

**Assessing the Efficacy and Safety of Bimodal Neuromodulation for the
Management of Symptomatic Tinnitus**

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Declaration

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Thavakumar Subramaniam

Summary

Tinnitus is defined as the perception of sound in the absence of an external auditory stimulus. It is a common symptom, affecting 5 – 30% of the general population, however only 1 – 3% of patients report the symptom to be intrusive or bothersome. The exact pathophysiology of tinnitus is not clearly understood, however it is hypothesized that a reduction in peripheral auditory input may result in discoordinated activity within the auditory neural pathways. Hence, tinnitus is commonly associated with sensorineural hearing loss and the prevalence of tinnitus has been observed to increase after 70 years of age due to presbycusis. Tinnitus is also frequently reported by patients with hearing loss secondary to chronic loud sound exposure, such as in the case with military personnel. Tinnitus is the most common disability affecting American military veterans, with an estimated 1.2 billion dollars spent in compensation annually.

There is a growing volume of evidence to support the involvement of non-auditory central structures in tinnitus activity such as the limbic system and dorsal cochlear nucleus. Hyperactivity within the limbic system may be linked to the strong psycho-emotional response often associated with tinnitus. The dorsal cochlear nucleus is a key site for neural convergence, receiving neural input from the auditory pathway, limbic system, cranial nerves and cervical spine nerve root ganglia. There is a growing volume of evidence to suggest that the dorsal cochlear nucleus is a key site involved in generating and sustaining tinnitus activity.

A gold standard treatment option for tinnitus remains illusive. To date, no drug therapy has been shown to be completely safe or clinically efficient. There is evidence to support the efficacy of cognitive behavioural therapy as a treatment option for tinnitus symptom control. However this modality aims to improve the patient's response to tinnitus, rather than eliminating or reducing the severity of the symptom.

Neuromodulation has emerged as a potential effective treatment option for tinnitus. In general, this novel therapeutic modality aims to alter neural activity by delivering a targeted stimulus. There is evidence from both animal and human studies that show modulation of tinnitus activity can be achieved, by stimulating the auditory neural pathways, either directly or via an interconnected neural network. Multiple neuromodulation stimulation techniques have been designed and investigated, however no modality has been shown to be superior in achieving optimal clinical gains for tinnitus.

However, there is emerging evidence to support the use of bimodal stimulation techniques to achieve greater therapeutic gains during tinnitus treatment. The benefits of bimodal stimulation were initially observed in animal studies. The pairing of auditory and electrical stimulation had the therapeutic advantage of suppressing neural hyperactivity in animals exhibiting tinnitus behaviour.

Neuromod Devices Limited (Neuromod Ltd) has developed a CE marked medical device called MutebuttonTM that enables bimodal neuromodulation for the treatment of tinnitus, combining auditory and electrical stimulation. Auditory stimulation in the form of frequency-adjusted tones, are used to stimulate auditory pathways involved in tinnitus. Electrical impulses stimulate the trigeminal nerve (via the lingual nerve) through an anterior tongue surface probe. Relevant to this design is evidence supporting the use of anterior tongue stimulation to drive greater auditory neuroplastic changes.

The efficacy of the MutebuttonTM device was initially assessed in the Tinnitus Alleviation Via Sensory Stimulation (TAVSS) pilot study. This was a single arm study in which the recruited participants, (n = 54) underwent a 10-week treatment period. The findings from this study were encouraging with treatment compliant participants reporting statistically significant improvements in Tinnitus Handicap Index scores (mean improvements of 11.7 points, $p < 0.001$).

The TAVSS study also established the feasibility of the MutebuttonTM device as a potential treatment option for symptomatic tinnitus.

The aim of this project was to build on the promising data observed in the TAVSS study. We designed a randomized double-blinded trial to assess the effects of three different bimodal stimulation settings on tinnitus severity. Based on both animal and human studies, variations in inter-stimulation settings (intensity and timing) have been shown to drive greater neuroplastic change that may be beneficial in reducing tinnitus activity.

The trial was conducted at two sites, Wellcome Trust-HRB Clinical Research Facility, St James's Hospital, Dublin, Ireland and Tinnituszentrum Regensburg, University of Regensburg, Germany. The participants underwent a 12-week treatment period and were assessed at five clinical visits over a 12-month period. Treatment outcome measures were recorded at each visit using validated tinnitus research questionnaires. A secondary aim of this trial was to assess the safety and feasibility of the MutebuttonTM device. Trained technicians at the clinical research facilities carried out device safety checks and relevant clinical examinations of the study participants during each assessment. All adverse events reported by participants were classified and logged for data analysis.

The outcomes reported in this study support the use of bimodal neuromodulation as a treatment option for symptomatic tinnitus. The variations in stimulations settings investigated during the trial have also shown to be beneficial in driving long-term therapeutic gains. These findings provide a strong basis upon which further research can undertaken.

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Finally, to my partner Emma Carroll, our daughter Sophia and to my parents whom I cannot express enough gratitude for their patience and love.

Abbreviations

AS	Acoustic stimulation
AE	Adverse event
ANP	Auditory neural pathway
BSI	British Standard Institute
CBT	Cognitive behavioural therapy
CE	Certification mark
CM	Complete masking
CN5	Trigeminal nerve
CN9	Glossopharyngeal nerve
CN10	Vagus nerve
CNS	Central nervous system
DCN	Dorsal cochlear nucleus
EEG	Electroencephalogram
ECRF	Electronic case report form
ENS	Electrical neural stimulation
FC	Fusiform cells
GRB	Glutamate receptor blocker
HAA	Hearing aid amplification
HL	Hearing loss
IE	Inner ear
IT	Intrusive tinnitus
LN	Lingual nerve
LSE	Loud sound exposure
MML	Minimum Masking Level
MRI	Magnetic resonance imaging
NMDA	N-methyo-D-aspartate
NPST	Non-pulsatile subjective tinnitus

PET	Positron emission tomography
PS	Parameter setting
PT	Pulsatile tinnitus
SAE	Serious adverse event
SBT	Sound based therapy
SNHL	Sensorineural hearing loss
SSRI	Selective serotonin reuptake inhibitor
SST	Somatosensory tinnitus
ST	Subjective tinnitus
TCA	Tricyclic antidepressants
TES	Transcranial electrical stimulation
TFI	Tinnitus Functional Index
THI	Tinnitus Handicap Inventory
TLM	Tinnitus Loudness Matching
TM	Tinnitus masking
TMS	Transcranial magnetic stimulation
TPE	Thermoplastic elastomer
TRI	Tinnitus Research Initiative
TRT	Tinnitus retaining therapy
UIC	Unique identified code

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Chapter 1

Introduction

1.1 Overview of Tinnitus

Tinnitus is a common otological symptom, defined as the perception of sound in the absence of an external auditory stimulus¹. Although ancient medical documents have made reference to tinnitus dating back to 1500 B.C, we still lack knowledge on the exact pathophysiological mechanisms that generate and drive tinnitus activity.

Producing best practice guidelines for the management of tinnitus has proven to be a challenge, given the heterogeneous nature of the symptom. Patients with tinnitus often report an array of aetiologies, fluctuations in symptom severity and inconsistent responses to treatment. This is also compounded by the major impact the patient's psycho-emotional state has on interpreting tinnitus severity.

In order to introduce a standardized approach to tinnitus assessment, the symptom is subtyped as either subjective tinnitus (ST) or objective tinnitus (OT). Subjective tinnitus is commonly encountered in clinical practice and is defined as tinnitus that is only perceived by the patient^{1 2}. Subjective tinnitus is often idiopathic, but can be caused by ototoxic medication, loud sound exposure, otological and neurological conditions². Objective tinnitus (OT) occurs due to sound generated by the body; hence, both the patient and assessor can detect it. This type of tinnitus can be caused by pathologies such as palatal muscle myoclonus, temporomandibular joint dysfunction, and turbulent flow within vessels or airway³.

It is pertinent to obtain details on the character of tinnitus described by the patient, as it may allude to a cause of the symptom^{1 2}. The character of tinnitus is defined as either pulsatile or non-pulsatile^{1 2}. Non-pulsatile tinnitus is common and patients often describe a ringing, hissing or buzzing sound. Patients with pulsatile tinnitus (PT) often describe a rhythmical sound resembling their heartbeat or pulse. Pulsatile tinnitus is likely attributed to a vascular origin and warrants further specialist investigation^{1 2}.

1.2 Epidemiology of Tinnitus

Obtaining accurate data on the prevalence of tinnitus can be challenging given the heterogeneous nature of the symptom and the lack of a standardized approach to reporting clinical data on tinnitus. This is reflected in a recently published systematic review that reported eight different definitions of tinnitus used to collect epidemiological data⁴.

Overall, the prevalence of tinnitus in the general population is reported to range between 5 – 30%⁴, however only 1-3% of patients report their symptom as severe or seek medical help. A large study from the United Kingdom on adult hearing loss (n = 48313), reported tinnitus prevalence of 10.1%, however only 0.5 – 1.6% of patients reported symptomatic or intrusive tinnitus⁵. A large cross sectional study from the United States in 2016 that obtained data from the National Health Interview Series, reported an estimated 9.6% of Americans had experienced tinnitus⁶.

Another cross sectional study from Korea (n= 19290), reported a tinnitus prevalence of 20.7%, however only 3% of recruits reported intrusive tinnitus (IT)⁷. Similar findings on tinnitus prevalence are also reported from epidemiological studies from Europe, Middle East, Asia and Africa⁸⁻¹³, proving the global burden of the condition. Currently, there is no available data on the prevalence of tinnitus in Ireland.

Although we collected demographic data during the trial, the cohort of participants recruited during this study was insufficient to accurately represent the national prevalence of tinnitus.

1.3 Aetiology and Risk Factors for Tinnitus

Although tinnitus is idiopathic in 40 – 50% of cases, any disorder of the auditory neural pathway can result in tinnitus³. In most population-based studies, hearing loss (HL) is reported as a significant risk factor for developing tinnitus. Furthermore, the prevalence of tinnitus has been reported to increase with age due to presbycusis^{1 3 4 7}. However, the relationship between hearing loss and tinnitus is not exclusive as 5-10% of patients with tinnitus have a normal audiological assessment^{14 15}.

Tinnitus may also be a symptom associated with other otological conditions such as Meniere's disease, otosclerosis, vestibular neuritis, labyrinthitis, temporal bone tumours and middle and inner infections. Indeed, inner ear conditions are reported to cause 24% of tinnitus cases¹⁶.

A history of loud sound exposure (LSE) is commonly associated with tinnitus. When compared to the general population, patients with a history of LSE have a higher incidence of developing tinnitus (40% vs 20%)^{1 2}. Occupational LSE has been shown to be a predictor of developing tinnitus, independent of the duration and intensity of LSE. Tinnitus is a common symptom amongst military personnel that have been deployed to warzones. The Veteran Affairs in the United States has reported spending over 1.2 billion dollars a year in tinnitus related compensation^{2 7}.

Cardiovascular risk factors such as obesity, smoking, hypertension, hyperlipidaemia and diabetes mellitus have been linked to tinnitus⁷. A reported 20 – 25% of the tinnitus population have co-existing cardiovascular risk factors. It is hypothesized that ischemic changes lead to oxidative damage within the inner ear. However there is limited data to clearly support these suggested findings⁷.

Certain drugs required for the treatment of malignancy and serious infections have ototoxic properties that can result in tinnitus. Drugs such as salicylate, platinum based cytotoxic drugs and aminoglycoside antibiotics have been well documented to be associated with tinnitus². Chemotherapeutic drugs such as cisplatin and carboplatin are extremely ototoxic. In a quality of life study following cisplatin treatment for testicular cancer, 20 - 25% of patients reported persistent tinnitus 2 years post treatment¹⁷. Similar rates of persistent tinnitus following cisplatin therapy for malignancy have been reported in other studies^{18 19}.

Cisplatin is capable of diffusing through plasma membranes and can also be transported into the cochlea by membrane receptors²⁰. Within the cochlea, cisplatin exhibits ototoxic effects by stimulating an inflammatory process driven by tumour necrosis factor and interleukin. Findings from animal studies suggest that the cisplatin induced inflammatory process appears to affect the organ of corti and stria vascularis. The cisplatin induced inflammatory process leads to free radical production, DNA damage and ultimately activation of the apoptotic pathways within the cochlea²¹.

Aminoglycosides have potent antimicrobial efficacy, but are associated with irreversible ototoxic damage. Aminoglycosides have been detected in animal cochlea within 10 minutes of administration²². Fluorescent labelled gentamicin has been detected in both outer and inner hair cells, diffusing through the stria vascularis of rat cochlea²². Inside the hair cells, aminoglycosides appear to cause ototoxic damage by promoting formation of free radicals and reactive oxygen that induces cell death through apoptosis²³.

Salicylate is a common drug with anti-inflammatory properties. At high doses, salicylate has the potential to be ototoxic, causing reversible hearing loss and tinnitus²⁴. High doses of salicylate have long been used in animal research to induce tinnitus in study subjects²⁵. Tinnitus activity in animals can be detected using a startle response or electrophysiological recordings. It is currently unknown if salicylate causes ototoxic changes in the cochlea or brain, as the drug actively crosses the blood brain barrier²⁶. Through animal and human studies, high dose salicylate has been found to affect cochlea function by reducing the function of cochlea outer hair cells^{27 28}. As a result, reduced levels of both stimulated and spontaneous otoacoustic emissions were detected in animal and human studies.

There is also evidence to suggest that salicylate may induce central ototoxicity prior to affecting the cochlea. In an early human study involving patients with rheumatoid arthritis receiving high dose salicylate, the affected patients reported the onset of tinnitus prior to hearing loss²⁹. More recent studies utilising radiolabelled functional imaging studies on animal models have detected hyperactivity in both auditory and non-auditory central structures following the induction of tinnitus with high dose salicylate^{30 31 32}.

Drugs that are ototoxic may be required to treat life-threatening conditions, however, secondary effects such as hearing loss and tinnitus can significantly impair a patient's quality of life. As there is currently no treatment to reverse tinnitus from ototoxicity, the use of ototoxicity monitoring protocols is key in preventing and reducing the incidence of drug-induced tinnitus.

The severity of tinnitus perceived by patients is strongly associated with their underlying emotional and stress factors^{1 4}. These negatively compounding factors have been well observed in clinical practice and reported in studies dating back to 1841 by Curtis et al³³. Furthermore, over the past decade, two large-scale publications (n = 10000) clearly demonstrated participants with a higher degree of emotional and occupational stress factors reporting an perceived increased tinnitus severity^{34 35}.

Interesting findings have been observed in studies analysing cortisol levels in subjects with tinnitus. A laboratory based study (n = 40) found lower salivary cortisol levels in participants with tinnitus and participants with a history of loud sound exposure, compared to participants in the control group³⁶. A similar finding of lower cortisol levels in tinnitus participants was also reported in two other studies investigating cortisol levels in tinnitus patients^{37 38}. The reported lower levels of cortisol in participants with tinnitus suggests that chronic tinnitus interacts with the central hypothalamic-pituitary axis, adapting towards a constant state of stress^{36 37 38}.

It is not uncommon for patients to report tinnitus following injuries to the craniofacial region and cervical neck¹. Some individuals also report the ability to temporarily modulate the loudness and pitch of tinnitus with cervical or mandibular manipulation^{39 40}. This subtype of subjective tinnitus has been termed somatosensory tinnitus (SST)^{39 40 41}. It is hypothesized that this subtype of tinnitus may be triggered following trauma to the neural structures within the head and neck region that are directly integrated with the central auditory pathways²⁷.

Neural networks have been mapped to show interconnections between cervical roots (C1-C4) trigeminal nerve (CN5), glossopharyngeal nerve (CN9), vagus nerve (CN10), auditory neural pathways and CNS²⁷.

The dorsal cochlear nucleus (DCN) has been reported to be the main site of convergence between these neural structures in both animal and human studies^{39 41-}

43

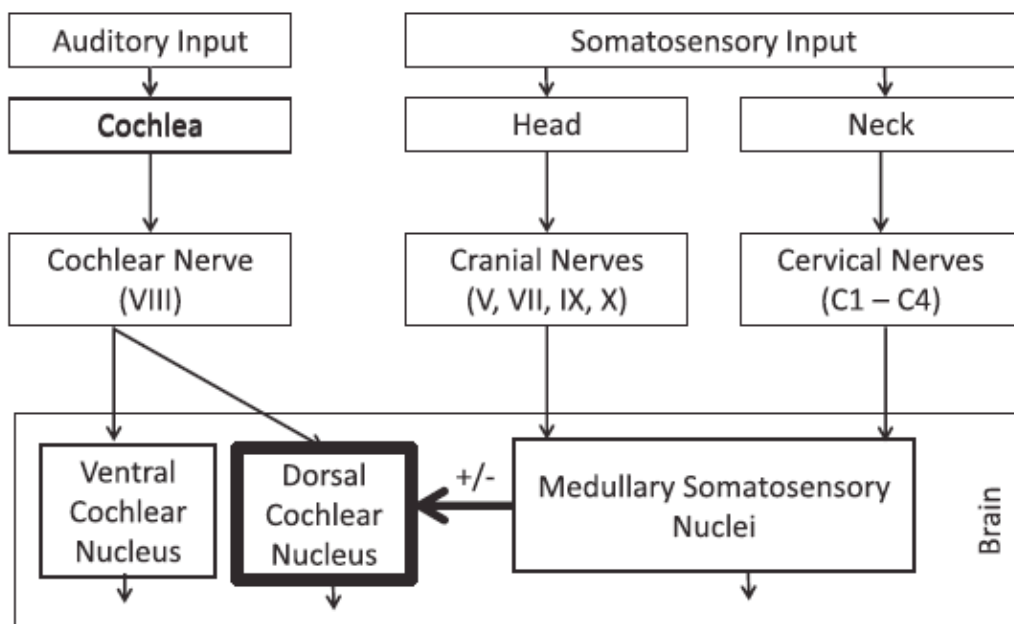


Figure 1: Integrated neural network in somatosensory tinnitus (Levine et al 2007)

Objective tinnitus	Subjective tinnitus
<p>Vascular type</p> <ul style="list-style-type: none"> • Arteriovenous malformation <ul style="list-style-type: none"> • Vascular tumours 	Idiopathic
	<p>Otological conditions</p> <ul style="list-style-type: none"> • Sensorineural hearing loss <ul style="list-style-type: none"> • Meniere's disease • Labyrinthitis & Vestibular neuritis • Middle & inner ear infections
	<p>Ototoxic medication</p> <ul style="list-style-type: none"> • Chemotherapeutic drugs <ul style="list-style-type: none"> • Aspirin • Diuretics
<p>Mechanical type</p> <ul style="list-style-type: none"> • Eustachian tube dysfunction <ul style="list-style-type: none"> • Palatal myoclonus • Tensor tympani myoclonus • Stapedius myoclonus 	<p>Neurological disorders</p> <ul style="list-style-type: none"> • Multiple sclerosis • Vestibular Schwannoma • Cerebrovascular accident
	<p>Metabolic disorders</p> <ul style="list-style-type: none"> • Diabetes mellitus • Hypothyroidism • Pregnancy (Hormonal changes)

Table 1: Aetiology, risk factors and conditions associated with tinnitus (Baguley et al 2013)

1.4 Pathophysiology of Tinnitus Pathways

The pathophysiology of tinnitus was originally assumed to be driven by inner ear and cochlear disorders, resulting in a “peripherally” generated symptom⁴⁴. This understanding was subsequently challenged as tinnitus was detected to be persistent in patients undergoing surgical division of bilateral auditory nerves⁴⁵. Recent advances in tinnitus research supports the hypothesis that abnormal neural activity within both the peripheral and central auditory structures are implicated in tinnitus generation^{1 2 44}. It appears that neural plasticity is the main factor in tinnitus generation and maintenance³.

Increased neural activity is a key factor driving tinnitus activity^{1 3 46}. Although hearing loss leads to reduced sensory input, the resultant chronic down regulation may inversely lead to hyperactivity within the central auditory cortex⁴⁷. These changes have been observed in several animal model studies and functional imaging studies⁴⁸. However, it is unclear if the neural changes are linked to tinnitus activity, as this data does not account for acute tinnitus¹.

Another proposed hypothesis for tinnitus generation is neural synchrony within the central auditory cortex¹. Neuroimaging studies involving patients with sensorineural hearing loss have shown increased activity within deprived regions of the auditory cortex. It is hypothesized that the hyperfunctioning neurons mimic adjacent neurons resulting in tinnitus, in order to compensate for the hearing loss. A retrospective study by Schecklmann et al involving 286 patients with hearing loss found significant correlation between tinnitus pitch and highest frequency of hearing loss. These findings may support the hypothesis of neural synchrony⁴⁹.

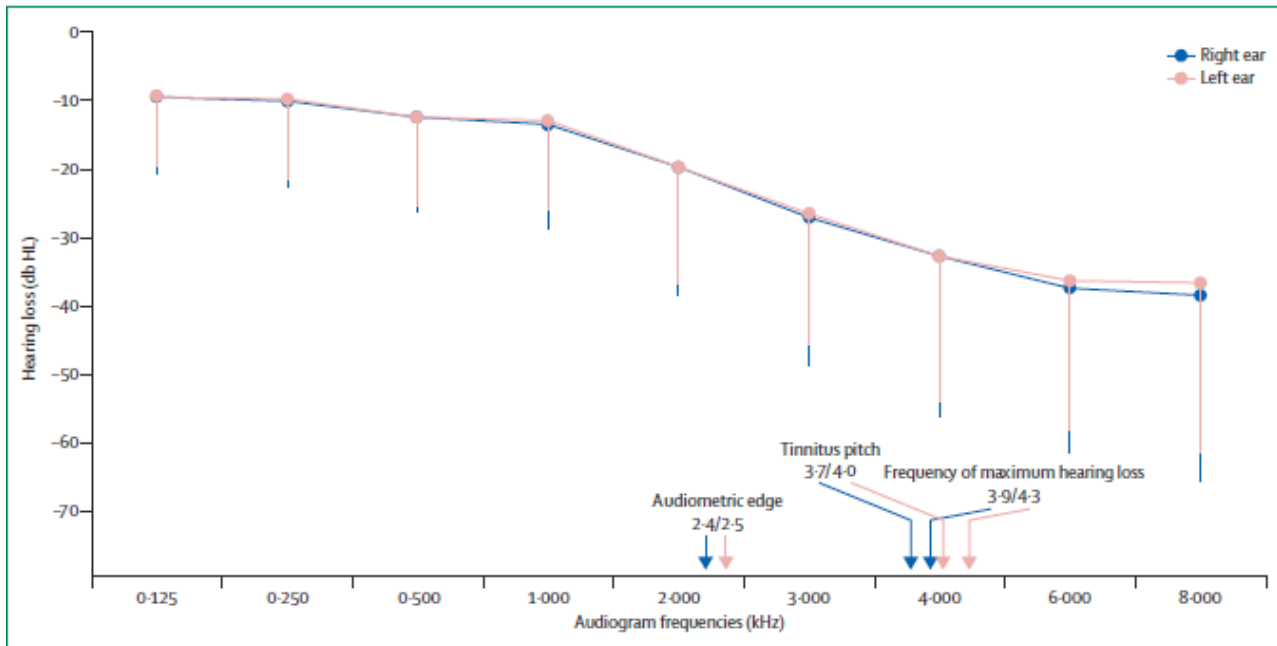


Figure 2: Tinnitus pitch in patients with hearing loss (Schecklmann et al 2012)

Functional magnetic resonance imaging (MRI) and electroencephalogram (EEG) studies on tinnitus patients have shown increased activity within non-auditory central structures, such as the limbic system, anterior insula, thalamus, hippocampus and amygdala. The increased activity within these structures may explain psycho-emotional links with tinnitus, as shared neural networks have been mapped between these structures and the auditory pathways^{1 6 50 51}. It is also suggested that the reticular thalamic nucleus plays a key role in the persistence of tinnitus, even with resolution of initial triggers^{52 53}.

The limbic system is made up of the limbic cortex, hippocampus, amygdala and hypothalamus. These structures play a key role in cognition, emotion and memory formation and have multiple synaptic projections with the ANP^{48 54}. Auditory-limbic interactions are necessary to allow for emotional and memory formation from auditory stimulation or input, which is key to evolution and survival. It is hypothesized that neuroplastic changes associated with tinnitus also affect the interconnected non-auditory structures such as the limbic system, affecting emotional cognitive function and reflex to phantom sound⁵⁵. The amygdala has been proposed as a key area in this model of tinnitus due to projections from the ANP.

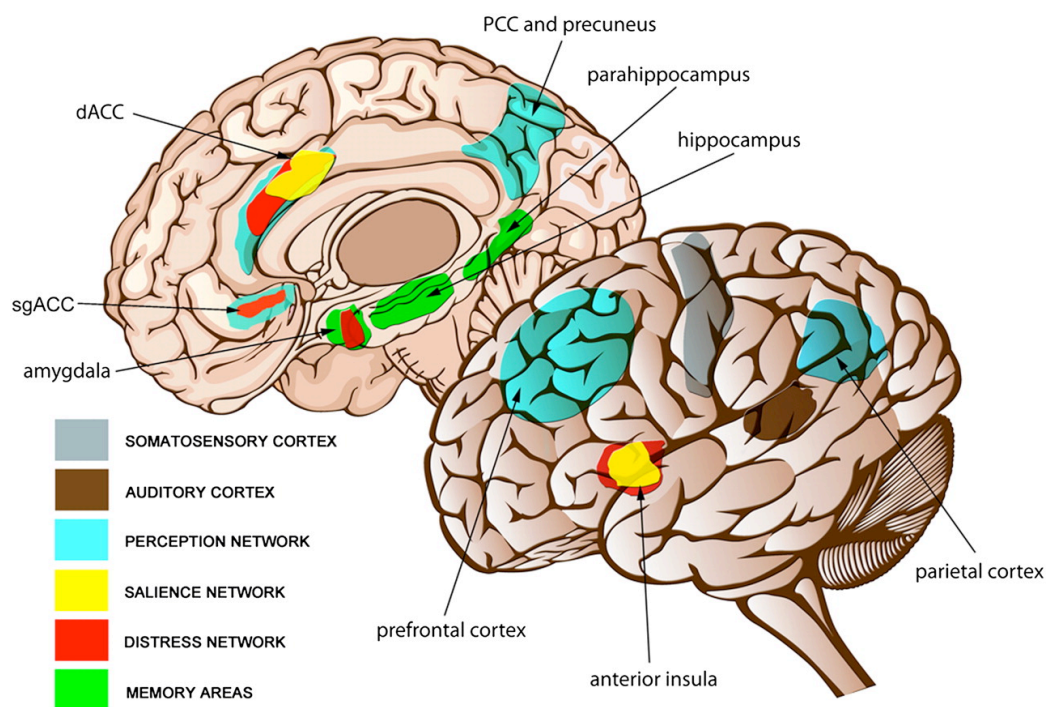


Figure 3: Brain networks involved in tinnitus (De Ridder et al 2011)

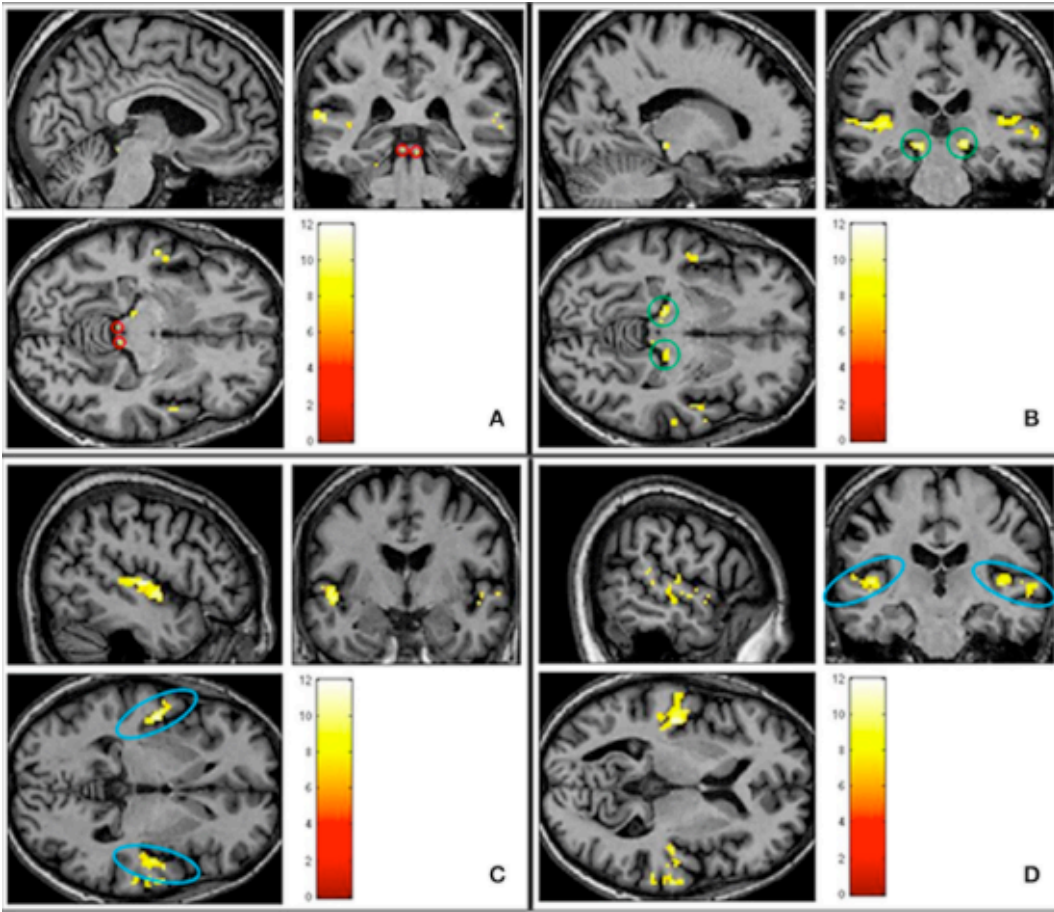


Figure 4: Functional MRI showing multisite neural activation in response to sound
(A) Inferior colliculus circled in red. **(B)** Medial geniculate body circled in green.
(C) Primary auditory cortex circled in blue. **(D)** Primary auditory cortex circled in blue. (Hall et al 2017)

The dorsal cochlear nucleus (DCN) is the first auditory nucleus, located on the dorso-lateral surface of the brainstem. The dorsal cochlear nucleus became an area of focus in tinnitus research, following the detection of DCN hyperactivity in animal subjects exhibiting tinnitus behaviour^{56 57 58}. Fusiform cells are the principle cells within the DCN and receive multisensory information (auditory, sensory and proprioception)⁵⁷. Hyperactive fusiform cells have been implicated in tinnitus activity. Electrophysiological recordings from animal studies have shown increased spontaneous activity in DCN fusiform cells, in animals exhibiting tinnitus activity⁵⁶. Using immunohistochemistry staining, studies have also detected upregulation of excitatory glutamate neurotransmitter in fusiform cells of animals exhibiting tinnitus activity⁵⁹.

Anatomical analysis have demonstrated similarities between human and animal DCN, indicating possible similarities in functional capabilities⁶⁰. To date, there is only one single human based study reporting on tinnitus outcomes following direct DCN stimulation. The study involved inserting auditory brain stem implants directly into the DCN following tumour removal (n = 10), in patients with preoperative tinnitus⁶¹. Six patients reported a significant reduction in tinnitus severity and one patient reported complete resolution of tinnitus⁶¹.

With the aid of modern investigative tools, neuroscientific research has significantly contributed towards existing models on the pathophysiology of tinnitus. Although not without limitations, there is a growing level of evidence to support the role of neuroplasticity, synaptic neurotransmitters and involvement of both auditory and non-auditory centres driving tinnitus activity. These findings have led to the development of novel therapeutic options for tinnitus. However, due to the heterogeneous nature of tinnitus, there is unlikely to be a single treatment modality for all tinnitus patients.

1.5 Current Perspectives on the Treatment of Tinnitus

Tinnitus is a common global medical condition, yet no effective or “gold standard” treatment option exists. Patients are often frustrated with the existing treatment options that are aimed at symptom control rather than cure. A survey carried out in the United States involving 230 tinnitus patients reported that 82.6% of patients had no effective outcome from the prescribed treatment option and only 3.5% of patients had satisfactory outcomes⁶². Studies from the United Kingdom and Sweden also reported similar findings of low satisfaction with treatment outcomes^{63 64}. Significant healthcare expenses are associated with the management of tinnitus. A cost analysis model from the United Kingdom estimates a cost of £717 for every patient that seeks medical help for tinnitus, and this totals to a sum of £750 million per year⁶⁵. Furthermore, these figures are not inclusive of disability benefits claimed for tinnitus, which in the United States amounts to over a billion dollars per year.

Although there is a vast array of treatment options utilised for the management of tinnitus, there is currently no standardized treatment protocol, leaving a significant void in clinical need. Common treatment methods used for tinnitus are discussed below.

1.5.1 Pharmacological

Various drug therapies have been prescribed for tinnitus, but there is currently no single FDA approved drug available. Intravenous lidocaine has been shown to suppress tinnitus activity⁶⁶. Lidocaine blocks sodium channels and has a transient inhibitory effect on the auditory cortex. However, lidocaine is not widely used for tinnitus treatment due to the associated side effect profile of cardiac arrhythmias, and the impracticality of requiring frequent intravenous doses⁶⁶.

Antidepressants are commonly used in treating tinnitus due to the often co-existing depressive disorder. The role of tricyclic antidepressants (TCA) has been investigated in a double-blinded placebo controlled study. This study reported a significant improvement in both depression and tinnitus scores compared to the placebo arm⁶⁷. Similar results were observed in a study utilising selective serotonin reuptake inhibitor (SSRI) antidepressants, with sertraline shown to be more effective in improving tinnitus severity scores when compared to placebo⁶⁸.

It is currently unclear if antidepressants act directly on the central pathways implicated in tinnitus activity or improve the underlying psycho-emotional state of the patient. A systematic review published in 2012 evaluated six clinical trials assessing antidepressants as a treatment option for tinnitus⁶⁹. The author concluded that the trials failed to prove the efficacy of tested drugs and advocated further research. A secondary finding from the systematic review was the benefits of antidepressants in improving mood and anxiety often associated with tinnitus⁶⁹. The British Tinnitus Association (BTA) recognizes these findings, and has recommended antidepressants as a treatment option for tinnitus in the appropriate clinical setting.

Chronic intrusive tinnitus often invokes a state of constant stress and anxiety amongst patients^{50 35}. Anxiolytics such as benzodiazepines have shown benefits in providing symptomatic relief of tinnitus. A small cohort double-blinded study (n = 36, following exclusions) reported 76% of subjects in the alprazolam treatment arm (15% in placebo arm) recorded improvements in tinnitus severity on a visual analogue scale⁷⁰. Apart from the small cohort, additional limitations to this study were the differing doses of alprazolam used by participants and the lack of outcomes from long term follow up⁷⁰. A retrospective study (n = 3000) assessing the use of clonazepam for the treatment of vestibular disorders, reported a secondary finding of 32% of patients reporting improvements in tinnitus severity⁷¹. However, no standardized treatment protocol, outcome measures or follow up details were reported in the study⁷¹. These positive findings were contradicted by a study by Kay et al (n = 21), reporting no significant improvements in tinnitus scores following treatment with diazepam⁷². Additional large, well-designed studies are required to further evaluate the potential therapeutic efficacy of anxiolytics as a treatment option for tinnitus.

Glutamate is the main excitatory neurotransmitter within the auditory neural pathway, acting on N-methyl-D-aspartate (NMDA) receptors⁷³. Glutamate receptor blockers (GRB) may have a role in tinnitus treatment, by suppressing the activity of the excitatory neurotransmitter, which may be driving neural hyperactivity in tinnitus patients⁷³. Drugs with GRB properties such as neramexane, caroverine, memantine and flupirtine have been assessed as a treatment option for tinnitus. A randomised double blinded clinical trial (n = 429) evaluated the therapeutic benefits of neramexane in tinnitus treatment⁷⁴. The study had four arms with varying doses of the drug (25mg, 50mg, 75mg) and a placebo group. Participants in all four-treatment groups reported improvements in tinnitus scores during the treatment phase of the trial. From week twelve onwards, recruits in the 50mg and

75mg treatment arm reported sustained improvement in tinnitus scores, however failed to reach statistical significance⁷⁴.

This latter study also reported 80% of recruits experiencing side effects secondary to GRB use, with headache and dizziness being the most common⁷⁴. The efficacy of memantine has also been assessed, but showed no improvement in tinnitus scores⁷⁵.

Non-selective NMDA antagonists have been evaluated as a treatment option for tinnitus⁷⁶. The drug acamprosate was recently assessed in a double-blinded clinical trial (n = 20)⁷⁷. Findings from this study were encouraging, with subjects in the acamprosate arm (n = 9) reporting significant improvements in tinnitus scores (p = 0.06). Further large-scale trials assessing the efficacy of GRB's and NMDA blockers as a therapeutic option for tinnitus are currently in progress.

The lack of conclusive evidence to support the use of pharmacotherapy for the treatment of tinnitus leaves a void in clinical need. Although some drugs have shown limited promise, evidence to support the wide scale use of these drugs is still lacking. There are a number of on-going clinical trials that may change the landscape of tinnitus treatment, but we currently await these findings.

1.5.2 Non-pharmacological

Non-pharmacological therapies are widely available for tinnitus. The two main options are sound based therapy (SBT) such as tinnitus retaining therapy (TRT) and tinnitus masking (TM). The second option is cognitive behavioural therapy (CBT).

Tinnitus retaining therapy is based on a publication by Jastreboff et al 2013 that proposes a treatment model that aims to alleviate tinnitus through education, habituation and neural sound masking⁷⁸. Patients are divided into 5 categories (0-5) depending on the severity of tinnitus and hearing loss. Protocols for counselling sessions dictate that patients should receive monthly sessions for the first 3 months, then at 3 monthly sessions over a period of 2 years. Treatment outcomes are documented using tinnitus evaluation questionnaires.

To date, the evidence to support TRT is lacking and is not derived from large-scale clinical trials. A Cochrane review on the efficacy of TRT included only a single study as other published trials on TRT did not follow strict counselling protocols⁷⁹⁸⁰. The trial of interest in the Cochrane review was a quasi-randomized trial comparing TM to TRT (n = 123)⁷⁹⁸⁰. The trial reported early benefits in both treatment groups, but superior and sustained tinnitus benefits in the TRT group at 12 months and 18 months post treatment⁷⁹⁸⁰. The Cochrane review however concludes that there is insufficient meaningful data to support the use of TRT, and further well designed trials are required⁸⁰.

Cognitive behavioural therapy aims to modify behaviours through education, relaxation and mindfulness training. A well designed clinical trial by Cima et al 2012 (n=492) showed the benefits of CBT⁸¹ as a treatment option for tinnitus. The trial reported significant improvement in tinnitus scores amongst recruits who received specialist delivered CBT when compared to community based CBT. Both treatment groups also reported a reduction in depression and anxiety scores, with no side effects. Cognitive behavioural therapy has several limitations. It is associated with high cost, is time consuming and has no direct effect on tinnitus activity, but instead improves patients coping mechanisms. There is also no evidence to support the long-term efficacy of CBT as a treatment option for tinnitus.

Tinnitus masking is based on the principle of distraction, utilizing background sound or “white noise” to diminish or render tinnitus inaudible. Sound therapy is a form of tinnitus masking and has been a long standing option used to provide symptomatic relief for tinnitus⁸². Vernon et al, (known as the father of tinnitus masking), concluded that, with appropriate patient selection, sound masking can alleviate distress from tinnitus in 60 – 80% of patients⁸³. Research has also shown that masking using sound that has been frequency matched to the patient’s tinnitus produces improved clinical outcomes⁸³. A placebo controlled trial (n = 63) reported clinically significant benefits in tinnitus outcome measures in 75% of recruits⁸⁴. Similar findings were reported by Williams et al (n = 66) reporting clinically significant improvements in tinnitus loudness (59%) and visual analogue scale (72%) after 22 – 26 weeks of therapy⁸⁵. A study by Hauptmann et al (n = 200), reported an average reduction of tinnitus severity scores by 38% from baseline and 66.9% of recruits reporting tinnitus improvement at 12 months post treatment⁸⁶. The studies reported here are limited due to the lack of randomization and placebo control groups^{85 86}.

Another form of tinnitus masking is complete masking (CM), where an adapted hearing aid produces a broad sound to match and mask tinnitus. However, the majority of treatment protocols for tinnitus masking recommend the use of low-level white noise rather than complete masking. This stems from evidence suggesting that low-level white noise compensates for sensory deprivation from hearing loss that may be driving tinnitus activity. This led to the development of noise generator machines that are used during TRT. The efficacy of TM was observed in a study using the Neuromonics tinnitus treatment protocol, that was developed utilising both auditory and behavioural therapy for tinnitus treatment (n = 47)⁸⁷. The treatment protocol utilises a NeuromonicsTM device designed to produce white noise to mask tinnitus and relaxing music to activate the limbic system. Following a six months treatment duration, 62% of recruits reported an improvement in tinnitus assessment scores⁸⁷. The study was limited by a large exclusion rate due to poor treatment compliance⁸⁷. Currently, there is no strong evidence to suggest that TM is effective in reducing tinnitus loudness or severity. However, TM may have a limited role in reducing the degree of distress caused by the symptom.

Hearing aid amplification (HAA) remains the most prescribed treatment option for patients with tinnitus and hearing loss in clinical practice. Corrective hearing amplification is hypothesised to alleviate tinnitus by restoring auditory stimulation and producing a “masking effect”⁸⁸. There is also the primary benefit of improving the patient’s hearing and ability to communicate. This has shown to significantly improve the patients quality of life and reduce social isolation^{57 89 90}. A prospective study (n=34) showed 90% of patients with hearing loss reported improvement in tinnitus handicap index (THI) scores following HAA⁹¹. There is also evidence to suggest that tinnitus counselling combined with HAA has significant benefits compared to tinnitus counselling alone^{89 90}. Hearing aids

remain a prominent therapeutic option for tinnitus, however limited by the lack of placebo-based comparison trials.

Cochlear implants (CI) aim to restore hearing by converting external sound into digital signals, which are then used to stimulate the cochlea⁹². Up to 80% of CI candidates are reported to suffer from tinnitus and outcomes relating to tinnitus activity following surgery are variable⁹³. There are also reports of onset of tinnitus post implant insertion, modulation of tinnitus when the speech processor is turned on/off and changes in characteristics of tinnitus following implantation.

Previous studies have shown positive findings in tinnitus outcomes following cochlear implantation. In a prospective study involving 50 CI patients with pre operative tinnitus, 28% of patients reported cessation of tinnitus post implantation⁹⁴. Cochlear implants have also been reported to have positive outcomes in patients with single sided deafness (SSD) and tinnitus⁹⁵. A systematic review assessing the influence of CI in patients with unilateral tinnitus and SSD reported 34.2% of patients had suppression of tinnitus, 53.7% had improvements in THI scores, 7.3% maintained stable tinnitus activity and 4.9% reported an increase in THI scores. There were no reports of iatrogenic tinnitus in this review⁹⁵. Although cochlear implants may produce secondary benefit in tinnitus outcomes, cochlear implantation devices are currently not approved for tinnitus treatment. Further research is required in large and well-designed studies to support the role of CI in tinnitus therapy.

Chapter 2

Neuromodulation

2.1 Introduction

In recent years, neuromodulation has emerged as a potential treatment option for symptomatic tinnitus⁹⁶. Neuromodulation is defined as an intervention that alters neural activity to produce a desired outcome for the patient^{96 97}. The first medical neuromodulation device was a spinal cord implant, used in a cancer patient with intractable pain^{97 98}. The device was pioneered by neurosurgeon Dr Norman Shealy in 1967⁹⁷, after he theorised that electrical impulses would travel along the spinal cord to the level of the affected dorsal root and alleviate pain. The first implantable spinal neuromodulation device was designed with Medtronic and aided with pain control for several months for the implanted patient^{97 98}. Since then, neuromodulation has been used to treat various other neurological conditions such as Parkinson's disease, epilepsy, depression and chronic pain⁹⁹. Neuromodulation invokes alterations within the nervous system by delivering repeated and dose controlled stimuli¹⁰⁰. As reported by Shealy et al in 1967, direct neural electrical stimulation creates a voltage gradient that results in ion exchange. Hence, with the appropriate electrical dosage neurons can be either stimulated or inhibited in an effort to produce a desired clinical outcome¹⁰⁰.

Alternative methods to deliver neuromodulation have been developed, including magnetic stimulation, optogenetic stimulation, thermal stimulation and acoustic modulation¹⁰¹. Currently, only magnetic stimulation and acoustic modulation have a role outside the realm of laboratory-based research. Magnetic stimulation is delivered transcutaneously and achieves neuromodulation by invoking a gradient across cells with rapid changes in magnetic currents^{101 102}.

The role of acoustic modulation is expanding in clinical practice, however the exact mechanism of action is not entirely understood¹⁰³. The available evidence suggests that repetitive pulsed acoustic stimuli may stimulate neural activity. Furthermore, the degree of neural activity can be altered according to the dose and character of the acoustics delivered^{101 102 103}.

Here we highlight, that independent to method of delivery, the objective of neuromodulation is to achieve neural stimulation to induce plasticity and functional change to produce clinical benefits.

2.2 Neuromodulation for the Treatment of Tinnitus

There is an increasing volume of evidence to suggest that neuromodulation may have a significant role in the treatment of symptomatic tinnitus^{96 99}. As discussed in Chapter 1, EEG and functional imaging studies have mapped a complex neural network involved in tinnitus activity⁴⁶. With strong evidence to support the theory of neural dysfunction as the main driving force behind tinnitus activity, neuromodulation may offer a potential solution¹⁰⁴. Neuromodulation has a potential to drive neuroplastic change, that may disrupt aberrant neural activity and reinstate controlled neural function⁹⁶. Clinically, this may reduce tinnitus severity and improve quality of life. For the treatment of tinnitus, neuromodulation may be delivered utilizing direct electrical stimulation with an implanted device or non-invasive transcutaneous methods (electrical and magnetic) and acoustic stimulation^{96 105}.

Neuromodulation utilizing electrical stimulation for the treatment of tinnitus has shown promising outcomes. As described below, several treatment protocols have been developed including variations in the method of delivery (transcutaneous or direct stimulation), electrode size and the location of electrode placement, amplitude and duration of electrical stimulation⁸⁷⁻⁸⁹. Cervical spine nerves (C1 – C4) are a potential site for targeted electrical stimulation, as these nerve roots have been mapped to form connections with the auditory cortex¹⁰⁶. Stimulation of cervical nerve root C2, has been shown to have an inhibitory effect on the auditory neural pathways¹⁰⁶. In a study using transcutaneous electrical stimulation of C2 nerve root for the treatment of tinnitus (n = 240), Vanneste et al reported 20% of recruits responded to treatment (p<0.0001) and six recruits reported complete resolution of tinnitus¹⁰⁶.

In another study using self-administered transcutaneous ear lobe stimulation (n = 26), 46% of recruits reported significant improvement in outcome measures¹⁰⁷. Similar findings were found in a placebo-controlled trial (n = 42), reporting improvements in 42.8% of recruits in the treated arm, however 28.5% of recruits in the placebo arm also reporting improvements¹⁰⁸. Findings from these studies indicate some tinnitus patients may benefit for electrical stimulation neuromodulation. However, the small number of recruits and placebo effects observed limit these studies.

Paired invasive vagal nerve stimulation (VNS) and acoustic stimulus (frequency range 170Hz – 16KHz) has been shown to potentially modulate electrical activity within the auditory neural pathways¹⁰⁵. A randomized blinded trial using VNS and auditory stimulation (n = 30) showed significant THI improvements (p=0.0012) in the VNS treatment arm compared to the control group¹⁰⁹. Auditory stimulation was delivered via headphones and a surgically implanted device (Serenity by MicroTransponderTM) was used to deliver direct vagal nerve stimulation. Clinically meaningful improvements were noted in 50% of participants in the VNS group compared to 28% in the control group. Although the study reported a high compliance rate of 96%, adverse events included two cases of vocal cord palsy. There was also one report of a vagal nerve stimulator lead fracture, requiring surgical retrieval¹⁰⁹.

Transcranial magnetic stimulation (TMS) is hypothesized to alter neural activity with strong impulses of magnetic currents. This method of neuromodulation is non-invasive, probably safe and can be used to target specific intracranial regions¹¹⁰. Neuroimaging studies have shown that magnetic stimulation may also alter neural activity at distant intracranial regions that are interconnected with the target site (limbic system activation with auditory cortex stimulation).

Repeated magnetic stimulation has demonstrated the potential to sustain or inhibit neural activity, depending on the parameter settings utilised^{110 111}. A high dose of 5 – 20 Hz has been shown to increase neural activity, while low frequencies of 1 -2 Hz may suppress neural activity, in regions that have been mapped to potentially drive tinnitus activity¹¹².

The potential therapeutic benefits of TMS in tinnitus treatment have been assessed. A study by Plewnia et al (n = 14) reported 57% of recruits responded immediately following magnetic stimulation to the temporoparietal cortex on a visual analogue severity scale ($p < 0.05$)¹¹³. However, the benefits achieved were transient¹¹³. Similar findings were reported by Fregni et al (n = 7) with 42% of recruits reporting significant tinnitus reduction ($p = 0.0024$) and in a study by De Ridder et al (n = 114), 25% of recruits reported positive outcomes^{114 115}. The study by De Ridder et al also reported recruits with long standing tinnitus showed greater response to low frequency TMS ($p < 0.001$)¹¹⁵. Limitations to these studies are small sample size, no placebo control and lack of evidence showing long-term sustained effects. There are currently no commercially available TMS devices that will allow patients to self-administer treatment.

2.3 The role of Paired Stimulation Techniques

With strong evidence to support the involvement of auditory and non-auditory neural pathways in tinnitus activity, paired or multisensory stimulation may have a potential to driving further therapeutic gains. Paired stimulation was first analysed in animal studies using guinea pigs. A study by Marks et al demonstrated that repeated bimodal audio-electrical stimulation may reduce synchrony and spontaneous neural activity in animal exhibiting tinnitus behavior¹⁰³. The positive findings in animal models prompted the assessment of bimodal stimulation in a human study. A double-blinded study carried out in the Kresge Hearing Research Institute, University of Michigan, USA, compared bimodal stimulation to single auditory stimulation in twenty participants with subjective tinnitus¹⁰³. Responsive participants in the bimodal stimulation arm reported improved Tinnitus Loudness Matching (TLM) scores and Tinnitus Functional Index scores. Pooled data from participants in the bimodal stimulation arm produced a mean decrease of 8.035 dB from baseline ($p < 0.05$) and a mean decrease in TFI scores by a significant 7 points from baseline¹⁰³.

The role of paired stimulation was also supported by findings from a study ($n = 20$) pairing auditory and transcranial magnetic stimulation (TMS)¹¹⁶. Electrophysiological recordings from this study suggests that paired stimulation had a greater inhibitory effect on neural activity within the auditory cortex, compared to unimodal (TMS only) stimulation¹¹⁶.

Paired acoustic and vagal nerve electrical stimulation has produced promising results in a randomized control trial involving 30 participants with tinnitus. The paired stimulation group reported a 17% mean improvement at 6 weeks (7.3% placebo arm)¹⁰⁹. Again, limitations observed in these studies include a small cohort of participants, placebo effects and variations in reporting outcomes measures.

2.4 Mutebutton™ Device

The investigational Mutebutton™ (MBT) device is manufactured by Neuromod Devices Limited. The MBT device is a CE Class 2a marked medical device for the treatment of symptomatic tinnitus. The device is fitted by a healthcare professional and can then be used at home. The recommended usage is for 30-60 minutes per day for 12 weeks. Daily device usage can be continuous or divided into 3 slots. The parameter setting of the device can be configured based on the clinical and audiological assessment of the user. Pre fitting assessment includes a detailed clinical assessment and audiometric studies. The device manufacturer has published contraindications to the use of the device including pregnancy, patients with pacemakers, defibrillators and patients with ulcerative disease within the oral cavity and certain neurological conditions.



Figure 5: Mutebutton™ device

2.5 Function and Description

The MBT device comprises of 3 main components. The main handheld controller is used to “control” the treatment session. The user may start, pause and resume the treatment session. The second component is an intraoral tongue tip probe, which is used to deliver gentle electrical stimulation to the anterodorsal surface of the tongue. The final component is a set of high fidelity, over the ear headphones used to deliver auditory stimulation.




Component	Description	Image
Controller	Polycarbonate device with control buttons, visual feedback and battery pack	
Tongue tip device	This component delivers the electrical stimulation to the tip of the tongue	
Headphones	Over the ear headphones delivering frequency adjusted auditory stimulation	

Table 2: Mutebutton™ device components and description

2.6 Mechanism of Action of the Mutebutton™ Device

The Mutebutton™ device is designed to alleviate symptomatic tinnitus via bimodal neuromodulation. The device produces auditory and electrical stimulation. Auditory stimulation is designed to stimulate bilateral auditory pathways and the electrical stimulation is designed to stimulate the dorsal cochlear nucleus, via the lingual and trigeminal nerves.

Auditory stimulation produced by the Mutebutton™ device comprises of therapeutic frequency adjusted tones that are delivered through high-fidelity headphones. There is an option to add background tones to make the listening experience more pleasant. Auditory stimulation is configured based on the users audiological assessment. Hearing thresholds for both ears are assessed to deliver adequate auditory input, simultaneously avoiding uncomfortable sound levels.

The tongue has a saliva coated mucosal surface, which enhances electrical stimulation due to its electrolyte content. The anterior surface of the tongue has a high density of nerve endings, with the lingual branch carrying taste and sensory information from the tongue to the trigeminal nerve. An animal model study by Markovitz and Lim et al reported important anatomical and functional integration between the trigeminal nerve and central auditory pathways¹¹⁷. Findings from this study support the role of stimulation of the trigeminal nerve to suppress hyperactivity within the central auditory pathways, potentially associated with tinnitus activity¹¹⁷.

A key function of the Mutebutton™ device is to drive neuroplastic change to improve on tinnitus severity. Neuroplasticity refers to a neurons ability to adapt and improve on its function. It is also possible for neurons to undergo maladaptive or discoordinated neuroplasticity resulting in an imbalance in function. It is hypothesized that this imbalance in neural function in both auditory and non-auditory pathways, drives tinnitus activity.

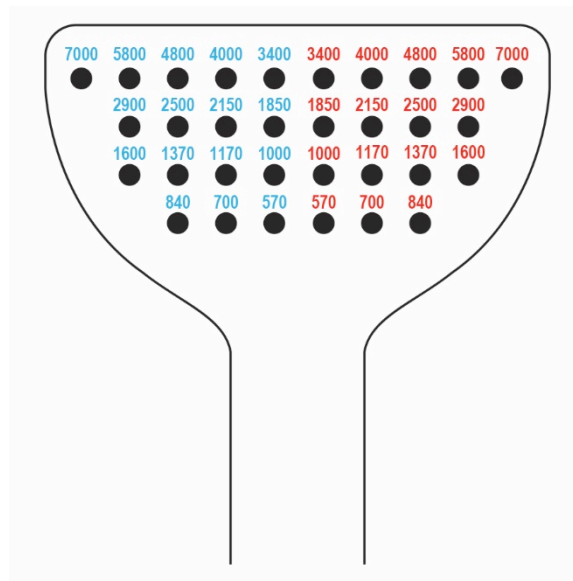


Figure 6: Surface probe of the tongue tip device with symmetrical arrays of 32 electrodes, delivering electrical stimulus to the anterior tongue.

2.7 Anticipated Clinical Benefit

A pilot study reported by Hamilton et al was designed to assess the efficacy of the MBT device for the treatment of symptomatic tinnitus¹⁰⁴. Outcome measures were recorded in the study using the Tinnitus Handicap Inventory (THI), Tinnitus Loudness Matching (TLM) and Minimum Masking Levels (MML). Tinnitus Loudness Matching and Minimum Masking Levels were measured in decibels (dB). Participants with chronic subjective tinnitus (n = 54) were recruited for the study. Data analysis was performed on 44 participants. Two participants withdrew from the study and eight participants failed to achieve minimum treatment compliance. The efficacy of the intervention was assessed by measuring changes in outcome measures between baseline and final scores. The average reductions in THI, TLM and MML were 11.7 (p<0.001), 7.5 dB (p<0.001) and 9.8 dB (p<0.001) respectively.

To further build on these encouraging findings, a randomized blinded trial was designed to assess the reproducibility of therapeutic gains observed in the pilot study, and assess the potential to drive further gains by introducing variations in device stimulation settings.

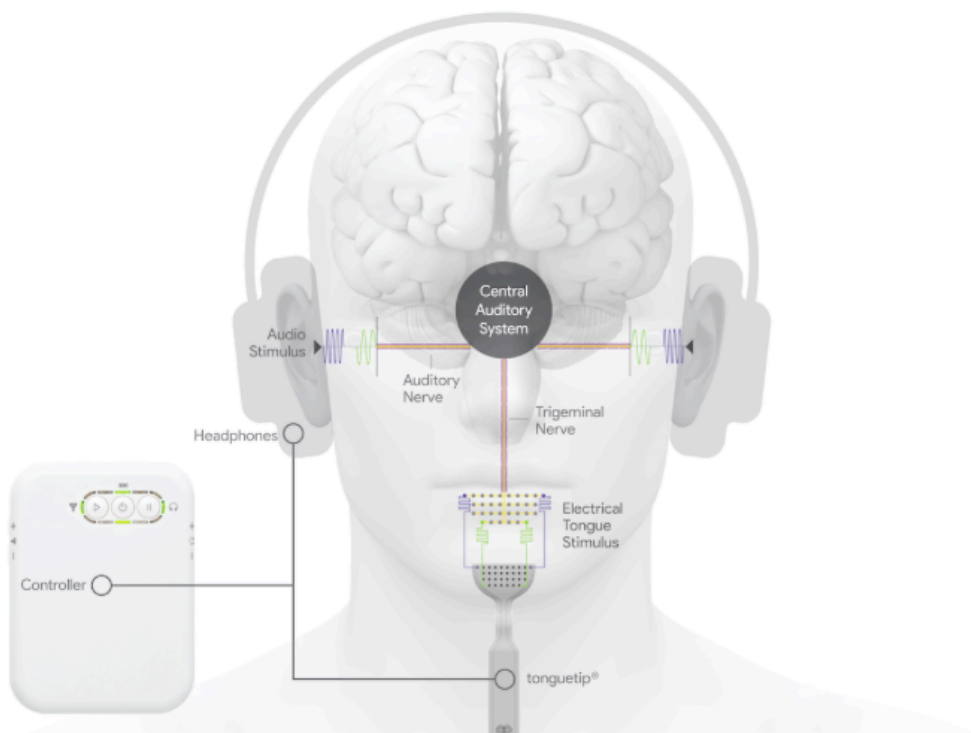


Figure 7: The Mutebutton™ device delivering bi modal auditory and somatosensory stimulation

Chapter 3

Methodology

3.1 Study Objectives

The title of this research project is Parameter Optimization for Bi-Modal Neuromodulation for the Treatment of Tinnitus. The specific aim of this study was to assess the potential benefits of introducing variations in dosage and inter-stimulation timing on the perception of tinnitus. We hypothesised that introducing variations in neuromodulation stimulation settings may drive further therapeutic gains. Outcome measures were recorded during the trial using validated subjective tinnitus assessment questionnaires, Tinnitus Handicap Inventory (THI) and Tinnitus Functional Index (TFI). A secondary aim of this study was to assess the feasibility and safety of MutebuttonTM device. Data on device safety and adverse events were logged throughout the treatment and follow up phase for analysis.

3.2 Study Design

A randomised double-blinded study was designed to examine outcomes from different combined auditory-electrical neuromodulation stimulation settings on participants with chronic subjective tinnitus. The MutebuttonTM device was used in this study to deliver bimodal neuromodulation. The study was designed with two phases, an investigative phase and a follow up phase. The investigative phase was a twelve-week treatment period. Treatment compliant participants were then invited to attend the follow up phase with clinical assessments at 6 months and 12 months post completion of treatment.

The study was conducted at two sites; Wellcome Trust-HRB Clinical Research Facility, St James's Hospital, Dublin, Ireland and Tinnituszentrum Regensburg, University of Regensburg, Germany. Ethical approval was obtained from the Research and Ethics committee of Tallaght Hospital/ St James's Hospital (Ref: 2016-03 List 11) and the University Clinic Regensburg (Ref: 16-101-0186). The trial was sponsored by Neuromod Devices Limited and registered on ClinicalTrials.gov on the 27th January 2016. Data reporting during the trial was in accordance to protocol items defined in the SPIRIT 2013 statement¹¹⁸.

3.3 Intervention

Participants with chronic subjective tinnitus were screened and randomised into three investigative arms (Arm 1, Arm 2 and Arm 3). Each participant enrolled in the trial received a MBT device. Auditory stimulation, consisting of pure tones was individualised to each participant, based on their audiological assessment. Adjustment controls on the MBT device allowed recruits to change the intensity of auditory stimulation, however limited between -12 to + 12dB (volume adjustment) across a frequency range of 0.25 – 8kHz.

Electrical stimulation was delivered through the anterior tongue surface probe. The intensity of electrical stimulation delivered was configured based on each individual recruit's tolerance assessment. Electrical stimulation settings are fixed and participants were not able to self adjust the intensity of electrical stimulation.

Each MBT device had a unique identifier code (UIC), which was specific to each participant. Participants were provided with a user's manual and a link to an instructional video. Intensive safety checks were performed in the research facility prior to allowing the participants to self-administer the treatment at home. Participants were observed using the device for a minimum of thirty minutes at the clinical site and checked for tolerance to the stimulation settings.

The software within the MBT device enables the device to be versatile and provide bimodal neuromodulation stimulation individualised to each user. A built in memory software logs details on date, time, duration of use and duration of contact between tongue tip device and tongue mucosa. Details on any adjustment made to the device by the user are also logged. All the data stored on the device can be downloaded onto a computer and be used for data analysis.

The MBT devices used in the trial were allocated three different stimulation settings (PS1, PS2 and PS3) based on the participants randomized treatment arm. Each parameter setting has varying synchronization or delays between auditory and electrical stimulation. Three different intensities of audio-electric stimulation were also assessed, respective to the treatment arm.

In Arm 1 (PS1), the audio-electric stimulations were synchronised and high frequency stimulation settings were used to represent a high treatment dose. In Arm 2 (PS2), a short 10 – 20 millisecond inter-stimulus delay and high frequency stimulation settings were used. In Arm 3 (PS3), orthogonal settings of longer 0.5 – 1 second inter-stimulus delays and low frequency stimulation settings were used, to represent a low treatment dose.

By incorporating three different parameter settings across three investigative arms, this trial was able to assess the role of synchronized and disrupted neuromodulation stimulation on the perception of tinnitus. We hypothesised that variations in stimulation settings may drive greater neuroplastic change and produce improved treatment outcomes¹¹⁹. Graphical representations of the parameter settings are summarized in Figure 8 - 10. Treatment arm parameter settings are summarised in Table 3 and Table 4.

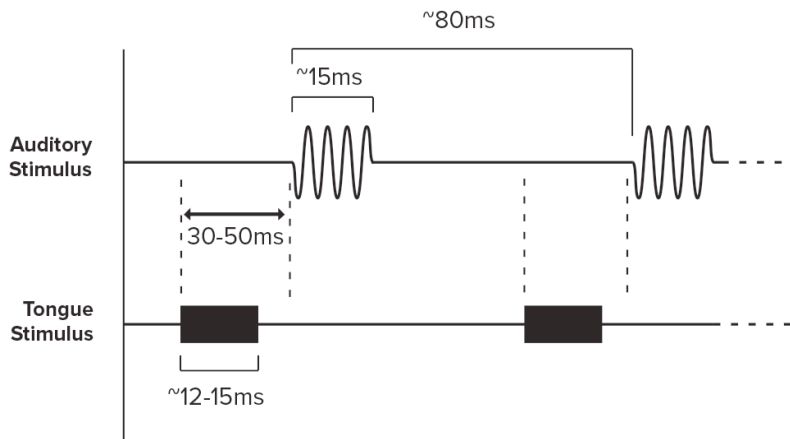


Figure 8: PS1 settings with synchronized bi modal stimulation.

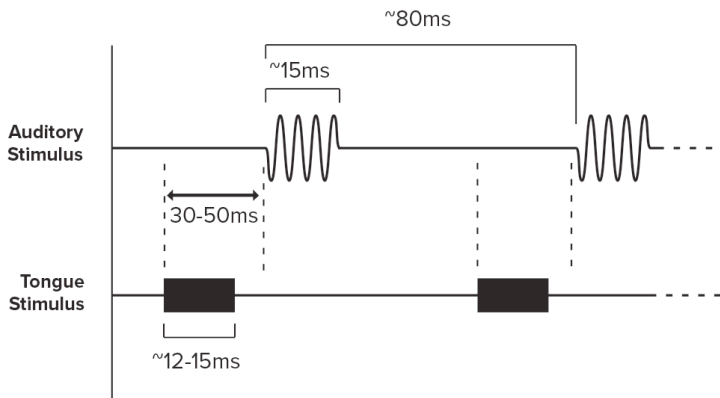


Figure 9: PS2 settings with 10 - 20 millisecond inter-stimulus delay.

Figure 10: PS3 settings with 0.5 – 1 second inter-stimulus delay.

Arm	Parameter Settings (PS)
Arm 1	High frequency auditory tones (500 – 8K Hz) Synchronized audio-electrical stimulation
Arm 2	High frequency auditory tones (500 – 8K Hz) Varying short 10 – 20 millisecond delay between audio-electric stimulation
Arm 3	Low frequency auditory tones (100 – 500 Hz) Long 0.5 - 1 second delay between audio-electric stimulation

Table 3: Summary of intervention between three treatment arms

Arm	Auditory frequency	Duration of auditory stimulation (Milliseconds)	Duration of somatosensory stimulation (Milliseconds)	Duration of inter stimulus delay
Arm 1	500 – 8kHz	20	20	30 – 50 milliseconds
Arm 2	500 – 8kHz	20	20	10 – 20 milliseconds
Arm 3	100 – 500 Hz	400 - 600	20	0.5 – 1 second

Table 4: Summary parameter settings used in each treatment arm

3.4 Outcome Measures

The Tinnitus Handicap Inventory (THI) and the Tinnitus Functional Index (TFI) were used as outcome measures during the study. Both the THI and TFI are validated research tools^{120 121 122}.

The THI questionnaire is composed of 25 questions, assessing the psychological impact of tinnitus. Each question is answered with either a yes, sometimes or no and the selected answer corresponds to a score of 4, 2 or 0 respectively. Total scores from the THI questionnaire range from 0 – 100, with a higher score indicating a greater degree of symptom burden¹²⁰.

The TFI questionnaire assesses participant's functional abilities over the previous seven days. The questionnaire contains 25 questions that are answered using an eleven point Likert scale (0 – 10)¹²¹. A high TFI score indicates a greater impact of tinnitus on daily function.

Tinnitus Handicap Inventory (THI)

This form is for informational purposes only and should not take the place of consultation and evaluation by a healthcare professional.

Your Name: _____

Date: _____

Instructions: The purpose of this questionnaire is to identify, quantify, and evaluate the difficulties that you may be experiencing because of tinnitus. Please do not skip any questions. When you have answer all the questions, add up your total score, based on the values for each response.

- | | | | |
|---|-------------------------------|-------------------------------------|------------------------------|
| 1. Because of your tinnitus, is it difficult for you to concentrate? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 2. Does the loudness of your tinnitus make it difficult for you to hear people? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 3. Does your tinnitus make you angry? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 4. Does your tinnitus make you feel confused? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 5. Because of your tinnitus, do you feel desperate? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 6. Do you complain a great deal about your tinnitus? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 7. Because of your tinnitus, do you have trouble falling to sleep at night? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 8. Do you feel as though you cannot escape your tinnitus? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 9. Does your tinnitus interfere with your ability to enjoy your social activities (such as going out to dinner, to the movies)? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 10. Because of your tinnitus, do you feel frustrated? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 11. Because of your tinnitus, do you feel that you have a terrible disease? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 12. Does your tinnitus make it difficult for you to enjoy life? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 13. Does your tinnitus interfere with your job or household responsibilities? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 14. Because of your tinnitus, do you find that you are often irritable? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 15. Because of your tinnitus, is it difficult for you to read? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 16. Does your tinnitus make you upset? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 17. Do you feel that your tinnitus problem has placed stress on your relationships with members of your family and friends? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 18. Do you find it difficult to focus your attention away from your tinnitus and on other things? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 19. Do you feel that you have no control over your tinnitus? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 20. Because of your tinnitus, do you often feel tired? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 21. Because of your tinnitus, do you feel depressed? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 22. Does your tinnitus make you feel anxious? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 23. Do you feel that you can no longer cope with your tinnitus? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 24. Does your tinnitus get worse when you are under stress? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |
| 25. Does your tinnitus make you feel insecure? | <input type="radio"/> Yes (4) | <input type="radio"/> Sometimes (2) | <input type="radio"/> No (0) |

The sum of all responses is your THI Score >>>

0

Newman CW, Jacobson GR, Spitzer JB. (1996) "Development of the Tinnitus Handicap Inventory." Archives of Otolaryngology - Head and Neck Surgery. 122(2):143-8.

McCombe A, Baguley D, Cole R, McKenna L, McEnery C & Windle-Taylor P. (2001). "Guidelines for the Grading of Tinnitus Severity: the Results of a Working Group Commissioned by the British Association of Otolaryngologists, Head and Neck Surgeons." Clinical Otolaryngology. 26, 388-393.

0-16: Slight or no handicap (Grade 1)

18-36: Mild handicap (Grade 2)

38-56: Moderate handicap (Grade 3)

58-76: Severe handicap (Grade 4)

78-100: Catastrophic handicap (Grade 5)

Figure 11: The Tinnitus Handicap Inventory (Henry et al 2016)

TINNITUS FUNCTIONAL INDEX

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

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

I Over the PAST WEEK...

1. What percentage of your time awake were you consciously **AWARE OF** your tinnitus?
Never aware ► 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% ◄ Always aware
2. How **STRONG** or **LOUD** was your tinnitus?
Not at all strong or loud ► 0 1 2 3 4 5 6 7 8 9 10 ◄ Extremely strong or loud
3. What percentage of your time awake were you **ANNOYED** by your tinnitus?
None of the time ► 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% ◄ All of the time

SC Over the PAST WEEK...

4. Did you feel **IN CONTROL** in regard to your tinnitus?
Very much in control ► 0 1 2 3 4 5 6 7 8 9 10 ◄ Never in control
5. How easy was it for you to **COPE** with your tinnitus?
Very easy to cope ► 0 1 2 3 4 5 6 7 8 9 10 ◄ Impossible to cope
6. How easy was it for you to **IGNORE** your tinnitus?
Very easy to ignore ► 0 1 2 3 4 5 6 7 8 9 10 ◄ Impossible to ignore

C Over the PAST WEEK...

7. Your ability to **CONCENTRATE**?
Did not interfere ► 0 1 2 3 4 5 6 7 8 9 10 ◄ Completely interfered
8. Your ability to **THINK CLEARLY**?
Did not interfere ► 0 1 2 3 4 5 6 7 8 9 10 ◄ Completely interfered
9. Your ability to **FOCUS ATTENTION** on other things besides your tinnitus?
Did not interfere ► 0 1 2 3 4 5 6 7 8 9 10 ◄ Completely interfered

SL Over the PAST WEEK...

10. How often did your tinnitus make it difficult to **FALL ASLEEP** or **STAY ASLEEP**?
Never had difficulty ► 0 1 2 3 4 5 6 7 8 9 10 ◄ Always had difficulty
11. How often did your tinnitus cause you difficulty in getting **AS MUCH SLEEP** as you needed?
Never had difficulty ► 0 1 2 3 4 5 6 7 8 9 10 ◄ Always had difficulty
12. How much of the time did your tinnitus keep you from **SLEEPING** as **DEEPLY** or as **PEACEFULLY** as you would have liked?
None of the time ► 0 1 2 3 4 5 6 7 8 9 10 ◄ All of the time

Figure 12: Page 1 of Tinnitus Functional Index (Newman et al 1996)

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

A	Over the PAST WEEK, how much has your tinnitus interfered with...	<i>Did not interfere</i>		<i>Completely interfered</i>
		▼		▼
	13. Your ability to HEAR CLEARLY ?	0	1 2 3 4 5 6 7 8 9 10	
	14. Your ability to UNDERSTAND PEOPLE who are talking?	0	1 2 3 4 5 6 7 8 9 10	
	15. Your ability to FOLLOW CONVERSATIONS in a group or at meetings?	0	1 2 3 4 5 6 7 8 9 10	
R	Over the PAST WEEK, how much has your tinnitus interfered with...	<i>Did not interfere</i>		<i>Completely interfered</i>
		▼		▼
	16. Your QUIET RESTING ACTIVITIES ?	0	1 2 3 4 5 6 7 8 9 10	
	17. Your ability to RELAX ?	0	1 2 3 4 5 6 7 8 9 10	
	18. Your ability to enjoy PEACE AND QUIET ?	0	1 2 3 4 5 6 7 8 9 10	
Q	Over the PAST WEEK, how much has your tinnitus interfered with...	<i>Did not interfere</i>		<i>Completely interfered</i>
		▼		▼
	19. Your enjoyment of SOCIAL ACTIVITIES ?	0	1 2 3 4 5 6 7 8 9 10	
	20. Your ENJOYMENT OF LIFE ?	0	1 2 3 4 5 6 7 8 9 10	
	21. Your RELATIONSHIPS with family, friends and other people?	0	1 2 3 4 5 6 7 8 9 10	
	22. How often did your tinnitus cause you to have difficulty performing your WORK OR OTHER TASKS , such as home maintenance, school work, or caring for children or others?			
	<i>Never had difficulty</i> ► 0 1 2 3 4 5 6 7 8 9 10 ◀ <i>Always had difficulty</i>			
E	Over the PAST WEEK...			
	23. How ANXIOUS or WORRIED has your tinnitus made you feel?			
	<i>Not at all anxious or worried</i> ► 0 1 2 3 4 5 6 7 8 9 10 ◀ <i>Extremely anxious or worried</i>			
	24. How BOTHERED or UPSET have you been because of your tinnitus?			
	<i>Not at all bothered or upset</i> ► 0 1 2 3 4 5 6 7 8 9 10 ◀ <i>Extremely bothered or upset</i>			
	25. How DEPRESSED were you because of your tinnitus?			
	<i>Not at all depressed</i> ► 0 1 2 3 4 5 6 7 8 9 10 ◀ <i>Extremely depressed</i>			

Figure 13: Page 2 of Tinnitus Functional Index (Newman et al 1996)

3.5 Sample Size

The sample size for the trial was calculated based on the defined clinically significant change of 7 THI points from baseline to endpoint¹²³. A minimum change of 7 THI points following an intervention, has been recognized as a clinically significant response and has been validated for use in clinical research¹²³. The power of the study was pre set at 95% with the probability of type 1 error set to 0.025. Sample size calculations were completed using MATLAB 2016a. The total number of participants was set at a minimum of 273 and a minimum of 91 within each treatment arm. Based on these figures, a further 10% of participants were recruited to compensate for the expected drop out rate. The number of participants was divided 80:20 between Ireland and Germany guided by funding allocations.

3.6 Randomization

Participants recruited for the study following the screening phase were randomized into three parallel arms. Both investigators and participants were blinded to treatment allocations. Stratified randomization based on hearing thresholds was applied to reduce subgroup imbalance. In order of priority, the strata are;

- I. Normal hearing thresholds (<20dB)
- II. Sensorineural hearing loss
- III. Hyperacusis (sound level intolerance <60dB)

Dice rolls emulated in MATLAB's Mersenne Twister algorithm (V.2016a) was used for the randomization process by coding the UIC of the MBT device allocated to each participant.

3.7 Data Collection and Analysis

The electronic case report form (ECRF) software was used to record data collected during the trial. Each participant was given a unique identifier code (UIC) that corresponds with MBT device used by the participant. The UIC for each participant was used to record all the data collected from each individual recruited during the trial and follow up phase. Device parameter settings were not recorded in order to maintain blinding.

Outcome measures were sampled using the THI and TFI questionnaires. The mean change in scores from baseline to endpoint was analysed to obtain within arm and inter-arm outcomes.

The safety and feasibility of the MBT device was performed during the trial by evaluating all recorded adverse events during the treatment and follow up phase. Safety monitoring and adverse events are discussed in Section 3.12 and 3.13.

3.8 Recruitment

Participants were recruited for the trial with the aid of media advertisements. Information on the clinical trial was also sent out to general practitioners, otolaryngologists and audiologists. Participants interested in volunteering for the study were welcomed to register their interest in a dedicated recruitment website.

Once participants completed the registration section, they were then re-directed to an online eligibility assessment survey hosted by SurveyGizmo. The online survey collected data on demographics, clinical details on tinnitus, oral health, oral piercings and current medical conditions. Participants who were eligible to partake in the trial based on the information provided on the online survey were then invited to engage in a formal screening assessment at the research facility.

3.9 Eligibility Criteria

The eligibility criteria for this trial was based on the TAVSS study and best practice guidelines recommended by the Tinnitus Research Initiative (TRI)¹²⁴. The eligibility criteria for the trial are listed below;

- Self reported subjective tinnitus for 3 months
- Self reported subjective tinnitus for less than 5 years
- Aged between 18 – 70 years
- Baseline THI score between 28 – 76 points
- Adequate language proficiency
- Able to commit to treatment compliance

Exclusion criteria for the study are listed below;

- Objective tinnitus
- Abnormal otological assessment on otoscopy or tympanometry
- SNHL of >40 dB in 1 ear at any frequency between 0.25 – 1 kHz
- SNHL of >80 dB in 1 ear at any frequency between 2 – 8 kHz
- Using hearing aids for under 3 months
- Implanted medical devices
- Cervical spine and mandibular disorders
- Anxiety inventory score of 120 – 160 points
- Mini mental state exam of <20 points
- Neurological conditions
- Meniere's disease
- Neurogenic medication
- Oral piercings
- Pregnancy

3.10 Clinical Site Screening

At the first screening visit, informed consent was obtained and participants underwent a detailed clinical assessment. The eligibility checklist was repeated and cross-referenced with the information provided on the online survey, to ensure consistency. The clinical assessment carried out on each participant involved a clinical history, ear exam, oral exam and an audiological assessment. Participants also completed the THI and TFI questionnaires.

Participants deemed eligible to partake in the study following the first assessment, then completed a comprehensive training session with the MBT device. The training session included instructions on device usage and troubleshooting. Participants were observed completing a single treatment session at the research facility to ensure recruits were able to self-administer treatment at home.

The first clinical assessment during the treatment phase of the study was performed at week-6. During this assessment, primary outcome measure questionnaires were sampled and a clinical assessment was carried out at the research facility. Device safety checks were performed on the MBT device and data on the device memory software was downloaded on the external ECRF software. A second assessment was performed at week 12, to mark the end of the treatment phase. Here again, primary outcomes measures, clinical assessment and audiological test were performed. Participants returned their allocated MBT device during this assessment.

During the follow up phase of the trial, participants were reviewed at 6 weeks, 6 months and 12 months post treatment. Primary outcome questionnaires and clinical assessments were repeated to obtain data on the long-term effects of the intervention in each study arm. The participant visit schedule is summarized in Table 5.

Visit	Visit 1 Week 0	Visit 2 Week 0	Visit 3 Week 6	Visit 4 Week 12	Visit Week 18	Visit 6 6 Months	Visit 6 12 Months
Informed consent	X						
Clinical assessment	X	X	X	X			
Audiometric assessment	X			X			
THI	X	X	X	X	X	X	X
TFI	X	X	X	X	X	X	X
Device fitting and training		X	X	X			
Device return				X			

Table 5: Summary of visit timeline and assessments.

3.11 Compliance

Participants recruited for the study were counselled on the importance of treatment compliance, as it was a key factor in producing clinically meaningful data from the trial. Participants were required to self-administer treatment daily for 30 – 60 minutes, either in a single session or three equally divided sessions. The treatment phase of the trial was 12 weeks, with an expected 5040 minutes of treatment time. For practical reasons, a minimum treatment compliance total time of 3326 minutes (66%) was set, to make allowances for any unexpected breaks during the 12-week treatment regime. Data used for the final statistical analysis was from participants who achieved the minimum treatment compliance or better. Accurate data on treatment compliance of each participant was collected during the trial by the memory software in the MBT device. As summarized in Table 5, data stored on the MBT device was downloaded and reviewed at each clinical assessment. Any issues that led to breaks in treatment during the treatment phase were addressed with urgency.

3.12 Safety Monitoring

The MBT device is CE marked as a Class 2 medical device used for the treatment of symptomatic tinnitus. Each device used during the trial was monitored based on existing quality standards and vigilance processes. Any risks, hazards or reported adverse events triggered an escalation procedure that requires a systematic evaluation by the investigative team. Every recruited participant was given an emergency contact number to report any adverse events during the treatment and follow up phase of the trial.

3.13 Adverse Events

Data on safety and adverse events (AE) were logged throughout the trial using the ECRF software. An adverse event was defined as any unfavourable and unintended sign, symptom or disease that may or may not be related to device use. Adverse events were subtyped into minor, major or serious. A serious adverse event was defined as death or critical deterioration in the health of a participant. The adverse events data logs contained information on the nature of the AE, device issues, instructions given to participant and follow up plan formulated.

The participants recruited for the trial were offered the option to withdraw from the study at any point. Participants who opted to withdraw from the study could request to have all their data removed and excluded from future data analysis. Participants could be removed from the study by the investigative team if there are found to have:

- Provided misleading information during the eligibility assessment.
- Developed any of the exclusion conditions during the trial.
- Not achieved defined minimum compliance.
- Disclosed details of the study, randomization or parameter settings.

3.14 Traceability

All MBT devices have a designated unique identifier code that can be tracked to the participant who used the device during the treatment phase. A tracking log was maintained to enable device tracing during the study and contained the following information:

- Serial number.
- Manufacture date.
- Allocated participant PIN.
- Date assigned to patient.
- Date returned by patient.
- Safety and AE logs.
- Device repair and replacements.

Chapter 4

Characteristics of Study Participants

4.1 Introduction

The demographic data and clinical characteristics of participants recruited for the study are analysed in Chapter 4. Minimization methods and equal distribution of participants across all three-treatment arms was performed to minimize statistical bias.

4.2 Patient Recruitment and Demographics

Participants were recruited for the trial through media advertising, directing them to the online eligibility survey. Information leaflets on the trial were also distributed to healthcare practitioners involved in tinnitus care. As anticipated, a large number of individuals ($n = 5826$) completed the online eligibility survey in Ireland and Germany. Based on the predefined exclusion criteria, 5128 participants who filled the online survey were excluded, and a further 372 were excluded following the first clinical assessment. Subsequent to the eligibility assessment phase, 326 participants were then randomized into three investigative arms as summarized in Figure 14. There was an unequal distribution of participants between Ireland and Germany due to funding available in each research facility. Two hundred and sixty one participants were assessed in the Clinical Research Facility in St James's Hospital, Dublin, Ireland and 65 participants were assessed in the University of Regensburg, Germany.

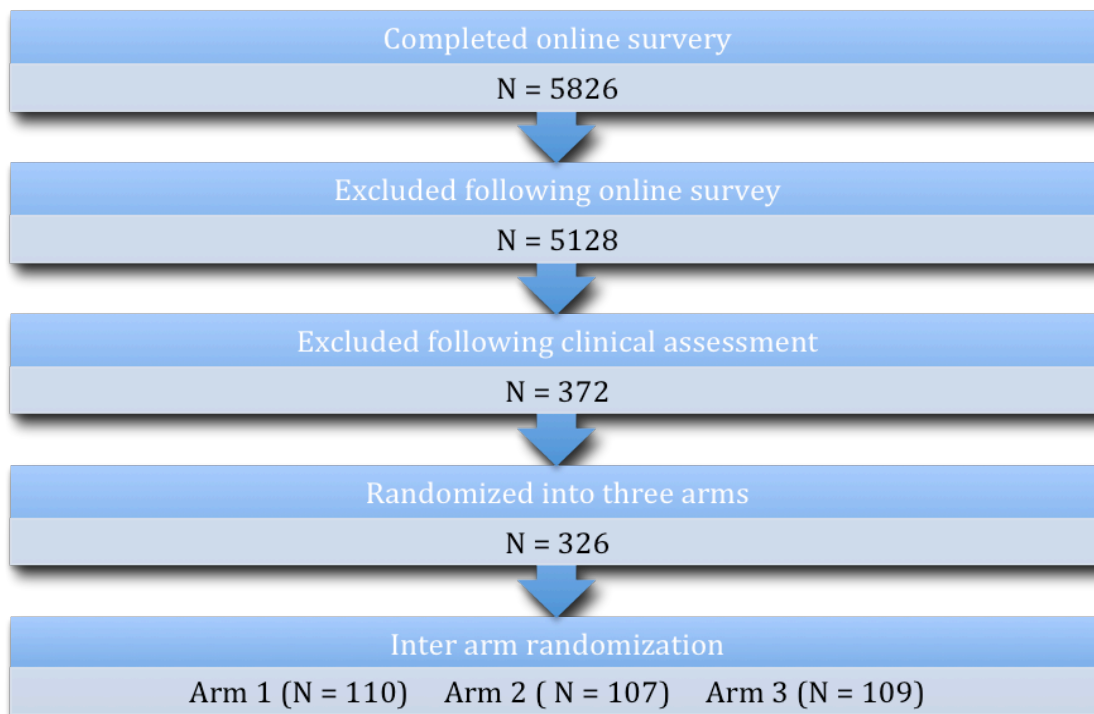


Figure 14: Participant flow diagram, from screening to randomization

From the 326 participants recruited for the study, 212 were males and 114 females (ratio 1: 1.8). The mean age of the participants was 48 years and the mean duration of tinnitus was 2 years. Complete and inter-arm patient demographics are summarized in Table 6

Characteristics	Units	Cohort	Arm 1	Arm 2	Arm 3	p-value
Total enrolled	Participants	326	110	107	109	0.990
Irish cohort	Participants	261	86	85	90	0.975
German cohort	Participants	65	24	22	19	0.883
Male	Participants	212	65	79	68	0.694
Female	Participants	114	45	28	41	0.351
Mean age	Years	48.1	46.3	48.7	49.5	0.102
Tinnitus mean duration	Years	2.6	2.5	2.7	2.6	0.77

Table 6: Patient demographics

4.3 Outcome Measures

The THI and TFI questionnaires were utilized to record outcome measures during the trial. The mean baseline THI and TFI scores for each treatment arm is summarized in Table 7. The mean baseline THI and TFI scores for all three arms were 43.5 and 47.9 points respectively. There were no significant differences in baseline scores across the three-study arms.

4.4 Minimization Characteristics

A minimization method was used during randomization of participants to reduce subgroup imbalances. The binary stratification categories included normal hearing thresholds ($<20\text{dB}$), SNHL and hyperacusis (sound level intolerance $<60\text{dB}$). The participants were distributed between the three treatment arms, with no significant difference between the stratification categories that would lead to primary endpoint bias. Baseline pre treatment outcome measures and minimization characteristics are summarised in Table 7.

Characteristics	Units	Cohort	Arm 1	Arm 2	Arm 3	p-value
THI @ Baseline	Mean points	43.5	44.5	44	42	0.325
TFI @ Baseline	Mean points	47.9	47.7	48.1	47.7	0.96
Stratification						
Normal hearing	Participants	78	26	26	26	1.0
SNHL	Participants	107	35	37	35	1.0
Hyperacusis	Participants	66	19	21	26	0.74

Table 7: Baseline pre treatment outcome measures and minimization characteristics

4.5 Follow up and Treatment Compliant Figures

At the end of the 12-week treatment period, 84% of participants (n = 274) were compliant in attending the two on site clinical assessments (week-6 and week-12). The minimum treatment compliance of 36 hours over 12 weeks was achieved by 95% of participants who were compliant with clinical attendance. Treatment compliant participants were invited to attend the follow up phase, with clinical assessments at 6 weeks (FU1), 6 months (FU2) and 12 months (FU3) post treatment. A drop out rate of 20% was expected during the follow up phase due to the prolonged timeline.

However, for participants who did not attend the on site follow up, the device safety monitoring was continued with telephone assessments. There were no significant differences in the treatment compliance rates and attendance across the treatment arms. Participant attendance figures in relation to time line of the clinical assessments are summarised in Table 8. Figures on participants lost to long-term follow up are summarised in Table 9.

Visits	Units	Cohort	Arm 1	Arm 2	Arm 3	p-value
Interim (6 weeks)	Participants	277	97	92	88	0.898
Final (12 weeks)	Participants	274	89	94	91	0.964
Treatment compliant cohort	Participants (Excluded)	260 (14)	85 (4)	89 (5)	86 (5)	
FU1	Participants	185	59	70	56	0.620
FU2	Participants	183	57	69	57	0.716
FU3	Participants	156	46	57	53	0.760

Table 8: Participant attendance figures, from enrolment to long-term follow up.

Visits	Units	Arm 1	Arm 2	Arm 3
Interim	Participants	10	10	14
Final	Participants	10	2	4
FU1	Participants	13	10	16
FU2	Participants	10	9	7
FU3	Participants	12	11	9

Table 9: Number of participants lost to follow up from interim visit to long-term follow-up.

Chapter 5

Therapeutic Effects of Treatment

5.1 Introduction

The primary end points used to assess the treatment efficacy of the MBT device comprised of changes in mean THI and TFI scores obtained from treatment compliant participants (minimum treatment of 36 hours over 12 weeks). Mean changes in scores were analysed using baseline and post treatment outcome measure scores.

5.2 Within Arm Changes in THI and TFI Scores

Scatter plots are used to represent changes in mean THI and TFI scores. Following 12 weeks of treatment, a total of 260 participants across all 3 arms were treatment compliant. Figures 15 and 16 display changes in average primary outcome measure scores across 3 arms. A total of 86.1% and 81.3% of participants reported an improvement in THI and TFI respectively.

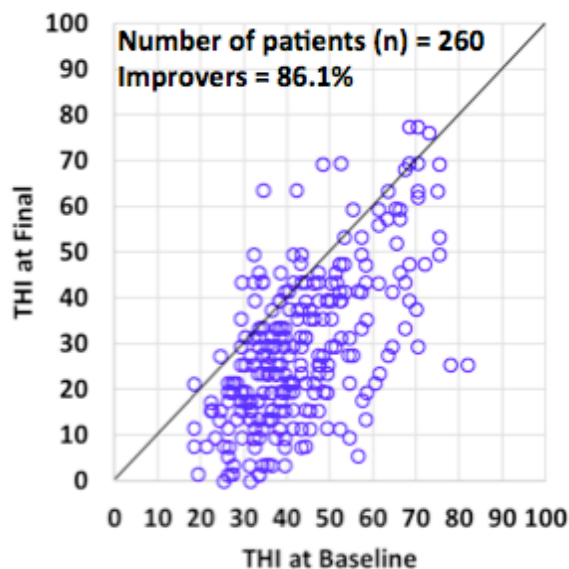


Figure 15: Scatter plot representing changes in average THI scores in all treatment compliant patients. Points below the diagonal black line indicate an improvement change in both scores.

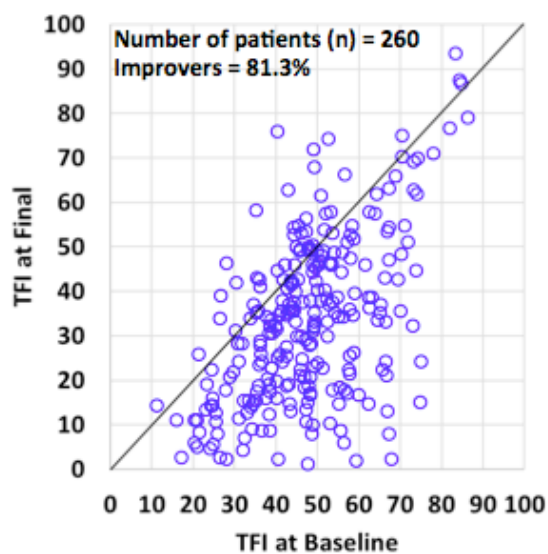


Figure 16: Scatter plot representing changes in average TFI scores in all treatment compliant patients.

Figure 17 displays 3 scatter plots (A – C) representing changes in THI scores in each treatment arm. The final THI score for treatment compliant participants is plotted against their baseline score. At week 12 (end of treatment), 85%, 88.8% and 83.7% of treatment compliant participants in arm 1, 2 and 3 respectively, recorded a reduction in outcome scores, indicating benefits from treatment. Participants in arm 1, 2 and 3 exhibited an average decrease of 14.6, 14.5, 13.5 points in THI respectively.

The mean changes in TFI scores are shown in Figure 18, scatter plots (D - F). Here again, the majority of participants recorded a reduction in TFI scores. Within the cohort of treatment compliant participants, 88.3% in arm 1, 80.7% in arm 2 and 74.7% in arm 3 reported improvements in TFI scores. The mean reductions in TFI scores were 13.9, 13.8 and 13.2 points in arm 1, 2, and 3 respectively. Statistical analysis using paired two-tailed t-test showed all within arm comparison of THI and TFI scores to be highly significant ($p < 0.001$). Within arm primary end points were successfully achieved and statistically significant in multiple comparisons.

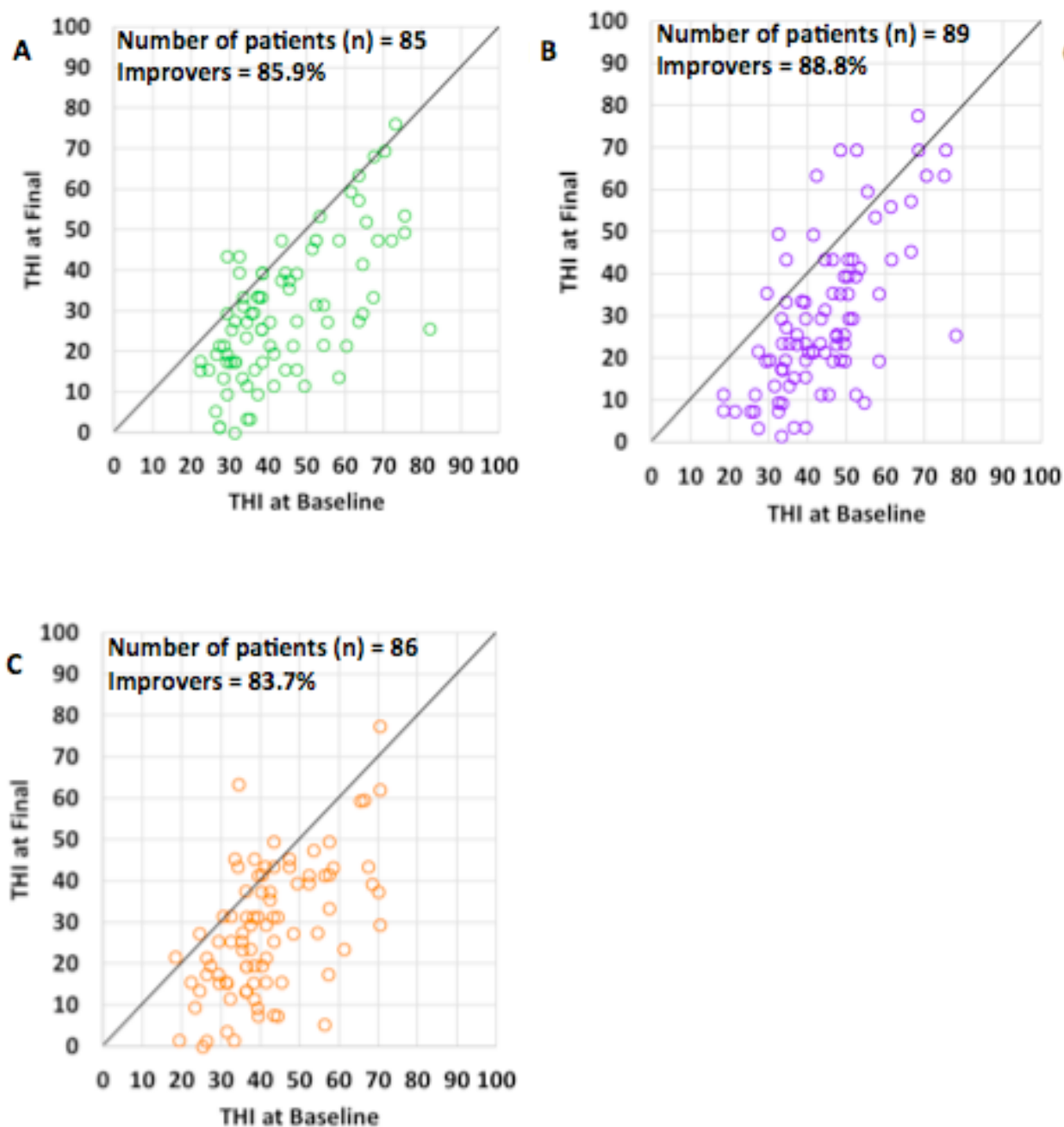


Figure 17: Scatter plots (A – C) showing changes in average change THI and TFI scores. Points below the diagonal black line indicate an improvement change in both scores.

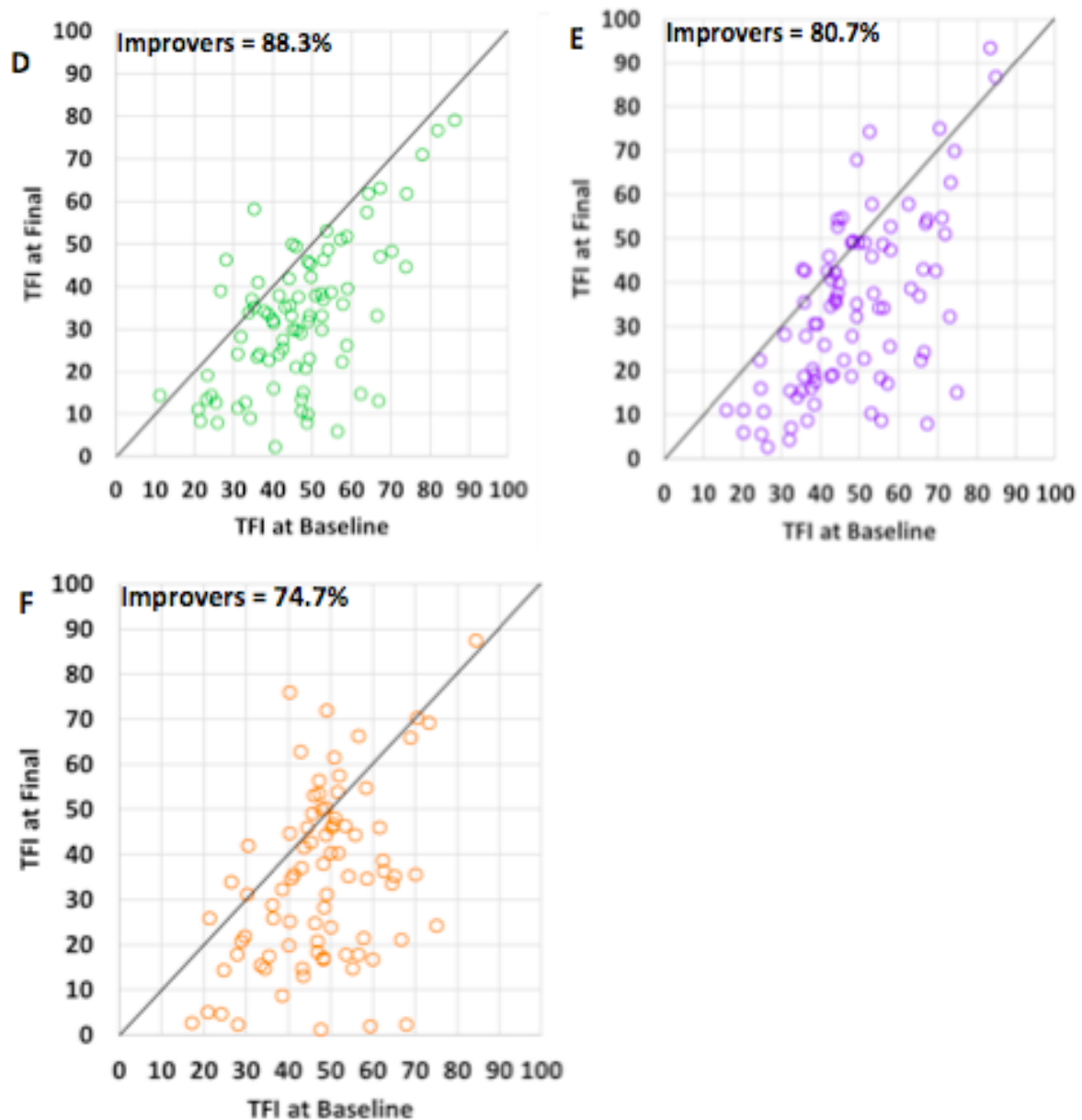


Figure 18: Scatter plots (D – F) showing changes in average change THI and TFI scores. Points below the diagonal black line indicate an improvement change in both scores.

5.3 Between Arm Changes in THI and TFI Scores

Between arm analyses were performed based on intention to treat estimates. The Markov chain Monte Carlo multiple imputation method was used to fill missing data. Multiple imputations and regression analyses were performed using baseline scores as covariates accounting for missing data. The imputation was based on a regression model with predictor variables of age, gender, duration of tinnitus, treatment arm, and compliance to treatment, hearing threshold, baseline and post treatment outcome measures. There were no significant differences in between arm analyses for primary outcome measures at 12 weeks ($p>0.05$; 95% CI crosses zero line). However, interesting between arm differences in tinnitus outcomes were observed during the 12-month post treatment follow up phase. These are discussed in Chapter 6.

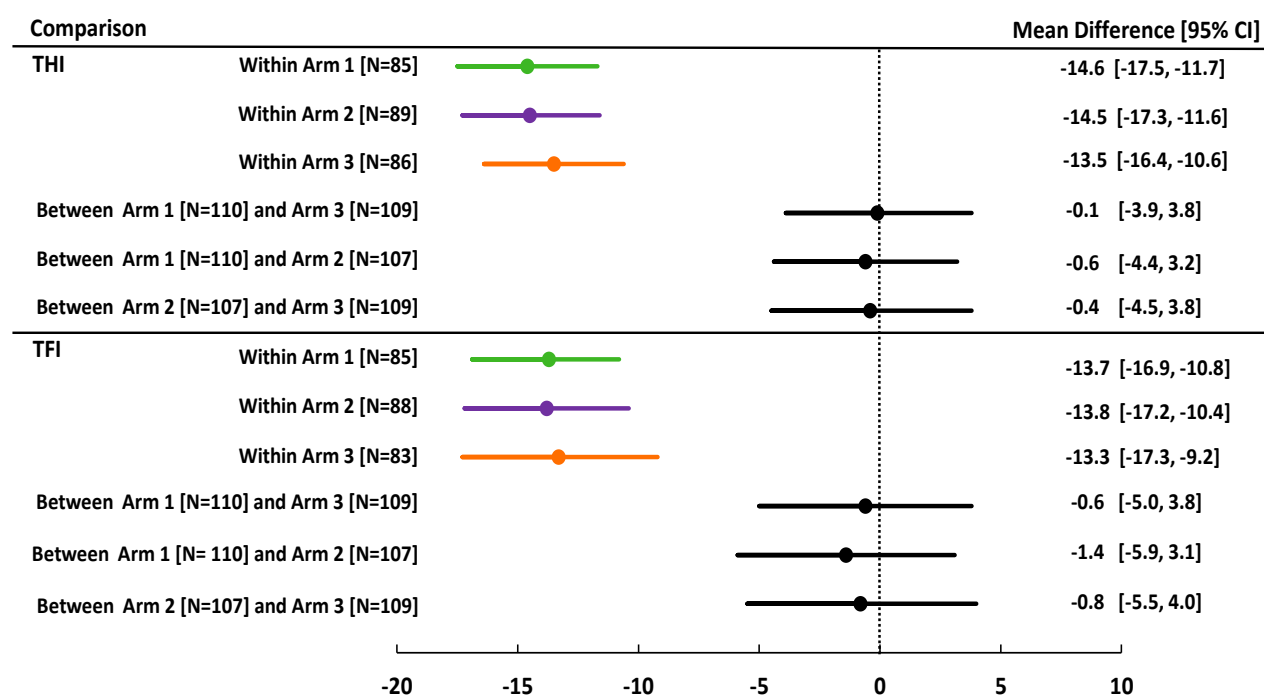


Figure 19: Within arm and between arm primary end point analyses. Primary within arm endpoints were highly significant ($p<0.001$). There were no significant differences between any arms ($p>0.05$)

Chapter 6

Long-term Treatment Outcomes

6.1 Introduction

This trial was designed with a follow up phase to obtain data on the long-term effects of bi-modal neuromodulation on tinnitus across three different stimulation settings. Treatment compliant participants were invited to attend clinical assessments during the follow up phase, at 6 weeks, 6 months and 12 months post treatment. Mean changes in THI and TFI scores were sampled as outcome measures, performed at each clinical visit

6.2 Changes in THI and TFI Scores

As discussed in Section 5.2, participants in all three-study arms recorded statistically significant improvements in THI and TFI scores during the treatment phase. Rapid improvements were observed during the first 6 weeks of treatment, followed by a period of minimal changes across all three investigative arms, as represented in Figure 20. We hypothesize that the plateau effect observed, was possibly a result of neural habituation.

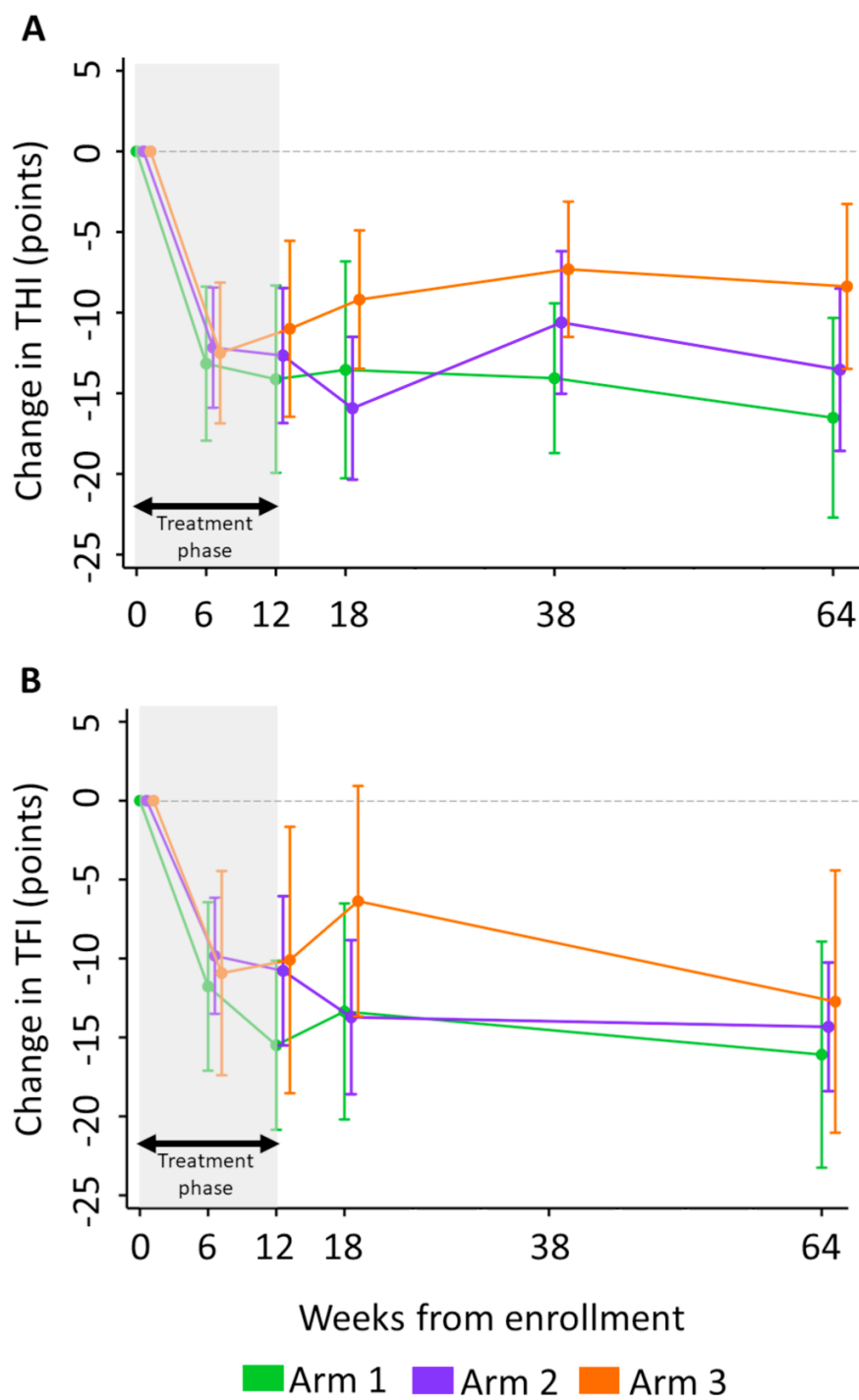


Figure 20: Line graph (A and B) comparing changes in THI and TFI scores between 3 treatment arms over 12 months.

To assess the long-term efficacy of the parameter settings in each treatment arm, only data from participants who attended every clinical assessment appointment during the follow up phase of the trial (6-weeks, 6 months, and 12 months post treatment) was analysed. The mean change in THI and TFI from baseline was plotted for each arm (Arm 1: n=31, Arm 2: n = 40, Arm 3: n = 31). Based on the analyses, responsive participants in Arm 1 sustained significant long-term improvements compared to Arm 3 ($p=0.031$ at 6 months and $p=0.042$ at 12 months) for THI. Arm 2 was significantly different from Arm 3 at 6-weeks post treatment ($p=0.033$).

Long-term data from this study suggest that bimodal neuromodulation with high frequency tones and short inter-stimulus delays are more effective in driving therapeutic benefits. Due to the shorter inter-stimulus delay, a greater number of stimulations per second were delivered in Arm 1 and Arm 2, which may have also contributed to the greater improvements in long-term outcomes. However, with the rapid improvements observed in all three arms, during the first 6 weeks of treatment, there is no clear evidence to support that a lower number of stimulations per second in Arm 3 reduces the efficacy of treatment. This needs to be investigated in a further study. Figure 20 (Graph A-B) summarises the changes in the pooled mean THI and TFI scores respectively, from baseline to 12 month follow up assessment.

Chapter 7

Safety and Acceptability of Device

7.1 Introduction

The close out process of the clinical trial was guided by a medical device research organisation, NAMSA (Minneapolis, Minnesota, USA). In conjunction with the medical review board of the study and ethics committee, NAMSA reviewed and categorised data on device safety.

7.2 Categorization of Adverse Events

Adverse events detected during the trial were classified according to guidelines recommended by MEDDEV 2.7-3¹²⁵. An adverse event was defined as any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs in a subject whether or not related to the investigated medical device. Adverse events were subdivided into anticipated or unanticipated. With regards to severity, AE were labelled either moderate or negligible. All adverse events were then subcategorized into three groups:

- I. Probably device related
- II. Possibly device related
- III. Probably not device related

A serious adverse event (SAE) was defined as an AE that led to death, injury or permanent impairment to a body structure or a body function or led to a serious deterioration in the health of the subject¹²⁵. We make note that a participant may report more than one adverse event.

7.3 Safety Data Analyses

There were a total of 155 adverse events reported during the trial. One hundred and six of the reported adverse events were expected and described in the user's manual. There were no serious AE reported during the treatment and follow up phase of the study. The most common AE recorded was an increase in tinnitus severity. This was an expected AE, and subdivided into either a dramatic increase or subjective increase. A dramatic increase was defined as an increase in tinnitus severity that was noted to be bothersome to the participant. A subjective increase was defined as a perceived increase in tinnitus severity that could be mild, occasional or non bothersome. Other reported adverse events include discomfort in the head, ear or mouth, ulceration in the oral cavity and tongue. Participants were counselled on these potential side effects of treatment during the consenting process.

Data on device safety is summarized in Table 10. Subcategories of data on device safety are listed in Table 10.1 Table 10.2 and Table 10.3. Seventeen unanticipated adverse events are subcategorised in Table 11.1 – 11.3. Table 12 summarises adverse events reported secondary to participant's own condition.

Potential adverse events	Total	Negligible	Moderate
Based on 326 enrolled patients	155	96	59

Table 10: Total adverse events

Potential adverse events	Total	Negligible	Moderate
Probably device related	33	18	15
Subjective increase in tinnitus	9	3	6
Dramatic increase in tinnitus	2	0	2
Fluctuating tinnitus	1	0	1
Pain in the head region	1	0	1
Pain in the ear or mouth	4	4	0
Temporary gum swelling	1	1	0
Sensitivity of oral mucosa	2	2	0
Transient tip of tongue discomfort	2	2	0
Ulceration of oral cavity	2	1	1
Ulceration of the tongue	4	1	3
Device mis-use	5	4	1

Table 10.1: Anticipated adverse events, probably device related

Potential adverse events	Total	Negligible	Moderate
Possibly device related	71	39	32
Subjective increase in tinnitus	45	26	19
Dramatic increase in tinnitus	3	0	3
Fluctuating tinnitus	9	5	4
Pain in the head region	3	2	1
Pain in the ear or mouth	6	4	2
Transient tip of tongue discomfort	2	2	0
Ulceration of oral cavity	2	0	2
Ulceration of the tongue	1	0	1

Table 10.2: Anticipated adverse events, possibly device related

Potential adverse events	Total	Negligible	Moderate
Probably not device related	7	5	2
Subjective increase in tinnitus	3	3	0
Dramatic increase in tinnitus	2	0	2
Pain in the ear or mouth	1	1	0
Increase in hearing threshold	1	1	0

Table 10.3: Anticipated adverse events, probably not device related

Unanticipated adverse events	Total	Negligible	Moderate
Probably device related	2	1	1
Small fissure buccal mucosa	1	1	0
Metallic taste tongue tip	1	1	0

Table 11.1: Unanticipated adverse events, probably device related

Unanticipated adverse events	Total	Negligible	Moderate
Possibly device related	11	6	5
Cold sore	4	0	4
Angular cheilitis	1	0	1
Increased anxiety	1	1	0
Lightheaded for seconds	1	1	0
Temporarily dizzy	1	1	0
Ear fullness	1	1	0
Ear tingling	1	1	0
Tiredness	1	1	0

Table 11.2: Unanticipated adverse events, possibly device related

Unanticipated adverse events	Total	Negligible	Moderate
Probably not device related	4	4	0
Lip ulceration post treatment	1	1	0
Difficulty swallowing saliva	1	1	0
Difficulty sleeping with common cold	1	1	0
Difficulty sleeping with alcohol detox	1	1	0

Table 11.3: Unanticipated adverse events, probably not device related

AE due to patients own condition	Total	Negligible	Moderate
Possibly device related	3	2	1
Eczema around ears	1	1	0
Low mood due to bereavement	1	1	0
Fluctuating hearing loss on background of Meniere's disease	1	0	1
Probably not device related	24	24	0
Long standing cold sores	1	1	0
Ear infection	1	1	0
Common cold	7	7	0
Accidental tongue biting	2	2	0
Conjunctivitis	1	1	0
Sinusitis	3	3	0
Incidental tongue lesion	1	1	0
Disorientated	1	1	0
Forgetfulness	1	1	0
Vomiting bug	1	1	0
Long standing poor sleep	1	1	0
Tiredness with new thyroid treatment	1	1	0
Existing anxiety	1	1	0
Palpitations	1	1	0
Short of breath on background of chronic lung disease	1	1	0

Table 12: Unanticipated adverse events, attributed to patients own condition

Statistical comparison of all adverse events across the three treatment arms was not possible due to the low number of events within each arm. An increase in subjective tinnitus was the most commonly reported AE, with 64-recorded events. This corresponds to 52 participants, given that a single participant may log more than one AE. Furthermore, there was no significant difference in the number participants reporting an increase in subjective tinnitus between the three study arms ($p=0.920$; Fisher's exact test).

The MBT device has proven to be safe, which concurs with the findings from the pilot study¹⁰⁴. Although there were adverse events or side effects of treatment that may have caused discomfort to participants, a high treatment compliance rate of 83.7% was achieved across a large cohort of recruits. A satisfaction survey performed at the final assessment found that 66.5% of participants reported benefits from the MBT device and 77.8% would recommend the device to someone else with tinnitus. This high compliance and satisfaction rate support strong benefit to risk profile for the MBT device for treatment of tinnitus.

Chapter 8

Discussion and Conclusion

8.1 Discussion

Tinnitus is a common and potentially debilitating symptom that occurs globally. There is currently no clinically efficient treatment option for symptomatic tinnitus. Furthermore, the exact mechanisms that generate and sustain tinnitus activity remain undefined.

Recent advances in neuroscientific research suggest that peripheral (otological) and central neural mechanisms (auditory and non-auditory) are likely to be involved. As tinnitus is commonly associated with sensorineural hearing loss (SNHL), it is hypothesized that the reduction in auditory input may result in maladaptive central changes to produce a compensatory sound in the form of “tinnitus”^{7 14 46 126 127}. However, 10 – 15% of tinnitus patients are found to have normal audiological thresholds and a large majority of patients with SNHL do not report tinnitus^{14 128}. It is possible that tinnitus in patients with normal hearing may have initiated following an insult to the cochlea, that subsequently recovered¹²⁹. An animal study utilising auditory brain responses (ABR) and histological analysis, reported normal hearing thresholds in rats that exhibited tinnitus behaviour following loud sound exposure (LSE)¹²⁹. Histological analysis of the study specimens found degeneration of neural synaptic junctions, but normal inner and out hair cell populations. The degeneration of neural junctions may result in high frequency loss not detected using standard audiological measurements¹³⁰. The possibility of a “hidden hearing loss” is supported by human ABR studies, reporting reduced Wave 1 (Cochlear nerve) activity following high frequency (supra-threshold) stimulation in subjects with tinnitus compared to control subjects¹²⁸. Subjects with tinnitus also projected increased activity in Wave 5 (Inferior Colliculus) suggesting auditory related central changes¹²⁸.

Although the exact underpinnings of tinnitus remain debated, current evidence supports the hypothesis that central changes and neural dysfunction are involved in tinnitus activity, encouraging the role of neuromodulation as a potential treatment modality.

Neuromodulation is a novel therapeutic modality, which has an emerging role in the management of conditions that respond to neural stimulation¹³¹. Furthermore, with an improved understanding of neural function and mapping of neural networks, advanced neuromodulation techniques have been developed. The application of neuromodulation in tinnitus treatment has shown promising results. It is hypothesised, that neuromodulation stimulation improves tinnitus severity by inhibiting or disrupting disordered neural activity mapped to drive tinnitus activity^{43 52 53 99 101 119 131 132}.

There are numerous techniques and protocols described in the literature on delivering neuromodulation for the treatment of tinnitus. However, there is emerging evidence to support the role of bimodal neuromodulation stimulation, targeting the dorsal cochlear nucleus (DCN) to potentially drive greater neuroplastic change that will result in improvements in tinnitus. The dorsal cochlear nucleus is the first site of integration between auditory and sensory neural input¹⁰³. The possible involvement of the DCN in tinnitus activity was first observed in animal studies. Utilising electrophysiological studies, changes in spontaneous neural activity within the DCN were recorded in guinea pigs exhibiting tinnitus behaviour, in response to loud sound exposure. These findings were absent in control study subjects¹³³. Another animal based study reported on the potential to invoke long term changes in synaptic activity, by introducing timing variations when stimulating the DCN.

Evidence from animal studies also report inhibitory effects detected following bimodal stimulation of the DCN, in animals exhibiting tinnitus behaviour, while the opposite of hyperactivity of the DCN was recorded in animals not exhibiting tinnitus behavior^{119 133}. A study by Marks and Shore et al investigated the role of non-invasive, bimodal audio-electric stimulation on guinea pigs exhibiting tinnitus behavior¹⁰³. Firstly the study detected neural hyperactivity within the DCN of guinea pigs exhibiting tinnitus behaviour. The study then recorded reduced neural synchrony and spontaneous activity following bimodal stimulation (audio-electric) with a 5 millisecond inter-stimulus delay, compared to animals undergoing unimodal stimulation. The animals with reduced neural activity also exhibited a reduction in tinnitus activity. The study animal model study by Marks and Shore et al provided evidence to support the role of bimodal audio-electric stimulation, with variations in inter-stimulus timing to drive neuroplastic change and decrease neural hyperactivity within the DCN and potentially produce improvements in tinnitus activity¹⁰³.

The main objective of the Parameter Optimization for Bi-Modal Neuromodulation for the Treatment of Tinnitus study; was to assess the role of introducing variations in inter-stimulation timings, on tinnitus related outcomes in participants with chronic subjective tinnitus. A large range of neuromodulation parameter settings can be evaluated for the treatment of tinnitus including types of acoustic stimuli, electrical pulse patterns and duration of inter-stimulus timings. The parameter settings assessed during our study were based on the positive findings observed in animal studies that suggest optimal therapeutic gains can be achieved by implementing a specific delay between auditory and electrical stimulation to drive beneficial central changes¹⁰³.

Both participants and investigators were blinded during the trial. Participants in Arm 1 (PS1) received simultaneous audio-electric (high frequency) stimulation and participants in Arm 2 (PS2) received disrupted (10 – 20ms) audio-electric stimulation. With the rationale that 10 – 20ms may not be sufficient to further disrupt neural activity, a longer inter-stimulus delay of 0.5 seconds, was used in Arm 3 (PS3). Neuromodulation stimulation was delivered using the MutebuttonTM (MBT) device in this study. The auditory stimulus was a sequence of tone burst and wide band noise frequency adjusted to each participant, based on their audiological assessment. The MBT device allowed participants to control the intensity of auditory stimulation by ± 12 dB, as evidence from the TAVSS trial reported supra-threshold auditory stimulation produced improved symptom benefits¹⁰⁴. Electrical stimulation intensity was also individualised to allow participants to sense the stimulation, but sub-uncomfortable levels.

All the 326 participants recruited for the study suffered from chronic subjective tinnitus. Eligible recruits were required to have a baseline THI score between 28 – 76 points. Recruits with a THI score of less than 28 were deemed to have mild tinnitus and are unlikely to experience a significant response to treatment¹²⁰. On the opposite end of the scale, recruits recording a baseline THI score of above 76 points have severe tinnitus and are likely to have psychological consequences secondary to the symptom. As the study did not include a psychological intervention arm, recruits with a THI score of >76 points were excluded from the study. Recruits with significant hearing loss were excluded from the study due to the upper sound limit of the headphones supplied to deliver auditory stimulation. Candidates with >40 dB hearing between 250 Hz to 1kHz (low frequency) or >80 dB between 2 – 8 kHz were excluded. These two hearing loss criteria resulted in the exclusion of 15.6% of the 698 screened participants.

The results on treatment outcomes and compliance from this trial are encouraging. From a cohort of 326 participants, 84% of participants achieved the predetermined minimum treatment compliance of 36 hours over 12 weeks. Between the three study arms, 75 – 89% of participants reported improvements in tinnitus severity. Responsive participants recorded a pooled mean improvement in THI and TFI scores of 14.2 points and 13.6 points respectively. Participants in Arm 1 recorded mean improvements of 14.6 THI points and 13.9 TFI points, which is comparable to the positive findings in the pilot study that utilized the same parameter settings, supporting reproducibility of the intervention¹⁰⁴. Interestingly, participants in Arm 2 and 3 recorded comparable improvements in THI and TFI scores during the treatment phase of the trial (week-12). These findings may prove the overall efficacy of bimodal neuromodulation, independent of the parameter settings. However, these findings are limited by the lack of a control arm in the study. Designing a placebo-controlled trial remains a challenge, as it is not possible to deliver a placebo auditory or electrical stimulation. Furthermore, suprathreshold stimulations are required to be supra-threshold to produce clinically noticeable improvements.

It is interesting to note that responsive participants in all three investigative arms recorded rapid improvements in THI and TFI scores following 6 weeks of treatment. However, responsive participants in arm 1 and 2 recorded significant improvements at the end of the treatment phase (week-12) that was sustained during the follow up phase. Participants in arm 1 recorded sustained improvements in mean THI and THI scores (16.5 and 16.1 respectively), nearly double to that of participants in arm 3 (8.4 and 12.7). Participants in arm 2 recorded sustained improvements in mean THI and THI scores 13.5 and 14.3 respectively. These findings support the use of high frequency neuromodulation stimulation settings with a short (10 – 20ms)

inter-stimulation delay to drive further beneficial therapeutic gains. The use of low frequency stimulation and long inter-stimulus delays (0.5 – 1 second) does not appear to produce long-term benefits in tinnitus treatment. To date, no other treatment modality for tinnitus has achieved long-term therapeutic gains in a clinical trial setting.

Cognitive behavioural therapy (CBT) is the only validated treatment option for tinnitus symptom control. In 2012, Cima et al published a randomized control trial comparing specialist delivered and non-specialist delivered CBT for tinnitus (n = 492) ⁸¹. The study reported significant improvements in primary outcome measures in the specialist delivered CBT group, with responsive participants recording average improvements of 10 points upon completion of the treatment phase⁸¹. A systematic review and meta-analysis on the efficacy of CBT for tinnitus treatment reported CBT to improve on tinnitus related distress and mood, compared to the control interventions¹³⁴. Cognitive behavioural therapy was also reported to have a secondary benefit of improving co-existing anxiety and depression in study participants. The meta-analysis however found a negative association between treatment effect and time, indicating therapeutic benefits decreased over time, particularly after 6 months¹³⁴. These findings were supported by a Cochrane review on the efficacy of CBT in tinnitus therapy¹³⁵.

When compared to CBT, results from this study show bimodal neuromodulation to produce greater improvements in tinnitus severity. Findings from our study also provide evidence on the long-term efficacy sustained following bimodal neuromodulation in responsive participants, compared to CBT. Treatment compliance in CBT has been shown to be low, due to the need for repeated sessions that are associated with a high cost in specialist centres. Bimodal neuromodulation using the MBT device has been shown to be feasible and associated with a high compliance rate¹⁰⁴.

The device parameter settings used in our study may have also driven the higher degree of therapeutic gains observed. Based on the positive findings from the animal model study, Marks and Shore et al designed a human study involving 20 recruits with chronic subjective tinnitus, randomized into two study arms. Participants either received auditory only (control group) stimulation or audio-electric stimulation. The electrical stimulation was delivered transcutaneously over the cervical spine and cheek, targeting the DCN via the cervical nerve roots and trigeminal nerve. The results from the study showed significant mean reductions of 6.3 TFI points ($p < 0.05$) in the bimodal stimulation arm. However, treatment benefits were only sustained for three weeks. There were no improvements recorded by participants in the control group¹⁰³.

There may be several factors contributing to the difference in long term efficacy observed in our trial. The trial by Marks and Shore et al utilised transcutaneous electrical stimulation on the neck and cheek. They also used tinnitus matched acoustic stimulus with a single 5 millisecond inter stimulus gap. In our study, electrical stimulation was delivered to the anterior aspect of the tongue. The parameter settings investigated in our study involved a wide range of acoustic frequencies and inter-stimulus delays. These variations

produced improved treatment outcomes in all three investigative arms. We also observed that the treatment period in our study was longer (36 hours minimum over 12 weeks) than the comparative trial (14 hours over 4 weeks). It is possible that the variations in parameter settings and the longer treatment period may have driven the greater beneficial neuroplastic changes observed in our study and other comparable studies^{46 99 103 119}.

A similar finding between our study and Marks and Shore et al was that paired stimulation improved tinnitus severity during the first 4 weeks of treatment. This was followed by a phase with minimum gains (over 8 weeks). We conclude that this plateau in treatment benefits may be due to neural habituation. We hypothesize that further variations in stimulation settings may reduce the likelihood of neural habituation.

Data on device safety obtained during the study confirmed that there were no serious adverse events (AE) reported. The most common AE reported during the study was an increase in tinnitus severity. We subdivided this to either a dramatic increase, whereby the participant noticed a substantial increase in tinnitus, or subjective; where the participant experienced a change in their tinnitus, but was mild and non bothersome. A change in tinnitus symptom was an expected AE. Tinnitus often fluctuates in most patients and it is inevitable to experience a change in tinnitus during neuromodulation stimulation. It is part of the mechanism of action that stimulation induces a change in neural activity that will lead to fluctuations in tinnitus activity prior experiencing the benefits of inhibitory action of the repeated stimulation. No participant reported a permanent worsening of tinnitus.

Another commonly occurring AE was pain and discomfort around the tongue. From our literature search, studies on other devices that have an electrical tongue stimulator component, such as the Portable Neuromodulator Stimulator Device (PoNSTM) did not report on the device side effects. We hypothesize that the discomfort reported during the treatment phase of the trial was likely due to transient irritation of the tongue surface papillae. Here again, all the participants who reported sensing oral discomfort continued with treatment and achieved the required compliance. Overall, we report a high compliance and satisfaction rates from this study, supporting a positive benefit-risk profile for the MutebuttonTM device.

The findings from our study are encouraging. A limitation to this study was the lack of a placebo control arm. It was not practical to design a neuromodulation study with a placebo control arm, as supra-threshold stimulation settings are required to potentially invoke clinically meaningful change in tinnitus activity. Furthermore, it would not be possible to maintain blinding in the placebo arm, as participants would be aware of the “non-functioning” MBT device. However, we conclude that it would not be possible to record sustained long-term treatment benefits from placebo effects.

To further build on the positive findings from our study, we are currently developing another large-scale clinical trial with four investigative arms to assess the effects of introducing different variations in stimulation settings mid treatment titled; Treatment Evaluation of Neuromodulation for Tinnitus – A2 (TENT-A2). Bimodal neuromodulation will be delivered using the MBT device over a 12-week treatment period with different parameter settings between the two halves of the treatment period. Primary outcome measures will be sampled utilizing the THI and TFI questionnaires.

8.2 Conclusion

Neuromodulation is a novel therapeutic modality with a proven potential to treat symptomatic tinnitus. Neuromodulation invokes beneficial neuroplastic change and “resets” dis-coordinated neural hyperactivity that may be driving tinnitus activity. The aim of this study was to build on encouraging findings from recent animal and human studies, highlighting the benefits of introducing variations in neuromodulation stimulation settings to further suppress tinnitus severity and obtain sustained outcomes.

The results from this study are encouraging, with a high rate of treatment compliance and clinically significant improvements in tinnitus outcomes in responsive participants. Furthermore, variations in parameter settings have shown the potential to sustain long-term treatment benefits. This novel approach is the first to open new frontiers in the management of a condition that has long eluded a recognised treatment modality.

Chapter 9

References

9 References

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