NUI MAYNOOTH
Ollscoil na hÉireann Má Nuad

IMPACT OF ACOUSTIC AND TACTILE MULTI-MODAL STIMULATION ON OBJECTIVE AND SUBJECTIVE MEASURES OF PERMANENT INTRACTABLE TINNITUS:

A PROSPECTIVE RESEARCH STUDY

Caroline Hamilton B.Sc.

Masters Thesis
Supervisor: Prof. Barak Pearlmutter
Head of Department: Prof. Douglas Leith

Hamilton Institute
National University of Ireland, Maynooth
Maynooth
Co. Kildare
June 2014

Dedicated to my parents, my inspiration.

DECLARATION

I hereby certify that this material which I now submit for assessment on the programme of study leading to the aware of Masters of Science is entirely my own work and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work .

This study was conducted through an independent collaboration between the National University of Ireland Maynooth, Hermitage Medical Centre and MuteButton Ltd.

Signed_____

ID No: 12251143

ACKNOWLEDGEMENTS

I'd like to express my deepest gratitude to Dr. Ross O'Neill for his constant support, encouragement and friendship over the course of this masters, without his expert advice and guidance, this work would not have been possible. I've learnt a lot from Dr. O'Neill and it has been a thoroughly positive experience.

I would also like to thank Prof. Barak Pearlmutter for providing me with such excellent direction and advice during my time in the Hamilton Institute. Special thanks to all the people I've met during my time here, in particular Rosemary Hunt and Kate Moriarty for making everything run so smoothly (and for many good laughs!). A special thanks to the Irish Research Council for the scholarship that allowed me to undertake this research.

Finally, I'd like to thank my husband Paul for his unwavering support and my two beautiful daughters Elly and Fia (for being such good sleepers). Thank you for being so understanding of my study and for all the encouragement.

ABSTRACT

Tinnitus is a complex condition comprising of three components, audiological, neurological and psychological which together produce the problems most commonly experienced by tinnitus suffers. It is believed that brainstem structures, such as cochlear nuclei, play a major role in tinnitus generation and that perception occurs at the cortical level. Studies suggest that hearing-loss causes a cascade of neuropathic effects in the central hearing system that is driven by maladaptive neuroplasticity. This model is supported by Eggermont et al. (2006); Kaltenbach et al. (2005); Weisz et al. (2007) which report that tinnitus patients with an underlying hearing-loss exhibited increased spontaneous firing rates, increased synchronicity and a reorganization of tonotopic maps in the auditory brainstem and auditory cortex. Similarly, Parra & Pearlmutter (2007) reports that individuals with tinnitus were more susceptible to the Zwicker tone auditory illusion, suggesting that tinnitus may be related to a central phenomenon of frequency dependent adaptive gains in their hearing-response.

Tinnitus may also partially involve the cranial somatosensory central nervous systems. Shore et al. (2005); Herraiz et al. (2007) demonstrated a functional interaction between auditory brainstem structures and input from the branches of the trigeminal nerve and that stimulation of these nerves can qualitatively and quantitatively influence tinnitus perception. Studies have shown that using Transcutaneous Electrical Nerve Stimulation (TENS) to stimulate the C2 dermatome can have a significant beneficial effect on the perception of tinnitus (Vanneste et al., 2010; Shore; 2005).

We present the findings of a research study into the impact of acoustic and tactile multi-modal stimulation on objective and subjective measures of permanent intractable tinnitus. This 16-week study was conducted with 54 patients suffering from permanent intractable tinnitus. Patients demonstrated statistically significant mean improvements in Minimum Masking level (-8.6dB); Tinnitus Loudness Matching (-7.2dB); and Tinnitus Handicap Inventory (-9.4pts). We discuss the implications of these findings for the clinical treatment of tinnitus and finally we make recommendations for the continued clinical investigation of this area of research.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

ABS	Auditory Brain Stem
AC	Alternate Contact
AHRQ	Agency for Healthcare Research and Quality
ANOVA	Analysis of Variance
ANS	Autonomic Nervous System
ATA	American Tinnitus Association
ATP	Adenotiphosphate
BA	Brodmann Area
CBT	Cognitive Behavioural Therapy
CC	Corpus Callosum
CG	Cingulate Gyrus
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DB	Decibels
DC	Direct Contact
DCN	Dorsal Cochlear Nucleus
EEG	Electroencephalography
EI	Expression of Interest
ENS	Enteric Nervous System
ES	Electrical Stimulation
ET	Eustachian Tube
fMRI	Functional Magnetic Resonance Imaging
GI	Gastrointestinal Tract
GP	General Practitioner

GM	Grey Matter
Hz	Hertz
IAA	Irish Academy of Audiologists
IAM	Internal Auditory Meatus
IC	Inferior Colliculus
IFU	Information for USE
IHCs	Inner Hair Cells
ISHAA	Irish Society of Hearing Aid Audiologists
ITT	Intention To Treat
KHz	Kilohertz
MA	Medical Advisor
MGB	Medial Geniculate Body
MML	Minimum Masking Level
MRC IHR	Medical Research Council Institute of Hearing Research
NHS	National Health Service
NUI	National University of Ireland
OHC	Outer Hair Cell
PFC	Prefrontal Cortex
PI	Principal Investigator
PNS	Peripheral Nervous System
PP	Potential Participant
RCT	Randomised Control Trial
RI	Residual Inhibition
rTMS	Repetitive Transcranial Magnetic Stimulation

SD	Standard Deviation
SFRs	Spontaneous Firing Rates
SNHL	Sensory Neural Hearing Loss
SNS	Somatic Nervous System
SOC	Superior Olivary Complex
SPSS	Statistical Packages for Social Sciences
tDCS	Transcranial Direct Current Stimulation
tACS	Transcranial Alternating Current Stimulation
TENS	Transcutaneous Electrical Stimulation
TFI	Tinnitus Functional Index
THI	Tinnitus Handicap Inventory
TII	Tinnitus Index Inventory
TLM	Tinnitus Loudness Masking
TM	Tinnitus Masking
TMJ	Temporomandibular Joint Dysfunction
TMS	Transcranial Magnetic Stimulation
TRI	Tinnitus Research Initiative
TRT	Tinnitus Retraining Therapy
UCD	University College Dublin
USA	United States of America
VA	Veteran Association
WM	White Matter

CHAPTER ONE

In this chapter, we give a brief overview of tinnitus and the underlying mechanisms involved. We introduce our Prospective Research Study using a novel Acoustic and Tactile Multi-modal Stimulation Tinnitus treatment.

1.1 Introduction

"Is my tinnitus going to get any worse? The single most common question asked of me a Clinician specialising in Tinnitus"

As a clinician specialising in tinnitus for over 10 years, I have been intrigued by the number of patients whom I meet every day with tinnitus, some extremely optimistic that their tinnitus may disappear whilst others live from day to day in fear of their tinnitus getting worse. The vast majority have been told that 'nothing can be done'. As a Tinnitus Specialist, my career to date has been rewarding but also very challenging. Sound therapy and counselling have been well defined and used routinely for treatment of tinnitus, but for the majority they have only given temporary relief. Unfortunately to date, no therapy has been currently found to be uniformly effective in the long term treatment of tinnitus. This motivated me to investigate how the current standard of care could be improved and help me to deliver better outcomes for my patients.

This thesis looks at the prevalence, pathophysiology and mechanisms of tinnitus, the current standard of care, and efficacy, of treatments available. It also reports on a novel multi-modal stimulation treatment for tinnitus which uses proprietary multi-sensory stimuli to drive neuroplasticity in an attempt to alleviate tinnitus.

Tinnitus is a common condition in which people experience a sound or noise which does not have a legitimate external source. Eggermont & Roberts (2004) defines tinnitus as an auditory phantom sensation (ringing in the ears) experienced when no external sound is present.

One in ten adults in Europe and in the USA has significant prolonged tinnitus, which is reported to have a severe effect on their quality of life as well as that of their families Hoffmann & Reid (2004). Studies from different countries have indicated that the prevalence of tinnitus in adults falls in the range of 10-15% (Henry et al., 2005). The Medical Research Council Institute of

Hearing Research (MRC IHR) carried out a robust and comprehensive study reported by Davis & El Rafaie (2000). This was a longitudinal study which sampled a large population in four major cities in UK. It revealed that 10.1% of adults experience tinnitus, 2.8% reported their tinnitus as moderately annoying, whilst 1.6% reported it as severe.

To date there is no agreed medical definition of what constitutes tinnitus; this is probably a crucial reason as to why different studies typically show different incidence and prevalence values (Moller et al., 2010: 30). Other studies have reported a wider range of outcomes, from 6% to 30% tinnitus prevalence, which could be accounted for by the lack of general agreement of the definition and assessment of the condition (Sanchez, 2004; Quaranta et al., 1996).

Tinnitus is known to occur as a concomitant of almost all the dysfunctions that involve the human auditory system (Naughton, 2004; Hoffman & Reid, 2004) but is most often associated with a sensory-neural or congenital hearing loss. People with no obvious audiological, neurological or psychological disorders may also present with tinnitus. Common risk factors include administration of certain medications, middle ear disease, and abnormalities in the vascular system, and ear surgery. The most significant effects of tinnitus tend to be psychological. According to McKenna et al. (1991), 45% of patients with tinnitus were in need of psychological help and 86% of these subjects accepted it. Such difficulties can include high levels of emotional stress such as depression, anxiety, irritability and anger; sleep difficulties; concentration problems; and disruptions to occupational, social, recreational, and interpersonal activities (Henry & Wilson, 2001).

In many respects, tinnitus is likened to chronic pain, portraying similar features in terms of physiology, assessment and management (Moller, 1997; 2000). Both tinnitus and chronic pain appear to be mediated by neuropathic mechanisms and seem to involve central generation in more severe cases (Henry et al., 2005; Tonndorf, 1987; Moller, 2007). In a review of tinnitus from a neurophysiological perspective, Jastreboff considers the perceptual, emotional and reactive systems involved in tinnitus. He claims that tinnitus does not always extend beyond the auditory system, and for these patients, tinnitus can be perceived only when the subject focuses on it. Chronic and disabling tinnitus, on the other hand, occurs when patients fixate on their symptoms, and is related to inappropriate activation of the limbic system (Jastreboff, 1999; Hallam et al., 1988; Naughton, 2004), as shown in Fig 1.
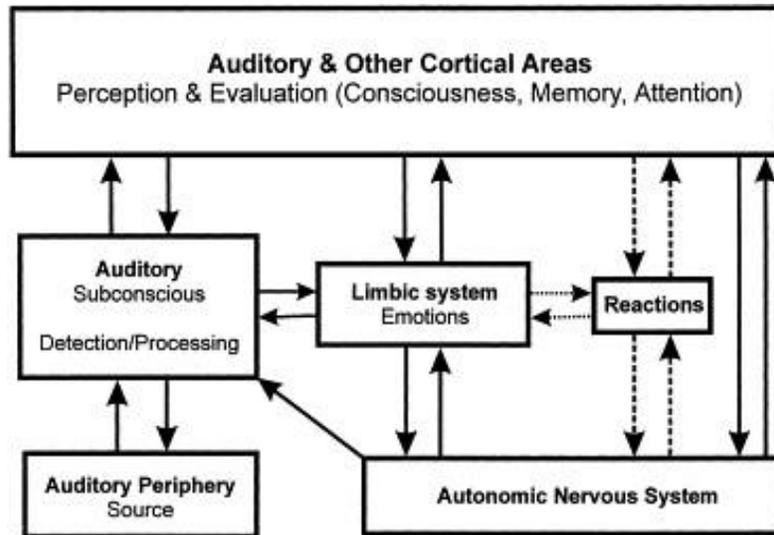
Figure 1 Block diagram of the Neurophysiological Model of Tinnitus. Image taken from Jastreboff (1999)

Tinnitus is broadly categorised into 'subjective' and 'objective' tinnitus. Subjective tinnitus is described as a sound or noise that has no external source and is audible only by the patient. Objective tinnitus, although quite rare, is an audible noise that emanates from the ear and is often measurable audiologically. Studies have shown that subjective tinnitus is most often associated with a high-frequency (noise or age-related) hearing loss (Nicolas-Puel et al., 2002; Pickles, 2008). Tinnitus may present itself unilaterally, experienced in one ear only, or bilaterally, experienced in both ears, which is more common. Unilateral tinnitus warrants further investigation as it is more likely to be a sign of an underlying pathology. Some patients perceive the tinnitus sound centrally, finding it difficult to pinpoint the exact location. Tinnitus is often qualitatively described as a single noise or tone, or as having two or more components. The noise may also be continuous or pulsatile. Although 'tinnitus' derives from the Latin word for 'ringing', it can take a variety of qualitative forms including, buzzing, whistling, hissing, whooshing, or humming. Some patients report experiencing tinnitus exclusively in quiet environments, whilst many others experience it even in noisy environments. Many individuals report daily variability in the overall intrusiveness of the condition, whilst some individuals report a similar daily variance in the pitch and quality of their tinnitus. Folmer et al. (2001) reports that chronic tinnitus is more persistent and can last for 6 months, in comparison to acute tinnitus which may last for days or weeks. Davis & El Rafaie (2000) reports that it is important to distinguish between clinically significant and non-significant tinnitus.

Due to the subjective nature of this disorder and general lack of understanding of the underlying pathophysiology, treatment of tinnitus has been limited, controversial, and quite often unsuccessful. Pharmacological treatment of tinnitus has proven ineffective, although some medications have been reported to relieve symptoms (Perry & Gantz 2000). There are currently no pharmacological agents specifically recommended for the purpose of treating tinnitus (Dobie, 1999). Non-pharmacological and surgical approaches have been used in certain cases with limited therapeutic effects. Other treatments that have been proposed for tinnitus are: Antioxidant Therapy, Tinnitus Retraining Therapy (TRT), Repetitive Transcranial Magnetic Stimulation (rTMS), Transcranial Direct Current Stimulation (tDCS), Transcranial Alternating Current Stimulation (tACS) Sound Therapy, and Cognitive Behavioural Therapy (CBT) (Clinical Policy Bulletin, 2013; Henry et al., 2005; Vanneste & De Ridder, 2012; Baguley, 2002; AHRQ, 2012).

1.2 Acoustic Approach to Tinnitus Treatment: - Acoustic and Tactile Multi-modal Stimulation

This thesis presents the findings of a research study into the impact of acoustic and tactile multi-modal stimulation on 'objective' and 'subjective' measures of permanent intractable tinnitus.

This intervention involves acoustic stimulation combined with tactile stimulation of the anterio-dorsal surface of the tongue, using an intra-oral electrode array. The study discusses the implications of these findings for the clinical treatment of tinnitus and makes recommendations for the continued clinical investigation of this area of research.

The prospective study was conducted over a 16-week period with 54 patients (34 male, 20 female with a mean age of 47 years), suffering from permanent intractable tinnitus (>6 months) and with an accompanying high-frequency hearing-loss.

Objective and subjective measures were used to measure and quantify the severity of tinnitus every two weeks for the duration of the study. 54 participants classified their tinnitus according to Visual Analogue Scale (VAS) and Tinnitus Handicap Inventory (THI). The objective measures used to quantify their condition were; Tinnitus matching (TM), Tinnitus Loudness Matching (TLM) and Minimum Masking Levels (MML) (Vernon & Meikle, 2000). Patients demonstrated statistically significant mean improvements in Minimum Masking level (-8.6dB);

Tinnitus Loudness Matching (7.2dB); and Tinnitus Handicap Inventory (-9.4pts). We discuss the implications of these findings for the clinical treatment of tinnitus and finally we make recommendations for the continued clinical investigation of this area of research.

1.3 Overview

In Chapter Two, we provide a general overview of the complex condition of tinnitus, its prevalence, pathophysiology and overall impact. We discuss the audiological, neurological and psychological components of tinnitus, which together produce the problems most commonly experienced by tinnitus sufferers. We also discuss the pharmacological and non-pharmacological treatments that are currently available. Chapter Three, briefly reviews the relevant parts of the Peripheral and Central Nervous systems that are relevant to our study. This includes the Peripheral and Central Auditory systems, somatosensory system and the cranial nerves. Chapter Four gives a brief overview of the auditory system and the mechanoelectrical transduction of sound pressure into neural action potentials.

We pay particular attention to the human sense of hearing, the relationship between tinnitus and high frequency hearing loss and neural pathologies in the central nervous system which drive neuroplasticity. Chapter Five discusses the anatomical and functional links between the auditory and somatosensory systems. We explore these cortical and subcortical links, how they influence the perception of sound, and their implications for the treatment of tinnitus. We propose two novel hypothetical treatments that utilise auditory-somatosensory interactions and outline our motivation for selecting and experimentally determining the clinical efficacy of one of these two treatments. Chapter Six provides the general methods of the clinical trial, including sample size and recruitment, eligibility criteria, trial procedures, outcome measures, data collection and analysis. Chapter Seven reports on the impact of acoustic and tactile multi-modal stimulation treatment for tinnitus. The results reported verify the clinical benefit and user tolerability of the treatment. Chapter Eight, the final chapter, highlights and examines the main findings of this research, discusses them in the broader clinical context and finally processes recommendations for further investigations.

CHAPTER TWO: OVERVIEW OF TINNITUS

In this chapter, we provide a general overview of the complex condition of tinnitus, its prevalence, pathophysiology, and overall impact. We make reference to the audiological, neurological, and psychological components of tinnitus, which together produce the problems most commonly experienced by tinnitus sufferers. We also discuss the pharmacological and non-pharmacological treatments that are currently available.

2.1 Tinnitus

Tinnitus is the perception of sound in the absence of external auditory stimulation. In both clinical and academic contexts, patients are described as presenting with symptoms of either 'objective' or 'subjective' tinnitus. As objective tinnitus is quite rare, some believe that all tinnitus should be defined as subjective and classified instead by origin, either as neurophysiologic or somatic tinnitus (Henry, 2011; AHRQ, 2012). In keeping with the prevalent practice this study will focus on subjective or neurophysiologic tinnitus which will be referred to simply as 'tinnitus'.

2.2 Prevalence

Numerous studies into the prevalence of tinnitus indicate that the condition is becoming an increasingly significant health problem. It is widely believed that the majority of people have some level of tinnitus however, given the lack of an accepted classification of the condition; accurately quantifying its prevalence is difficult (Heller, 2003). The largest longitudinal study was carried out by the Medical Research Council Institute of Hearing Research (Davis & Rafaie, 2000). The study interviewed 48,313 people, 10.1% reported that their tinnitus is spontaneous, lasting for 5 or more minutes at a time and 5% described their tinnitus as moderately annoying or severely annoying. 0.5% reported that their tinnitus had a severe effect on their quality of life. These figures are consistent with data collected by the American Tinnitus Association (ATA) which reports that tinnitus may be experienced by approximately 50 million Americans (ATA 2004). Hoffman & Reed (2004) made reference to six large studies in different countries and reported prevalence of prolonged tinnitus, varying between 4.4% and 15.1% for adults. Comparable prevalence rates have been reported in several studies from the UK, Sweden, Norway and the US. Moller et al (2010: 29-34) reported the prevalence of tinnitus in these studies were not the same for the different age groups however the majority of studies agreed that the

6

risk of developing tinnitus increases with age up to about 65 to 70 years, after which it becomes constant or decreases slightly (Moller et al., 2010: 29-34; Henry et al., 2005; Davis & El Rafaie, 2000: 1-24).

The association between presbyacusis and tinnitus contributes to the misconception that tinnitus is exclusively a complaint of the elderly. However, many people develop tinnitus in their middle age and younger (Naughton, 2004). Baguley (2002) reported that women are also more likely to report tinnitus than men and occupational noise and lower socio-economic class are also associated with increased tinnitus, however further studies are required to determine these factors.

Meikle (2003) reviewed the prevalence of tinnitus, and reports that it is much higher than the number of patients who seek treatment (Davis, 1995, Hinchcliffe, 1961; Leske, 1981), thus indicating that many individuals who experience tinnitus do not find it to be a significant or debilitating problem. Nearly 50 million Americans experience tinnitus with 10-12 million seeking medical attention due to chronic symptoms. According to the American Tinnitus Association (ATA) 1-2 million American tinnitus sufferers are debilitated by their condition where their cognitive abilities are compromised and quality of life seriously impacted. This year, 840,000 Veterans were in receipt of disability compensation, costing $1.28 billion annually, which the Department of Veterans Affairs (VA) expects will increase to $2.75 billion by 2016 (ATA, 2013). The Royal National Institute for the Deaf (RNID) estimates that there were 12.6 million chronic tinnitus suffers worldwide in 2007 and predicted that this would grow to 22.3 million by 2015 (RNID, 2005).

2.3 Pathophysiology of Tinnitus

According to McKenna et al., (2011) tinnitus is an extremely common symptom affecting 'humanity'. The greatest challenge is determining a clear definition and classification of tinnitus due to its multiple aetiologies and highly subjective presentation of its symptoms. It can range from an intermittent tinnitus perception to a constant intrusive tinnitus; it may present itself unilaterally or bilaterally, or may be perceived in the head. Tinnitus may be linked to a range of physiological conditions or psychological experiences particularly if the onset is sudden. However the exact mechanism is still not fully understood. For some individuals, the loudness, pitch and quality of the tinnitus can vary from day to day.

As a symptom, tinnitus may be associated with a number of audiological conditions including impacted wax, adverse reactions to ototoxic medications, or acoustic tumours. It is most commonly associated with sensory-neural hearing loss; in particular, noise induced or age related hearing loss (Coles, 2000; Davis & El Rafaie et al., 2000; Saunders, 2007). It may also be associated with symptoms such as hyperacusis (Andersson et al., 2001; Dauman & Bouscau-Faure, 2005). As noted, tinnitus is most commonly associated with hearing loss. According to the Tinnitus Archive of the Oregon Health and Science University the most common cause of tinnitus is noise exposure (approx. 24%) followed by head and neck injuries (approx18%) (Eggermont, 2006). The causal relationship between hearing loss and tinnitus will be discussed in further detail. However, tinnitus has also been reported in individuals with normal hearing within the recommended audiological range of 250 to 8 kHz (Barnea et al., 1990). However Salvi et al. (2009) state that when testing is carried out above 8 kHz, cases of individuals with tinnitus without hearing loss are quite rare. Several tinnitus classifications have been proposed (McCoombe, 2001; Dauman, 1992; Davis & El Rafaie, 2000). Davis & Rafaie (2000) reports that it is important to distinguish between clinically significant and non-significant tinnitus. Dauman (1992) makes a distinction between 'normal' (lasting less than five minutes, occurring less than once a week and experienced by most people) and 'pathological' tinnitus (lasting more than five minutes, occurring more than once a week and usually experienced by people with hearing loss.

Figure 2 TRI Flowchart for Patient Management. Image taken from TRI Tinnitus Clinic Network, Biesinger et al. (2010)
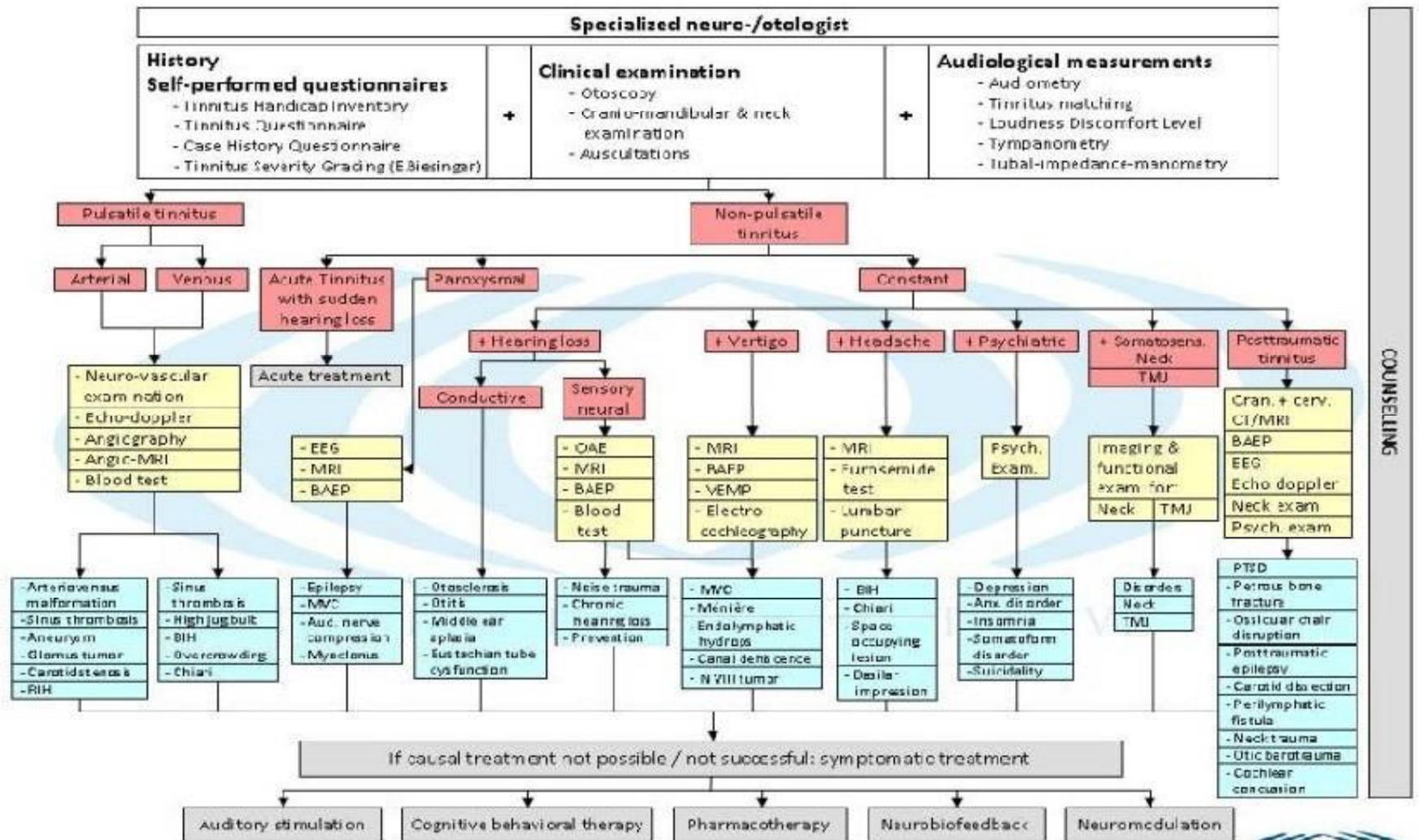
2.4 Mechanisms

Numerous pathophysiological mechanisms and models have been proposed as contributors to tinnitus (Baguley, 2002; Eggermont & Roberts, 2004; Kaltenbach et al., 2005; Weisz et al. 2007). Tyler et al., (2008); Landgrebe (2010) report that efforts towards establishing tinnitus subgroups are currently underway. Based on these subgroups the Tinnitus Research Initiative (TRI) is already recommending different patient pathways for these subgroups that encompasses treatment and management strategies as shown in Fig 2.

Cochlear damage is believed to be the initiating factor which leads to altered patterns of neural activity along the central auditory pathway (Bauer et al., 2008). Some suggest that after cochlear damage a cascade of changes occurs in central auditory pathways, and some of these may serve as 'neural codes' for tinnitus (Eggermont & Roberts, 2004). Recent studies have demonstrated enhanced spontaneous firing rates (SFRs) in central acoustic pathways (Kaltenbach et al., 2005), tonotopic reorganisation, and altered synchronous cortical activity (Seki and Eggermont, 2003; Weisz et al., 2007).

2.5 Limbic System

Reviews of tinnitus from a neurophysiological perspective (Jastreboff, 1990; Jastreboff, 2004) consider the perceptual, emotional and reactive systems involved. It is claimed that for many patients neurological involvement does not extend beyond the auditory system, and for these patients, tinnitus can be perceived only when the subject focuses on it. Chronic and disabling tinnitus, on the other hand, occurs when patients fixate on their symptoms and thus cause inappropriate activation of the limbic system (Naughton, 2004; Hallam et al., 1988). The lemniscal pathways use the ventral part of the medial geniculate body, the neurons of which project to the primary auditory cortex, whereas the extralemniscal pathways otherwise known as the non-classical pathways use the dorsal part of the medial geniculate body that projects to the secondary auditory cortex and association cortices, thus bypassing the primary cortex. The non-classical pathways can be modulated by somatosensory input and studies have shown evidence of extralemniscal cross-modal interaction in both children and adults with tinnitus. Moller & Rollins (2002); Moller et al. (1992); Lockwood et al. (1998) demonstrated that the limbic structures which support the involvement of the extralemniscal auditory system are more active

10

in response to sound stimulation in some patients with tinnitus. The limbic system mediates the emotional and sympathetic nervous system activity which drives maladaptive neuroplasticity which may be a contributing factor to tinnitus (Saunders, 2007; Kaltenbach et al., 2005). Activation of the limbic system produces changes in mood, arousal and thoughts which may be associated with major depression, anxiety, and other psychosomatic and or psychological problems that lead to progressive deterioration of quality of life (Sullivan, 1993; Lockwood, 1998; Langguth et al., 2011).
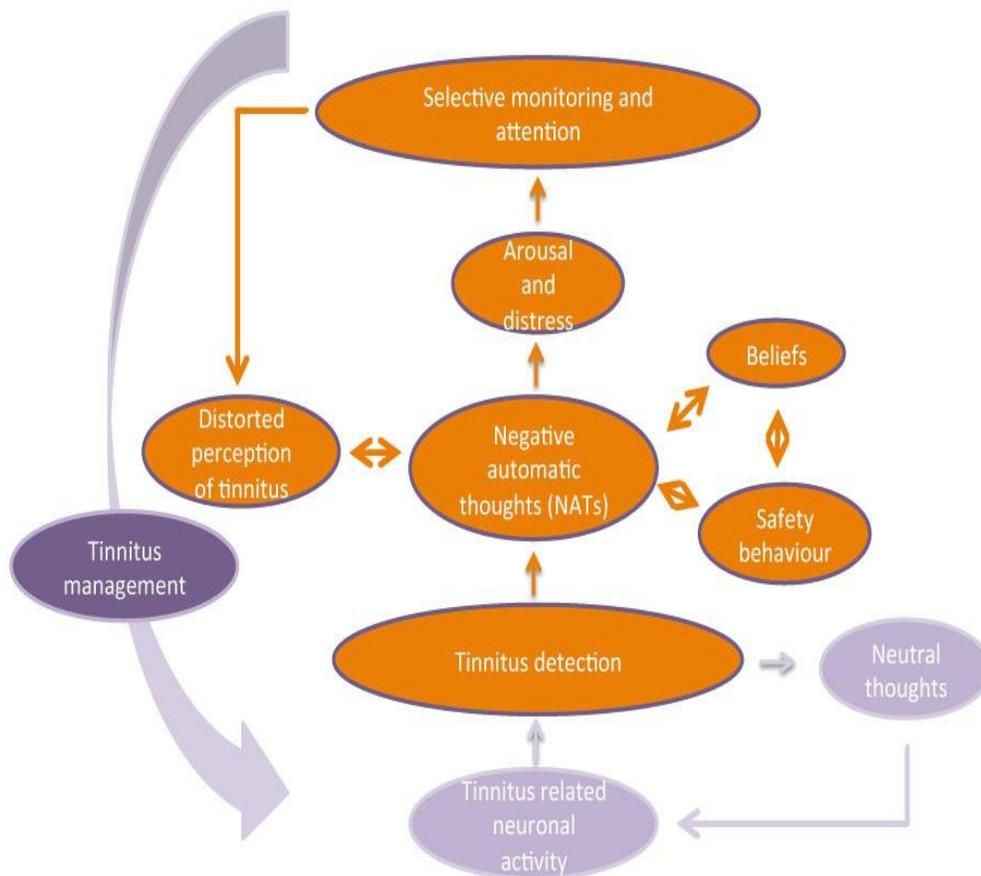
Figure 3 Vicious Cycle of Tinnitus. Image taken from Holt Hearing & Balance (2013)

2.6 Impact

The initial onset of tinnitus is quite often associated with stress, which can lead to negative thoughts and emotions, particularly if the tinnitus persists (Schmidtt et al., 2000). Tinnitus also

becomes a problem when it is perceived as a threat, appears continuously intrusive, or when patients have difficulty coping (Hazell, 1998). Tinnitus can lead to a repeating cycle of annoyance, mood changes, fear, and anxiety, all of which are associated with tinnitus severity (Henry et al., 2005), as displayed in Fig 3 above.

The effects of Tinnitus include both medical and psychological components. Regardless as to the underlying diagnosis it is believed that the brain generates the 'illusory sound', and psychological factors begin to emerge that determine how the person copes with their tinnitus. Distress caused by the initial onset or continued intrusiveness of tinnitus may negatively exacerbate underlying physical or psychological issues. Physical effects include disruption of daily activities, disturbance of sleep, or new side effects to their long term medications.

Hallam (1988) reports difficult in hearing, emotional stress and sleep as the three most commonly made complaints about tinnitus. Sanchez & Stephens (1997) concluded that the single most common problem in everyday life for tinnitus patients was sleep disturbance, with 71% reporting it as their main issues. Davis et al. (1995) reported 5% of individuals in a normal population have sleep disorders with tinnitus as the casual factor. Patients' anecdotally reported that tinnitus wakens them from their sleep, but Folmer and Griest (2000) and Axelsson (1989) report that this may not be the case as patients with insomnia often appear to experience more severe tinnitus in comparison to patients who do not have problems sleeping.

Psychological effects include learned helplessness, anxiety depression, decline in memory and concentration and emotional self-neglect. Several studies have discussed similarities between the patient profiles and therapeutic approaches for chronic pain and tinnitus sufferers (Moller, 2000; Tonndorf 1987). McKenna et al. (2011) state that although individuals with intrusive tinnitus perceive a sound, it often behaves more like pain especially in terms of the variety of reactions. The brain continues to develop perceptual experiences even after the loss of function of peripheral sensory cells (Rauschecker, 1999). Both disorders are subjective, intractable, and distressing, which can have a major impact on the quality of life of the sufferers (Kirsch et al., 1989; Meikle et al., 1995).

Sullivan et al. (1988) studied the association between disabling tinnitus and affective disorders. The results demonstrated that tinnitus sufferers presented a greater lifetime prevalence of major depression than a control group of subjects with hearing loss and no tinnitus. The authors concluded that the results were in accordance with the hypothesis that disability is strongly associated with depression. Scott & Lindberg (2000) also confirmed the link between anxiety, depression, stress, and chronic tinnitus.

It has been reported that tinnitus loudness rarely correlates with distress. Hallum et al. (1988) suggested that perception of and reaction to tinnitus is not one and the same. A study by Erlandsson et al. (1992) suggested that the patients' perception of the condition and their management of it can predict the level of impact. This supports Jastreboff's theory (1990) that tinnitus is perceived only when the individual focuses and reacts to it. Conversely Willebrand et al. (2001) suggest that failing to acknowledge the condition can increase the associated distress.

As only a small proportion of people who experience tinnitus are affected by it, it is important to make a distinction between awareness of and distress caused by tinnitus (McKenna et al., 2010).

2.7 Measurement

It is widely acknowledged that there are a lack of objective tools to measures and quantify tinnitus. As a condition, tinnitus is highly subjective and influenced by a range of complex factors including cultural and social. Tinnitus is a complex and multidimensional condition which can impact physical, psychological and social aspects of a patient's life. Various measures can be used to determine the presence and severity of tinnitus (McCoombe et al., 2001). A thorough clinical examination, including a complete patient history, audiological assessment and in some cases further investigation, is paramount in determining potential causes.

The assessments of tinnitus severity and its impact also depend on valid and reliable self-report instruments. Self-report measures are increasingly used in tinnitus research and in the management of tinnitus patients. The use of robust outcome measures is of great importance. There are a number of validated questionnaires and inventories for the assessment of tinnitus impact (Andersson et al., 2007: 92). Psychological grading scales can also aid in the

13

discrimination between clinically significant and non-significant tinnitus (Erlandsson, 2000). The Tinnitus Functional Index (TFI) is a new self-report questionnaire that has documented validity both for scaling the severity and negative impact of tinnitus and for measuring treatment-related changes in tinnitus (Meikle et al., 2012).

2.7.1 Subjective Measurements:

Visual Analogue Scale (VAS)

The VAS is a well-known psychometric measure of subjective attitudes and is used frequently in pain management (Wewers and Lowe, 1990) and also recommended for use in tinnitus research (Axelsson et al., 1993). The VAS provides consistent and reliable results and is used to evaluate the self-perceived loudness pitch and severity of tinnitus on a rating scale of 1 to 10, with 1 being 'barely audible' and 10 being 'intolerable (Miekle, 2008). The VAS has been validated for use in a number of tinnitus studies (Axelsson et al., 1993). Adamchic et al. (2012) reported that VAS annoyance and VAS loudness are valid and effective measurements and provide good test-retest reliability.

Tinnitus Hearing Inventory (THI)

THI measures are used to assess the impact of tinnitus on the participant and reports have confirmed its test-retest reliability (Newman et al., 1998) and a high convergence with other questionnaires (Baguley et al., 2000). This is a 25-item self-administered questionnaire for the measurement of tinnitus handicap and the impact of tinnitus on everyday functioning (total score ranging from 0 to 100, with a higher score indicating greater handicap). Based on the (confidence intervals) CI estimates, it is suggested that treatment is effective if a change of 20 points is noted pre-post treatment (Newman et al., 1998).

THI is valuable in assessing tinnitus severity, however it is limited in that it is not designed or validated to measure effectiveness of tinnitus interventions (Kamalski et al., 2010). Meikle et al. (2008) acknowledges the THI to be both valid and reliable in measuring self-reported tinnitus handicap. Although verified, it does have areas of weakness. There are a wide variety of questions regarding sleep, stress, etc., but as a measure the THI doesn't separate out these confounding factors. Henry et al. (2005) recommend open ended questionnaires which could

help improve this, however Schwartz (1999) reports that open ended questionnaires present with a number of discrepancies.

2.7.2 Objective Measurements

Psychoacoustic assessment, including Tinnitus Matching (TM), Tinnitus Loudness Matching (TLM), and Minimum Masking Levels (MML), are determined by establishing the frequency, intensity, and minimum masking level of the patient's tinnitus. These measurements are expressed in Hertz (Hz) and Decibels (dB), respectively (Henry & Meikle 2000). Another assessment is Residual Inhibition (RI), which measures the temporal duration of tinnitus suppression immediately following a period of masking.

2.8 Management

Currently both pharmacologic and non-pharmacologic treatments as described below are used for managing tinnitus. These range from different forms of Sound Therapy; Tinnitus Retraining Therapy, Cognitive Behavioural Therapy, Neuro-feedback, and various forms of Electrical Stimulation. These therapies tend to provide symptomatic relief, but tend not to be overly effective in eliminating tinnitus. The chosen treatment modality is often a function of the severity of the condition. There are a diverse range of available treatments, the benefit and limitations of which have been discussed in numerous articles Langguth et al (2011). However many of the studies have come under criticism as they were not considered well-controlled trials and lacked a common outcome measure (Dobie, 2004; Henry, et al., 2005). As tinnitus has a vast range of aetiologies (Hoffman & Reid, 2004) patients tend to be grouped mainly by the severity of their tinnitus, based on one of many questionnaires (Newman & Sandridge, 2004; Eggermont et al 2011).

Vanneste & De Ridder (2012) report that many studies only evaluate transient changes in tinnitus perception without the analysis of long-term effects, and other studies only report on improvement of tinnitus distress, without verifying the improvement in tinnitus intensity, and some studies report statistically significant improvements with low effect sizes revealing only 'marginal clinical relevance'. Dobie (1999) further suggests that by adopting an agreed outcome measure the range of therapeutic approaches could be compared more effectively.

2.9 Pharmacotherapy Treatment Approaches

Studies refer to a range of pharmacological treatments which have been proposed to relieve tinnitus, albeit with limited success (Perry & Gantz, 2000; Patterson & Balough, 2006; Nobel, 2008; Henry et al., 2005; Langguth, 2009). Pharmacological agents specifically administered for the treatment of tinnitus include; *antidepressants, vasodilators, intravenous lidocaine, barbiturates, antihistamines, beta histamine,* and *benzodiazepines*. However, Dobie (1999) states that the use of drugs should only be considered in the treatment of symptoms which can co-exist with the tinnitus, i.e., sleep deprivation, depression, and anxiety. Sziklail et al. (2011) referred to a recent study of the drug Pramipexole a dopaminergic agent which is a newer medication that has been reported to be an effective agent against tinnitus with presbyacusis and is currently being further investigated (Henry et al., 2005). Langguth et al. (2009) stressed that a drug that produced only a small but significant effect would have an enormous therapeutic impact and urged for more effective pharmacotherapies for this huge and growing market (Vanneste & De Ridder, 2012).

Fornaro & Martino (2010) reported that for some individuals the use of alternative medications have reduced the severity of tinnitus. These treatments include ginkgo biloba, zinc, melatonin, lidocaine, magnesium, botulinum toxins, and B vitamins, but as discussed below much of the evidence is anecdotal (Pandey, 2011).

2.10 Non- Pharmacotherapy Treatment Approaches

2.10.1 Cochlear Implants

Cochlear implants have been reported to suppress tinnitus in nearly 50-80% of patients (House, 1976; Berliner et al., 1987; Henry et al., 2005). Cochlear implants were found to be effective for reducing tinnitus (Vernon, 2000; Ruckenstein & Tyler, 2004) an effect which may arise from masking by the newly perceived sound or from electrical stimulation of the auditory nerve (Dauman, 2000). Cochlear implants are a viable treatment option for individuals who are profoundly deaf with severe intractable tinnitus (Henry et al., 2005). The reorganising of the central auditory nervous system after restoration of peripheral sensory input may help in reducing tinnitus (Moller, 2003; Del Bo & Ambrosetti, 2007). Although it has been reported that cochlear

implants exacerbate tinnitus (Tyler, 1995), an interesting fact is that unilateral cochlear implantation has been associated with reduction in contralateral tinnitus in up to 67% of individuals (Andersson et al., 2007: 130).

2.10.2 Complementary Therapies

Complementary therapies over the years have been recommended for relieving tinnitus, but few studies have been published regarding their efficacy. Therapies range from herbalism, homeopathy, aromatherapy, massage, osteopathy (include cranial sacral therapy), acupuncture, biofeedback, hypnosis, magnets, oxygen yoga, prayer, and meditation. Acupuncture is widely used to treat tinnitus (Zhang, 2002) and controlled trials carried out recently report it be an effective treatment (Tan, 2007) however Park (2000) carried out a systematic review of acupuncture and concluded that there was insufficient randomised control trial (RCT) evidence to demonstrate its effectiveness. Although many therapeutic effects are attributed to Ginkgo biloba (Morgenstern, 1997), there is very little evidence to support this (Hilton, 2004).   Due to its subjective nature, tinnitus may be particularly amenable to placebo-based therapies.

2.10.3 Temporomandibular Joint Dysfunction (TMJ)

TMJ disorder is a very common disorder which arises from the temporomandibular joints and associated structures. It is also known as temporomandibular pain dysfunction or craniofacial disorder. Symptoms of TMJ include pain, tenderness, abnormal bite, headaches and facial sensitivity. Tinnitus can also be a symptom of temporomandibular joint dysfunction.   In most cases, changing to a soft diet, jaw muscle exercises or use of anti-inflammatory or analgesic drugs can help. For those that grind their teeth, dental treatment or bite realignment can help relieve the symptoms of TMJ pain and associated tinnitus for some individuals (Morgan, 1996). This can be disposed of when normal functional is restored. Anderson et al. (2007) made reference to studies by Erlandsson et al. (1991); Wright & Bifano (1997) who have shown that treatment of TMJ improves associated tinnitus.

2.10.4 Laser therapy

Laser powered or soft lasers have been suggested as a potential treatment for tinnitus.   They are believed to stimulate the mitochondria in the cells of the ear to produce energy through the

production of ATP (adenosine triphosphate) and in return repairs the damaged tissue. Laser therapy can offer significant benefit in treatment of tinnitus, but further experimental studies are needed to assess the efficacy (Gungor et al., 2008). In addition to different pathophysiological mechanisms of inner ear disease and diverse theories on the nature of tinnitus, the methodical differences in study design, treatment schedules, and irradiation parameters could cause a wide range of outcomes (Tauber et al., 2003). Nakashima et al. (2002) and Teggi et al. (2009) concluded that Transmeatal laser irradiation was ineffective for treatment of tinnitus.

2.10.5 Transcranial magnetic stimulation

Transcranial Magnetic Stimulation (TMS) and Repetitive Transcranial Magnetic Stimulation (rTMS) are techniques that scientists are now refining for tinnitus patients. Depending on the stimulation frequency, this magnetic field can either decrease or increase the electrical excitability of the brain. A number of studies have shown that TMS may be effective in the treatment of tinnitus (Khedr et al., 2008; Kleinjung et al., 2005; Pridmore et al., 2006; Smith et al., 2007). However Meng et al. (2011) in Cochrane Review evaluated the effectiveness of rTMS versus placebo in patients with tinnitus and reported that it is a safe treatment for tinnitus in the short term, however there was insufficient evidence regarding long term treatment. They concluded that more prospective, randomised placebo controlled double blind studies with larger samples are needed with uniform, validated tinnitus specific questionnaires as well as measurement scales (Clinical Policy Bulletin, 2013).

2.10.6 Educational Therapy

For a lot of people with tinnitus, reassurance and explanation is all that is required. Simply understanding what is causing the problem is a great help in hastening the problem. This is because when tinnitus begins, it is common to feel anxious and fearful, but then it usually settles down as the brain gradually "habituates" to this new sensation and through its central auditory system gradually learns to ignore it (McKenna et al., 2011).

2.10.7 Relaxation Therapy

Relaxation therapies such as biofeedback aim to manage stress by changing the body's reaction to it by teaching individuals to manage their automatic body functions such as muscle tension and body temperature. Therapists offer strategies to divert the individual attention away from

their tinnitus-related symptoms. Although this may not eliminate tinnitus, the main aim is to improve an individual's quality of life (Ireland, 1985) by providing them with behavioural and relaxation techniques.

2.10.8 Tinnitus Retraining Therapy (TRT)

Tinnitus Retraining Therapy (TRT) which was developed by PJ Jastreboff in the 1990's, is a commonly used habituation programme which combines sound therapy with directive counselling. Sound is used to make the tinnitus less noticeable as opposed to masking it out, and it is used in conjunction with an intense form of direct counselling based on the Jasstebroff's 'neurophysiological model' (McKenna et al., 2010). The combination of sound therapy and counselling with TRT is designed to lead to habituation, which means that the tinnitus-related neuronal activity is blocked from reaching the limbic and autonomic nervous system and consequently there are no negative reactions to the tinnitus (Jastreboff & Hazell, 2006). The long term impact of TRT is limited (Dobie, 1999) and it can take 1-2 years to observe stable effects. It has been noted that there is need for better experimental designs in the studies of TRT efficacy (Wilson et al., 1998; Kroner-Herwit et al., 2000; Henry et al., 2005).

2.10.9 Neuromonics Treatment

Neuromonics combines the use of broadband noise and relaxing music with a structured programme of counselling and support by clinicians specially trained in tinnitus rehabilitation. It claims 90% success rates for patients who persist with the treatment and a 40% reduction in tinnitus intensity. Davis et al. (2007) (2008) found that the treatment provided rapid and profound improvements to the severity of tinnitus symptoms and their effect on the individual quality of life. The difference between the two groups was statistically significant. Goddard et al. (2009) confirmed that Neuromonics appears to be useful as a means of significantly reducing the effects of tinnitus on an individual's daily life, but future studies are needed to look at larger groups of subjects and longer follow-up regarding the efficacy of this device.

2.10.10 Cognitive Behavioural Therapy (CBT)

Tinnitus is associated with many psychological problems as previously discussed (Langguth et al., 2011). An intervention like Cognitive Behavioural Therapy (CBT) by itself does not influence the subjective loudness of tinnitus or improve the associated depression, but it may

19

effectively increase an individual's quality of life by increasing the patient's ability to deal with chronic tinnitus (Martinez-Devesa et al., 2010). The goal of CBT in tinnitus treatment is to recognise and then correct any negative thoughts and emotions an individual has about their tinnitus, (Henry & Wilson, 2001).   Studies have demonstrated that CBT has helped patients reduce tinnitus related distress Zachriat & Kroner-Hewrig (2004) and a Cochrane Review has also demonstrated CBT can have an overall effect on the qualitative aspects of tinnitus and also improve how the patients manage the condition (Martinez-Devesa et al., 2007).

2.10.11 Transcutaneous Electrical Stimulation (TENS)

Transcutaneous Electrical Stimulation (TENS) machines are commercially available devices which apply pulsed electrical stimuli to provide pain relief. Siedman & Jacobson (1996), in a review of tinnitus, indicated Electrical Stimulation (ES) as a possible treatment modality for patients with severe tinnitus. ES for suppression of tinnitus has been researched for many years and it has been indicated as a promising area of investigation (Dauman, 2000; Rubinstein & Tyler, 2004). The exact mechanism by which ES suppresses tinnitus is still unclear and the effects reported have varied considerably (Moller, 2010: 727). Shulman (1987) were one of the first to describe the results from cutaneous ES around the ear. Various types of ES have been used, such as high frequency electrical current, direct current (DC), and pulse trains at different rates (Moller, 2011: 727).

Commercial electrical stimulation tinnitus suppression devices were developed, but are no longer available (Henry et al., 2005). A number of studies were conducted with a tinnitus suppression device, the Audimax Theraband (Audimax Corp), which was developed during the 1980's. This wearable device used a headband to hold electrodes which deliver low level alternative current (AC) against each mastoid. The best controlled study of the theraband showed some limited therapeutic benefit Dobie et al. (1986), but the device is no longer being produced. Henry et al. (2005) also made reference to other electrical stimulation studies which reported some limited effectiveness, although he reports that placebo effects could have influenced the results (Dauman, 2000).

The use of ES has demonstrated some positive findings and the general consensus is that the DC is the most effective type of current, but causes tissue damage (Dobie et al., 1986; Hazell et al., 1989; Staller, 1998). AC does not cause tissue damage, but is only effective for a limited number of patients. ES is therefore still considered an experimental treatment and has not been demonstrated to be useful for common clinical practice (Henry et al., 2005). For the purpose of this study, we shall discuss ES of the trigeminal nerve in further detail in Chapter Five.

2.10.12 Sound Therapy

Various treatment strategies for tinnitus use sound therapy in the form of wearable devices such as hearing aids and maskers and non-wearable devices such as table top sound generators or maskers (Schechter & Henry, 2002; Henry et al, 2005). When used over long periods, noise generators which are set to masking sound levels can produce an overall reduction in tinnitus symptoms. Roberts (2010) reports that sound therapy has little effect once the external stimulus is discontinued with 'residual inhibition' (temporary relief when stimulus is turned off) lasting for approximately 2 minutes, resulting in short-term habituation effects. If the noise generator is set to produce sound levels below the masking level, the patient is conscious of both the noise from the masker and their tinnitus, which tends to result in greater improvements, particularly if the device is continually used for over a year. Typically between 60 and 70% of patients receiving this type of treatment will experience a useful reduction in their tinnitus symptoms (Baracca, 2007; Newman, 2012).

Hearing Aids have long been recognised to reduce the bothersome effects of tinnitus (Saltzman & Ersner, 1947; Surr et al., 1985; Melin et al., 1987; Newman, 1996; Henry et al., 2006). Masking devices in combination with amplification have been recommended for about 60% of patients treated in a major tinnitus clinic (Vernon & Miekle, 2000) and hearing aids alone are sometimes sufficient to provide masking relief (Del & Ambrosetti (2007); Trotter & Donaldson (2008). Vanettse & De Ridder (2012) make reference to hearing aids having only a marginal effect on the intensity of tinnitus and referred to studies where the perception of tinnitus was affected only weakly in a conventional amplification group and not at all affected in a high-bandwidth amplification regime (Moffat et al., 2009).

The efficacy of tinnitus masking is difficult to assess from the current literature, as the majority of studies only report the outcomes of treatment for those who purchased and used the devices, there are no reports on those who are not referred for treatment, who don't actually purchase devices, who purchase devices but don't use them, or those patients who return their devices for various reasons (Henry et al., 2005), and only a few authors include placebo control studies (Hobson et al., 2010).

CHAPTER THREE: NERVOUS SYSTEM

In this chapter, we briefly review the relevant parts of the Peripheral and Central Nervous systems that are relevant to our study. This includes the Peripheral and Central Auditory systems, somatosensory system and the cranial nerves.
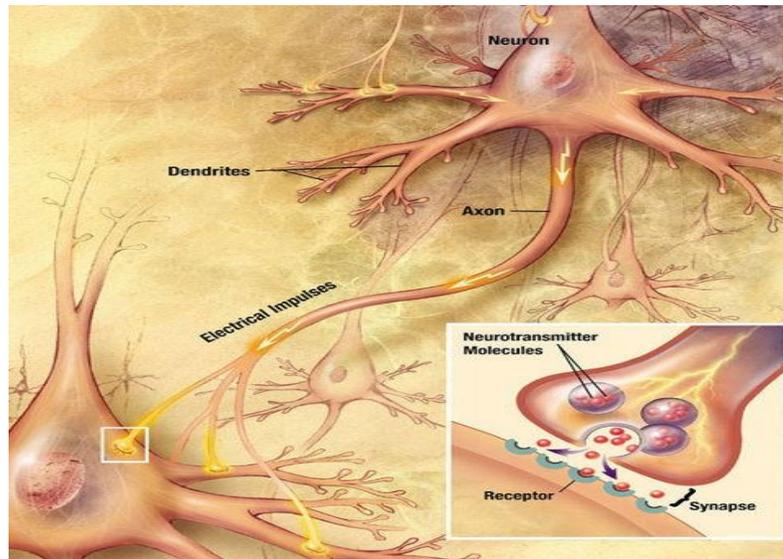
Figure 4 The Neuron: Chemical Synapse. Image from Wikipedia Commons (2013)

3.1 Neurons

Neurons contain nerve processes called dendrites and axons and a cell body called the soma which, transmit signals between different parts of the body, as shown in Fig 4. They release chemicals known as neurotransmitters at junctions called synapses, which give a command to the cell and the entire communication process typically takes only a fraction of a millisecond.

Neurons create electric impulses known as action potentials (spikes hereafter) which play a central role in cell to cell communication. A neuron that emits an action potential is often said to 'fire'. The spike occurs in response to an electrical charge inside the cell membrane. This change is due to channels opening in the dendrites in response to electrical (voltage gated channels), chemical (ligand gated channels) or mechanical (mechanical gated channels) stimuli, allowing mobile charges to enter the cell.

The generation of spikes is controlled by a region of the neuron called the trigger zone. These spikes travel right through the long distance an axon can span to the target cells. When action potentials arrive at the synapse (junction between two neurons) it triggers a complex chain of biochemical processing steps that lead to a release of neurotransmitters from the presynaptic terminal into the post synaptic cleft. Some neurons emit action potentials constantly, at rates of 10-100 meters per second. Some neurons are quiet but occasionally emit a burst of spikes (Barnes, 2007). The sensory areas receive information (nervous impulses) from all body parts and the association areas analyse the impulses and make decisions. Sensory neurons capture information about their environment and express it in terms of language of the nervous system.

In engineering terms, the human senses are essentially a set of analogue to digital converters. They convert the analogue signals of the world such as light and sound, into the digital signals of the nervous system, the spikes. This process is known as sensory transduction. The motor areas send impulses (orders) to muscles or glands. These impulses are carried by 43 pairs of cranial nerves, 31 pairs of nerves are in the spinal cord and 12 are in the brain stem. Due to the nature of this study, the trigeminal nerve and vestibular cochlear nerve will be discussed in more detail later in this chapter.

3.2 Central Nervous System (CNS)

The Central Nervous System (CNS) which is the most complex part of the Nervous System (NS) is made up of the brain and spinal cord and contains the majority of nerve cells and synaptic connections. It sends and receives sensory info to and from the Peripheral Nervous System (PNS) via sensory and motor cells. The CNS is responsible for receiving, processing and transmitting information by means of electrical and chemical interactions.

3.2.1 Spinal Cord

The spinal cord is the main pathway which connects the brain and peripheral nervous system (PNS). It is approximately the diameter of a human finger which extends from the brain down the middle of the back and is protected by the bony vertebral column. The Spinal cord consists of 31 pairs of spinal nerves consisting of fibres. It is surrounded by cerebrospinal fluid which protects the nerves against damage from the vertebral column. Between the vertebrae the spinal

nerves enter the spinal column and join with the spinal cord. Each junction has a sensory and motor connection. The spinal nerves are divided into 4 main groups of nerves which exit at different levels of the spinal cord. In descending order, they range from the cervical nerves (nerves in the neck) which supply movement and feeling to the arms, neck and upper trunk and also control breathing; the thoracic nerves (nerves in the upper back) which supply the trunk and abdomen and lumbar nerves, and sacral nerves (nerves in lower back) which supply the legs, bladder, bowel and, sexual organs.
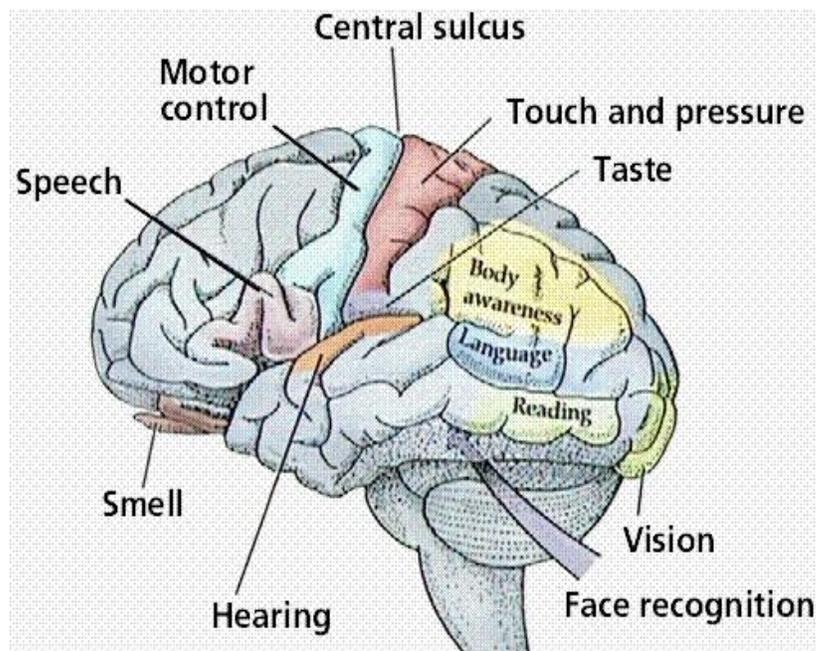
Figure 5 The functional area of the brain. Image taken from Purves et al (2008)

3.2.2 Brain

The brain is the most complex organ which controls most of the body's activities, as displayed in Fig 5 above. It is protected by the bones of the skull and by three thin membranes called meninges. It is also protected and cushioned by cerebrospinal fluid. It is the only organ able to produce 'intelligent' action based on past experience, present events and, future plans and is divided into the hindbrain, midbrain and, forebrain. The brain processes and interprets sensory information sent from the spinal cord.

The forebrain, (cerebrum) is the largest and most highly developed part of the brain. The cerebrum is categorised into areas according to their function - sensory, motor or associative. It

25

consists of the thalamus, hypothalamus and, two cerebral hemispheres which are joined by the corpus callosum (a band of nerve fibres). The cerebral hemispheres are separated into two halves by the sagittal fissure. They consist of four components; cerebral cortex; basal ganglia's; hippocampus formations and amygdala. The outer layer of the cerebral hemisphere is the cerebral cortex which is made up of grey matter and is responsible for receiving and processing sensory information such as decision making, speech, learning, memory and imagination and, controlling motor and autoimmune functions. Most of the information processing takes place in the cerebral cortex which is separated into 4 major lobes. These are the frontal, temporal, parietal and occipital lobes. These are shown in Fig.6 below.
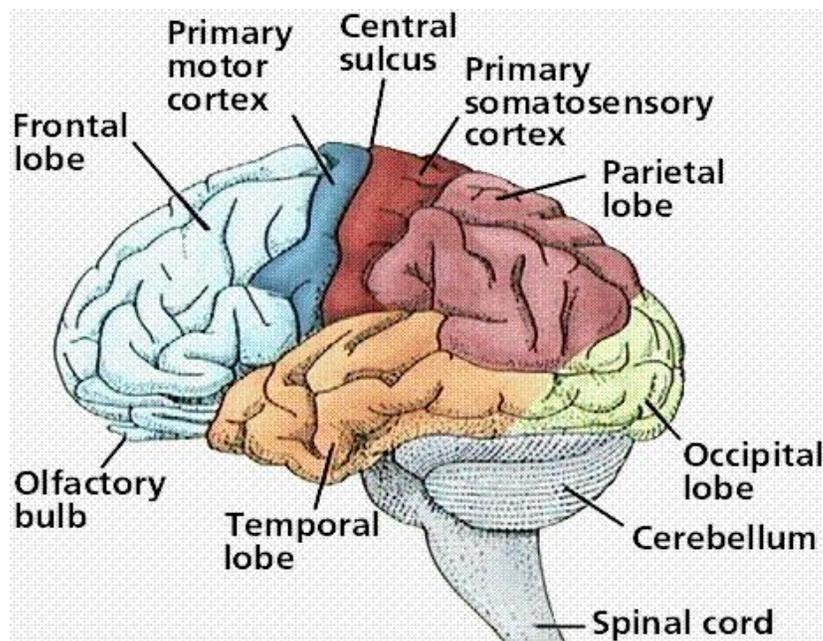
Figure 6 The major brain areas and lobes. Image taken from Purves et al. (2008)

3.2.3 Brain Stem

The Brain stem is a collective term for midbrain, pons and medulla and is a continuation of the spinal cord. It provides the main motor and sensory innervation to the face and neck via cranial nerves and is an extremely important component of the brain as the nerve connections of both motor and sensory systems from the brain to the rest of the body pass through it. The brain stem assists in the regulation of respiratory and cardiac function and also forms part of the auditory pathway.

26

3.3 Peripheral Nervous System (PNS)

The Peripheral Nervous System (PNS) connects to various organs and structures of the body through cranial and spinal nerves. It includes all of the nervous system outside the brain and spinal cord. The PNS consists of sensory neurons, and nerves that connect to one another and to the central nervous system. There are two types of cells in the PNS which transport information to (sensory nervous cells) and from (motor nervous cells) the CNS. Sensory neurons react to physical stimuli such as light, sound and touch and send feedback from the nerves to the central nervous system about the body's surrounding environment. Motor neurons, located in the central nervous system or in peripheral ganglia, transmit signals from the brain and spinal cord to muscle fibres throughout the body. The PNS is divided into three systems, Autonomic Nervous System (ANS), Somatic Nervous System (SNS) and, Enteric Nervous System (ENS).

3.3.1 Somatic Nervous System (SNS)

The Somatic Nervous System (SNS) is responsible for transporting motor and sensory information to and from the CNS and is made up of nerves that connect to the skin, sensory organs and skeletal muscles. Neurons of the somatic system project from the CNS system directly into the muscles and sensory organs. The body of the neurons are situation in the CNS and the axons project and terminate in the skin, sense organs or muscles. Electrochemical impulses then travel along the axon to the brain and spinal cord. The SNS is responsible for nearly all voluntary movements as well as the processing of sensory information that arrives via external stimuli including hearing, touch and sight. It consists of spinal nerves which carry sensory information into the spinal cord, cranial nerves that carry info in and out of the brain stem and association nerves that integrate sensory input and motor output.

3.3.2 Autonomic Nervous System (ANS)

The Autonomic Nervous System (ANS) is part of the nervous system that controls the functions of our internal organs (the Viscera) such as heart, stomach and intestines and also carries signals to the involuntary muscles, such as cardiac and smooth muscle. It has two main parts; The Sympathetic Nervous System and Parasympathetic Nervous System which tend to have opposing effects. The sympathetic nervous system is responsible for the 'fight or flight' response, in which blood pressure and heart rate rise. The synapse in the sympathetic pre-ganglion neuron use

acetylcholine as a neurotransmitter and the synapse between the post-ganglionic neuron with the target organ uses a neurotransmitter called norepinephrine. The parasympathetic nervous system tends to act in opposition to the sympathetic nervous system, by slowing down the heartbeat and dilating the blood vessels. It regulates the function of many glands, such as those that produce saliva and tears, and also stimulates digestive secretions.

3.4 Cranial Nerves

As previously mentioned, there are a total of twelve bilaterally paired cranial nerves originating from the brain and brain stem. Each of them carries different functions related to different senses of body. Apart from sensory functions there are also some that work as motor nerves or mixed nerves.
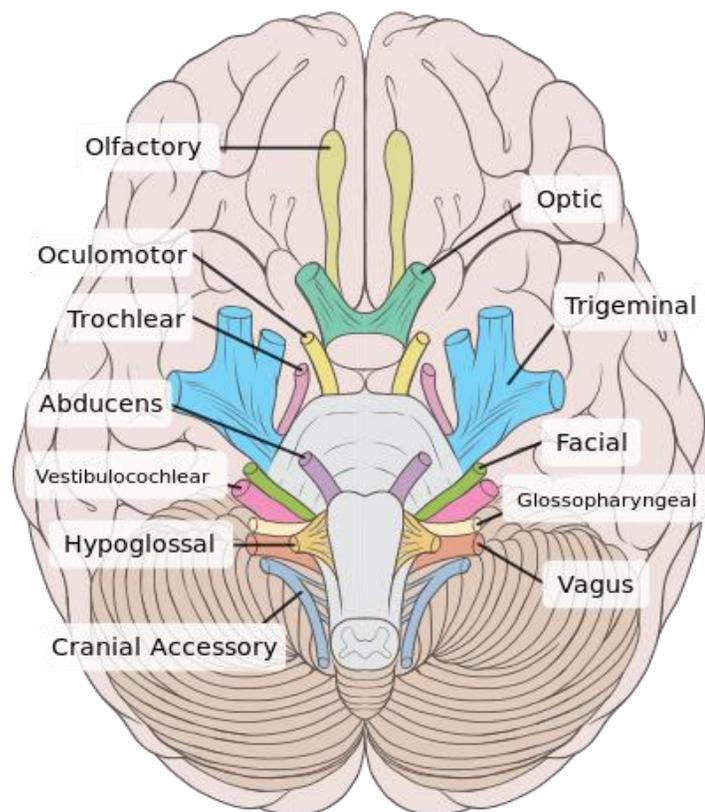
Figure 7 Ventral brain showing labelled cranial nerves. Image taken from WikiCommons (2012)

3.4. 1 Trigeminal Nerve

The trigeminal nerve is known as the 5th (V) and largest cranial nerve. It contains both sensory and motor components. Fibres carrying general sensory information (touch, pressure, pain and temp) from the head enter the brain through the trigeminal nerve at the level of the pons and terminate in the trigeminal sensory nucleus. This is the largest nucleus that runs the whole length of the brain stem and extends into the cervical spinal cord. The trigeminal nerve is responsible for general sensation in face and motor functions such as biting and chewing. Sensory functions of the trigeminal nerve are to provide the tactile, proprioceptive and nociceptive inference to the face and mouth. The nerve consists of three major branches, ophthalmic nerve, maxillary nerve which are purely sensory and mandibular nerve which consists of both sensory and motor functions.

The mandibular nerve carries touch/position and pain /temp sensation form the mouth. It is not responsible for taste sensation, chorda tympani is responsible for taste but one of its branches the lingual nerve carries multiple types of nerve fibres that do not originate in the mandibular nerve. The branches intersect on the trigeminal ganglion, which contains the cell bodies of incoming nerve fibres. From the trigeminal ganglion a single large sensory root enters the brain stem at the level of the pons and motor fibres pass through the trigeminal on their way to the peripheral muscles. In classical anatomy the trigeminal nerve is said to have general somatic afferent (sensory) components, as well as special visceral efferent motor components.

3.4. 2 Vestibularcochlear Nerve

The vestibularcochlear nerve is the 8th cranial nerve (VIII) and is responsible for transmitting sound and equilibrium information from the inner ear to the brain. It is a sensory nerve along which the sensory cells of the inner ear convey information to the brain and consists of two component parts, the cochlear nerve carrying information about hearing and the vestibular nerve carry information about movement and balance. Both nerve parts pass through the internal acoustic meatus in the temporal bone which also contains the facial nerve and attach to the brain stem.

The cochlear nerve fibres make contact with the hair cells in the organ of Corti within the cochlear duct of the inner ear. The cell bodies of these fibres are known as the spiral ganglion. These

fibres end in the dorsal and ventral cochlear nuclei and the next stage of neural processing in the auditory system begins.

3.5 Auditory System
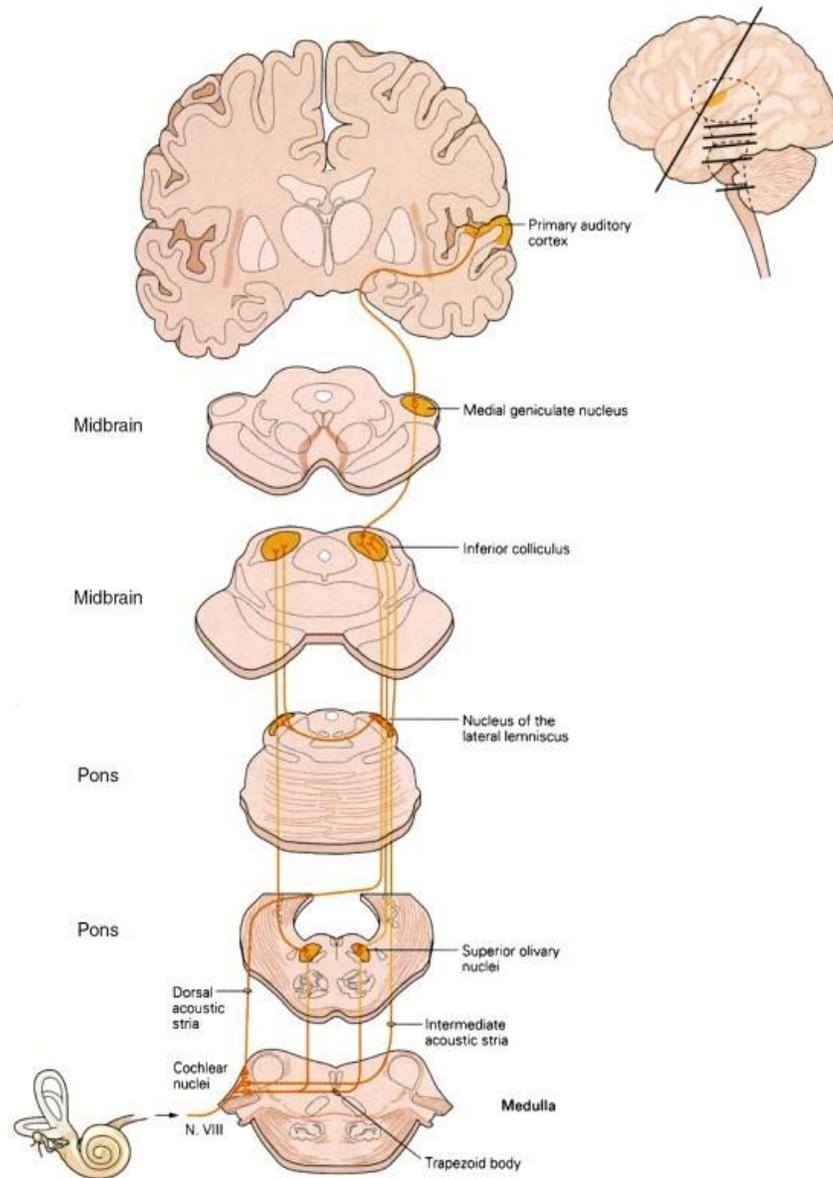
Figure 8 Principal ascending connections of the auditory component of the vestibulocochlear nerve.

Image taken from Kandel et al. (2000)

3.5.1 The Auditory System

The auditory system is a sensory system which is responsible for the sense of hearing and is divided into the peripheral auditory system and central auditory system as shown in Fig.7. The peripheral system which shall be discussed further in Chapter Four consists of the outer, middle and inner ear which performs mechanoelectrical transduction of sound pressure waves into neural action potentials. This is the first stage of sound transduction which feeds directly into the nervous system. The re-encoded sound travels down the vestibulocochlear nerve to the central auditory system which consists of the cochlear nuclei, trapezoid body in the ventral pons, superior olivary complex (SOC) of the brain stem, lateral lemniscuses in the brainstem, inferior colliculus (IC) of the midbrain, medial geniculate nucleus and the primary auditory cortex which is the first region of the primary auditory cortex to receive auditory input as shown in Fig. 7 above.

3.5.2 Dorsal Cochlear Nucleus

The cochlear nucleus (CN) is the first synapse or relay point in the auditory system and receives information directly via the 8th nerve and somatosensory input indirectly from the 5th nerve via granule cells. Auditory signals go through the CN on their way to the auditory cortex for further processing via the cochlear nerve. It is split anatomically and physiological into 2 regions, the dorsal cochlear nucleus (DCN) and ventral cochlear nucleus (VCN). The CN receives auditory signals from the hair cells in the cochlea, where sound is detected, as well as signals related to eye movements. It also receives signals from muscle position sensors and relays these to other areas of the brain. Sensory data from muscles and acoustic data from the ears are both relayed to the brain at very nearly the same point in the brain stem. The cochlear nucleus receives input from each spiral ganglion, but also receives input from *other* parts of the brain, such as auditory cortex, pontine nuclei, trigeminal ganglion and nucleus, dorsal column nuclei and the second dorsal root ganglion. The inputs from these other areas of the brain probably play a role in sound localisation. It is also believed that the DCN plays a role in tinnitus perception, which will be discussed in more detail in Chapter Five.

3.5.3 Superior Olivary Complex

The superior olivary complex (SOC) is the second major relay in the brain stem. Located in the pons, on either side of the brain, it is tonotopically organised and receives projections

from the ventral cochlear nucleus (VCN) and the dorsal cochlear nucleus (DCN) via the ventral acoustic stria. The nuclear complex can localise sound in acoustic space by discriminating the differences between the intensity of sound to each ear or in the timing of sounds arriving at the ear. They have an inhibitory function and monitor the transmission of auditory information to the cochlear nerve.

3.5.4 Lateral Lemniscus

Ascending fibres comprise the lateral lemniscus which, carry information regarding sound from the central nuclei to various brain stem nuclei and contralaterally to the inferior colliculus (IC) of the mid brain.

3.5.5 Inferior Colliculus (IC)

The dorsal portion of the inferior colliculus (IC) receives projections from the neurons that respond to low frequencies of sound, as opposed to the ventral portion which responds to high frequencies of sound. The auditory information is then processed and relayed by the IC to the medial geniculate nucleus (MGN) of the thalamus.

3.5.6 Thalamus

The thalamus sits deep in the brain on top of the brain stem, between the cerebral cortex and midbrain. It is an area which carries out the first basic sorting of incoming impulses and directs them to the different parts of the cerebrum. It also directs some outgoing impulses. It is one of four main parts of the diencephalon, and connects to the hippocampus via the mammillo-thalamic tract. It has multiple functions, and is mainly thought to act as a relay between a range of subcortical areas and the cerebral cortex. It is the largest part of the diencephalon and plays an important role in cognitive, sensory and motor functions. Apart from the olfactory system, every sensory system includes a thalamic nucleus that receives sensory signals and sends them to primary cortical areas. The medial geniculate nucleus (MGN) which is tonotopically arranged acts as a key auditory relay between the inferior colliculus (IC) of the midbrain and the primary auditory cortex of the temporal lobe. It relays precise information about frequency, intensity and binaural properties of sound. It is the gateway to the cerebral cortex as nearly all sensory inputs pass through it to the higher levels of the brain.

3.5.7 Primary Auditory Cortex

The auditory cortex is divided into three main parts, primary secondary and tertiary cortices with the primary being located between the two others. It is comprised of two areas named Brodmann areas 41 and 42, which together are referred to as the A-1 region. The human primary auditory cortex is located on the superior part of the temporal lobe just above the ear. It is responsible for processing signals from the auditory sensory system and is believed to be mainly responsible for processing the more simple elements of sound, such as pitch in comparison to the secondary auditory cortex which is believe to process more complex sounds such as rhythmic patterns. It does not function in isolation but interacts with other cortical and neocortical structures and receives projections directly from the medial geniculate nucleus. Like most of the ascending auditory structures, it is characterised by its tonotopic organisation which arises in the cochlea and is maintained throughout the auditory system (Truex & Carpenter, 1969; Aldhafeeri, 2012).

Auditory information is further processed and interpreted in the auditory association cortex. Part of the temporal lobe is curled inwards and forms the hippocampus which is part of the limbic system. It main function is in relation to memory and emotional behaviour. The amygdala which is also part of the limbic system lies close to the anterior end of the hippocampus. The amygdala receives sensory information from the various sensory modalities, including the auditory, somatosensory, visual and olfactory stimuli. The amygdala is anatomically and functionally connected to brain regions which include; the basal forebrain, hypothalamus, hippocampal formation and striatum.
This will be further discussed in Chapter Five.

3.6 Somatosensory Cortex

The postcentral gyrus of the parietal lobe is referred to as the somatosensory cortex. It processes input from various regions of the body which are sensitive to touch, pressure, pain, itching, proprioception and temperature. It is located next to the motor cortex and both are quite similarly organised in terms of their functional relation to various body parts. The cortex processes information contralaterally. Impulses from the body associated with sensation of pain, temp etc. run across nerves to the thalamus which passes the signals to the somatosensory system. The

cortex receives afferents from the ventral posterior nucleus of the thalamus, which is when the spinothalamic tract, trigeminothalamic tract and medial lemnisucs terminate. The somatosensory cortex has also the ability to reorganise or rewire itself in response to external events, this is known as neuroplasticity. Behind the cortex lies the sensory association cortex which is responsible for interpreting general sensory information.

An area that resides between the somatosensory, visual and auditory association areas is referred to as the common integrative area. It is thought to be involved in the integration of signals from all these areas, as well as from the olfactory and gustatory areas, the brain stem and thalamus (Crossman & Neary, 2010).

CHAPTER FOUR: NEURAL PATHOLOGIES

Chapter Four gives a brief overview of the auditory system and the mechanoelectrical transduction of sound pressure into neural action potentials. We pay particular attention to the human sense of hearing, the relationship between tinnitus and high frequency hearing loss, and neural pathologies in the central nervous system which drive neuroplasticity.

4.1 Peripheral Auditory System
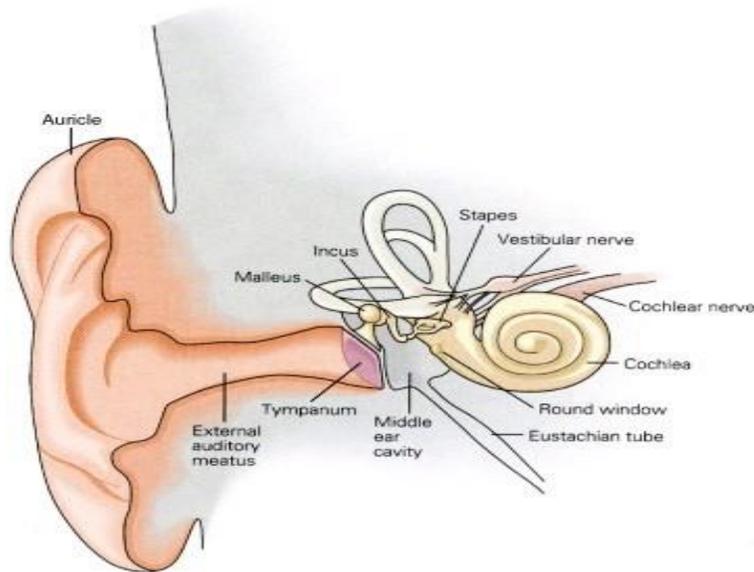
Figure 9 The Peripheral Auditory System. Image taken from E.R. Kandel et al. (2000)

4.2.1 Outer Ear

The outer ear consists of the pinna, a flexible oval shaped structure attached to the ear, and the ear canal or meatus, which leads to the middle ear, see Figure 8 above. Before sound reaches the middle ear it is picked up by the outer ear. The pinna is responsible for funnelling sounds into the ear canals. Sound travels along the ear canal, and causes the eardrum to vibrate. The human ear can comfortably perceive mechanical disturbances in the air in the amplitude range of 0dB to 80dB and in the frequency range of 20Hz to 20 kHz.

4.1.2 Middle Ear

This vibration is passed through to the tiny bones of the middle ear known as the ossicles; these include the malleus, incus, and stapes which are responsible for amplifying sound and transmitting vibrations to the inner ear. Two muscles in the middle ear, the tensor tympanic which is supplied by a branch of the trigeminal nerve and the stapedius muscle which is supplied by the facial nerve, are responsible for reducing transmission of some sounds. The middle ear is filled with air and the pressure on each side of the eardrum needs to be similar so that the eardrum can vibrate correctly. The Eustachian Tube (ET) is responsible for equalising pressure in the middle ear, it connects the middle to the back of the throat and pressure is normally maintained by swallowing as this opens and closes the tube. The middle ear also contains the oval and round windows which are miniature versions of the eardrum and separate the middle ear from the inner ear.

4.2.3 Inner Ear

The inner ear is where sound is converted to mechanical energy and then to nerve impulses which travel to the brain. It consists of a spiral fluid-filled cochlea which contains the organ of Corti, the most important component of hearing which contains receptors of hearing called stereocilia. The Corti sits in the Basilar Membrane, which is a very sensitive membrane (Ballantyne et al., 1993:24-44). Sounds of different frequencies cause different parts of the membrane to vibrate. The basilar membrane of perilymph is compressed inwards by the movement of the stapes. When the basilar membrane vibrates, the stereocilia and small sensory hair cells inside the Corti begin to move. The organ of Corti pivots in response to the movements of the basilar membrane, see Fig. 9 below.

4.2 Central Auditory Pathway

The human cochlea is a tonotopically-organised structure that decomposes complex sounds into a collection of frequency components which are neutrally encoded and transmitted centrally through the auditory nerve. Situated at the end of the hair cells are tips of nerve fibres. As hair cells are bent, nerve impulses are stimulated in the nerve fibres. These nerve fibres together make up the auditory nerve. Nerve pulses are transmitted from the ear to the brain via auditory nerves, one of the several sensory nerves which are part of the group of nerves known as the cranial

nerves. The re-coded sound travels along the vestibulocochlear nerve through the cochlear nuclei which is the first sign of neuronal processing from the inner ear. The cochlear nuclei are anatomically and physiologically split into the dorsal cochlear and ventral nucleus. The cochlear nucleus is thought to sharpen features of the now highly compressed signal.

Neural information continues to the superior olivary complex (SOC) of the brainstem which is responsible for lateralisation of sound sources, and onto the inferior colliculus (IC) of the midbrain, being further processed at each point. Information reaches the thalamus and is relayed to the cortex. The primary auditory cortex interacts with the secondary auditory cortex which surrounds it. The secondary areas interconnect with further processing areas in the superior temporal gyrus, in the dorsal bank of the superior temporal sulcus, and in the frontal lobe, which are individually important for speech perception as well as for distinguishing between speech, music, and noises.
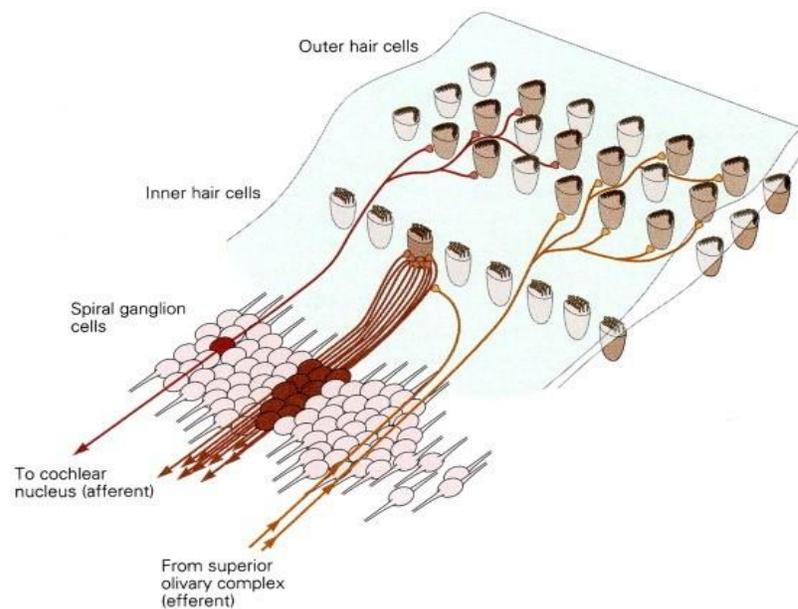
Figure 10 Innervation of the Organ of Corti. Image taken from E.R. Kandel et al. (2000)

The auditory sensory hair cells are the focal point of the hearing mechanism (Ballantyne et al., 1993:36). Sensory-neural hearing loss tends to occur when there is damage to the inner ear, or the nerve pathways. Sensori-nerual hearing-loss is most commonly characterized by a high-

frequency loss that may involve loss of both outer hair cells (OHC) and inner hair cell (IHC) function. OHC, which are controlled by the olivocochlear efferents, are believed to provide dynamic range compression by modulating cochlear amplification gain within the associated frequency-bands Guinan (1996). IHC mechanically transduce the associated frequency component and neutrally encode it by modulating the stochastic firing rates of the auditory nerve fibres that innervate them, where there is a linear relationship between stimulus intensity and firing rates (Kiang, 1975). Loss of OHC function results in a loss of dynamic range compression within the associated band, while loss of IHC function results in loss of general sensitivity within the band.

4.3 Hearing Loss Related Tinnitus

As discussed in Chapter One, hearing loss related tinnitus is the most common form of the condition and is currently considered untreatable (Eggermont, 2006). There is a clear relationship between tinnitus and high frequency sensorinerual hearing loss (Eggermont & Roberts, 2004; Moore et al., 2010; Davis & Rafaie, 2000; Henry & Wilson, 2001) in particular age related (Vernon & Meikle, 2000) and noise related (Axelsson & Prasher, 2000) with the pitch of the phantom sound often correlating to the frequency of the hearing loss (Norena et al., 2002). Although many areas along the auditory pathway have been linked to tinnitus generation (Weisz, 2007; Wei et al., 2010) it believed that damage to the peripheral organ (cochlea) is the trigger point and generation occurs in the central nervous system (Jastreboff, 1990; Schaette & Kempter, 2006). Noise induced tinnitus has been reported to correlate with increased activity in many auditory regions, from the dorsal cochlear nucleus (DCN) to the cortex (Norena & Eggermont, 2003; Finlayson & Kaltenback, 2009; Shore et al., 2008). This hyperactivity is thought to occur due to the reduced auditory nerve activity which performs an inhibitory role in the auditory brain stem structures. Reduced or degraded peripheral input is believed to be associated with increased neuronal activity, increased synchronicity and functional reorganisation in the auditory cortex (Norena & Eggermont, 2003; Weisz, 2007; Eggermont & Roberts, 2004; Seiki & Eggermont, 2003; Moller, 2007).

4.4 Central Gain Adaptation

Jastreboff (1990) suggested that damage to the peripheral organ serves as a trigger for tinnitus which is sustained by events occurring in the central auditory pathway (Saunders 2007). This 'deafferentation' subsequently leads to reorganization of tonotopic maps as the effected neurons begin to express the tuning preference of frequencies adjacent to the partial hearing loss (Dietrich et al. 2001) altered firing rates and synchronicity. It is believed that this may be driven by a 'central gains' phenomenon that seeks to preserve mean firing rates and neural homeostasis (Norena, 2011; Schaette & Kempter, 2006) at the expense of perceptual accuracy. In order to compensate for loss of input and normalise the wider frequency response, the central auditory system naturally adapts frequency dependent gains within the affected bands. This mechanism is also consistent with the finding that unilateral cochlear implants generally reduce contralateral tinnitus (Quaranta et al 2004).

Schaette (2006) also refers to a computational model of this "central gain mechanism", suggesting that reduced cochlear compression increases the required natural gain adaption and Parra and Pearlmutter (2007) similarly reports that tinnitus patients are more likely to exhibit such frequency-dependant gains.

4.5 Zwicker Tone

The Zwicker tone which was discovered by Eberhand Zwicker is an auditory illusion similar to tinnitus and therefore cannot be explained by known properties of the auditory periphery alone (Zwicker, 1964). In their 2006 study, Parra and Pearlmutter proposed a model of central gains that seeks to compensate for loss of outer hair cells (OHC) dynamic range compression. They demonstrated that individuals with tinnitus exhibit independent gain control in frequency-bands of significant hearing loss. They postulated that the auditory mechanisms increase internal gains when confronted with silence in selected frequency bands which then amplify neuronal noise to the point that it is perceived as phantom sounds such as Zwicker tones.

4.6 Lateral Inhibition

Dominguez et al. (2006) describes a theoretical model of decreased lateral inhibition and increased lateral excitation in thalamocortical afferents that could underlie such 'central gains' and may give rise to the illusory perception of tinnitus, as shown in Fig. 10.

Roberts et al. (2010) refers to high frequency, hearing loss and the cortical neurons which start to respond preferentially to frequencies at the edge of normal hearing, which as a result become overrepresented in the cortical tonotopic map (Eggermont & Komiya, 2000). This reorganisation of the tonotopic map has been detected in human tinnitus sufferers by neuromagnetic braining imaging (Roberts et al., 2010). Loss of input to the auditory cortex from peripheral ototrauma can also lead to areas of missing frequencies in the cortical tonotopic map (Lockwood et al., 2002; Moller, 2006). Our understanding of tonotopic remodelling in the auditory cortex comes from the somatosensory system where there is a well-known response to the elimination of peripheral input (Salvi et al., 2000).

Animal studies have shown that when a region of the tonotopic map is disconnected from the ear by cochlear damage, this region reorganises itself as the affected neurons begin to express the tuning preference of their neighbours (Roberts, 2011; Eggermont & Komiya, 2000). The lost

40

sideband inhibition model proposed by Dominiguez et al. (2006) suggests that spectral modification or enrichment of auditory input may compensate for peripheral loss and reverse these central gains in the affected frequency bands. Norena & Eggermont (2006) examined these effects of such spectrally modified sound in felines after induced hearing loss and found that those which were kept in high frequency enriched environments did not develop the neural correlates of tinnitus. Tonotoptic maps, spontaneous firing rates and synchrony remained unchanged post hearing-loss. Similar studies suggest that sound enrichment may reverse such neural pathologies in humans (Stracke et al., 2010; Okamoto et al., 2010). Hearing aids and other sound therapies are used to treat tinnitus patients on this basis (Moffat, 2009), yet questions remain about their efficacy (Hobson et al., 2010); Roberts et al., 2008).

4. 7 Neuroplasticity

Neural plasticity refers to the brains ability to adapt its neural networks on the basis of new experience. The brain has the ability to constantly optimise itself, reorganise itself and transfer cognitive abilities from one lobe to the other, particularly as we age.

Neuroplasticity may be "adaptive or positive" in terms of learning or memory allowing us to adapt to changes in the environment. It can also be "negative or maladaptive" resulting in an imbalance in excitatory and inhibitory events in the brain resulting in neural hyperactivity (Kaltenbach et al., 2005; Saunders, 2007).

Maladaptive neuroplasticity can be seen in various pathologies such as limb amputation and focal hand dystonia. The somatosensory cortex is not expected to respond to any stimulus following amputation of a limb and damage to the neural networks; however neighbouring neural inputs are believed to be able to stimulate this particular area of the brain and is recognised in the affected somatosensory cortex. The brain compensates for damage by reorganising and forming new connections between intact neurons (O'Neill, 2008).

Deprivation of input to the nervous system is the main factor that can activate neuroplasticy. Many studies agree that neuroplasticity plays a major role in the tinnitus pathogenesis (Baguley, 2002; Eggermont, 2003; Moller, 2003; Eggermont, 2005). Kaltenbach et al. (2005) describes tinnitus as a perceptual manifestation of plastic changes that result in neural hyperactivity.

Following hearing loss, the area of missing frequencies reappears in the reorganised tonotopic map (Saunders 2007) and it is has been conjectured that tinnitus occurs due to this reorganisation. In other words, the brain rewires itself due to the brain cells being deprived of acoustic stimulation. It is also believed that neuroplasticty may be involved in the disorders that often accompany tinnitus, such as hyperacusis, phonophobia and depression (Nelson & Chen, 2004; Cacace, 2003).

CHAPTER FIVE: AUDITORY-SOMATOSENSORY INTEGRATION AND IMPLICATIONS FOR THE TREATMENT OF TINNITUS

Chapter Five discusses the anatomical and functional links between the auditory and somatosensory systems. We explore these cortical and subcortical links, how they influence the perception of sound, and their implications for the treatment of tinnitus. Finally, we propose a novel treatment that utilises auditory-somatosensory interactions.

5.1 Subcortical Auditory-Somatosensory Interaction

There is long-established evidence of auditory-somatosensory integration in the midbrain structure known as the inferior colliculus (IC) and in the brainstem structure known as the superior olivary complex (SOC) (Aitkin et al., 1978; Eliades & Wang 2003; 2005). However, more recent studies have shown that the subcortical auditory structure with perhaps the greatest levels of somatosensory interaction is the cochlear nucleus (CN). The CN receives input from the ipsilateral auditory nerve (8th nerve), from the contralateral nucleus and also from trigeminal sensory structures (Shore et al., 2000; Zhou & Shore 2004; Shore & Zhou 2006). It is believed that the trigeminal projections are associated with systems that control vocalisation, chewing and breathing (Shore & Zhou, 2006). Furthermore, it has been shown that electrical stimulation of these projections can suppress acoustically driven activity in CN and IC. It has been suggested that the function of these anatomical and physiological auditory-somatosensory connections are to suppress responses to endogenous sounds, such as vocalisations, chewing and breathing relative to responses to more exogenous sounds (Shore & Zhou, 2006).

The involvement of the dorsal cochlear nucleus (DCN) has been implicated in the generation of the illusory sounds of tinnitus. In addition to changes observed in the peripheral hearing systems, neural hyperactivity has been observed in the DCN following hearing loss (Kaltenbach et al., 2005, Sachaete & Kempter. 2008). It is believed that this is a neural correlate of the 'central gains' phenomenon discussed in Chapter Four. It is unclear what contribution, if any, somatosensory inputs into the DCN make to the generation of this neural hyperactivity.

However, it has been suggested that somatosensory inputs are relayed to DCN neurons via a series of excitatory fibres, which may contribute to increased neural activity (Levine, 1999; Weinberg, 1987; Eggermont & Roberts, 2004; Brozoskin & Bauer, 2005; Shore, 2005). Shore et al. (2006) found that tinnitus percepts may be qualitatively and quantitatively modulated through physical manipulation of the head, neck and jaw and proposed a model, which suggests this modulation is the result of complex auditory-somatosensory spike timing. Tzounopoulos (2004) suggested that these auditory-somatosensory interactions drive synaptic plasticity in the DCN that could underlie the 'ignition' and 'maintenance' of tinnitus. Conversely, Shore et al. (2006) demonstrated that auditory evoked activity in DCN neurons can be suppressed by electrically stimulating the trigeminal system. Harnessing the trigeminal capability to suppress sound through electrical stimulation may be the basis for a novel technological intervention for tinnitus, which we will discuss in further detail in Section 5.5. This hypothesis is supported by promising findings in human studies that electrically stimulated the C2 dermatome using Transcutaneous Electrical Nerve Stimulation (TENS) (Vanneste et al., 2010).

5.2 Cortical Auditory-Somatosensory Interaction

There is a growing body of evidence of cortical-level auditory-somatosensory integration. Brain-imaging studies with primates have shown that auditory broadband sound combined with tactile stimulation of the hand elicited auditory-somatosensory integration in the area posterior to and along the lateral side of the primary auditory cortex in the caudal auditory belt (Kayser et al., 2005). Similar studies with humans showed enhanced auditory cortical responses to somatosensory stimuli in hearing-impaired humans (Auer et al., 2007). Perhaps the most well-known example of auditory-somatosensory integration is the 'Parchment Skin Illusion' (Jousmaki & Hari 1998), which shows that sound strongly, modulates tactile sensations. Similarly, touch has been shown to have a corresponding influence over auditory sensations. Studies showed that simultaneous vibrotactile stimulation attenuates loudness perception in normal hearing adults (Schurmann et al., 2004). Similar studies showed that simultaneous audio-tactile stimuli bias the perceived location of sounds (Caclin et al., 2002). Furthermore, animal studies demonstrated that simultaneous audio-tactile stimuli can alter the frequency responses of rodent and chiropteran cortical, collicular and corticofugal neurons for periods longer than twenty-four hours (Gao & Suga, 2000; Kilgard & Merznich, 1998; Bao et al., 2001). Weinberger

(1998) postulates that auditory and somatosensory stimuli are associated in the medial division of the medial geniculate body (MGB) and intralaminar nucleus and that the associated signal is sent to the basal forebrain via the amygdala. The basal forebrain plays a critical role in the production of acetylcholine, which has been shown to improve cortical information processing and enhance conditioned learning (Kuo, 2007; Laviolette & van der Kooy, 2004; Changeaux, 2010). This hypothesis was experimentally verified in animal studies that used simultaneous audio tones and electrical vagus nerve stimulation to reverse the neural correlates of tinnitus in rodents (Engineer, 2011).
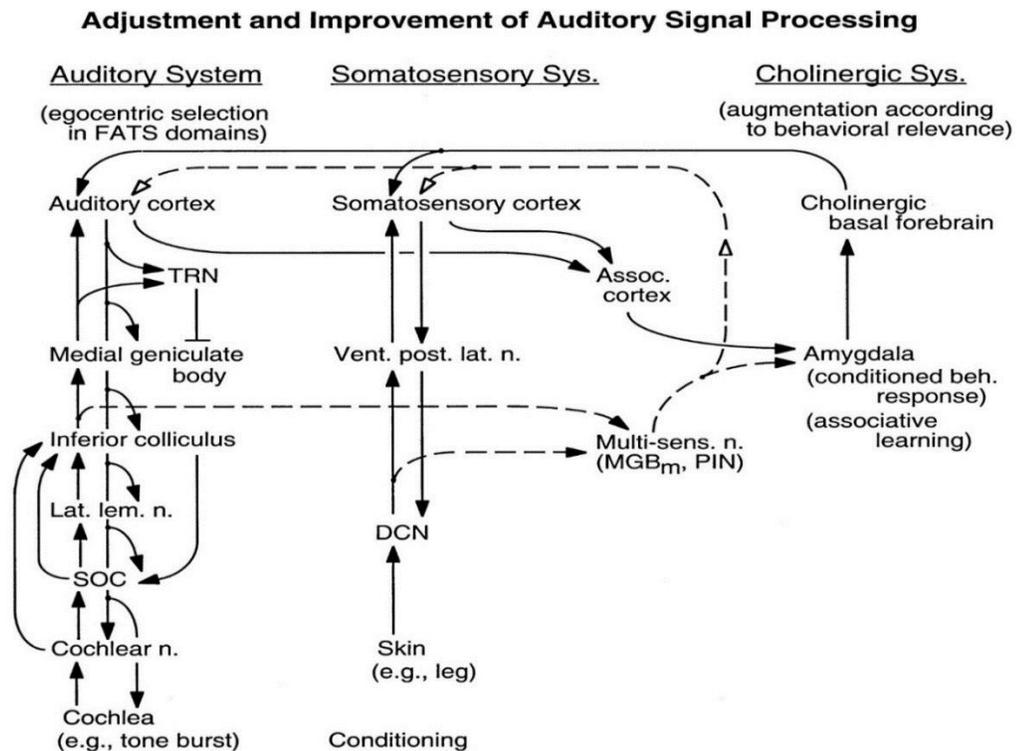
Figure 12 Working Hypothesis for the Adjustment and Improvement of Auditory Signal Processing according to Associative Learning (Auditory Fear Conditioning). Image taken from Suga et al. (2002)

The findings that audio-tactile stimuli can modulate the frequency and loudness of auditory perception constitutes a compelling and growing case for the multisensory approach to treating tinnitus. In the following sections, we will discuss the optimal forms of sound and tactile stimulation that might form the basis for such a multisensory treatment.

5.3 Auditory Stimuli

5.3.1 Tonal Stimuli

Tonal stimuli have been widely used in both unisensory and multisensory tinnitus interventions. In animal studies, tones have been used in combination with simultaneous electrical stimulation of the cutaneous surface of the foot to alter the frequency responses of rodent and chiropteran cortical, collicular and corticofugal neurons for periods longer than twenty-four hours (Gao & Suga, 2000; Kilgard & Merznich, 1998; Bao et al., 2001). Similarly, simultaneous audio tones and electrical vagus nerve stimulation have been used to reverse the neural correlates of tinnitus in the auditory cortices of rodents (Engineer, 2011). Tones have also been used to disrupt cortical synchrony in the auditory cortices of humans (Tass et al., 2012).

While the use of tonal stimuli shows promising results in animal and human research, the practical clinical use of such stimuli faces major challenges. The repetitive mechanistic nature of the sounds are unlikely to be well tolerated by patients in the long-term and may even further contribute to tinnitus related stress.

5.3.2 Sound Enrichment

The lateral inhibition model proposed by Dominguez et al. (2008) and frequency dependent central gains model proposed by Parra & Pearlmutter (2007) suggest that spectral modification or enrichment of auditory input may compensate for peripheral loss and reverse central gains in affected frequency bands. Norena & Eggermont (2006) examined the neurologic benefit of introducing sound enrichment immediately after high-frequency hearing loss was induced in felines and found that animals that were kept in high-frequency enriched environments did not develop neural correlates of tinnitus. Tonotopic maps, spontaneous firing rates and synchrony remained unchanged post-hearing-loss. Similar studies suggest that sound enrichment may reverse such neural pathologies in humans a priori (Stracke et al., 2010; Okamoto et al., 2010). Hearing aids and other sound therapies are used to treat tinnitus patients on this basis (Saltzman & Ersner, 1947; Surr et al, 1985; Moller et al., 2011; Melin et al., 1987; Moffat, 2009; Roberts et al., 2008; Hobson et al., 2010).

Hearing aids are widely used and are generally well tolerated by patients. Modern digital hearing aids adjust amplification in independent frequency bands according to the patient's audiogram. Sound is amplified in bands where there is a loss and not amplified in bands where hearing is normal. This approach should theoretically compensate for frequency-dependent peripheral losses and thus alleviate the resulting central gains phenomenon.

The practical clinical experience of digital hearing aids is that many patients find the lack of dynamic compression frustrating, especially when moving from noisy to quiet environments. Patients often begin to manually adjust amplification levels to suit their environment thus negating the settings made by their audiologist and undermining any derived therapeutic benefit for their tinnitus.

5.4 Tactile Stimuli

5.4.1 Trigeminal Stimulation

As discussed in Section 5.1, studies have shown that electrical stimulation of the trigeminal system can suppress acoustically-driven activity in the cochlear nucleus (CN) and inferior colliculus (IC). Shore et al. (2006) demonstrated that when acoustic tones were preceded by electrical pulses delivered to the trigeminal nerve, the DCN responses to the acoustic tones were suppressed. Furthermore, Tzounopoulos (2004) suggested that these auditory-somatosensory interactions drive synaptic plasticity in the DCN.

This inhibitory mechanism could potentially be harnessed through broad transcutaneous electrical stimulation of the trigeminal system (Opthalmic, Maxillary or Mandibular) or through more subtle auditory-trigeminal stimuli that utilise pulse/tone timing to manipulate DCN plasticity.

Auditory-trigeminal pulse/tone timing is technically challenging and currently not well understood in humans. This approach would require extensive further research to determine the latencies of the human trigeminal and auditory systems and is beyond the scope of this project.

Broad trigeminal stimulation has the advantages of being technologically and clinically practical and its use is supported by the findings of studies using transcutaneous electrical stimulation of the C2 dermatome to treat tinnitus (Vanneste et al., 2010). As previously mentioned in Chapter Four, TENS is a very safe, non-invasive method, and a method used to reduce pain (Herraiz, 2007; Vanestte & De Ridder, 2012). For tinnitus, it was initially shown that TENs of the median nerve could modulate tinnitus perception in a number of patients (Moller et al., 1992). A number of clinical studies have been conducted over the years to investigate the use of electrical cutaneous stimulation as a potential treatment for tinnitus (Dobie, 1986; Thedinger, 1987; Shulman, 1987; Vanneste, 2010; Engelberg & Baucer, 1985; Steenerson, 2003; Herraiz, 2007; Kapkin, 2008). These studies focussed on the stimulation of the inhibitory inputs of the trigeminal nerve into the dorsal cochlear nucleus through surface electrodes. In a recent study by Vanneste et al. (2011) it was shown that there is variability in the response to TENS as well as tDCS and TMS. Based on such results it is argued that TENS only modulates the tinnitus brain circuit indirectly via the C2 nerve, activation of which modulates signal transmission in the dorsal cochlear nucleus, whereas TMS and tDCS have a dual working mechanism, a TENS-like indirect mechanism via somatosensory influences mediated through the C2 and/ or the trigeminal nerve plus a direct brain modulating mechanism. There is evidence that electrical stimulation works for some patients and although there are reports of some minor adverse effects, (Theringer, 1987; Steerenson, 2003), other studies report of continued tinnitus treatment after electrical stimulation (Steenerson, 2003; Engleberg, 1995).

5.4.2 Paired Stimulation

As discussed in Section 5.2, brain-imaging studies have shown enhanced auditory cortical responses to somatosensory stimuli (Kayser et al., 2005; Auer et al., 2007). It has been suggested that these enhanced cortical responses may be due to elevated cholinergic activity Kuo (2007); Laviolette & van der Kooy (2004); Changeaux (2010) resulting from limbic system and basal forebrain engagement triggered by multisensory stimuli (Weinberger, 1998). The cutaneous surface of the hands or feet are the preferred non-invasive stimulation sites for the vast majority of paired stimulation studies (Kayser et al. 2005; Auer et al. 2007; Schurmann et al. 2004; Gao & Suga, 2000; Levanen, 1998).

Another stimulation site that has been used in vestibular prosthesis studies is the mucosal surface of the tongue (Tyler et al., 2003). The anterio-dorsal surface of the tongue is an optimal site for stimulation for the following reasons: Firstly, the tongue is a mucosal surface, which is beneficial because it does not have an electrically impeding epidermal layer and it is coated with a replenishing electrolyte (saliva) that enhances transcutaneous electrical stimulation. Secondly, the anterio-dorsal surface of the tongue possesses one of the highest somatic nerve densities in the human body and as a result has a disproportionately large representation in the somatosensory homunculus. Finally, the lingual branch of the trigeminal nerve innervates the anterior surface of the tongue. Shore et al. (2006) demonstrated that there are important anatomical and functional links between the trigeminal nerve and central auditory structures, such as the cochlear nuclei. To date there has been no publications covering the effects of electrical stimulation delivered via the tongue. However, a purpose-designed tongue stimulator, the BrainPort (Wicab) have been used to treat vestibular balance disorders (Tyler et al., 2003). This device is connected to a tilt-sensor on the head, and produces error signals to the left or right of a central band if the head position control deteriorates. Significant balance improvements have been reported using this modality (Tyler et al., 2003).

More invasive approaches to paired stimulation have included vagus nerve stimulation (VNS) and deep brain stimulation of the basal forebrain (Engineer, 2011; Kilgard & Merznich, 1998). While these approaches showed promising results, they are unlikely to be clinically adopted given their highly invasive nature.

5.5 Hypothesis

Tinnitus interventions can be broadly categorised into top-down and bottom-up approaches. Top-down approaches seek to reverse cortical-level correlates of tinnitus, such as altered characteristic frequency responses, hyperactivity and synchronicity, in the belief that corticoefferent mechanisms will propogate recovery caudally. Examples of such top-down approaches were discussed Section 5.3, where tones paired with electrical stimulation pulses on the foot were used to alter the characteristic frequencies of cortical and corticofugal neurons (Gao & Suga, 2000; Kilgard & Merznich, 1998; Bao et al., 2001). Other similar approaches utilised paired tone / pulses targeting the Vagus nerve to alter characteristic frequencies of cortical

neurons (Engineer, 2011) and demonstrated promising results in reversing cortical correlates of tinnitus.

Bottom-up approaches seek to address the underlying cause of tinnitus, such as sensory deafferentation or sensori-neural hearing loss, in the belief that afferent mechanisms will propagate recovery dorsally. Examples of such bottom-up approaches were discussed in Section 5.4, where deficits in affected frequency bands were addressed through sound amplification. Studies using sound enrichment to compensate for deficient frequency bands demonstrated promising results in preventing the onset of tinnitus correlates (tonotopic reorganisation, spontaneous firing rates, synchrony) (Norena & Eggermont, 2006) and in reversing them (Stracke et al., 2010; Okamoto et al., 2010).

We postulate that paired tone / pulse approaches, while useful in demonstrating the principle that auditory-somatosensory stimuli can alter characteristic frequencies of cortical neurons, face a number of fundamental challenges:

- Multiplexing – most paired tone / pulse approaches involve permutations of many independent frequency tones with a single tactile stimulation point. Tones must be multiplexed with this single simultaneous point in order to tune the characteristic frequencies of each of the corresponding neurons.
- Channel bandwidth maximisation – tones only partially utilise channel bandwidth in deficient frequency bands, especially if these tones are multiplexed across many bands, as described above.

We propose a novel approach that seeks to address the multiplexing and channel maximisation issues highlighted above. This hypothetical treatment for tinnitus combines band-pass filtered acoustic stimuli, where the filter is characterized by the patient's hearing loss, with simultaneous transcutaneous electrical stimulation of the anterio-dorsal surface of the tongue, where the electrical stimulus is a spatio-temporal encoded pattern that represents the instantaneous frequency-domain coefficients of the auditory stimulus. Such an approach should theoretically reap the benefits of both the top-down and bottom-up approaches described above.

The filtered sound compensates for channel deficiencies and ensures channel bandwidth maximisation, while the simultaneous electrical stimulus is delivered through an array, such that each frequency channel has a dedicated stimulator, thus negating the need for multiplexing.

We propose that this novel multisensory approach should compensate for peripheral hearing loss and thus alleviate central gains, and similarly, elicit enhanced auditory cortical responses and alter characteristic frequencies. In the following chapters, we discuss a prospective pilot study to investigate the effect of this theoretical approach on the objective and subjective measures of permanent intractable tinnitus.

CHAPTER SIX: METHODOLOGY

Chapter Six, provides the general methods of the clinical trial, including recruitment, eligibility criteria, trial procedures, outcome measures, data collection and analysis.

6.1 Study Design

This study was a prospective single arm pilot study. It was conducted with approval from the Research Ethics Committee of NUI Maynooth and The Hermitage Medical Clinic Lucan in collaboration with MuteButton Ltd, Nova UCD.

The study was designed to establish 'Baseline' values in objective (MML, TLM, TM) and subjective (THI) tinnitus measures over the 4-week run-in period and to determine efficacy by comparing measured values with those Baseline values over the 10-week treatment and 2-week follow-up periods. A secondary objective was to assess usage and tolerance of the device over the duration of the trial.

6.2 Study Objective

The objective of the study was to determine the impact of acoustic and tactile multi-modal stimulation on symptoms of permanent intractable tinnitus as measures by objective and subjective measures including Minimum Masking Level (MML), Tinnitus Loudness Masking (Tinnitus Loudness Masking), Tinnitus Handicap Inventory (THI) and Visual Analogue Scale (VAS).

6.3 Study Duration

This study was conducted over a 16-week period with 54 patients (34 male, 20 female with a mean age of 47 years), suffering from permanent intractable tinnitus (>6 months) and with an accompanying high-frequency hearing-loss. Patients were screened for 4 weeks, they receive treatment for 10 weeks and they were followed up 2 weeks post treatment. For the duration of the study they were assessed every 2 weeks in the clinical environment.

6.4 Study Supervision

The study was conducted by a Clinical Audiologist who is registered with the Irish Society of Hearing Aid Audiologists (ISHAA) and the Irish Academy of Audiology (IAA), under the clinical supervision of a Senior Consultant Otolaryngologist Head & Neck Surgeon who is a member of the Association for Research in Otolaryngology, European Academy of Otology and Neuro-otology, Royal Society of Medicine: Otology, Laryngology & Rhinology, Prosper Meniere Society, Irish Otolaryngology Society and the American Auditory Society.

6.5 Identification of Patients

Tinnitus patients were referred by ENT Consultants and Audiologist from 4 hospitals in the Dublin area; Hermitage Medical Clinic, St James's Hospital, Tallaght Hospital and Beaumont Hospital. A considerable cohort of tinnitus patients were recruited and screened for participation in the research study through the Hermitage Medical Clinic.

6.6 Recruitment and Randomisation and Selection

Patient recruitment was limited to the greater Dublin. Patients were allocated to the study on random basis of attendance at the clinic. Patients were informed that participation in this research study was entirely voluntary, and they were free to withdraw from the study at any time without having to give a reason. Their GP was also informed by letter if they were eligible to participate in the study (Appendix 1).

6.6.1 Eligibility

Patient data were deemed eligible if they complied with the following;

- minimum total use of the device should be 30 minutes per day, i.e. 3.5 hours per week
- the level of stimulus should be greater than zero
- acceptable timing for visit dates
- Baseline interview to be conducted within 4 weeks from the start of the new treatment

6.6.2 Non eligible and withdrawals

Participants deemed not eligible to take part in this particular study were referred back to their GP and advised of further therapies available that may be beneficial. They also received a letter of refusal (Appendix 2).

Any participant who dropped out of this study was analysed according to the intention to-treat (ITT) method, i.e. all eligible patients who conducted any part of the study and provided follow-up data for at least one time-point.

6.7 Patient Selection Criteria

The eligibility of study participants was determined by inclusion and exclusion criteria, as listed below.

6.7.1 Inclusion criteria:

- Aged <65 years
- Suffering from subjective intractable tinnitus
- Tinnitus > 6 months
- Tinnitus associated with an age or noise related sensory-neural hearing loss
- Have sound English reading, comprehension and written skills
- Able and willing to participate in the study for the 16 weeks duration
- Informed consent

6.7.2 Exclusion criteria:

- Ulceration of oral cavity or tongue, oral mucosa or significant intra oral disease - to mitigate risk of further aggravation these symptoms
- Meniere's Disease - due to the fluctuating hearing loss
- Hyperacusis - to avoid further aggravation of sensitivity of sound
- Current medical legal cases regarding tinnitus or hearing - in order to avoid any conflict of interest

- Undergoing any treatment for tinnitus - in order to accurately measure the independent effect of the intervention
- Pacemakers - due to potential magnetic interference

6.8 Minimising Bias

Bias was minimised through anonymised participation and the use of objective and subjective internationally recognised outcome measures.

6.9 Assessment of Outcome Measures and Compliance

Primary outcome measures were assessed across the duration of the study in the clinical environment at review visits. Participant compliance was measured using embedded data logging within the tolerability assessed on completion of the study through a questionnaire.

6.9.1 Subjective Outcome Measures

The Tinnitus Hearing Inventory (THI) was used as the main outcome measure (Appendix 3). The THI is a 25-item self-administered questionnaire for the measurement of tinnitus (Newman 1998). The THI scoring takes 5-10 minutes, with a score of 4 for a 'yes', 2 for 'sometimes' and 0 for 'no'. Accordingly results are categorised into 5 main grades of severity from slight, to catastrophic (McCoombe, 2001). Participants were also asked to rate the intensity level of their tinnitus on a Visual Analogue Scale (VAS) of 10 cm length with 1 being 'barely audible' and 10 being 'intolerable' (Appendix 4). Participants were given clear instructions and asked to complete both the THI and VAS independently every two weeks prior to review visits in the clinic waiting area.

6.9.2 Objective Measures

Participants completed a psychoacoustic assessment, including Tinnitus Matching (TM) which determines the frequency and pitch of their tinnitus, Tinnitus Loudness Matching (TLM) which determines the intensity of their tinnitus and Minimum Masking Levels (MML) which determines the lowest level of noise required to mask the tinnitus. Participants did not have access to the measurements recorded throughout the study.

TM and TLM were determined by establishing the frequency level of the tinnitus and the intensity level of the tinnitus frequency in the contralateral ear or binaurally if there was no difference between both ears. Both measurements were expressed in Hertz (Hz) and Decibels (dB) respectively. The MML and TLM were determined using 1 dB steps (Henry & Meikle, 2000). Participants underwent TM, TLM and MML assessments every two weeks at review visits.

6.10 Treatment

6.10.1 Pre-Treatment Phase

Pre-treatment Phase consisted of a four week run-in period prior to commencement of treatment where baseline measures were obtained and sampled every 2 weeks at Week 0, Week 2 and Week 4.

Potential Participants (PP) who expressed an interest in participating in the study and met the basic selection criteria were identified and contact via mail, email or phone and given a time/date for their first appointment of the pre-treatment phase at the Hermitage Medical Clinic, Dublin (Appendix 5). They were sent a copy of the Patient Information Leaflet to read prior to their visit (Appendix 6). PP met with our Medical Advisor (MA) Mr Brendan Conlon, and Principal Investigator (PI) Ms Caroline Hamilton who discussed the study in detail and obtained written consent (Appendix 7) from participants prior to obtaining baseline measures (screening tests).

Those eligible to participate in the study were subsequently contacted by phone and advised within 1-2 weeks after the first initial screening visit and invited to attend a 2nd screening appointment. Following the run-in period, participants were enrolled on the treatment study.

As part of the enrolment appointment, participants were given clear verbal instructions on how to use the device as well as instructions regarding maintenance of the device. They were advised to thoroughly read the Information for Use (IFU) and sterilisation instructions prior to leaving the clinic. Under the supervision of both the PI and MA, all participants were instructed to use the device for 30 minutes whilst in the clinic.

6.10.2 Treatment Phase

The treatment Phase consisted of a 10 week period were participants were advised to use the device for a recommended minimum of 60 minutes per day in their home. All Participants' usage of the device was logged on an internal SD card.

Objective and subjective tests as described above were carried out at the enrolment visit and every 2 weeks for the duration of the study. Patients were given an information pack which included details of their appointment dates/times for duration of study (Appendix 8), copy of informed consent, copy of information leaflet regarding the study, contact details regarding medical issues or adverse effects relating to the device (Appendix 9) and Information for Use booklet (Appendix 10).

6.11 Risk Analysis

Participants were advised to terminate use and to contact the Hermitage Clinic if they experienced any side-effects or adverse effects. They were also instructed to contact a member of the research team regarding any device malfunction.

6.12 Materials
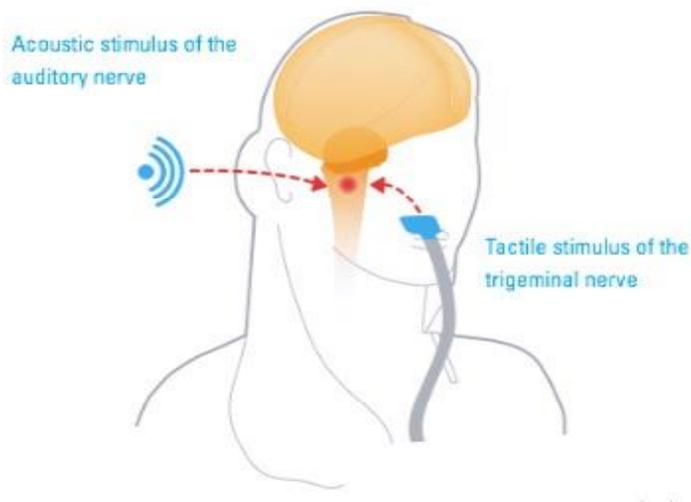
Figure 13 The MuteButton device combining spectrally modified sound with simultaneous transcutaneous stimulation of the anterior dorsal surface of the tongue. Image taken from MuteButton (2013)

6.12.1 MuteButton Multi-Modal Stimulation Device

MuteButton is a non-invasive device which combines two existing tinnitus treatment approaches, sound therapy and transcutaneous electrical nerve stimulation (TENS) into one single treatment, as shown in Fig. 13 above. It simultaneously stimulates the senses of hearing and touch using band-pass filtered 'pink noise' and random transcutaneous electrical stimulation delivered to the tongue. The centre-frequency of the band-pass filter is set to correspond with the frequency of steepest gradient or hearing deficit in the patient's audiogram. The patient wears the device, (which is approximately the size of an iPhone), using a lanyard around their neck and it hangs at the chest area. It consists of two outputs, a set of headphones and an intra-oral device.

6.12.2 Headphones

It involves stimulation in the form 'pink noise' played through a set of hi-fidelity headphones (Sony model "MDR-XD200) which are placed over the ears.

6.12.3 Intra Oral Device

Simultaneous to the audio stimulus, tactile patterns consisting of small electrical pulses are delivered to the tip of the tongue. They receive transcutaneous stimulation on the tongue using a 'lollypop' sensor that sits on the anterior section (tip) of the tongue. The lollypop is approximately 1.5cm^2 in surface area and less than a centimetre in profile depth. It is positioned just behind the front teeth, such that the tongue lies against it when the jaws are in a relaxed state and lips are closed. It has 21 transcutaneous electrodes that electrically stimulate the nerve endings in the tongue. The intra-oral device to be used is non-invasive: a tongue-based carbon electrode array previously used for sensory substitution, with low voltages and waveforms designed to be perceptible but not painful.

6.12.4 Battery

The device is battery operated and comes with an internal rechargeable battery which is a Lithium-Polymer type and a supplied charger (XP Power model VEP08US05) which plugs into the socket to charge the battery.

6.12.5 Micro-SD Card

A micro-SD card is inserted into the slot on the device. It contains information relating to the specific audio and stimulation patterns that is deemed most suitable for particular tinnitus characteristics. The device will not function if this card is removed or if an alternative card is inserted. It records the hours/days used, volume and audio settings over time.

6.13 Data Collection and Analysis

6.13.1 Data Collection

Data was collected during baseline, treatment stage and follow-up stage. All raw data from the THI, VAS and psychoacoustic measures were entered directly into computerised spread sheets. After the calculation of weekly means and variances, data were exported to Statistical Package for Social Sciences (SPSS, version, 13.0 for Windows) for statistical analysis.

The statistical analysis undertaken in this study can be summarised as follows:

- Establishment of baseline scores: The profile of the patients in the study and the severity of their condition.
- Comparison analysis: The effectiveness of treatment as change from baseline, over a period of 16 weeks, in terms of objective and subjective measures
- Usability and Tolerance: The profile of the usage and tolerability of the device, recorded in terms of hours/days used volume and audio settings over time.

6.13.2 Data Analysis

The data were summarised as mean +/- standard deviations (SD). Per protocol analysis was performed for participants who completed the study. Data missed was left blank. In addition, participants who dropped out during study were also recorded, and their primary outcome measure was analysed using the intention-to-treat analysis.

Boxplots and repeated ANOVA for all visits have been carried out for each score. If overall repeated ANOVA shows statistical significance, paired t-test analysis is carried out to compare main effect, i.e. change between Baseline V2 (Week 4/1st week of treatment)and V7 (Week

59

14/10th week of treatment), and interim effect, change between Baseline and V4 (Week 8/4th week of treatment).

The potential placebo/context effect has been analysed in an exploratory manner. The scores have been measured at Screening Visit and at Baseline. This is a 4-week period in which intervention is not administered, but some beneficial effect may be observed due to the subjective nature of the tinnitus condition. Paired t-tests comparing Screening visit and Baseline are run to test for evidence of potential placebo/context effect.

When the probability value was less than 0.05, the difference was considered to be statistically significant.

CHAPTER SEVEN: RESULTS AND ANALYSIS

Chapter Seven reports on the impact of acoustic and tactile multi-modal stimulation treatment for tinnitus and verifies the clinical benefit and user tolerability of the treatment.

7.1 Results and Analysis

7.1.1 Analysis Population and Compliance

The statistical analysis was based on all subjects including the intent-to-treat subjects.

Participant data was deemed eligible if participants met the following compliance and minimum appliance requirements.

- Minimum total use; 30 minutes per day or 3.5 hours per week.
- Minimum level of stimulus; greater than zero
- Review visits within one week of scheduled dates

7.1.2 Demographics and Baseline Characteristics

Baseline measures and basic demographic data (age/gender) were obtained during pre-treatment phase. Summary tables and figures are presented below for each characteristic:

Age

Table 1 **Age - Summary Statistics**

	Total number	Mean (years)	Std. Dev (years)	Min age (years)	Max age (years)
Age	54	47	11	21	64

Age Category (years)	Frequency	Percentage (%)	Cum. Percentage (%)
<30	4	7.41	7.41
30-39	11	20.37	27.78
40-49	16	29.63	57.41
50-59	15	27.78	85.19
60-69	8	14.91	100%
Total	54	100%	

Table 2 **Age – Distribution**

Average age of the group was 47. The youngest patient was 21 and the eldest is 64. Over half of the patients (57%) were under the age of 50.

Gender

Thirty four (63%) patients were male and 20 (37%) patients were female.

7.1.3 Hearing Loss Profile

Hearing loss profile was measured for left and right ears individually using GN Otometrics Madsen Astera Clinical Audiometer, calibrated in accordance with BS EN 60645-1 (IEC 60645-1) and the relevant BS EN ISO 389 (ISO 389) series standards. Hearing loss was classified according to severity; Normal, Mild, Mild to Moderate, Moderate, Moderate to Severe, Severe. The distribution of severity is summarised in Table 3 and 4 below.

Table 3 **Hearing Loss Profile at Screening – Left Ear**

Grade	Frequency	Percentage (%)	Cum. Percentage (%)
Normal	4	7.41	7.41
Mild	19	35.19	42.59
Mild to Moderate	25	46.30	88.89
Moderate	4	7.41	96.30
Moderate to Severe	1	1.85	98.15
Severe	1	1.85	100.00
Total	54	100.00	

Table 4 **Hearing Loss Profile at Screening – Right Ear**

Grade	Frequency	Percentage (%)	Cum. Percentage (%)
Normal	2	3.77	3.77
Mild	20	37.74	41.51
Mild to Moderate	27	50.94	92.45
Moderate	4	7.75	100.00
Moderate to Severe	0	0.00	
Severe	0	0.00	
Total	53	100.00	

In the majority of cases the severity of hearing loss at screening ranges between mild and moderate. Very few cases are diagnosed as severe.

7.1.4 Tinnitus Profile

Tinnitus profiles of patients were measured at screening using the following scores: THI, MML, TLM and TM. Summary statistics are shown in Table5 below.

Table 5 **Tinnitus Scores at Screening - Summary Statistics**

Score	N	Mean	Std. dev.	Min	Max
THI	54	41.1	22.4	6	94
MML	54	50.8	17.1	15	85
TLM	54	42.9	19.7	10	85
TM	54	6518	3387	250	12500

7.1.5 Analysis

Scores were obtained at screening V0 and Baseline V2 and every 2 weeks for duration of study. Comparisons were made between Baselines V2 and V7 (Week 4/1st week of treatment) and V7 (Week 14/10th week of treatment) for main effect and between Baseline V2 and V4 (Week 8/4 weeks of treatment) for interim effect. A placebo/context effect was explored as a comparison between screening visit V0 and baseline V2, where participants have not yet received treatment.

Short term effects of treatment were measured as a comparison between the last week of treatment V7 (Week 14) and V8 (Week 16/2nd week post treatment).

Boxplots and repeated ANOVA were carried out for all sampled measures to determine statistical significance. Paired t-tests were carried out to compare the main effect (change between Baseline V2 and V7 (Week 14/10th week of treatment) and interim effect (change between baseline V2 and V4 (Week 8/4th week of treatment).

The potential placebo/context effect was analysed in an exploratory manner comparing measures at V0 and Baseline V2. This was a 4 week run-in period in which intervention is not administered, but some beneficial effect may have been observed due to the subjective nature of tinnitus. Paired t-tests compared Screening visit V0 and Baseline V2 to test for evidence of a potential placebo/context effect.

7.1.6 Tinnitus Handicap Inventory (THI)

Change in THI score over time is shown in Figure 13 below. Overall repeated ANOVA was statistically significant (p-value <0.001). Paired t-test comparison between Baseline V2 and V7 (Week 14/10th week of treatment) was also determined to be significant (p-value <0.001). THI score decreased from an average value of 34.3 (95% CI: 27.3 – 41.2, N=46) at Baseline V2 to 24.9 (95% CI: 19.8 – 30.7, N=46) at V7 (Week 14/10th week of treatment). Interim effect (average change in THI from baseline V2 to V4 (Week 8/4th week of treatment), was also significant (p-value = 0.0052), decreased from 34.42 (95% CI: 27.5-41.3, N = 50) at Baseline V2 to 31.12 (95% CI: 24.2 – 38.1, N= 50) at V4 (Week 8/4th week of treatment).
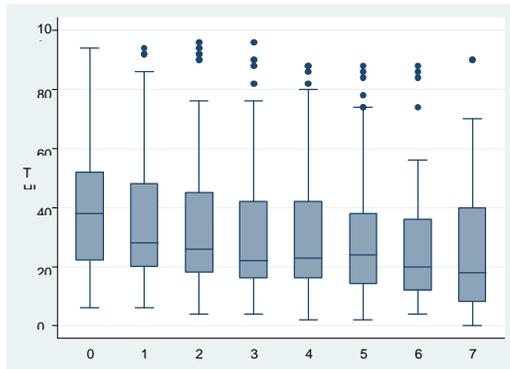
Significant placebo/context effect was determined for THI score. Average THI score dropped from 41.1 (SD 3.04) to 34.4 (SD 3.2) (N = 54) from V0 screening visit to V2 Baseline visit and the change was statistically significant (p-value <0.001).

7.1.7 Minimum Masking Level (MML)

Change in MML score over time was shown in Figure 14 below. Overall repeated ANOVA was statistically significant (p-value <0.001). Paired t-test comparison between Baseline V0 and V7 (Week 14) was also significant (p-value <0.001). MML score decreased from an average value of 47.4 (SD=2.54, 95% CI: 42.3 – 52.6, N=39) at Baseline V2 to 38.8 (SD = 2.7, 95% CI: 33.4 – 43.34, N=39) at V7 (Week 14/10th week of treatment). Interim effect, (average change in MML from Baseline V2 to V4 (Week 8), was also significant (p-value = 0.0088), it decreased from 48.15 (SD= 2.69, 95% CI: 42.66 – 53.64, N = 33) at Baseline V0 to 43.79 (SD = 3.13, 95% CI: 37.4 – 50.16, N= 33) at V4 (Week 8).
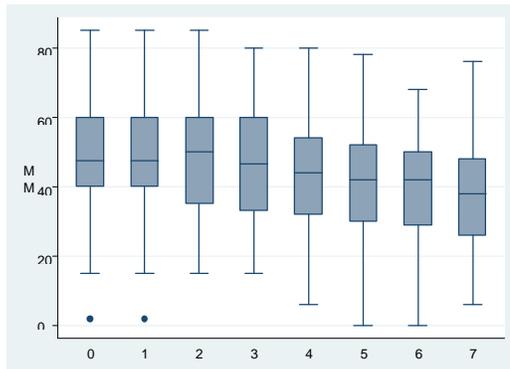
There was evidence of a placebo/context effect for the MML score, which was significant (p-value = 0.01). Between screening visit V0 and Baseline V2 the average MML score changed from 50.8 (SD 2.3) V0 to 46.7 (SD 2.2) (N = 54) V2.

7.1.8 Tinnitus Loudness Matching (TLM)

The change of TML score over time is shown in Figure 15 below. The overall repeated ANOVA is statistically significant (p-value <0.001). The paired t-test comparison between V2 Baseline and V7 (Week 14/10th week of treatment) was also significant (p-value = 0.001). The TLM score decreased from an average value of 45.3 (SD=2.5, 95% CI: 40.2 – 50.4, N=39) at Baseline (V2) to 38.1 (SD = 2.75, 95% CI: 32.5 – 43.6, N=33) at V7 (Week 14/10th week of treatment). The interim effect, (average change in TLM from Baseline V2 to V4 (Week 8/4th week of treatment), was also significant (p-value = 0.045), it decreased from 44.63 (SD= 2.61, 95% CI: 39.31 – 50, N = 33) at Baseline V2 to 40.18 (SD = 3.28, 95% CI: 33.5 – 46.85, N= 33) V4 (Week 8/4th week of treatment).

There was no evidence of a placebo/context effect for TLM score. Average change between screening visit V0 and Baseline V2 was less than 1 point, changing from 42.9 (SD 2.68) to 43.4 (SD 2.1), and was not significant.

7.1.9 Tinnitus Matching

Change of TM score over time is shown in Figure 16 below. Overall repeated ANOVA showed some trend of decreasing values, but was not significant. Summary values for each visit are presented in Table 6 below.

Table 6 TM Scores – Summary Statistics

Visit	N	Mean	Std. Dev.	Min	Max
0	40	7265	3472.5	250	12500
1	40	7265	3472.5	250	12500
2	52	6043	3253.5	250	12500
3	40	6344	3380.1	250	12500
4	33	5454	3326.9	1000	10000
5	35	5493	3143.9	250	10000
6	40	5756	3105.8	250	10000
7	35	6000	2897.8	1000	10000

7.2 Clinical Efficacy

The patient group demonstrated a statistically significant mean improvement in objective measures, exhibiting a reduction of 8.6dB in MML and 7.2dB in TLM after 10 weeks of 1-hour daily treatments between Baseline Visit (V2/4th week of treatment) and End of Treatment Visit (V7/14th week of treatment).

Similarly, the patient group demonstrated a statistically significant mean improvement in the THI self-reduction from 41.1pts to 24.9pts (-16.2pts). This reduction included a statistically significant placebo/context effect that constituted 6.9pts of the overall improvement.

The device also demonstrated significant user tolerability in marketing questionnaires, with 34 (77.3%) (N=44) respondents saying they 'would recommend to a friend with tinnitus' and 38 respondents (86.3%) (N=44) rating the treatment as either 'effective' or 'highly effective'.

These results provide further positive evidence and tangible efficacy for the multisensory approach to the treatment of tinnitus. The MuteButton device previously demonstrated efficacy in studies using subjective measures with similar patients (O'Grady et al., 2012). In 2011, 20 patients were recruited to a 4 week study. The primary objective of this study was to assess the effect of transcutaneous electrical stimulation of the tongue on the symptoms of tinnitus, assessed by mean Tinnitus Handicap Inventory (THI) and Tinnitus Reaction Questionnaire (TRQ). Patient

68

compliance was measured by logging when the computer programme was activated; this was not adequate as the patient could have run the programme without engaging with the device. Although objective measures were not administered during this study, the subjective results reported further verify the clinical benefit and user tolerability of the MuteButton treatment.

CHAPTER EIGHT: DISCUSSION, CONCLUSION AND FUTURE WORK

Chapter Eight, the final chapter, highlights and examines the main findings of this research, discusses them in the broader clinical context and finally, processes recommendations for further investigations.

8.1 Discussion

As a Tinnitus Specialist, my career to date has been rewarding but also very challenging. I spend a great deal of my clinical time providing information about tinnitus recommendations for rehabilitation and persuading patients about the possible benefits. Although sound therapy and counselling have been well defined and used routinely for the treatment of tinnitus, for the majority this have only given temporary relief. To date, no therapy has been found to be uniformly effective in the long term treatment of tinnitus. This motivated me to investigate how the current standard of care could be improved and help me to deliver better outcomes for my patients.

The literature review in Chapter Four identifies two main strategies for treating tinnitus, both of which have achieved moderate levels of success. Auditory and electrical stimulation for tinnitus treatment are reported as being most effective. There is also evidence to suggest that psychological factors play an important part in the treatment of tinnitus and Cognitive Behavioural Therapy (CBT) is considered an effective strategy for tinnitus management.

Currently, there is no commercially available electrical stimulation treatment for tinnitus. However, Transcutaneous Nerve Stimulation (TENS) in general has demonstrated some good results. Auditory stimulation in the form of maskers and hearing aids is currently the conventional treatment for tinnitus. It has been proposed that sound enrichment or sound therapy including Tinnitus Retraining Therapy (TRT), hearing aids or maskers prevent or even reverse the neuropathologies that give rise to tinnitus. There is mixed evidence as to whether or not hearing aids provide relief from tinnitus, in some instances it has been found that hearing aids provide

only transient rather than enduring relief. However, for many patients, they do not tend to acknowledge their hearing loss until after the onset of these neuropathologies and the symptoms of tinnitus; unfortunately at this stage it may be too late to lastingly treat tinnitus simply through sound enrichment.

TRT which uses counselling and sound enrichment to help people habituate to their tinnitus has been successful, however its main problem is motivating people to persist, as it can take up to 1-2 years to observe stable effects (Dobie, 1999). There is also a need for better experimental designs in the studies of TRT efficacy (Wilson et al., 1998; Kroner-Hewitt et al., 2000; Henry et al, 2005). The Neuromonics Treatment System is a treatment that combines regular use of a noise-masker device with structured psychological counselling. The Minimum Masking levels (MML) obtained in our study compare favourably to studies of the Neuromonics Treatment System, and although Goddard et al. (2009) confirmed that Neuromonics appears to reduce the effects of tinnitus on an individual's daily life, future studies are needed to look at larger groups of subjects and longer follow-up regarding the efficacy of this device. ANM's T30 Coordinated Reset device is a sound therapy aimed exclusively at treating 'tonal' tinnitus. The subjective results obtained in our study compare favourably with studies using ANM device (Tass et al., (2012); Adamchic et al., 2012). Electroencephalograph testing (EEG) was used as their objective measure, however there is little evidence to support its efficacy and in my opinion additional evidence is needed to evaluate the value of including quantitative EEG testing for tinnitus.

Studies have also demonstrated that CBT has helped patients reduce tinnitus related distress (Zachriat & Kroner-Hewitt, 2004) and a Cochrane review demonstrated that CBT can have an overall effect on the qualitative aspects of tinnitus and also improve how the patients manage the condition (Martinez-Devesa et al., 2007). While we believe that psychological counselling could provide additional benefit, we did not include counselling in this study of our treatment. However we did measure subjective benefit under the philosophy that verifiable objective improvement without tangible subjective relief to the patient is of little treatment value.

The aim of the study described in this thesis was to evaluate the impact of acoustic and tactile multi-modal neuromodulation on objective and subjective measures of permanent intractable

tinnitus. The results of the study demonstrated positive evidence and tangible efficacy for the multisensory approach in the treatment of tinnitus following 10 weeks of 60 minute daily treatments. Bias was minimised through anonymised participation and use of objective and subjective internationally recognised outcome measures.

Table 7 Comparative treatments and results

MEASURES	MUTEBUTTON	NEUROMONICS	ANM T30
Objective Measures			
MML (dB)	-8.6 dB @ 10 weeks	-12dB @ 52 weeks	-
TML (dB)	-7.2 dB @ 10 weeks	-	-
TM (Hz)	Decreasing trend (not significant)	-	-
Subjective Measures	-	-	-
THI (Pts)	-16.2 pts @ 10 weeks	-	-
TRQ (Pts)	-	-39 pts @ 52 weeks	-12 pts @16 weeks

Despite the positive results we acknowledge there are several limitations in this study that need to be addressed. The most important of these include blinding and post-treatment results. Successful blinding is a challenge in multi-modal stimulation as the patient needs to hear and feel both the acoustic and tactile stimuli respectively, in other words turning the stimuli down or off would not be an appropriate option for such studies. The participant and Principal Investigator (PI) in this study were unable to be blinded as the PI was involved in prescribing and clinically supervising the participants whilst using the device in the clinic prior to taking it home.

To ensure credibility of the novel multisensory treatment, a placebo/context effect was applied. This is a 4-week period in which intervention is not administered, but some beneficial effect may be observed due to the subjective nature of the tinnitus condition. However many authors still highlight the need for placebo controlled studies, to assess the actual "placebo effect" in tinnitus

treatments as expectation alone can stimulate a placebo response (Benedetti et al., 2011; Mielczarek et al., 2013). This is difficult to evaluate in electrical stimulation because the patient can feel the electrical current and it is difficult to give non-treatment as a placebo (Kuk et al., 1989).

A better controlled study would be to carry out the acoustic-tactile training with a sham tactile stimulus or to present the acoustic and tactile stimuli separately for 15 minutes each and compare either of these conditions to the 30 minute multi-modal stimulation.

It is widely acknowledged that there is a lack of objective tools to measures and quantify tinnitus. The assessment of tinnitus severity and its impact depends on a number of valid and reliable self-report instruments which are increasingly used in tinnitus research and management of tinnitus patients. The use of robust outcome measures is of great importance (Andersson et al., 2007: 92). As discussed in Chapter Two, the Tinnitus Hearing Inventory (THI) although verified to be useful in measuring tinnitus in a number of studies, does have many areas of weakness. Kamalski et al. (2010) report the THI to be valuable in assessing tinnitus severity; however it is limited in that it is not designed or validated to measure effectiveness of tinnitus interventions. Furthermore, it consists of a range of questions which may not be relevant to a patient's particular experience and may result in an outcome that does not reflect the patient's distress. It is possible that the use of open-ended questionnaires (Henry et al., 2005) or alternatively the Tinnitus Functional Index (TFI) could assist in improving these issues particularly for research purposes (Miekle, 2012).

8.2 Conclusion

One of the greatest difficulties a clinician faces is an understanding of the neurological component associated with tinnitus. However, I am fortunate that my literature and clinical research has enabled me to gain a greater understanding of the condition from a neurological perspective.

It is believed that brainstem structures, such as cochlear nuclei, play a major role in tinnitus generation and that perception occurs at cortical level. Studies suggest hearing-loss causes a

cascade of neuropathic effects in the central hearing system that is driven by maladaptive neuroplasticity. Shore et al. (2005); Herraiz et al. (2007) demonstrated a functional interaction between auditory brainstem structures and input from the branches of the trigeminal nerve and that stimulation of these nerves can influence tinnitus perception.

There is long-established evidence of auditory-somatosensory integration. This thesis focused on the involvement of the subcortical auditory structure with possibly the greatest level of somatosensory integration, the dorsal cochlear nucleus (DCN), which has been implicated in the generation of the illusory sounds of tinnitus (Kaltenbach et al., 2005; Sachaete & Kempter 2008). It is believed that this is a neural correlate of the 'central gains' phenomenon as discussed in Chapter Four and Chapter Five.

There is also evidence of cortical-level auditory-somatosensory integration in the medial 1division of the medial geniculate body (MGB) and intralaminar nucleus and that the associated signal is sent to the basal forebrain via the amygdala. This relationship between tinnitus, the prefrontal cortex and the limbic system has been emphasised. As previously discussed, the limbic system mediates the emotional and sympathetic nervous system activity which drives maladaptive neuroplasticity which maybe also be a contributing factor to tinnitus (Saunders, 2007; Kaltenbach et al., 2005).

Many areas still need to be addressed in relation to tinnitus, particularly in developing an appropriate and specific training for clinical professional, establishing good methodology for carrying out assessments, clinical studies and ongoing research and also in developing patient education (Vanneste & De Ridder, 2012).

In terms of developing a suitable and effective treatment, tinnitus interventions can be categorised as top-down and bottom-up approaches, with top-down seeking to reverse cortical-level correlates of tinnitus and bottom-up approaches addresses the underlying cause of tinnitus, such as sensory deafferentation or sensori-neural hearing loss using sound amplification. As previously mentioned in Chapter 5, hearing aids are the conventional treatment for tinnitus and are generally well-tolerated bottom-up approaches. However lack of dynamic range compression

can be a major problem for some patients who eventually end up rejecting their hearing aids completely. As discussed, the efficacy of tinnitus masking is difficult to assess from current literature. A systematic review of the evidence of tinnitus treatment reported that hearing aids and tinnitus masking are of "unknown effectiveness" (Savage et al., 2011). However, Hobson et al (2010) stated that this should not be interpreted as evidence of lack of effectiveness, but that these results demonstrate lack of good quality research as well as a lack of tinnitus management approaches.

Even with recent medical advances, no therapy has been found to be uniformly effective in the treatment of tinnitus. It may be considered that no single theory, model or hypothesis will ever explain the presence of tinnitus in all those affected. The most probable future scenario is that there will be different treatment approaches for different forms of tinnitus Eggermont (2006). However, MuteButton seems to offer the potential for additional assistance to tinnitus patients, and could easily be incorporated in a multidisciplinary tinnitus management programme. MuteButton's multi-modal approach should theoretically reap the benefits of the both the top-down and bottom-up approaches described above.

The findings, that audiotactile stimulation can modulate the frequency and loudness of auditory perception constitutes a compelling and growing case for multisensory approach to treating tinnitus. From a clinical perspective, this non-invasive multi-modal stimulation treatment carries very few risks and is very easy to apply. The technology is compact, portable and easy to operate, and should be considered as a treatment tool in clinical practice in conjunction with hearing aids.

As mentioned in Chapter Two, the initial onset of tinnitus is quite often associated with stress, leading to negative emotions particularly if the tinnitus persists. It can lead to a repeating cycle of annoyance, mood changes, fear and anxiety, all of which are associated with tinnitus severity (Henry et al. 2005). Although CBT by itself does not influence the subjective loudness of tinnitus or improve the associated depression, it may effectively increase an individual's quality of life by increasing their ability to deal with their tinnitus (Martinez-Devesa et al., 2010).

8.3 Future Work

Due to the subjective nature of this disorder and general lack of understanding of the underlying pathophysiology, treatment of tinnitus has been limited, controversial and quite often unsuccessful. There are currently no pharmacological agents specifically recommended for the purpose of treating tinnitus (Dobie, 1999). Non-pharmacological and surgical approaches have been used in certain cases with limited therapeutic effects.

Although neuromodulation has been reported as a promising treatment for tinnitus, much more research is required to analyse and determine its potential, determine exactly the method by which it works as well as the brains response to such treatment. More research on neruomodulation in tinnitus is focusing on TMs, in particular repetitive transcranial magnetic stimulation (rTMs) which has recently been reported to improve tinnitus related distress (Kleinjung et al., 2005; Vanneste & De Ridder, 2012). TMs delivers short but high-intensity current pulse through a coil which penetrates the scalp and brain with little attenuation. A number of studies have been carried out and results have been promising, however there is still some controversy over the duration of treatment and its efficacy and also on the sub-groups of patients who may benefit most. In some studies effects outlasted the stimulation period up to a year (Kleinjung et al., 2005; Khedr e al., 2008), whilst others could not demonstrate any after-effects (Moller et al., 2010: 702-707). However TMs is more expensive and more difficult to apply in comparison to transcutaneous electrical nerve stimulation (TENs) and transcranial direct current stimulation (tDCS). tDCS is a non-invasive cortical stimulation technique which can modulate cortical activity and has been reported in several studies to influence working memory, decision making and emotional responsiveness. Its effect in treating tinnitus depends on the stimulation site and intensity, and duration of treatment. Pilot studies have demonstrated that tDCS applied to the temporal lobe and the dorsal lateral prefrontal cortex can supress tinnitus (Vanneste & DeRidder 2012). Although different techniques introduced show promising results, other neuromodulation techniques such as transcranial alternative current stimulation (tACS) and vagus nerve stimulation (Schnupp, 2011; Engineer et al., 2011; Vanneste & De Ridder 2012) might also show benefits in the future.

The majority of these studies rely on patient's self-evaluation of their tinnitus. Auer et al (2007) describe brain-imaging studies which show enhanced cortical responses to somatosensory stimuli in hearing impaired humans. Such functional and structural MRI analysis may be provide promising objective diagnostic tools for future research, particularly when distinguishing between normals and tinnitus suffers, and could be utilised as objective clinical measurements before and after treatment.

A logical continuation of this study is to have a double-blind randomised control trial (RCT) examining the benefits of using multisensory stimulation or a comparative study with hearing aids comparing the efficacy of both treatments for tinnitus. To ensure successful blinding, an assessor would be allocated to collect and summarise the data and be blinded to the treatment allocation which would be consistent with current quality assessment of Randomised Control Trial (RCT) recommendations (Jadad et al., 1996).

Given the positive results of this study, we intend to follow up with further studies to determine the benefits of longer treatment periods in addition to measuring retention at three and six-month intervals post-treatment and also include a larger tinnitus population with different hearing statuses, including normal, mild, moderate and severe hearing loss.

REFERENCES

Adamchic, I., Langguth, B., Hauptmann, C. & Tass, P.A, (2012), "Psychometric Evaluation of Visual Analogue Scale for the Assessment of Chronic Tinnitus", American Journal of Audiology, **21**, 215-225.

Agency for Health and Research Quality (AHQR), (2013), "Evaluation and Treatment of Tinnitus: Comparative Effectiveness" http://effective_healthcare.ahrq.gov/search-for-guides-reviews-and-?reports/ (accessed 22/08/13).

Aigner, M., Lukas, J. R., Denk, M., & Mayr, R., (1997) "Sensory innervation of the guinea pig extraocular muscles: A 1, 1′-dioctadecyl-3, 3, 3′ 3′-tetramethylindocarbocyanine perchlorate tracing and calcitonin gene-related peptide immunohistochemical study", Journal of Comparative Neurology, **380**(1), 16-22.

Aitkin, L. M., Dickhaus, H., Schult, W., & Zimmermann, M., (1978), "External nucleus of inferior colliculus: auditory and spinal somatosensory afferents and their interactions", Journal of Neurophysiology, **41**(4), 837-847.

Aldhafeeri, F. (2012), "An investigation into the neural substrates of tinnitus", Doctoral dissertation, University of Liverpool.

Andersson, G., Vretblad, P. Larsen, H.C. & Lyttkens, L. (2001), "Longitudinal Follow Up of Tinnitus Complaints", Archives of Otolaryngology – Head and Neck Surgery, **127**, 175-179.

Andersson, G., Baguley, D.D., McKenna, L. & McFerran D, (2005), "A cognitive Behavioural Treatment Programme", Tinnitus: A Multidisciplinary Approach, London: Whurr Publishers, pp. 145-158, (3rd Ed).

American Tinnitus Association (ATA), (2004), http//www.ata.org (accessed 23/04/13).

American Tinnitus Association (ATA), (2013), http//www.ata.org (accessed 22/03/13).

Auer Jr, E. T., & Bernstein, L. E., (2007), "Enhanced visual speech perception in individuals with early-onset hearing impairment", Journal of Speech, Language and Hearing Research, **50**(5), 1157.

Axelsson, A., & Ringdahl, A. (1989), "Tinnitus: A study of its Prevalence and Characteristics", British Journal of Audiology, **23**, 53-51.

Axelsson, A., & Prasher, D. (2000), "Tinnitus induced by occupational and leisure noise", Noise and Health, **2**(8), 47.

Axelsson, A., Coles, R., Erlandsson, S., Meikle, M. & Vernon, A. (1993), "Evaluation of Tinnitus Treatments: Methodological Aspects", Journal of Audiological Medicine, **2**, 141-150.

Baguley, D.M, (2002), "Mechanisms of Tinnitus", British Medical Bulletin, **63**, 195212.

Baguley, D.M., Stottart, R.L. & Hodgson, C.A., (2000), "Convergence validity of the Tinnitus Handicap Inventory and the Tinnitus Questionnaire", Journal of Laryngology and Otology, **114**, 840-843.

Baguley, D. M., McKenna, L., & McFerran, D., (2005), Tinnitus: a multidisciplinary approach, London: Whurr Publishers, (3rd Ed).
Ballanytne, J., Martin, M.C., Martin, (1993), Deafness, Whurr Publishers Ltd, London, (5th Ed).

Bao, S., Chan, V. T., & Merzenich, M. M., (2001), "Cortical remodelling induced by activity of ventral tegmental dopamine neurons", Nature, **412**(6842), 79-83.

Baracca, G. N., Forti, S., Crocetti, A., Fagnani, E., Scotti, A., Del Bo, L., & Ambrosetti, U. (2007), "Results of TRT after eighteen months: our experience", International Journal of Audiology, **46**(5), 217-222.

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

Barnes, A. P., Lilley, B. N., Pan, Y. A., Plummer, L. J., Powell, A. W., Raines, A. N. & Polleux, F. (2007), "LKB1 and SAD kinases define a pathway required for the polarization of cortical neurons", Cell, **129**(3), 549-563.

Benedetti, Fabrizio, and Martina Amanzio (2011), "The placebo response: How words and rituals change the patient's brain", Patient education and counselling, **84**(3), 413-419.

Berliner, K.I., Cunningham, J.K., House, W.F., & House, J.W., (1987), "Effect of the Cochlear Implant on Tinnitus in Profoundly Deaf Patients", in Feldman, H. (eds), Proceedings of the Third International Tinnitus Seminar 1987, Munster, Germany (pp. 451-453). Karlsruhe, Germany: Harsch Verlag.

Biesinger E, Del Bo L, De Ridder D, Goodey R, Herraiz C, Kleinjung T, Lainez JM, Landgrebe M, Langguth B, Londero A, Paolino M, Questier B, Sanchez T, Searchfield G., (2010), "Algorithm for the diagnostic and therapeutic management of tinnitus", Tinnitus Clinic Network, Tinnitus Research Initiative. Available: www. tinnitus research. Org/en/documents/downloads/TRI _Tinnitus _Flowchart. pdf (accessed 09/08/2013).

Brozoski, T. J., & Bauer, C. A. (2005), "The effect of dorsal cochlear nucleus ablation on tinnitus in rats", Hearing Research, **206**(1), 227-236.

Cacace, A. T., (2003), "Expanding the biological basis of tinnitus: crossmodal origins and the role of neuroplasticity", Hearing Research, **175**(1), 112-132.

Caclin, A., Soto-Faraco, S., Kingstone, A., & Spence, C., (2002), "Tactile "capture" of audition", Perception & Psychophysics, **64**(4), 616-630.

Changeux, Jean-Pierre., (2010), "Nicotine addiction and nicotinic receptors: lessons from genetically modified mice." <u>Nature Reviews Neuroscience,</u> **11**(6), 389-401.

Clinical Policy Bulletin (2013), "Tinnitus Treatments" <u>http://www.aetna.com/cpb/medical/data/400_499/0406.html</u> Clinical Policy Bulletin (accessed 11/08/13).

Coles, R.R.A., (2000), "Medicolegal Issues", in Tyler, R.S. (eds), <u>Tinnitus handbook</u>. San Diego, CA: Singular, 399-417.

Crossman, A.R., Neary, D., (2004), <u>Neuroanatomy</u> (4th Ed.), Churchill Livingstone.

Dauman, R., & Tyler, R. S., (1992), "Some considerations on the classification of tinnitus", <u>In Proceedings of the Fourth International Tinnitus Seminar</u>. Amsterdam/New York: Kugler Publications, (225-229).

Dauman, R., (2000), "Electrical Stimulation for Tinnitus Suppression", in Tyler, R. (eds), <u>Tinnitus handbook</u>, San Diego, CA: Singular, 377-398.

Dauman, R., Bouscau-Faure, F. (2005), "Assessment and amelioration of hyperacusis in patients", Acta Oto-Laryngologica, **125**(5), 503-509.

Davis, A.C., (1995), <u>Hearing in Adults</u>, London: Whurr Publishers.

Davis, A. & El Refaie, A. (2000), "Epidemiology of Tinnitus", in Tyler, R.S. (eds), <u>Epidemiology of Tinnitus San Diego</u>, CA: Singular, pp 1-24.

Davis, P.B., Paki, B. & Hanley, P.J., (2007), "Neuromonics Tinnitus Treatment: Third Clinical Trial", <u>Ear Hear,</u> **28**(2), 242-259.

Davis, P.B. Wilde, R.A., Steed, L.G. & Hanley, P.J., (2008), "Treatment of Tinnitus with a Customized Acoustic Neural Stimulus: A Controlled Clinical Study", <u>Ear Nose Throat Journal,</u> **87**(6), 330-339.

Dehmel, S., Cui, Y. L., & Shore, S. E., (2008). Cross-modal interactions of auditory and somatic inputs in the brainstem and midbrain and their imbalance in tinnitus and deafness. , <u>American journal of audiology</u> **17**(2), S193.

Del Bo, L., Forti, S., Ambrosetti, U. (2007), "Hearing Aids for the Treatment of Tinnitus", <u>Progress in Brain Research</u>, **166**, 341-345.

Dobie, R.A., Hoberg, K.E. & Rees, T.S., (1986), "Electrical Tinnitus Suppression A Double-Blind Crossover Study". <u>Otolaryngology – Head and Neck Surgery,</u> **95**, 319323.

Dobie, R.A., (1999), "A Review of Randomized Clinical Trials in Tinnitus", <u>The Laryngoscope</u> **109**(8), 1202-1211.

Dobie, R.A., (2004), "Suffering from Tinnitus", in Snow, J.B. (eds), <u>Tinnitus Theory and Management</u>, Ontario: BC Decker, pp. 1-8.

Dominguez, M., Becker, S., Bruce, I. and Read, H. (2006), "A spiking neuron model of cortical correlates of sensori-neural hearing loss: spontaneous firing, synchrony and tinnitus", <u>Neural Computation</u>, **18**(12), 2942-2958.

Eggermont, J. J., & Komiya, H., (2000), "Moderate noise trauma in juvenile cats results in profound cortical topographic map changes in adulthood", <u>Hearing research</u>, **142**(1), 89-101.

Eggermont, J.J., (2003), "Central tinnitus", <u>Auris Nasus Larynx</u>, **30**, 7-12.

Eggermont, J.J. & Roberts, L.E., (2004), "The Neuroscience of Tinnitus", <u>Trends in Neurosciences,</u> **27**(11), 676-682.

Eggermont, J. J., (2005), "Tinnitus: neurobiological substrates", Drug discovery today, **10**(19), 1283-1290.

Eggermont, J.J., (2006), "Cortical Tonotopic Map Reorganization and its Implications for Treatment of Tinnitus", Acta Oto-Laryngologica, **126**(10): 9-12.

Eliades, S. J., & Wang, X., (2003), "Sensory-motor interaction in the primate auditory cortex during self-initiated vocalizations", Journal of Neurophysiology**, 89**(4), 21942207.

Eliades, S. J., & Wang, X., (2005), "Dynamics of auditory–vocal interaction in monkey auditory", Cerebral Cortex, **15**(10), 1510-1523.

Engelberg, M. & Bauer, W., (1985), "Transcutaneous Electrical Stimulation for Tinnitus", Laryngoscope, **95**, 1167-1173.

Engineer, N. D., Riley, J. R., Seale, J. D., Vrana, W. A., Shetake, J. A., Sudanagunta, S. P. & Kilgard, M. P., (2011), "Reversing pathological neural activity using targeted plasticity", Nature**, 470**(7332), 101-104.

Erlandsson, S. I., Rubinstein, B., & Carlsson, S. G., (1991), "Tinnitus: evaluation of biofeedback and stomatognathic treatment", British Journal of Audiology, **25**(3), 151161.

Erlandsson, S. I., Hallberg, L. R., & Axelsson, A., (1992), "Psychological and audiological correlates of perceived tinnitus severity", International Journal of Audiology, **31**(3), 168-179.

Erlandsson, S., (2000), "Psychological Profiles of Tinnitus Patients", in Tyler, R.S.
(eds), Tinnitus handbook San Diego, CA: Singular, pp. 25-57.

Finlayson, P. G., & Kaltenbach, J. A., (2009), "Alterations in the spontaneous discharge patterns of single units in the dorsal cochlear nucleus following intense sound exposure", Hearing research, **256**(1), 104-117.

Folmer, R. L., & Griest, S. E., (2000), "Tinnitus and insomnia", <u>American Journal of Otolaryngology</u>, **21**(5), 287-293.

Fornaro, M., & Martino, M., (2010), "Tinnitus psychopharmacology: A comprehensive review of its pathomechanisms and management". <u>Neuropsychiatric Disease and Treatment,</u> **6**, 209.

Gao, E. & Suga, N (2000), "Experience-dependent plasticity in the auditory cortex and the inferior colliculus of bats: role of the corticofugal system", <u>Proceedings of the National Academy of Sciences</u>**, 97**(14), 8091-8086

Goddard, J. C., Berliner, K., & Luxford, W. M., (2009), "Recent experience with the neuromonics tinnitus treatment", <u>The International Tinnitus Journal</u>, **15**(2), 168.

Goldstein, B. A., Shulman, A., Lenhardt, M. L., Richards, D. G., Madsen, A. G., & Guinta, R., (2001), "Long-term inhibition of tinnitus by UltraQuiet therapy: Preliminary report". <u>International Tinnitus Journal</u>, **7**(2), 122-127.

Guinan, J. J. Jr., (1996), "Physiology of olivocochlear efferents", in <u>The Cochlea</u>, 435– 502 (Springer).

Gungor, A., Dogru, S. & Cincik, H., (2008), "Effectiveness of Transmeatal Low Power Laser Irradiation for Chronic Tinnitus", <u>Journal of Laryngology and Otology</u>, **122**(5), 447-451.

Hallum, R. S., Jakes, S. C. & Hinchcliffe, R., (1988), "Cognitive Variables in Tinnitus Annoyance", <u>British Journal of Clinical Psychology,</u> **27**, 213-222.

Hanley, Peter J., et al., (2008), "Treatment of tinnitus with a customized, dynamic acoustic neural stimulus: clinical outcomes in general private practice." <u>Annals of</u> <u>Otology, Rhinology & Laryngology,</u> **117**(11), 791.

Hazell, J. W. P., & Wood, S., (1981), "Tinnitus masking-a significant contribution to tinnitus management", British Journal of Audiology, **15**(4), 223-230.

Hazell, J. W., Meerton, L. J., & Conway, M. J., (1989), "Electrical tinnitus suppression (ETS) with a single channel cochlear implant". The Journal of laryngology and otology. Supplement, **18**, 39.

Hazell, J., (1998), "Management of tinnitus", In H. Ludman & T. Wright (Eds.), Diseases of the ear (pp. 202–215). London: Arnold.

Heller AJ., (2003), "Classification and epidemiology of tinnitus". Otolaryngol Clin North America, **36**(2), 239–48.

Henry, J. A., & Meikle, M. B., (2000). Psychoacoustic measures of tinnitus. Journal of the American Academy of Audiology, **11**(3), 138-155.

Henry, J. L. & Wilson, P., (2001), "The Psychological Management of Chronic Tinnitus, A Cognitive-Behavioural Approach", Needham Heights, **36**, 337-348.

Henry, J. L., Dennis, K. & Schechter, M. A., (2005), "General Review of Tinnitus: Prevalence, Mechanisms, Effects and Management", Journal of Speech, Language and Hearing **48,** 1204-1235.

Henry, J. A., Schechter, M. A., Zaugg, T. L., Griest, S., Jastreboff, P. J., Vernon, J. A. & Stewart, B. J., (2006), "Clinical trial to compare tinnitus masking and tinnitus retraining therapy", Acta Oto-Laryngologica**, 126**, 64-69.

Henry, J.A. (2011), "Key Informant Interview" 26th July.

Herraiz, C. et al., (2007), "Trans-Electrical Nerve Stimulation (TENS) for Somatic Tinnitus", Progress in Brain Research, **166**, 389-553.

Hilton, M., & Stuart, E. (2004), "Ginkgo biloba for tinnitus", <u>Cochrane Database Syst Rev</u>**, 2**.

Hinchcliffe, R., (1961), "Prevalence of the Commoner Ear, Nose, Throat Conditions in the Adult Rural Population of Great Britain", <u>British Journal of Preventive and Social Medicine, </u>**15**, 128-140.

Hobson, Jonathan, Edward Chisholm, (2010), and Amr El Refaie."Sound therapy (masking) in the management of tinnitus in adults." <u>Cochrane Database Syst Rev</u> **12**.

Hoffman, H. J. & Reed, G. W., (2004), "Tinnitus: Theory and management", <u>Epidemiology of Tinnitus</u>, 16-41.

House, W. F. (1976), "Cochlear Implants", <u>Annals of Otology Rhinology and Laryngology</u>, **85**(27), 3-91.

House, J. W., & Brackman, D. E., (1981), "Tinnitus: surgical treatment", <u>In Ciba Foundation Symposium</u>, **85**, 204-212.

Ireland, C. E., Wilson P. H., & Tonkin, J. P., (1985), "An Evaluation of Relaxation Training in the Treatment of Tinnitus Management", <u>Behavioural Research and Therapy</u> **23**(4), 423-30.

Jadad, Alejandro R., et al., (1996), "Assessing the quality of reports of randomised clinical trials: is blinding necessary?", Controlled clinical trials, **17**(1), 1-12

Jastreboff, P. J. (1999, September), "The neurophysiological model of tinnitus and hyperacusis". In <u>Proceedings of the sixth international tinnitus seminar</u> (pp. 32-38).

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

Jastreboff, P. J., (2004), "Tinnitus Retaining Therapy: An Implementation of the Neurophysicological Model of Tinnitus", Cambridge University Press.

Jastreboff, P. J. & Hazell, J. W., (2006), "The Neurophysiological Model of Tinnitus and Decreased Sound Tolerance", Tinnitus Treatment: Clinical Protocols, 32-36.

Jousmäki, V., & Hari, R., (1998), "Parchment-skin illusion: sound-biased touch", Current Biology, **8**(6), R190-R191.

Kapkın, O., Satar, B., & Yetiser, S. (2008), "Transcutaneous electrical stimulation of subjective tinnitus", ORL, **70**(3), 156-161.

Kaltenbach, J. A. & Zhang, J., (2005), "Tinnitus as a Plastic Phenomenon and its Possible Neural Underpinnings in the Dorsal Cochlear Nucleus", Hearing Research, **206**, 200-226.

Kamalski, D.M. Hoekstra, C.C. & Van Zanten, B.G., (2010), "Measuring Disease Specific Health-Related Quality of Life to evaluate treatment outcomes in tinnitus patients: A systematic Review Journal of Otolaryngology – Head and Neck Surgery, **143**/2 181-185

Kandel, E.R Schwartz, J.H., Jessel, T.M.l (Eds.), Principles of neural science (4th ed.), McGraw-Hill, New York (2000), pp. 606–610

Kayser C., Petkov CI, Augath M., Logothetis N.K., (2005), "Integration of touch and sound in the auditory cortex", Neuron, **48**,373-384.

Khedr, E.M., Rothwell, J.C., Ahmed, M.A. & El-Atar, A. (2008), "Effect of Daily Repetitive Transcranial Magnetic Stimulation for Treatment of Tinnitus", Journal Neurology Neurosurgery Psychiatry, **79**(2), 212-215.

Kiang, N. Y. S., (1975), "Stimulus Representation in the Discharge Patterns of Auditory Neurons", in The Nervous System: Human Communication and Its Disorders, **(3)**81-96

Kilgard M.P. and Merznich M.M, (1998) "Cortical map reorganization enabled by nucleus basalis activity", <u>Science</u>, **279**(5357), 1714-1718.

Kirsch, C. A., Blanchard, E. B. & Parnes, S. M., (1989), "Psychological Characteristics of Individuals High and Low in Their Ability to Cope with Tinnitus", <u>Psychosomatic Medicine, </u>**51**, 209-217.

Kleinjung, T., Eichhammer, P. & Langguth, B., (2005), "Long-Term Effects of Repetitive Transcranial Magnetic Stimulation (rTMS) in Patients with Chronic Tinnitus", <u>Otolaryngology Head Neck Surgery, </u>**132**(4), 566-569.

Kroener-Herwig, B., Biesinger, E. & Gerhards, F., (2000), "Retraining Therapy for Chronic Tinnitus. A Critical Analysis of its Status", <u>Scand Audiol, </u>**29**(2), 67-78.

Kuk, Francis K., et al, (1989). "Alternating current at the eardrum for tinnitus reduction", <u>Journal of Speech, Language, and Hearing Research</u>, **32**(2), 393-400.

Kuo, M. F., Grosch, J., Fregni, F., Paulus, W., & Nitsche, M. A., (2007), "Focusing effect of acetylcholine on neuroplasticity in the human motor cortex", <u>The Journal of Neuroscience</u>, **27**(52), 14442-14447.

Landgrebe, M, Zeman, F., Koller, M., Eberl, Y., Mohr, M., Reiter, J. & Langguth, B., (2010), "The Tinnitus Research Initiative (TRI) database: a new approach for delineation of tinnitus subtypes and generation of predictors for treatment outcome", <u>BMC medical informatics and decision making</u>, **10**(1), 42.

Langguth, B., Salvi, R., & Elgoyhen, A. B., (2009), "Emerging pharmacotherapy of tinnitus", <u>Expert opinion on emerging drugs</u>, **14**(4), 687-702.

Langguth, B., Landgrebe, M., Kleinjung, T., Sand, G. P., & Hajak, G., (2011), Tinnitus and depression, <u>World Journal of Biological Psychiatry</u>, **12**(7), 489-500.

Langguth, B., Biesinger, E., Del Bo, L., De Ridder, D., Goodey, R., Herraiz, C. & Searchfield, G. D., (2011), "Algorithm for the diagnostic and therapeutic management of tinnitus", In Textbook of tinnitus (pp. 381-385). Springer New York.

Laviolette, S. R., Gallegos, R. A., Henriksen, S. J., & van der Kooy, D., (2004), "Opiate state controls bi-directional reward signaling via GABAA receptors in the ventral tegmental area", Nature neuroscience, **7**(2), 160-169.

Leske, M. C., (1981), "Prevalence Estimates of Communicative Disorders in the US. Language, Hearing and Vestibular Disorders", American Speech and Hearing Association, **23**, 229-37.

Levine, R. A., (1999, September), "Somatic modulation appears to be a fundamental attribute of tinnitus", In Proceedings of the Sixth International Tinnitus Seminar, London: The Tinnitus and Hyperacusis Center, (pp. 193-7).

Lockwood, A.H., Salvi, R.J. & Burkard, R.F., (2002), "Tinnitus", New England Journal of Medicine, **347**, 904-910.

Lockwood, Alan H., et al., (1998), "The functional neuroanatomy of tinnitus Evidence for limbic system links and neural plasticity." Neurology, **50** (1), 114-120.

Martinez Devesa, P., Waddell, A., Perera, R., & Theodoulou, M., (2007), "Cognitive behavioural therapy for tinnitus", Cochrane Database Syst Rev, **1**.

Martinez-Devesa, P., Perera, R. & Theodoulou, M. (2010), "Cognitive Behavioural Therapy for Tinnitus", Cochrane Database System Revision **8**(9).

McCombe, A. Baugley, D. & Coles, R. (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 1999", <u>Clinical Otolaryngology & Allied</u> <u>Science</u> **26**(5), 388-393.

Martinez-Devesa, P., Perera, R. & Theodoulou, M. (2010), "Cognitive Behavioural Therapy for Tinnitus", <u>Cochrane Database System Revision</u> **8**(9),

McKenna, L., Hallam R.S. & Hinchcliffe R., (1991), "The Prevalence of Psychological Disturbance in Neuro-Otology Outpatients", Clinical Otolaryngology, **16,** 452-456.

McKenna, L., Baguley, D., & McFerran, D., (2011), "<u>Living with tinnitus and hyperacusis,</u> Sheldon, London.

Meikle, M. B., Griest, S. E., Stewart, B.J., & Press, L. S. (1995), "Measuring the Negative Impact of Tinnitus: A Brief Severity Index", <u>Midwinter Meeting: Association</u> <u>for Research in</u> <u>Otolaryngology,</u> **167**.

Meikle, M. B., (2003), "A Conceptual Framework to Aid the Diagnosis and Treatment of Severe Tinnitus", <u>The Australian and New Zealand Journal of Audiology,</u> **21**, 59-67.

Meikle, M. B., Stewart, B. J., Griest, S. E., & Henry, J. A. (2008), "Tinnitus Outcomes Assessment", <u>Trends in Amplification,</u> **12**(3), 223-235.

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

Melin, L., Scott, B., Lindberg, P. & Lyttkens, L., (1987), "Hearing Aids and Tinnitus An Experimental Group Study", <u>British Journal of Audiology,</u> **21**, 91-97.

Meng, Z., Liu, S., Zheng, Y., & Phillips, J. S., (2011). Repetitive transcranial magnetic stimulation for tinnitus, Cochrane Database Syst Rev, **10**.

Mielczarek, M., Konopka, W., & Olszewski, J., (2013), "The application of direct current electrical stimulation of the ear and cervical spine kinesitherapy in tinnitus treatment", Auris Nasus Larynx, **40**(1), 61-65.

Moffat, G., et al., "Effects of hearing aid fitting on the perceptual characteristics of tinnitus." Hearing research, **254**.1 (2009): 82-91.

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

Moller, A. R., (2000), "Similarities Between Severe Tinnitus and Chronic Pain", Journal of the American Academy, **11**, 115-124.

Moller, A. R. (2003), "Pathophysiology of Tinnitus", Otolaryngologic Clinics of North America, **36**, 249-266.

Moller, A. R., Rollins, P.R., (2002), "The non-classical auditory pathways are involved in hearing in children but not in adults", Neuroscience Letters, **319**(1), 41-44

Møller, A. R. (2006), "Neural plasticity in tinnitus", Progress in Brain Research, **157**, 365-372.

Møller, A. R., (2007), "Tinnitus and pain", Progress in Brain Research, **166**, 47-53.

Moller, A.R., (2007), "The role of neural plasticity in tinnitus", Progress in Brain Research, **166:** 37-544.

Moller, A.R. & Langguth, B., (2010), Textbook of Tinnitus, London: Springer New York Dordrecht Heidelberg.

Moore, B. C. (2010), "The relationship between tinnitus pitch and the edge frequency of the audiogram in individuals with hearing impairment and tonal tinnitus", *Hearing research*, **261**(1), 51-56.

Morgan, D. H., (1996), "Tinnitus Caused by a Temporomandibular Disorder", Proceedings of the Fifth International Tinnitus Seminar, 653-654.

Morgenstern, C. & Biermann, E., (1997), "Ginkgo- Spezialextrakt Egb 761", Tinnitus aurium Forschr der Medizin **115**, 7-11.

Mulders, W. H. A. M., & Robertson, D., (2009), "Hyperactivity in the auditory midbrain after acoustic trauma: dependence on cochlear activity", Neuroscience, **164**(2), 733-746.

MuteButton: http://www.mutebutton.ie (accessed 12/12/2013).

Nakashima, T., Ueda, H. & Misawa, H., (2002), "Transmeatal Low-Power Laser Irradiation for Tinnitus", Otology & neurology **23**(3), 296-300.

National Institute of Neurological Disorders and Stroke (NINDS), (2013), www.ninds.nih.gov (accessed 30/08/2013).

Naughton, P., (2004), "The quest for quiet: people's experience of tinnitus in Ireland", A Research Study for the Irish Tinnitus Association.

Nelson, J. J., & Chen, K., (2004), The relationship of tinnitus, hyperacusis, and hearing loss", Ear, nose, & throat journal, **83**(7), 472.

Neuromonics: http://www.neuromonics.com (accessed 12/12/2013).

Newman, C. W., Jacobson, G. P., & Spitzer, J. B., (1996), "Development of the tinnitus handicap inventory", <u>Archives of Otolaryngology—Head & Neck Surgery</u>, **122**(2), 143

Newman, C.W., Sandridge S.A. & Jacobson, G., (1998),"Psychometric Adequacy of the Tinnitus Handicap Inventory (THI) for Evaluating Treatment Outcome", <u>Journal of the American Academy of Audiology,</u> **9**, 153-160.

Newman, C. W., & Sandridge, S. A., (2004), "Tinnitus Questionnaires", In J.B Snow (Ed.), <u>Tinnitus theory and management,</u> 237-254.

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

Nicolas-Puel, Cécile, et al. "Characteristics of tinnitus and etiology of associated hearing loss: a study of 123 patients. "<u>The International Tinnitus Journal</u> **8.1** (2002): 37.

National Institute of Neurological Disorders and Stroke, http//www.nip.gov (accessed 09/09/2013).

Noble, W. (2008), "Treatments or Tinnitus", <u>Trends Amplif</u>, **12**(3), 236-41.

Norena, A., Micheyl, C., Chéry-Croze, S., & Collet, L. (2002), "Psychoacoustic characterization of the tinnitus spectrum: implications for the underlying mechanisms of tinnitus", "Audiology and Neurotology", **7**(6), 358-369.

Norena, A. J., & Eggermont, J. J., (2003), "Changes in spontaneous neural activity immediately after an acoustic trauma: implications for neural correlates of tinnitus", <u>Hearing research,</u> **183**(1), 137-153.

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

Noreña, A. J., & Eggermont, J. J., (2006), "Enriched acoustic environment after noise trauma abolishes neural signs of tinnitus", Neuroreport, **17**(6), 559-563.

Okamoto, H., Stracke, H., Stoll, W. & Pantev, C., (2010), "Listening to tailor-made music reverses maladaptive auditory cortex reorganization and alleviates tinnitus", Proc Natl Acad Sci U S A, **107**(3), 1207-1210.

O'Grady, P., O'Neill, R., & Pearlmutter, B.A., (2012), "Method and apparatus for sensory substitution", WIPO Patent No. 2012069429.

O'Neill, R., (2008), "Modality Specific Optimally Encoded Sensory Substitution Techniques: Hardware and Signal Processing Developments", PhD Thesis, Hamilton Institute, NUI Maynooth, Ireland. [bibtex].

Parra, L. and Pearlmutter, B., (2007) "Illusory Percepts from Auditory Adaptation", Journal of Acoustic Society of America, **121**, 1632

Patterson, M. B., & Balough, B. J., (2006), "Review of Pharmacological Therapy for Tinnitus", The International Tinnitus Journal, **12**, 149-160.

Park, J., White, A. R., & Ernst, E., (2000), "Efficacy of acupuncture as a treatment for tinnitus: a systematic review", Archives of Otolaryngology—Head & Neck Surgery, **126**(4), 489.

Pandey, S., (2011), "Bhramari Pranayama and Alternative Treatments of Tinnitus: In Pursuit of the Cure", UP TO DATE ON TINNITUS, **153**.

Perry, B. P., & Gantz, B. J., (2000), "Medical and surgical evaluation and management of tinnitus", Tinnitus handbook, 221-241.

Pickles, J. O., (1988), "An introduction to the physiology of hearing", London: Academic press, **2**.

Pridmore, S., Kleinjung, T., Langguth, B. & Eichhammer, P., (2006), "Transcranial Magnetic Stimulation: Potential Treatment for Tinnitus?" Psychiatry Clinical Neuroscience, **60**(2), 133-138.

Purves, D. Augustine, G.J., Fitzpatrick, D., Hall W. C., LaMantia A.S., McNamara, J.O. and White L.E., (2008), "Functional areas of the brain". Life: The Science of Biology, by Sinauer Associates (4th Ed), www.sinauer.com (accessed 09/09/2013).

Quaranta, A., Assennato, G., & Sallustio, V., (1996), "Epidemiology of Hearing Problems Among Adults in Italy", Scandinavian Audiology **42**, 7-11.

Quaranta, N., Wagstaff, S., & Baguley, D. M., (2004), "Tinnitus and cochlear implantation", International Journal of Audiology, **43**(5), 245-251.

Rauschecker, J. P., (1999), "Auditory cortical plasticity: a comparison with other sensory systems", Trends in Neurosciences, **22**(2), 74-80.

Holt Hearing & Balance (2013), http//www.holthearingandbalance.co.uk (accessed 12/08/2012).

Roberts L.E., Moffat G., Baumann M., Ward L.M., Bosnyak D.J., (2008), "Residual inhibition functions overlap tinnitus spectra and the region of auditory threshold shift". J Assoc Res Otolaryngol, **9**:417–435.

Roberts, Larry E., et al. (2010) "Ringing ears: the neuroscience of tinnitus." The Journal of Neuroscience, **30**(45), 14972-14979.

Royal National Institute for the Deaf (RNID), (2005), <u>Tinnitus Market Report</u>, pp 5 (not avail online).

Rubinstein, J. T., & Tyler, R. S., (2004), "Electrical Suppression of Tinnitus", In J. B. Snow, Jr. (eds), <u>Tinnitus: Theory and Management</u>, Lewiston, NY: BC Decker.

Saltzman, M. & Ersner, M. S., (1947), "A Hearing Aid for Relief of Tinnitus Aurium", <u>The Laryngoscope,</u> **57**, 358-366.

Salvi, R. J., Lobarinas, E. & Sun, W., (2009), "Pharmacological Treatments for Tinnitus: New and Old", <u>Drugs of the Future,</u> **34**, 381-400.

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

Sanchez, L. & Stephens, D., (1997), "A Tinnitus Problem Questionnaire", <u>Ear and</u> <u>Hearing,</u> **18**, 210-217.

Sanchez, L., (2004) "The epidemiology of tinnitus." <u>Audiological Medicine,</u> **2**(1), 8-17.

Saunders J. C., (2007), "The Role of the Nervous System Plasticity in Tinnitus", <u>Journal</u> <u>of Communication Disorders,</u> **40**, 409-417.

Savage J, Waddell A., (2011) "Tinnitus", In <u>BMJ Clinical Evidence.</u> London, UK, BMJ Publishing Group.

Schaette, R., & Kempter, R., (2006), "Development of tinnitus-related neuronal hyperactivity through homeostatic plasticity after hearing loss: a computational model". <u>European Journal of Neuroscience</u>, **23**(11), 3124-3138.

Schaette, R., & Kempter, R., (2008), "Development of hyperactivity after hearing- loss in a computational model of the dorsal cochlear nucleus depends on neuron response type", <u>Hearing research</u>, **240**(1), 57-72.

Schechter, M. A., & Henry, J. A., (2002), "Assessment and Treatment of Tinnitus Patients Using a" Masking Approach", <u>Journal of the American Academy of Audiology</u>, **13**(10), 545-558.

Schmidtt, C., Patak, M. & Kroner-Herwig, B., (2000), "Stress and the Onset of Sudden Hearing Loss and Tinnitus", <u>International Tinnitus Journal,</u> **6**, 41-49.

Schürmann, M., Caetano, G., Jousmäki, V., & Hari, R., (2004), "Hands help hearing: facilitatory audiotactile interaction at low sound-intensity levels", <u>The Journal of the</u> <u>Acoustical Society of America</u>, **115**, 830

Schurmann M, Caetano G, Hlushchuk Y, Jousmaki V,Hari R., (2006) "Touch activates human auditory cortex", <u>NeuroImage</u>, **30**(4), 1325-1331.

Schwartz, N. (1999), "Self-Reports. How the Questions Shape the Answers", <u>American Psychologist,</u> **54,** 93-105.

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

Seki, S. & Eggermont, J. J., (2003), "Changes in Spontaneous Firing Rate and Neural Synchrony in Cat Primary Auditory Cortex after Localised Tone-induced Hearing Loss", <u>Hearing Resolution</u> **180**, 28-38.

Shore, S. (2005), "Multisensory Integration in the Dorsal Cochlear Nucleus: Unit Response to Acoustic and Trigeminal Ganglion Stimulation", <u>European Journal of Neuroscience</u>, (**21**) 334-348.

Shore, S. & Zhou, J., (2006), "Somatosensory Influence on the Cochlear Nucleus and Beyond", Hearing Research, 216-217.

Shore, S. E., Koehler, S., Oldakowski, M., Hughes, L. F., & Syed, S., (2008), "Dorsal cochlear nucleus responses to somatosensory stimulation are enhanced after noise-induced hearing loss" European Journal of Neuroscience, **27**(1), 155-168.

Shulman, A., (1987), "External electrical tinnitus suppression: a review", Otology & Neurotology, **8**(6), 479-484.

Smith, J.A., Mennemeier, M. & Bartel, T., (2007), "Repetitive Transcranial Stimulation for Tinnitus: A Pilot Study", Laryngoscope, **117**(3), 529-534.

Staller, S. J., (1998), "Suppression of tinnitus with electrical stimulation", Tinnitus: Treatment and relief, 77-90.

Stracke, Henning, Hidehiko Okamoto, and Christo Pantev, (2010), "Customized notched music training reduces tinnitus loudness." Communicative & integrative biology, **3**(3), 274-277.

Steenerson, R. L., & Cronin, G. W., (2003), "Tinnitus reduction using transcutaneous electrical stimulation", Otolaryngologic Clinics of North America, **36**(2), 337-344.

Suga, N., Xiao, Z., Ma, X., & Ji, W., (2002), "Plasticity and corticofugal modulation for hearing in adult animals", Neuron, **36**(1), 9-18.

Sullivan, M. D., Katon, W., Dobie, R., Sakai, C., Russo, J., & Harrop-Griffiths, J., (1988), "Disabling tinnitus: association with affective disorder", General hospital psychiatry, **10**(4), 285-291.

Sullivan, M., Katon, W., Russo, J., Dobie, R., & Sakai, C., (1993), "A randomized trial of nortriptyline for severe chronic tinnitus: effects on depression, disability, and tinnitus symptoms", <u>Archives of internal medicine</u>, **153**(19), 2251.

Surr, R. K., Montogomery, A. A. & Muller, H. G., (1985), "Effect of Amplification on Tinnitus Among New Hearing Aid Users", <u>Ear and Hearing,</u> **6,** 71-75.

Sweetow, R. W., & Sabes, J. H, (2010), "An overview of common procedures for the management of tinnitus patients", <u>The Hearing Journal</u>, **63**(11), 11-12.

Sziklai, I., Szilvássy, J., & Szilvássy, Z., (2011), "Tinnitus control by dopamine agonist pramipexole in presbyacusis patients", A randomized, placebo-controlled, double-blind study, <u>The Laryngoscope</u>, **121**(4), 888-893.

Tan, K. Q., Zhang, C., Liu, M. X., & Qiu, L. (2007), "Comparative study on therapeutic effects of acupuncture", Chinese herbs and Western medicine on nervous tinnitus].
Zhongguo zhen jiu= <u>Chinese acupuncture & moxibustion</u>, **27(**4), 249.

Tass, P. A., Adamchic, I., Freund, H. J., von Stackelberg, T., & Hauptmann, C, (2012), "Counteracting tinnitus by acoustic coordinated reset neuromodulation", <u>Restorative</u> <u>neurology and neuroscience</u>, **30**(2), 137-159.

Tauber, S., Schorn, K., Beyer, W. & Baugartner, R., (2003), "Transmeatal Cochlear Laser (TCL) Treatment of Cochlear Dysfunction: A Feasibility Study for Chronic Tinnitus", <u>Lasers Medical Science,</u> **18**(3), 154-161.

Teggi, R., Bellini, C &, Piccioni, L.O., (2008), "Transmeatal Low-Level Laser Therapy for Chronic Tinnitus with Cochlear Dysfunction", <u>Audiology and Neurology,</u> **14**(2), 115-120.

Thedinger, B. S., Karlsen, E., & Schack, S. H., (1987), "Treatment of tinnitus with electrical stimulation: an evaluation of the Audimax Theraband", <u>The Laryngoscope</u>, **97**(1), 33-37.

Tonndorf, J., (1987), "The Analogy between Tinnitus and Pain: A Suggestion for a Physiological Basis of Chronic Tinnitus", <u>Hearing Research,</u> **28**, 271-275.

Trotter MI., Donaldson I., (2008) "Hearing aids and tinnitus therapy: a 25 year experience", <u>J Laryngol Otol</u>, **122**, 1051-1056.

Truex, R. C. (1969), "Human neuroanatomy", Balimore Waverly Press.

Tzounopoulos, T., & Kraus, N. (2009), "Learning to encode timing: mechanisms of plasticity in the auditory brainstem", <u>Neuron</u>, **62**(4), 463-469.

Tyler, R. S., (1995), "Tinnitus in the Profoundly Hearing-impaired and the Effects of Cochlear Implants", <u>The Annals of otology, Rhinology & Laryngology Supplement</u> **165**, 25-30.

Tyler, R., Coelho, C., Tao, P., Ji, H., Noble, W., Gehringer, A., & Gogel, S., (2008), "Identifying tinnitus subgroups with cluster analysis", <u>American Journal of Audiology</u>, **17**(2), S176.

Vanneste, S., Plazier, M., Van de Heying, P. & De Ridder, D., (2010), "Transcutaneous Electrical Nerve Stimulation (TENS) of Upper Cervical Nerve (C2) for the Treatment of Somatic Tinnitus", <u>Experimental Brain Research,</u> **204**(2), 283-287.

Vanneste, S. & De Ridder, D., (2012), "Noninvasive and invasive neuromodulation for the treatment of tinnitus: an overview", <u>Neuromodulation: Technology at the Neural Interface</u>, **15**(4), 350-360.

Vernon, J.A., (2000), "Masking of Tinnitus through a Cochlear Implant", <u>Journal of the American Academy of Audiology,</u> **11**, 293-294.

Vernon, J.A. & Meikle M.B., (2000) "Tinnitus masking". In: Tyler RS (Ed.). <u>Tinnitus Handbook.</u> San Diego, Calif: Singular, Thompson Learning, 313-356.

Wei, L., Ding, D., & Salvi, R. (2010), "Salicylate-induced degeneration of cochlea spiral ganglion neurons-apoptosis signalling", <u>Neuroscience</u>, **168**(1), 288-299.

Weinberger, D. R. (1987), "Implications of normal brain development for the pathogenesis of schizophrenia", <u>Archives of general psychiatry</u>, **44**(7), 660.

Weinberger, N.M., (1998), "Physiological memory in primary auditory cortex: Characteristics and Mechanisms", <u>Neurobiology of learning and memory,</u> **70**(1), 226251.

Weisz, N., Muller, S., Schlee, W., Dohrmann, K., Hartmann, T. & Elbert, T., (2007), "The Neural Code of Auditory Phantom Perception", <u>Journal of Neuroscience,</u> **27**(6), 1479-1484.

Wewers, M. E., & Lowe, N. K. (1990), "A critical review of visual analogue scales in the measurement of clinical phenomena", <u>Research in Nursing & Health</u>, **13**(4), 227236.

WikiCommons, (2012), Ventral brain showing labelled cranial nerves, http://en.wikivet.net/Cranial_Nerves_-_Anatomy_%26_Physiology (accessed 10/05/2014).

Wikipedia Commons, Neuron: Chemical Synapse, http://en.wikipedia.org/wiki/File:Chemical_synapse_schema_cropped.jpg (accessed 10/03/2013).

Willebrand, M., Kildal, M., Ekselius, L., Gerdin, B. & Andersson, G., (2001), "Development of the Coping with Burns Questionnaire", <u>Personality and Individual Differences,</u> **30**, 1059-1072.

Wilson, P.H., Henry, J.L., Andersson, G., Hallam, R.S. & Lindberg, P. (1998), "A Critical Analysis of Directive Counselling as a Component of Tinnitus Retraining Therapy", <u>British Journal of Audiology</u>, **32**, 273-287.

Wright, E. F., & Bifano, S. L., (1997), "Tinnitus improvement through TMD therapy", The Journal of the American Dental Association, **128**(10), 1424-1432.

Xiaozhe, Z., (2002), "Comparative Study on Clinical Therapeutic Effects of Electroacupuncture and Acupuncture on Tinnitus" [J]. Chinese Acupuncture & Moxibustion**, 2,** 009.

Zachriat, C. & Kroner-Herwig, B., (2004), "Treating Chronic Tinnitus: Comparison of Cognitive Behavioural and Habituation-Based Treatments", Cognitive Behaviour Therapy, **33**(4), 187-198.

Zhang XZ., (2002), "Comparative study on clinical therapeutic effects of electroacupuncture and acupuncture on tinnitus, Zhongguo Zhen Jiu, **22**(2), 91-2.

Zhou, Jianxun, and Susan Shore, (2004), "Projections from the trigeminal nuclear complex to the cochlear nuclei: a retrograde and anterograde tracing study in the guinea pig." Journal of Neuroscience Research, **78**(6), 901-907.

Zwicker, E., (1964), ""Negative afterimage" in hearing." The Journal of the Acoustical Society of America, **36**, 2413-2415.

APPENDICES

Date _____

Dear Dr _____

RE: Tinnitus Research Study

Your patient _____ **(DOB___ / ___/____)** has consented to participate in a Tinnitus Research study. This study is been conducted by a team of researchers at NUI-Maynooth in collaboration with the Hermitage Clinic in Lucan.

The duration of the study is 12 weeks. The recruitment period for this study is June to Sept 2012. The aim of the study is to investigate whether a novel, experimental sound to touch translation device, called MuteButton, can affect the patient's awareness of tinnitus. It involves using the device every day for a period of 2 hours. The stimulation involves audio patterns played through a set of headphones and tactile patterns consisting of small electrical pulses delivered to the tip of the tongue. The patient will be invited to attend The Hamilton Institute, NUI-Maynooth or Hermitage Medical Clinic, Lucan every two weeks. They will be given relevant contact details if they have any questions during the 12 week period. Should they develop any side effects or unusual symptoms they will be advised to contact us direct.

Should you have any questions, please do not hesitate to contact me direct at 0879976995 or via email: caroline.hamilton@nuim.ie. If you require any further information regarding this study, or have any concerns about your patient's condition, please do not hesitate to contact Mr. Brendan Conlon MD, Hermitage Medical Clinic, Lucan, Co Dublin. Tel: (01) 6459601 or via email: bconlon@ent.ie.

Yours sincerely

_____

Caroline Hamilton
Audiologist/Researcher

APPENDIX 2 – LETTER OF REFUSAL

Patients name/address

Date_____

Dear _____

I write to you regarding your recent interest in our Tinnitus Research Study. As previously discussed, The Hermitage Medical Clinic in collaboration with NUI Maynooth are running a tinnitus research study using a device developed by researchers at the University. Having reviewed your data, it would appear that you do not fit the inclusion criteria for this particular study.

However, we intend running further tinnitus studies in due course and if interested we would be happy to contact you. While we cannot guarantee your participation in future studies, should you wish to be assessed for inclusion, please contact a member of the research team direct @ **087 9976995** or email caroline.hamilton@nuim.ie**.**

Sincerely,

_____

Caroline Hamilton
Audiologist/Researcher

APPENDIX 3 – APPOINTMENT LETTER

Patients name/address: Date_____

Appointment Date:

Dear _____

I write to you regarding your recent interest in our Tinnitus Research Study. As previously discussed, The Hermitage Medical Clinic in collaboration with NUI Maynooth are running a tinnitus research study using a device developed by researchers at the University. Having reviewed your data, it would appear that you fit the participant profile for this study.   A further screening appointment would however be required to verify that you meet all the inclusion criteria. This appointment will take place at the Hermitage Medical Clinic, Lucan, Co Dublin. Please check in at main reception and you will be directed to our Suite.

You will be required to complete 2 questionnaires on arrival. Hearing and tinnitus matching tests will also be carried out. The study will be discussed with you and you will be asked to sign a consent form. Duration of this appointment will be approximately 30 - 45 minutes. Please arrive approximately 15 minutes prior to your appointment.

Following your screening appointment you will be contacted within 1-2 weeks and advised as to whether or not you have been recommended for inclusion in the study which will take place over a 12 week period, commencing July 2012. As part of this study, you will be required to attend a review appointment every 2 weeks during this 12 week period.

While we cannot guarantee your participation in the study, should you wish to be assessed for inclusion and are available to attend at the above date and time, please contact a member of the research team direct @ **087 9976995** or email caroline.hamilton@nuim.ie**.**
Sincerely,

_____

Caroline Hamilton, Audiologist/Researcher

APPENDIX 4 – TINNITUS HEARING INVENTORY (THI)

		4	0	2
		Yes	No	Someti mes
1	Because of your tinnitus is it difficult for you to concentrate?			
2	Does the loudness of your tinnitus make it difficult for you to hear people?			
3	Does your tinnitus make you angry?			
4	Does your tinnitus make you confused?			
5	Because of your tinnitus are you desperate?			
6	Do you complain a great deal about your tinnitus?			
7	Because of your tinnitus do you have trouble falling asleep at night?			
8	Do you feel as though you cannot escape from your tinnitus?			
9	Does your tinnitus interfere with your ability to enjoy social activities?			
10	Because of your tinnitus do you feel frustrated?			
11	Because of your tinnitus do you feel you have a terrible disease?			
12	Does your tinnitus make it difficult for you to enjoy life?			

13	Does your tinnitus interfere with your job or household responsibilities?			
14	Because of your tinnitus do you find that you are often irritable?			
15	Because of your tinnitus is it difficult for you to read?			
16	Does your tinnitus make you upset?			
17	Do you feel that your tinnitus has placed stress on your relationships?			
18	Do you find it difficult to focus your attention away from your tinnitus and onto other things?			
19	Do you feel that you have no control over your tinnitus?			
20	Because of your tinnitus do you often feel tired?			
21	Because of your tinnitus do you feel depressed?			
22	Does your tinnitus make you feel anxious?			
23	Do you feel you can no longer cope with your tinnitus?			
24	Does your tinnitus get worse when you are under stress?			
25	Does your tinnitus make you feel insecure?			

APPENDIX 5 – VISUAL ANALOGUE SCALE (VAS)

Over the last 2 weeks, can you rate the severity of you tinnitus (please circle)

1   2   3   4   5   6   7   8   9   10

MILD   **SEVERE**

Tinnitus Research Study

Introduction

You are being invited to take part in a research study. Before you decide to take part it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and feel free to discuss it with others. Ask us if anything is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

The aim of this study is to investigate whether a novel, experimental device "MuteButton" can affect the awareness of tinnitus. Sound that arrives at the ears naturally will be presented in the form of touch patterns on the tongue. By learning to associate the sounds in the ears with the sound patterns on the tongue, we aim to demonstrate that the brain will learn to discriminate the real sounds from legitimate external sources from the imaginary tinnitus sounds that are created inside the brain.

Why have I been invited?

You have been invited to participate because you experience tinnitus. Up to 100 Participants will be invited to be pre-screened for the study. Based on the inclusion/exclusion criteria, the first 60 participants who meet the criteria will be recommended for the 12 week study.

Do I have to take part?

Participation in this study is entirely voluntary. It is up to you to decide whether to take part or not. If you do decide to take part, you are free to leave the study at any time without giving a reason. This will not affect your future medical care in any way. Any participation you had in the study previous to your departure from the study will be stricken from the record and destroyed if you so wish.

Your doctor may withdraw you from the study if he/she feels this is in your best interest or in case of stopping the study early.

What will happen to me if I take part?

You will meet with the Consultant and research team who will discuss the study with you in detail and you will be asked to sign a consent form.

If you agree to take part in this study, you will be invited to attend The Hamilton Institute, NUI-Maynooth to have certain examinations and tests (called "screening tests") to help determine whether you are eligible to participate. The duration of the first visit will be approximately 45 minutes. The screening tests include a review of your tinnitus medical history; complete 2 questionnaires (Tinnitus Handicap Inventory and Visual Analogue Scale).You will undergo a tinnitus matching test. The purpose of this test is to help identify the frequency and intensity of your tinnitus. The test is similar to having your hearing tested. You will be asked to wear a set a headphones connected to an audiometer (used for hearing tests) and you will be asked to identify which of the tones of the audiometer match the tone of the ringing in your ear(s). This is a simple procedure in which the researcher adjusts the sound until you indicate that it is the same as your tinnitus.

It is possible that after these tests are reviewed, you will not be eligible to take part in this study. You will be referred back to your GP and advised of further therapies available that may be beneficial.

If you are eligible to participate in the research study you will advised within 1-2 weeks after the screening visit. You will be invited to attend the enrolment visit at the Hermitage Medical Clinic, Lucan. The duration of your second visit will be approximately 1 hour 30 minutes.

At the enrolment visit you will receive an information pack, which will include a user manual and instruction of usage for MuteButton, the required accessories for maintenance which include harness, mouth piece, headphones and charger. An appointment card, detailing location, date and times of each of your follow-up visits as well as a map for Hermitage Medical Clinic, Lucan and the Hamilton Institute – NUI Maynooth.

The instructions for use will include information on how to charge, maintain, clean and store the device. It is important your device is fully charged before you start to use it. Ensure the charger is disconnected before use (or it will not switch on).

At this visit you will be instructed on how to use the device and as to the frequency/duration of use. During this initial training session you will be instructed on how to insert the device into the oral cavity and depress against the tongue. You will be advised to use it for 30 minutes whilst under the supervision of Ms. Caroline Hamilton, Audiologist and Mr. Brendan Conlon, MD, Ear Nose and Throat Consultant.

Once the enrolment session is complete, you will be given the MuteButton device to take home for 12 weeks. You will be advised during your first visit to use the device for 2 hours a day, preferably at the same time and in the same place every day. (Advise morning or evening time, in a quiet room, no other sounds or distractions in the room. Avoid any distractions or interruptions, such as door bells, phones etc. If possible avoid turning off the device during the 2 hours).

The MuteButton device (which is about the size/weight of a mobile phone) has a neck harness on it so you can hang it around your neck, close to your chest. It involves stimulation in the form of audio/sound patterns played through a set of headphones which are placed over the ears. It will have a volume control to allow you to increase and decrease volume, as well as a pause and a play button.

At the same time tactile patterns consisting of small electrical pulses will be delivered to the tip of the tongue. You will place the mouthpiece end, just behind the front teeth, such that the tongue lies against it when your mouth and jaw are in a relaxed state. Your lips will close around the bottom of the mouth piece. You can also adjust the stimulus level of the mouth piece.

Your participation will terminate if you experience any of the following side-effects - pain, swelling, erythema (redness), tongue or oral mucosa (patchy or dark oral mucous) or dramatic increase in tinnitus symptoms. Any participants who experience mild symptoms will be observed in the out-patient setting until complete resolution of symptoms. Once the enrolment session is complete, you will be given the device for 12 consecutive weeks

Following your enrolment visit, you will be asked to meet with a member of the research team every two weeks during the 12 week period, for 30-45 minutes for follow-up visits (6 follow-up visits in total). At each visit you will be asked to complete 2 Questionnaires (Tinnitus Handicap Inventory and Visual Analogue Scale) on arrival as well as the tinnitus matching test. At the final visit, you will meet with a member of the research team who will provide you with a debriefing of the study and will give you an opportunity to ask further questions if required.

You will be requested to return the information pack (given to you on the enrolment visit) and the MuteButton device. The debriefing session will complete your involvement in the study and your interaction with the research team. Approximately 3 months after your final appointment, the questionnaires will be emailed to you, once completed you will be asked to return them via post/email.

What is the device that is being tested?

The MuteButton is a device that is being used in experimental research trials to evaluate the effect of stimulation on the symptoms of tonal tinnitus. You have been chosen for this study as you experience tinnitus and have also been diagnosed with a high frequency sensory-neural hearing loss. When used according to the instructions the perceived loudness of the tinnitus may be reduced for several hours following a treatment session. It involves stimulation in the form of audio/sound patterns played through a set of headphones which are placed over the ears. At the same time tactile patterns consisting of small electrical pulses will be delivered to the tip of the tongue.

What are the alternatives for treatment?

There are a number of other treatments/therapies available for your condition that your Consultant, Audiologist or GP will discuss with you.

What are the possible risks of taking part?

Patients who previously participated in the initial study to evaluate this device did not experience any adverse events. There is no guarantee this device will be of any benefit to you. . If you feel

any pain, discomfort, worsening of tinnitus symptoms or any adverse reactions while using the device at any stage, you must stop using the device immediately and contact Mr. Brendan Conlon MD, ENT Consultant at the Hermitage Hospital at (01) 6459601 or via email: bconlon@ent.ie or a member of the research team at 0879976995 or via email: caroline.hamilton@nuim.ie during clinic hours. Outside of clinic hours, contact the Emergency Department at the Hermitage Hospital at (01) 6459016.

What are the possible benefits of taking part?

The potential benefits if participating in this research study is, that the perceived loudness of your tinnitus maybe reduced for several hours following a treatment session. A previous study using the same treatment device for 4 weeks, resulted in 60% of patients reported their symptoms had 'improved' or 'greatly improved'. The knowledge gained from this study may also be of help to other patients in the future.

What happens if new information becomes available?

If any new information becomes available during the course of the study that may affect your willingness to participate, you will be informed of this. If you decide to withdraw, your research doctor will advise you on alternative treatment if available or return to your GP or ENT surgeon or whoever was treating patient initially. If you decide to continue in the study you will be asked to sign and date an updated consent form. Your doctor may decide based on the new information it may not be in your best interest to continue in the study. He/she will explain the reasons and arrange for your care to continue.

Will my taking part in this study be kept confidential?

If you agree to take part, your GP will be informed of your participation in the study. Your study doctor and staff will collect information about you. A code will replace your name on all the data collected about you. All the data collected will be kept strictly confidential within the limitations of the law. All information relating to your personal data will be anonymised will have your name and address removed so as to preserve confidentiality. Any information that will identify you in any way will also be removed.

The data collected will be used for the evaluation of the study, and may be used in the future in related or other studies. The data may be submitted to the health authority/notified body for registration purposes. Members of health authorities, of Research Ethics Committees or other persons required by law may review the data provided. This data may also be used in publications about the medical device. However, your identity will not be revealed in any compilations, study reports or publications. In order to verify the accuracy of collected data, it is necessary for the sponsor to directly compare them with your medical records. Such checks will only be done by qualified and authorized personnel. All such persons are required to and will keep the data confidential.

Who is organising and funding the research?

The research is being organised by a research team from the National University of Ireland Maynooth in collaboration with the Hermitage Medical Clinic. The research is funded by Irish Research Council for Science Engineering and Technology.

Who has reviewed the study?

The study has been reviewed and given a positive opinion by the Hermitage Medical and NUI-Maynooth Ethics Committee.

Who do I contact if I have a question?

Please feel free to address any questions to Mr. Brendan Conlon MD, ENT Consultant at the Hermitage Hospital at (01) 6459601 or via email: bconlon@ent.ieor a member of the research team at 0879976995 or via email: caroline.hamilton@nuim.ie during clinic hours.

Contact for further information:

If you or your relative(s) have any questions regarding the study or in case of study related injuries you may contact Mr. Brendan Conlon MD, ENT Consultant at the Hermitage Hospital at (01) 6459601 or via email: bconlon@ent.ie or a member of the research team at 0879976995 or via email: caroline.hamilton@nuim.ie during clinic hours. Outside of clinic hours, contact the Emergency Department at the Hermitage Hospital at (01) 6459016.

If during your participation in this study you feel the information and guidelines that you were given have been neglected or disregarded in any way, or if you are unhappy about the process please contact the Secretary of the National University of Ireland Maynooth Ethics Committee at research.ethics@nuim.ie or +353 (0)1 708 6019. Please be assured that you concerns will be dealt with in a sensitive manner.

You will receive a copy of the information leaflet and consent form to keep.

APPENDIX 7 – CONSENT FORM

Tinnitus Research Study

Name of Study Doctor:

Patient Identification Number for this trial:

Patient's full name and date of birth:

I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions.

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

I understand that sections of any medical notes may be looked at by responsible individuals from the sponsor company or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

I agree that the data collected for the study will be used for the purpose set forth above, and processing by the sponsor company in an anonymous form with respect of the confidentiality of my data. This will not waive any rights that I have under local law.

I agree to take part in the above study. To be signed simultaneously, i.e. same date, by all parties:

Print Name of Patient

Date (to be entered by Patient)

Signature

Print Name of person <u>obtaining the consent</u>

Date (to be entered by the person obtaining the consent)

Signature

Title of person <u>obtaining the consent</u>

Distribution: original for study file, copy to Patient and copy to hospital notes.

APPENDIX 8 - APPTOINTMENT SCHEDULE

If for some reason you cannot attend your appointment please contact us at your earliest convenience on **0879976995** or email caroline.hamilton@nuim.ie

It may not be possible to reschedule appointment(s) due to the number of subjects attending, as appointments are all booked in advance.

APPOINTMENT	DATE	TIME	LOCATION

APPENDIX 9 – CONTACT DETAILS FOR TINNITUS RESEARCH STUDY

Who to contact regarding medical concern(s)?

If you feel any pain, discomfort, worsening of tinnitus symptoms or any adverse reactions while using the device at any stage, you must stop using the device immediately and contact (during clinic hours);

- **Mr. Brendan Conlon MD, ENT Consultant at the Hermitage Hospital at (01) 6459601** or via email: bconlon@ent.ie or
- A member of the **Research Team** at **0879976995** or via email: caroline.hamilton@nuim.ie or caroline.hamilton@nuim.ie
- The **Emergency Department at the Hermitage Hospital** at **(01) 6459016** (Mon-Fri: 8am-5pm, Sat/Sun and Bank hols: 10am-5pm).
- Outside of clinic hours, please go to your nearest **Accident and Emergency Department**, contact a member of the **Research Team** at **0879976995** and leave a message/contact details. A member of the team will return your call.

Who to contact regarding general question(s)?

Please feel free to address any questions (during clinic hours) to;

- **Mr. Brendan Conlon MD, ENT Consultant at the Hermitage Hospital at (01) 6459601** or via email: bconlon@ent.ie or
- A member of the **Research Ream** at **0879976995** or via email: caroline.hamilton@nuim.ie

Who to contact regarding further information?

If you or your relative(s) have any questions regarding the study or in case of study related injuries you may contact (during clinic hours);

- **Mr. Brendan Conlon MD, ENT Consultant at the Hermitage Hospital at (01) 6459601** or via email: bconlon@ent.ie or
- A member of the **Research Team** at **0879976995** or via email: caroline.hamilton@nuim.ie or

119

- The **Emergency Department at the Hermitage Hospital** at **(01) 6459016** (<u>Mon-Fri: 8am-5pm, Sat/Sun and Bank hols: 10am-5pm).</u>
- <u>Outside of clinic hours</u>, please go to your nearest **Accident and Emergency Department,** contact a member of the **Research Team** at **0879976995** and leave a message/contact details. A member of the research team will return your call.

If during your participation in this study you feel the information and guidelines that you were given have been neglected or disregarded in any way, or if you are unhappy about the process please contact;

- The **Secretary of the National University of Ireland Maynooth Ethics Committee** at <u>pgdean@nuim.ie</u> or **01 708 6018**. Please be assured that you concerns will be dealt with in a sensitive manner.

MuteButton Model MB2011

Instructions For Use

Please read instructions carefully before using MuteButton

Purpose of the MuteButton Device:

The MuteButton is a device that will be used in experimental research trials to evaluate the effect of stimulation on the symptoms of tonal tinnitus. The stimulation involves audio patterns / music played through a set of headphones and tactile patterns consisting of small electrical pulses delivered to the tip of the tongue.

When used according to the instructions contained herewith, the perceived loudness of the tinnitus may be reduced for several hours following a treatment session.

This device is only to be used under direct instructions from your physician / trial clinician. He/she will guide you on the optimal usage pattern and monitor your symptoms progress throughout the trial period.

Contraindications:

- This device should not be used if you have a pacemaker, pulse regulator or any other electronic implanted medical devices unless directed to by a physician.
- This device should not be used if you have diagnosed or suspected heart problems unless directed to by a physician
- This device should not be used if you have any lesions, sores or inflammation of the tongue, gums or inside of the mouth.
- This device should not be used during pregnancy unless directed to by a physician.
- This device should not be used if you suffer from Epilepsy unless directed to by a physician.
- This device should not be used if you are immunocompromised in any way such as if undergoing chemotherapy or infected with HIV unless directed to by a physician.

Precautions:

- Only use with the supplied headphones, Sony model "MDR-XD200"
- During use make sure that the electrode contacts do not come into contact with other equipment or conductive parts.
- Do not use in very cold or warm climates (below +5 or above +50 degrees Celsius) or in very humid environments (above 90% Relative Humidity)
- Do not use at altitudes greater than 2000m

- Do not use for more than one hour per day unless directed to do so by your physician / clinician.

- Do not connect any other equipment to the headphone socket.

- Do not use this device while sleeping or napping.

- Keep away from children.

- Portable radio equipment such as mobile phones may interfere with the performance of the MuteButton device and should be kept at least 30cm away from it when in use.

Description of the MuteButton Device - Controls, Indicators and Connections:

Power Button (doubles up as Play/Pause button)

This button is used for powering the device up when it is off, and also for pausing and re-starting treatment when it is on. It can also be used to power the device off by holding it down for 2 seconds.

Forward Button and Reverse Button

In certain circumstances your health care professional may include multiple sound tracks on the memory card. In this case these buttons allow you to skip forward or backwards to select different tracks. If there is only one track on the memory card then pressing these buttons will have no effect.

Charger Socket

The supplied charger plugs into this socket to charge the battery.

Charger Lamp

This lamp indicates the state of battery charging. It will illuminate green when the battery is charging, and orange when the battery is fully charged.

Headphone Socket

The supplied headphones should be plugged into this socket when in use, and they can be unplugged when the device is stored away.

Mouthpiece interconnecting cable

During normal use the mouthpiece (see figure 4) should be placed just behind your front teeth such that the tongue lies against it when your mouth and jaw are in a relaxed state. This is illustrated in figure 1.

Volume control dial

This dial adjusts the volume of sound in the headphones. Rotate the dial away from you to increase the volume and vice versa.

Stimulus control dial

This dial allows you to increase or decrease the tongue stimulation level. Rotate away from the mouthpiece cable to increase the stimulation level and vice versa.

Micro-SD card Slot

Your physician / clinician will insert a micro-SD card into this slot on your device. It contains information relating to the specific audio and stimulation patterns that is deemed most suitable for your particular tinnitus characteristics. The device will not function if this card is removed or if an alternative card is inserted.

Electro-tactile stimulus indicator lamp

This lamp indicates the state of electro-tactile stimulation. It will illuminate yellow when stimulation is active.

Using the MuteButton Device:

- The MuteButton device is designed to hang from a neck harness close to the chest. The supplied headphones are placed over the ears, and the mouthpiece is then to be placed just behind the front teeth such that the tip of the tongue makes contact with the electrodes and the lips close around the connecting cable.

- Before the device can be used, the charger must be disconnected or it will not switch on. Press the Play button briefly to power the device on. The light in the 12 O'clock position will illuminate immediately and two seconds later a clockwise rotating pattern of blue lights will coincide with the start of stimulation playback.

- At this point the audio volume and tongue stimulus level can be adjusted to comfortable levels.

- The stimulus will continue for the duration of the treatment session. A slowly rotating light in the anti-clockwise direction indicates the time remaining in the treatment session – when that light rotates one full circle back to 12 O'clock the session is complete and the device will automatically shut down.

- The treatment session can be paused at any stage by pressing the Play button, and resumed by pressing the play button again. If the session is paused for more than 10 minutes it will automatically shut down.

- The device can be manually shut down at any stage by holding the Play button down for 2 seconds.

- The Forward and Back buttons will only operate if your treatment profile contains multiple stimulation tracks and in that case can be used to skip forward or back to select different tracks.

- The device will automatically shut down if the micro-SD card is removed as this is essential to the operation of the device.

- The slowly rotating light will change colour from green to orange when the battery goes low. When this happens there is still enough energy in the battery to complete the current treatment session but once the session is complete the supplied charger should be connected to re-charge the battery.

- When the charger is connected the device will not operate (it will remain shut down) for safety reasons. The charge light adjacent to the charger socket will be green then the battery is charging and orange when the battery is fully charged.

Cleaning and Sterilization:
- The control device should only be cleaned with a dry cloth, or if that is not effective iso-propyl alcohol can also be used. If the control device does get wet, please contact MuteButton for a replacement to minimize the risk of electrical shock.

- Sterilization should not be required often during normal use, where no other person or property comes into contact with it. If you suspect that something else may have come into contact with it then the intra-oral device (mouthpiece) can be sterilized by immersing the mouthpiece part in Milton Sterilizing Fluid at room temperature (20 degrees Celsius) for a minimum of 15 minutes.

Maintenance, Storage and Disposal:

- A weekly visual inspection should be carried out to ensure there is no physical damage or for evidence of liquids ingress into the control device and for any discolouration or damage of the intra-oral part.

- When not in use the device should be kept in the supplied case.

- Ensure that the device is stored in a dry location that is not colder than -5 degrees Celsius or warmer than 50 degrees Celsius or has a relative humidity level that is more than 90%.

- The internal battery B1 is a lithium-Polymer type and as such does not contain environmentally damaging chemicals. If should be returned to MuteButton for safe disposal at end of it's useful life and should not be disposed o as domestic waste.

Troubleshooting:

- Below are a few common problems and suggestions on how they may be circumvented. If attempting these does not solve the problem please contact MuteButton.

Device does not power on:

- The device will not operate while the charger is connected, please disconnect the charger before pressing the power button.

- Check that the device is charged by connecting the charger and waiting until the charge LED is the colour orange. Make sure that you press the power button for at least a half of one second, very short presses may not cause the device to latch on.

- Make sure that the supplied micro-SD card is fully inserted with the text side facing up.

The sound level is too low:

- Try to adjust the audio volume level by rotating the volume control dial anti-clockwise.

The sound is distorted:

- Check that the headphone connector is fully inserted and that the headphone connector is clean.

- Try adjusting the audio volume level to be lower by rotating the volume control dial clockwise.

- Ensure you are using the supplied headphones: Sony model "MDR-XD200"

The tongue stimulation level is too low:

- Try to adjust the stimulation level by rotating the stimulation control dial anti-clockwise.

The lights turn green, then orange briefly when powered up and then shuts down again:

- This occurs when the charger is connected, please disconnect the charger and try to power the device on again.

The lights turn red briefly when powered up and then shuts down again:

- This is the indication that the device has not passed its own self-testing and is indicative of a hardware failure or a micro-SD card error. This device should be returned to MuteButton.