes (215), Schaette et al. (49), and Parazzini et al. (50)) and small

sample sizes may limit generalisation of the findings. There was a wide range of sample size across the studies: there were two case studies (Saltzman & Ersner (46), and Stacey St (490),); eight studies had 50 or fewer participants (Melin et al. (487), Del Bo et al. (245), Herraiz et al. (482), Zagolski (485), Ferrari et al. (484), Moffat et al. (439), Sweetow & Sabes (215), and Schaette et al. (49)); three studies had between 50 and 150 participants (Folmer & Carroll (48), Searchfield et al. (51), and Parazzini et al. (50)) four surveys had 150 - 250 participants (Brooks & Bulmer (489), Surr et al. (488), Sanchez & Stephens (486), and Kochkin & Tyler (446)); and one study retrospective study by Trotter & Donaldson (483) had 2153 participants. An appropriate sample size is dependent on the power of the study assessment tools; it does not appear that statistical power calculations were undertaken for any of the studies reviewed.

Randomised and blinded trials are considered the gold standard for evaluation of clinical treatments. There is a need for more RCTs; there was only one RCT in this scoping review, that of Melin et al. (487) (1987) and one randomised blinded cross over trial (Ferrari et al. (484), 2007). There were two retrospective studies (Trotter & Donaldson (483), and Searchfield et al. (51)) and eight studies were of prospective research design (Del Bo et al. (245), Folmer & Carroll (48), Herraiz et al. (482), Zagolski (485), Moffat et al. (439), Schaette et al. (49), Sweetow & Sabes (215), and Parazzini et al. (50)). Across most studies, tools used to assess impact on tinnitus were limited to questionnaires (Brooks & Bulmer (489), Surr et al. (488), Sanchez & Stephens (486), Folmer & Carroll (48), Herraiz et al. (482), Ferrari et al. (484), Kochkin & Tyler (446), Trotter & Donaldson (483), Searchfield et al. (51), Schaette et al. (49), and Sweetow & Sabes (215)) or interview and questionnaires (Melin et al. (487), Del Bo et al. (245), and Parazzini et al. (50)). Using psychoacoustic tinnitus assessments pre and post hearing aid use, such as measurement of tinnitus pitch and loudness, would possibly be informative as to any change in tinnitus characteristics which might be modifiable by sound stimulation as opposed to changes in quality of life. Only two studies (Zagolski (485), and Moffat et al. (439)) recorded psychoacoustic measures of tinnitus pitch. The pitch of tinnitus is potentially an important factor to consider when fitting hearing aids. If the pitch of tinnitus falls in the range of amplification it leads to better results (49). However it has not been considered, or reported, in the majority of studies during hearing aid fitting. It is difficult to distinguish the extent of impact hearing aids are having on tinnitus, per se, as opposed to psychosocial benefits from improving hearing; hence further studies should consider the

use of hearing inventories to assess improvement in hearing (Andersson et al. (6)) along with tinnitus questionnaires to determine the degree of covariance. Studies should use questionnaires that have both hearing and tinnitus subscales. Searchfield et al. (51) were able to show improvement in the social and emotional subscales of the tinnitus handicap questionnaire, greater than tinnitus and hearing subscales, suggesting the benefit seen with hearing aids were not purely related to improved hearing. Electrophysiological or imaging studies may also contribute to understanding hearing aid effects by examining potential to modify cortical networks (Billings et al. (494)).

Another set of variables that could contribute to the difference in hearing aid effectiveness is the hearing aid technology used. Studies undertaken before 2000 (Melin et al. (487), Surr et al. (488), Brooks & Bulmer (489), and Saltzman & Ersner (46)), with the exception of Stacey (490), did not mention the details of the hearing aids, but it appears that they were analogue hearing aids with linear amplification, potentially not providing sufficient amplification of low level sounds to interfere with tinnitus in quiet environments and more likely to have distortion in loud environments. Recent studies have often used open fit digital hearing aids with wide dynamic range compression (Del Bo et al. (245), Searchfield et al. (51), and Parazzini et al. (50)) potentially providing more normal loudness perception, greater amplification of soft compared to loud sounds; less distortion and reduced occlusion as well as other features potentially useful in tinnitus management (Searchfield (53)). The study undertaken by Trotter & Donaldson (483) looked at retrospective data obtained from the previous 25 years and documented the use of digital as well as analogue hearing aids. They authors report significant improvement in tinnitus perception with digital hearing aids' compared to analogue hearing aids. It was concluded that the improvement in technology may account for superior results obtained with digital hearing aids (Trotter & Donaldson (483)).

It has been hypothesised (438) that increasing bandwidth (the frequency range of sounds amplified) may improve effectiveness, however Moffat et al's (439) group III (9 participants, fitted with high-bandwidth amplification) did not show any significant effect of amplification on tinnitus. However this extended bandwidth group received comparatively less low frequency amplification, thought to be very important for interference with tinnitus due to the spectrum of background noise. Additional high frequency amplification might have proven beneficial if low frequencies were preserved.

The approach that was taken in fitting the aids varied between studies. For example in the Melin et al. (487) study hearing aids' were not fitted in the ear with worst tinnitus, rather the ear where enhanced hearing ability was needed. Five studies used binaural fittings (Stacey (490), Brooks & Bulmer (489), Ferrari et al. (484), Moffat et al. (439), and Parazzini et al. (50)). A case study by Saltzman et al. (46) described five participants with tinnitus and all of them were reported to experience tinnitus relief with a unilateral hearing aid. One study did not mention if the participants used monaural or binaural hearing aids (486). Most of the studies used a combination of binaural and monaural fittings (Surr et al. (488), Melin et al. (487), Folmer & Carroll (48), Herraiz et al. (482), Del Bo et al. (245), Zagolski (485), Trotter & Donaldson (483), Sweetow & Sabes (215), and Schaette et al. (49)); hearing aids were fitted binaurally when hearing loss/tinnitus was present in both ears and monaural aids were fitted in participants with unilateral hearing loss/tinnitus. Brooks and Bulmer (489) showed that binaural amplification is more effective than monaural hearing aids for tinnitus suppression. Binaural amplification not only allows better spatial localisation of sounds but may also stimulate the entire auditory nervous system which in turn helps in reducing the annoyance of tinnitus and facilitating better communication.

The most effective hearing aid setting for tinnitus suppression may not be the same as the one used for enhancing communication. Hearing aid prescription procedures are commonly used to determine hearing aid amplification for a given hearing loss. Two common methods are based on loudness normalisation; DSL (I/O) and loudness equalization; National Acoustic Lab Non Linear (NAL-NL1). These prescribe different hearing aid amplification characteristic. In general the DSL (I/O) method provides more low and high frequency amplification at lower intensities (192). Schaette et al. (49) used the NAL-NL-1 prescriptive procedure and Searchfield et al. (51) followed the recommendations of Searchfield (53) based around amplification of low level sound with the DSL (I/O) prescriptive procedure as a reference. For the majority of studies the information about prescriptive procedure used for fitting hearing aids was missing [Melin et al. (487), Sanchez & Stephens (486), Folmer & Carroll (48), Herraiz et al. (482), Del Bo et al. (245), Zagolski (485), Ferrari et al. (484), Trotter & Donaldson (483), Moffat et al. (439), Sweetow & Sabes (215), and Parazzini et al. (50)). Specially designed prescriptive procedures for tinnitus may be useful (53). If hearing aids' are fitted for assisting hearing rather than tinnitus, which appears the case in majority of the studies, they may not be set

optimally for amplification of quiet environmental sounds thought to be important for reducing tinnitus audibility (53). Still more research is needed for developing special prescriptive procedures targeting tinnitus suppression.

Although a direct comparison is not possible because of the range of scales used, the severity of tinnitus varied across studies (Melin et al. (487), Del Bo (245), Herraiz et al. (482), Searchfield et al. (51), and Parazzini et al. (50)). Some studies used very well defined inclusion criteria about the tinnitus severity. All participants in Parazzini et al. (50) study were borderline between category I and II (Jasterboff classification). Similarly all participants in Del Bo et als' (245) study were in Jasterboff categories I and II, and had a THI score of ≥ 38. In Herraiz et al. (482) study, inclusion criteria was a score of > 36% on THI. Searchfield et al. (51) included participants with a tinnitus handicap score of ≥ 15 on the THQ. The severity of tinnitus in Melin et al. (487) study, was graded in to three categories (Grade I – audible in quiet environment, Grade II – audible in ordinary; but not in noisy environments, Grade III – constantly noticed in all ordinary acoustical environments and causing severe disturbances of concentration and continuous disturbance of sleep), only 2 out of 20 participants were in Grade III in the experimental group and none in control group. Many studies did not mention any details about the tinnitus severity inclusion criteria of participants (Brooks & Bulmer (489), Surr et al. (488), Sanchez et al. (486), Folmer and Carroll (48), Zagolski (485), Ferrari (484), Trotter & Donaldson (483), Moffat et al. (439), Sweetow & Sabes (215), and Schaette et al. (49)). There has been a movement towards developing a set of standard methods for evaluating tinnitus treatment outcomes (495) and the TFI is a new questionnaire developed with this intention (496) but this has yet to be trialed across different cultures and languages.

The amount of time that participants used hearing aids appeared to vary between studies. Some researchers instructed participants to use hearing aids' for certain number of hours (Del Bo et al. (245), Schaette et al. (49), Parazzini et al. (50)) others did not report their instructions (Melin et al. (487), Herraiz et al. (482), Zagolski (485), Folmer & Carroll (48), Ferrari et al. (484), Trotter & Donaldson (483), Moffat et al. (439), Searchfield et al. (51), and Sweetow & Sabes (215)). Brooks & Bulmer (489) reported that those participants who used hearing aids for more than 2 hours per day experienced significant reduction in tinnitus. However details are not mentioned about the regularity of hearing aid usage for all the participants (whether majority of participants used it for less than 2 hours a day or irregular usage of hearing aids).

Hearing aids are also not normally used on their own and are provided alongside guidance and counselling for more effective results (51). An examination of the research studies show varied amount of counselling was provided, for example in the Del Bo et al. (245) Schaette et al. (49) and Parazzini et al. (50) studies all the participants underwent counselling during fitting and on each follow up (up to 4 follow ups in 6 month duration). Certain studies did not provide counselling (Melin et al. (487) and Sweetow & Sabes (215)). Others did not mention the details of counselling provided (Surr et al. (488), Folmer & Carroll (48), Herraiz et al. (482), and Trotter & Donaldson (483)) and some studies simply did not mention counselling (Brooks & Bulmer (489), Sanchez & Stephens (486), Zagolski (485), Ferrari et al. (484), and Moffat et al. (439))

Reviews of sound therapy (164) have identified the difficulties in determining benefits of sound versus the counselling provided. Also the majority of studies in the present review involved combined approaches (hearing aids/counselling/maskers/tinnitus retraining therapy) making it difficult to extract the role of individual intervention approach. Similar observations were made by Hobson et al. (447). Although counselling alongside hearing aids' appears an appropriate combination for clinical practice (51) few have considered which element accounts for what effects.

We are unsure as to the exact mechanism by which hearing aids are beneficial to participants with tinnitus: masking of tinnitus by amplification of speech, background noise and internal noise of the aids, improvement in communication, reduction of stress related to hearing impairment and overall improvement of quality of life are plausible mechanisms by which hearing aids could contribute in tinnitus relief (162, 437, 438). Searchfield et al. (229) suggest that tinnitus magnitude can be explained by an adaptation level theory in which it is the weighted product of the tinnitus signal, context and psychological/cognitive factors. Hearing aids' may exert positive effects on tinnitus by: improving quality of life related to hearing difficulties (497, 498), reducing attention to tinnitus and facilitating masking from ambient sound (499) and compensating for deafferentation to reduce central gain (15). The masking achieved by hearing aids, may have a different mechanism from noise based maskers, amplification of information containing sounds, such as speech might draw on cognitive resources and result in informational masking effects (500, 501) while noise maskers may exert an effect through a simpler neural suppression mechanism. Combination aids (hearing aids and maskers) may conceivably achieve masking by different, potentially complementary, effects.

In this scoping review we followed the guidelines of Arksey & O'Malley (435). The final stage of a scoping review (consultation with key stake holders) is an optional stage. We did not include a consultation process as it was thought that without sampling a very wide range of opinions the risk of bias might out weight any advantage. However we hope this paper will promote discussion and debate, contributing to engagement of clinicians and researchers who use amplification in managing tinnitus.

4.7. Conclusions

Although the quality of evidence for hearing aids' effects on tinnitus is not strong, the weight of evidence (17 research studies for, 1 against) suggests merit of hearing aids in tinnitus treatment. Clinicians should feel reassured that some evidence shows support for the use of hearing aids but there is still a need for stronger methodology and randomised control trials in future research. Further research is needed to understand how hearing aids' can be optimised for tinnitus relief. RCTs are needed which specify type of counselling, hearing technology, prescription, and tinnitus characteristics in detail.

Chapter 5. Prescription of Hearing Aid Output for Tinnitus Relief

5.1. Preface

Publication

This chapter includes content from the article “Prescription of hearing aid output for tinnitus intervention” published in the International Journal of Audiology, volume 52, page no 617 – 625, 2013. The latest available impact factor of the journal was 1.396 (2011).

What was undertaken?

This study was carried out to identify a prescription of amplification optimised for tinnitus relief. Prescriptive procedures are a systematic and organised approach for hearing aid fitting. The DSL (I/O) is a loudness equalisation technique aimed at providing audible and comfortable signal in entire frequency region of hearing loss. Recordings of three cut off frequencies (2 kHz, 4 kHz and 6 kHz) and four gain settings (+6 dB, +3 dB, -3 dB and -6 dB) were used to simulate the effect of change in DSL(I/O) v5.0 on high frequency perception and the impact of these manipulated speech files on tinnitus audibility was documented.

Why it was needed?

Existing research in the area of hearing aids and tinnitus has supported the use of hearing aids for tinnitus. The majority of these studies have programmed hearing aids for optimising hearing and communication, neglecting tinnitus perception. There is a lack of research about the best prescription of amplification for targeting tinnitus relief. Hence this study was carried out.

How does it contribute to the objectives of the PhD?

This study recommends DSL(I/O) v5.0 as a good starting point for the prescription of amplification for tinnitus relief and tinnitus pitch is a factor to consider when programming hearing aids. These findings were used in programming hearing aids for the clinical trial using multi-session tDCS and hearing aids for tinnitus management (Chapter 7).

5.2. Abstract

Objectives – Tinnitus is a perceived sound that cannot be attributed to an external source. This study attempts to identify a prescription of amplification that is optimised as a first-fit setting for tinnitus relief.

Design - Participants compared the effect of high frequency amplification on their tinnitus. Stimuli were speech files (13 stimuli) with different amounts of high frequency amplification (3 cut off frequencies and 4 gain settings) to simulate the effects of a change in DSL(I/O) v5.0 prescription in the high frequencies.

Study Sample – Twenty five participants (mean age 59 years) with chronic tinnitus (minimum 2 years) participated in the study.

Results – A 6 dB reduction to prescribed gain at 2 kHz, emerged as the most preferred output (26.47% participants) to interfere with participants' tinnitus. Over all 70.58% participants' preferred a 3 to 6 dB reduction in output while 29.42% participants preferred a similar increase across all cut off frequencies. A trend was observed in which the higher the tinnitus pitch the more similar the preferred output to DSL(I/O) v5.0.

Conclusions – DSL(I/O) v5.0 appears to be a good starting point for prescription of hearing aid output for tinnitus management. Long-term benefits of different prescriptions for tinnitus still need to be ascertained.

5.3. Introduction

Tinnitus is a perceived sound that cannot be attributed to an external source (60). Sensorineural hearing loss underlies the majority of tinnitus cases (502) and due to frequent co-existence of tinnitus and hearing loss, hearing aids are often used for tinnitus management (47, 446, 492). Hearing aids are believed to have a positive impact on tinnitus by: reducing attention towards hearing loss and tinnitus, which in turn reduces associated stress (437); complete or partial masking of tinnitus by amplified ambient noise/instrumental noise (438); counselling associated with hearing aid fitting providing benefit through improved understanding of tinnitus (51); and reduction of central gain by increasing auditory nerve activity (439).

A scoping review regarding the role of hearing aids in tinnitus intervention has recently been conducted (47). Twenty nine studies were included in the review, with the majority of studies (27 out of 29) supporting the use of hearing aids for tinnitus management, except two (447, 487). Melin et al. (1987) (487) recommended controlled trials to study the separate impact of counselling and hearing aids on tinnitus. Hobson et al. (447) (2010) reviewed six RCTs and found they used multiple approaches (including different hearing aids) for tinnitus intervention, making it difficult to assess the exclusive impact of hearing aids on tinnitus. The majority of studies included in the scoping review had methodological limitations such as missing control groups, small sample size and lack of randomization. Hearing aids were programmed to assist hearing instead of a focus on tinnitus in most of these studies. Since tinnitus was not the main focus, it is hard to determine whether the observed tinnitus relief was a byproduct of counselling, improved hearing and other psychosocial aspects associated with it. Only two of the studies reviewed mentioned the prescriptive procedure used for hearing aid programming (49, 51). Prescriptive procedures are a systematic and organised approach for hearing aid fitting (503). They aim to provide the most appropriate amplification based on a person's hearing loss. Commonly used conventional prescriptive procedures for hearing aid fitting include the DSL (I/O) (504) and the national acoustic lab (NAL) (505) prescriptions. Schaette et al. (2010) used the national acoustic lab –nonlinear (NAL-NL 1) prescription and Searchfield et al. (2010) used DSL(I/O) v5.0 in their respective studies. DSL (I/O) is a loudness-equalisation technique (504) which tries to equalise loudness for each frequency channel separately (506). DSL (I/O) attempts to provide audible and comfortable signal in

each frequency region (507). NAL-NL1 is a loudness-normalisation technique that attempts to optimise intelligibility and tries to normalise overall loudness rather than for each frequency channel (506). NAL-NL1 is a modified and advanced version of the NAL series of prescriptive procedures. The original NAL procedure prescribed too little low frequency and too much high frequency gain for steep high frequency hearing loss. It underwent series of modifications leading to development of national acoustic lab revised which provided slightly less than half-gain across the entire audiometric frequency; it was a popular linear prescriptive approach for patients with mild to moderate hearing loss (508). The national acoustic lab revised, profound was a modification of national acoustic lab revised; it was identical to national acoustic lab revised, profound except that it provided additional considerations for severe to profound hearing loss configurations (509) NAL-NL-1 was developed as a non-linear prescription procedure; its main purpose is to prescribe hearing aid gain for several input levels that would result in maximal effective audibility. 'Effective audibility' refers to the extent of information which can be extracted from speech sounds once they are audible (506).

The most effective setting of hearing aid for tinnitus relief may not be the same as the one used for enhancing communication (53). Hearing aids may affect tinnitus audibility through many potential mechanisms such as partial masking (431) or lateral inhibition (436). Wise (2003) (52) investigated amplification of sound for tinnitus management and compared the use of DSL(I/O) v4.0 vs. NAL-NL1 on tinnitus audibility. The audibility of tinnitus is the ease with which the participant hears their tinnitus. DSL(I/O) v4.0 with low compression knee-points resulted in reducing tinnitus awareness in 80 % of participants; however this setting caused more annoyance to environmental sounds than NAL-NL1 (52). NAL-NL1 resulted in higher word recognition scores than DSL(I/O) v4.0 on a speech in noise test. Wise (2003) (52) recommended the use of a multi-programmable hearing aid with separate programs for optimising communication and reducing tinnitus awareness. This fitting approach is described in detail by Searchfield (2006) (53). The impact of standard and high bandwidth amplification on psychoacoustical measures of tinnitus has also been investigated (439). The standard amplification regime significantly altered the tinnitus spectrum within 1 month of hearing aid use, whereas the high bandwidth amplification regime did not change the tinnitus perception. The tinnitus spectrum was the psychoacoustical characterisation of tinnitus in which participants were asked to rate the contribution of tones (250 - 8000 Hz) to their tinnitus percept on a rating scale from 0 (not

at all similar) to 10 (completely the same). After one month of hearing aid use by participants the normal amplification group showed a significant reduction in the low frequencies of their tinnitus spectrum (439).

There is a lack of research in the area of optimising hearing aid settings for tinnitus intervention. If the first fit settings of hearing aids can be optimised for tinnitus relief, this may result in improved hearing aid efficiency in tinnitus management. This study was planned with the specific goal to examine the effects of high frequency modification of the DSL(I/O) v5.0 prescriptive procedure on short-term tinnitus perception. Speech files (13 stimuli) simulating different amounts of high frequency amplification (3 cut off frequencies and 4 gain settings) were used to ascertain the effects of a change in DSL(I/O) v5.0 prescription on participants tinnitus. The focus of this study was to investigate the immediate impact of change in prescription setting on tinnitus perception.

5.4. Methods

This study was approved by the University of Auckland Human Participant's Ethics Committee.

Participants

Twenty five participants (mean age of 59 years, age range 34 - 81 years) completed the study. Participants were recruited through the University of Auckland Hearing and Tinnitus Clinic research database. All the participants were candidates for hearing aid use, none of them had used hearing aids before, but they all indicated interest in potential use of hearing aids to manage their tinnitus. Inclusion in the research was based on an intention to use basis, not on a predetermined level of tinnitus handicap.

There were 9 females (36%) and 16 males (64%) with mean Tinnitus Functional Index (TFI) (496) score of 39.30 (SD = 19.11). The range of possible scores with TFI is 0 to 100. All participants had experienced chronic bothersome tinnitus for a minimum of 2 years with average tinnitus duration of 18.71 years (ranging from 2 - 54 years). Mean self-perception of tinnitus loudness was 62.6 (on a rating scale from 1 to 100, where 1 = very faint and 100 = very loud). Fifteen participants had bilateral tinnitus [R = L (9 participants), L > R (4 participants), R > L (2 participants)], 6 participants had unilateral tinnitus localised to the left side and 4 participants had tinnitus localised to the centre of

the head. Tinnitus quality was documented for each participant, and 40% rated it as tonal, 28% as noise, 20% as cricket, and 12% as combination of other qualities. Mean measured tinnitus pitch was 7.892 kHz (range 0.8 to 14.5 kHz). On a self-perception measure 64% of participants rated their tinnitus to be high pitched, 20% as very high pitched and 16% as medium pitched.

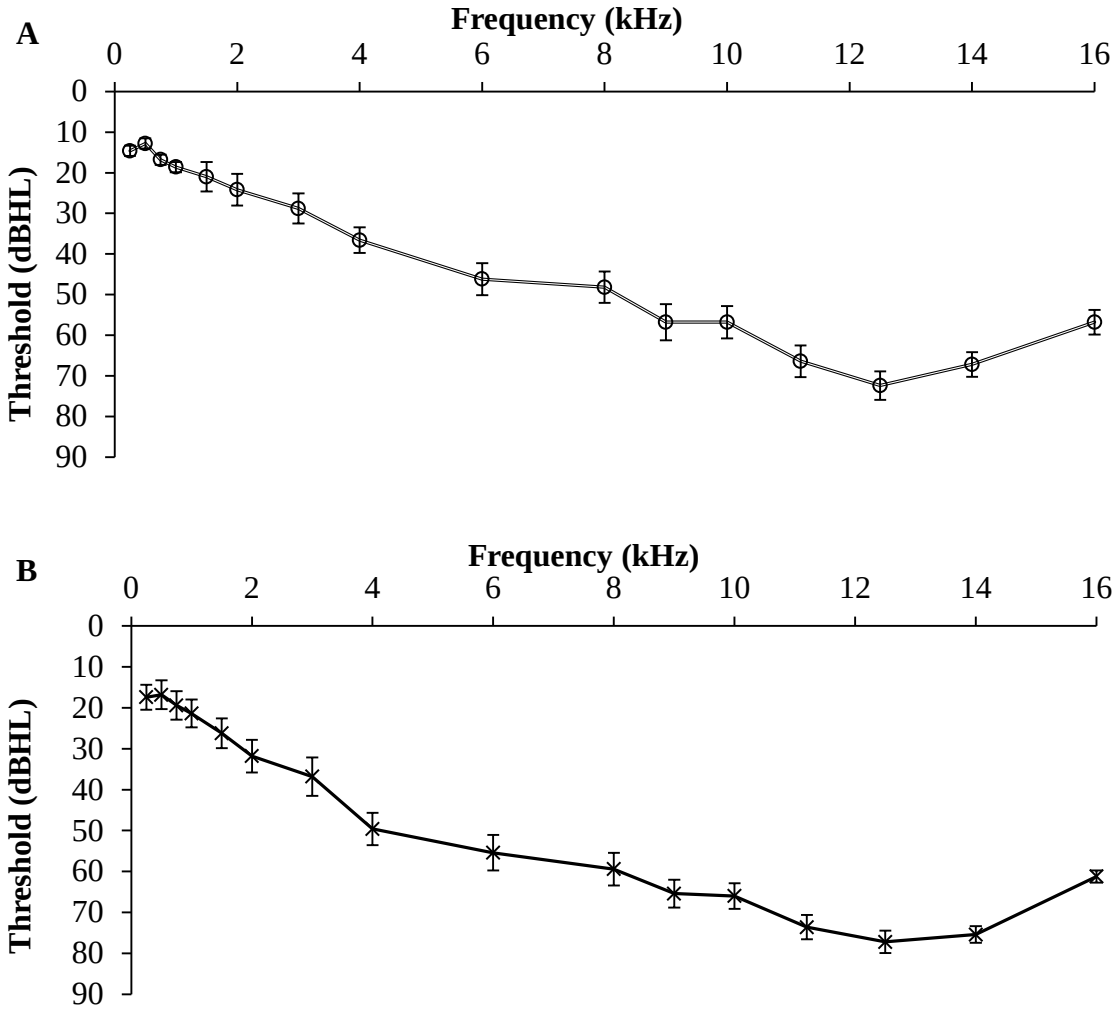


Figure 5:1. The mean hearing thresholds for twenty five participants (A) right ear (circles) and (B) left ear (crosses). The error bars represent ± 1 standard error of the mean.

All participants had mild to moderate high-frequency sloping sensorineural hearing loss in the audiometric range of 0.25 to 8 kHz and it became moderately severe to severe in the extended high frequencies (9 to 16 kHz). Mean hearing thresholds of the left ear were worse than the right ear; however they were not significantly different. All the participants had aidable hearing loss (Figure 5:1).

Hearing Assessment

Audiometry (0.25 - 16 kHz) was undertaken using a two-channel audiometer (either Grason Stadler GSI-61 or Interacoustics AC40). Measurements were undertaken using supra-aural (Telephonics, TDH - 50P) or insert headphones (E.A.RTONE 3A) (0.25 – 8 kHz) and high frequency circumaural headphones (Sennheiser HDA 200) (9 - 16 kHz). Audiometry was performed using the modified Hughson-Westlake procedure (424).

Tinnitus Testing

Tinnitus pitch was assessed using testing software (© The University of Auckland) throughout the test frequency range of 0.25-16 kHz. For tinnitus pitch measurement a 2AFC method was used, in which pairs of tones were presented based on the configuration of audiogram and perceptual feedback (participants were asked to choose if their tinnitus pitch was low, mid, high or very high frequency and, based on that, a frequency was chosen to represent tinnitus pitch and it was increased or decreased based on participants further feedback). The starting frequency and order of testing varied for participants based on the above mentioned two factors (configuration of audiogram and perceptual feedback about tinnitus pitch). High frequency circumaural headphones (Sennheiser HDA 200) were used for the entire pitch matching procedure. Participants were asked to identify the tone which matched the best with their tinnitus pitch. Each tone was presented at a sensation level of 15 dBSL. Once the settings for a given pair of tones were established, the two tones were presented in alternating manner until the participant indicated which one was closest to the pitch of their tinnitus. Pitch match was then compared to tones 1 octave above and below to rule out octave confusion. The measurement was repeated until two repeatable responses were obtained.

Research Protocol

The research design was in the form of a paired round robin tournament using different stimulus parameters (comparing 13 speech files) with ratings to ascertain the winner for each participant. Participants compared the effect of high frequency amplification (using a master hearing aid programmed to DSL(I/O) v5.0 prescription) on their tinnitus, by comparing tinnitus audibility to speech files with different amounts of high frequency energy (3 cut off frequencies and 4 gain settings) to simulate the effects of a change in DSL(I/O) v5.0 prescription in the high frequencies.

Round Robin Tournament

Participants' perceptions of tinnitus in response to the 13 speech files sounds were tested by a round robin (paired comparison) tournament (2AFC) in a quiet room. Speech files (a "flat" response + 12 filtered) were paired and presented in random order (total 78 times) using Lab VIEW 8.0 software (National Instruments Ltd.).

Master Hearing Aid

Amplification to compensate for hearing loss was provided by a master (non-wearable) hearing aid (Wolverine™ Hybrid Jig with Inspiria™ Extreme [Software number SA3286], Sound Design Technologies Ltd). The hearing aid was programmed to match DSL(I/O) v5.0 real-ear prescription targets based on each participant's hearing loss. A front-end microphone (AM4011) was engineered to work with the test rig. The microphone frequency response was 0.5 - 12.5 kHz. The SA3286 is a hybrid DSP system with adaptive algorithms that run on the Voyageur™ hardware platform. This hardware platform consists of a combination of a DSP core and a high fidelity audio CODEC. Insert earphones, ER-5A (Etymotic research Ltd) were used through the buffer in the board as the transducer. The acoustic frequency responses of the ER-5A earphones were 0.1 - 10 kHz, and they were used bilaterally.

Speech Files

The speech files were recorded from a speech track on the New Zealand cochlear implant assessment tests disc, which is used for the Hearing in Noise Test assessments in the University of Auckland Audiology Clinic. The speech file comprised of 5 sentences spoken by a female and was recorded in 13 patterns (boost and cut) through a second-order shelving filter program (Matlab R2009b) based on (510). The modifications in the speech files were done in advance for three cut off frequencies (2, 4 & 6 kHz) and four gain settings (+6, +3, -3 and -6 dB) respectively for the 12 speech files and then they were presented to each participants and the gain was adjusted based on their hearing loss, through the master hearing aid programming. The winning setting was obtained for each participant.

The speech files were presented at the desired comfortable level of each participant and the long term average spectrum was computed by Adobe Audition using 2048-point FFTs (Blackmann window) (Figure 5:2).

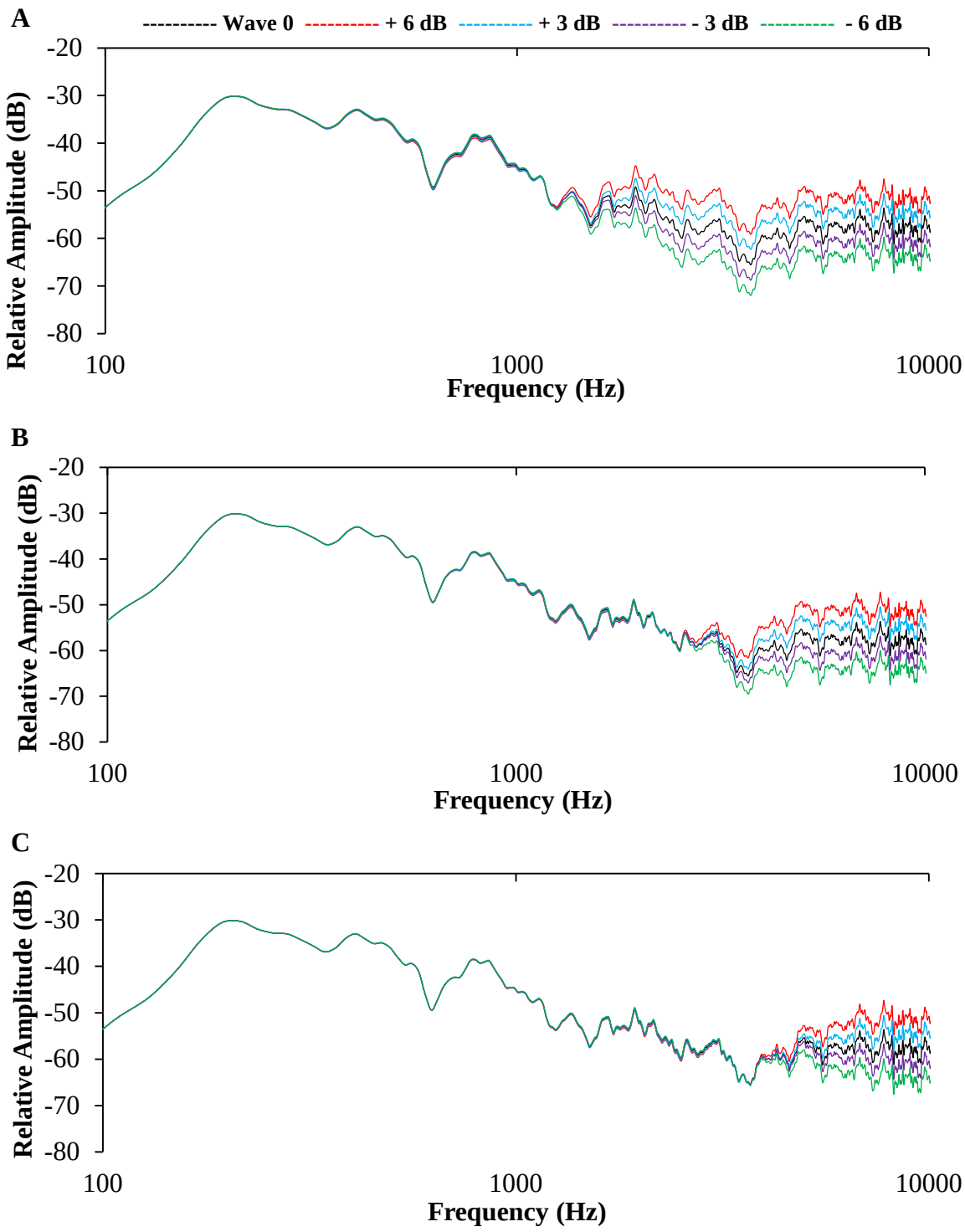


Figure 5:2. The long-term average amplitude spectra of 13 speech files measured by adobe audition using 2048-point FFTs (Blackmann window). Wave 0 is speech file with no change to frequency response. Gains relative to original file for +6, +3, -3 and -6 dB are shown for (A) cut off frequency = 2 kHz, (B) cut off frequency = 4 kHz, (C) cut off frequency = 6 kHz.

Participants' Task & Instructions

The master hearing aid was programmed for each participant based on their latest hearing test results. The participant's task was to choose the preferred setting that interfered most with their tinnitus percept and made the tinnitus least audible. Their task was to focus on the immediate impact of the sound settings on their tinnitus perception.

Instructions given to participants were:

"You will be hearing a pair of speech files. Listen to them carefully and choose the speech file which interferes the most with your tinnitus and makes it least audible by pressing either ↑ (up), ↓ (down) keys on a computer keyboard. If you can't differentiate between them or feel they are equally effective/not effective in interfering with your tinnitus then choose any one speech file randomly. There will be 78 presentations in total. This task can take approximately 20 to 30 minutes of your time."

The computer program counted the number of "wins" for each stimulus. Results were then collapsed to provide an over-all winner.

Real Ear Measures

An Audio Scan Verifit (version 3.4) real-ear measurement system was used for real ear measurements. A silicon probe tube was inserted in participants' ear canals 25 mm beyond the intertragal notch and then the insert earphone was inserted carefully so as not to move the probe tube. The master hearing aid output was measured in the ears matched to the DSL(I/O) v5.0 prescribed gain and with the winning setting on (post the analysis of round robin tournament of all the settings). Output (dBSPL) was recorded from 0.25 – 6 kHz.

Data Analysis

The data were analysed using SPSS software (IBM Version 19). A three-way repeated measure analysis of variance (ANOVA) was undertaken, using real ear measures, tinnitus pitch (> 8 kHz, 4 to 8 kHz and < 4 kHz) and hearing threshold at 2 kHz (< 30 dBHL and > 30 dBHL) as factors. A criterion for statistical significance of 0.05 was chosen. A non parametric test (Fisher's exact) was used to analyse participant's choice of winning settings.

5.5. Results

A 6 dB reduction at 2 kHz emerged as the most preferred output to interfere with participants' tinnitus (26.47% participants), followed by 6 dB reduction at 4 kHz and 3 dB reduction at 2 kHz (14.71% and 11.76% participants respectively) however, Fisher's exact test did not reveal a significant difference in the number of people choosing a particular setting as compared to others. Overall 70.58% of participants' preferred a 3 to 6 dB reduction in output and 29.42% of participants' preferred 3 to 6 dB increment in output across all cut off frequencies (Table 5:1).

Table 5:1. Cut off frequency preferred by participants [Three cut off frequencies (fc) (2 kHz, 4 kHz and 6 kHz) at four gain settings (+ 6 dB, + 3 dB, - 3 dB, & - 6 dB)] as a percentage of total choices.

Cut off Frequency	**2 KHz**				**4KHz**				**6KHz**			
Gain	+ 6	+ 3	- 3	- 6	+ 6	+ 3	- 3	- 6	+ 6	+ 3	- 3	- 6
Number of participants	3	3	4	9	2	2	2	5	0	0	2	2
%	8.82	8.82	11.76	26.47	5.88	5.88	5.88	14.71	0	0	5.88	5.88

Real ear measurements showed a small difference in hearing aid output between DSL(I/O) v5.0 and the most preferred setting. Across the entire frequency range the winning setting prescribed less (but statistically insignificant) output compared to DSL(I/O) v5.0 (Figure 5:3).

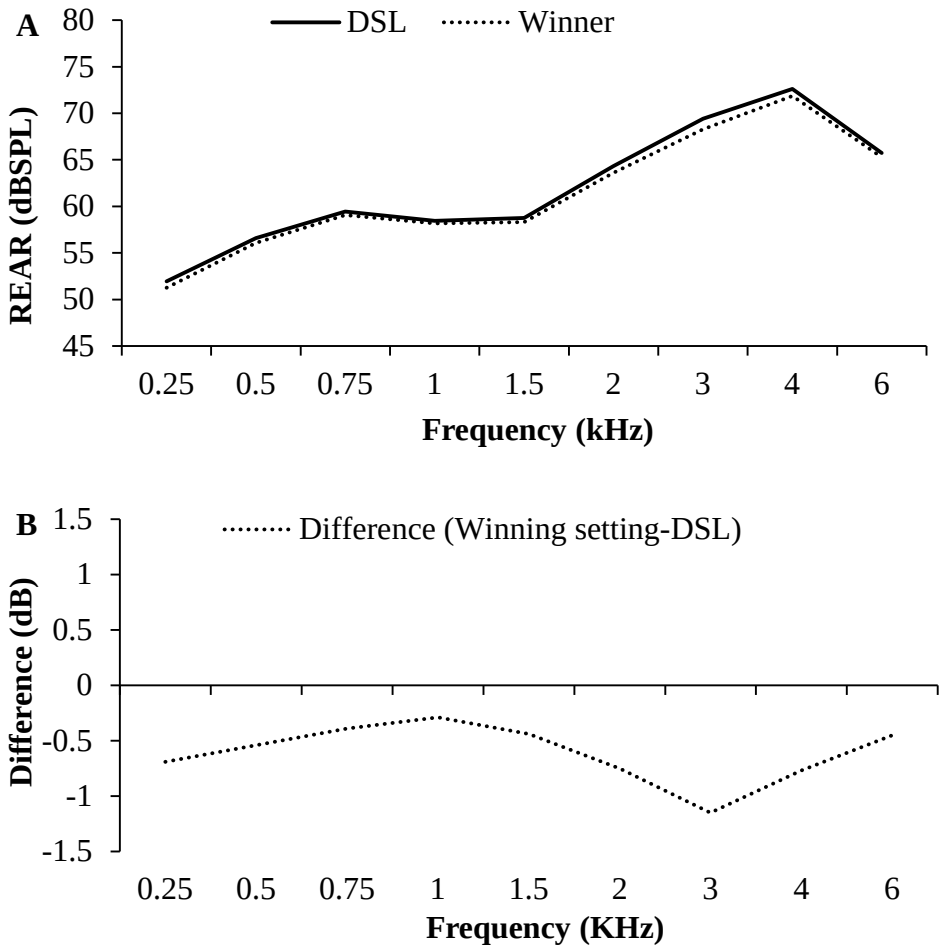


Figure 5:3. (A) Real-ear SPL measured for the overall winning output (dashed line) and DSL(I/O) v5.0 setting (solid line). (B) Difference between overall winning output and DSL(I/O) v5.0 prescribed output.

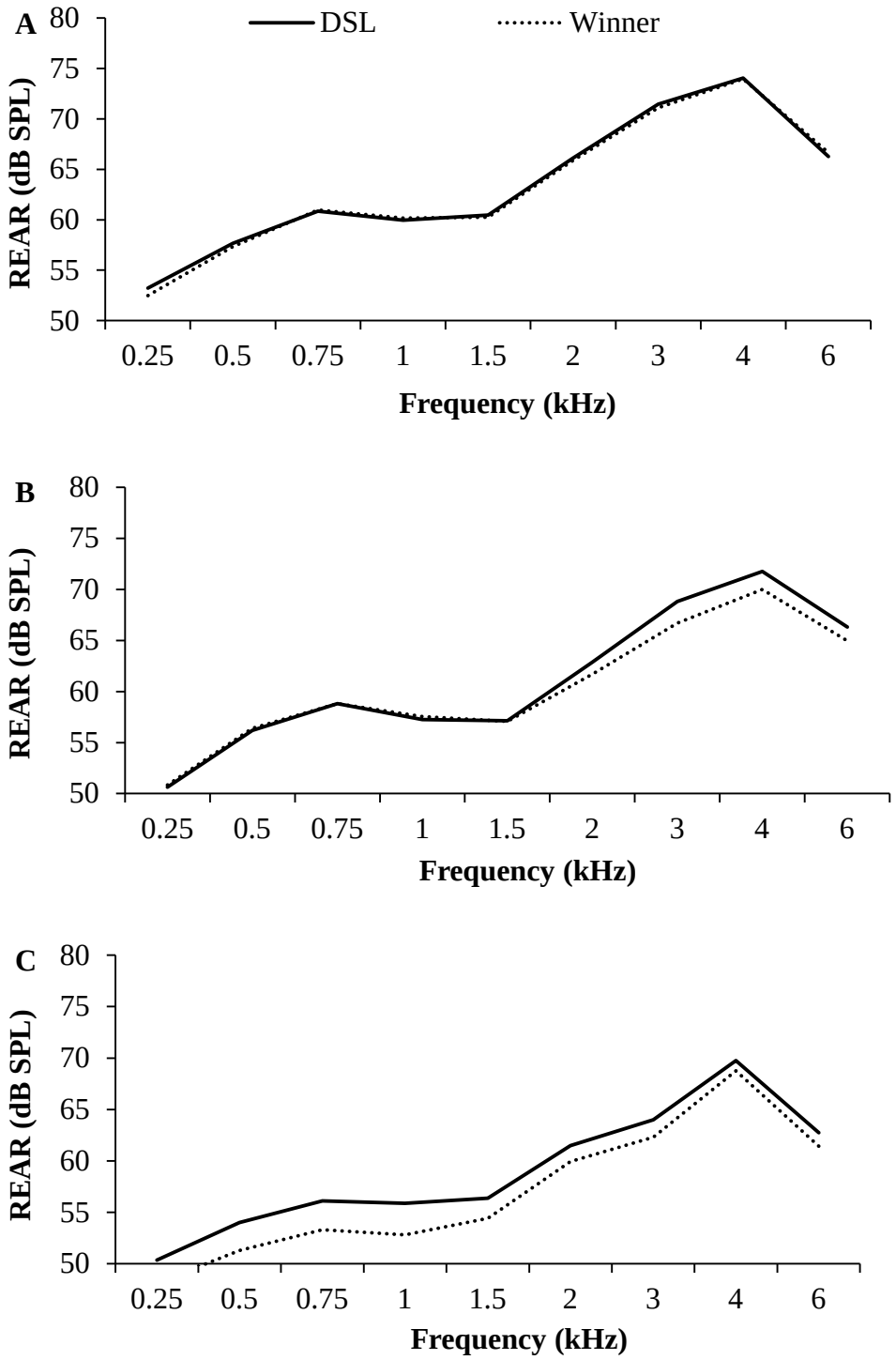


Figure 5:4. REAR for DSL(I/O) v5.0 at 65 dBSPL input (solid lines) and overall winning setting (dashed lines) (A) Participant's tinnitus pitch > 8 kHz, (B) 4 kHz to 8 kHz (C) Tinnitus pitch < 4 kHz.

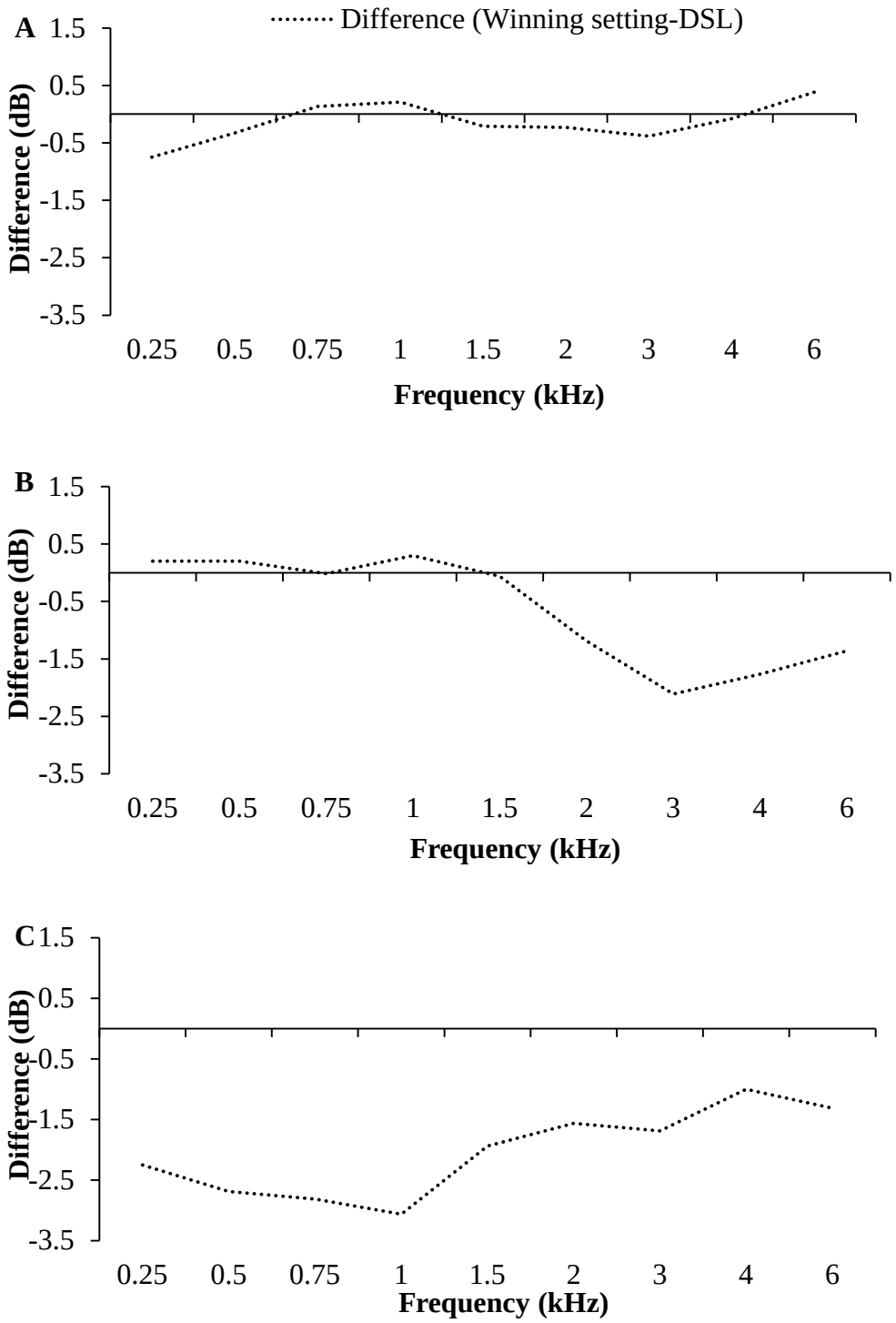


Figure 5:5. Difference between overall winning prescribed output and DSL(I/O) v5.0 to 65 dBSPL input (A) Participant's tinnitus pitch > 8 kHz, (B) 4 kHz to 8 kHz (C) Tinnitus pitch < 4 kHz.

Measurement results were classified into three categories based on tinnitus pitch (> 8 kHz, 4 kHz to 8 kHz, and <4 kHz). The difference between DSL(I/O) v5.0 prescribed settings and the overall winning setting across the frequency range were compared (Figure 5:4 and Figure 5:5). The output prescribed by the winning setting was less (but not at statistically significant level) than those of DSL(I/O) v5.0 across the entire frequency range for the

participants with tinnitus pitch less than 4 kHz. The difference was in the range of 1 to 3 dB, and was smaller as tinnitus pitch increased.

When the tinnitus pitch was greater than 8 kHz, the preferred output was slightly more than DSL(I/O) v5.0 at three frequencies 750 Hz, 1 kHz and 6 kHz) and slightly less than DSL(I/O) v5.0 at the other frequencies measured. However this difference was not more than 1 dB (Figure 5:4 A and Figure 5:5 A).

When the participants tinnitus pitch was between 4 kHz to 8 kHz, the preferred gain was up to 2 dB less than DSL(I/O) v5.0 across the entire high frequency (2 kHz and above) but more than DSL(I/O) v5.0 at the low and mid frequency (from 250 Hz to 1.5 kHz) however this difference was minimal (less than 0.5 dB) (Figure 5:4 B and Figure 5:5 B).

When tinnitus pitch was less than 4 kHz, the preferred setting was between 1 to 3 dB less than DSL(I/O) v5.0 across entire frequency range. This was the largest difference obtained when tinnitus pitch was considered (Figure 5:4 C and Figure 5:5 C).

A trend was observed between tinnitus pitch and the difference between DSL(I/O) v5.0 setting and winning setting; as tinnitus pitch decreased the winning settings become lower than DSL(I/O) v5.0; however this difference was not statistically significant.

5.6. Discussion

The majority of studies investigating the role of hearing aids for tinnitus management have considered neither tinnitus pitch nor the prescription approach for hearing aid fitting aiming at tinnitus relief (47). In this study twenty five participants with chronic tinnitus compared the effectiveness of sound files with various levels of high frequency amplification for reducing short-term tinnitus audibility. The higher the tinnitus pitch, the more the preferred real ear output tended to match DSL(I/O) v5.0. For low-pitched tinnitus (< 4 kHz) the preferred output tended to be lower than that of DSL(I/O) v5.0 across the entire frequency range.

Wise (2003) (52) documented that participants experienced less audible tinnitus when hearing aids were programmed according to the DSL(I/O) v4.0 compared to NAL-NL1 prescription. A plausible explanation for this could be the fact that most noise is concentrated in the low frequency region (511) and DSL (I/O) generally prescribes more low intensity and low frequency gain than NAL-NL1 (512). Participants preferred NAL-

NL-1 prescription for speech perception (52). This resulted in the proposal of having separate programs for hearing and tinnitus relief. The relative long term benefits of these and newer (NAL-NL 2) (513) prescriptive formulae need to be ascertained. The present study revealed that participants' high frequency preference was not significantly different from the DSL(I/O) v5.0 prescription. However the lower the tinnitus pitch the lower the output that was preferred. These results support Wise's (2003) (52) and Searchfield's (2006) (53) recommendation that DSL (I/O) can be used as a first-fit prescription for tinnitus.

This research ascertained first fit benefits of different settings in a controlled environment. There is no doubt that differences in background noise, environment, individual difference and auditory scene analysis etc. would influence tinnitus perception as it does for use of hearing aids for hearing purposes. Hearing aid trial periods remain important with subsequent fine tuning, or in the future, hearing aid learning paradigms.

Tinnitus pitch may be an important factor to consider when programming hearing aids. There is large inter- and intra-session variability associated with pitch matching (410). Pitch matching needs to be repeated a number of times to achieve greater reliability. Schaette et al. (2010) (49) showed that participants with tinnitus pitch less than 6 kHz showed significant reduction in tinnitus loudness with hearing aids compared to those with pitch higher than 6 kHz. Participants with tinnitus pitch falling within the range of acoustic stimulation showed better results. Similarly hearing aids appeared most effective in managing tinnitus when tinnitus pitch was within the frequency response of hearing aid (431).

From this study and the limited existing literature it appears that tinnitus pitch and hearing aid prescription may be important variables to explore in future research. Although this study has focused on one aspect of hearing aid fitting (prescribed output) other factors are likely to be significant for hearing aid success in tinnitus management as well (53). Clinicians should consider these when prescribing hearing aids for tinnitus relief. Some of these factors are: minimizing or turning off settings recommended for noise reduction; low compression knee points; physical comfort; occlusion; type of hearing aids; and counselling.

Most modern hearing aids have features to reduce environmental noise and internal noise. These programs to suppress background noise should be disabled for tinnitus management

(53). Continuous exposure to ambient noise levels may lead to reduction of gain in the auditory pathway. Low compression thresholds, turning off expansion and noise reduction algorithms and using omnidirectional microphone settings may facilitate greater amplification of low level background sound for partial masking effects. Low compression knee points (less than 40 dBSPL) without expansion have been shown to help in the amplification of low intensity sounds to interfere with tinnitus detection without the fear of over amplifying loud sounds (52). These recommended changes should not be at the expense of listeners comfort (53). When amplification of environmental sound is not sufficient to distract or achieve some degree of masking (such as when low frequency hearing loss is too great or tinnitus pitch is too high) combination hearing aid and sound generators may be necessary (50).

In this study the master hearing aid was programmed based on the DSL(I/O) v.5.0 prescriptive approach, many manufacturers software allows the choice of DSL as a first fit option while other manufacturers use other prescriptions e.g. NAL-NL 2 or proprietary manufacturers' prescription. There is clear evidence that following selection of prescription within hearing aid software, hearing aid output /gain should be verified using real ear measurements (514). We would strongly recommend that undertaking verifications and adjusting to prescribed response is an important aspect of hearing aid provision for persons with tinnitus.

Any aspect of the hearing aid which focuses client's attention/awareness towards their ear (e.g. physical discomfort) and consequently tinnitus, should be minimised (53, 515). Excessive occlusion of the ear canal can heighten tinnitus awareness (515); hence either open fit hearing aids or appropriate venting should be used to overcome occlusion related issues (53, 245). Binaural hearing aid fittings are also more effective than monaural fitting for tinnitus suppression (489).

Even with optimisation of hearing aids for tinnitus therapy, counselling is always necessary. Counselling plays a pivotal role in tinnitus management, including when used along with hearing aids (51).

This is one of the first studies to examine the effects of changes in hearing aid prescription on tinnitus perception. Different protocols could be explored using lower cut off frequencies and higher gain settings. This study was focused on the immediate impact of change in sound settings on tinnitus perception, long term change in the tinnitus annoyance

and other non-perceptual characteristics of tinnitus were beyond the scope of this study and should be considered for future research. Short to long term effects of different hearing aid settings on tinnitus relief and the broader psychological and perceptual aspects of tinnitus need to be ascertained.

Every client has different needs and a unique tinnitus and hearing profile, hence it is important to offer an individualised approach to each client based on their personal preferences. We believe there is merit in using hearing aids for tinnitus management but the way they are programmed for tinnitus relief is significant and we suggest that:

1. DSL(I/O) v5.0 is a good starting point for prescription for tinnitus.
2. For tinnitus pitch identified ≤ 4 kHz we recommend a starting point of 3 dB below DSL(I/O) v5.0 across the frequency range.
3. Individual tuning based on listeners preference is recommended that considers comfort as well as reduced tinnitus audibility.

5.7. Conclusions

The results of the present study indicate that DSL(I/O) v5.0 appears to be a good starting point for prescription of hearing aid output for tinnitus management. The present study also indicates that for participants with tinnitus pitch ≤ 4 kHz slightly less high frequency output than DSL(I/O) v5.0 is preferred. Tinnitus pitch is a factor to consider when fitting hearing aids for tinnitus relief and individual fine-tuning based on listeners preference is strongly recommended for better results. More research is needed in this area of prescription of gain for hearing aids targeting tinnitus relief. Long-term benefits of different prescriptions for tinnitus still need to be ascertained.

Chapter 6. Transcranial Direct Current Stimulation (tDCS) Intensity and Duration Effects on Tinnitus Suppression

6.1. Preface

Publication

This chapter includes content from the article “Transcranial direct current stimulation intensity and duration effects on tinnitus suppression” published in Neurorehabilitation and Neural Repair, volume 27, page no 164 – 172, 2012. The latest available impact factor of the journal was 4.495 (2013).

What was undertaken?

This study examined tDCS dose (current intensity and duration) and response effects for tinnitus suppression. The impact of intensity (1 mA and 2 mA) and duration (10 min, 15 min and 20 min) on tinnitus suppression was investigated.

Why it was needed?

tDCS is a promising tool for tinnitus research. However none of the existing studies addressed the issue of optimisation of tDCS parameters (intensity and duration) for tinnitus relief. Hence this study was carried out, prior to commencing a RCT of tDCS and hearing aids (Chapter 7)

How does it contribute to the objectives of the PhD?

The study found that 2 mA current delivered for 20 minutes duration was the most effective combination for anodal tDCS of the LTA for transient tinnitus suppression. This is one of the first studies to evaluate the effects of a 2 mA current intensity on tinnitus symptoms and based on this study, the most effective setting (2 mA current intensity and 20 minutes duration) of tDCS was used in the clinical trial (Chapter 7) where multisession tDCS and hearing aids were used for tinnitus management.

6.2. Abstract

Background - Perception of sound in the absence of an external auditory source is called tinnitus, which may negatively impact quality of life. Anodal tDCS of the LTA was explored for tinnitus relief.

Objectives - This pilot study examined tDCS dose (current intensity and duration) and response effects for tinnitus suppression.

Methods – Twenty-five participants with chronic tinnitus and a mean age of 54 years took part. Anodal tDCS of LTA was carried out. Current intensity (1 mA and 2 mA) and duration (10 min, 15 min and 20 min) were varied and their impact on tinnitus measured.

Results - tDCS was well tolerated. Fifty six percent of participants (14) experienced transient suppression of tinnitus, 44% of participants (11) experienced long term improvement of symptoms (overnight - less annoyance, more relaxed and better sleep). There was an interaction between duration and intensity of the stimulus on the change in rated loudness of tinnitus ($F(2, 48) = 4.355$, $p = 0.018$) and CGI score ($F(2, 48) = 3.193$, $p = 0.050$) after stimulation.

Conclusions - Current intensity of 2mA for 20 minutes was the more effective stimulus parameter for anodal tDCS of LTA. tDCS can be a potential clinical tool for reduction of tinnitus, although longer-term trials are needed.

6.3. Introduction

Perception of sound in the absence of an external auditory source is called tinnitus. In the United States approximately 50 million people experience some form of tinnitus and 16 million experience frequent tinnitus (69). It can lead to anger, frustration, tension, poor communication, and lack of sleep (5, 6) and can have a devastating impact on overall QOL (3, 4). The underlying mechanisms of tinnitus and its most effective treatment are as yet unresolved (40).

In the past 5 years attention has been drawn towards the use of non-invasive brain stimulation for tinnitus management (39-41). The history of non-invasive electrical brain stimulation dates back to 43 AD when electric torpedo fish were used for the treatment of headaches and gout (366). It was not formally investigated until the 1960s when experiments started applying mild direct current to the exposed cortex to study its impact on the neuronal activities (369, 370). While the majority of early work was performed on animals, similar neural effects are expected in humans as well.

More recently, the effects of tDCS have been explored in humans, in both healthy and neurological populations. Depending upon the polarity of the stimulation, tDCS can increase or decrease the excitability of the underlying cortex. Anodal stimulation increases excitability due to neuronal depolarisation and cathodal stimulation decreases excitability due to neuronal hyperpolarisation (372-374). It is postulated that the after-effects of tDCS could possibly be due to change in intracortical inhibition or facilitation which is controlled by synaptic activity (516).

Not all of the current applied at the scalp reaches the cortex, some of it is shunted through the scalp tissue and cerebrospinal fluid; the balance reaches the brain (374, 376) Miranda and colleagues (377), modelled the current distribution during tDCS and found that based on: the location, size and number of electrodes used, the percentage of current reaching the brain varied from 39% to 59%. While tDCS might potentially be a powerful strategy for tinnitus intervention (41, 42, 382), it requires optimisation of stimulation parameters (40). As yet there is no consensus as to the optimal parameters for tinnitus modulation using tDCS (Table 6:1).

Table 6:1. Research studies using tDCS for tinnitus management. (A-Anodal, C-Cathodal, S-Sham)

Authors / Year	Stimulus Parameters					Session	Interval	Sample Size	Electrode Size
	Polarity	Stimulation electrode position	Reference electrode position	Duration	Current (mA)				
Fregni F et al. (39)	A/C/S	LTA	Contra lateral supra orbital area	3 Min	1mA	6 sessions (2 for each A/C/S)	6 Min	7 (4M, 3F)	Anode & Cathode = 35cm^2
Vannesteste S et al. (41)	A/C	DLPFC	Contra DLPFC	20 Min	1.5mA	1 session	-	(543-195M, 348F) 448 A 30 C 65 no	Anode & Cathode = 35cm^2
Garin. P et al. (40)	A/C/S	LTA	Contra Lateral Frontal scalp	20Min	1mA	3 sessions of tDCS (A/C/S)	2Weeks	21(16 M, 5F) 1 F dropout	Anode= 35cm^2 Cathode= 50cm^2
Frank. E et al. (42)	A/C	DLPFC	Contra DLPFC	30 Min	1.5mA	6 sessions (2 per week)	3-4 days	32 (25M, 7F)	Not mentioned
Faber. M et al. (43)	A/C/S	DLPFC	Contra DLPFC	20 Min	1.5mA	6 sessions	8 weeks	15 (11 M, 4 F)	Anode & Cathode = 35cm^2
Vannesteste S et al. (44)	A/C	DLPFC	Contra DLPFC	20 Min	1.5mA	1 session	-	153 (92 M, 61 F)	Anode & Cathode = 35cm^2

Anodal tDCS of the LTA and DLPFC are potentially the most favourable polarity and sites of stimulation for tinnitus relief (39-44). tDCS of LTA results in more widespread diffused impact on cortical areas larger than the target region, However tDCS of DLPFC results in to more localised impact on target region itself (390). Since tinnitus can have widespread underlying causes (42), LTA was chosen as site of stimulation for this study.

There have been few if any dose-response studies in tDCS (383). The aim of the present study was to explore tDCS dose (current intensity and duration) response effects for tinnitus suppression for LTA stimulation. Anodal tDCS of the LTA has led to transient suppression of tinnitus in 42% (39), and 35% (40), of participants. A comparatively long lasting impact on tinnitus perception, lasting up to few days, was observed in a recent double blind, sham controlled study conducted by Garin et al. (40), where the duration of tDCS was 20 min with 1 mA current intensity. Anodal tDCS produced more favourable effects compared to cathodal or sham tDCS. Compared to previous work (39, 41), this study had a longer interval between tDCS sessions (2 weeks), and the size of the reference

electrode was larger than the stimulating electrode (Table 6:1). Vanneste and colleagues (41) explored whether tDCS of DLPFC would lead to tinnitus suppression. They used a slightly higher current intensity (1.5 mA) than other authors (39, 40), and reported a 29.9% positive response rate with bifrontal tDCS (anode on the right DLPFC and cathode on the left DLPFC).

The primary goal of the present study was to optimise parameters for anodal tDCS of LTA. We selected anodal stimulation for investigation, as previous studies have established that anodal tDCS is more effective in tinnitus suppression than cathodal or sham (39, 40). We investigated six combinations of stimulus intensity and duration, in order to optimise these tDCS parameters for future studies. This is one of the first studies to evaluate the effects of a 2 mA current intensity on tinnitus symptoms.

6.4. Methods

Participants

Participants were recruited through the University of Auckland Hearing and Tinnitus Clinic. Volunteers were eligible for inclusion if they were aged at least 18 years, and had experienced bothersome tinnitus for at least 18 months. Volunteers were excluded if they had any contraindications to tDCS, such as: previous brain surgery, metal or electronic implants, pregnancy, and a history of seizures as determined by a neurologist (Appendix A). Each participant provided written informed consent in accordance with the Declaration of Helsinki, and this study was approved by the University of Auckland human participant's ethics committee.

Twenty five participants with mean age of 54 years (range 28 to 78 years) completed the experiment. There were 8 females (32%) and 17 males (68%) with mean TFI (496) score of 47.76 (SD = 20.94). All participants had chronic bothersome tinnitus lasting for at least 18 months with average tinnitus duration of 16.18 years (ranging from 1.5 years to 54 years). Twenty one participants had bilateral tinnitus and 4 had unilateral tinnitus (3 left sided and 1 right sided). Two participants had normal hearing sensitivity and 23 had hearing loss. Tinnitus quality was documented for each participant, and 25.9% rated it as hissing, 22.9% as ringing, 17.1% as buzzing, 11.4% as high pitch whistling and 22.9% as other qualities (see Table 6:2).

Table 6:2. Participant Characteristics.

S.No	Age (Yrs.)	Sex	TFI score	Tinnitus			Hearing status
				Quality*	Laterality	Duration (Yrs.)	
1	63	M	81.6	R+B	R=L	18	High frequency hearing loss
2	56	M	57.2	HPW	R=L	3	High frequency hearing loss
3	78	M	32.8	R+T	R=L	10	High frequency hearing loss
4	28	F	26.8	HPW+TH	R>L	26	Moderately Severe Hearing loss
5	28	M	58.4	H+B	Centre of head	21	High frequency hearing loss
6	43	M	75.6	R	R=L	6	Normal hearing
7	41	F	39.6	C	L>R	6	High frequency hearing loss
8	55	F	26	R+H	L	6	High frequency hearing loss
9	57	M	38.8	H+B	R=L	10	Normal Hearing
10	50	F	39.2	HU	R>L	20	High frequency hearing loss
11	28	M	80.8	R	R>L	10	High frequency hearing loss
12	54	M	92	HPW	L	11	High frequency hearing loss
13	68	M	30.4	H	R=L	2	High frequency hearing loss
14	72	M	23.6	H+B	Back of head	5	High frequency hearing loss
15	49	F	54	B	L>R	10	High frequency hearing loss
16	62	F	44.8	HU	R	10	High frequency hearing loss
17	52	M	20.8	C	L>R	10	High frequency hearing loss
18	51	M	45.6	R	R=L	30	High frequency hearing loss
19	66	F	44.4	R+H	L>R	30	High frequency hearing loss
20	59	M	65.2	C+H	R=L	5	High frequency hearing loss
21	58	M	38.4	P	R>L	30	High frequency hearing loss
22	70	F	27.2	R	L>R	50	High frequency hearing loss
23	72	M	58	H	R=L	54	Moderate hearing loss
24	45	M	72.8	HPW	L	1.5	High frequency hearing loss
25	49	M	20	H+B	R>L	20	High frequency hearing loss

*Tinnitus Quality codes - R=Ringing, B=Buzzing, H=Hissing, HU=Humming, T=Ticking, HPW=High pitch whistling, TH=Thumping, C =Cicadas, P = Pulsating

Procedure

Experiments were conducted in a sound treated room (ISO 8253-1:2010). Six combinations of stimulus intensity and duration were used in the following incremental order: 1 mA for 10 min, 15 min and 20 min followed by 2 mA for 10 min, 15 min, and 20 min. In total each participant received 6 tDCS stimulations. Participants were blinded to the intensity and duration of the stimulation and were told that the six settings would be presented randomly and these could suppress, elevate or have no effect on their tinnitus. Each participant rated their tinnitus twice before stimulation, and twice after, each tDCS stimulation. The first rating was immediately after stimulation and second rating 10 minutes after the first rating. The rationale for doing the rating twice before stimulation was to document the effect of change in environment (day-to-day environment to sound treated room) on the tinnitus. The second rating, after arriving in the sound treated room, was used as the baseline measure to compare with post stimulation ratings.

Tinnitus suppression was defined as a minimum 1 point decrease in a 10 point loudness-visual analogue scale (LVAS). If, following stimulation, no tinnitus suppression was observed participants received the next stimulation following a 10 minute break (up to a maximum of all 6 stimulations in one session). If total tinnitus suppression was obtained (defined as not able to hear tinnitus at all), participants returned for the next stimulation a minimum of 24 hours following the previous stimulation (to allow for an extinction of effect) (Figure 6:1).

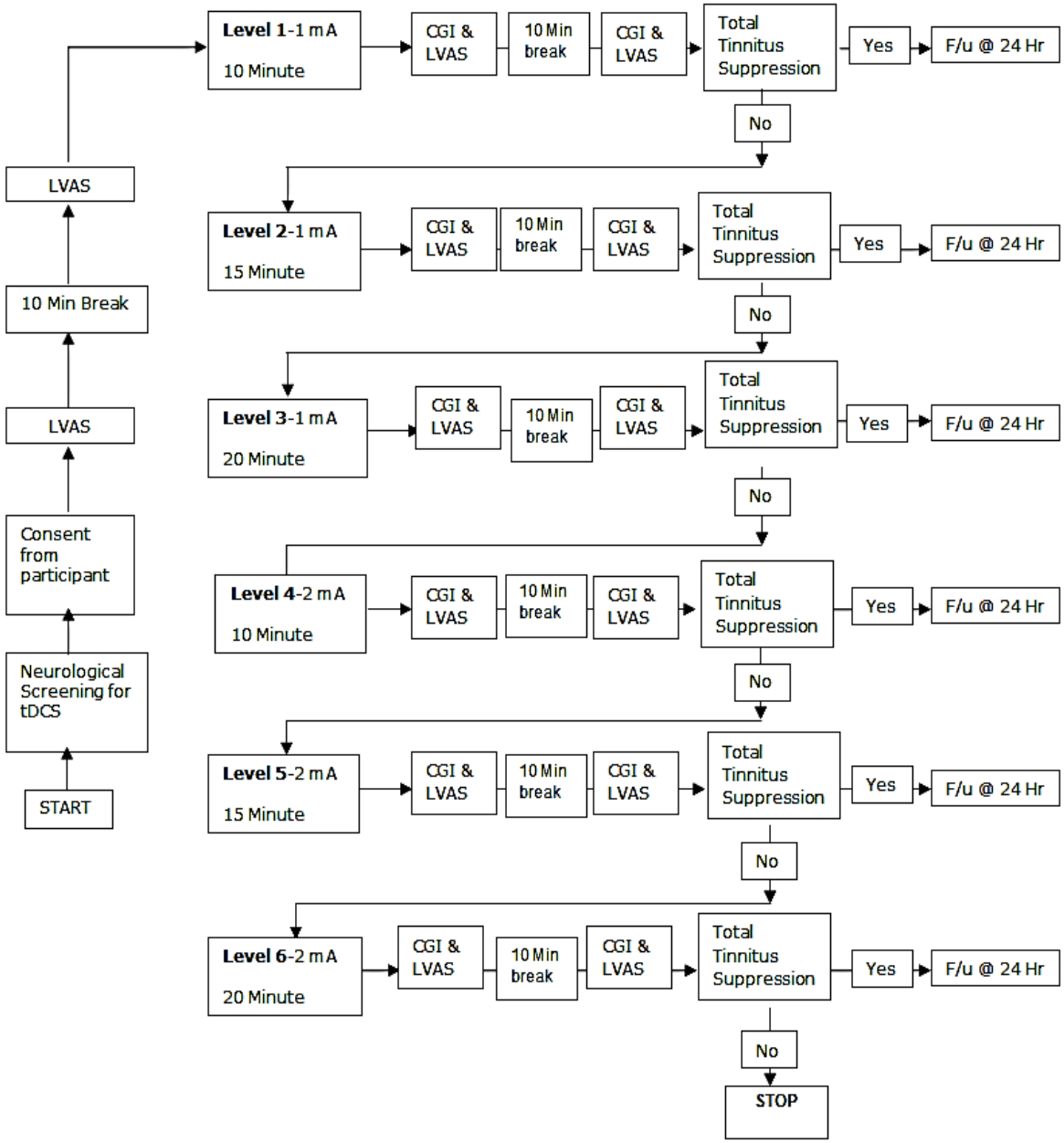


Figure 6:1. Protocol used for tDCS

Clinical Evaluation

A Clinical Global Impression (CGI) measure (517) was used to assess the total change in tinnitus complaint compared to before stimulation. The CGI is a 7 point rating scale where 4 means 'No change', 3 means 'minimally better', 2 means 'much better', 1 means 'very much better', 5 represented 'minimally worse', 6 means 'much worse' and 7 means 'very much worse'. A loudness measurement of tinnitus was made with a 10 point LVAS (518) where 1 to 10 represented a spectrum of tinnitus from very quiet (1) to very loud (10). Patient-reported ratings and any incidental observations were recorded after every stimulation.

Transcranial Direct Current Stimulation

tDCS was applied in accordance with the recommendations of international guidelines (389, 519, 520) (Appendix B). A NeuroConn DC stimulator (Germany) was used for all procedures. The rubber electrodes had a surface area of 35 cm^2 (anode) and 50 cm^2 (cathode) as a smaller stimulating electrode can lead to a more focused stimulation area and a larger reference electrode has minimal physiological effects (378). Electrode sponges were soaked in NaCl solution (0.85%) based on Dundas et al. (16). The anode was placed at LTA and the cathode was placed at the contralateral frontal scalp.These locations were identified using the interenational 10-20 system. LTA was defined as being the halfway point between C3 and T5 (39, 323). The contralateral frontal scalp site was defined as being halfway between F8 and T4 (40). All stimulation protocols included a fade in/out time of 8 seconds. Impedance and voltage were monitored and maintained < 6 kΩ and < 6 V respectively across all the stimulation settings used.

Data Analysis

The CGI ratings and the change in tinnitus loudness rating were analysed using SPSS software. Tinnitus LVAS rating and CGI scores were analysed using two separate three-way repeated measure ANOVAs with, current intensity (1 mA, 2 mA), stimulation duration (10 min, 15 min, and 20 min), and time (immediately and 10 minutes after stimulation) as the factors. A criterion for statistical significance of 0.05 was chosen. Where significant interaction effects were detected, post-hoc comparisons were made using two-tailed paired t-tests. No attempt was made to control the type-1 error rate for

repeated comparisons. Mauchly's test for sphericity was performed to validate interactions between current intensity, stimulation duration, CGI score and rated loudness of tinnitus.

6.5. Results

tDCS was very well tolerated by all participants. Mild headache was reported by two participants after first stimulation (1 mA current intensity and 10 minutes duration). We assumed this was because of tension in the Velcro straps, as the headache resolved within 15 minutes of readjusting the Velcro straps and participants did not experience it further with the rest of the stimulations.

Fourteen (56%) out of 25 participants experienced a transient suppression in tinnitus loudness (Figure 6:2). This suppression was compared with a reference loudness rating obtained in the sound treated room by participants 10 minutes after arrival. For this study suppression in tinnitus loudness was defined as a minimum 1 point decrease in the VAS loudness rating of tinnitus (39, 41).

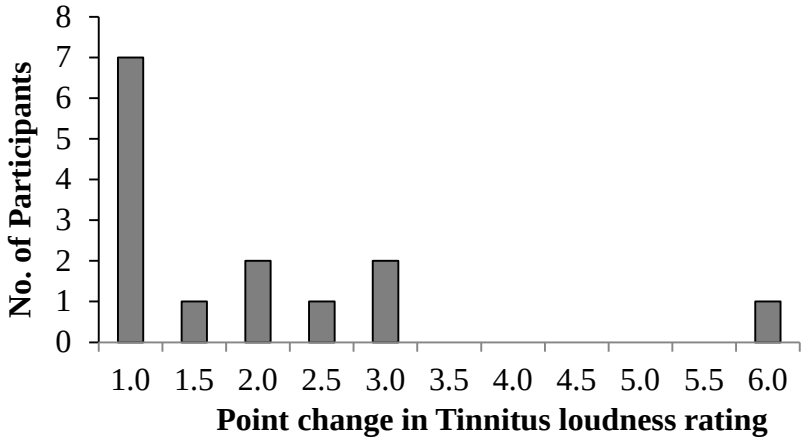


Figure 6:2. Point change in the loudness rating of participants (14 participants out of 25, remaining 11 participants did not experience any change). Point changes were collapsed across both intensities and all durations.

The majority of participants (13) reported a 3 point or less suppression in tinnitus, one participant reported a 6 point suppression on the LVAS. The mean loudness rating before treatment was 5.9 (SD = 2.2) after 1 mA, 10 mins stimulation was 6.1 (SD = 2.3), 1 mA, 15 mins stimulation was 5.8 (SD = 2.3), 1 mA, 20 mins stimulation was 5.7 (SD = 2.3), 2 mA, 10 mins stimulation was 5.5 (SD = 2.2), 2 mA, 15 mins stimulation was 5.2 (SD = 2.1) and 2 mA, 20 mins stimulation was 5 (SD = 2.2). There was no statistically significant difference for the mean loudness rating for any of the stimulation parameters.

Longer term (24 hours) improvement of tinnitus symptoms was reported by 11 participants, 10 reported no change and 4 reported worsening of their tinnitus symptoms (report by emails from participants). The beneficial effects were described as “less annoyance of tinnitus”, “more relaxation” and “good sleep during the night”. Four participants reported negative effects; they felt the tinnitus was more annoying, obvious and loud. An important point to note is that both the positive and negative effects lasted only for 24 hours.

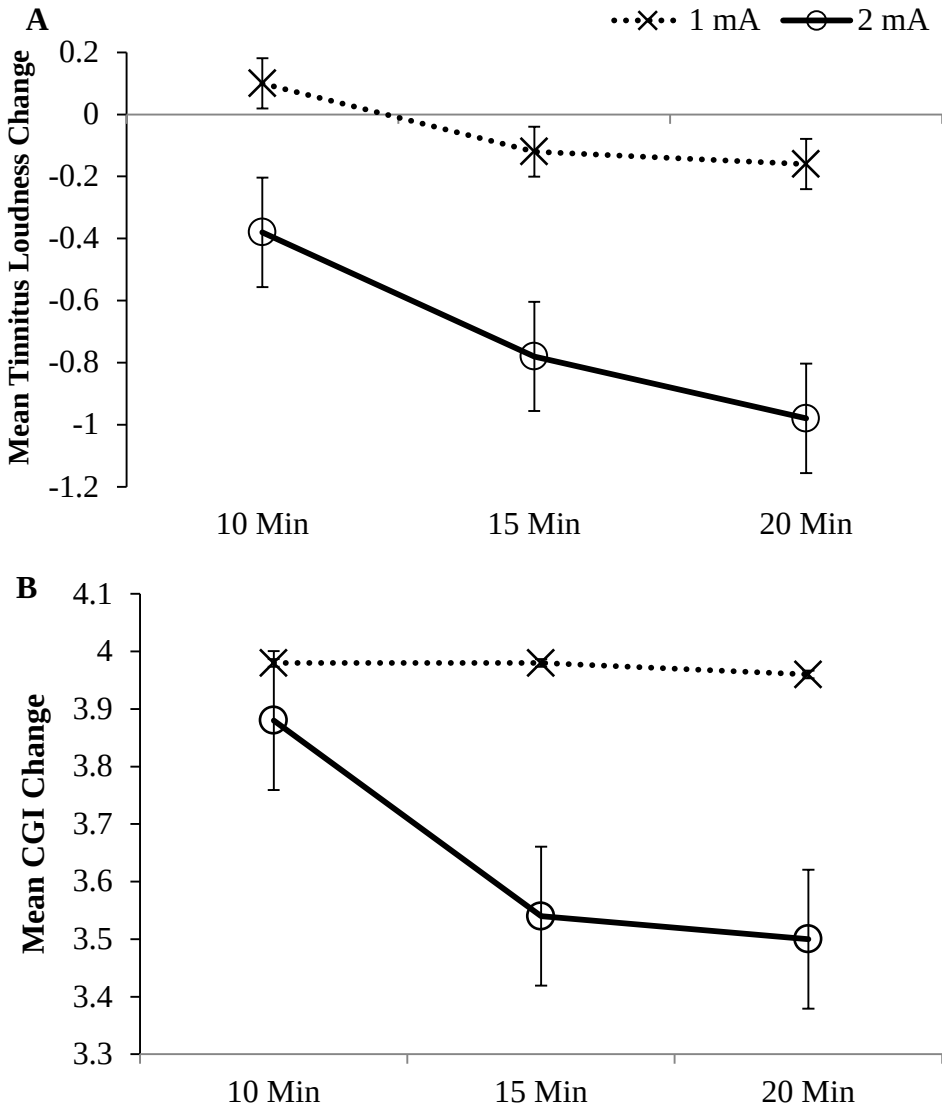


Figure 6:3. A) Interaction between duration and intensity for tinnitus loudness score change. B) - Interaction between duration and intensity for CGI score change. The error bars represent ± 1 standard error of the mean.

Two separate three-way repeated measure ANOVAs were used to investigate tinnitus LVAS ratings and CGI scores. Mauchly’s test for sphericity indicated that the sphericity assumption of the repeated measures ANOVA was met. There was an interaction between

duration and intensity of the stimulus on the change in the rated loudness of tinnitus after stimulation ($F(2, 48) = 4.355$, $p = 0.018$, Figure 6:3 A) and CGI score ($F(2, 48) = 3.193$, $p = 0.050$, Figure 6:3 B). The maximum amount of loudness change was observed following 2 mA stimuli for 20 minutes. There was no three-way interaction between duration, intensity, and time, ($F(2, 48) = 0.673$, $p = 0.472$).

A stimulus intensity of 2 mA delivered for 15 minutes and 20 minutes led to a greater decrease in CGI scores than a 1 mA stimulus intensity of any duration (10, 15, 20 minutes) and a 2 mA stimulus intensity for 10 minutes. There was a significant difference between CGI scores with 2 mA for 10 minutes and 2 mA for 15 and 20 minutes ($p < 0.05$). There was no three-way interaction between duration, intensity, and time ($F(2, 48) = 0.842$, $p = 0.437$).

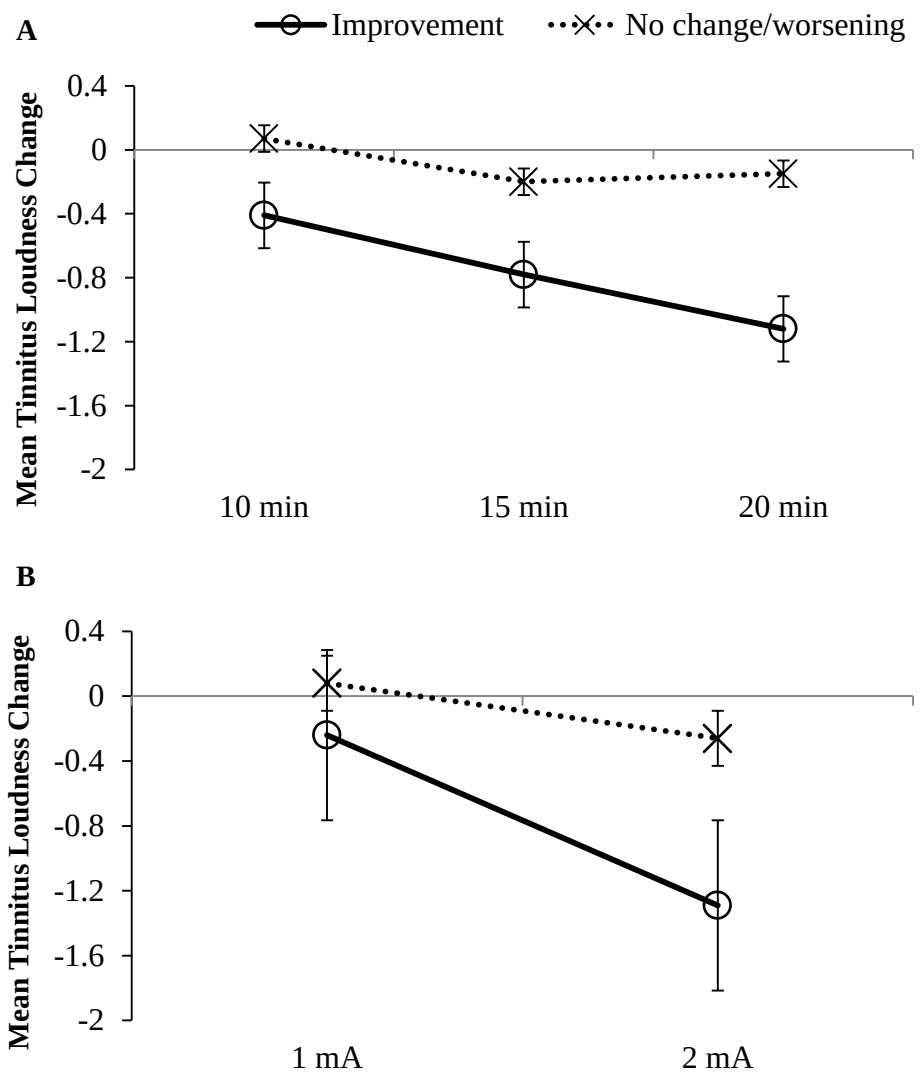


Figure 6:4. A) Interaction between tDCS duration and long term improvement of tinnitus symptoms (overnight) collapsed across intensity. B) Interaction between tDCS Intensity and long term improvement of tinnitus symptoms (overnight).The 11 participants who experienced overnight positive impact were in the 'improvement' group and 'no change/worsening' group was comprised of 4 participants who experienced worsening of tinnitus symptoms and 10 participants who did not experience any change overnight. The error bars represent ± 1 Standard Error of the mean.

There was marginal, but non-significant, evidence of an interaction between long term improvement of tinnitus symptoms (overnight) and duration of stimuli ($F(2,46) = 2.943$, $p = 0.063$, Figure 6:4 A). Overnight improvement in tinnitus appeared to be associated with the longer duration settings of tDCS. The participants who experienced a greater effect of the tDCS in the short term (0 to 10 minutes) were also those whose tinnitus improved longer-term (Figure 6:4 B).

6.6. Discussion

This study is one of the first attempts to optimise tDCS parameters (intensity and duration) for tinnitus suppression, and the first to evaluate the effects of a 2 mA current intensity on tinnitus symptoms. The positive response rates in previous studies investigating LTA as stimulation site were 42% (39), and 35% (40). A slightly higher positive response rate (56%) was obtained in the present study, possibly because a higher current intensity (2 mA) was used. The present results indicate that higher intensity and longer duration anodal tDCS of LTA (2 mA and 20 minutes) more effectively suppressed tinnitus symptoms than low intensity stimulation of any duration (1 mA for 10 min, 15 min, and 20 min). Longer term (overnight) effects were also observed following stimulation: 11 participants reported less annoyance, more relaxation and good sleep, 4 participants felt that they were more aware of their tinnitus and found it to be louder than usual. Interestingly, all participants experiencing positive or negative effects reported a return to baseline after 24 hours. This is in contrast to a previous study reporting transient tinnitus suppression for several days in some participants (40), a result that could be attributed to the altered plasticity induced by tDCS however the exact mechanism remains to be determined.

The present study supports LTA as an effective site of stimulation for tinnitus. Underneath the LTA lies a neural network that probably plays a significant role in tinnitus perception such as areas BA 41, 42 (primary auditory cortex), BA areas 21, 22 (auditory association areas), and part of the limbic system (amygdala and hippocampus) (237, 317, 521). A possible explanation for transient suppression of tinnitus by tDCS could be that depolarisation of neurons at the various cortical and subcortical structures facilitate a reduction in abnormal hyperactivity in the cortex via inhibitory networks and competition (39), and once the impact of stimulation fades away the tinnitus comes back to its usual state. It is likely that the current flow through LTA towards the contralateral frontal site has a widespread impact on various cortical and subcortical structures, [for example, the para-limbic system and subcallosal areas which play a role in long term habituation to tinnitus (154)].

Another interesting point for consideration is that if higher intensity stimulation leads to better results, could current intensities higher than 2 mA be used? A review of studies since 1998 using tDCS in humans across various clinical conditions found that none used a current intensity of greater than 2 mA (383). Hence the current intensity chosen in this

study did not exceed 2 mA. Use of current higher than 2 mA would require a preparatory investigation of safety issues which was beyond the scope of this study.

Potential Limitations

The washout period between the stimulation sessions was 10 minutes which may not have completely eliminated the impact of previous stimulation. It is therefore not possible to rule out a cumulative impact of brain stimulation on tinnitus perception. A relatively large electrode (50 cm^2, cathode) was used on the contralateral frontal scalp; it is possible that this electrode site provided stimulation at a high (2 mA) dose. Although a physiological effect cannot be completely ruled out it is hypothesized to be minimal compared to the intended stimulation site.

Another potential limitation is that no sham control was used. Patients were told before the stimulation that it could suppress, elevate or have no effect on their tinnitus. They were told that 6 different tDCS settings will be randomly used to study the impact of those settings. If suppression were a placebo effect it would be reasonable to expect that participants would have reported changes with the first stimulation settings as well as last, however we did not observe any perceptual change with the initial settings of tDCS, and there was no evidence that participants could distinguish low from high dose tDCS based on the feedback given by them however, they were not specifically asked if they could differentiate between different current intensities in the present study. The majority of the positive effects were observed with higher intensity and longer durations of stimulation. Further sham controlled trials of tDCS use in tinnitus are desirable.

6.7. Conclusions

The current study reveals that anodal tDCS of LTA using a 2 mA current intensity delivered for 20 minutes was the most effective combination of tDCS parameters for transient suppression of tinnitus. tDCS can be a potential clinical tool for patients with tinnitus although more research is needed in this area.

Chapter 7. Priming for Tinnitus Sound Therapy: A Double blind, Sham-control, Randomised Clinical Trial of Transcranial Direct Current Stimulation (tDCS) and Hearing Aids for Tinnitus Management

7.1. Preface

Publication

A modified version of this chapter (to meet the word and figure limits) has been accepted for publication in Neurorehabilitation and Neural Repair, 2013. The latest available impact factor of the journal was 4.495 (2013).

What was undertaken?

This study was a double blind, sham control, randomised clinical trial, investigating the combined impact of multi-session tDCS (5 sessions of anodal tDCS of LTA with 2 mA current intensity and 20 minutes duration) and hearing aids (binaural open fit, used for 6 months) for tinnitus management.

Why it was needed?

Research supports the effectiveness of tDCS for transient tinnitus suppression (few minutes to few days) and longer-term impact of hearing aid use for tinnitus management. This clinical trial was planned to investigate if the combination of tDCS and hearing aids could enhance management.

How does it contribute to the objectives of the PhD?

This is one of the first reported attempts to prime the auditory central nervous system for hearing aid based tinnitus relief. Hearing aids (without tinnitus counselling) irrespective of tDCS lead to significant reduction in tinnitus handicap at 3 months and 6 months of sustained use. The benefits of tDCS combined with hearing aids over hearing aids alone were limited. More research is needed with variations in tDCS protocol to assess its long term effectiveness in priming the auditory system for sound therapy based tinnitus management.

7.2. Abstract

Background/Aims – The perception of sound in the absence of an external sound is tinnitus. Tinnitus can have a severe negative impact on QOL. This study investigated whether multi-session anodal tDCS of the LTA might enhance sound therapy from hearing aids.

Methods - Forty participants with a mean age of 54 years, experiencing chronic tinnitus (minimum two years) completed a seven-month long double-blind clinical trial. Participants were randomised into two groups: control (sham tDCS) and experimental (tDCS). Each group underwent multisession (five consecutive sessions with 24 hour wash out period) anodal tDCS (2 mA intensity and 20 minutes duration) of the LTA, followed by hearing aid use for six months. The impact of tDCS and hearing aid use on tinnitus was assessed using questionnaires (primary measure (TFI)) and psycho-acoustic tinnitus measurements.

Results –There was a significant reduction in the overall TFI score with time ($F [2, 37] = 11.9$, $p = 0.0001$) for both the groups. Similar patterns were seen for secondary measures. tDCS appeared to have a positive effect on MMLs but not questionnaire responses.

Conclusions – After three months of hearing aid use, there were significant improvements in tinnitus which were sustained six months of use. The hearing aid effects were mainly independent of tDCS. Further investigations of tDCS or other neuromodulators priming the auditory system for sound therapy based tinnitus treatments are warranted.

7.3. Introduction

Tinnitus is defined as the perception of sound that does not occur in the environment (522). Multiple overlapping and parallel brain networks such as the auditory cortex, somatosensory cortex, memory area, perception, salience, and distress networks are believed to be involved in tinnitus perception and reaction (146). Tinnitus can lead to anger, frustration, poor communication, tension, lack of sleep (5, 6), and negatively influences the overall QOL of its sufferers (3, 4). Tinnitus has also been linked to suicidal tendencies (7, 8).

Traditionally, hearing aids have been used for tinnitus management (46) and more recently various neuromodulation techniques such as rTMS (323, 334), neurofeedback (293, 302), TENS (357, 360), and tDCS (39-43, 523) have been used with varying degrees of success. In this study, we hypothesised that priming of the central nervous system might achieve a stronger and faster acting benefit from hearing aids. Priming is an effect in which exposure to a stimulus influences a response to a later stimulus. Priming has been used in stroke patients for better clinical results (56, 57). Facilitating ipsilesional motor cortex excitability prior to motor practice with the paretic upper limb leads to greater functional improvements than motor practice alone (57). According to Norena's central gain model of tinnitus, a reduction of central gain and peripheral drive might facilitate tinnitus management (15). We hypothesised that tDCS might assist in reducing central gain of tinnitus signal by facilitating the peripheral stimulation effects of hearing aids.

tDCS is a painless, safe and non-invasive neuromodulation technique (379, 382). Either the anode or cathode can be positioned over the target area, to facilitate or suppress cortical activity (372-374). Anodal tDCS of LTA (39, 40, 523) and DLPFC (41-44) has been effective in transient tinnitus suppression. The LTA montage stimulates various cortical and subcortical areas, which, either by competition or inhibition results in the reduction of abnormal hyperactivity caused by tinnitus (39). Underneath the LTA lies the primary auditory cortex (BA 41, 42), auditory association areas (BA 21, 22), and parts of the limbic system (amygdala and hippocampus) which are thought to be parts of the proposed neural network involved in tinnitus (237, 317, 521).

Studies undertaken in the area of tinnitus and tDCS have usually investigated the effect of a single session (40, 382) or two sessions (39) of tDCS on tinnitus. Frank et al. (42) and

Faber et al. (43) investigated whether multiple sessions of bifrontal tDCS of DLPFC could lead to longer-lasting reduction of tinnitus. The study conducted by Faber et al. (43) was a double-blind, sham-controlled, cross-over design comprised of six sessions of bifrontal tDCS (current intensity 1.5 mA and duration 20 minutes) with an 8-week wash-out period, which observed a reduction in tinnitus annoyance with no change in tinnitus loudness. Frank et al. (42) used six sessions of bifrontal tDCS, 1.5 mA current intensity, and 30-minutes duration, and reported positive results on numeric ratings of: tinnitus loudness, discomfort, and unpleasantness, however no effect was seen in tinnitus questionnaire scores. Both Frank et al. (42) and Faber et al. (43) stimulated the DLPFC with 1.5 mA current intensity and there is a possibility that not enough current reached other cortical and sub-cortical areas (auditory cortex and limbic system) due to the focal nature of the electric field and current density distribution offered by the DLPFC montage (390). Recently, Shekhawat et al. (523) conducted a dose–response study to optimise tDCS parameters for tinnitus and proposed 2 mA current intensity and 20 minute duration as the most favourable intensity and duration settings for transient tinnitus suppression.

Tinnitus is usually associated with hearing loss (11, 12) and hearing aids have been commonly used for tinnitus management for the last six decades (46). Shekhawat et al. (47) conducted a scoping review of the role of hearing aids for tinnitus management, and found that although the evidence supporting hearing aid use was poor in quality, there was a large quantity of evidence for the benefits of hearing aid use for tinnitus. There are several proposed mechanisms of effect for which hearing aids might assist in tinnitus management. These mechanisms include: masking tinnitus, reversing tinnitus related cortical reorganisation (45, 439, 440), providing compensation for the degree of hearing loss, down regulating central gain (54, 439), and reducing the communication stress associated with hearing loss (214, 437, 438). Hearing aid use can lead to long lasting tinnitus reduction, but its full effectiveness is often only achieved after 6-12 months of use (48, 50, 51).

It is well-established that long-term hearing aid use can improve tinnitus. It has also been shown that tDCS can lead to transient tinnitus suppression. Modifying the stimulation parameters by using a higher current intensity, and changing the site of stimulation from DLPFC to LTA, could improve the effectiveness of tDCS. We hypothesised that multiple sessions of anodal tDCS of LTA would augment the plasticity of the brain to facilitate greater hearing aid benefit in a shorter period of time.

7.4. Methods

This study was approved by the University of Auckland human participant's ethics committee and was registered as a clinical trial on the Australian New Zealand Clinical Trial (Registry number – ACTRN12612000277842, http://www.anzctr.org.au/).

Participants

Forty Participants (mean age 59.18 years, ranging from 45 years to 76 years) were recruited through the University of Auckland Hearing and Tinnitus Clinic and researchstudies.co.nz. 'Research studies' is an online participant recruitment portal that connects research volunteers with research opportunities. Inclusion criteria for the participants were chronic tinnitus (more than two years), aidable hearing loss with no previous experience of hearing aid use, and a minimum score of 25 on the TFI (496). Volunteers were excluded if they had any contraindications for undergoing tDCS (personal or family history of seizures, metal and electronic implants, pregnancy, heart conditions, brain surgery, and others) as screened by a neurologist (Appendix A). Twenty volunteers not meeting the inclusion criteria were excluded. Written informed consent was provided by all participants as per the Declaration of Helsinki.

Research Protocol

This was a double-blind, sham-controlled, randomised clinical trial. The first author undertook all stimulation and data analysis before being unblinded. A minimisation method was used by the third author to randomise participants to a treatment group (20 participants) or control group (20 participants). Randomisation was based on age, gender, TFI score, tinnitus duration, and severity of tinnitus. Both groups underwent five sessions of brain stimulation (real or sham tDCS) followed by hearing aid fitting and use for six months. Multiple evaluations were carried out at the following time points: one month pre-treatment (1st baseline), one week pre-treatment (2nd baseline), before and after each tDCS session (five tDCS/sham sessions), before hearing aid fitting, three months and six months following hearing aid use (Figure 7:1 and Table 7:1).

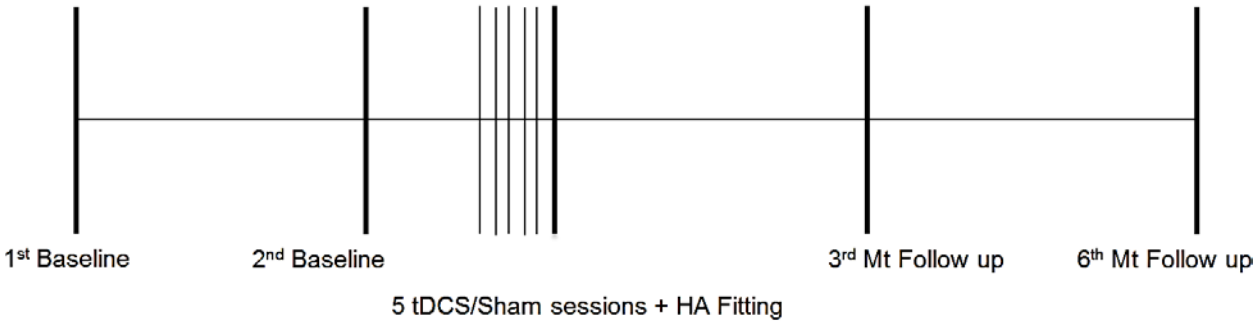


Figure 7:1. Protocol for data collection. Multiple evaluations were undertaken at the following time points: 1 month pre-treatment (1st baseline), 1 week pre-treatment (2nd baseline), before and after each brain stimulation session (five tDCS/Sham sessions), before hearing aid fitting, three months and six months following hearing aid use.

Table 7:1. Outcome assessments undertaken across the 7 month long clinical trial.

	1st Baseline	**2nd Baseline**	**During 5 stimulation sessions**	**Before hearing aid fitting**	**3 Mt Fu**	**6 Mt Fu**
Questionnaires used	TCHQ, HADS, TFI, TSNS, THQ.	TFI, TSNS, THQ, HHI	VAS-loudness, CGI	TFI, TSNS, THQ and HHI	HADS, TFI, TSNS, THQ and HHI	HADS, TFI, TSNS, THQ and HHI
Psychoacoustic tinnitus measurement (MML/ tinnitus pitch/ tinnitus loudness)	-	MML/tinnitus pitch/ tinnitus loudness	-	MML/ tinnitus pitch/ tinnitus loudness	MML/ tinnitus pitch/ tinnitus loudness	MML/ tinnitus pitch/ tinnitus loudness

The progress of the clinical trial through various phases (enrolment, allocation, follow-up and analysis) is shown in Figure 7:2 as per the consolidated standards of reporting trials protocol proposed by Schulz et al. (524).

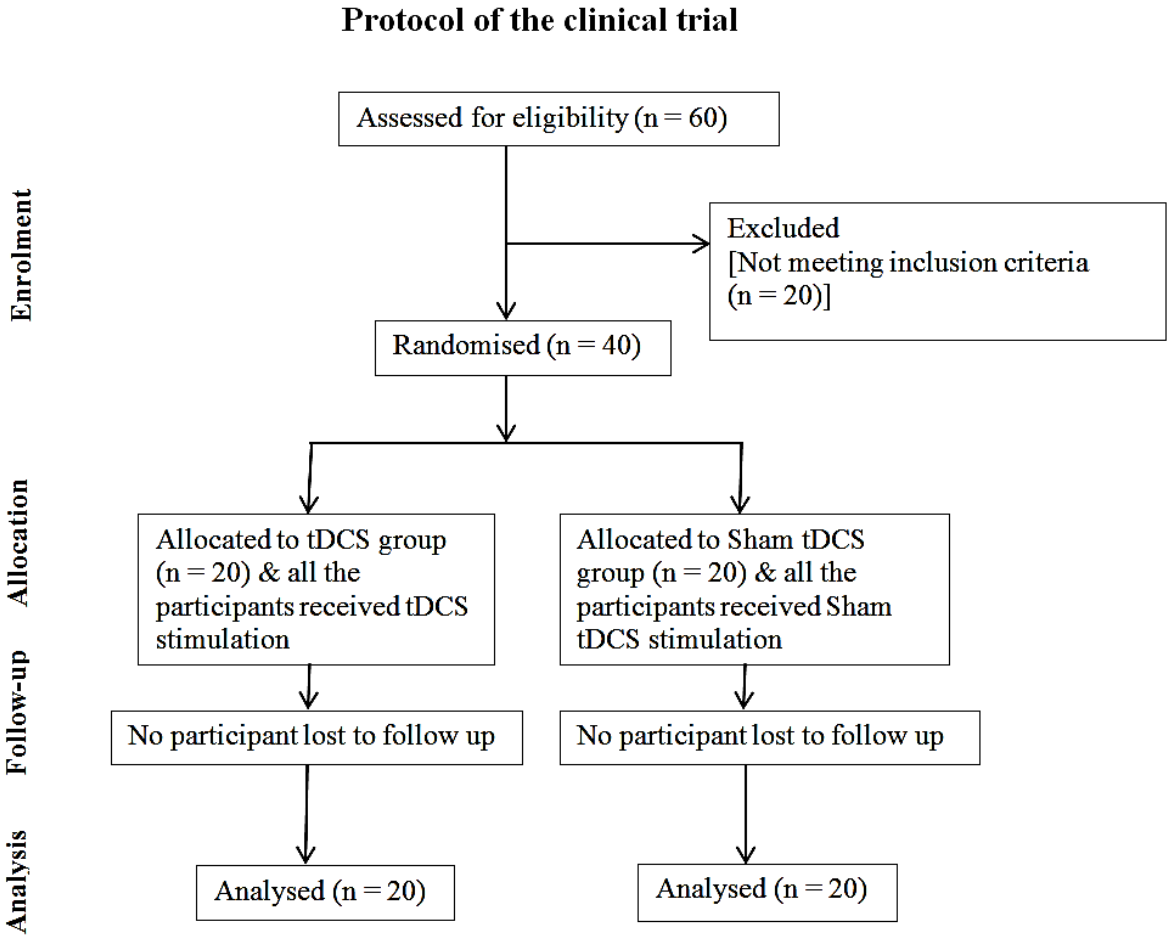


Figure 7:2. Flow diagram of the progress through the phases (enrolment, allocation, follow-up and analysis) of the randomised clinical trial of tDCS and Sham tDCS groups.

Hearing Assessment

Hearing assessment was conducted in a sound treated room (ISO 8253–1:2010). Pure tone audiometry (0.25–16 kHz) was undertaken using a two-channel audiometer (either GSI - 61, Grason Stadler; or AC40, Interacoustics). Measurements (0.25–8 kHz) were made using standard ear phones (TDH - 50P; Telephonics) or insert headphones (E.A.RTONE 3A) and high frequency (8–16 kHz) headphones (Sennheiser HDA 200). Audiometry was obtained using the modified Hughson-Westlake procedure (424). Tympanometry was undertaken using a GSI (Grason Stadler) Immittance audiometer, and DPOAEs were measured using an ILOV 6 (Otodynamics, Ltd.) OAE analyser.

Questionnaires Used for Clinical Evaluation

The following questionnaires: tinnitus case history questionnaire (TCHQ), TFI, tinnitus severity numeric scale (TSNS), hospital anxiety and depression scale (HADS), THQ,

hearing handicap inventory (HHI), CGI, and the VAS were used. The HADS is a 14-item, self-report screening scale developed to detect the presence of anxiety and depression symptoms (525). There are seven anxiety symptoms and seven depression symptoms, and each item uses a 4-point Likert type scale: never (0), sometimes (1), most of the day (2), almost all day (3). The maximum score for both scales (anxiety and depression) was 21 points. Scores 0–7 would be considered normal, 8–10 would indicate mild anxiety and/or depression and ≥11 would indicated clinically relevant anxiety and/or depression. The TCHQ is a standard tinnitus case history questionnaire developed during the first Tinnitus Research Initiative meeting in 2006 (495). It consists of 35 items (14 essential and 21 highly desirable) and assists in collecting in-depth information about participant's tinnitus. The THQ was developed and psychometrically validated by Kuk and colleagues (477). Two factors were examined: the physical, emotional, and social consequences of tinnitus (Factor 1), and the hearing ability of the patient (Factor 2). The TFI is a relatively new self-report questionnaire, which has documented validity for scaling the severity and negative impact of tinnitus and for measuring treatment-related changes in tinnitus (496). The TFI has 25 items and 8 sub-scales (intrusiveness, sense of control, cognitive, sleep, auditory, relaxation, quality of life, and emotional). The HHI is a 25-item hearing handicap self-assessment scale composed of two sub-scales: emotional and social/situational (526). It has high internal consistency reliability and low standard error of measurement. The TSNS is a 6-item scale (527), where the first item assess the overall impact of tinnitus on a 5-point scale where '1' is 'not a problem' and '5' is 'a very big problem' and the other five items assess related problems induced by tinnitus (loudness of tinnitus, uncomfortable, annoyance, ability to ignore and unpleasantness of tinnitus) on a 10-point scale where 1 represents the least amount of problem and 10 represents the maximum amount of trouble. The CGI measure (517) was used to assess the total change in tinnitus complaint compared to before brain stimulation. The CGI is a 7-point rating scale which ranges from 1 (very much better) to 7 (very much worse). A loudness measurement of tinnitus was made with a 10-point loudness VAS (518) where 1 to 10 represented a spectrum of tinnitus from very quiet (1) to very loud (10). Patient-reported ratings and any incidental observations were recorded at every assessment.

Psychoacoustic Tinnitus Assessment

Tinnitus pitch, loudness & MML were assessed using testing software (© The University of Auckland). Tinnitus pitch was assessed throughout the test frequency range of 0.25–16

kHz using a 2AFC method, in which pairs of tones were presented based on the configuration of audiogram and perceptual feedback. High frequency circumaural headphones (Sennheiser HDA 200) were used for the entire pitch matching procedure. Participants were asked to identify the tone which matched the best with their tinnitus pitch. Each tone was presented at a sensation level of 15 dBSL. Once the settings for a given pair of tones were established, the two tones were presented in an alternating manner until the participant indicated which one was closest to the pitch of their tinnitus. Pitch match was then compared to tones 1 octave above and below to rule out octave confusion. The measurement was repeated until two repeatable responses were obtained.

The sensation level (loudness, dBSL) of tinnitus was measured by presenting sound at the tinnitus pitch and gradually increasing its intensity. Participants were instructed to indicate the level at which the loudness of the presented tone was equal to that of their tinnitus. This was repeated three times and the average of three trials was taken as the loudness match.

The MML measurement was similar to that of loudness measurement except that participants were instructed to indicate the level at which the presented sound masked or covered their tinnitus perception. This was repeated three times and the average of three trials was taken as the MML. MML was recorded in sensation level (dBSL).

Transcranial Direct Current Stimulation

tDCS was applied in accordance with the recommendations of international guidelines (389, 519) (Appendix B). A NeuroConn DC stimulator (Germany) was used for tDCS. The rubber electrodes had a surface area of 35 cm^2 (anode) and 50 cm^2 (cathode) as a smaller stimulating electrode can lead to a more focused stimulation and a larger reference electrode has minimal physiological effects on proximal structures (378). NaCl solution (0.85%) was used to soak the electrode sponges (16). The anode was placed above the LTA (halfway between C3 and T5 (39, 323)) and the cathode was placed at the contralateral frontal scalp (halfway between F8 and T4 (40)) identified using the international 10–20 system. Impedance and voltage were monitored and were less than 5 kΩ and less than 5 V respectively across all stimulation settings used. The NeuroConn DC stimulator had a ‘study mode’ where input codes were used (the researcher was blinded to these codes) and the settings generated were either a sham or actual stimulation. In both cases the display of the device showed the same settings (2 mA current intensity and 20

minutes duration). The settings used for sham-stimulation were a fade in time of 8 seconds, followed by 30 seconds of direct current, followed by a fade out time of five seconds (followed by no further stimulation, just impedance control). This was as per previous recommendations for effective sham setting for tDCS and did not lead to any significant effect on the underlying neuronal activity (379, 383). In the real stimulation the constant current was maintained through the duration of stimulation.

Hearing Aid Fitting

All the participants were fitted bilaterally with GN ReSound Live 571 open-fit hearing aids on the day following the final brain stimulation session (irrespective of which group they were in). A modified DSL(I/O) v.5.0 was used as the amplification prescription target (528) and the fitting was modified according to participant's comfort and preference. Care, maintenance and use of the hearing aids was explained to participants during the hearing aid fitting session and they were recommended to use the hearing aids for a minimum of 8 hours per day in a variety of everyday listening situations. Participants were told to contact the researcher if they required any further assistance before the next follow up (after 3 months). No tinnitus counselling was provided to either group. Hearing aids were well received. One participant lost one of his hearing aids and it was replaced.

Data Analysis

The data were analysed using the statistical analysis system (SAS) version 9.3. Outcome variables measured at follow up (post tDCS, three month and six month) were analysed using a mixed-effects model for repeated measures (SAS 9.3 MIXED procedure). Group, visit (as categorical variable), group and visit interaction, tinnitus duration, age, tinnitus severity and baseline TFI were assessed as fixed effects, baseline measure as a covariate, and participants were assessed as a random effect in the mixed-effects model. The within-subject errors were modelled using an unstructured (co)variance structure. The Kenward-Roger method was used to estimate the denominator degree of freedom for fixed effects. A generalised linear mixed effects model technique (SAS 9.3 GLIMMIXED procedure) was used to analyse ordinal variables (TSNS, CGI and VAS-Tinnitus loudness) measured at follow up (post tDCS, three month and six month). Multinomial distribution with cumulative logit link function was used. Measurements from the same person were analysed as if the measurements were taken from the same cluster. T-tests were used to assess if the participants in the two groups differed on the baseline measures (hearing

threshold, age, gender, handedness, family history, tinnitus onset and duration). Delta values were calculated to plot graphs (change in TFI and THQ) and for measures where two baselines were not measured (HHI and psychoacoustic tinnitus measures such as MML, tinnitus pitch and loudness).

7.5. Results

The tDCS and sham tDCS groups did not differ significantly in their baseline measures (mean age, gender, family history of tinnitus, tinnitus severity, duration, onset, DPOAE, real ear aided response (REAR), laterality of tinnitus, handedness) indicating that both groups were well balanced (Table 7:2). The overall hearing status of participants in the two groups is shown in Figure 7:3.

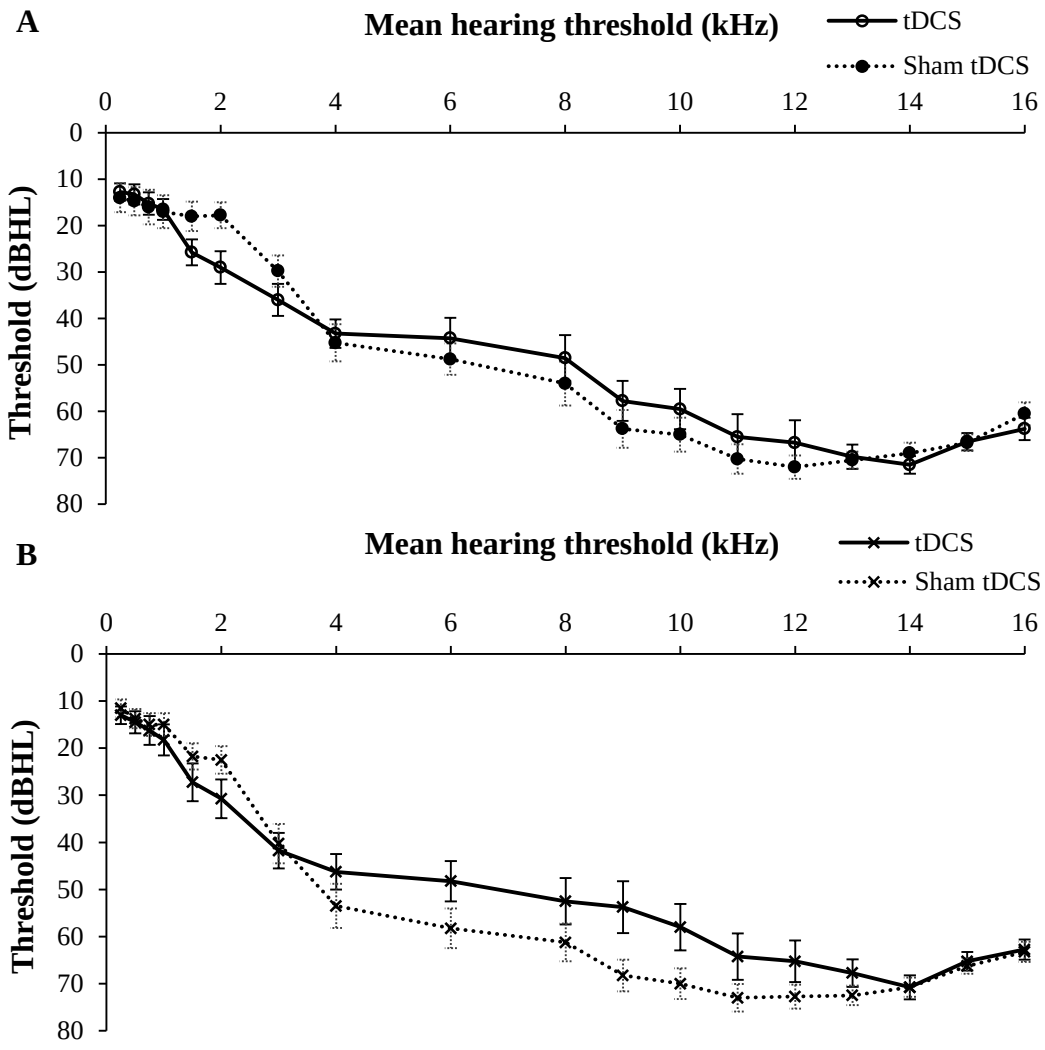


Figure 7:3. The mean hearing thresholds of right (A) and left ear (B) for participants in sham tDCS and tDCS groups. The error bars represent ± 1 standard error of the mean.

Table 7:2. Profile of research participants in sham tDCS and tDCS group. Both the groups were well matched and there was no significant difference between the two groups on all the mentioned parameters.

	Sham tDCS	**tDCS group**
Mean Age Years	58.5 (SD 6.4)	59.85 (SD 9.6)
Male	18	18
Female	2	2
Right - Handed	16	18
Left-Handed	3	1
Ambidextrous	1	1
Positive Family History of Tinnitus	7	8
Gradual Beginning of Tinnitus	15	17
Abrupt Beginning of Tinnitus	5	3
Mean Tinnitus Duration (Years)	16.55	19.78
'A' Tympanogram	27	26
'Ad' Tympanogram	13	14

Participants in both the groups had a sloping mild to severe sensorineural hearing loss and the two groups did not differ from each other significantly except for the right ear at 2 kHz, where the sham tDCS group had significantly better hearing than the tDCS group [$t(38) = -2.51$, $p < 0.05$] and for left ear at 9 kHz [$t(38) = 2.25$, $p < 0.05$] and 10 kHz [$t(38) = 2.04$, $p < 0.05$], where the sham tDCS group had significantly worse hearing than the tDCS group. All the participants had aidable hearing loss with no history of hearing aid use. Participants were fitted with binaural open fit hearing aids using the DSL (I/O) v0.5 prescriptive procedure. The two groups (sham tDCS and tDCS) did not differ from each other in the overall REAR measured with the inputs of 65 dB, 55 dB and maximum power output measured with a 80 dB input. There were individual variations in hearing aid use in both groups. Eleven participants in the tDCS group and the 14 in the sham tDCS group used hearing aids for eight or more hours per day. The mean hearing aid use for tDCS and sham tDCS group was 7.97 hours/day and 9.35 hours/day respectively; however this difference was not statistically significant.

During the five stimulation sessions, participants in both groups rated their tinnitus loudness using the VAS on a 10 point rating scale. Loudness rating was undertaken three times in each session. The first rating was done immediately after arrival and then after 10 minutes the second rating was done, the rationale for doing the rating twice before stimulation was to document the effect of change in environment (day-to-day environment to sound treated room) on the tinnitus. The second rating, after arriving in the sound treated room, was used as the baseline measure to compare with post stimulation ratings

(third rating) which was done immediately after the stimulation. The average loudness rating for both the groups is shown in Figure 7:4.

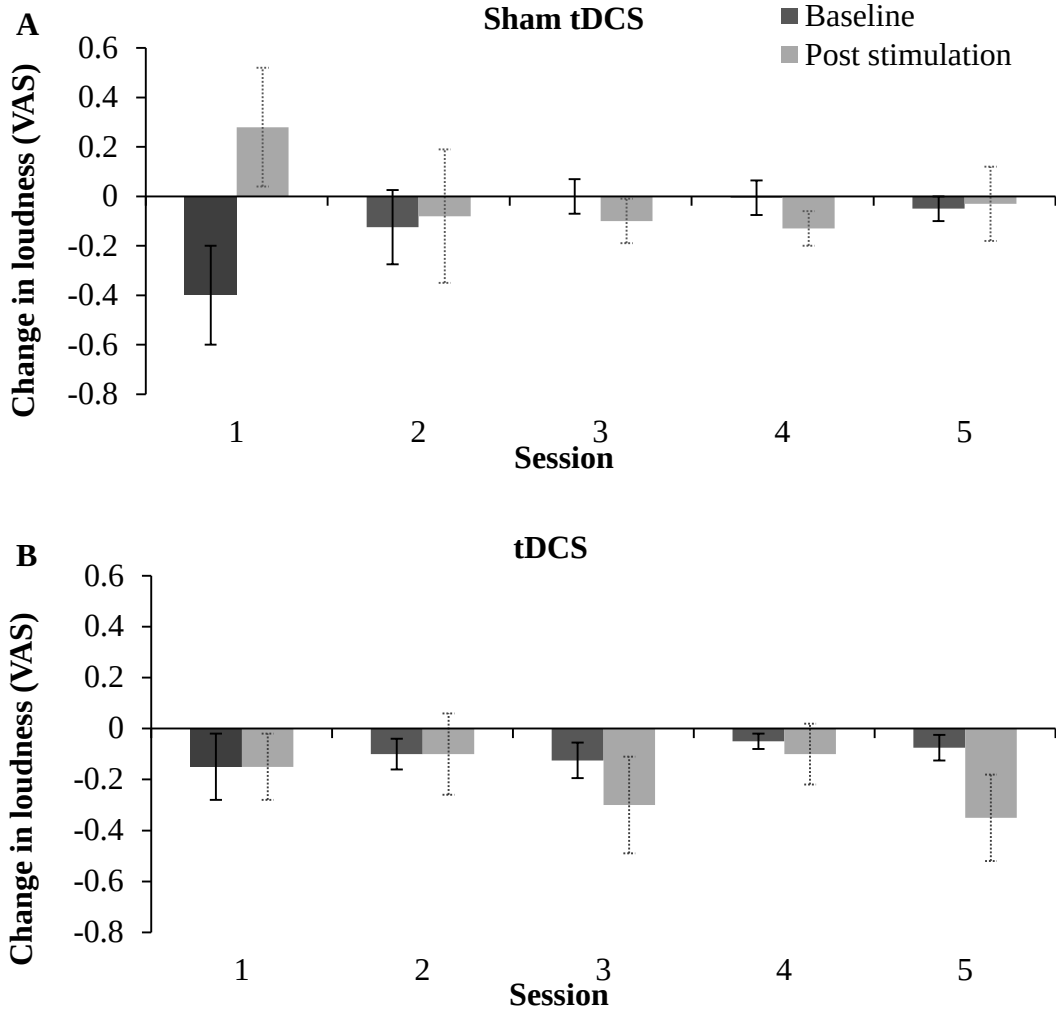


Figure 7:4. Change in loudness in sham tDCS group (A) and tDCS group (B) followed by five sessions of stimulation. Change in loudness was calculated as follow: baseline change was calculated by subtracting loudness rating immediately after arrival (baseline 1) from loudness rating after 10 minutes of arrival (baseline 2); post stimulation loudness change was calculated by subtracting loudness rating immediately before stimulation from loudness rating immediately after stimulation. Positive values represent increase in tinnitus loudness (worsening), negative values represents reduction in tinnitus loudness (improvement). The error bars represent ± 1 standard error of the mean.

There was no statistically significant difference between the two groups for loudness change during the five stimulation sessions. However there was a consistent trend of reduction in tinnitus loudness with maximum loudness change occurring after the fifth stimulation session for the tDCS group. The sham tDCS group failed to show a consistent reduction in tinnitus loudness; during the first session the loudness increased (tinnitus worsened) after stimulation, during the second to fourth sessions there was some reduction

in tinnitus loudness and finally after the fifth session the post stimulation rating was worse than the pre-stimulation baseline.

The CGI was measured after completion of each stimulation session to document participant's perception of the effectiveness of stimulation on their tinnitus (Figure 7:5).

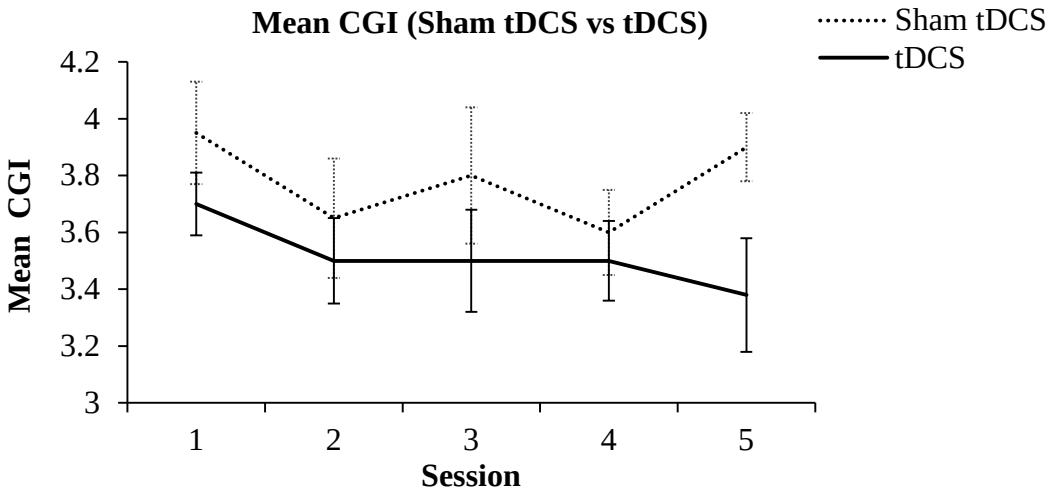
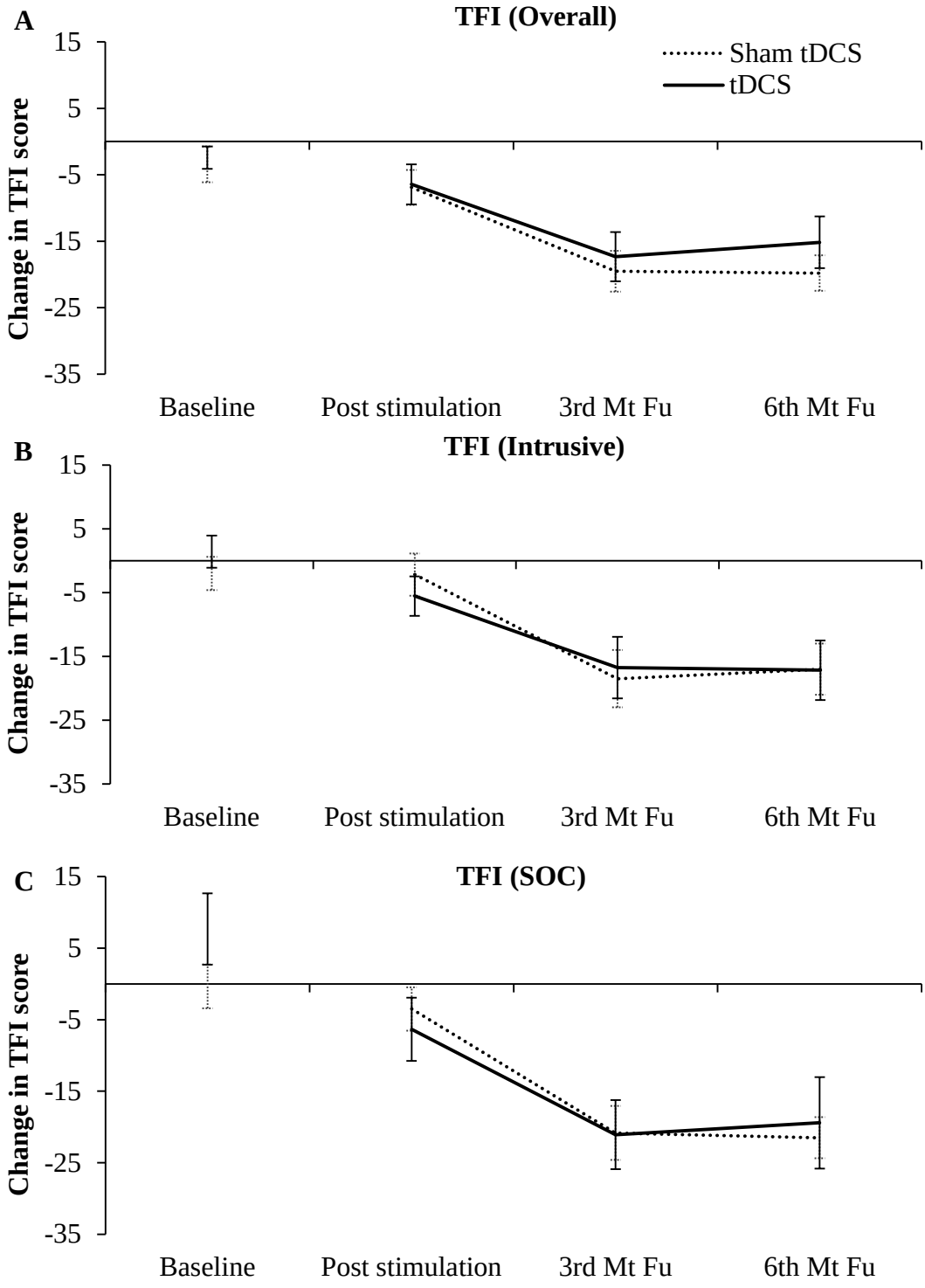


Figure 7:5. Mean CGI for sham tDCS and tDCS group during five sessions of stimulation. On the CGI rating scale point 4 represents 'no change' and point 3 represents 'minimally better'. The error bars represent ± 1 standard error of the mean.

There was no significant difference in the two groups in their mean CGI ratings, although the mean CGI ratings for tDCS group decreased with the lowest rating at the end of the fifth stimulation session. The average ratings for the sham tDCS group were close to '4' reflecting no change.

The primary outcome measure used in this trial was the TFI and there was a significant reduction in the overall TFI score with time ($F [2, 37] = 11.9$, $p = 0.0001$) (Figure 7:6). The maximum amount of reduction happened after 3 months of hearing aid use. There was a marginal, but not statistically significant, difference between sham tDCS and tDCS groups for the overall change in TFI score with the sham tDCS group showing more change ($F [1, 52.3] = 3.14$, $p = 0.08$) compared to tDCS group at the three month and six month follow up after hearing aid fitting.


A
TFI (Overall)
Sham tDCS
tDCS
Change in TFI score
15
5
-5
-15
-25
-35
Baseline
Post stimulation
3rd Mt Fu
6th Mt Fu
B
TFI (Intrusive)
Change in TFI score
15
5
-5
-15
-25
-35
Baseline
Post stimulation
3rd Mt Fu
6th Mt Fu
C
TFI (SOC)
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15
5
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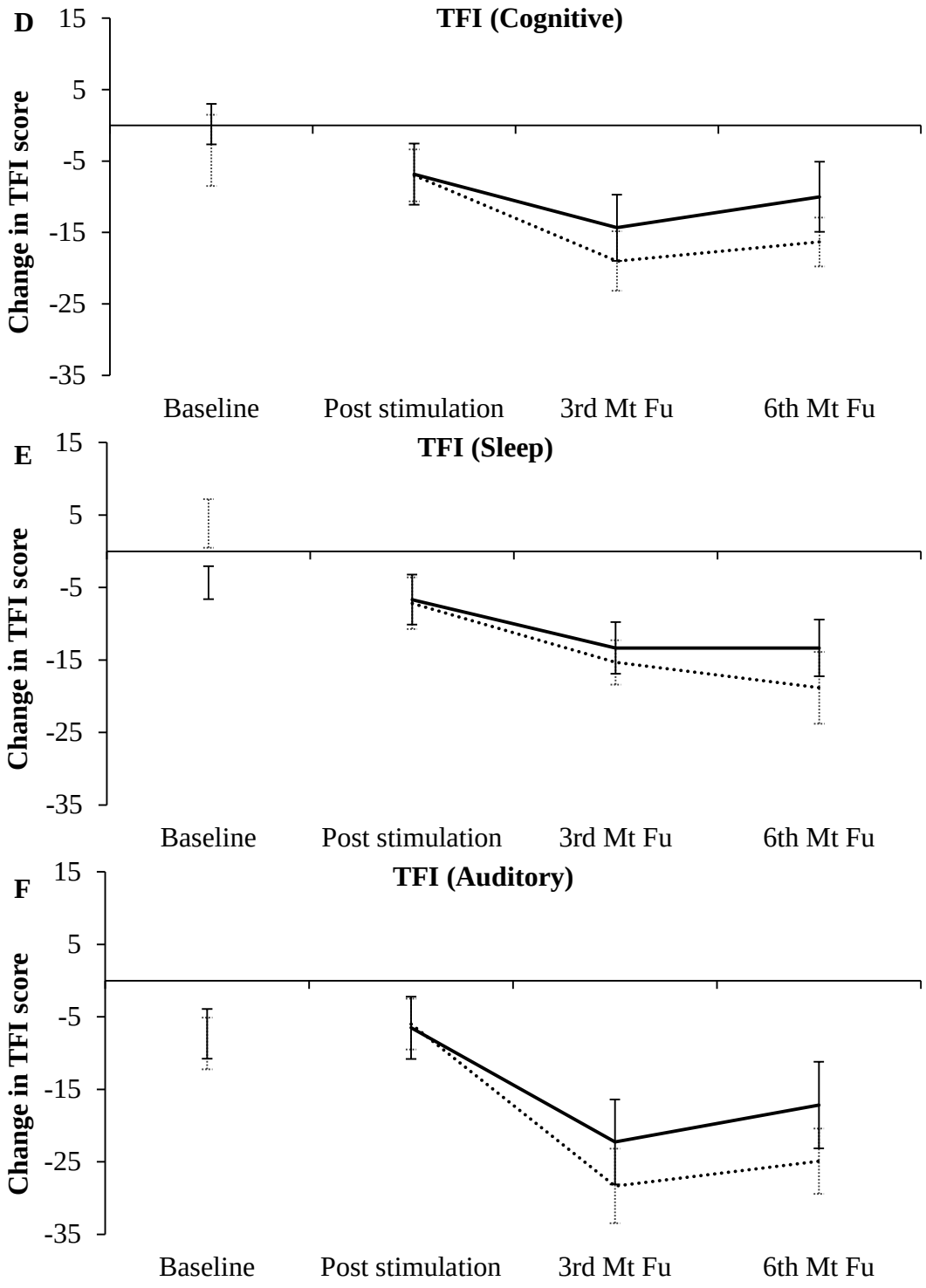
-25
-35
Baseline
Post stimulation
3rd Mt Fu
6th Mt Fu


D
TFI (Cognitive)
Change in TFI score
15
5
-5
-15
-25
-35
Baseline
Post stimulation
3rd Mt Fu
6th Mt Fu
E
TFI (Sleep)
Change in TFI score
15
5
-5
-15
-25
-35
Baseline
Post stimulation
3rd Mt Fu
6th Mt Fu
F
TFI (Auditory)
Change in TFI score
15
5
-5
-15
-25
-35
Baseline
Post stimulation
3rd Mt Fu
6th Mt Fu

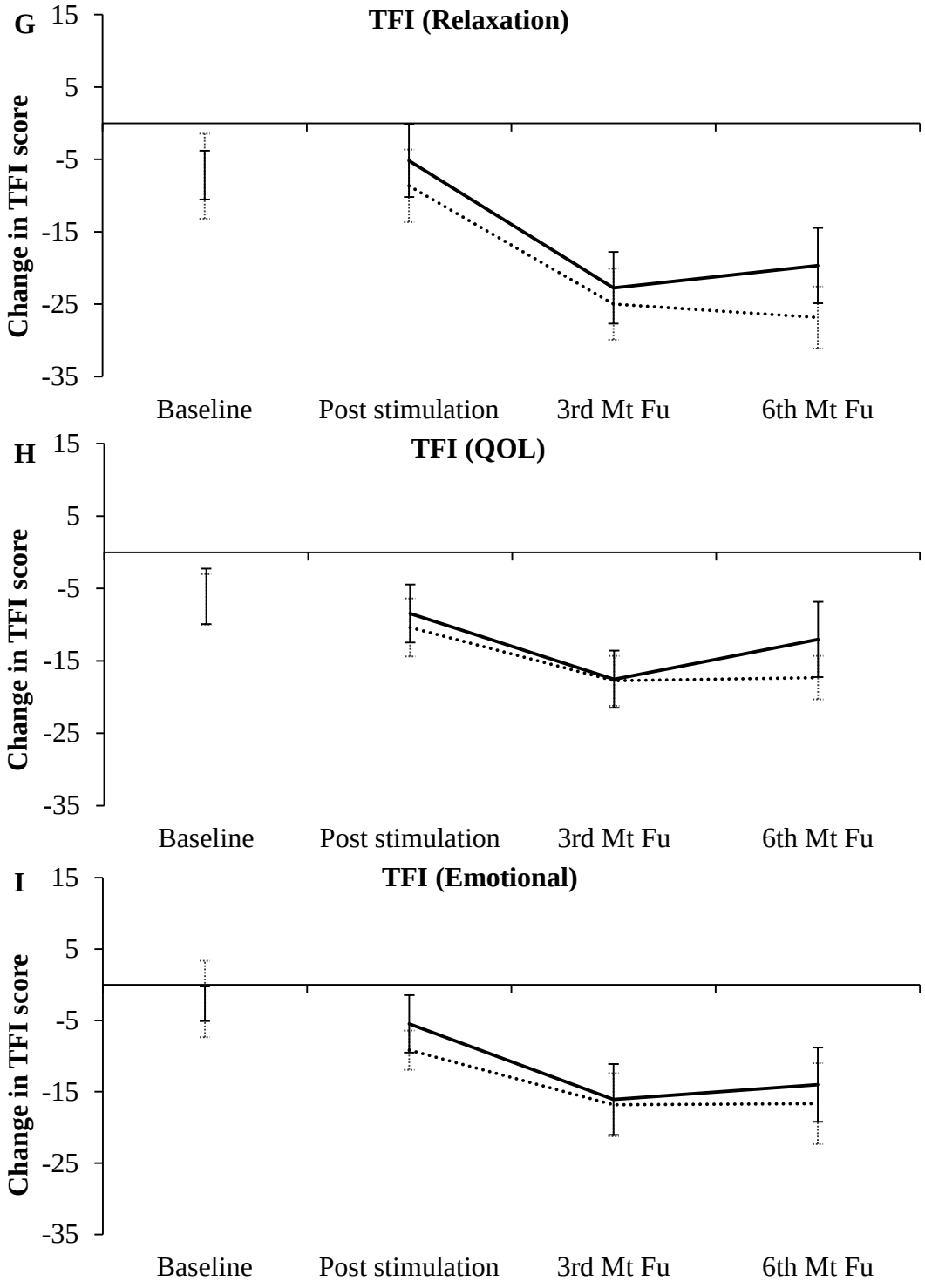


Figure 7:6. Change in TFI baseline, post stimulation, 3rd month and 6th month follow up in sham tDCS and tDCS group. TFI has an overall score and eight sub scales as follow: (A) Overall, (B) Intrusive, (C) Sense of control [SOC], (D) Cognitive, (E) Sleep, (F) Auditory, (G) Relaxation, (H) Quality of life [QOL], (I) Emotional. Change in TFI baseline was calculated by subtracting first baseline TFI obtained one month prior to stimulation session from second baseline TFI obtained one week before starting stimulation. Change in TFI (post stimulation, 3rd month and 6th month follow up) was calculated by subtracting the second baseline TFI obtained one week before starting stimulation from post tDCS, 3rd month and 6th month follow ups. Positive values represent worsening in tinnitus symptoms, negative values represents improvement in tinnitus symptoms. The error bars represent ± 1 standard error of the mean.

Along with the TFI, several other questionnaires (THQ, HHI, TSNS, HADS) were used as secondary measures. The change in THQ was correlated with change in TFI. There was a marginal difference between the two groups on THQ factor 1 (physical health, emotional status and social consequences) (F [1, 32] = 3.26, p = 0.08), however no statistically significant difference was observed on factor 2 (hearing difficulty) (Figure 7:7).

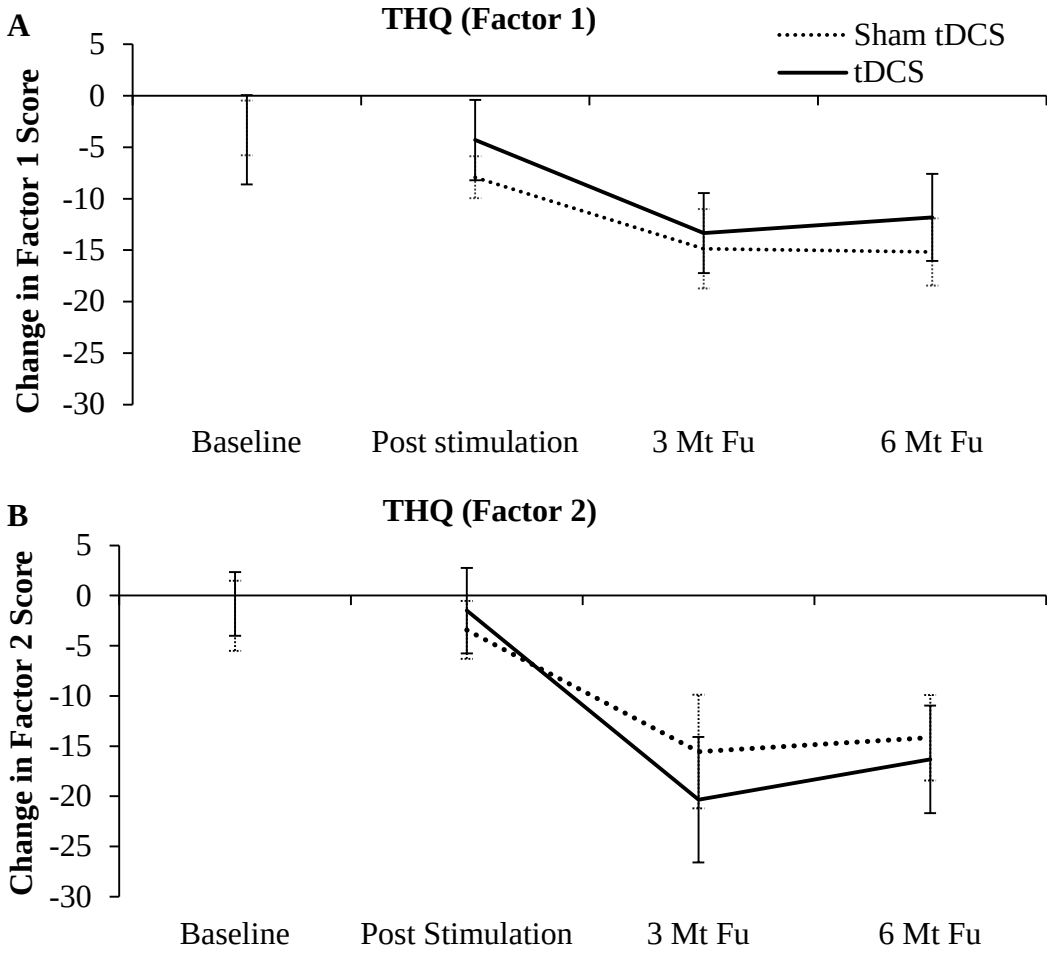


Figure 7:7. Change in THQ baseline, post stimulation, 3rd month and 6th month follow up in sham tDCS and tDCS group (A) factor 1, (B) factor 2. Change in THQ baseline was calculated by subtracting first baseline THQ obtained one month prior to stimulation from second baseline THQ obtained one week before starting stimulation. Change in THQ (post stimulation, 3rd month and 6th month follow up) was calculated by subtracting the second baseline THQ obtained one week before starting stimulation from post stimulation, 3rd month and 6th month follow ups. The error bars represent ± 1 standard error of the mean.

For the HHI-social factor (Figure 7:8), there was a significant reduction in the score with time (F [2, 37] = 4.99, p = 0.01). A similar result was seen for the HHI-emotional factor as well (F [2, 37] = 8.02, p = 0.001). The change in TFI scores (both groups) were significantly correlated with change in HHI scores (r was 0.59 for social, 0.56 for emotional at < 0.001 level) after 3 months of hearing aid use (Figure 7:9).

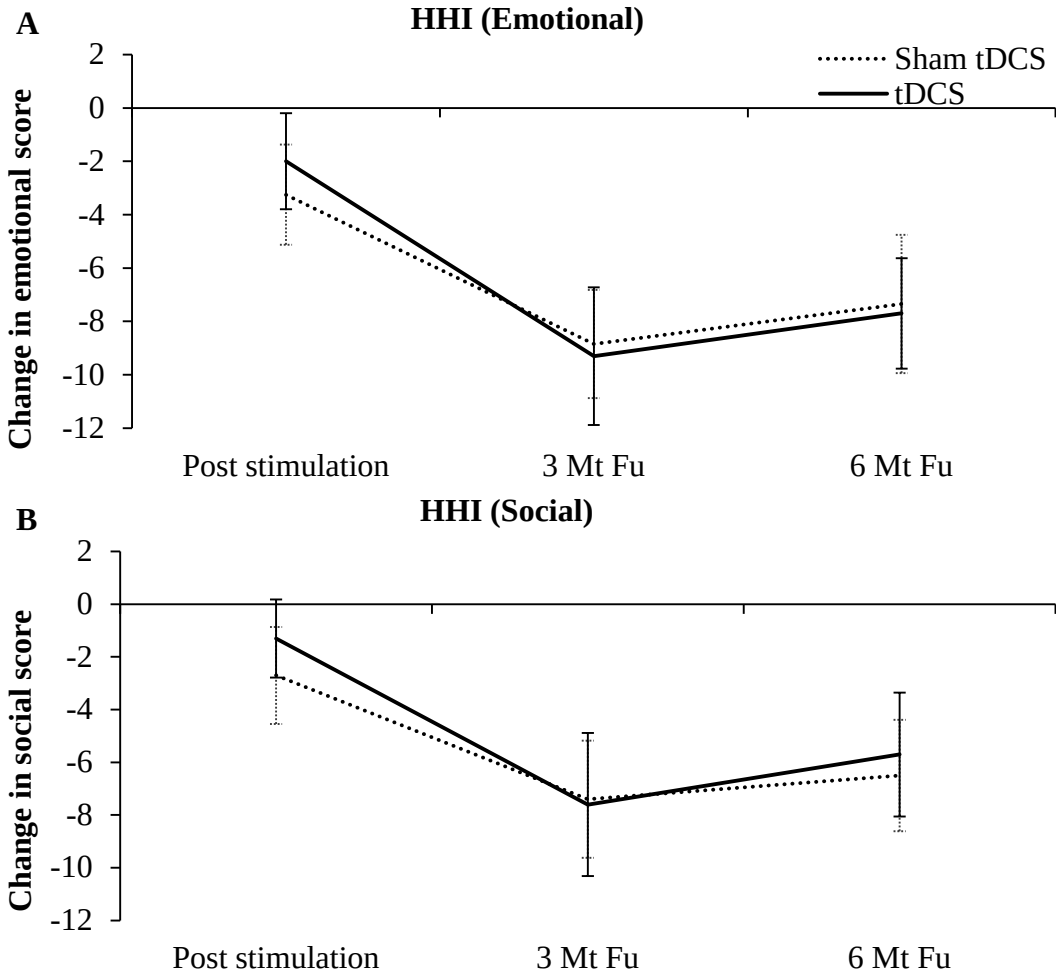


Figure 7:8. Change in HHI post stimulation, 3rd month and 6th month follow up in sham tDCS and tDCS group (A) emotional, (B) social. Change in HHI (post stimulation, 3rd month and 6th month follow up) was calculated by subtracting the baseline HHI obtained one week before starting stimulation from post stimulation, 3rd month and 6th month follow ups. The error bars represent ± 1 standard error of the mean.

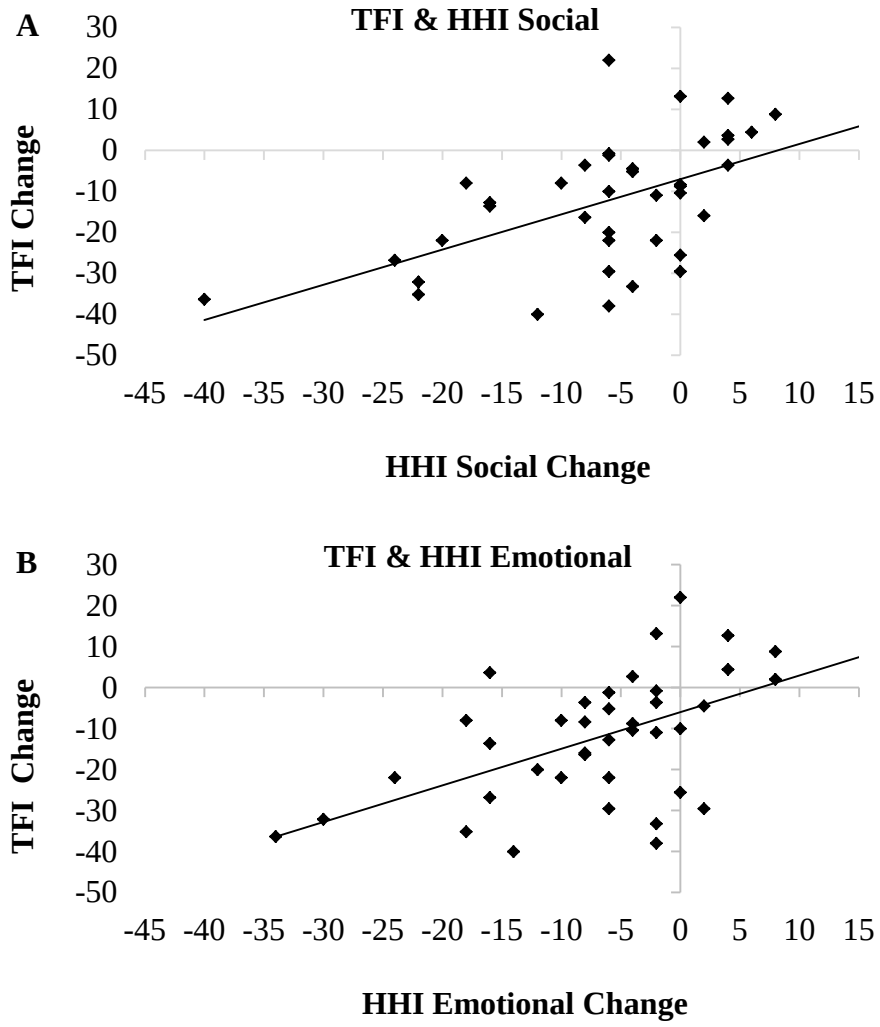
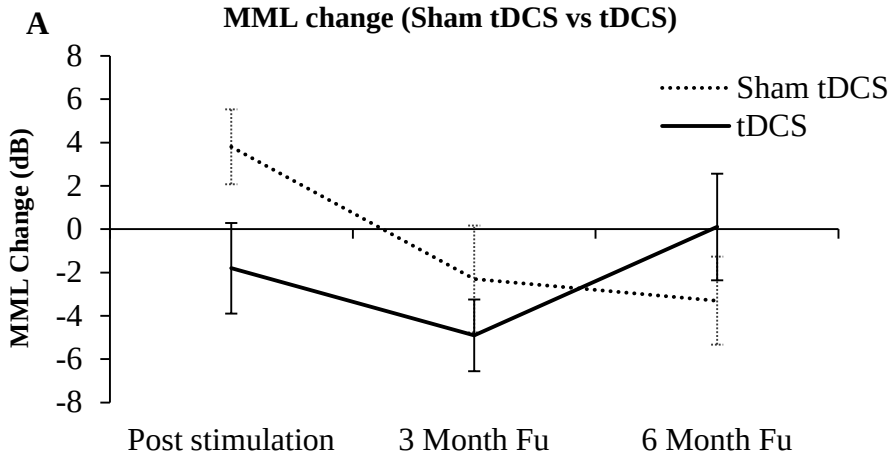
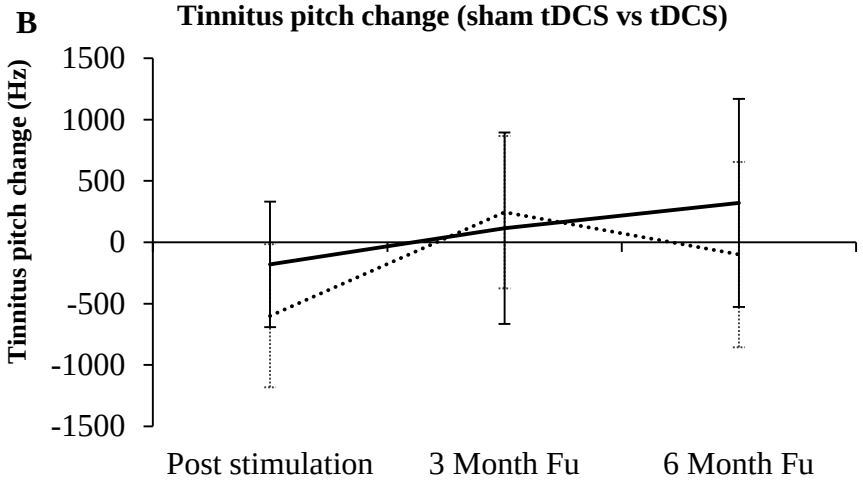


Figure 7:9. Scatterplot for change in TFI scores with change in HHI social (r = 0.59) (A) and emotional (r = 0.56) (B) factors before hearing aid fitting and after 3 month hearing aid use, for 40 participants in this study. Change in TFI and HHI was calculated by subtracting the 3 month follow up scores (after using the hearing aid for 3 months) from the post-stimulation scores (before hearing aid fitting).

For the TSNS, there was a significant reduction in the overall tinnitus score with time ($F [2, 106] = 10.96$, $p < 0.0001$). There was a significant interaction between the factors group and time for MML ($F [2, 37] = 5.43$, $p = 0.008$). This interaction arose because the measured MML for the two groups was different at the three time points; for the treatment group, MML reduced post-treatment and at the 3 month follow up (relative to baseline), while the control group MML was higher than baseline immediately after treatment, then reduced at the two follow-up time points (Figure 7:10 A). There was a significant interaction between the two groups and three time points (post stimulation, three month and six month follow up) for measured tinnitus loudness ($F [2, 37] = 4$, $p = 0.02$) (Figure 7:10 C).





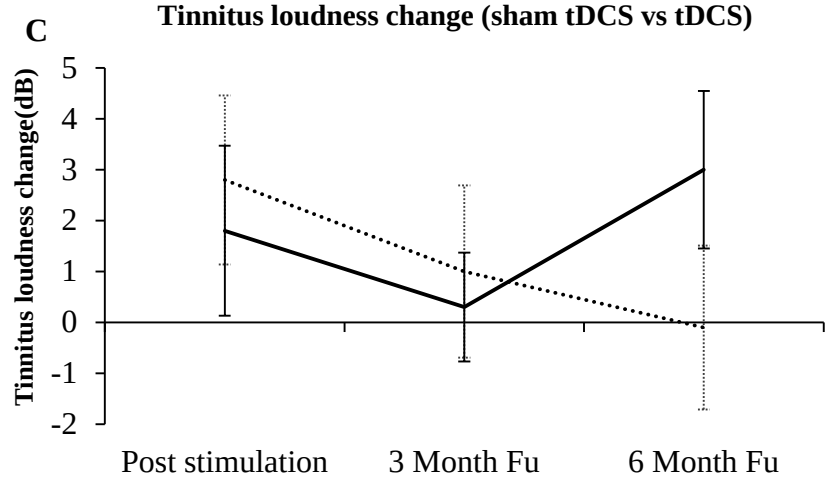


Figure 7:10. Change in MML (A), tinnitus pitch (B) and tinnitus loudness (C) post stimulation, 3rd month and 6th month follow up in sham tDCS and tDCS group. Changes in MML, tinnitus pitch and loudness was calculated by subtracting baseline values measured before starting stimulation sessions from post stimulation, 3rd month and 6th month follow up values. The error bars represent ± 1 standard error of the mean.

In our trial we did not find any significant difference between the tDCS and sham tDCS group in the overall HADS scores for anxiety and depression. All the recruited participants in this study had normal scores on the depression and anxiety scales of HADS at baseline.

7.6. Discussion

The main finding of this study was that hearing aids can significantly reduce the negative impact of tinnitus on quality of life. There was some preliminary evidence suggesting that tDCS may have resulted in lower MMLs (reducing the amount of sound need to cover tinnitus), however such results need to be replicated. It was hypothesised that multiple sessions of tDCS might diminish peripheral drive; by modulating neural correlates of tinnitus at various cortical and sub-cortical areas possibly through a top-down approach (529, 530); hearing aids were used for six months in an attempt to reduce central gain, likely through a bottom-up approach, by increasing afferent activity diminished by hearing loss.

The use of hearing aids led to a significant reduction in tinnitus handicap as measured with the TFI. The maximum amount of benefit was achieved after 3 months of hearing aid use, unlike many other studies which observed maximum benefit after 6 to 12 months of hearing aid use (48, 50, 51). The three sub-scales of TFI showing the largest reductions after hearing aid use were: auditory, sense of control and relaxation. This suggests that along with providing benefit in hearing, the hearing aids were also beneficial in inducing relaxation and a sense of control for coping with tinnitus. The THQ also reduced in a similar manner to the TFI. The sham tDCS group experienced a 9.53 point reduction in THQ score, which is comparable to masking alone (Henry et al. (531)) and counselling alone (Searchfield et al. (51)). The tDCS group experienced a 13.94 point decrease. This study addressed a number of short comings of previous tinnitus focused hearing aid studies (47). In the present study hearing aids were programmed specially for tinnitus instead of optimising them for communication only (49, 483), this trial was a controlled trial, purely assessing the impact of hearing aids and tDCS not a combination of hearing aids with counselling (164, 447) and multiple measurement methods including psycho-acoustic tinnitus assessment were used providing convergent validity (49, 215). All participants were fitted with binaural hearing aids of the same design. The hours of hearing aid use were recorded using data-logging, enabling control for participant compliance.

We hypothesised that tDCS might improve the effectiveness of hearing aids; for the majority of measures this hypothesis was not supported. The one measure showing a difference between tDCS and sham groups three months following hearing aid fitting was the MML. The MML was at its lowest for the tDCS group at the three month follow up, while the maximum reduction for the sham tDCS group was measured at six months follow up. A possible interpretation is that tDCS hastened the maximum suppression possible by sound achieved by the hearing aids, but this advantage disappeared after six months. The likely reason for the long term effect of tDCS on MML but, no effect on tinnitus loudness, is that the neuromodulation may affect attention, so that sounds more easily disrupt tinnitus perception, but loudness (the signal) remains unaffected, research is needed to confirm this hypothesis.

The change in measured tinnitus loudness mirrored the MML change (i.e. was in the opposite direction). An increase in measured tinnitus loudness for both the groups could be due to the attention drawn to their tinnitus as suggested by adaptation level theory (229) rather than a true increase in tinnitus magnitude. While the hearing aids effects on tinnitus dominated any improvement due to tDCS there were trends towards reduction in subjective tinnitus loudness, mean CGI and MML with tDCS.

All the brain stimulation sessions were well tolerated and none of the participants reported any discomfort or side effects. So far only two clinical studies (42, 43) have investigated the impact of multi-session tDCS on tinnitus perception. Both these studies have used DLPFC as the site of stimulation and neither of them found any lasting impact of tDCS on tinnitus perception.

In our trial all the six items of the TSNS (overall, strong, uncomfortable, annoying, ignore and unpleasant) reduced with a maximum effect after three months of hearing aid use, however the two groups (tDCS and sham tDCS) did not differ from each other significantly. The post brain stimulation differences in the ratings were small. The hearing aids had a strong effect; any tDCS effects may have been “washed-out” by larger effects of the acoustic stimulation. There was large variability between participants in the results, which has also been seen in other trials (39-42) and it could potentially be due to various forms of tinnitus and the likelihood of differences in the neural networks and connections in participants with tinnitus (400).

All the participants in our trial had hearing loss; the tDCS group had significantly worse hearing at 2 kHz in the right ear (in the conventional frequency range) compared to the sham tDCS group. Fregni et al. (39) found an inverse relationship between severity of hearing loss and responsiveness towards tDCS. The slightly greater hearing loss in our tDCS group and three years higher average tinnitus duration (though not statistically significant) may have reduced the magnitude of benefit from the brain stimulation sessions. Further trials could be undertaken on tinnitus sufferers with normal or near normal hearing to explore the potential of this effect.

This trial is the first reported attempt to prime the auditory centre nervous system for hearing aid based tinnitus relief. It showed little beneficial effect of priming; however it's too early to comment on the potential effectiveness of tDCS for priming the auditory system for change given that only one tDCS stimulation protocol was used. Different options for tDCS need to be explored for use with hearing aids. One possibility could be to try variations in the spacing of tDCS sessions, such as every two to four weeks along with hearing aid use. This protocol might increase the possibility of regular modulation of brain plasticity that could be exploited by hearing aid use. The impact of tDCS and acoustic stimulation on residual inhibition (RI; brief tinnitus suppression following cessation of the masker (223)) could also be investigated to explore whether the use of tDCS could prolong RI. RI usually lasts for less than a minute, but the brief respite patients can have from their tinnitus can be strong (complete absence of tinnitus) (532). Research investigating the impact of tDCS on RI might provide further insight into the better utilisation of tDCS with sound therapy.

7.7. Conclusions

Hearing aids (without tinnitus counselling) resulted in significant improvement in tinnitus related QOL after three months of use. The hearing aid benefits were independent of tDCS. This trial did not reveal any statistically significant benefit of tDCS over hearing aid use alone. Further investigations of tDCS, or other neuromodulation techniques, may find that priming the auditory system for hearing aid use can be clinically beneficial. Different tDCS protocols along with hearing aids and/or other auditory stimulation should be explored to further test the hypothesis that priming may improve hearing aid effectiveness.

Chapter 8. Discussion

This thesis explored a novel approach for tinnitus management, by combining techniques that directly (tDCS) and indirectly (hearing aids) modulate the plasticity of brain. The primary findings of this thesis were: hearing aids, irrespective of tDCS, significantly improved tinnitus related QOL; tDCS had a positive effect on MML and provided transient suppression of the subjective tinnitus loudness, without adding significant benefits to QOL achieved with the aids alone. Five studies were conducted as part of this thesis. The major findings of these studies are discussed which also include implications for clinical practice and research.

Chapter 3 was a pilot study with the aim of finding the relationship between the audiogram and tinnitus pitch. A retrospective evaluation of 192 participants with chronic tinnitus revealed the significance of high frequency audiometry as a part of tinnitus assessment battery. All the participants had normal to mild hearing loss in the conventional audiometric frequency range (0.25 to 8 kHz); however the level of hearing loss increased up to a severe degree at extended high frequencies (9 to 16 kHz). Seventy-three percent of participants matched their tinnitus pitch between 8 to 16 kHz. Since tinnitus pitch is significant for programming hearing aids (49, 431) and as a predictor for tinnitus management (137), it would seem essential to conduct high frequency audiometry for all tinnitus participants as part of routine clinical practice. There have only been a few studies that explore the relationship between tinnitus pitch and edge frequency (409, 425-427) or the frequency with maximum degree of hearing loss (135, 138, 426); with these studies producing mixed results. None of these studies conducted extended high frequency audiometry, which is likely to influence the findings, especially the calculation of the edge frequency and frequency of maximum hearing loss. This study was one of the first attempts to explore the relationship between tinnitus pitch and the frequency where the hearing loss is 50 dBHL (T50). The reason a relationship between tinnitus pitch and T50 was proposed, was due to T50 being the level of hearing loss associated with the beginning of damage to IHCs (421). IHCs provide most of the afferent input to the auditory areas in the brain (533) and damage to them (beginning at approximately hearing thresholds of 50 dBHL) may contribute to tinnitus pitch as a consequence of central plastic changes at the frequency of initial deafferentation. Cochlear deafferentation is believed to be the peripheral driver for central adaptation mechanisms creating tinnitus (115). A statistically significant positive correlation was found between tinnitus pitch and T50 ($r = 0.161$, $p < 0.030$).

Since tinnitus pitch is essential for tinnitus assessment and management, finding the best tinnitus pitch predictor could assist in better management of tinnitus. Findings of this study may be translated to a better and quicker tinnitus pitch matching protocol. Based on existing practice, tinnitus pitch matching is considered a tedious task with questionable reliability (410), as it is a time consuming process and can be tiresome for participants. If we could build a tinnitus pitch assessment protocol based around T50, pitch prediction at T50 could not only make the process of tinnitus pitch matching less time consuming, but also more reliable. However, further research is needed to confirm this hypothesis. Another possible implication of this study could be its impact on hearing aid fitting protocol for participants with tinnitus. While programming hearing aids, attention should be given to ensure enough gain at T50. This will increase the likelihood of stimulation reaching the region of tinnitus pitch match and might assist in better gain adaptation or reversing tinnitus related cortical reorganisation (431). Limited output of hearing aids in the high frequency range is certainly a hurdle for participants with T50, falling in high frequencies beyond the range of hearing aids output. However this might change with further research and advancements in hearing aid technology. Another possibility for such participants could be the use of sound generators to deliver extended high frequency outputs, and exploring the possibility of extended high frequency stimulation and its impact on tinnitus perception. It would be too early to comment on the implication of T50 on a tDCS protocol, however, there have been some early indications that the severity of hearing loss is inversely linked with the responsiveness to non-invasive stimulation (39). Incorporating extended high frequency audiometry in routine tinnitus assessment would assist in early identification of overall severity of hearing loss. Such participants could be referred for neuromodulation at an early stage instead of later when the severity of hearing loss has increased further and much stronger tinnitus related cortical organisation has been established, which might reduce their chances of positively responding to neuromodulation. It would be interesting to conduct a study to investigate the impact of severity of hearing loss and responsiveness towards neuromodulation, along with finding other possible clinical co-variables such as age, gender, tinnitus severity, duration, types, pitch, genotypes, and causes. Some or all of these factors may determine the responsiveness to neuromodulation, or candidacy for neuromodulation. This study had some limitations: all the participants had sloping configuration of hearing loss and therefore the findings may not be generalised to other configurations of hearing loss. The

study also differed in the way edge frequency was calculated (409, 425). The highlight of this study was the correlation between tinnitus pitch and T50.

Hearing aids are one of the most popular and oldest management options used for people with tinnitus (446). They have been used for over 60 years (46). Tinnitus is usually associated with hearing loss (12) and studies have proposed the following mechanisms underlying effectiveness of hearing aids for managing tinnitus and hearing loss: gain adaptation (439), reversing tinnitus related cortical reorganisation (45, 440), masking, positive psychosocial impact, and reducing communication stress as examples (162, 437, 438). A scoping review was undertaken (Chapter 4) in an attempt to gather available literature on tinnitus management with hearing aids. Scoping reviews are relatively new in the area of hearing sciences but they have been used in various other disciplines such as nursing (463, 469-471), education (470, 471), business (472), and public services (473). A unique feature of a scoping review (unlike a systematic review) is that it does not exclude a study based on its quality (460). It includes as many studies as possible (which assist in studying the spread of literature in a particular area) as long as they are relevant. This thesis includes one of the very first scoping reviews to explore the spread of literature in the area of hearing aids' role in tinnitus management. In total, 29 studies were included after an intensive search and filtering of the literature was conducted to chart the data (out of 277 shortlisted studies). These studies comprised of surveys, case studies, investigational studies, and review studies. Although there were differences within studies based on their methods, such as the use of a prescriptive approach, sample size, outcome measures used, counselling, rationale and technology used, the majority of the studies (27, out of 29) supported the use of hearing aids for tinnitus management. The scoping review also identified some significant areas that were lacking in research, such as a need for studies with much stronger methodology and more RCTs in the area of hearing aids and tinnitus. The need for more research towards prescription of hearing aids gain for tinnitus management and optimisation of hearing aids for tinnitus relief were also identified. In this thesis I addressed these two areas with a study of prescription of hearing aid output for tinnitus relief (Chapter 5) and undertook a RCT (with tDCS stimulation) of hearing aid effects (Chapter 7).

This scoping review highlighted certain important factors which one should consider when planning further research about hearing aids and tinnitus management. They are discussed here; all the research studies have prescribed the hearing aid gain for optimising

communication and tinnitus relief was a reported by-product of this process. Hearing aids should be programmed specifically for tinnitus, based on participants' tinnitus profile such as tinnitus pitch along with their hearing status (49). Prescriptive approaches for programming hearing aids for tinnitus management should be carefully selected and documented, and this scoping review revealed a lack of information in the majority of studies about the prescription and the rationale for its use. RCTs should be encouraged in effectively studying the impact of hearing aids for tinnitus management. The majority of studies in this scoping review were lacking control groups (49, 50, 215, 245, 446, 482-485) and the methodology of research studies could have been stronger. Many studies used multiple interventions along with hearing aids such as guidance, counselling, and sound generators (164, 447) which made it difficult to extract the impact of an individual management strategy. It would be more appropriate to avoid multiple interventions, and therefore be able to study the effect of a specific intervention. Outcome measures were limited to only questionnaires and interviews (48-51, 215, 245, 446, 482-484, 486-489) in the majority of the studies, combining other outcome majors such as psycho-acoustic measurements involving assessing tinnitus pitch, loudness, MML, and questionnaires could be a more comprehensive approach and likely to give more insight about the effect of intervention used on tinnitus characteristics. A difference of opinion was observed in fitting hearing aids to one ear or both; binaural amplification would appear to be appropriate in participants with binaural tinnitus and hearing loss (489). Another significant factor was the inclusion–exclusion criteria of participants, having more uniform groups at the baseline would lead itself to identifying treatment, rather than selection, effects. Conclusions as to effectiveness must however be applied to the trial population, with caution as to how results might apply to persons with different characteristics in the general population. The scoping review identified gaps, especially around hearing aids selection, programming, and use towards tinnitus management. Although hearing aids have been used for a long time, there is a mismatch between the purpose and the way they have been used to address that purpose. This study indicated the need to optimise the process of hearing aid fitting for tinnitus management and to opt for a research design based on the factors highlighted above such as participants' inclusion, prescriptive approach, and outcome measures.

The above mentioned insights were derived from the scoping review and were implemented in the other research studies planned as part of this dissertation (Chapter 5

and Chapter 7). A clinical trial (Chapter 7) was planned based on the findings of the scoping review, and hearing aids were programmed for tinnitus, psycho-acoustic measurement of tinnitus characteristics (tinnitus pitch, loudness, MML) were conducted along with questionnaires, participants were randomised and it was a controlled trial. Participants were fitted with the same model of hearing aids binaurally. Multiple interventions such as counselling were avoided which allowed us to focus on the exclusive impact of hearing aids and brain stimulation.

Chapter 5 explored the prescription of hearing aid output for tinnitus relief. Prescriptive procedures are a systematic and organised approach for hearing aid fitting (503). This thesis includes an attempt to explore the modifications of a prescription approach [DSL (I/O) v.5.0] and study its effectiveness for tinnitus relief (Chapter 5). Prescriptive approaches are used to programme hearing aids and are a quick and effective way to cater for the needs of people with different configurations of hearing loss. Two important points to remember are : 1) prescriptive formulae offers a guideline, it is necessary to verify the gain using real ear measurements (514), and 2) they are targeted to optimise communication based on the hearing loss. Wise 2003 (52) compared the effectiveness of NAL–NL1 and DSL (I/O) v.4.0 prescription for tinnitus relief and found that DSL (I/O) v4.0 was effective in reducing tinnitus awareness in 80 % of participants. Chapter 5 explored high frequency modification of DSL (I/O) v.5.0 and its effect on tinnitus relief. The impacts of sound files, simulating changes in DSL(I/O) v5.0 prescribed output, on tinnitus audibility were documented. Overall, 70.58 % of participants preferred a 3 to 6 dB reduction in output at three different cut-off frequencies. Tinnitus pitch was linked to the preference of hearing aid output. Based on tinnitus pitch, all 25 participants were divided in to three categories (> 8 kHz, 4 kHz to 8 kHz, and < 4 kHz). For tinnitus pitch lower than 4 kHz, the overall winning preference setting was 1 to 3 dB lower than DSL (I/O) v.5.0 (although this difference was not statistically significant). As the tinnitus pitch increased, the preferred setting became more similar to DSL (I/O) v.5.0. If we wish to use prescription procedures for tinnitus management, we need to adjust and modify them based on participants' tinnitus profiles and individual needs. The majority of research done in this area of hearing aid use for tinnitus management appears to have overlooked this important factor. Some studies have confirmed the significance of tinnitus pitch when programming hearing aids for tinnitus management (49), however other factors such as tinnitus loudness, MML and laterality of tinnitus have not been considered for hearing aid

programming. It would be interesting to plan studies focussing on these dimensions for better tinnitus management. Chapter 5 showed that overall, DSL (I/O) v.5.0 is a good starting point for prescribing hearing aid output for tinnitus management, and that tinnitus pitch is a significant factor to consider when programming hearing aids for tinnitus relief. These recommendations were used in the clinical trial (Chapter 7).

tDCS has been used extensively for various clinical conditions such as stroke, depression, migraine, pain, and craving (383) with varied amount of success. Its use for tinnitus management has been relatively recent. The first published study came in 2006 (39) and to date there have been only a handful of published studies about the use of tDCS for tinnitus management (40-44, 395). All these studies have supported the effectiveness of tDCS in transient tinnitus relief. These studies differ in the use of tDCS parameters such as intensity, duration, site of stimulation, and have used different protocols. Prior to this thesis there was no existing study optimising tDCS intensity and duration parameters for tinnitus suppression. A dose-response study (Chapter 6) was undertaken to optimise the parameters of tDCS for tinnitus suppression. Based on existing literature on tDCS the, three most frequently used durations (10 min, 15 min, and 20 min) and intensities (1 mA and 2 mA) were combined to produce six settings to study. The LTA was chosen as the site of stimulation based on the quantity of evidence at the time of planning this study, and research undertaken by Plewnia et al. 2003 (323) revealed LTA as the winning site of stimulation when compared with seven other sites on the head. The results of Chapter 6 revealed that 2 mA current intensity and 20 minute duration as the most effective settings in transient tinnitus suppression. The positive response rate in Chapter 6 (2 mA current intensity and 20 minute duration) was 56%, which was higher than previous studies. Fregni et al. (39) and Garin et al. (40) used LTA as the site of stimulation and used 1mA current intensity and 3 minutes and 20 minutes duration. They found a positive response rate of 42% and 35% respectively. Vanneste et al. (41) and Frank et al. (42) used anodal tDCS of DLPFC with 1.5 mA current intensity and 20 minute and 30 minute duration. They achieved a positive response rate of 29.9% and 15.6%. I speculated that the use of higher current intensity resulted in higher positive response rate in Chapter 6. It's also hard to rule out the cumulative impact of multiple sessions used in my study. Variations in the positive response rate across various studies could be attributed to the difference in methods used in these studies as there were differences in the amount of current intensity,

duration, site of stimulation, washout periods, and research design used across these studies.

Two hypotheses as to the mechanisms leading to effective transient tinnitus suppression by tDCS are provided by Fregni et al. 2006 (39): stimulation of various cortical and sub-cortical areas underlying LTA, either by inhibition and competition reduces the abnormal hyperactivity generated by tinnitus leading to transient benefit; and Vanneste et al. 2010 (41): inhibitory effect of the DLPFC on the auditory areas, results in the reduction of abnormal hyperactivity caused by tinnitus. The stimulation of the LTA leads to more widespread, generalised stimulation and distribution of electric field and current density at various cortical and sub-cortical areas along with the target structure (534). Underneath the LTA lies various cortical and sub-cortical structures such as the primary auditory cortex (BA 41, 42), auditory association area (BA 21, 22) and parts of limbic system (amygdala and hippocampus) (317, 521, 535). The amount of stimulation reaching the DLPFC was comparable when stimulating LTA or DLPFC (390). Hence, the possible reason for transient tinnitus suppression using anodal tDCS of LTA could be a combination of both the hypothesis proposed by Fregni et al. (39) and Vanneste et al. (41).

The winning setting from the pilot study (Chapter 6) was used for the brain stimulation sessions in the clinical trial and consisted of multi-session tDCS along with hearing aids use (Chapter 7). The impact of tDCS on tinnitus is transient, ranging from a few minutes to a few days. While hearing aids can have immediate masking benefits, most researchers believe lasting benefits (without aids in) may take 6 months or longer (536). Although the mechanism underpinning hearing aid benefits is unclear (these may include psychological benefit), physiological explanations include changes in auditory plasticity. Auditory plasticity is the ability of auditory nerve cells to conform to environmental influence, and there is some evidence that rapid plastic changes can occur (231) with evidence from hearing aid use suggesting many months of use before plastic changes are observed (see Chapter 2 and Chapter 4). Hearing aids assist participants with tinnitus by a proposed mechanism of reversing the tinnitus related centrally controlled gain or central reorganisation and synchronisation; however, this process may take several months', as it's an indirect modulation of brain plasticity through acoustic stimulation. The reason to use multi-session tDCS before hearing aid fitting is based on speculation that it would accelerate the modulation of brain plasticity and hence prime the brain for effective and quicker impact of hearing aids on tinnitus related pathological activity through acoustic

stimulation. Forty participants completed a seven-month-long clinical trial aimed to study the effectiveness of combining direct (multi-session tDCS) and indirect (hearing aids) modulation of brain plasticity for tinnitus management. The parameters for brain stimulation were based on the findings of Chapter 6, and hearing aids were programmed as per the findings of Chapter 5. Chapter 7 was a double-blind, sham-controlled, randomised clinical trial with the TFI as the primary outcome measure (496), and several other questionnaires were used as secondary measures (CGI, THQ, HHI, HADS, TSNS, and VAS). Tinnitus pitch, loudness, and MML were measured with tinnitus tester software developed at the University of Auckland. The first baseline measure was obtained one month before starting stimulation; a second baseline was obtained one week before starting stimulation. Forty participants were randomised into sham tDCS and tDCS groups (20 participants in each group). During the stimulation, participants underwent five sessions of stimulation with a 24 hours washout period. During the stimulation sessions, tinnitus loudness was measured with VAS before (twice) and after the simulation and at the end of each session participants completed a CGI scale to rate their overall perception of the effectiveness of the treatment. On the sixth day, at the end of five stimulation sessions, binaural open fit, hearing aids were programmed using DSL (I/O) v.5.0 based on participants' hearing loss and tinnitus profile (based on the recommendations from Chapter 5). Participants were recommended to use hearing aids for a minimum of eight hours per day and for a minimum of six months' time and two more follow-ups were done using questionnaires and psycho-acoustic measurements at the third and sixth month following fitting. This was the first clinical trial combining hearing aids with brain stimulation. The effectiveness of hearing aids for tinnitus management was evident after three months of use and was sustained at six months. Hearing aid use lead to significant reduction in TFI scores for both the sham and tDCS group, and were independent of brain stimulation sessions. The beneficial effects of tDCS were not very clear. There was some preliminary evidence of a greater reduction of MML for tDCS group compared to the sham tDCS group after the stimulation sessions and third month follow-up. There was also a consistent trend of tinnitus loudness reduction and better CGI ratings during the five sessions of stimulation for the tDCS group, but for the sham tDCS group tinnitus loudness increased after the first session, inconsistent loudness reduction for the remaining sessions and CGI ratings tending more towards 'no change' were observed. It was hypothesised that six months of hearing aid use might have reduced the central gain by increasing the afferent activity which was diminished by hearing loss, possibly through a bottom-up approach and

multi-sessions of tDCS might diminish peripheral drive; by modulating neural correlates of tinnitus at various cortical and sub-cortical areas possibly through a top-down approach (529, 530). More research evidence is needed before making confirmatory conclusions about the effectiveness of tDCS for tinnitus management and exploring different protocols of tDCS for tinnitus relief is required.

8.1. Future Implications

This thesis raised questions which need to be addressed by future research. The benefits of tDCS are not very clear based on the clinical trial (Chapter 7) and the possibility of converting the transient benefits of tDCS into lasting results should be explored using different protocols. One possibility would be that instead of using multisession tDCS only at the beginning of the trial before hearing aid fitting, it should be spaced throughout the hearing aid use, e.g., after every two or three months of hearing aid use. This protocol might show better results, as there is a possibility that it might modulate the plasticity of brain at regular intervals. Another possibility could be to use tDCS along with acoustic stimulation to study its impact on RI. A combination of different protocols could be trialled to see if the use of tDCS can elongate RI, which may give further insights regarding better incorporation of tDCS sessions along with hearing aid use. The tinnitus laboratory at the University of Auckland plans such experiments in the future.

tDCS could also be tried as an additional intervention along with various other intervention approaches used for tinnitus; for CBT, guidance, and counselling, and the transient improvement in tinnitus from tDCS may encourage participants towards acquiring a more positive attitude towards their condition especially for chronic tinnitus sufferers.

Further research is also needed in the area of hearing aids. Although hearing aids have been used for more than 60 years for tinnitus management, the major focus has been towards the effect of hearing aids in optimising communication and reducing hearing handicap. Optimisation of hearing aids for tinnitus management is needed. This thesis is a step in this direction. Chapter 3, Chapter 4, Chapter 5, and Chapter 7 were aimed at optimising and exploring hearing aid use for tinnitus management. Additional research is needed towards prescriptive approaches for programming hearing aids or combination devices for tinnitus relief, and studying the long-term benefits of different prescription formulas for tinnitus management. It would be interesting to study the effect of programming hearing aids exclusively for tinnitus relief, or to have a programme dedicated for tinnitus relief and one for optimum communication. Improvements in the high frequency gain of hearing aids may assist the 76% of participants (see Chapter 3) that had their tinnitus pitch $\geq$ 8 kHz. Tinnitus pitch may significantly contribute towards tinnitus management decisions, hence future research towards exploring better predictors of

tinnitus pitch based on audiometric assessment may assist in developing improved management strategies for tinnitus sufferers.

8.2. Conclusions

Hearing aids (without tinnitus counselling) resulted in significant improvement in tinnitus related QOL after three months of use. The hearing aid benefits were independent of tDCS. Our clinical trial did not reveal any statistically significant benefit of tDCS over hearing aid use alone at 3 and 6 months following tDCS. However significant reduction in MMLs compared to sham, and a consistent (but not statistically significant) trend for lower loudness and CGI scores were obtained immediately after the tDCS sessions. Further research is needed to evaluate the effectiveness of neuromodulation for sound therapy. Anodal tDCS of LTA with 2 mA current intensity and 20 minutes duration appears to be the most effective tDCS setting for providing transient tinnitus suppression for some patients. Tinnitus pitch plays an important part in assessment as well as management of tinnitus.

Appendix A. Participant Screening Checklist and Interview Guideline for tDCS

Participant screening checklist and interview guidelines, developed by Dr Winston Byblow (PhD), Dr Alan Barber (PhD, MBChB, FRACP Neurology) and Dr Cathy Stinear (PhD), University of Auckland, for use in the Movement Neuroscience Laboratory. Updated: July 2009

Last name: _____

First names: _____

Please take a moment to carefully answer all questions.

	Question:	**Your answer:**
1.	Do you suffer from epilepsy, or have you ever had an epileptic seizure?	Yes ☐ No ☐
2.	Does anyone in your family suffer from epilepsy?	Yes ☐ No ☐
3.	Do you have any metal implant(s) in any part of your body or head? (Excluding tooth fillings)	Yes ☐ No ☐
4.	Do you have an implanted medication pump or any other implanted electronics?	Yes ☐ No ☐
5.	Do you have a pacemaker or defibrillator?	Yes ☐ No ☐
6.	Do you suffer from any form of heart disease or had heart surgery?	Yes ☐ No ☐
7.	Do you suffer from recurring headaches?	Yes ☐ No ☐
8.	Have you ever had a skull fracture or head injury?	Yes ☐ No ☐
9.	Have you ever had any head or brain surgery?	Yes ☐ No ☐
10.	Is there any chance you could be pregnant?	Yes ☐ No ☐
11.	Do you take any medication?	Yes ☐ No ☐
12.	Do you suffer from any neurological or other medical conditions?	Yes ☐ No ☐

Please turn over

Comments _____

_____

_____

Participant:		Researcher:	
Name	_____	Name	_____
Signature	_____	Signature	_____
Date	_____	Date	_____

Important information

_____

_____

_____

_____

_____

_____

_____

_____

_____

OUTCOME: ☐ INCLUDE ☐ EXCLUDE

Consultation with Study Physician:

Name: _____

Date: _____

Supervisor:

Name: _____

Date: _____

Additional Comments

_____

_____

Name _____

Signature_____

Date _____

Name _____

Signature_____

Date _____

Name _____

Signature_____

Date _____

Name _____

Signature_____

Date _____

Name _____

Signature_____

Date _____

Name _____

Signature_____

Date _____

Medication Recommendations Checklist

Medication (generic)	**Medication (brand or tradename)**	
Amantadine	Symmetrel®	Consult study physician
Alprazolam	Xanax®	Consult study physician
Baclofen	Pacifen ®	Consult study physician
Benztropine	Benztrop® (tab) Cogentin® (injection)	Consult study physician
Carbamazepine	Tegretol® Teril®	Exclude
Citalopram	Celapram® Arrow-citalopram® Citalopram-Rex® Cipramil	Consult study physician
Clobazam	Frisium®	Exclude
Clonazepam	Rivotril® (oral drops & injection) Paxam® (oral)	Exclude
Fluoxetine	Fluox® Prozac® (not funded)	Consult study physician
Gabapentin	Neurontin® Nupentin®	Exclude
Haloperidol	Haldol® (injection) Serenace®	Exclude
Hyoscine	Scopaderm® (patch) Buscopan®	Consult study physician
Ketamine		Exclude
Lamotrigine	Lamictal® Arrow-lamotrigine® Mogine®	Exclude

Medication (generic)	**Medication (brand or tradename)**	
Levodopa + benserazide	Madopar®	Consult study physician
Levodopa + carbidopa	Sinemet®	Consult study physician
Lisuride	Dopergin®	Consult study physician
Lorazepam	Ativan® Lorapram®	Consult study physician
Mertazapine	Remeron®	Exclude
Methylphenidate	Ritalin	Exclude
Moclobemide	Apo-moclobemide® Aurorix	Consult study physician
Paroxetine	Loxamine® Aropax	Consult study physician
Pergolide	Permax®	Consult study physician
Phenytoin	Dilantin®	Exclude
Quetiapine	Seroquel® Quetapel®	Exclude
Selegiline	Apo-selegiline® Eldepryl	Consult study physician
Sertraline	Zoloft®	Consult study physician
Sodium valproate	Epilim®	Exclude
Temazepam	Normison® Euhypnos	Consult study physician
Tolcapone	Tasmar®	Consult study physician
Topiramate	Topamax®	Exclude
Triazolam	Hypam® Halcion®	Consult study physician
Venlafaxine	Efexor®	Exclude
Vigabatrin	Sabril®	Exclude
	None of the above	

Interview guidelines for tDCS checklist

1. *Do you suffer from epilepsy, or have you ever had an epileptic seizure?*
Exclude.

2. *Does anyone in your family suffer from epilepsy?*
Ask: Does anyone in your family (related by birth) suffer from epilepsy?

Ask: Do you know if their epilepsy is caused by something in particular,

such as a head injury or stroke?

If they are related by marriage to someone with epilepsy, rather than genetically related, they can be included.

If they are genetically related to someone with epilepsy, but it was caused by a specific event, such as head trauma, stroke, brain tumour or brain surgery, they can be included.

If they are genetically related to someone with epilepsy, but they aren't sure whether it was caused by trauma, stroke, brain tumour or brain surgery **consult study physician.**

If they are genetically related to someone who experiences epilepsy, with no known cause, **consult study physician.**

3. *Do you have any metal implant(s) in any part of your body or head? (Excluding tooth fillings)*
Ask: Where in your body?

If the metal is implanted in the head or neck, **exclude.**

If metal is implanted at the level of the shoulders or below, they can be included.

4. *Do you have an implanted medication pump or any other implanted electronics?*
Exclude.
5. *Do you have a pacemaker or defibrillator?*
Exclude.

6. *Do you suffer from any form of heart disease or had heart surgery?*
Ask: What sort of heart disease or heart surgery?

Ask: If heart surgery, did they implant anything, such as a new valve?

If they have had a valve replacement, or any other cardiac implants **consult study physician.**

7. *Do you suffer from recurring headaches?*
Ask: How often do you experience a headache?

Ask: Do you know what triggers your headaches?

Ask: Does the headache respond to over the counter medications?

Ask: Have you consulted your doctor about these headaches?

If they experience headaches more than once per week or the headaches don't respond to over the counter medications, **consult study physician.**

8. *Have you ever had a skull fracture or head injury?*
If skull fracture, **exclude.**

If head injury with loss of consciousness, **consult study physician.**

If head injury with no loss of consciousness, within last six months, **exclude.** If they experience ongoing symptoms as a result of their head injury, **exclude.**

If the head injury did not result in a loss of consciousness, and was more than six months ago, and they don't experience any ongoing symptoms, they can be included.

9. *Have you ever had any head or brain surgery?*
If brain surgery, **exclude.**

Ask: What type of head surgery?

Ask: When was the surgery?

Ask: Was any metal implanted, such as screws, plates or pins? If YES, **exclude.** If NO, **consult study physician**.

10. *Is there any chance you could be pregnant?*
Exclude.

11. *Do you take any medication?*
Ask them to list all medications they take on the checklist

Ask them to fill in the 'Medication Recommendation Checklist', follow its criteria, to check for any medication contraindications.

Do you suffer from any neurological or other medical conditions?

Ask them to fill in the 'Medication Recommendation Checklist', follow its criteria, to check for any medication contraindications.

If they take medication that is not on the 'Medication Screening Checklist', **consult study physician**.

Appendix B. tDCS Guidelines

Based on recommendations from Loo et al. and Norris et al. (389, 519) here are some important guidelines which one should consider before, during and after conducting tDCS.

Factors related to tDCS equipment

- One must ensure that the tDCS battery is fully charged to avoid power supply interruption (519).
- All the stimulus parameters (such as current intensity, duration, ramping, stimulus mode, impedance limits etc.) should be pre-programmed before the arrival of participant (519).
- Equipment should be placed out of view of the participant to create non-threatening environment (519).
- If equipment fault arises the delivery of current should be stopped immediately and one should avoid troubleshooting the equipment while delivering the current (519).

Factors related to participant

- Detail information about the procedure and research should be provided to the participant and their questions, concerns and doubts should be addressed (519).
- Informed consent should be taken in writing.
- Conduct neurological screening with the help of participant checklist for transcranial electrical stimulation (Screening checklist attached Appendix B). Only those passing the screening should undergo the procedure.
- Skin under the potential placement of electrode should be carefully examined to rule out any cuts, lesions or skin infections. Avoid tDCS if there is any kind of skin lesion or infection (389, 519).

Factors related to examiner during stimulation

- Examiner should wear gloves for good hygiene (519).

- After locating the electrode placement, the site should be cleaned with alcohol swab gently. Avoid abrading the skin during cleaning (389, 519).
- Electrodes and sponges should be cleaned and disinfected (389, 519).
- Participant should be provided a protective sheet or towel to prevent dripping of saline solution which is used to dampen the electrode to fall on them (519).
- Electrode placement should be marked and elastic/velcro straps should be placed across the forehead and under the chin perpendicular to each other. Examiner should ensure that the straps are firmly placed at the same time it should not be uncomfortable for the participant (519).
- Use NaCl (sodium chloride) solution to dampen the sponge and rubber electrodes should be inserted in it.
- Place the dampened electrodes under the straps on the marked locations. Adjust them to ensure the placement on the desired location. Further apply the NaCl solution as per the need (519).
- Ensure firm and even electrode-skin contact over the entire surface of the electrode. The long end of the electrode should be placed parallel to the strap to ensure even pressure on the electrode to maintain good contact with skin (519).
- Impedance should be measured and it should be within the recommended levels provided by the manufacturers. If not carefully review above points and measure the static impedance. Stimulation should not proceed with levels outside the recommend range (389, 519).
- Before starting the stimulation instruct the participant to indicate if the stimulation feels anything other than itchy or tingling sensation or it is painful (389).
- If it is painful apply NaCl solution on the sponges and check the tightness of the straps and if the pain persists then stop the stimulation (389).
- Apply NaCl solution routinely to avoid drying of the electrode and good electrode-skin interface (after every 10 minutes) (389).
- Examiner should be very alert and vigilant for any sign of discomfort (519).

Factors to consider post stimulation

- After the stimulation carefully examine the skin under the electrode for any sign of redness or injury (389).
- Clean the electrode and the headbands with disinfectant and wash the sponges (389).

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