AN INVESTIGATION OF TINNITUS USING BEHAVIOURAL AND FUNCTIONAL IMAGING MEASURES

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A wise old lady once told me to remain in education for as long as possible…well Nan, I took your advice.

In loving memory of Teresa Bentley

ABSTRACT

Tinnitus is the phantom perception of sound. For some people tinnitus can have a detrimental impact on their quality of life. Negative emotional feelings associated with tinnitus play a major role in enhancing and maintaining its continued presence. Despite its high prevalence across the world, its neurophysiological underpinnings remain elusive and there is no universal cure.

This thesis utilises data derived from an open-label, non-randomised clinical trial whose original aim was to evaluate the effect of hearing aids for hearing-impaired individuals with tinnitus. To achieve this, a range of patient-reported clinical measures, as well as functional magnetic resonance imaging (fMRI) were used to identify both clinical and neurophysiological markers of treatment-related change over a six-month period.

Evidence for clinical impact of hearing aid provision in the management of tinnitus was examined. In study 1, tinnitus handicap was compared amongst two groups of chronic tinnitus patients; those opting for hearing aids (n=42) and age-matched controls who were not (n=14). A small statistically significant reduction in tinnitus handicap as measured by the Tinnitus Handicap Questionnaire was observed in the hearing aid group six months post-fitting compared to controls. However this was not

clinically significant. Given the lack of evidence for strong clinical benefit, three further investigations were conducted to identify objective neurophysiological markers associated with the presence of tinnitus. These used baseline fMRI data (i.e. prior to any hearing aid provision) derived from the same age and hearing-matched groups (chronic tinnitus, n=12 and no tinnitus controls, n=11). Independent Component Analysis, region of interest analysis and Patel's conditional dependence measures were used to investigate resting-state brain activity across the auditory network (study 2) and within the amygdala (study 3). Neither study found any between-group differences. Study 4 examined sound-evoked differences between groups by measuring the amygdala response to emotionally evocative soundscapes using a general linear model approach. Soundscapes rated as very pleasant or very unpleasant elicited stronger amygdala activity than neutral soundscapes (replicating a previous finding). However, activity in the tinnitus group was reduced compared to controls, contrary to our expectations.

While results demonstrate that the objective quantification of tinnitus is possible, this nevertheless remains a challenging field. The investigation of resting-state and sound-evoked fMRI data derived from the same participant groups illustrates how neurophysiological markers of tinnitus may only become apparent

given the right choice of experimental paradigm. The identification of a potential tinnitus-related biomarker in limbic, not auditory, brain regions leads us to speculate that functional imaging may be more sensitive to the emotional consequences of the tinnitus than the neural signature of the sound perception itself. Challenges and recommendations for future tinnitus research are identified.

PUBLICATIONS

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J. Davies, P. E. Gander, M. Andrews and D. A. Hall (2014). Auditory network connectivity in tinnitus patients: a resting-state fMRI study. Int J Audiol 53(3): 192-198.

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P. E. Gander and J. Davies. (2012). How to help residents who are troubled with tinnitus. *Nursing and Residential Care* 14 (7): 1-5.

Oral Presentations

J. Davies (2015). An investigation of tinnitus using behavioural and functional imaging measures: a summary of four years. British Tinnitus Association conference, Manchester.

J. Davies (2015). An investigation of tinnitus using behavioural and functional imaging measures: a summary of four years. British Academy of Audiology student conference, Leicester.

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J. Davies (2013). A PhD or an Audiology post; why not do both? British Academy of Audiology conference, Manchester.

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J. Davies, P. Gander, M. Andrews, and D.A. Hall (2012). Auditory network connectivity in tinnitus patients: a resting-state fMRI study. British Society of Audiology conference, Nottingham.

DECLARATION

I certify that this is my own work, except where indicated by referencing. No part of this thesis has been submitted elsewhere for any other degree or qualification.

Jeff Davies:  Date: 21/04/16

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ABBREVIATIONS

ANOVA	Analysis Of Variance
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BOLD	Blood Oxygen Level Dependant
CBT	Cognitive Behavioural Therapy
CSQ	Coping Styles Questionnaire
dB	Decibel
DMN	Default Mode Network
EEG	Electroencephalography
ENT	Ear Nose Throat
EPI	Echo Planar Imaging
FDR	False Discovery Rate
fMRI	functional Magnetic Resonance Imaging
FOV	Field Of View
FWE	Family Wise Error
HL	Hearing Loss
HQ	Hyperacusis Questionnaire
ICA	Independent Component Analysis
MEG	Magnetoencephalography
MHLC	Mental Health Locus of Control Form C
MRI	Magnetic Resonance Imaging

NH	Normal Hearing
NHS	National Health Service
NRES	National Research Ethics Service
PCA	Principle Component Analysis
PET	Positron Emission Tomography
ROI	Region Of Interest
RSN	Resting State Network
SCA	Seed-based Correlation Analysis
SF-36	Short Form 36 Health Survey
SPL	Sound Pressure Level
TCHQ	Tinnitus Case History Questionnaire
TE	Echo Time
TFI	Tinnitus Functional Index
THI	Tinnitus Handicap Inventory
THQ	Tinnitus Handicap Questionnaire
TR	Repetition Time
UK	United Kingdom

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1 OVERVIEW

1.1 THESIS SCOPE

Tinnitus is the phantom perception of sound which does not relate to any external sound source. Despite its high prevalence across the world (Tyler, 2000), relatively little is known about its underlying neural mechanisms. Although originally thought to result from damage to the peripheral auditory structures, more recent evidence suggests central mechanisms may play a key role in the manifestation and persistence of tinnitus. Over the last two decades, novel neuroimaging techniques such as functional magnetic resonance imaging (fMRI) have emerged which may provide new insight into this enigmatic condition. This non-invasive method is sensitive to changes in blood oxygenation levels which are associated with neural activity, making it a well-suited tool in the investigation of brain function.

The work presented has taken place at the Nottingham Hearing Biomedical Research Unit, University of Nottingham between September 2011 and January 2016. I was awarded a PhD studentship by Deafness Research UK (now merged with Action on Hearing Loss) to study the neurophysiological mechanisms of tinnitus using objective neuroimaging methods. I took a multi-

faceted approach in my investigation of tinnitus, conducting four studies which examined both behavioural and neurophysiological markers associated with tinnitus and the treatment of tinnitus using hearing aid interventions. Choosing both modalities made it possible to correlate subjective data such as a participant's perceived level of tinnitus distress with objective fMRI data.

All data within this thesis was sourced from an unpublished controlled clinical trial whose primary aim was to assess the longitudinal benefit of hearing aid provision for the management of tinnitus using a variety of behavioural and objective outcome measures collected at baseline, then again at 3 and 6 months post hearing aid intervention. I had sole responsibility for processing and analysis of the behavioural and objective measures data.

Chapter 2 introduces the underpinning concepts, theories and methods which are central to this thesis. Tinnitus is described in terms of its epidemiology and proposed neural mechanisms. Functional MRI is broadly described in the context of auditory brain research before introducing the two key experimental paradigms which feature in this work; resting-state and sound-evoked fMRI. Analytical approaches and clinical applications of both are detailed.

Chapter 3 describes the unpublished clinical trial data on which this thesis is entirely based. The original study design and

participant flow for the behavioural and neuroimaging data utilised in the subsequent chapters are provided.

Chapter 4 presents the first of four studies conducted as part of this PhD studentship. This first study used the behavioural questionnaire-based outcome data to investigate the longitudinal effects of hearing aid amplification on tinnitus handicap over a 6 month study period. The influence of perceived tinnitus pitch on tinnitus handicap in hearing aid users was also evaluated. In comparison to age-matched controls, individuals who received a hearing aid showed a small but statistically significant reduction in tinnitus handicap in the 6 month period post-intervention. Dominant tinnitus pitch did not influence this reduction in handicap amongst hearing aid users.

The three fMRI studies featured in Chapters 5-7 use the same group of tinnitus participants and no tinnitus 'controls'. This subset of participants was retrospectively selected from the unpublished clinical trial data set described in Chapter 3. This allowed me to carefully match both groups on a number of important demographic, psychological and audiological characteristics thus reducing the risk of confounding variables. These characteristics are detailed fully in Chapter 5.

In Chapter 5, I present a resting-state fMRI study which investigates auditory network activity in individuals with and

without chronic tinnitus. Methods of independent component analysis and region of interest analysis from a previously published pilot study were replicated in an attempt to consolidate early findings in this newly emerging area of tinnitus research. Contrary to previous literature, baseline measures of resting-state auditory network activity did not differ between tinnitus participants and controls.

Based on the findings of the first two behavioural and neuroimaging studies; which show only a small reduction in tinnitus handicap following hearing aid intervention and a lack of baseline between-group neurophysiological differences in auditory brain regions, no further longitudinal investigation of treatment-related change was undertaken. Instead, my attention was shifted towards the investigation of the limbic system and its reported involvement in tinnitus.

Chapter 6 describes a follow-up analysis using the same resting-state data featured in chapter 5. This study applied a data-driven Bayesian approach known as Patel's conditional dependence measures to determine both strength and directionality of neural network connectivity between auditory and limbic brain regions.

Chapter 7 presents the final study which targets the sound-evoked fMRI data. Here, we used emotionally evocative soundscapes to investigate potential differences in amygdala

activation in individuals with and without chronic tinnitus. To enhance detectability of subcortical structures such as the amygdala, we applied a novel double-echo imaging sequence. We found a strong modulatory effect of emotional valence on the amygdala's response in a smooth U-shaped manner. This pattern of activation was reduced in individuals with tinnitus.

Chapter 8 summarises all four studies. Challenges of this research area are discussed and recommendations for future fMRI tinnitus studies are proposed.

During my PhD studies I was also involved in an industry-funded feasibility study in which the Oticon Alta hearing aid with tinnitus sound generator was evaluated for feasibility, usability and acceptability. As this study was not part of the original thesis dataset, the submitted manuscript is presented separately in Appendix A.

1.2 AIMS OF THESIS

The research aims of the original clinical trial were primarily focussed on investigating the benefits of different sound and psychological-based tinnitus intervention strategies (see section 3.1.2. original research questions). In addition to this, we devised other research questions to better reflect the broader scope of this

thesis as well as utilise all data domains. Our research questions were as follows:

1) How effective is amplification for hearing loss in alleviating tinnitus handicap?
2) Does perceived tinnitus pitch affect hearing aid efficacy in the management of tinnitus?
3) Does chronic tinnitus reliably alter patterns of resting-state auditory network activity?
4) Is the amygdala engaged with the auditory network in chronic tinnitus patients during rest?
5) Does the amygdala respond differently to emotionally evocative sound in chronic tinnitus patients?

Questions 1 and 2 are addressed in chapter 4, questions 3, 4 and 5 are addressed respectively in chapters 5, 6 and 7.

2 INTRODUCTION

2.1 DEFINING TINNITUS

In the UK, around 10-15 % of the general population will experience tinnitus, with an estimated 1-3% reporting a detrimental impact on their quality of life (Davis and El Rafaie, 2000). The prevalence of tinnitus is reported to be higher in males, and increases with advancing age (Axelsson and Ringdahl, 1989; Lockwood et al, 2002, McCormack et al. 2014). Tinnitus comes from the Latin term "tinnire" which means "to ring". Appearing in early written medical records, the 1693 edition of Blanchard's Physician's Dictionary describes tinnitus as "a certain buzzing or tingling in the ears". However, a more exhaustive description of tinnitus comes from Eggermont and Roberts (2004) who define tinnitus as "an auditory phantom sensation experienced when no external sound source is present". This tinnitus definition makes no attempt to describe the type or source of sound that the individual may experience, in recognition of its heterogeneous nature.

The perceptual characteristics of tinnitus can vary significantly from one person to the next. It may be perceived centrally, in one or both ears, it may be constant or intermittent and can vary in both pitch and loudness. Common sound descriptors for tinnitus include 'ringing', 'humming', 'buzzing' or

'whistling'. Tinnitus may be broadly classified into two groups depending on etiology; objective and subjective. Objective tinnitus describes an atypical circumstance whereby a person's tinnitus has a physical, traceable sound source originating from within the body. This is sometimes called a somatosound. These sound sources are often pathological in nature with a vascular or muscular origin. Pulsatile blood flow from vascular tumours within or adjacent to the middle or inner ear may be audible to the affected individual (Sonmez et al. 2007). Involuntary contractions of the middle ear muscles known as myoclonus may also be heard as a 'beating' type sound (Howsam et al. 2005). In the case of objective tinnitus, Lanting et al. (2009) describe it as the normal perception of an abnormal sound source. In contrast, subjective tinnitus is far more common and is characterised by the fact that there is no apparent physical sound source. Chronic subjective tinnitus is most frequently featured in tinnitus research and is the main focus of this thesis.

Tinnitus is often referred to as a symptom rather than a disease (Passi et al. 2008). Given its complexity and variability between and even within individuals, it is not surprising that most cases of tinnitus cannot be ascribed to a specific etiology (Henry et al. 2005). However, there are a number of otological diseases and disorders of the auditory system which have been reported to

cause or accompany the tinnitus percept. Common examples include Ménière's disease and retrocochlear tumours such as vestibular schwannomas (Minor et al. 2004; Gimsing, 2009). Although various common co-morbid predictors of tinnitus have been presented in the literature, it is important to recognise the distinction between what may cause tinnitus and what mechanisms may be responsible for its perpetuation. According to the UK National Study of Hearing, the presence of high frequency hearing impairment (which is also common in age-related hearing loss), excessive noise exposure and a history of ear discharge were all dominant factors in predicting the occurrence of prolonged spontaneous tinnitus (Davis, 1995). In a more recent large scale study of over 2000 tinnitus patients, Henry et al. (2005) reported that prolonged noise exposure and/or trauma were also the most common associating factors, accounting for 22% of cases. This was followed by head and neck injury (17%), drugs and other medical conditions (13%) and infections and neck illness (10%). Remaining patients were unable to identify a cause for their tinnitus, as is the case for many individuals. Perhaps considered to a lesser extent, medications are also frequently associated with temporary or chronic tinnitus. According to DiSorga (2001), tinnitus is listed as a side effect in over 300 prescription and over-the-counter drugs. However, as Cianfrone et al. (2011) point out in

their review of pharmacological drugs inducing ototoxicity, the effects of such drugs depend on many pharmacological and patient factors including dosage, pharmaco-kinetic interactions, body size, metabolism and genetic predispositions. Some people possess the ability to modulate their tinnitus pitch or loudness through various somatic movements such as jaw clenching or changing lateral gaze position (Abel and Levine, 2004; Kaltenbach, 2011). This would suggest input via certain somatosensory modalities may influence neural activity in the auditory system. Although convergence of somatosensory and auditory neural inputs occur at several levels of the auditory system, the dorsal cochlear nucleus is thought to be the most likely site (Shore et al. 2008).

Of the many people who experience tinnitus, not all may find it sufficiently bothersome to warrant seeking medical help. For some it may be of no concern, others may be mildly disturbed by it and in extreme cases some individuals may regard the percept as severely distressing, having a profound impact on quality of life (Vanneste et al. 2010). This can lead to stress, anxiety, depression, insomnia and concentration deficits (Halford & Anderson, 1991; Dobie, 2003; Cronlein et al. 2007; Hallam et al. 2004). With its high prevalence and potentially devastating impact on a person's psychological wellbeing, the demand for an effective clinical treatment of tinnitus is highly prioritised. However, at

present there is no universal cure or any licensed drugs specifically tailored for alleviating the tinnitus percept. Despite first appearing in medical records many centuries ago, our knowledge of tinnitus as a recognised disorder is still limited in terms of its underlying neural mechanisms and causes. Reasons for this may be down to its heterogeneous nature and the possibility that tinnitus may be born out of multiple etiologies. Given this level of complexity and heterogeneity, it is conceivable that no single theory of tinnitus will ever be able to adequately explain its occurrence.

2.2 MECHANISMS OF TINNITUS

2.2.1 From animal studies to human models of tinnitus

Several models exist that attempt to explain the neural substrates of tinnitus in humans. These models have largely been informed through behavioural and electrophysiological animal studies. Animal models of tinnitus often seek to induce tinnitus through ototoxic drugs such as salicylates or excessive noise exposure. These will cause sufficient cochlear trauma. Following this, psychoacoustic characteristics of the tinnitus percept can then be measured through behavioural paradigms such as the gap detection method (Ison, 1982; Turner and Brozoski, 2006). Such methods require conditioning the animal to produce a particular behavioural response when they detect a gap in a presented sound

stimulus prior to tinnitus induction. In addition to this, *in vivo* and *in vitro* electrophysiological recordings can be obtained providing spatial and temporal signal information at a neuronal level. Since the introduction of animal models of tinnitus in the 1980's (Jastreboff and Sasaki, 1986), a great deal of valuable and converging information has been gathered. This emergence has served to catalyse and inform our understanding of tinnitus mechanisms in humans today.

Before going on to highlight such proposed mechanisms of tinnitus in humans, one should consider the potential limitations of applying theory from animal models to human models of tinnitus. Firstly and perhaps most obviously, whilst obtaining basic estimates of tinnitus pitch and loudness in animals are supposedly possible through behavioural methods (Jastreboff and Sasaki, 1994), humans are clearly able to communicate their own perceptions in much greater detail (Adjamian et al. 2009). A second consideration relates to the nature in which tinnitus is induced in animals. Commonly through noise trauma, ototoxic drugs or anaesthetics, these methods of induction may manifest themselves in unique and complex ways, which may prove to be incomparable to the common etiological causes observed in humans. A final consideration addresses the differences in methodological techniques adopted by animal and human studies.

Whereas animal studies will use more invasive methods of recording neuronal activity from single or multiple neurons, this rarely occurs in human studies which often utilise non-invasive methods such as electroencephalography (EEG) or functional Magnetic Resonance Imaging (fMRI). These measure neuronal activity on a macroscopic level. Consequently, it is vital when interpreting the findings of animal and human tinnitus studies to recognise the use of different techniques, which may in turn, target different aspects of tinnitus-related neuronal activity (Eggermont, 2014).

Although no single theory has been unequivocally proven to account for all tinnitus forms, the current consensus would be that tinnitus may arise through changes in neuronal firing patterns in the central auditory system following damage to peripheral auditory structures (Eggermont and Roberts, 2004; Roberts et al. 2010). This peripheral damage is commonly expressed as a hearing loss, which in turn, is often associated with tinnitus (Eggermont and Roberts, 2004). This frequent observation in co-morbidity between tinnitus and hearing loss formed the basic idea that peripheral auditory damage may be responsible for the tinnitus origin. Despite this, several studies have suggested that tinnitus may exist in individuals with no apparent hearing loss (Stouffer and Tyler, 1990; Jastreboff and Jastreboff, 2003).

However, detection of a hearing loss is not always sensitive through standard clinical procedures such as pure tone audiometry (Fabijańska et al. 2012). House and Brackmann (1981) found that even after sectioning the eighth auditory nerve in some tinnitus patients, tinnitus was still present. This suggests that although peripheral damage may be responsible for initial tinnitus onset, central mechanisms must facilitate in its continued presence.

A contemporary and summative model of tinnitus which draws on evidence from both animal and human tinnitus studies has been offered by Kaltenbach (2011). This proposes that tinnitus may be triggered by damage to the auditory periphery, often cochlear hair cell damage caused through noise exposure, aging or ototoxicity (Heffner and Harrington, 2002; Caspary et al. 2008; Guitton et al. 2003). In turn, this may decrease auditory nerve activity leading to 'plastic changes' in higher central auditory regions (Salvi et al. 2000). More specifically, this reduction in afferent input shifts the balance between excitatory and inhibitory activity resulting in a decline in inhibition and an increase in hyper-excitatory activity within the central auditory system. It is this change in spontaneous activity following sensory deafferentation that is suggested to be the neural correlate of tinnitus. A number of neural mechanisms have been identified from the animal literature. These include (i) changes in stochastic spontaneous firing rate

within the central auditory system during rest (Norena and Eggermont, 2003), (ii) changes in the temporal pattern of spontaneous activity; either as burst firing in single neurons or synchronous firing in groups of neurons, known as neural synchrony (Norena and Eggermont, 2003; Seki and Eggermont, 2003) and (iii) reorganisation of the cortical tonotopic map (Muhlnickel et al. 1998; Eggermont and Komiya, 2000; Norena et al. 2003). However, a recent fMRI study in humans with tinnitus did conclude that tonotopic map reorganisation is not necessary for tinnitus to occur (Langers et al. 2014). But, as Eggermont (2014) points out this study did use participants with clinically normal hearing (< 20dB thresholds up to 8 kHz). Figure 2.1. displays a normal and reorganised tonotopic map in the primary auditory cortex of two cats.

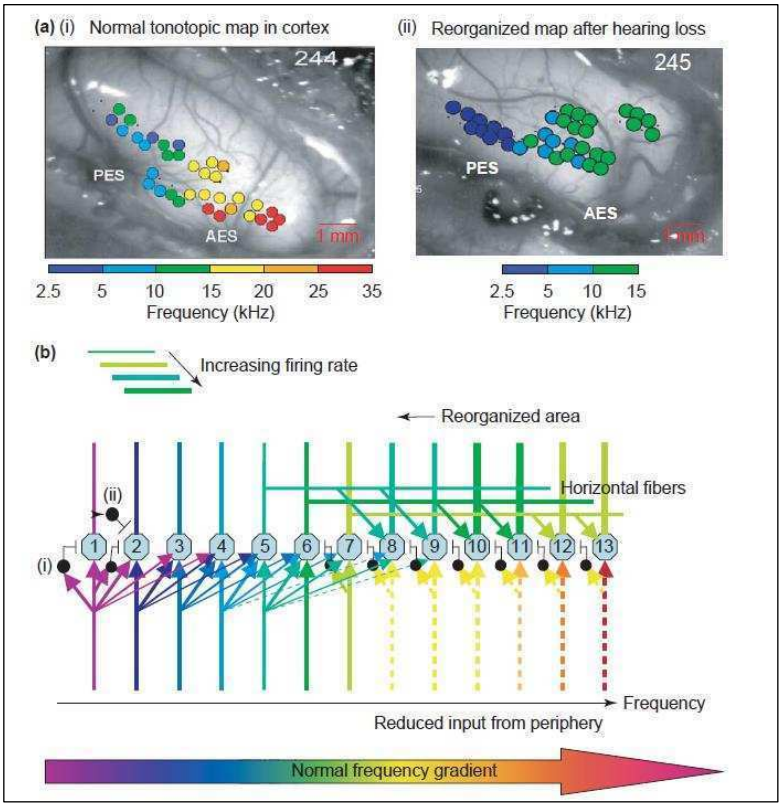


Figure 2.1 Cortical reorganisation of the tonotopic map following noise exposure. Following significant noise exposure, a loss of peripheral input in the lesioned frequency range leads to organisational changes of the cortical neurons. Neurons which correspond to frequencies in the region of the hearing loss become responsive to the frequency tuning of their less affected neighbours. This results in an over-representation of the lesion edge frequency. Taken from Eggermont and Roberts (2004).

Given the presented evidence for numerous classifications of neural activity in the animal literature, it is possible that multiple mechanisms may be responsible for the tinnitus percept. Crucial questions yet to be answered relate to whether these mechanisms work independently from one another or combine in complex ways

to form specific types of tinnitus. Not only this, more is needed to be known about where such activity takes place within the brain and how this may be linked to other non-auditory components of tinnitus such as emotion and attention. After all, if individuals did not perceive tinnitus as being bothersome, there would be little demand for clinical management or the need for further research and ultimately a cure.

2.3 NON-AUDITORY MECHANISMS OF TINNITUS

Interactions with the environment occur constantly within everyday life. These interactions may be presented as various stimuli which in turn are 'sensed' and then 'perceived'. Our interpretation of such stimuli is a subjective process heavily influenced by our previous experiences. The conscious perception of tinnitus is one such example. This section presents two complimentary theories which attempt to explain how and why tinnitus can be attributed to strong emotional and attentional properties.

2.3.1 Neurophysiological model of tinnitus

In 1990, Pawel Jastreboff published a paper entitled "Phantom auditory perception (tinnitus); mechanisms of generation and perception". His proposed neurophysiological model of tinnitus introduced the contribution of the autonomic nervous system and

limbic system in tinnitus (see Figure 2.2.). The model attempts to explain how the perception of tinnitus can vary between individuals.

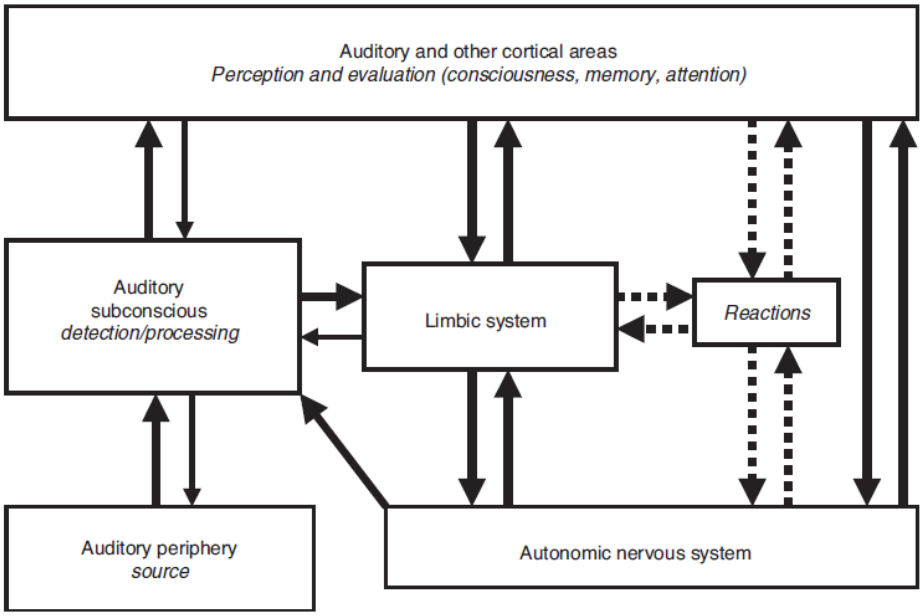


Figure 2.2. The neurophysiological model of tinnitus; interactions between major anatomical sites are indicated. Taken from Jastreboff (1990).

When a new sound is presented, it ascends from the peripheral auditory system to higher auditory cortical areas where it is then evaluated and perceived. Its relevance is compared to other signals stored in memory then appropriately "labelled" as being positive, negative or neutral. As a new signal, it evokes reaction and activation of both the limbic and autonomic systems. If the signal was neutrally labelled then a future representation of the same

signal will not activate such systems. Thus our attention will not be attracted and we will not be aware of its presence. In this instance, we are said to have 'habituated' to the signal.

In the case of tinnitus, which for some people may be bothersome, annoying or perhaps associated with a given pathology, a negative association may be assigned. In this instance, rather than subconsciously filtering out the signal upon its next occurrence, instead the limbic and autonomic systems are activated inducing the fight or flight mechanism. This reaction brings about feelings of annoyance or fear and further enhances our awareness of the signal. Subsequent activations of these systems reinforce the conditioned reflex loop and can often be described as "the vicious circle".

This idea that sound stimuli (be they phantom or physical) attributed with strong emotional meaning can prompt autonomic involvement ultimately leading to the conscious awareness of sound has been adopted by De Ridder and his team in a more recent tinnitus model.

2.3.2 Multiple parallel overlapping brain networks

De Ridder et al. (2011) present a theoretical model of tinnitus which involves the integration of multiple brain networks including auditory, memory, distress, perception and salience. Interestingly, this model was conceived with a dual application in mind: as a model of tinnitus and also phantom limb pain, a condition which is believed to share a number of parallels to tinnitus.

Supporting the previous work of Jastreboff (1990) and others, this model suggests that following peripheral deafferentation, neuroplastic changes take place leading to activity within the auditory cortex. However, at this stage there is not yet a conscious perception of the tinnitus sound. This occurs when the auditory activity becomes functionally connected to the perceptual network (anterior cingulate cortex, precuneus, frontal and parietal cortices). Salience to the tinnitus is reflected through activation of the anterior cingulate cortex and anterior insula. Tinnitus can become associated with distress as a consequence of a constant learning process. This is reflected by the presence of a nonspecific distress network consisting of the anterior cingulate cortex, anterior insula, and amygdala. The continued presence of the tinnitus percept is due to memory mechanisms involving the parahippocampal area, amygdala, and hippocampus. These

networks are mapped out onto a brain sliced in the sagittal plane to reveal medial and lateral viewpoints (see Figure 2.3.).

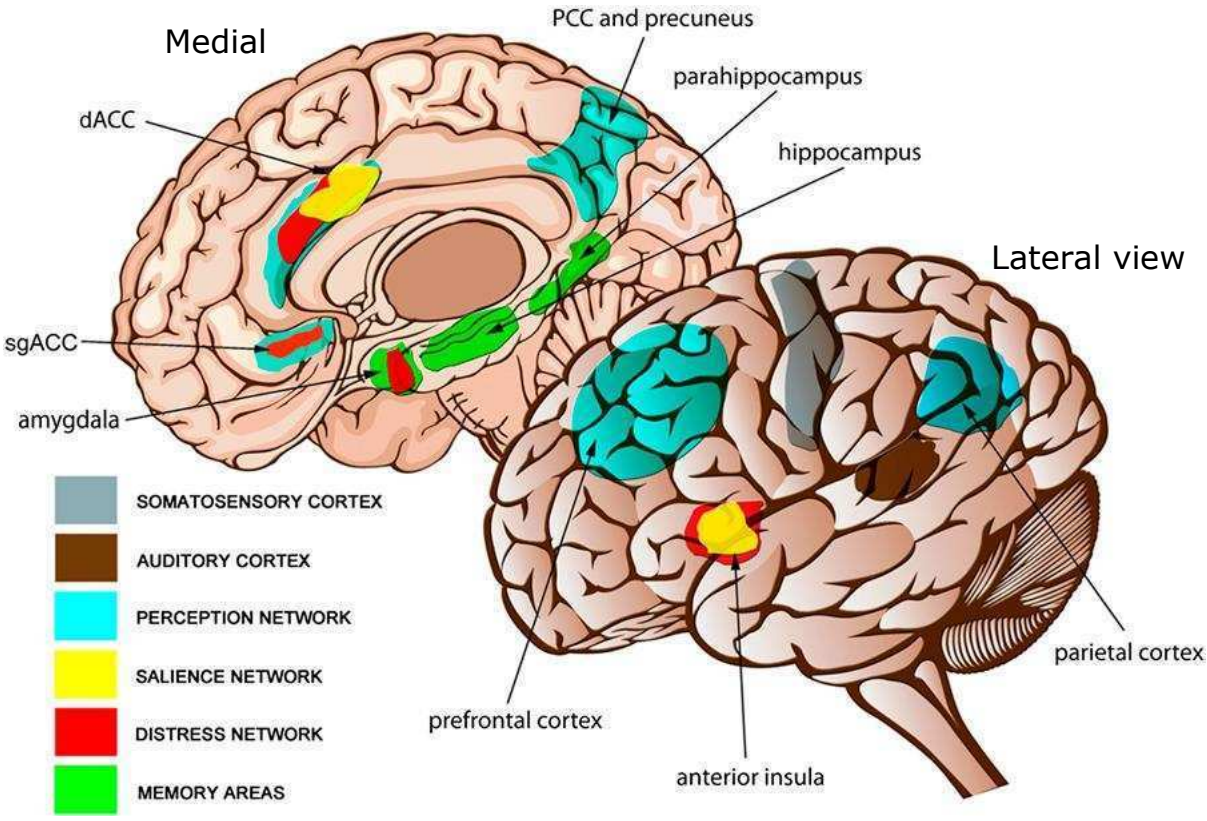


Figure 2.3 Multiple parallel overlapping brain networks. Taken from De Ridder et al. (2011).

The central theme of this theory suggests that tinnitus is born out of the perceptual states of continuous learning, where in the absence of an external input (due to sensory deafferentation), the tinnitus percept is reinforced and strongly linked with negative emotional associations which are continuously updated. This potential involvement of multiple parallel overlapping brain

networks in the perception and persistence of tinnitus offers new research avenues to explore. Detection and investigation of these various networks will undoubtedly involve the use of connectivity measures applied through fMRI, a method which may prove instrumental in advancing our knowledge in this area.

2.4 FUNCTIONAL MAGNETIC RESONANCE IMAGING

2.4.1 Introduction

Developed in the early 1990s, fMRI is a complex method of neuroimaging that has vastly facilitated the study of *in vivo* brain function (Ogawa et al., 1990; Kwong et al., 1992; Bandetti et al., 1992; Frahm et al., 1992; Ogawa et al., 1992). Extending from the use of MRI which enables the capture of high resolution anatomical images, fMRI is sensitive to haemodynamic changes arising from underlying neural activity and thus provides information about biological and cognitive brain function. Given its non-invasive nature and ability to deliver images with high spatial resolution, fMRI research has become increasingly popular over the last two decades replacing less favourable methods such as Positron Emission Tomography (PET) which rely on the use of exogenous radioactive contrast agents which are often administered intravenously and may be harmful to humans.

2.4.2 What is being measured in fMRI?

Functional MRI takes advantage of two important details; increased blood flow in response to metabolically active neurons and the different magnetic properties of the blood depending on its state of oxygenation.

2.4.3 The BOLD signal

Blood contains the oxygen carrier haemoglobin which has a ferrous core, naturally colouring it red. The iron contained within the haemoglobin protein is magnetically sensitive. When the haemoglobin binds with oxygen its magnetic susceptibility is poor, having little effect on the local magnetic field. However, when in a state of deoxygenation, haemoglobin is paramagnetic meaning that the local magnetic field is increased in the presence of an applied external magnetic field (Weisskoff and Kiihne, 1992). These small haemodynamic changes can be detected in image brightness on the MRI scan. On a T2* weighted image (which typically uses longer echo times and repetition time), pixels containing mainly oxygenated haemoglobin will appear brighter than pixels containing deoxygenated haemoglobin. This is used as a contrast mechanism in fMRI and may be termed the blood oxygenation level dependant (BOLD) contrast (Ogawa et al. 1990).

Changes in the BOLD signal in response to underlying neuronal activity can to some extent be illustrated by the haemodynamic response function (refer to Figure 2.4.). However this relationship is complex and as of yet, has not been clearly quantified.

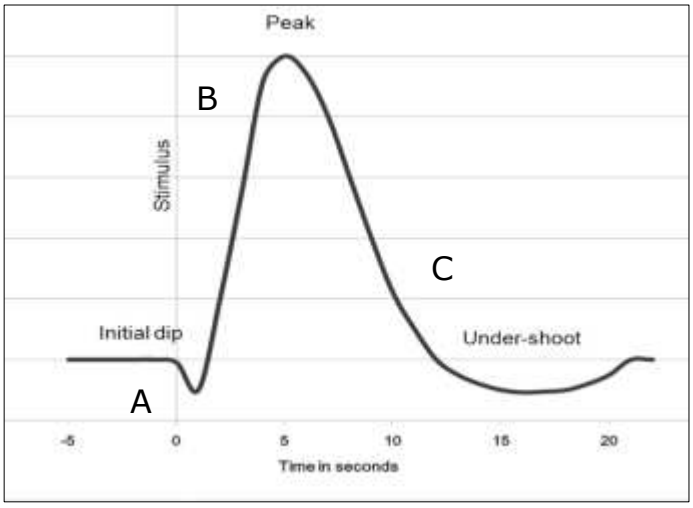


Figure 2.4. Haemodynamic response function. A; initial dip, B; rise and peak and C; fall and undershoot.

When neurons within the brain become active, say in response to external stimuli or internal cognitive processes, blood flow is increased in that area. This increase in local blood flow is required to meet the metabolic demand produced by synaptic activity. During neuronal activity, oxygen will be removed from the blood thereby increasing the concentration of deoxyhaemoglobin. This causes a small initial dip in the intensity of the MR image contrast (see Figure 2.4. A). In response to this, local blood flow

and volume increases, delivering blood that is rich in oxyhaemoglobin to the metabolically active neurons. This over-compensating response peaks approximately six seconds after neural activity has occurred and results in a large increase in MR image intensity (Figure 2.4. B). Buxton and Frank (1997) suggested that this overshoot was biologically necessary in order to deliver sufficient oxygen levels to the mitochondria. 'Activations' measured in most fMRI experiments arise from targeting this specific part of the BOLD signal. The signal then falls back towards its baseline as blood flow and volume return to normal, this is accompanied by a large undershoot (Figure 2.4 C). In summary, fMRI is sensitive to changes in T2* weighted MR image contrast resulting from haemodynamic changes or the 'BOLD signal'. This is brought about by metabolically active neurons responding to external stimuli or internal cognition.

2.4.4 What is not being measured in fMRI?

As previously mentioned, the relationship between the BOLD signal and neuronal activity is not well defined, and given that only the former is actually being measured, one should be mindful of this when using fMRI for investigation of cognitive brain function. Functional MRI is an indirect measure of neuronal activity (Lanting

et al. 2009). There are several contributing factors which may explain why this is the case.

Firstly, the temporal lag in peak BOLD signal activation (often several seconds) makes the method less sensitive to detect an exact onset of neural activation (often a few milliseconds). Also, this temporal lag in peak BOLD signal is known to vary across tissue types, making comparison and interpretation of BOLD signal timing differences between regions potentially more difficult (Hall et al. 2002; Chang et al. 2008). A further consideration is the vascular source from which the BOLD signal is derived. Peak BOLD activity could be some distance from the true site of activation (Kim et al., 1994). Not only this, active neurons may be masked by larger signals coming from adjacent major draining blood vessels. This spatial conundrum may be prevented if an anatomical map of vein location is used when interpreting the origins of peak signal activation (Clare, 1997). Finally, some thought should be given to the neuronal signal that precipitates such fMRI activation. Only mass neuronal activity arising from increases in both excitatory and inhibitory synaptic activity rather than spiking activity is sufficient enough in magnitude to evoke a detectable fMRI signal (Li et al. 2009; Logothetis, 2008). Therefore, although cognitive processes may be taking place, not all will be manifested into a detectable signal.

Given both the physical and biological constraints of these aforementioned factors, it should not be assumed that neuronal activity and the resulting fMRI signal share direct proportionality. Despite this, fMRI offers the means to obtain information regarding cognitive brain function with high spatial precision.

2.4.5 Contraindications of human MRI

The underlying physics of MRI are fundamentally based on the application of an extremely strong static magnetic field. As a consequence, metallic implantable devices such as pacemakers, medical prostheses, hearing aids or cochlear implants have long been known to be incompatible with the scanning environment. The strength and rapid switching of the applied magnetic field may affect the implantable device in a number of ways which include; heating of the device, dislocation and loss of function (Hsu et al. 2012). Some clinical studies have demonstrated no untoward complications in patients with certain implantable devices undergoing MRI (Roguin et al. 2004; Martin et al. 2004) albeit at lower field strengths (1.5 tesla for example). However, this practice is not risk free and MRI is still considered largely unsuitable as a method of investigation where patients with implantable devices are concerned.

2.5 CONNECTIVITY AND RESTING-STATE NETWORKS

2.5.1 Introduction

The human brain is a complex network. Even when in a so called 'state of rest' the brain is still very much active, constantly processing and exchanging information between spatially distributed but functionally connected anatomical regions. In recent years there has been a growing interest in these patterns of brain activity during rest. Resting-state fMRI has been able to facilitate such interest, providing innovative new ways of characterising these intrinsic networks of brain activity. Moreover, these measures have given insight into the strength and direction of functionally connected brain regions and offer information on the overall functional organisation of the brain.

2.5.2 Connectivity

The relationship of information exchange between different anatomical brain regions can be referred to as 'functional connectivity'. Friston et al. (1993) define functional connectivity as the "temporal correlations between spatially remote neurophysiological events". In the context of fMRI, functional connectivity may be quantified by first measuring the low frequency (~ 0.01 - 0.1 Hz) spontaneous fluctuations in the haemodynamic BOLD signals derived from different brain regions

(Rogers et al. 2010). The level of co-activation between each BOLD signal time series is then statistically compared. Refer to Figure 2.5. for a schematic illustration.

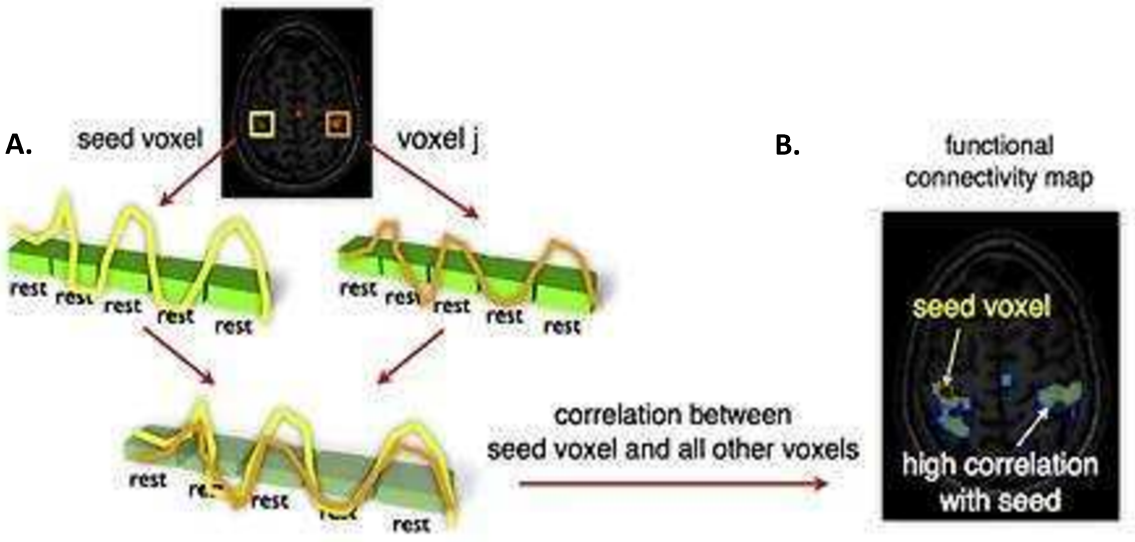


Figure 2.5. Schematic diagram illustrating two regions which are functionally connected (A). Extracted BOLD signal time-series from each region showing high temporal correlations are projected onto a functional connectivity map (B). Adapted from; van den Heuvel and Hulshoff (2010).

It is important to note that functional connectivity is only concerned with temporal correlations between neuronal events occurring in spatially independent brain regions. As Buxton points out (2016), these correlation measures of BOLD signals pay no attention to the BOLD signal amplitude itself. To quantify this,

other methods such as arterial spin labelling are needed (Dai et al. 2016). Furthermore, functional connectivity measures make no statements regarding the direction of the relationship or how one region may influence another. Directional modelling is known as effective connectivity and relies on a mechanistic model which can explain data causation. Effective connectivity describes the causal influences that one region may exert over another (Friston, 1994; Friston et al. 2014). When considering how one region may be connected to another, it is important to address the types of interactions which can be present (see Figure 2.6.).

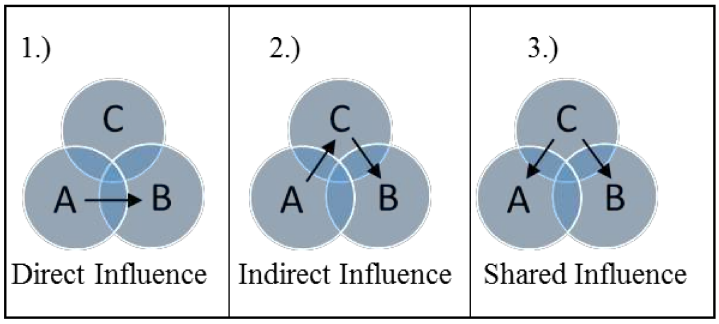


Figure 2.6. Three different types of connectivity relationships. In the direct influence scenario (Figure 2.6. panel 1), there is a direct causal influence between regions A and B. In the indirect influence scenario (Figure 2.6. panel 2), region A has an indirect relationship with region B via a third mediating region C. Lastly, the shared influence scenario (Figure 2.6. panel 3) diagram refers to two regions with a shared common input. Here regions A and B may not even be related other than through their common input source C. Given these possibilities,

selection and interpretation of specific methods of connectivity analyses should be handled with care.

2.5.3 Resting-state networks

Patterns of spatially independent, temporally correlated signals have since been termed 'resting-state networks' and are thought to reflect functional systems supporting core perceptual and cognitive processes (Cole et al. 2010; Lee at al. 2013). Biswal et al. (1995) were the first group to identify these coherent blood oxygen level dependent fluctuations using resting-state fMRI. They were able to demonstrate positive correlations between spontaneous BOLD signals in the left and right somatomotor cortices. However, this viewpoint was not always shared by the neuroscience community. Even now there is on-going debate regarding the true origin of the resting-state BOLD signal. Some studies have suggested that the BOLD signals may arise from respiratory or myogenic physiological processes (Birn et al. 2006; Chang et al. 2009). Contradictory to this, Cordes et al. (2000; 2001) report that BOLD signal oscillations are separable to both respiratory (0.1-0.5 Hz) and cardiac oscillations (0.6-1.2 Hz) which tend to be higher in frequency. Further support that BOLD signals have a neuronal origin stems from their physical origin within areas of cortical gray matter that have known functional relevance (Damoiseaux et al. 2006). Several resting-state networks have now been identified (refer to

Figure 2.7.) including visual, attention, default mode and auditory (Beckmann et al. 2005; Damoiseaux et al. 2006; Mantini et al. 2007).

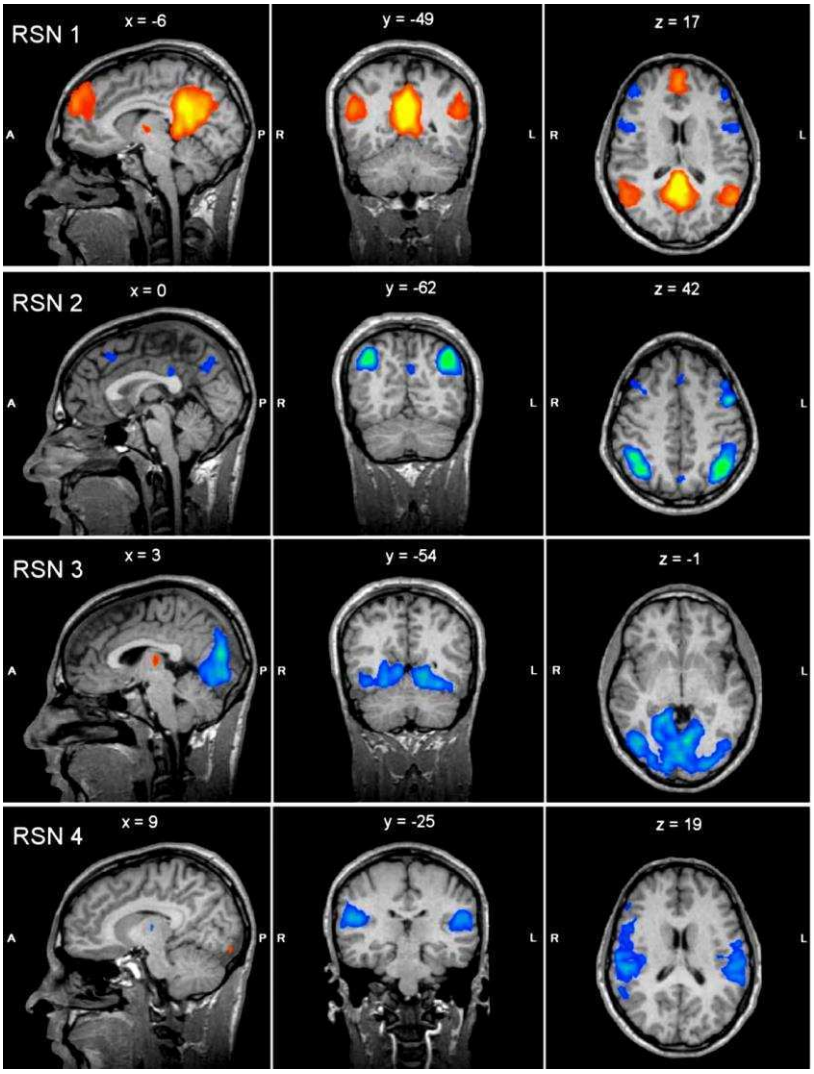


Figure 2.7. Four common resting-state networks (RSN). RSN 1 default mode network; RSN 2 dorsal attention network; RSN 3 visual network; and RSN 4 auditory network. Figure taken from Mantini et al. 2007.

For example, the Default Mode Network (DMN) has been identified as a group of anatomically separate but functionally connected brain regions which are believed to be linked with self-referential thought, reflection and attending to internal and external stimuli (Raichle et al. 2001). The DMN is found to be active in the absence of task-related, goal-directed behaviours. Conversely, this default mode activity is suspended when the individual is engaged in a task, leading to the notion that the default mode network exists to support internally orientated mental processes (Harrison et al. 2008). McKiernan and colleagues (2003) found that by increasing the difficulty of a given cognitive task they were able to observe a larger deactivation in DMN activity. The main brain regions involved in the DMN are the posterior cingulate cortex, precuneus, inferior parietal cortices and the dorsal and ventral areas of the medial frontal cortex (see Figure 2.8.) (Harrison et al. 2008).

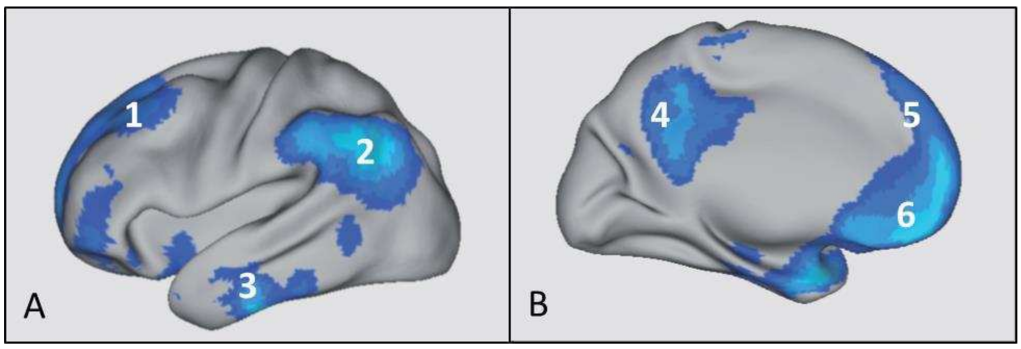


Figure 2.8 Default mode network displayed onto a brain sliced in the sagittal plane to reveal lateral (A) and medial (B) viewpoints. 1 =

prefrontal cortex, 2 = inferior parietal lobe, 3 = lateral temporal cortex, 4 = posterior cingulate, 5 = dorsal medial prefrontal cortex, 6 = netral medial prefrontal cortex. Adapted from Buckner (2013).

Resting-state networks are generally reported to show reliable and consistent patterns of functional connectivity (Zhang et al., 2008). Several studies have looked at the effects of aging on connectivity and resting-state networks. Age related reductions in long range functional connectivity in the default mode network and dorsal attention network have been reported (Wu et al. 2011; Tomasi & Volkow, 2012). However, given the various and complex neurological, chemical and vascular changes which take place in the brain as we age, it is difficult to infer an exact causal link. Given the presence of these coherent and robust resting-state networks in healthy individuals, there has been great interest in investigating such networks in individuals with psychological disorder and disease. This will be discussed further in the following section.

2.5.4 Clinical Applications

The exploration of resting-state networks has been applied to clinical populations as a potential biomarker for detecting

underlying connectivity differences in those with chronic neurological and psychological disorder (Lee et al. 2013). Examples include investigation of Alzheimer's disease (Greicius et al. 2004; Dennis and Thompson, 2014), depression (Veer et al. 2010) and schizophrenia (Garrity et al. 2007). In 2007, Garrity et al. investigated the differences in default mode network activity in schizophrenic patients and healthy age-matched controls using independent component analysis. Significant spatial and temporal aberrant activity was found in the default mode networks of the patient group. Figure 2.9. presents a schematic diagram of the DMN.

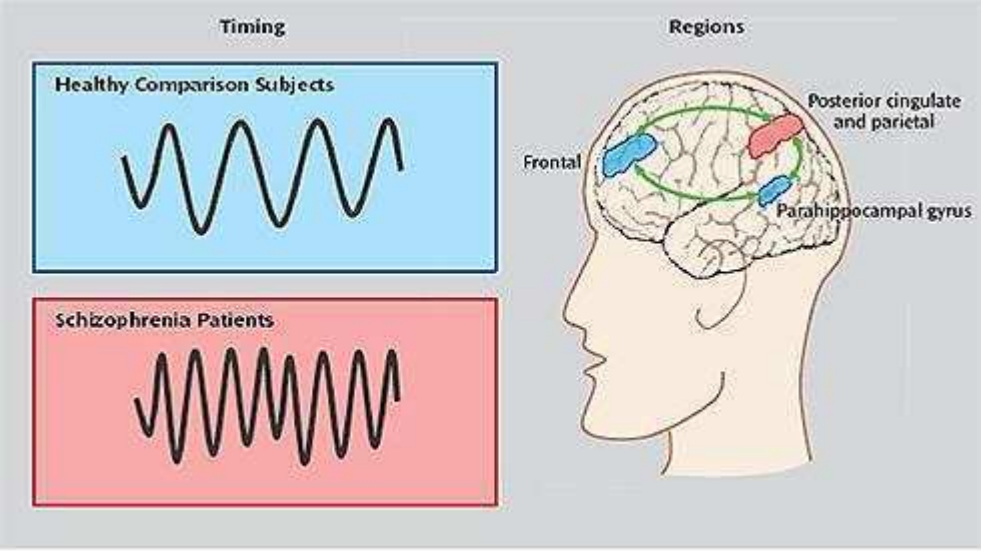


Figure 2.9. Schematic diagram of the DMN (right). Temporal BOLD oscillatory activity differences between schizophrenic patients and healthy controls are also present (left). Diagram taken from Pearlson, (2007).

Spatial network differences were found in the frontal, anterior cingulate and parahippocampal gyri. The DMN of the healthy control group correlated more significantly to the DMN spatial template than that of the patient group, perhaps indicating greater variability in the patient group. The patient group also had significantly more power in high frequency oscillations (0.08 - 0.24 Hz) as compared to the controls that had more power in low frequency oscillations (0.03 Hz). The authors suggested that this result may indicate a loss of temporal synchrony either within the DMN brain regions or between the DMN and other brain regions.

Abnormal connectivity patterns have also been found in patients suffering from depression (Veer et al. 2010). Resting-state independent component analysis performed on a group of severely depressed non-medicated individuals found evidence for major depression-related decreases in functional connectivity in three resting-state networks. Decreased connectivity was found bilaterally in the amygdala and left frontal pole and bilateral lingual gyrus. These decreases were putatively thought to reflect emotional, attentional and cognitive deficiencies as commonly found in patients with depression.

Being able to understand the dynamic interactions between different neural networks in healthy and diseased states is vital. Knowing which networks are active, be it *hyper* or *hypo*, and how

they interact with other networks in certain disease states may help inform future treatment strategies or be used as biomarkers when measuring the effects of new treatments (Narayanan, 2010). On a practical level, the investigation of resting-state networks offers a very simplistic experimental paradigm where the participant is required only to lie in wakeful rest within the scanner, usually with eyes closed. This makes resting-state fMRI an attractive method particularly for individuals with cognitively debilitating diseases or psychological disorders whereby performing certain tasks may not be possible. So far, only a limited number of studies exist which investigate resting-state networks and connectivity differences using fMRI in participants with tinnitus. A critical review of these studies will be given in Chapter 5.

2.6 USING FMRI TO MEASURE RESTING-STATE CONNECTIVITY

There are several analytical approaches which serve to explore resting-state brain connectivity. These can be broadly categorised as hypothesis-driven and data-driven methods (Rogers et al. 2007). Hypothesis-driven approaches require, as the name suggests, prior knowledge to highlight a particular brain region of interest (ROI) or 'seed' as they are often termed. Coversely, data-driven approaches are unbiased in that they do not make any *a*

priori assumptions about the data and attempt to map whole brain functional connectivity. These approaches have also been respectively referred to as 'model-dependent' and 'model-free' methods (van den Heuvel and Hulshoff, 2010).

2.6.1 Hypothesis-driven methods

Hypothesis-driven methods of connectivity analysis such as seed-based correlation analysis (SCA) or ROI analysis are considered to be relatively simple to perform and interpret. In SCA, *a priori* regions of interest or seeds are chosen, their fluctuating resting-state time-series are then extracted and correlated against the time-series of all other voxels within the brain resulting in a functional connectivity map (see Figure 2.5. part B). The functional connectivity map shows which brain regions share strong temporal coherence in resting-state time series with the selected ROI. The chosen region of interest or seed could be an individual voxel, a cluster of voxels or an entire brain region. Regions are often based on the findings of previous anatomical literature or functionally defined using the activation maps of separate localiser experiments. Another common approach is to simply correlate the time-series of several different ROIs (Poldrack, 2007). This approach often relies on strong *a priori* information based on

animal or human neuro-anatomical models and may be termed ROI analysis.

Seed-based correlation analysis is an elegant technique providing simple mapping of brain regions which are most strongly functionally connected with a pre-defined region of interest. However, the main strength of SCA, that is its simplistic rationale, is also in some respects its weakness. Given the near infinite number of neural connections which may take place within the brain at any one time, choosing just one seed region and interpreting its functional relationship with other brain regions results in a large proportion of data going uninvestigated. Another important consideration relates to the size and location of the chosen seed region. As pointed out by Buckner et al. 2008, even small variations in seed selection can result in large variations in SCA results and subsequent interpretations, making comparisons between studies more challenging. Nevertheless, SCA continues to be a popular choice of connectivity analysis amongst researchers offering simple answers to simple questions about the functional connectivity relationships of pre-defined brain regions. The functional connectivity maps generated by SCA are constrained by and relate solely to the number of chosen seed regions. To evaluate whole-brain functional connectivity patterns, data-drive approaches are required.

2.6.2 Data-driven methods

Data-driven methods seek to explore whole-brain functional connectivity patterns without having to define focal seed regions. One such prominent method is independent component analysis (ICA). Originally used in electroencephalography (EEG) data, ICA was first applied to resting-state fMRI data by Kiviniemi et al. (2003). Spatial ICA is a whole-brain method of blind source signal separation analysis which can be used to extract functionally related but spatially independent patterns of brain activity (referred to as components), each with an associated time course and spatial map (Margulies et al. 2010; Calhoun and Adali, 2012). A common analogy used to describe blind source separation would be the ability to separate the voices of different speakers recorded via a single microphone (Calhoun et al. 2001). Apart from discovering spatially independent components, ICA can also be used to extract temporally independent components (temporal ICA). However this method is less preferred as temporal components are orthogonalised, typically leading to a reduced number of observations and thus increasing the possibility of noise contamination (Cole et al. 2010).

Despite not requiring any *a priori* assumptions, ICA does rely on post-analysis experimenter selection of meaningful components, be it through visual inspection or other automated methods. An important advantage that ICA perhaps holds over SCA, is its ability to account for structured artifactual noises e.g. those arising through respiration, within components separate to meaningful resting-state networks (Birn et al. 2008). On the down side, ICA may decompose resting-state networks into further sub-networks, contributing to the production of additional components and making the analysis significantly more difficult to interpret. The adoption of both hypothesis and data-driven approaches in the investigation of brain connectivity has produced vital information about the functional organisation of the brain. In summary, both approaches possess contrasting strengths and weaknesses with neither one being the superior choice. Results from these two approaches have reassuringly been able to provide a high level of overlap that is consistent and complimentary.

2.7 USING FMRI TO MEASURE SOUND-EVOKED ACTIVITY

2.7.1 Challenges associated with auditory fMRI

Functional MRI has been applied across a wide range of research areas, offering information about brain function. This is most

commonly achieved through the purposeful modulation of neural activity using a controlled experimental stimulus; such as a sound clip in the case of auditory research. However, compared with other sensory domains such as vision, the practical application of auditory experimentation within the MRI scanning environment is complicated by a number of technical and anatomical factors. This is further obscured by our targeted demographic of tinnitus patients as will be explained.

Perhaps most obvious, are the interfering effects of the acoustically noisy scanner environment created by the gradient switching during image acquisition. This noise can reach levels of around 110 dB SPL (Hedeen & Edelstein, 1997) and has the ability to mask a participants perceived tinnitus as well as any experimental sound stimuli presented to them in the scanner. Not only can this increase cognitive load, it also changes the nature of the task by making it harder to detect the target stimuli amongst the scanner noise (Ulmer et al. 1998; Hall et al. 2001). Furthermore, the loud scanner noise can activate the auditory system itself (Ulmer et al. 1998; Bandetti et al. 1998; Hall et al. 2000). This may mean that during a typical "on and off" sound block design, the auditory system may still be stimulated by the scanner acoustic noise in baseline periods where no sound stimuli is being delivered. Consequently, this can lead to saturation effects

and difficulties in interpreting stimulus-induced activations versus baseline activations. An additional challenge comes as a consequence of the strong magnetic fields which prohibit the use of magnetic materials in or near the scanner. As a result of this, experimental sound stimuli are often presented through tubes housed within protective ear-defenders. However, the tubing affords resonant properties of its own thus affecting the phase and amplitude of the sound stimulus (Hall et al. 1999). Finally, the small size and variable location of the primary auditory cortex within Heschl's gyrus makes it difficult to identify accurately (Penhune et al. 1996).

Fortunately, several strategies have been developed to address the problems associated with auditory fMRI. These include (i) using "silent" MRI sequences, (ii) attenuating scanner acoustic noise through ear protection, (iii) using a "sparse" temporal imaging sequence. The latter two were applied in the fMRI studies of this current thesis and will now be discussed.

2.7.2 Noise attenuation

Firstly, scanner noise can be passively reduced through the combined use of ear defenders and ear plugs. These can provide up to 50 dB of attenuation dependant on the type of ear defender and specific frequency spectrum created by the scanner itself (Salle et

al. 2003). However, this approach would not allow the optimal presentation of sound stimuli and would therefore be better suited to resting-state and other non-auditory tasks. An alternative method would be active noise cancellation headphones. These can help to further reduce scanner noise by up to an additional 35 dB (Hall et al. 2009). Bullock and colleagues (1998) developed an MR compatible headphone system which can deliver calibrated sounds whilst implementing active noise cancellation of the scanner environment. One important consideration applicable to all noise attenuation methods; be they passive or active, is that they cannot eliminate scanner noise completely. Sound may still reach the cochlea via bone conduction.

2.7.3 Sparse temporal imaging

An alternative approach would be to modify the fMRI acquisition parameters such that scanner noise is separated from the delivery of auditory stimuli; a method referred to as sparse temporal imaging or clustered volume acquisition (Hall et al. 1999; Peelle, 2014). This is achieved by increasing the time in-between scans (repetition time), allowing sound stimuli to be presented in a more favourable acoustic environment without the noise from the gradient switching system. Slice acquisition is then clustered towards the end of the long 'silent' period, taking advantage of lag

between neural stimulation onset and its associated haemodynamic effects. Because of this delayed response (peaking around 4-7 seconds), the proceeding scan still measures activity relating to the stimulus. Figure 2.10. provides a schematic illustration of this approach.

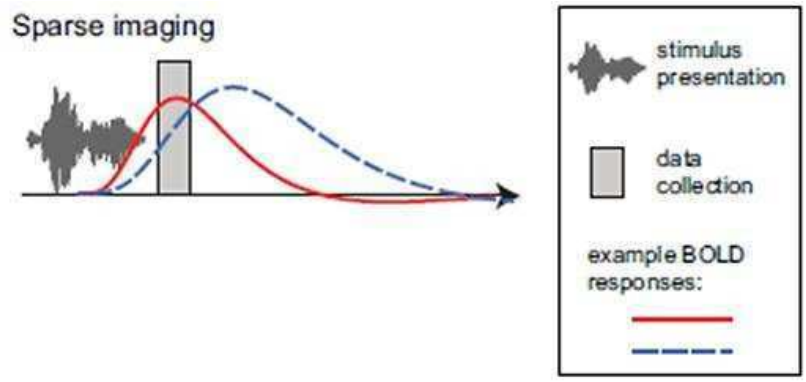


Figure 2.10. Schematic of sparse imaging approach. Sound stimuli presented in the absence of gradient switching noise. The resulting BOLD response is then measured after the sound stimuli have been presented. Two examples of individual differences in haemodynamic response latency are illustrated by the blue and red lines. Here, peak activation is captured for the red response line only. Adapted from Peelle (2014).

Sparse imaging reduces perceptual masking and the possible saturation effects within the auditory brain created by the response to scanner noise (Hall et al. 2000). According to Peelle (2014) the

primary disadvantage of sparse imaging is the reduction in time course information resulting from the reduced sampling rate/ extended repetition time. However, Hall et al. (1999; 2000) argue that the reduced number of data averages within sparse imaging does not compromise its ability to detect activation because (1) BOLD percentage signal change is maximised by contrasting the peak response with the post-stimulus negative phase of the response, (2) BOLD signal-to-noise ratio is increased as a result of greater MR signal recovery between scans afforded by the longer interscan interval.

At first glance the application of fMRI in the investigation of auditory brain function appears to be littered with a number of unsurmountable obstacles. The influence of acoustic scanner noise on auditory brain function, not to mention the participant's perceived levels of tinnitus is far reaching and must be considered carefully. But, by modifying the scanner acquisition parameters and employing other aforementioned methods of noise attenuation, many of these challenges can be overcome, permitting the collection of valuable functional brain data.

3 DATA SUMMARY

3.1 INTRODUCTION

This thesis is based entirely on secondary data sourced from an unpublished pre-existing clinical trial which ran between April 2010 and March 2012. Ethical approval was granted by the National Research Ethics Service (NRES) Committee, East Midlands, Nottingham (REC: 09/H0407/8). The author of this thesis was involved in participant recruitment and data collection of the original clinical trial, working in his capacity as an audiologist at Nottingham Audiology Services. All participants were anonymously coded prior to any secondary data analyses conducted for the purposes of this thesis.

3.1.1 Background of unpublished clinical trial

The original aim of the clinical trial was to evaluate psychological and sound-based intervention strategies for the treatment of tinnitus, the phantom perception of sound heard in the ears or head with no external source. Despite the widespread prevalence of tinnitus, it remains poorly understood with no uniformly effective treatment.

The degree to which tinnitus impacts on a person's quality of life is heavily influenced by mechanisms involving selective attention, emotional state, and memory (Hiller et al., 1997;

Andersson and McKenna, 1998; Andersson et al., 2006). Negative emotional feelings attributed to tinnitus play a major role in enhancing and maintaining long term tinnitus (Jastreboff, 1990). This model is supported by neuroscientific evidence that the emotional and memory centres of the brain in the limbic system are abnormally elevated in tinnitus (Zhang et al., 2003). Some treatments for tinnitus try to prevent the negative emotional reinforcement and hence reduce the emotional significance of the sounds the person hears. Psychological therapies, for example cognitive behavioural therapy (CBT), have been particularly significant in this respect, since they target the thoughts and beliefs surrounding tinnitus. The original trial sought to examine the efficacy of such types of intervention, not simply in terms of reducing self-reported distress from tinnitus, but also in reducing the involvement of limbic system activity. To answer such questions, a combination of self-report questionnaires and functional magnetic resonance imaging were used. Findings from the trial would give insight into the effective mechanisms that maintain tinnitus and how these can be best ameliorated.

3.1.2 Original Research Questions

1) Are there further benefits to be gained by the provision of sound or psychological intervention, in addition to the standard

audiological treatment of hearing aid provision? And if so, what is the nature of the benefit?

- tinnitus loudness and spectral quality?
- self-reported handicap from tinnitus?
- self-reported psychological state (anxiety and depression)?
- involvement of limbic system activity in tinnitus?

2) Are there any differential benefits of the additional psychological versus sound-based intervention?

3.1.3 Participant selection

Potential participants attending Nottingham Audiology Services or the Ear Nose and Throat (ENT) Centre, Queen's Medical Centre, Nottingham were targeted for study recruitment. Advertisements were placed in these clinical departments. Willing participants were given a study information sheet and asked to sign a consent form prior to taking part. All participants were made aware that they could withdraw from the study at any moment, without reason and that their future medical care would not be affected.

3.1.4 Participant groups and eligibility criteria

Four participant groups were selected for the trial:

1) Forty individuals with tinnitus receiving hearing aids

After 3 months, individuals from group (1) were randomly divided into 3 sub-groups, 2 of which were given an additional sound intervention in the form of a "nature sounds" CD or an "instructive relaxation" CD. The third group which did not receive any additional sound intervention served as the "control" group.

2) Twenty individuals with tinnitus not receiving hearing aids

3) Twenty individuals without tinnitus receiving hearing aids

4) Twenty individuals without tinnitus not receiving hearing aids

A number of inclusion and exclusion criteria were applied to ensure appropriate recruitment and participant safety (see Table 3.1.)

Table 3.1. Inclusion/exclusion criteria.

Inclusion criteria for tinnitus group
Men and women aged between 18-75 years
Chronic subjective tinnitus
English speaking
Currently seeking hearing aid provision (assigned to hearing aid group)
Not currently seeking hearing aid provision (assigned to no hearing aid group)
Inclusion criteria for no tinnitus group
Men and women aged between 18-75 years
No tinnitus
English speaking
Currently seeking hearing aid provision (assigned to hearing aid group)
Not currently seeking hearing aid provision (assigned to no hearing aid group)
General exclusion criteria
MRI incompatible metal implants, claustrophobia and pregnant women
Reported history of neurological disorder
Reported cardiovascular or respiratory problems
Reported alcohol or drug problems
Reported back pain or neck pain that precludes the person from lying still

3.2 DESIGN

This was a single-centre, unblinded, non-randomised parallel-group observational study conducted over a six month period in Nottingham. Eligible participants were scanned at 0, 3 and 6 months in a Philips Achieva 3T MRI scanner. Each visit included a five minute MPRAGE anatomical scan, a five minute whole-brain resting-state scan and a 15 minute functional scan, during which participants were asked to listen to a variety of emotionally evocative soundscape clips. A sparse sampling method was used for the sound evoked experiment. A gradient-echo echo-planar imaging (EPI) sequence was used for all functional scans (all fMRI parameters are detailed in the proceeding relevant chapters). Behavioural tests included an extended frequency (0.125-14 kHz) audiogram and a battery of tinnitus and psychological questionnaires. These included: Tinnitus Handicap Questionnaire (THQ; Kuk et al. 1990), Tinnitus Case History Questionnaire (TCHQ; Langguth et al. 2007), Hyperacusis Questionnaire (HQ; Khalfa et al. 2002), Short Form 36 Health Survey (SF-36), Beck Depression Inventory (BDI; Beck et al. 2000), Beck Anxiety Inventory (BAI; Beck et al. 1998), Mental Health Locus of Control Form C (MHLC) and Coping Styles Questionnaire (CSQ). Table 3.2.

displays the behavioural test battery and Table 3.3. highlights key information about each questionnaires.

Table 3.2. Behavioural test battery

Visit 1 (0 months)	Visit 2 (3 months)	Visit 3 (6 months)
Audiogram	-	-
Tinnitus tester	Tinnitus tester	Tinnitus tester
TCHQ	-	-
THQ	THQ	THQ
CSQ	-	-
SF36	-	SF36
MHLC	MHLC	MHLC
BAI	BAI	BAI
BDI	BDI	BDI
	-	HQ

Table 3.3. Questionnaire information

Tinnitus Handicap Questionnaire	This 27-item (0-100 scale) self-assessment questionnaire contains three factors which reflect physical, emotional and social consequences of tinnitus (Factor 1), tinnitus and hearing (Factor 2) and the patient's view on tinnitus (Factor 3). Scores from each factor were summated and divided by 27 to produce a scaled score between 0-100. A higher score indicates a greater degree of distress.
Tinnitus Case History Questionnaire	This 30-item self-assessment questionnaire provides descriptive information on tinnitus history and characteristics.
Hyperacusis Questionnaire	This 14-item (0-3 scale) questionnaire was designed to quantify and evaluate various hyperacusis symptoms. Three dimensions are isolated: attentional, social and emotional. A score of >28 is indicative of hyperacusis.
Short Form 36 Health Survey (SF-36)	The Short Form (36) Health Survey is a 36-item, patient-reported survey of patient health. SF-36 provides an eight scale health profile, (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health) and two component summary scores representing Physical health and Mental Health. Summary scores are converted into a norm-based scare based on a US population where a score of 50 is considered average with a standard deviation of 10.
Beck Depression Inventory – fast screen	This 7-item (0-3 scale) self-report inventory measures the severity of depressive symptoms, whilst excluding symptoms which may relate to medical problems. Scores are between 0-21 and can be interpreted as follows: 0-3 = minimal, 4-8 = mild, 9-12 = moderate and 13-21 = severe depression.
Beck Anxiety Inventory	This 21-item (0-3 scale) self-report inventory measures the severity of anxiety. Scores are between 0-63 and can be interpreted as follows: 0-7 = minimal; 8-15 = mild, 16-25 = moderate and 26-63 = severe anxiety.
Mental Health Locus of Control Form C	This 18-item (1-6 scale) self-report questionnaire was designed to investigate health-related control beliefs of persons with an existing medical condition. It can therefore be adapted for use with any medical condition.
Coping Styles Questionnaire	This is a 60-item (0-3 scale) self-report questionnaire which measures an individual's ability to cope with threat-related information.

3.3 PARTICIPANT FLOW OVERVIEW

Data collection in this trial comprised of two key domains: neuroimaging data and behavioural / questionnaire-based data. Most individuals recruited on to the trial participated in both domains, as was the intention of the study. However, there were several individuals who were not eligible for MRI scanning but still participated in the behavioural / questionnaire-based aspects of the study. For this reason, participants who took part in MRI and behavioural measures will be described separately.

3.3.1 Participant flow for MRI

Ninety eight participants were assessed for eligibility to take part in the trial. From this, 19 did not meet the study inclusion criteria (see Table 3.1. for criteria), 6 withdrew before the first visit and 2 consented too late to be scanned (27 exclusions in total prior to visit 1). Figure 3.1. shows the flow of participants from initial eligibility assessment through to study completion. Here we define study completion as a participant who attended all three MRI scanning sessions over a 6 month period.

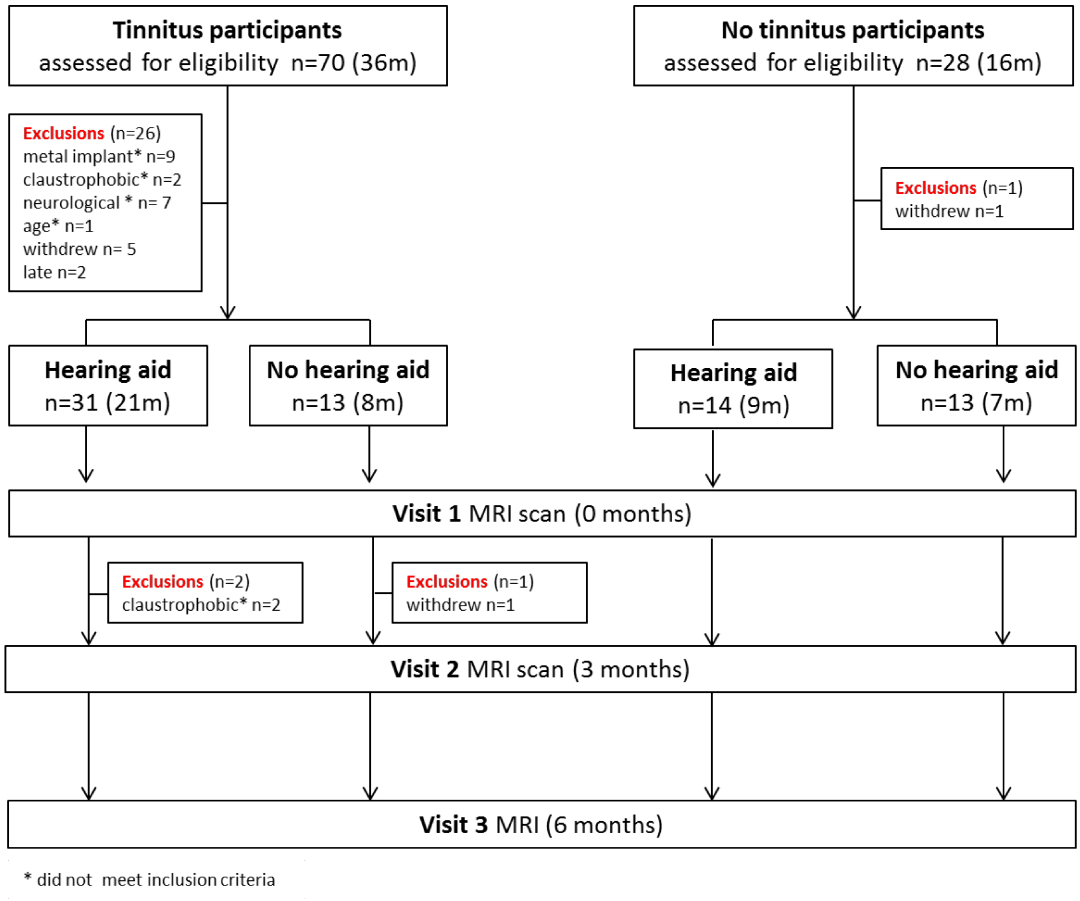


Figure 3.1. The flow of participants from initial eligibility assessment through to study completion for MRI scanning. Of the participants with tinnitus, 29 hearing aid users and 12 non-users completed the study. In the no tinnitus group, 14 hearing aid users and 13 non-users completed the study.

3.3.2 Participant flow for behavioural measures

Of the 27 participants "excluded" prior to visit 1 MRI scans (see Figure 3.1.), 15 were able to continue their participation in the study by completing the behavioural tests only. The remaining 12 did not take part in any aspect of the trial. Here we define study

completion as a participant who completed all three behavioural test batteries over the 6 month period. Figure 3.2. shows the participant flow for the behavioural tests only.

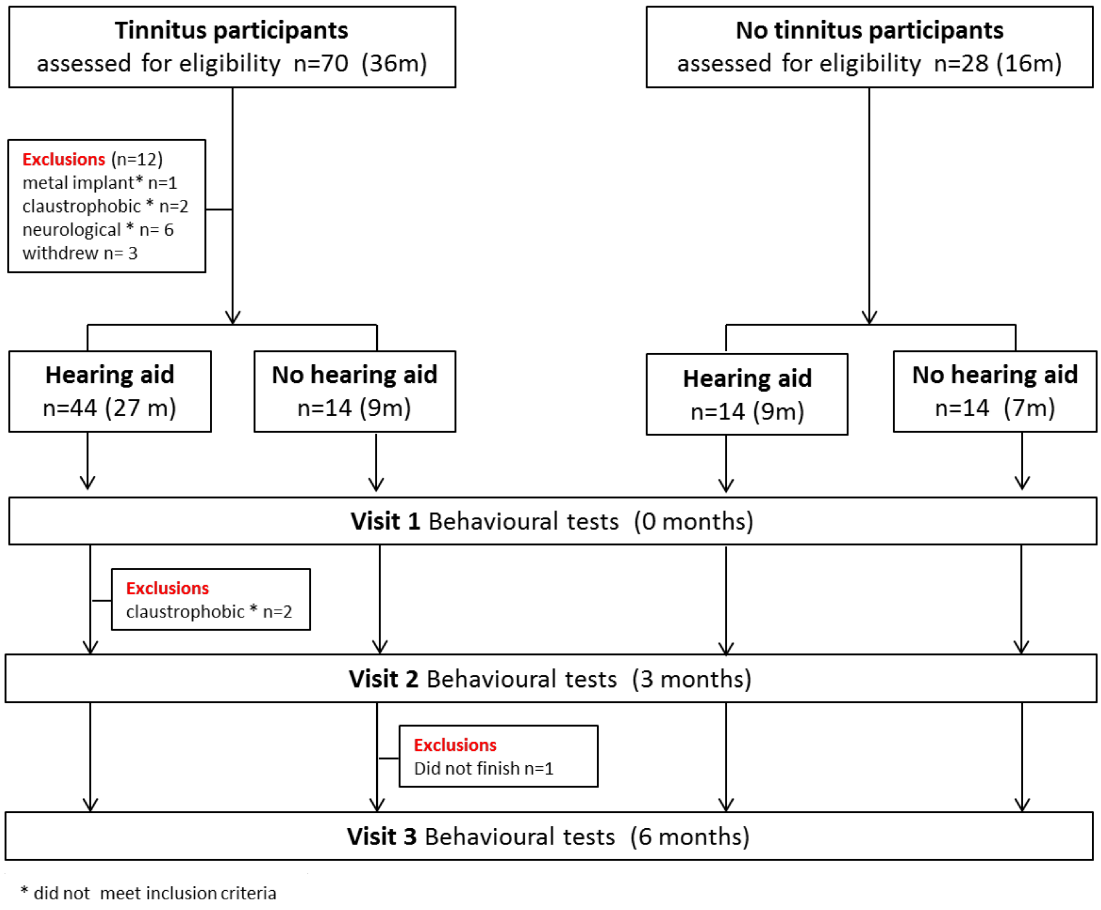


Figure 3.2. Participant flow for behavioural tests. Of the participants with tinnitus, 42 hearing aid users and 13 non-users completed the study. In the no tinnitus group, 14 hearing aid users and 14 non-users completed the study.

4 HOW EFFECTIVE IS AMPLIFICATION FOR HEARING LOSS IN ALLEVIATING TINNITUS HANDICAP? : A PROSPECTIVE QUESTIONNAIRE-BASED EVALUATION WITHIN A UK CLINIC

4.1 INTRODUCTION

For those who report tinnitus, an underlying clinical hearing loss often co-exists (Davis & El Rafaie, 2000; Nicolas-Pueal et al. 2002; Nondahl et al. 2011). Unsurprisingly then, hearing aid provision is a common management strategy amongst clinicians, with Saltzman and Ersner (1947) first reporting on the provision of hearing aids for tinnitus relief. Since this time, major advancements in hearing aid technology have been made (Kim and Barrs 2006) and the use of hearing aids for tinnitus management has continued to be an integral part of audiological care within the National Health Service (NHS) (Department of Health Good Practice Guidelines, 2009), as well as elsewhere (Tunkel et al. 2014; Shekhawat et al., 2013).

A recent Cochrane Review (Hoare et al., 2014) found that high quality evidence for the efficacy of amplification is limited, with only one published randomised controlled trial meeting inclusion criteria (Parazzini et al. 2011). This study compared the effects of bilateral open ear hearing aids versus sound generators, using measures of tinnitus handicap (THI) and loudness (self-

reported scale of 0 to 10). While tinnitus handicap and loudness improved over time in both groups, there was no difference in efficacy between the two interventions. This included study had potential bias in allocation and blinding, as well as using a sub-optimal outcome measure (Tinnitus Handicap Inventory) that has been criticised for its lack of sensitivity to treatment-related change (see Fackrell et al. 2014). A recent scoping review of tinnitus and hearing aid intervention used broader inclusion criteria (Shekhawat et al., 2013). The authors reviewed 18 research studies and found that 17 supported the benefit of hearing aids in tinnitus management. One of those studies targeted a UK-based group of patients within the National Health Service (NHS) - the main provider of hearing aids in the UK (iDATA, 2011). This was a retrospective observation of clinical data spanning the eras of both analogue and digital devices (Trotter and Donaldson 2008). The group found a statistically significant improvement in tinnitus perception as measured by a visual analogue scale of symptomatic improvement, following the introduction of digital hearing aid technology. Another reviewed study suggested that the dominant tinnitus pitch could be an important factor to consider when fitting hearing aids (Schaette et al., 2010). This study found that amplification was most beneficial at reducing tinnitus loudness and distress if the tinnitus pitch fell within the stimulated region

constrained by the device performance, i.e was lower than the upper cut-off of 6 kHz. However, the sample was small (n=10 with a pitch <6 kHz and n=5 with a pitch ≥6 kHz). Shekhawat et al. (2013) point out that the question concerning tinnitus pitch and amplification has not been considered, or reported, in other trials.

The authors of the scoping review also noted the general poor quality of study design and reporting, and uncontrolled variability that limits interpretation. Adding further complexity, are the many variances in the parameters of hearing aid fitting such as amplification strategy (Moffat et al. 2009) or ear mould type (Munhoes dos Santos Ferrari, Sanchez et al. 2007), not to mention differences in accompanying counselling strategies (Searchfield et al. 2010) and participant demographics (Schaette et al. 2010), all of which may influence reported benefit. The Cochrane Review authors call for future trials to consider randomising specific hearing aid features, whilst controlling for hearing loss in an attempt to unravel their individual contributions to reported outcome (Hoare et al., 2014).

While randomised controlled trials are considered the gold standard for evaluating healthcare interventions (Cochrane Handbook, 2011), in the case of tinnitus trials, it is not always possible or ethical to randomly allocate patients into different audiological intervention arms. Tinnitus often co-occurs with a

hearing loss, and amplification is primarily offered as an intervention for the hearing loss rather than for the tinnitus. Hearing aids are known to be beneficial for moderate-to-severe hearing loss (Bertoli et al. 2010) and so it would be unethical to recruit patients into a tinnitus trial for which they may be withheld from receiving an intervention already known to be effective for their hearing loss. The conflict between best clinical practice for hearing loss and gold standard research design to assess tinnitus management poses certain moral dilemmas regarding randomised treatment allocation and could explain the current lack of such trials in this field.

In the current trial, we present a prospective six month evaluation of hearing aid efficacy using a non-randomised controlled trial design. We recruited individuals with hearing loss and chronic subjective tinnitus who were seeking audiological management through the NHS. This recruitment strategy was attractive as it offered good ecological validity. An age-matched control group comprised members of the general population who had chronic tinnitus but were not seeking audiological management. Our main objective was to establish how effective were digital hearing aids in alleviating tinnitus handicap, using the THQ as a primary outcome measure. This tool is validated for sensitivity to treatment-related change (Kuk et al. 1990). It was

hypothesised that individuals fitted with hearing aids would experience a greater reduction in their tinnitus handicap compared to controls. As two secondary objectives, we also investigated the effects of perceived tinnitus pitch and self-reported hearing aid usage on tinnitus handicap.

4.2 METHODS

4.2.1 Participant groups

The original context of this study also required participants to be eligible for a Magnetic Resonance Imaging (MRI) brain scan. The MRI data will not be reported here.

In total, 58 individuals with chronic subjective tinnitus were recruited. Two individuals withdrew after their initial visit due to claustrophobia within the MRI scanner. The remaining 56 individuals completed the trial, these comprised of two groups. The hearing aid group included 42 individuals (25 males, 17 females; mean age 63.5 years) who were referred to NHS services and were prescribed digital hearing aids. The no hearing aid group included fourteen age-matched controls (9 males, 5 females; mean age 60.8 years) who were not currently seeking hearing aid provision. All participants completed a battery of behavioural measures (refer back to table 3.2.) at baseline (pre-hearing aid fitting) then again at 3 and 6 months (post-intervention).

4.2.2 Intervention

All hearing aids were fitted by qualified audiologists as part of a routine NHS treatment pathway. Eighteen individuals were fitted bilaterally, with the rest opting for a single aid. Four models of hearing aid were fitted during the trial. Twenty nine individuals (69%) were fitted with Oticon Zests (Oticon A/S, Denmark), eight (19%) were fitted with Siemens Reflex M's (Siemens Hearing Instruments, Inc, USA), four (9.5%) were fitted with Phonak Nathos micro's (Phonak Holding AG, Switzerland) and one individual (2.5%) was fitted with an Oticon Spirit 3 D (Oticon A/S, Denmark). Hearing aid fitting parameters were tailored to each individual's audiometric profile and subjective requirements. Hearing aid gain was set to the NAL-NL1 prescription (Dillon, 1999) and verified using real-ear measures. Hearing aid bandwidth was 6.4 kHz on average (Oticon Zest = 6 kHz, Siemens Reflex M = 4.5 kHz, Phonak Nathos micro = 8.2 kHz and Oticon Spirit 3D = 7 kHz). Participants were instructed to wear their hearing aids as often as possible. Data logging was used where possible to record average daily hearing aid use.

4.2.3 Additional sound intervention at 3 months

As part of the trial, individuals fitted with hearing aids were alternatively allocated with an additional sound intervention after 3

months. Group 1 (n=14) received a "water and nature sounds" CD, group 2 (n=14) received an instructive "deep relaxation" CD and group 3 (n=14) did not receive any further intervention. Individuals were instructed to listen to the CD as often as possible. As any change in tinnitus handicap from 3 to 6 months could be influenced by the introduction of the additional sound intervention over and above the hearing aid. We specified that listening to the CD at least 24 times (twice a week for 3 months) would constitute reasonable usage that might bring about additional benefit. Listening to the CD less than this would constitute intermittent usage that would be less likely to provide benefit over and above regular hearing aid usage.

4.2.4 Primary Outcome

Our primary endpoint with respect to efficacy in alleviating tinnitus was the difference in mean global THQ scores between the hearing aid and no hearing aid groups from baseline (pre-hearing aid fitting) to either 3 or 6 months (post-intervention) dependant on compliance of the additional sound intervention at 3 months.

The THQ was selected because it constitutes one of the better validated English-language measures of tinnitus severity with good responsiveness to treatment-related change, good internal consistency and high test-retest reliability for factors 1 and 2 (Kuk

et al. 1990; Newman et al. 1995; Meric et al. 1997). Participants were instructed to rate each of the 27 statements relating to tinnitus based on their level of agreement. A visual analogue scale from 0 (strongly disagree) to 100 (strongly agree) was used. Global scores ranged from 0 to 2700, with a high global score indicating substantial tinnitus handicap. This global score was scaled (i.e. divided by 27) to give a range of 0-100 for ease of interpretation.

4.2.5 Secondary Outcomes

The HQ, BAI, BDI and SF-36 questionnaires were also included in the test battery. Self-reported tinnitus pitch and loudness were characterised using an automated, computerised procedure, termed the Tinnitus Tester (Roberts et al. 2006, 2008). The concepts of pitch and loudness were first introduced through a computer program. Participants quantified their perceived level of tinnitus in two ways; through a visual analogue scale and secondly by adjusting the level (dB SPL) of eleven different frequencies (ranging from 0.5 kHz up to 12 kHz) so that it matched the loudness of their own tinnitus. Participants were asked to indicate which of these eleven different frequencies best matched the frequency spectrum of their own tinnitus percept. Each frequency was presented three times, with the mean average being used to

represent the participant's own tinnitus pitch. The TCHQ was administered for a general assessment of tinnitus characteristics at baseline (pre-hearing aid fitting) only (see Table 3.2.). Self-reported hearing aid usage was measured at 6 months. Individuals were asked to indicate how often they wore their hearing aids during waking hours using a visual analogue scale. This scale ranged from 0 (did not wear the aid) to 100 (wore the aid all the time). All outcome assessments were administered by a trained researcher (Jeff Davies or Phillip Gander).

4.2.6 Randomisation and blinding

Hearing aid provision was not randomised in this trial. Candidacy was decided jointly by the participant and audiologist assessing the participant as part of a routine NHS clinic. This decision was based on a number of factors specific to each individual, including severity of hearing loss, hearing and tinnitus-related problems and the participant's readiness to trial a hearing aid. The audiologists, participants and researchers involved in this trial were all unblinded to the interventions received.

4.2.7 Monitoring data entry

To check for accuracy in transcribing data from the paper-based case report forms to the electronic records, a process of source data verification was conducted independently by two team

members (Jeff Davies and Phillip Gander). Questionnaire scores (at 0, 3 and 6 months) were checked to ensure accurate data entry in all participants involved in the trial. No transcription errors were found and reasons for withdrawal were also verified.

4.2.8 Statistical methods

Data analyses were performed in SPSS (v20.0) and R (v3.0). Descriptive statistics were generated for primary and secondary outcomes at baseline (pre-hearing aid fitting) and 3 and 6 month visits using the available (i.e. non-imputed) data. A varying-intercept and varying-slope general linear model was used to assess the effects of hearing aid intervention on global THQ handicap scores from 0 to 6 months. This approach uses the pre-fit global THQ scores as a covariate, allowing an unbiased assessment of post-intervention scores (6 months) between groups, adjusting for baseline (pre-hearing aid fitting) scores. Global THQ scores were also modelled as a linear function of all three visits (i.e. modelling the rate of increase/decrease of THQ scores with time) using a varying-slope random effects regression model. Age, sex and average hearing level dB HL (0.25, 0.5, 1, 2, 4 kHz) were used as covariates. The slope was modelled as a function of a binary variable indicating whether the subject had a hearing aid or not.

To calculate significant differences in HQ, BAI, BDI and tinnitus loudness scores, a Mann-Whitney test was used for between-group analysis and a Wilcoxon signed-rank test was used for within-group analysis. These tests were chosen due to the unequal sample sizes and non-parametric distributions. Effect sizes (r) were calculated using Rosenthal's (1991: 19) equation: $r = \frac{Z}{\sqrt{N}}$ in which z is the z-score produced during the non-parametric test in SPSS, N is the total number of observations and r is an effect size estimate which may be interpreted using Cohen's d as r = 0.1 (small effect), r = 0.3 (medium effect) and r = 0.5 (large effect). To assess the effect of tinnitus pitch relative to hearing aid amplification bandwidth, individuals receiving a hearing aid were categorised according to their dominant tinnitus pitch measured at baseline (either ≥6 kHz or <6 kHz). A varying-intercept general linear model was then applied. The slope was modelled as a function of a binary pitch variable indicating whether the participant fell into the high (≥6 kHz) or low (<6 kHz) pitch tinnitus category. Again, this approach uses the baseline (pre-hearing aid fitting) global THQ scores as a covariate.

To investigate the effects of the additional CD sound intervention on global THQ scores from 3 to 6 months, a 2 x 3 mixed model ANOVA was used. The model had one within-subject

factor 'time' with two levels: global THQ score at '3 months' and '6 months' and one between-subjects factor 'intervention group' with three levels: 'no CD', 'nature sounds CD' and 'relaxation CD'.

4.3 RESULTS

4.3.1 Characteristics of the participants

Participant demographics and clinical characteristics as measured at baseline (pre-hearing aid fitting) are reported in Table 4.1.

			Between-group differences		
	Hearing aid group (mean, SD)	No hearing aid group (mean, SD)	P value	Z score	Effect size
Age	63.5 (9.3) years	60.9 (8.6) years	2.52	-1.15	-0.15
Gender	25 male: 17 female	9 male: 5 female			
Hearing level (low frequency) dB HL	31.07 (12.6)	15.79 (10.0)	<0.001*	-3.81	-0.51
Hearing level (high frequency) dB HL	51.09 (15.13)	30.28 (17.5)	<0.001*	-3.55	-0.47
THQ global score	38.87 (16.20)	42.8 (20.04)	0.51	-0.66	-0.09
BAI score	4.6 (4.8)	9.9 (12.4)	0.14	-1.47	-0.20
BDI score	0.98 (1.22)	4.21 (4.66)	0.02*	-2.30	-0.31
HQ score	13.92 (6.77)	14.92 (8.8)	0.86	-0.18	-0.02
Tinnitus pitch (kHz)	6.94 (3.23)	6.82 (3.48)	0.99	-0.01	-0.00
Tinnitus loudness (VAS scale)	44.04 (21.13)	46.57 (15.98)	0.43	-0.80	-0.11

Table 4.1. Participant characteristics at baseline assessment (pre-hearing aid fitting). A Mann-Whitney test was used to calculate significant differences. Effect sizes and standard deviations (SD) are also given. Note: * indicates statistical significance at p< 0.05.

There was no statistical difference in HQ scores or BAI scores between groups prior to intervention (see Table 4.1.). Average BDI scores were higher in the no HA group as compared to the HA group at baseline (see Table 4.1.). This was statistically significant ($p=0.022$).

All participants had an extended frequency hearing test (0.125-14 kHz). On average, participants in the hearing aid group displayed a greater degree of hearing impairment than those in the no hearing aid group (see Figure 4.1.). Better-ear low frequency hearing average (0.25, 0.5, 1, 2, 4 kHz) was significantly higher ($p<0.001$) in the hearing aid group (31 dB HL) as compared to the no hearing aid group (16 dB HL). Better-ear high frequency hearing average (2, 3, 4, 6, 8 kHz) was also significantly higher ($p=0.000$) in the hearing aid group (51 dB HL) as compared to the no hearing aid group 30dB HL).

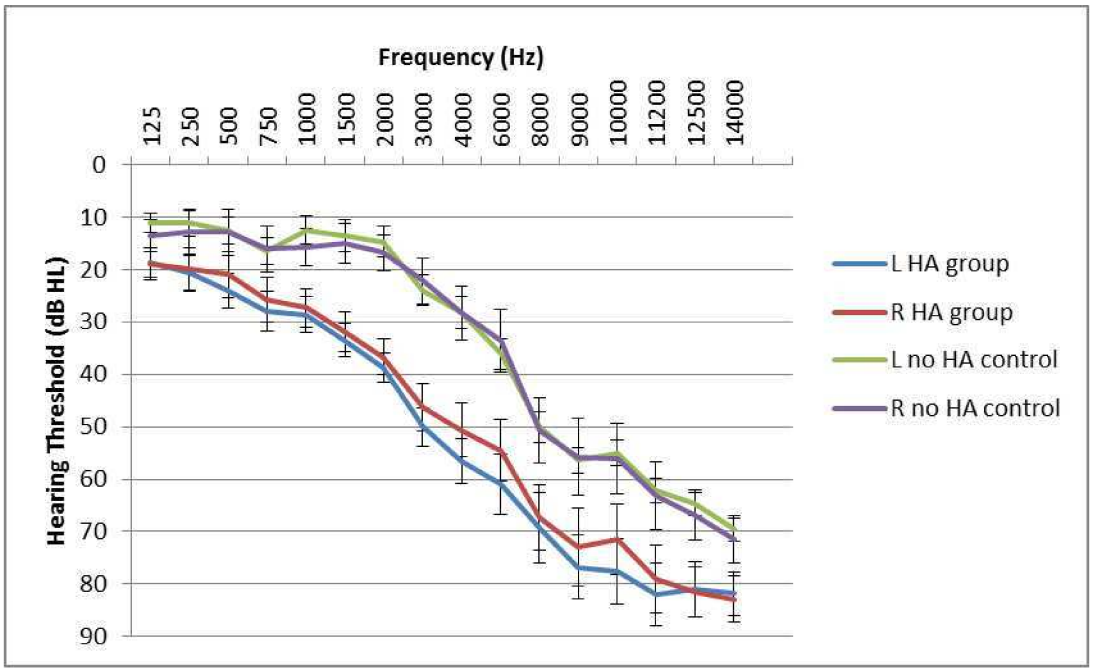


Figure 4.1. Mean average hearing thresholds for the hearing aid and no hearing aid groups. Error bars represent one standard error of the mean. L = LEFT, R = RIGHT, HA = Hearing Aid.

From the TCHQ at baseline, all participants reported chronic tinnitus with an average duration of 16.6 years (SD = 17.84) in the hearing aid group and 11.4 years (SD = 12.76) in the no hearing aid group. Tinnitus was constant for 93% of the hearing aid group and 71 % of the no hearing aid group. Fifteen individuals reported unilateral tinnitus (hearing aid group n=14, no hearing aid group n=1).

4.3.2 Compliance with additional sound intervention

Hearing aid usage is reported later in section 4.3.6. Overall, CD usage after 3 months (reviewed at 6 months) was extremely low,

with group 1 listening to the water and nature sounds CD 4.1 times and group 2 listening to the deep relaxation CD just 2.8 times on average. Three individuals from group 1 and six individuals from group 2 did not listen to the CD at all. Usage data for one individual in group 2 was not known and therefore not included when calculating average usage.

Such a poor compliance rate would indicate a non-significant impact of CD usage on tinnitus outcome at 6 months. Nevertheless to test the effects of the additional CD sound intervention on global THQ scores from 3 to 6 months, a 2 x 3 mixed model ANOVA was conducted. The model had one within-subject factor 'time' with two levels (global THQ score at '3 months' and '6 months') and one between-subjects factor 'intervention group' with three levels ('no CD', 'nature sounds CD' and 'relaxation CD'). There were no significant effects of intervention group (p= 0.986) or time (p=0.126), nor were there any significant interactions between time and group (p=0.372). This was unsurprising given the low compliance rate and confirms that the additional sound interventions did not impact on global THQ score.

4.3.3 Effect of hearing aid use on THQ

Average THQ scores (global, factor 1 and factor 2) at 0, 3 and 6 months are reported in Table 4.2. Factor 3 (outlook on tinnitus)

was not included due to its poor psychometric properties and reliability (Fackrell et al. 2014: Kuk et al. 1990).

Table 4.2. Average THQ scores at 0, 3 and 6 months.

	Hearing aid group (mean, SD)			No hearing aid group (mean, SD)		
	0 months	3 months	6 months	0 months	3 months	6 months
THQ global score	38.87 (16.20)	34.43 (17.0)	32.10 (15.10)	42.8 (20.04)	48.27 (20.81)	48.74 (23.28)
Factor 1 score	31.81 (17.88)	28.84 (19.51)	25.24 (16.47)	38.34 (27.10)	46.64 (26.89)	45.74 (28.39)
Factor 2 score	44.21 (24.85)	38.10 (20.71)	37.81 (20.53)	43.29 (22.08)	47.65 (19.70)	52.38 (23.65)

There was no statistical difference in mean global THQ scores between groups prior to intervention (Hearing aid group THQ = 38.87, S.D= 16.20; No hearing aid control group = 42.81, S.D = 20.04, p=0.508, effect size =-0.09). Global THQ scores were modelled as a linear function of visit number (i.e. the rate of increase/decrease of THQ scores with time was modelled) using a varying-slope random effects regression model. Age, sex and average hearing level dB HL (0.25, 0.5, 1, 2, 4 kHz) were used as covariates. The slope was modelled as a function of a binary variable indicating whether the subject had a hearing aid or not (see Figure 4.2.). There was a significant effect of hearing aid on the value of the slope, ChiSq(df=1) = 12.664, p< 0.001, with the global THQ score of subjects with a hearing aid dropping on average by 3.4 THQ points per visit (6.8 points in total). Although

there was an increase in global THQ score for the no hearing aid group, this was not significant. Overall, the results suggest that hearing aid amplification for hearing loss can help to reduce tinnitus handicap.

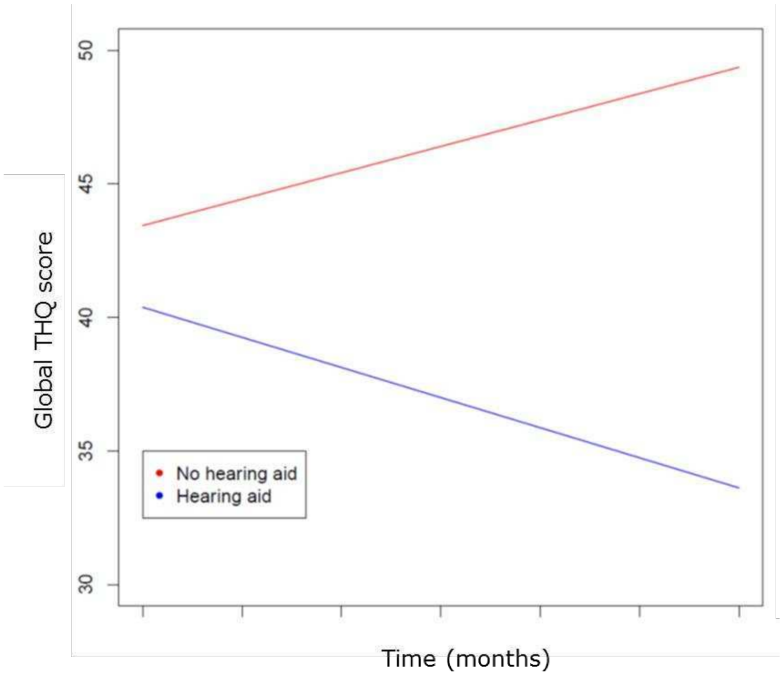


Figure 4.2. Varying-slope random effects regression model showing predicted change in THQ score over time. Age, sex and average hearing level dB HL (0.25, 0.5, 1, 2, 4 kHz) were used as covariates. THQ scores were modelled as a linear function of visit number: 0, 3 and 6 months for each group.

Global THQ scores were also modelled as a linear function of time (0 months to 6 months) for each group using a varying-slope, varying-intercept general linear model (see Figure 4.3.). The value of the slope describing the linear relationship between baseline and

6 months was significantly different for the hearing aid and no hearing aid group (p = 0.0373). Compared to the no hearing aid group, the hearing aid group had a reduced slope gradient, indicating a greater pre-post reduction in tinnitus handicap.

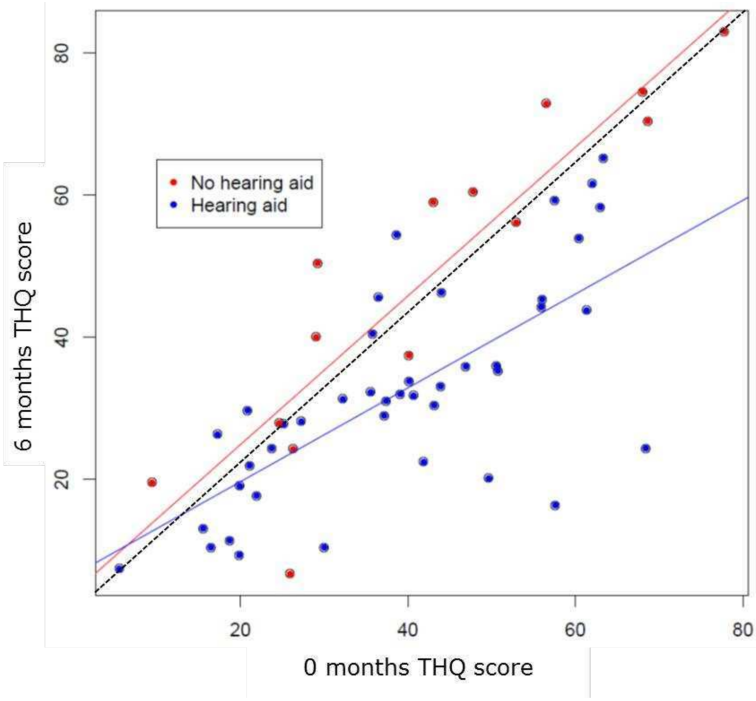


Figure 4.3. Varying slope, varying intercept general linear model. THQ scores modelled as a linear function of time for each group. Scores below the black dashed line indicate a reduction in tinnitus handicap.

4.3.4 THQ factor 1 and 2 scores

A Wilcoxon signed-rank test was used to calculate within-group differences in factor 1 and 2 scores between 0 and 6 months. Refer back to Table 4.2. for average THQ scores (global, factor 1 and factor 2) at 0, 3 and 6 months. Factor 1 (psychosocial) reduced significantly by 6.57 points in the hearing aid group (p=0.001,

effect size= -0.36). Factor 2 (hearing) reduced by 6.4 points in the hearing aid group however this was not statistically significant (p=0.108, effect size= -0.18). Factor 1 (psychosocial) increased by 7.4 points in the no hearing aid group however this was not statistically significant (p=0.096, effect size= -0.31). Factor 2 (hearing) increased by 9.09 points in the no hearing aid group, this was statistically significantly (p= 0.016, effect size=-0.46).

4.3.5 Tinnitus pitch

There was no statistical difference in tinnitus pitch between groups prior to intervention p> 0.05 (see Table 4.1.). To assess the effect of tinnitus pitch relative to hearing aid amplification bandwidth, subjects within the hearing aid group were grouped according to their dominant tinnitus pitch as measured at baseline (pre-hearing aid fitting). Figure 4.4. displays a histogram of dominant tinnitus pitch for participants in the hearing aid group. The first group comprised tinnitus pitch of less than 6 kHz (n=16) and the second group comprised tinnitus pitch of 6 kHz or greater (n=26).

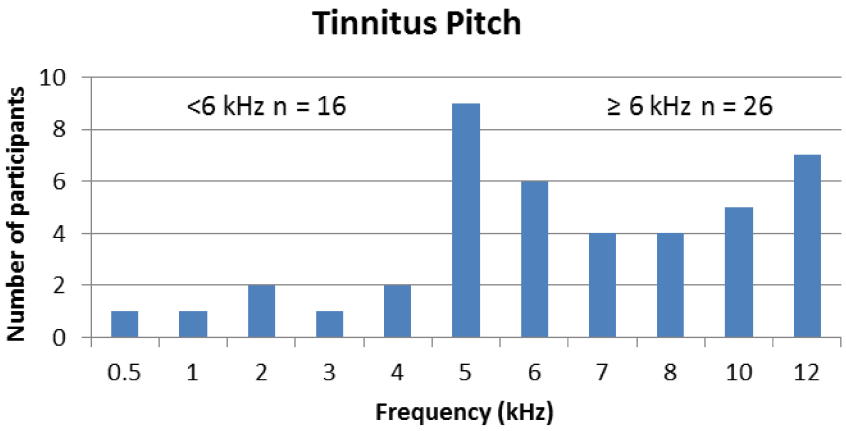


Figure 4.4. Histogram of dominant tinnitus pitch for participants in the hearing aid group.

Dividing the HA group according to their dominant tinnitus pitch (≥6 kHz or <6 kHz) had no significant effect on THQ change over 6 months (p=0.302). See Figure 4.5.

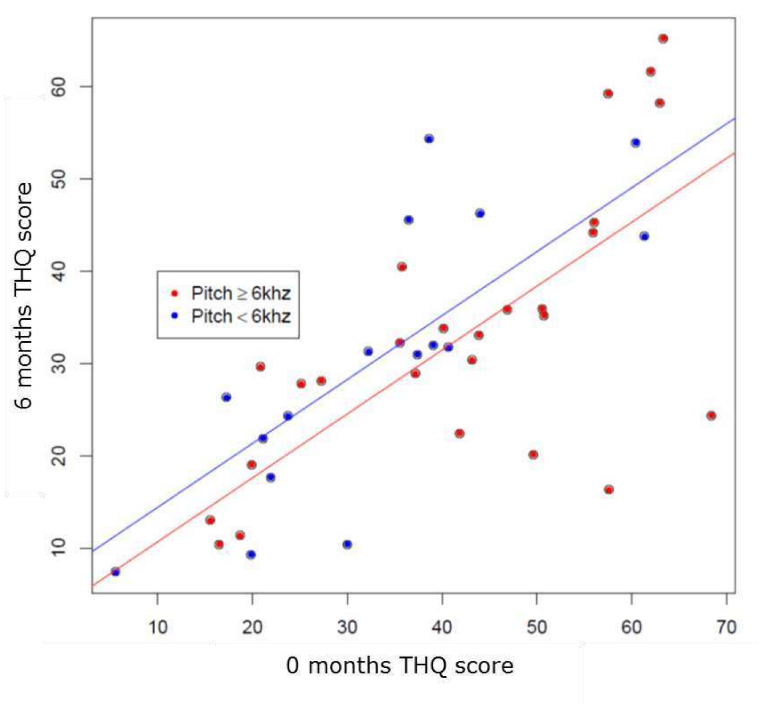


Figure 4.5. Varying-intercept general linear model shows no significant change in intercept value as a function of high (≥ 6 kHz) or low (< 6 kHz) tinnitus pitch, t(df=39) = 1.046, p=0.302001.

4.3.6 Hearing aid usage

After 6 months, average self-reported hearing aid usage was 47%. Only one individual reported 0% hearing aid usage. Overall, hearing aid use was high with 21 individuals wearing their hearing aids for at least 50 % of their waking day. Figure 4.6. shows a histogram of hearing aid use as reported at 6 months.

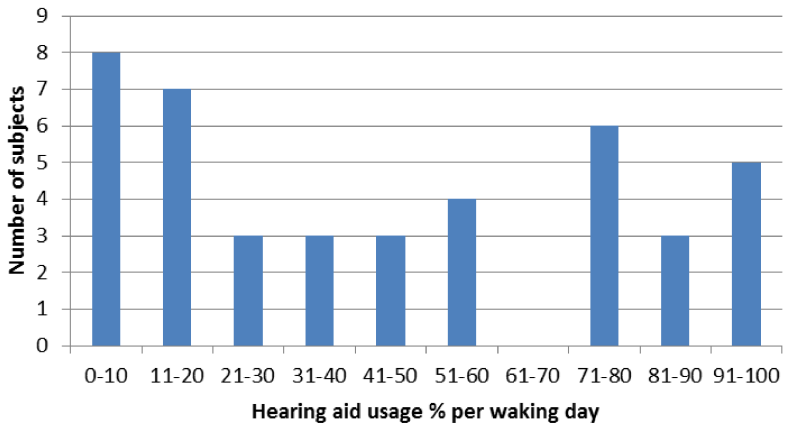


Figure 4.6. Histogram of hearing aid usage as reported at 6 months.

A scatterplot of hearing aid usage data collected at 6 months versus global THQ change over 6 months is given in Figure 4.7. The flat regression line (R^2 = 0.00008) indicates no correlation between hearing aid usage and change in global THQ score over the 6 month study period.

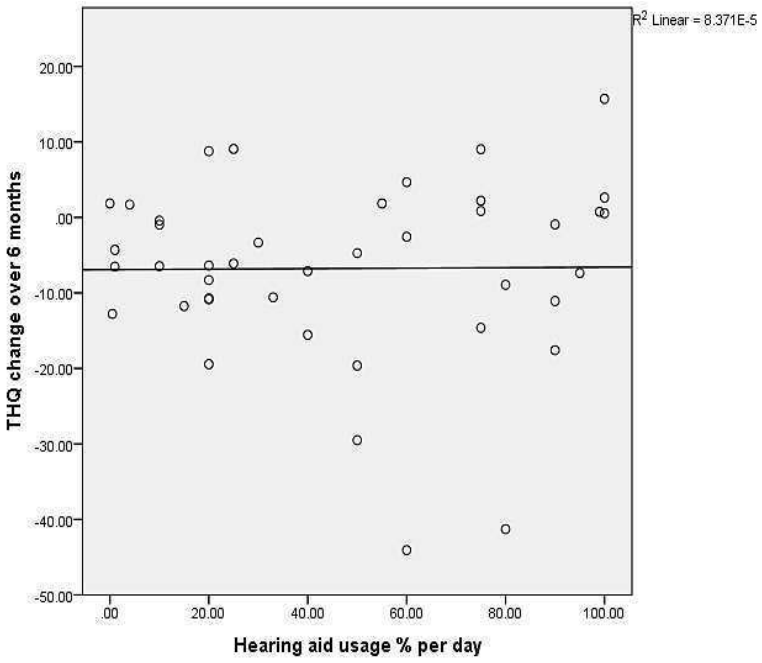


Figure 4.7. A scatterplot of hearing aid usage vs. global THQ change over 6 months. Individuals were asked to indicate how often they wore their hearing aids during waking hours using a visual analogue scale. This ranged from 0 (did not wear the aid) to 100 (wore the aid all the time).

4.3.7 Tinnitus loudness

There was no statistical difference in tinnitus loudness between groups prior to intervention $p>0.05$ (see Table 4.1.). After 6 months, tinnitus loudness did not change significantly within (see Table 4.4.) or between groups (see Table 4.5.) although a general reduction in loudness was observed in both groups.

Table 4.3. Descriptive statistics for secondary outcome measures (BAI, BDI, HQ, pitch and loudness).

	Hearing aid group (mean, SD)			No hearing aid group (mean, SD)		
	0 months	3 months	6 months	0 months	3 months	6 months
BAI score	4.6 (4.8)	5.83 (5.32)	6.12 (5.78)	9.9 (12.4)	9.35 (12.40)	9.93 (9.01)
BDI score	0.98 (1.22)	1.16 (1.62)	1.14 (1.69)	4.21 (4.66)	4.38 (4.45)	4.07 (4.94)
HQ score	13.92 (6.77)		12.66 (5.91)	14.92 (8.8)		16.85 (8.57)
SF-36 (physical)	45.72 (11.10)		44.22 (10.72)	46.25 10.25)		47.35 (10.05)
SF-36 (mental)	52.62 (8.34)		53.22 (8.85)	43.80 (11.50)		44.27 (12.63)
Tinnitus pitch (kHz)	6.94 (3.23)			6.82 (3.48)		
Tinnitus loudness (VAS scale)	44.04 (21.13)	41 (17.13)	39.76 (17.95)	46.57 (15.98)	44.43 (22.67)	44.64 (19.0)

Table 4.4. Within-group comparison of secondary outcome measures in hearing aid and no hearing aid group. A Wilcoxon signed-rank test was used to calculate significant differences. Effect sizes are also given. Note: * indicates statistical significance at p< 0.05.

		Within-group differences 0-3 months			Within-group differences 0-6 months		
		P value	Z score	Effect size	P value	Z score	Effect size
Hearing aid group	BAI	0.21	-1.26	-0.14	.045*	-2.0	-0.22
	BDI	0.85	-0.19	-0.02	0.74	-0.34	-0.04
	HQ				0.10	-1.63	-0.18
	SF-36 (physical)				0.2	-1.29	-0.14
	SF-36 (mental)				0.62	-0.49	-0.05
	Tinnitus loudness (VAS scale)	0.14	-1.47	-0.16	0.12	-0.54	-0.17
No Hearing aid group	BAI	0.82	-0.22	-0.04	0.62	-0.49	-0.09
	BDI	0.87	-0.17	-0.03	0.78	-0.28	-0.05
	HQ				0.23	-0.20	-0.23
	SF-36 (physical)				0.22	-1.22	-0.23
	SF-36 (mental)				0.6	-0.52	-0.09
	Tinnitus loudness (VAS scale)	0.78	-0.28	-0.05	0.78	-0.28	-0.05

Table 4.5. Between-group comparison of 0-6 month change scores. A Mann-Whitney test was used to calculate significant differences. Effect sizes are also given.

	Between-group differences 0-6 months		
	P value	Z score	Effect size
BAI	0.76	-0.30	-0.04
BDI	0.97	-0.04	-0.01
HQ	0.07	-1.78	-0.24
SF-36 (physical)	0.07	-1.80	-0.24
SF-36 (mental)	0.72	-0.36	-0.05
Tinnitus loudness (VAS scale)	0.68	-0.42	-0.06

4.3.8 Hyperacusis Questionnaire

The mean HQ scores of both groups at baseline were comparable to that of the general population (≈15) and far below the cut-off score of >28, which might be indicative of hyperacusis according to Khalfa et al. (2002). After 6 months, HQ scores did not change significantly within (see Table 4.4.) or between groups (see Table 4.5.).

4.3.9 Beck Anxiety Inventory

With reference to the BAI categories of anxiety, the hearing aid group had "minimal" levels of anxiety and the no hearing aid group had "mild" levels of anxiety at baseline. After 6 months, BAI scores remained the same for the no hearing aid group and increased by an average of 1.52 for the hearing aid group (see Table 4.4.). Whilst this increase was statistically significant ($p = 0.045$) the hearing aid group still remained within the 0-7 "minimal" anxiety category according to the scale specified by Beck & Steer (1993). This would suggest that the observed increase was not clinically meaningful.

4.3.10 Beck Depression Inventory

With reference to the BDI categories of depression, the hearing aid group had "minimal" depression and the no hearing aid group had "mild" depression at baseline. After 6 months, BAI scores did not

change significantly within (see Table 4.4.) or between groups (see Table 4.5.).

4.3.11 Short Form (36) Health Survey

The mean component summary measures of physical health at baseline were similar between groups. The mean component summary measures of mental health were significantly higher in the hearing aid group ($p = 0.004$). After 6 months, physical and mental component scores did not change significantly within (see Table 4.4.) or between groups (see Table 4.5.).

4.4 DISCUSSION

In this study we asked how effective is amplification for hearing loss in alleviating tinnitus handicap using the THQ as our primary outcome measure. We targeted a UK population who received NHS digital hearing aids as part of a routine care pathway. In comparison to age-matched controls with comparable levels of tinnitus distress, we found that individuals who received a hearing aid showed a statistically significant reduction in their global THQ scores in the 6 month period post-intervention. We also assessed whether perceived tinnitus pitch relative to hearing aid frequency bandwidth would influence global THQ scores over time following the findings of Schaette et al. (2010). A within-group comparison

of hearing aid users based on their dominant tinnitus pitch (≥6 kHz or <6 kHz) revealed no significant effect on THQ change over 6 months.

Our main finding of reduced tinnitus handicap following hearing aid intervention is reflective of the general consensus reached by a recent scoping review which supports the use of hearing aids for tinnitus management because they give patient benefit (Shekhawat et al. 2013). Despite the weight of evidence favouring hearing aids for tinnitus management, Hoare et al. 2014 point out that the general quality of studies is low, requiring better methodology and randomisation of interventions. An important consideration when using questionnaire outcomes to measure intervention efficacy concerns how to distinguish between clinically meaningful change and statistical change (Tyler et al. 2007). The ease to which this is accomplished may be dependent on the choice of outcome measure. For example, creators of the Tinnitus Functional Index (TFI) questionnaire suggest that a 13 point reduction on the 0-100 scale constitutes a clinically significant benefit (Meikle et al. 2012). The THQ used in the present study has a scoring range of 0-2700 which can be scaled down to 0-100. Based on data from a large clinical trial which compared two different tinnitus therapies (Henry et al., 2006), Hoare et al. (2013) reported that if a mean change in global THQ of 194 points

indicated a clinically meaningful change, with a medium effect size, then a scaled score equivalent would be 7.19 (using the 0-100 scoring criteria). Using this criteria, the 6.8 unit mean reduction in global THQ score over 6 months observed in the hearing aid group falls just short. However, Tyler et al. (2007) argue that if the questionnaire used is properly validated and designed to measure real issues related to the given condition, then a statistical difference for an individual should also be clinically meaningful. Some tinnitus questionnaires use smaller scales and therefore are not as sensitive to treatment related change (Fackrell et al. 2014). For example, the Tinnitus Handicap Inventory (THI: Newman et al. 1996) which uses a 3-point ordinal scale.

4.4.1 THQ factors 1 and 2

In this study, the provision of hearing aids improved the psychosocial aspects of tinnitus (factor 1) by an average of 6.57 points (over 6 months) suggesting a therapeutic benefit which goes beyond the hearing aid's ability to improve hearing, although as expected, this effect was also present (evidenced by an average reduction in factor 2 scores by 6.4 points over the same time frame). This supports the previous work of Searchfield et al. (2010) who also reported reductions in both factor 1 and 2 scores of their hearing aid cohort. A general increase in both factor 1 and 2 scores

was observed in the no hearing aid group by 7.4 points and 9.09 points respectively. This reached statistical significance for the factor 2 (hearing) scores. As this was a longitudinal study spanning 6 months, a plausible explanation for this increase in hearing-related problems might just reflect the natural course of age-related hearing loss which is known to be progressive (Kim and Chung, 2013).

4.4.2 Tinnitus pitch

Several recent studies have investigated tinnitus pitch as a predictor of success when fitting hearing aids. The pilot study of Schaette et al. (2010) found that tinnitus loudness and distress reduced significantly in hearing aid users whose dominant tinnitus pitch was less than 6 kHz. From this, they concluded that acoustic stimulation devices (i.e. hearing aids) might be more effective when tinnitus pitch is within the stimulated frequency range. However, in our group of 42 hearing aid users we did not find any influence of tinnitus pitch (≥6 kHz or <6 kHz) on tinnitus related distress or loudness. Here it is worth noting that Schaette et al. (2010) used the German Tinnitus Questionnaire (Goebel and Hiller, 1994) to assess tinnitus related distress. Moffat et al. (2009) took the different approach of examining the influence of hearing aids with varying bandwidths on the tinnitus spectrum. No differences in

psychoacoustic properties of tinnitus (loudness and pitch) were found when comparing standard hearing aid amplification to high bandwidth amplification regimes after 1 month of use. However this period of use may not have allowed adequate acclimatisation time. As Schaette et al. (2010) point out, tinnitus-related distress was not measured making it difficult to draw meaningful comparisons between the two studies. In a retrospective study of 70 tinnitus patients fitted with hearing aids, McNeill et al. (2012) examined the relationship between tinnitus pitch and the effectiveness of hearing aids in masking their tinnitus. They found that masking was more likely to be achieved in patients who had good low-frequency hearing thresholds and where the dominant tinnitus pitch fell within the hearing aid bandwidth. They also found that patients who reported greater subjective tinnitus masking showed a larger reduction in tinnitus distress as measured by the Australian Tinnitus Reaction Questionnaire (Wilson et al. 1991). This study was unique in that it considered the degree of effective masking as rated subjectively by each hearing aid user. This intricate relationship between tinnitus pitch, residual hearing levels and effective masking levels is not fully understood and requires careful consideration in future studies.

4.4.3 Hearing aid use and THQ score

Hearing aid usage in the present study was generally high with 21 individuals reporting to wear the hearing aids for at least 50% of their waking day. Only one individual did not wear their device. This contrasts with UK hearing aid usage figures which indicates that 30 % of individuals who have hearing aids do not use them (Action on Hearing Loss, 2011). High device compliance in this study may have been encouraged by the prospect of improving not only hearing but also tinnitus alleviation. Electronic data logging of average daily usage (in hours) would have been useful however this feature was only available in two out of the four hearing aid models fitted in this study. Upon assessing the relationship between self-reported hearing aid usage and global THQ score change over time, we found no correlation. This was surprising as hearing usage is known to be positively associated with higher levels of patient satisfaction and listener benefit in terms of an improvement in speech perception (Uriarte et al. 2005; Roup et al. 2009). However, this relationship has not yet been studied in the context of a tinnitus population and so should be carefully considered in future studies. The varying pattern of hearing aid usage in relation to global THQ change observed in this study seem to suggest that different people may require different amounts of hearing aid usage to receive similar reductions in tinnitus handicap.

4.4.4 Study limitations

The intervention group within this study consisted of individuals who self-opted to trial hearing aids. As they were compared against individuals who were not actively seeking audiological intervention, one must consider the influence of self-selection bias on the results. Furthermore, our sample was unbalanced between groups. This was partly because of the self-selection process regarding intervention and partly because no attempt was made in the study design to equalise baseline characteristics.

Although the primary intervention in this study was a hearing aid, participants would have also received some education and information counselling to compliment the fitting process. This aspect of the fitting was not standardised between clinicians. Despite how common this combined approach is in hearing aid management, it can cloud interpretation as to the true cause of any treatment-related change in outcome. Searchfield et al. (2010) sought to address this issue by retrospectively studying 58 individuals with hearing loss and tinnitus. Participants elected themselves into one of two management groups; group 1 received counselling and group 2 received a hearing aid in addition to counselling. Participants who received a hearing aid in addition to counselling showed a greater reduction in tinnitus handicap as

measured by the THQ. They concluded from this that individuals with tinnitus and hearing loss should try a hearing aid.

4.5 CONCLUSIONS

This is the first prospective study to target a UK-based NHS population using current digital hearing aids. The study provides further evidence to support the use of hearing aids in the management of chronic tinnitus and hearing loss. Individuals who opted to try hearing aids experienced a statistically significant reduction in their tinnitus handicap, regardless of perceived tinnitus pitch. Whether this change is deemed to be clinically meaningful depends on the definition used (e.g. Hoare et al. 2013; Tyler et al. 2007). Although not randomised, I feel our choice of methodology in this current study provides useful and ecological insight into current NHS practice. Future studies are encouraged to target NHS audiology clinics in an effort to better understand tinnitus management efficacy within the UK.

5 AUDITORY NETWORK CONNECTIVITY IN TINNITUS PATIENTS: A RESTING-STATE fMRI STUDY

The study featured in this chapter was published in the *International Journal of Audiology*, 2014, March, 53 (3) in modified form. This study considers the resting-state fMRI tinnitus studies which had been published at the time of writing. However, since 2012 a number of resting-state fMRI tinnitus studies have been published. This subsequent literature will be addressed and summarised in section 5.5.

5.1 INTRODUCTION

So far, many neuroimaging tinnitus studies have used sound-evoked paradigms (Golm et al. 2013; Husain et al. 2011; Gu et al. 2010; Melcher et al. 2009; Adjamian et al. 2009) or focussed on anatomical differences in brain structure (e.g., Melcher et al. 2012). However, in the case of chronic health conditions such as depression and schizophrenia, there is a growing interest in investigating the patterns of brain activity during rest (Veer et al. 2010; Garrity et al. 2007). Being able to understand the dynamic interactions between different neural networks in healthy and diseased states may help inform future treatment strategies or be used as biomarkers when measuring the efficacy of new treatments

(Narayanan, 2010). Moreover, in the context of tinnitus research, the use of resting-state neuroimaging may be better suited as an experimental paradigm to record activity relating to the "typical" on-going experience of the tinnitus percept.

Human brain function is not localised but engages spatially distributed, functionally linked anatomical regions which are in constant exchange of information. This inter-relationship can be referred to as 'connectivity' and can be quantified in humans using neuroimaging methods such as fMRI, PET, EEG and MEG. The present study investigates connectivity using resting-state fMRI which is sensitive to low frequency (< 0.1 Hz) spontaneous fluctuations in the blood oxygenation level dependent (BOLD) signal (Ogawa et al. 1990; Fox and Raichle, 2007) and offers a high-degree of spatial resolution.

Biswal et al. (1995) were the first group to use fMRI to identify coherent patterns of spatially independent, temporally correlated BOLD signal fluctuations during a resting-state. That is, when no explicit task is being performed by the participant. These patterns have since been termed 'resting-state networks' (Greicius et al. 2003) and are thought to reflect functional systems supporting core perceptual and cognitive processes (Cole et al., 2010). Several resting-state networks have been identified including visual, attention, auditory and DMN (Beckman et al.

2005). Resting-state networks are generally reported to show reliable and consistent patterns of functional connectivity (Zhang et al., 2008). Rogers et al. (2007) define the term 'functional connectivity' as the quantification of the operational interactions of multiple spatially-distinct brain regions that are simultaneously engaged. See van den Heuvel & Pol (2010) for a review of resting-state fMRI functional connectivity.

Recently, the application of resting-state fMRI has been used to investigate functional connectivity differences in those with tinnitus (Burton et al. 2012; Kim et al. 2012; Lee et al. 2012; Maudoux et al. 2012a; 2012b; Wineland et al. 2012). In a preliminary study of four people with tinnitus and six controls, Kim et al. (2012) used resting-state fMRI to investigate underlying brain activity within the auditory cortex of people with tinnitus. Results from an independent component analysis (ICA) followed by bivariate correlation between regions of interest indicated a reduced functional connectivity between left and right auditory cortices in the tinnitus group. The authors interpret this finding as indicative of a loss of coherence in intrinsic oscillatory activity, potentially indicating disequilibrium between neural excitation and inhibition across the hemispheres. Two further studies (Maudoux et al., 2012a; 2012b) also adopted ICA with a customised automated component selection approach. Both studies describe results for the

same cohort of 13 people with chronic tinnitus and 16 age-matched controls. A large number of connectivity differences were observed between the two groups in auditory and distributed non-auditory regions. Tinnitus individuals showed increased connectivity in the brainstem, basal ganglia, cerebellum, parahippocampal, right prefrontal, parietal, and sensorimotor areas and decreased connectivity in the right primary auditory cortex, left prefrontal, left fusiform gyrus, and bilateral occipital regions. Overall, Maudoux and colleagues (2012a; 2012b) concluded that the presence of tinnitus was able to modify functional connectivity in networks which encompass memory, attention and emotion. A pair of studies targeted larger samples of people with bothersome (n = 17) and non-bothersome tinnitus (n = 18), adopting the same methodology (Burton et al., 2012; Wineland et al., 2012). Their research investigated potential correlations between the auditory network and other brain networks using an exploratory seed correlation approach. The main finding was a negative connectivity correlation between auditory and visual networks only in those with bothersome tinnitus. The authors thought these findings may reflect neuroplastic adaptations to reduce phantom noise salience and conflict between non-auditory tasks.

Although all of these studies found that the presence of tinnitus modifies brain connectivity, the results differ markedly

between studies. Many fMRI tinnitus studies have identified some potential confounds which might explain difficulties in replication of findings across studies. These include factors such as age and gender (Lanting et al. 2009), laterality of the tinnitus percept (Melcher et al. 2000; Smits et al. 2007), severity of symptoms (Burton et al., 2012; Wineland et al., 2012), hearing loss (Husain et al., 2011) and hyperacusis (Gu et al., 2010). The present study therefore sought to address some of these design limitations by using a larger cohort of age, sex, and hearing-matched participants. Differences in analysis methodology could certainly be sufficient to explain much of the variability in findings. In the present study, we made an *a priori* decision to follow the same analysis steps described by Kim et al. (2012), as they used widely available proprietary software, naturally lending itself to replication. By doing this, we could ensure that this aspect of the analysis methodology was comparable between studies. We also employed additional analyses to more fully explore the data: 1) we defined regions that separated primary and secondary auditory cortex, and 2) we included a partial correlation approach, which allowed us to assess functional connectivity relationships between two auditory regions both within and between hemispheres, whilst controlling for the effects of the remaining ROIs specified in the model (e.g. Smith et al. 2011).

5.2 METHODS

5.2.1 Participants

All participants were recruited through Nottingham Audiology Services or the ENT department, Queen's Medical Centre, Nottingham. Twelve participants (7 male, 5 female; mean age 65.8 years) all with chronic (2 years minimum duration), constant subjective tinnitus participated in the study. Two of the twelve participants had lateralised tinnitus, the remaining ten had bilateral (n = 7) or central (perceived in the centre of the head) (n = 3) tinnitus. We also recruited eleven age and hearing matched controls (8 male, 3 female; mean age 68.5 years). All participants were aged 49-75 years without a history of neurological disorder. The study was approved by the National Research Ethics Committee (REC: 09/H0407/8). All participants gave written informed consent prior to taking part. See Table 5.1. for participant demographics and tinnitus characteristics.

5.2.2 Audiological profile

Participants had an extended frequency hearing test (125 Hz-14 kHz) prior to scanning. Participants with unilateral or asymmetrical hearing loss (as indicated by a between-ear air conduction threshold difference of 15 dB at two or more consecutive frequencies) were excluded from the study. Those with

hyperacusis, as indicated by a score of ≥ 29 on the hyperacusis questionnaire (Khalfa et al. 2002) were also excluded. Post-hoc t-tests of average hearing thresholds revealed no significant differences between or within participant groups (P> 0.05). The general hearing status of both groups could be described as a bilateral, mild to moderately severe sloping sensorineural hearing loss, typical of presbyacusis (see Figure 5.1.).

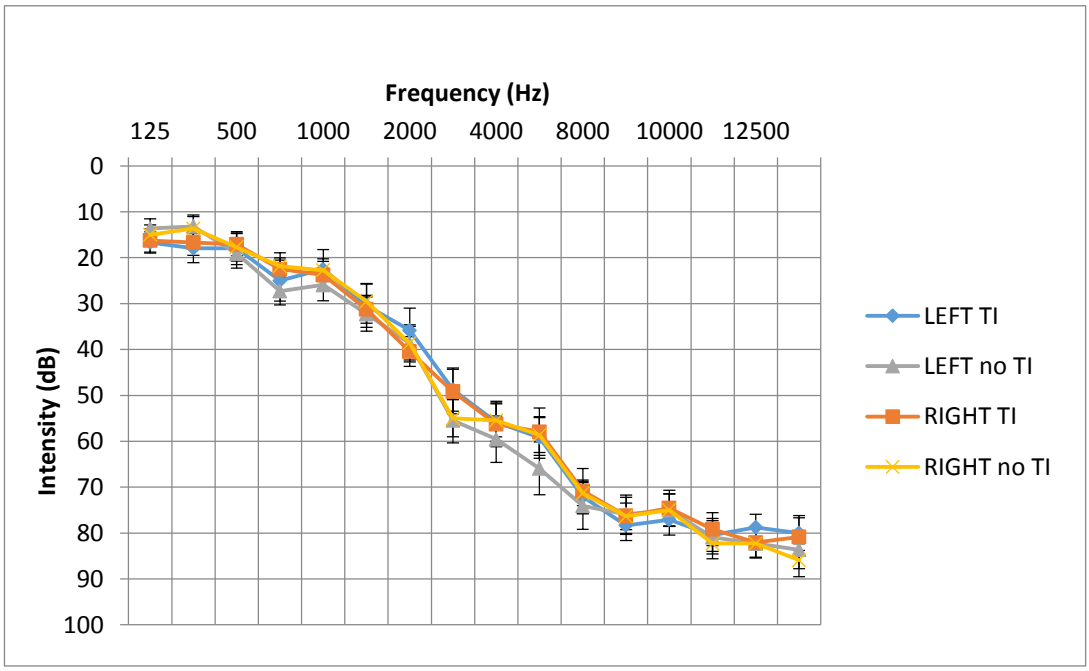


Figure 5.1. Mean average hearing thresholds for tinnitus and no tinnitus groups. Error bars represent one standard error of the mean.

5.2.3 Behavioural profile

All participants completed the following questionnaires; HQ, BAI and the BDI. Tinnitus participants also completed the THQ and the

TCHQ. Questionnaire scores are given in Table 5.1. For the tinnitus group, BAI and BDI scores were not significantly different from the control group. On average, BAI and BDI scores were minimal in severity for both groups. For the tinnitus group, HQ scores were significantly higher (P = 0.031) than the control group. However, the mean HQ score for the two groups were comparable to the mean score of the general population (i.e., 15) and no participant in either group had a HQ score of > 28, which according to Khalfa et al. (2002) indicates the presence of hyperacusis.

Table 5.1. Group demographics, questionnaire scores and tinnitus characteristics

	No tinnitus group					Tinnitus group					Tinnitus characteristics			
	Sex	Age	HQ	BAI	BDI	Sex	Age	HQ	BAI	BDI	Laterality	Duration (yrs)	THQ	TCHQ % annoy
	F	68	6	2	0	M	72	24	10	4	L	15	25.1	28
	F	71	9	8	3	M	64	14	2	2	L&R	2	35.5	10
	M	58	13	2	0	M	72	14	2	2	L&R	2	60.4	70
	M	68	19	0	3	F	67	8	6	0	L&R	4	61.3	50
	M	75	8	3	0	F	73	11	4	2	IN HEAD	70	21.1	5
	M	68	9	0	0	F	57	18	11	0	IN HEAD	2	63.3	50
	M	60	2	0	0	M	71	22	3	0	IN HEAD	6	68.4	30
	F	75	18	13	4	M	71	11	5	0	L&R	10	32.2	20
	M	66	8	0	0	M	64	11	0	0	L&R	20	30	20
	M	74	2	0	1	F	72	17	3	0	R	13	50.6	35
	M	70	11	14	0	M	49	10	4	2	L&R	2	57.5	50
	~	~	~	~	~	F	58	15	1	1	L&R	40	18.7	25
mean	8 M/3 F	68.5	9.6	3.8	1	7 M/5 F	65.8	14.6	4.3	1.1	~	15.5	43.7	32.8
SD	~	~	5.54	5.34	1.55	~	~	4.9	3.36	1.31	~	20.4	18.32	19

Abbreviations: M = male, F = female, L = left, R = right, HEAD = central tinnitus.

5.2.4 fMRI acquisition

Data were obtained from a Philips Achieva 3T MR scanner (Philips Medical Systems, The Netherlands) using an 8-channel SENSE receiver head coil. Whole brain functional images were acquired continuously for each participant during a five minute period of

wakeful rest using a double-echo gradient echo EPI sequence for optimal detectability of subcortical activity (echo times: 20, 45 ms, interscan interval 2700 ms, 36 slices, 0 mm slice gap, FOV = 240 x 240 mm, voxel size 3x3x3 mm, 112 volumes, descending slice order, sense factor 2.3). The participants had no explicit task to perform, rather they were instructed to keep still and alert with their eyes closed. During scans, participants wore ear plugs as well as circum-aural headphones which employed active noise control to reduce noise generated by the scanner (Hall et al. 2009). A five minute MPRAGE anatomical image was also acquired for each participant (160 slices, FOV = 256, voxel size 1x1x1 mm).

5.2.5 Double-echo imaging sequence

We were interested in two distinct brain regions; bilateral auditory cortex and amygdala. We applied a novel 'double-echo' imaging sequence. This approach captures two images at different echo times for every radio-frequency excitation and has been reported to provide wider brain coverage and improved BOLD sensitivity across a range of tissues (Marciani et al., 2006; Posse et al., 1999). Choice of echo time (TE 20ms and TE 45 ms) was intended to maximise detectability of our two regions of interest as previously demonstrated (Irwin et al. 2012). Echo 1 and echo 2 acquisitions were combined using a custom script in MATLAB

version 8 (http://www.mathworks.com/products/matlab/) to produce a weighted average using the T2* maps from each echo. The first echo EPI images were motion corrected to median volume data space (volume 56). These motion parameters were subsequently applied to the second echo images prior to co-registration. Each participant's motion parameters for the fMRI data were inspected to ensure no participant's head movement of greater than 1 voxel (3 mm). No participants were excluded based on this criteria.

5.2.6 Preprocessing steps

Functional MRI data were preprocessed using statistical parametric mapping software SPM8 (http://www.fil.ion.ucl. ac.uk/spm /software/spm8/). Images were realigned, co-registered with the participant's high resolution anatomical scan, normalised to the Montreal Neurological Institute (MNI152) template and spatially smoothed (4 mm full-width at half maximum).

5.2.7 Analysis approach summary

Analysis of resting-state functional data in this present study involved two stages. Firstly, group ICA was used to extract the auditory component of interest. This largely incorporated bilateral auditory cortex. Four seed ROIs within the auditory component were then selected: bilateral primary auditory cortex and

nonprimary auditory cortex within the lateral part of planum temporale. Bivariate correlation and partial correlation analyses were then used to assess levels of functional connectivity between each ROI. With the exception of the partial correlation analysis, all steps followed Kim et al. (2012).

5.2.8 Group ICA and auditory component selection

Group ICA was performed using the 'Group ICA for fMRI Toolbox' v1.8 (GIFT, http://mialab.mrn.org/software/gift/index.html) in MATLAB version 7.14. GIFT applies ICA as an unbiased, whole-brain analysis method of blind source signal separation, on either single or group level data. It allows the extraction of functionally related, spatially independent brain sources (referred to as components), each with an associated time course and spatial map.

Group ICA was first used to estimate the number of components using concatenated data from both tinnitus and no tinnitus groups. Of the 23 components identified, the component which most resembled the auditory network (component 14) was visually selected (see Figure 5.3. A). To support this selection, the independent components (ICs) were spatially sorted by performing a correlation analysis against a spatial template of the auditory network. The auditory template was taken from the SPM anatomy

toolbox v1.8 (http://www.fz-juelich.de/inm/inm-1/DE/Forschung/_docs/SPMAnatomyToolbox/SPMAnatomyToolbox_node.html, Eickhoff et al. 2005) which incorporated bilateral primary auditory cortex and nonprimary auditory cortex. Component 14 was found to be most highly correlated with the auditory template (Figure 5.3. A) and will henceforth be putatively referred to as the 'auditory network' component. Within SPM8, a one-sample t-test was used to derive the auditory network functional connectivity maps for the tinnitus group (n=12), no tinnitus group (n=11) and both groups combined (n=23). A further two-sample t-test was used to assess between group differences in the auditory functional connectivity maps.

5.2.9 Defining and constructing ROIs

ROIs were functionally defined using concatenated data from both tinnitus and no tinnitus groups. Within SPM8, a one-sample t-test was performed on the extracted auditory network component. Results were masked using the same auditory template used previously and thresholded at $P< 0.05$, uncorrected. Voxel co-ordinates for peak activity in bilateral primary auditory and nonprimary auditory cortices were extracted and used as the centre co-ordinate for each of the four, 5 mm radius, spherical auditory ROIs (see Figure 5.2 for a schematic of the four auditory

ROIs). The ROIs were constructed within the MarsBar toolbox (http://marsbar.sourceforge.net/) and used in the functional connectivity analyses.

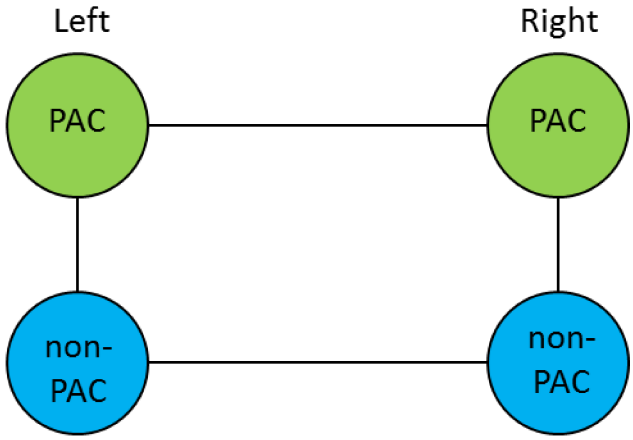


Figure 5.2 Schematic of the four auditory ROI's

5.2.10 Correlation analysis

As in Kim et al.'s study (2012), the 'Functional Connectivity toolbox' v12.1 (SPM8, http://web.mit.edu/swg/software.htm) was used to compute Fisher-transformed bivariate correlation coefficients (beta values) between the low frequency BOLD fluctuations of each ROI pair. To reduce any possible confounding sources of noise, cerebrospinal fluid motion, participant motion parameters and white matter signals were used as nuisance covariates. The BOLD signal was also band-pass filtered (0.009-0.08 Hz) to facilitate exclusion of respiratory or myogenic artifacts (Cole et al., 2010).

Partial correlation analysis was also performed to exclusively assess functional connectivity relationships between selected ROI pairs at the same time as accounting for the influence of activity from the other two ROIs. Fisher-transformation was also applied to the partial correlation coefficients to ensure measures were approximately normal in distribution. A two-sample t-test was then used to evaluate group level differences between all Fisher-transformed bivariate and partial correlation coefficients generated from each auditory ROI pair. Heterogeneous inter-hemispheric auditory ROI pairs e.g. left primary auditory cortex to right nonprimary auditory cortex, were not investigated as commissural projections in primary and nonprimary auditory cortices arise predominantly from contralateral homotopic regions (Lee and Winer, 2008). Bonferonni corrections were applied to all correlations to control for familywise error.

5.3 RESULTS

5.3.1 ICA

A one-sample t-test of the auditory network component combined across both tinnitus and no tinnitus control groups ($p < 0.001$, uncorrected) revealed robust functional connectivity between bilateral auditory cortical areas (Figure 5.3. C). A two-sample t-test of the auditory network component adopting the same statistical

thresholding as Kim et al. (2012) (i.e. $p < 0.01$, uncorrected for multiple comparisons, 48 voxel extent threshold) showed increased functional connectivity in the right supramarginal gyrus and left posterior middle temporal gyrus for the tinnitus group (Figure 5.3. D). However, after correcting for multiple comparisons using the more stringent family-wise error (FWE) corrected statistical thresholding, these areas of enhanced functional connectivity did not survive. These results differ from Kim et al. (2012) who reported increased functional connectivity in tinnitus participants between the auditory network and the left amygdala and between the auditory network and dorsomedial prefrontal cortex. No suprathreshold clusters of voxels were found in the auditory network for the 'reverse contrast' two-sample t-test comparison (no tinnitus > tinnitus).

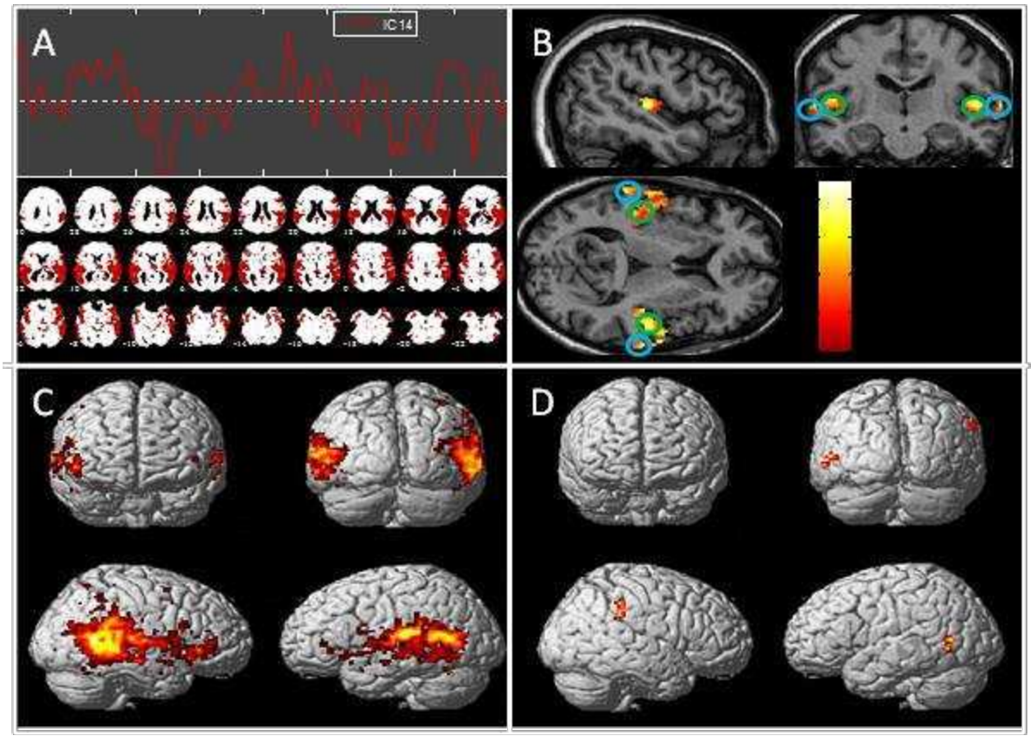


Figure 5.3. (A) Auditory network component and time-course. (B) Whole group one-sample t-test of auditory component, masked with auditory template (p< 0.05, uncorrected). Primary auditory cortex seed regions (green). Auditory association cortex seed regions (blue). (C) Whole group one-sample t-test of auditory network component (p< 0.001, uncorrected). (D) Ti > No Ti two-sample t-test (p< 0.01, uncorrected, 48 voxel extent threshold) showing increased connectivity in the right supramarginal gyrus and increased connectivity in the left posterior middle temporal gyrus.

5.3.2 Correlation analyses

Average bivariate correlation coefficients were not significantly different between the tinnitus group and controls (Figure 5.4. A). For the partial correlation analysis (Figure 5.4. B), only the average partial correlation coefficient between the left primary auditory

cortex and the left auditory association cortex was significantly lower (P = 0.029) in the tinnitus group. However, this did not survive statistical thresholding following Bonferonni adjustment of the alpha level (0.05/4).

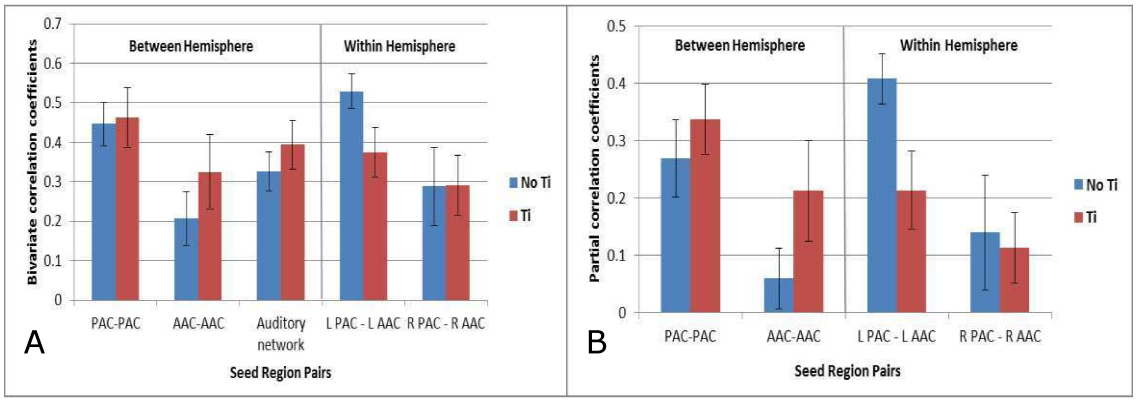


Figure 5.4 (A) Average bivariate correlation coefficients (beta values) for each paired ROI. The 'auditory network' refers to a combined mean average derived from the BOLD time-series of primary auditory and auditory association cortical seed regions. (B) Average partial correlation coefficients for each paired ROI. Error bars represent one standard error of the mean. PAC = primary auditory cortex, AAC = auditory association cortex, L = left, R = right.

5.4 DISCUSSION

We sought to consolidate early findings regarding resting-state fMRI in chronic subjective tinnitus, by controlling for a number of important factors; namely age, sex, BAI/BDI scores and audiometric profile. Using methods based on Kim et al. (2012), we

chose to assess auditory functional connectivity both between and, in addition to Kim et al. (2012), within brain hemispheres. We also employed methods of partial correlation which have recently been found to be a powerful analysis approach (Smith et al. 2011), allowing functional connectivity relationships between two chosen auditory regions to be assessed whilst controlling for the effects of the remaining ROIs. In the present study, whole-brain ICA and bivariate correlation analyses resulted in similar patterns of auditory network connectivity between tinnitus and no-tinnitus groups. Our additional methods of partial correlation and exploring connectivity within hemispheres revealed no significant differences between groups indicating that auditory cortical functional connectivity is not modified by the experience of tinnitus.

5.4.1 Connectivity within the auditory cortex network

Kim et al. (2012) found a significant reduction in bilateral auditory cortical functional connectivity in their tinnitus participants compared to controls. They hypothesised that this reduction may imply a loss of coherence in spontaneous resting state neural activity between the left and right auditory cortices. While our null result for auditory network functional connectivity contradicts Kim and colleagues, it is supported by reports from Burton et al. (2012) and Wineland et al. (2012). Interpreting these mixed findings is

challenging because of the many methodological differences (participants, analysis etc.). One pertinent factor which may explain the differences in auditory network connectivity between studies is hearing acuity. According to Husain et al. (2011), compensatory mechanisms for hearing loss may differ to those of tinnitus, resulting in differences in functional neural responses unless hearing status is carefully controlled as a potential confound. We note that Kim et al. (2012) matched hearing between their tinnitus and control groups based on a three point average hearing threshold (0.5, 1 and 2 kHz), leaving high frequency hearing loss unaccounted for. The present study carefully matched hearing status between tinnitus participants and controls across a wide range of frequencies 125 Hz -14 kHz. We acknowledge differences in tinnitus laterality between the present study cohort and that of Kim et al. (2012). Kim recruited people with lateralised tinnitus, while our cohort was mixed with a majority experiencing bilateral tinnitus. There have been several sound-evoked fMRI studies investigating tinnitus laterality (Melcher et al. 2000; Lanting et al. 2008; Smits et al. 2007). However, there is no systematic evidence to indicate an effect of tinnitus laterality on the patterns of resting-state brain activity and connectivity.

5.4.2 Connectivity between auditory and emotional networks

De Ridder et al. (2011) suggest that distress associated with tinnitus results from a constant learning process and is reflected by the presence of a non-specific distress network consisting of the anterior cingulate cortex, anterior insula and the amygdala (refer back to Figure 2.3.). In their tinnitus participants, Kim et al. (2012) reported reduced functional connectivity between left and right auditory cortices and increased functional connectivity between the auditory network and the left amygdala and dorsomedial prefrontal cortex. Although these data plausibly suggest that tinnitus is associated with increased functional connectivity in brain regions which sub-serve emotion and attention, Kim et al. (2012) did not report the degree of tinnitus distress experienced by their participants and the statistical reliability of their findings is also questionable. Our results throw doubt on this interpretation because this finding was not replicated in the present study, although we do acknowledge that our participants had relatively low levels of tinnitus distress (THQ mean score was 43.7 out of 100) and tinnitus annoyance (TCHQ mean score was 32.8 %).

Several other recent resting-state fMRI studies have found alterations in networks associated with emotion and attention, with findings tending to indicate this depends on the bothersome nature of the tinnitus symptoms. For example, Maudoux et al. (2012b)

observed a positive correlation between the resting-state activity of the posterior cingulate/precuneus regions and THI scores (an indicator for emotional distress). Burton et al. (2012) found that the right anterior insula and left frontal gyrus of their distressed tinnitus group showed significantly greater functional connectivity with the auditory network than controls, while data from the same research group reported in a separate paper (Wineland et al., 2012) found no differences in functional connectivity in those with non-bothersome tinnitus compared against age and hearing matched controls. Although these results might imply that only bothersome tinnitus alters functional connectivity in brain regions related to attention and emotional processing, direct statistical comparisons need to be made between subgroups with low and high levels of tinnitus distress in order to confirm any such claims.

Independent replications of experimental findings in tinnitus represent an important way to validate claims made about the underpinning neural mechanisms of this enigmatic condition, seeking to separate truth from myth. Just as there has recently been a call for an international standard in clinical trial methodology for tinnitus research (Landgrebe et al., 2012), we would argue that the same concerted collaborative efforts would benefit this newly emerging field of resting-state fMRI. Transparency in the details of the methods and analysis and

sharing of customised analysis software would help us all as a community to obtain reliable information about the neural circuitry in the tinnitus brain.

5.5 RESTING-STATE fMRI TINNITUS: RE-VISITED

Husain and Schmidt (2013) present a comprehensive review of the resting-state fMRI tinnitus literature from 2012. However since this time, other relevant studies (including this current study) have been published. Experimental details and major findings of these later resting-state fMRI tinnitus studies along with the original ones discussed previously in this chapter have been summarised in the following table.

Table 5.2. Resting-state fMRI tinnitus summary table. Major findings are reported in tinnitus participants relative to controls. Functional connectivity between two regions is indicated by "-".

Study	Participant groups	Age of participants	Tinnitus distress	Hearing loss of tinnitus participants	Methods	Major findings in tinnitus participants, relative to controls
Kim et al. (2012)	4 T (1 f) 6 NHC (2 f)	45 ± 2.76 45 ± 3.92	?	<25dB HL between 0.5-2kHz	group ICA seed-to-seed seed-to-voxel	Decreased AN FC Increased FC: AC-Amyg, AC-dmpgfc
Maudoux et al. (2012a)	13 T (6 f) 15 NHC (6 f)	52 ± 11 51 ± 13	THI 16-84 mean 43.5	Mild to severe	group ICA	Increased FC: AC-BS, AC-BG, AC-C, AC-P, AC-right Pf, AC-Pa, AC-S Decreased FC: AC-Pf, AC-Fg, AC-bilateral Oc
Maudoux et al. (2012b)	13 T (6 f) 15 NHC (6 f)	52 ± 11 51 ± 13	THI 16-84 mean 43.5	Mild to severe	Graph connectivity	Increased FC: AC-left P
Burton et al. (2012)	17 T (6 f) 17 NHC (10 f)	53.5 ± 3.6 50.6 ± 2.5	THI 38-76 mean 53.5	None to severe	seed-to-seed seed-to-voxel	Decreased FC: AC-VC, VC-tpj, VC-IFG, VC-ins, OC-ins, OC-IFG
Wineland et al. (2012)	18 T (6 f) 23 NHC (11 f)	54 median 46 median	THI 0-24 mean 9.67	None to severe	seed-to-seed seed-to-voxel	No differences
Husain and Schmidt (2013)	12 T (6 f) 15 NHC (6 f) 13 HLC (8 f)	55 ± 6.9 52.9 ± 8.6 57.62 ± 9.4	THI 0-22 mean 8.33	Mild to moderate in T, HLC matched	seed-to-voxel	Increased FC: AC-Phip, fef-Phip Decreased DMN FC Decreased FC: ips-right smg
Davies et al. (2013)	12 T (5 f) 11 HLC (3 f)	65.8 ± 5.6 68.5 ± 7.7	THQ 18.7-68.4 mean 43.7	Mild to moderate in T, HLC matched	group ICA seed-to-seed	No differences
Ueyama et al. (2013)	24 T (7 f) No control group	50.3 ± 14.6	THI 4-100 mean 60.3	Normal to moderate	PCA seed-to-voxel	Only correlations between brain regions and questionnaire scores considered
Chen et al. (2014)	31 T (14 f) 32 NHC (15 f)	41.9 ± 10.8 46.5 ± 12.6	THQ 17.41-278.15 mean 100.6 (not scaled)	<25dB HL between 0.25-16kHz	VBM 2 sample T test of whole brain FC maps	Increased FC: right MTG, right SFG, right AG Decreased FC: left Cu, right middle OG, bilateral Th
Zhang et al. (2015)	31 T (13 f) 33 NHC (15 f)	40.8 ± 13.2 45.2 ± 11.9	THQ mean 41.4 (range not given)	<25dB HL between 0.25-16kHz, NHC matched	VBM seed-to-voxel	Increased FC: left Th-right MTG, left Th-right middle OFG, left Th-left MFG, left Th-right PG, left Th-bilateral CC Decreased FC: right Th-left STG, : right Th-left Amyg, right Th- right SFG, right Th- left PG, right Th- left middle OG

Abbreviations: T = tinnitus, NHC = normal hearing control, HLC = hearing loss control, f = female, ? = data not provided by author, ICA = independent component analysis, PCA = principal component analysis, AN = auditory network, DMN = default mode network, FC = functional connectivity, THI = tinnitus handicap inventory, THQ tinnitus handicap questionnaire, AC = auditory cortex, dpfmc = dorsomedial prefrontal cortex, BS= brainstem, BG = basal ganglia, C = cerebellum, P = parahippocampal, Pf = prefrontal, Pa = parietal, S = sensorimotor areas, Fg = fusiform gyrus, Oc = occipital regions, VC = visual cortex, tpj = temporoparietal junction, IFG = inferior frontal gyrus, ins = insula, OC= occipital cortex, Phip = parahippocampus, fef = frontal eye field, ips = intraparietal sulci, smg = supramarginal gyrus, MTG = middle temporal gyrus, SFG = superior frontal gyrus, AG = angular gyrus, Cu = cuneus, OG = occipital gyrus, Th = thalamus OFG = orbitofrontal gyrus, MFG = middle frontal gyrus, PG= precentral gyrus, CC = calcarine cortex, Amyg = amygdala.

5.5.1 Summary of resting-state literature

Collective observation of the resting-state fMRI tinnitus literature to date further illustrates a high degree of variability in results, with little specific agreement amongst studies. Several variables which might explain such differences will now be addressed. Effects of these variables will be considered in greater detail in chapter 8.

Hearing loss

Out of the ten studies presented in Table 5.2. only Husain and Schmidt (2013) and Davies et al. (2013) use hearing loss matched controls. Most studies recruited normal hearing controls despite enrolling tinnitus participants with hearing loss (Kim et al. 2012; Maudoux et al 2012a; 2012b; Burton et al. 2012; Wineland et al. 2012). This leaves findings vulnerable to the confounding effects of hearing loss (Husain et al. 2011). Alternatively, Chen et al. (2014) and Zhang et al. (2015) both chose to target only participants with normal hearing (audiometric thresholds < 25 dB HL between 0.25-16 kHz), despite hearing loss being the main risk factor of tinnitus (Nondahl et al. 2011).

Comparison group

Ueyama et al. (2013) were the only group who did not directly compare against a control group. Instead, they controlled for the effects of hearing loss, tinnitus distress, tinnitus loudness and

levels of depression using methods of partial correlation in their seed to voxel analyses.

Age

The mean average participant age group was 51 years across all ten studies (known disclosed age range was 21-76 years). As tinnitus is associated with advancing age (Lockwood et al, 2002) it is important to compare tinnitus participants with aged-matched controls. In doing so, this may protect against confounds often associated with age; such as hearing loss and brain atrophy. All studies reported in Table 5.2. (with the exception of Ueyama et al. 2013) compared against an aged-matched control group.

Sample size

All studies used more than ten participants in each group with the exception of Kim et al. (2012) who only included four tinnitus participants and six controls. As will be discussed further in section 8.3.1, increasing participant numbers will help to increase statistical power which is needed to make credible inferences about given groups or populations.

Levels of distress

Tinnitus distress levels varied considerably within and between studies. Only Burton et al. (2012) and Wineland et al. (2012) chose *a priori* to target high and low tinnitus distress groups respectively. Kim et al. (2012) were the only group not to measure tinnitus

distress, all others used either the THI or THQ to measure reported tinnitus distress. Measuring distress through behavioural questionnaires should be considered a crucial first step in the quantification of tinnitus, allowing correlation with underlying brain activity.

Analysis Methods

A variety of analysis methods are used in all ten studies to analyse the resting-state data, with many favouring hypothesis-driven methods of connectivity analysis such as SCA or ROI. Specific ROIs vary between studies but common ones include auditory, limbic and emotional brain regions. Eight of the ten studies show alterations in functional connectivity which are thought to represent the neural signature underlying tinnitus. However, location, stength and pattern of functional connectivity vary considerably from study to study. Only Wineland et al. (2012) and Davies et al. (2013) report no connectivity differences between participants with and without tinnitus.

Whilst most claim to measure tinnitus-related alterations in functional connectivity, few adequately match audiological and demographic characteristics amongst patients and controls. And although many seem to choose a ROI approach for analysis of resting-state data, independent replication of identical analysis methods has so far only been executed by our own research group,

despite offering a sensible way of validating results. Given these variations one must ask: are the observed tinnitus-related alterations in functional connectivity related to the perception of tinnitus or do they perhaps reflect a wider more complex story composed of varying patient demographics and analysis methods?

6 INVESTIGATING AUDITORY-AMYGDALA CONNECTIVITY IN CHRONIC TINNITUS PATIENTS: AN EXPLORATORY FOLLOW UP ANALYSIS

6.1 INTRODUCTION

Tinnitus is a highly subjective condition which can be distressing for many individuals. Interestingly, the psychoacoustic properties of tinnitus do not predict the severity of related distress (Henry and Meikle, 2000; Hiller et al. 1994). One frequently adopted model of tinnitus distress proposed by Jastreboff and colleagues (1996) suggests that an initial negative emotional evaluation of tinnitus may determine the level of related distress. For example, where the initial perception of tinnitus is associated with something negative such as the onset of deafness. Negative affect in turn can activate limbic brain regions such as the amygdala which is engaged in emotional processing (De Ridder et al., 2011; Golm et al., 2012). The amygdala is a small neural structure ≈ 1.7cm^3 within the human brain, whose chief function is considered to be processing emotional stimuli from all sensory modalities (see Irwin et al. 2012 for a review). Many studies have targeted the amygdala's response to emotionally salient auditory stimuli, investigating how these signals are processed and what resulting behavioural responses emerge.

While functional associations indicate anatomical linkages, direct structural evidence for auditory-amygdala pathways has arisen from early neuro-anatomical animal studies. LeDoux and colleagues (1990) found direct auditory inputs into the lateral nucleus of the lateral amygdala from the auditory thalamus and auditory association cortex of rats. A later study by the same group found that fear conditioning to a simple auditory stimulus can be mediated through either of these two pathways (Romanski and LeDoux, 1992). These auditory-amygdala pathways have also been identified in the macaque monkey (Yukie, 2002).

More recent neuroimaging studies in humans have supported these findings from the animal literature. In a diffusion tensor imaging study of the human auditory system, anatomical pathways were found between auditory cortex and the amygdala (Crippa et al., 2010). These white matter tracts where found to have increased fractional anisotropy (thought to reflect fibre density, axonal diameter and white matter myelination) in individuals with tinnitus as compared to healthy controls. However, due to the resolution constraints of this technique, further spatial precision could not be given. Roy et al. (2009) examined the functional connectivity patterns of the amygdala in 65 healthy native English speaking individuals using resting-state fMRI. Specific spontaneous connectivity patterns were found for each of the three main groups

of amygdala subnuclei: superficial (SF), centromedial (CM) and laterobasal (LB) suggesting that each subdivision performs a disparate role. Consistent with the amygdala's reported involvement in fear conditioning (Romanski and LeDoux, 1992), Roy et al. (2009) found the LB nuclei to be functionally connected to the superior temporal gyrus, hippocampus and parahippocampal gyrus. Kim et al. (2012) were the first to report increased functional connectivity between auditory cortices and the amygdala in four tinnitus patients using resting-state fMRI methods. However, this was preliminary data derived through post-hoc analysis and was not corrected for FWE.

To date, no resting-state fMRI study has investigated, *a priori,* auditory-amygdala connectivity in chronic tinnitus sufferers. To determine functional connectivity relationships between auditory cortex and amygdala brain regions (see Figure 6.1.), we applied Patel's conditional dependence measures to the same group of chronic tinnitus patients and matched controls as in our previous study (see Chapter 5.). This novel Bayesian method offers a data-driven approach to determine neural network connectivity (Patel et al. 2006) and has been found to offer excellent sensitivity in estimating the presence of a network connection, as well as a reasonable ability to estimate directionality of true connections

(Smith et al. 2011). A description of the method is given in section 6.2.3.

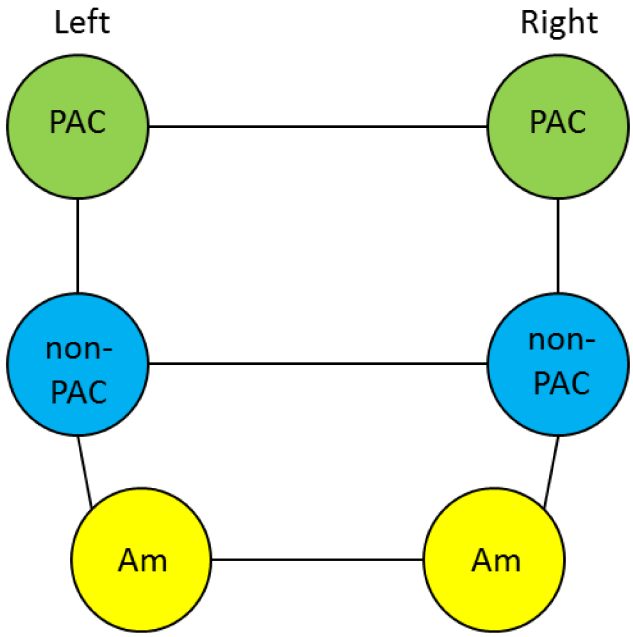


Figure 6.1. Schematic of auditory-amygdala network model. Neural pathways of primary interest are indicated by the black connecting lines. PAC = primary auditory cortex, non-PAC = nonprimary auditory cortex, Am = amygdala.

6.2 METHODS

6.2.1 Participants

Twelve individuals with chronic subjective tinnitus and eleven age and hearing-matched controls took part (refer to sections 5.2.1. to 5.2.3. for full patient demographics and audiological

characteristics). All participants were aged 49 – 75 years without a history of neurological disorder.

6.2.2 fMRI parameters

Resting-state fMRI data were derived from the same cohort of individuals used in Chapter 5. Details of fMRI acquisition parameters and preprocessing steps can be found in sections 5.2.4. to 5.2.6.

6.2.3 Patel's conditional dependence measures

Patel's conditional dependence measures offer a Bayesian approach to determine neural network connectivity (Patel et al. 2006). The method determines hierarchical network connectivity by assessing the relative probability of elevated activity levels amongst voxel pairs (e.g. voxel x and voxel y). By looking at the imbalance between $P(x|y)$ and $P(y|x)$ one can determine two measures: kappa (κ) the amount of functional connectivity between two brain regions and tau (τ), the degree of ascendancy that one region has over another. This is achieved by binarising each voxel or region of interest according to whether or not it is active. Criteria for determining activity is as follows; if a voxel's corresponding time-series is one standard deviation above what is expected under the null hypothesis, then it is labelled active. This threshold is based on

Patel's (2006b) study which investigated functional connectivity in the auditory cortex in response to speech.

Calculating κ is based on the conditional activation of probabilities $P(A_a|A_b)$ and $P(A_b|A_a)$ and the corresponding marginal distributions $P(A_a)$ and $P(A_b)$ where $P(A_a|A_b)$ is the probability that a exhibits elevated activity given that b also exhibits elevated activity, after controlling for any confounding effects. When voxels a and b are functionally connected, κ will differ significantly from 0 and the degree of ascendancy τ can be derived by measuring the degree of dissimilarity between $P(A_a)$ and $P(A_b)$. If voxel a exhibits elevated activity for a sub-period of time in which voxel b is active, then voxel b is considered to be ascendant to a in a hierarchical network.

6.2.4 Interpretation of kappa and tau

Both measures of κ and τ are normalised to fall within a range of -1 to 1. Where two ROIs are functionally connected, κ will differ significantly from 0 (as indicated by lower and upper 95% High Posterior Density [HPD] intervals which will be entirely positive or entirely negative). A κ value close to -1 or 1 suggests a high degree of functional connectivity between ROI pairs. On the condition that $\kappa \neq 0$, τ can be calculated. A positive value of τ indicates that voxel a is ascendant to b and a negative value

indicates that voxels b is ascendant to a. Patel et al. (2006) do caution against the interpretation of ascendancy as a direct measure of influence or effective connectivity as the measures are based on probability and therefore do not necessarily imply physiological influence.

6.2.5 Defining and constructing regions of interest

Regions of interest were functionally defined using sound-evoked data averaged from both tinnitus and no tinnitus groups (as previously described in section 5.2.9.). Voxel co-ordinates with peak activity in bilateral primary auditory cortex, non-primary auditory cortex and amygdala were extracted and used as the centre co-ordinate for each spherical 5 mm radius ROI (see Figures 6.2. and 6.3.). Selection of these ROI's was largely informed by the work of LeDoux et al. (1990) outlined in section 6.1. All ROIs were constructed within the MarsBar toolbox (http://marsbar.sourceforge.net/). Using the Functional Connectivity Toolbox v12.1 (SPM8, http://web.mit.edu/swg/software.htm), the resting-state BOLD time-series of each ROI were band-pass filtered (0.009-0.08 Hz) and had the following noise sources removed: spinal fluid motion, participant motion parameters and white matter signals. The ROI time-series data were then exported in preparation for Patel's analysis.

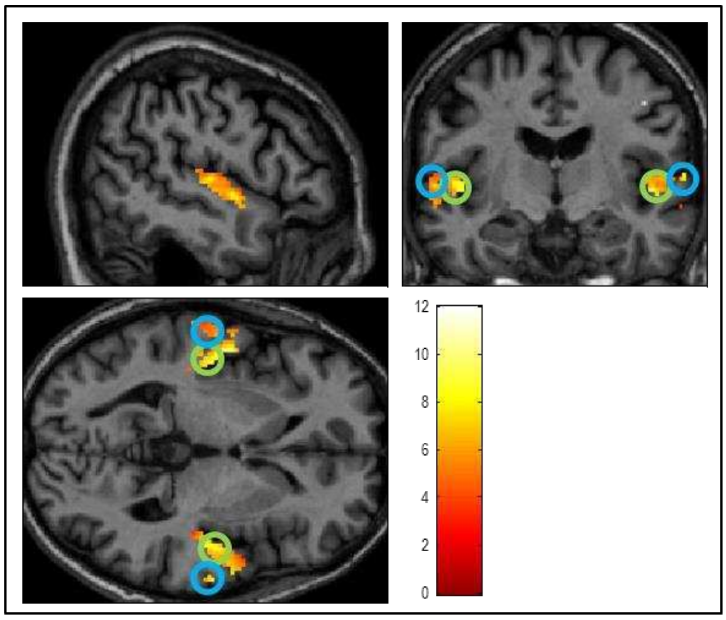


Figure 6.2. Group averaged (n=23) activity to sound vs. silence condition p<0.01 uncorrected. Inclusive auditory mask applied: bilateral primary auditory cortex (circled in green) and nonprimary auditory cortex (circled in blue).

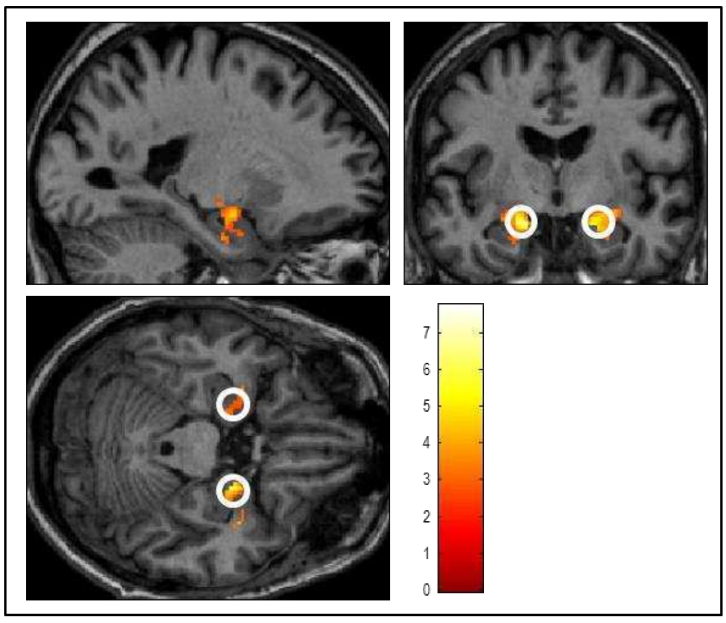


Figure 6.3. Group averaged (n=23) activity to sound vs. silence condition p<0.01 uncorrected. Inclusive amygdala mask applied: bilateral amygdala (circled in white).

Table 6.1. Centre MNI co-ordinates for ROIs based on peak-voxel activity.

	Peak voxel activity co-ordinates		
	X	Y	Z
Left primary auditory cortex	-54	-26	10
Right primary auditory cortex	50	6	6
Left non- primary auditory cortex	-62	4	4
Right non- primary auditory cortex	68	5	5
Left Amygdala	-24	-8	-18
Right Amygdala	20	-8	-18

Patel's conditional dependence measures were computed using R (v3.0), generating a measure of functional connectivity (κ) and ascendency (τ) for every combination of ROI pair. Heterogeneous inter-hemispheric ROI pairs, e.g. left primary auditory cortex to right nonprimary auditory cortex, were disregarded as commissural projections in primary and nonprimary auditory cortices arise predominantly from contralateral homotopic regions (Lee & Winer, 2008).

6.3 RESULTS

All significant kappa and corresponding tau values along with lower and upper 95% High Posterior Density (HPD) intervals are given in Tables 6.2. and 6.3.

Table 6.2. Significant Kappa values and corresponding tau values for no tinnitus group. Lower and upper 95% HPD intervals are given.

ROI pairs	Kappa median	HPD lower	HPD upper	Tau median	HPD lower	HPD upper
01:02	0.28	0.19	0.38	-0.05	-0.21	0.11
01:03	0.39	0.3	0.48	-0.11	-0.25	0.04
01:04	0.27	0.17	0.37	-0.1	-0.24	0.07
02:03	0.2	0.11	0.3	-0.06	-0.21	0.1
02:04	0.24	0.15	0.34	-0.05	-0.2	0.12
03:04	0.14	0.04	0.23	0.02	-0.14	0.18
03:06	0.15	0.06	0.25	0.01	-0.15	0.16
05:06	0.25	0.16	0.34	0.02	-0.13	0.17

Table 6.3. Significant Kappa values and corresponding tau values for tinnitus group. Lower and upper 95% HPD intervals are given.

ROI pairs	Kappa median	HPD lower	HPD upper	Tau median	HPD lower	HPD upper
01:02	0.38	0.29	0.46	0.02	-0.12	0.16
01:03	0.28	0.19	0.36	-0.04	-0.18	0.11
01:04	0.27	0.18	0.35	-0.01	-0.16	0.14
02:03	0.27	0.18	0.35	-0.06	-0.2	0.09
02:04	0.31	0.22	0.4	-0.04	-0.18	0.11
03:04	0.26	0.17	0.34	0.02	-0.13	0.16
05:06	0.32	0.23	0.41	-0.1	-0.24	0.04

1=left Primary Auditory Cortex, 2= right Primary Auditory Cortex, 3=left Nonprimary Auditory Cortex, 4=right Nonprimary Auditory Cortex, 5=left Amygdala, 6=right Amygdala.

Schematic representation of these results are provided in Figure 6.4. Overall, no significant differences in functional connectivity strength (kappa) or ascendancy (tau) were found between groups. Both tinnitus and no tinnitus groups showed similar levels of

significant functional connectivity between left and right primary and non-primary auditory cortices. Likewise, significant within-hemisphere functional connectivity between primary and non-primary auditory cortex was found in both groups. Significant functional connectivity between bilateral amygdalae was also found in both groups. These connectivity relationships did not engage any auditory ROI in the tinnitus group, although one significant functional connection was measured between the left non-primary auditory cortex and the right amygdala for the no tinnitus group. However, as this was a non-homologous inter-hemispheric ROI pairing it was discounted based on our *a priori* assumptions. No significant tau values were found between any ROI pair defined in our model, indicating a lack of ascendancy amongst our chosen brain regions.

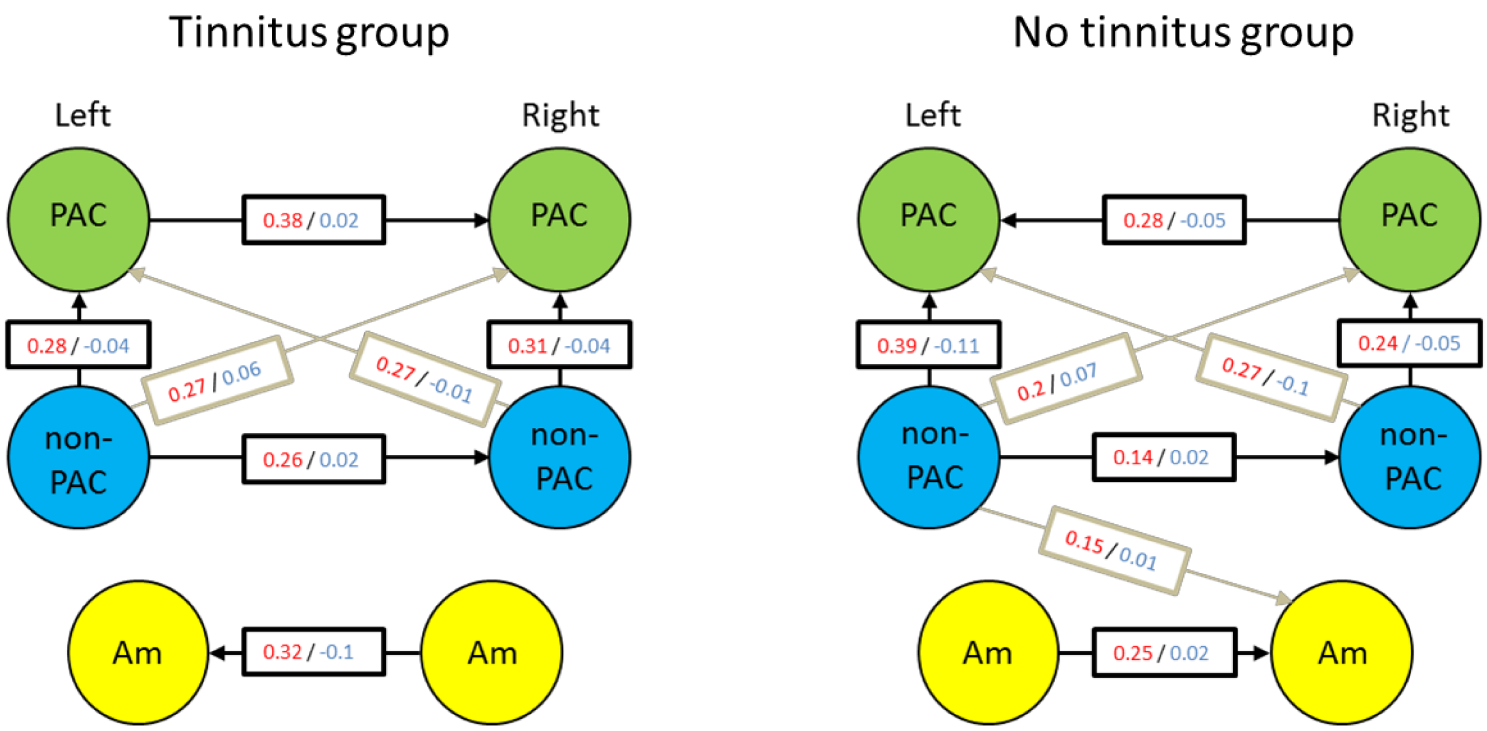


Figure 6.4 Significant Kappa values and corresponding Tau values (direction of ascendancy indicated by arrows). No significant Tau values were found in either group. Grey lines indicate non-homologous inter-hemispheric ROI pairs of no interest.

6.4 DISCUSSION

In this exploratory follow-up study we applied Patel's conditional dependence measures to determine auditory-amygdala connectivity in individuals with chronic tinnitus. This *a priori* exploration of auditory-amygdala connectivity in tinnitus patients is the first of its kind using resting-state fMRI.

We found a strong degree of functional connectivity (as indicated by significant kappa values) between homologous auditory and amygdala ROI pairs, which was similar for both groups. This finding corroborates our initial resting-state study which used independent component analysis and partial correlation methods to show robust auditory network connectivity in the same group of participants. Although bilateral amygdala connectivity was significant for both groups, it did not differ between groups nor did either amygdala engage with any other auditory region specified within the model. This disagrees with Kim et al. (2012) who, using a seed to voxel correlation approach, found increased connectivity between auditory cortices and the amygdala in their tinnitus patients when compared to age-matched controls. This functional involvement of the amygdala exclusive to Kim's study might be explained by the use of different methods or indeed by differences in tinnitus distress amongst participant groups in the two studies.

The present study featured individuals with relatively low global THQ scores, rather than individuals with severe or catastrophic levels of tinnitus distress which have previously been found to alter functional connectivity (Wineland et al. 2012; Burton et al. 2012). However, this remains speculative as tinnitus distress was not measured in the study of Kim et al. (2012).

No significant tau values were found between any ROI pair defined in our model. This indicates a lack of ascendancy amongst our chosen brain regions, most likely because ROI pairs showed strong functional connectivity and were therefore co-actively engaged rather than ascendant to one another. When interpreting these results one must also consider the sensitivity of the applied method. Smith et al (2011) compared a number of connectivity estimation approaches, including Patel's measures, using a variety of simulated fMRI datasets. Approaches were assessed on their ability to determine network connectivity and directionality. Whilst Patel's tau method performed the best in estimating directionality, its degree of accuracy was still only around 15 % greater than chance alone. Patel's kappa on the other hand was very sensitive in predicting connectivity strength, achieving around 90 % accuracy. Applying Patel's conditional dependence measures to our auditory-amygdala model provided a means to quantify relationships amongst specified ROI pairs in terms of connectivity strength

(kappa) and directionality (tau). This allowed us to compare against previously applied methods of partial correlation and independent component analysis, corroborating our earlier findings and providing additional information about ascendancy.

7 EXPLORING THE AMYGDALA RESPONSE TO EMOTIONALLY EVOCATIVE SOUNDSCAPES IN PEOPLE WITH TINNITUS: A SOUND-EVOKED FMRI STUDY

7.1 INTRODUCTION

The limbic system is a convenient way of describing a number of functionally and anatomically connected brain structures that regulate autonomic and endocrine function, particularly in response to emotional stimuli. The limbic system forms the "feeling and reacting brain" but many of the brain areas within the limbic system are also implicated in memory, particularly emotional memory. Cortical parts of the limbic system include (the hippocampus, insula cortex, orbital frontal cortex, subcallosal gyrus, cingulate gyrus and parahippocampal gyrus). Subcortical parts of the limbic system include the olfactory bulb, hypothalamus, amygdala, septal nuclei and some thalamic nuclei.

One limbic structure in particular, the amygdala, is believed to play a role in processing subjective 'phantom' sounds and has been proposed in models of tinnitus to account for the emotional distress that can occur for some sufferers. Jastreboff's neurophysiological model of tinnitus (1990) includes the amygdala as a key component. Central to this model is the concept that sounds which evoke strong emotional reactions activate limbic and

autonomic systems. Sounds can be real physical sounds or phantom sounds such as tinnitus. Typically, repeated exposure to the same sound results in habituation, where the person becomes less aware of the sound. However when there is an emotional reaction to the sound, any subsequent exposure to the same sound stimulus maintains a conscious awareness of the sound, without habituation. For de Ridder et al. (2011), a key factor in chronic tinnitus concerns the role of emotional memories (Figure 2.3.). Such memory mechanisms play a role in persistent tinnitus because they result in an extended state of hypervigilance which promotes a sustained state of awareness about the tinnitus. The amygdala is highlighted as a structure of major functional importance because it is not only part of the 'distress network' but it also overlaps with brain areas involved in central control of the autonomic system, consistent with Jastreboff's neurophysiological model (see Figure 2.2).

Despite its projected role in tinnitus, the involvement of the amygdala has not been directly measured until more recently. For example, Shulman et al. (1995) found a decrease in cerebral perfusion in the amygdala of two patients with severely bothersome tinnitus using single-photon emission computed tomography (SPECT). Regardless of the study's small sample size, interest in this area has grown and further evidence has emerged

from both the animal (Romanski and LeDoux, 1992; Yukie, 2002) and human literature (Roy et al. 2009; Crippa et al. 2010; Irwin et al. 2011; Kumar et al. 2012) which implicates the amygdala and auditory brain regions in the perception of emotionally evocative sounds (both real sounds and phantom sounds).

The emotional experience of stimulus perception can be described by two main factors (Mauss & Robinson, 2009). The first factor relates to ratings of pleasantness (valence) and the second factor relates to ratings of vibrancy (arousal). Stimuli may be separated into three categories of pleasantness (unpleasant, neutral and pleasant) to assess the influence of valence (Carpenter-Thompson et al. 2014). Alternatively, analysis may collapse unpleasant and pleasant stimuli into one 'affective/emotionally evocative' category.

To decipher specifically how information is relayed between the auditory cortex and amygdala and whether it is modulated by valence or the acoustic features of the stimulus, Kumar et al. (2012) used dynamic causal modelling, an effective connectivity measure. The study used a group of 16 young adults (aged 22-35) with normal hearing. According to the models tested, they concluded the following: unpleasant sound stimuli are first processed and decoded in the auditory cortex before any emotional response can be assigned by the amygdala. Forward connections

from the auditory cortex to the amygdala are modulated by acoustic features. The amygdala then modulates the auditory cortex in accordance with the pleasantness of sounds. It should be noted however that Kumar et al. (2012) only investigated unpleasant sounds. Studies have indicated functional associations between sensory and emotional centres of the brain (Murphy et al. 2003; Janak and Tye, 2015). The amygdala is significant as it mediates emotional responses to sensory stimuli. Urban soundscapes have been used successfully in normal hearing adults (aged 21-55 years) to examine the role of auditory and limbic brain networks in processing unpleasantness. For example, Irwin et al. (2011) found that highly pleasant or highly unpleasant soundscapes relative to neutral soundscapes evoked greater activation of a number of auditory brain regions including the auditory cortex and the posterior insula, and non-auditory brain regions such as the amygdala (see Figure 7.1. for amygdala response activation). A direct between-hemisphere comparison of amygdala response activation revealed no differences. In contrast to the substantial changes with pleasantness, ratings of vibrancy had little effect on the overall brain response.

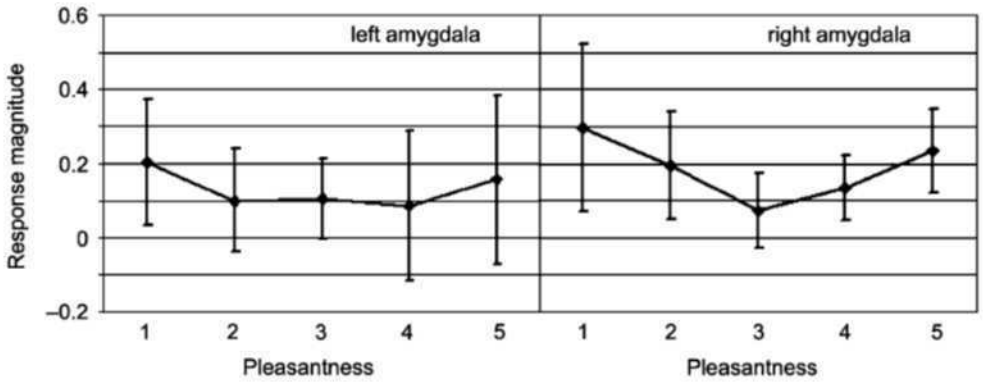


Figure 7.1. Plots of mean response magnitude for the left and right amygdala across the five categories of pleasantness (1 = very pleasant, 3 = neutral, 5 = very unpleasant). The scale on the y-axis represents the parameter estimate of brain activity, and error bars represent the 95% confidence intervals. Taken from Irwin et al. (2011) with permission.

A majority of the studies examining the response to the emotional dimension of stimulus processing have enrolled young healthy participants (Kumar et al. 2012; Irwin et al. 2011; Costa et al. 2010; Bradley and Lang, 2000). However, it has been shown that age can affect the way in which the brain responds to emotional stimuli (an example from Mathers et al., 2003 is described below). Explanations for this range from the neurophysiological; such as age-related atrophy of neural systems (Tsai et al. 2000), to the psycho-social; such as the theory of socio-emotional selectivity which predicts that decreasing time horizons in old age motivates the older person to prioritise positive information and ignore negative information (Carstensen et al. 2003). Since many people

with tinnitus are older, not younger, any studies that consider emotional coding in people with tinnitus need to consider the potential confounding impact of age. One example in the visual domain may be relevant here. Mathers et al. (2003) compared amygdala activation in seventeen younger (aged 18-29) and seventeen older (aged 70-90) adults using event-related functional MRI. Using positive, negative and neutral emotionally evocative images, it was found that older adults showed a reduced signal change in the amygdala when presented with negative images, whilst maintaining or increasing reactivity to positive images relative to a baseline signal, averaged across all trials. Although as a visual study expectancy of a similar result within the auditory domain should be tentative. Nevertheless, visual and auditory emotional stimuli have previously been found to evoke the same brain networks. For example, Bradley and Lang (2000) conducted an electrophysiology experiment measuring autonomic and facial electromyographic activity in response to naturally occurring sounds. They found that the general pattern of physiological reactions elicited when listening to emotionally evocative sounds were similar to previous studies of emotionally evocative picture viewing. Another study by Pourtois et al. (2005) used positron emission tomography (PET) to explore which brain regions were activated in response to images of facial expressions and auditory

sound clips of emotional voices. Results of this study suggested that multisensory perception of emotion from visual and auditory modalities converged in heteromodal brain regions. Taken together, these two studies provide some evidence to suggest that age differences found in the emotional coding of visual stimuli as reported by Mathers et al. (2003), could also be relevant in the auditory domain.

Only two studies have targeted a tinnitus population thus far. The first used an emotional sentence listening task in an attempt to stimulate cognitive emotional processing in individuals with varying degrees of tinnitus distress (Golm et al. 2013). The task comprised three verbal sentence types, neutral (e.g. regularly I look at my watch), negative (e.g. I often feel sorry for myself) and tinnitus-related (e.g. I will never get rid of the noise). Compared to healthy age- and hearing-matched controls, tinnitus patients showed stronger activations when reading tinnitus-related sentences relative to neutral sentences in several parts of the limbic system. Brain regions included anterior cingulate cortex, mid-cingulate cortex, posterior cingulate cortex, retrosplenial cortex and insula as well as frontal areas. The tinnitus group were also divided according to levels of perceived tinnitus distress. Individuals with a score of 31 or higher on the Tinnitus Questionnaire were assigned into the high distress group. Direct group comparisons (high

distress versus low distress) revealed stronger activity in the left middle frontal gyrus in the high tinnitus distress group, a brain region which Jastreboff (1990) had previously implicated in the integration of sensory and emotional characteristics of tinnitus. Although this study showed some limbic activity, specific amygdala involvement was not found.

The second and most recent study by Carpenter-Thompson et al. (2014) used emotionally evocative sounds chosen from the International Affective Digital Sounds database to assess the effects of tinnitus on emotional processing. The stimulus set was 30 pleasant (P), 30 unpleasant (U) and 30 neutral (N) sound clips. In an effort to control for hearing loss, three participant groups were included: hearing loss with tinnitus (TIN group, n=13), hearing loss without tinnitus (HL group, n=12) and no hearing loss without tinnitus (NH group, n=12). All groups were age and gender matched. The authors expected to measure an elevated response in the amygdala, parahippocampus and insula regions of the tinnitus group in response to emotionally evocative sounds, relative to the control groups. They also hypothesised that the tinnitus group would show a heightened response in auditory regions relative to the other two groups. Contrary to the author's hypothesis, the tinnitus group did not show an elevated amygdala response in either the P>N or U>N contrasts. Instead, a decreasing

trend in amygdala activations across groups was observed such that NH>HL>TIN for the two emotionally evocative sound contrasts (P>N and U>N). Here the amygdala response was significant only at an uncorrected threshold level of $p<0.001$ in the NH group for emotionally evocative sounds. Direct between-group statistical comparison of emotionally evocative sound contrasts (P>N and U>N) failed to show any significant differences in amygdala reponse. The authors suggested two reasons for this: (1) individuals with tinnitus might re-route their emotional signalling pathway to avoid the amygdala and its connections to the auditory cortex, (2) because their participants had mildly bothersome tinnitus, and so may have habituated to the tinnitus. However, we propose a third explanation; it is well known that detecting signal from the amygdala is challenging with fMRI due to its size and location (Irwin et al. 2012; Chen et al. 2003). It is therefore conceivable that their results were restricted by their choice of fMRI parameters, which were not optimally suited for detection of activity in the amygdala.

Both tinnitus studies (Golm et al. 2013; Carpenter-Thompson et al. 2014) consider the amygdala as a single homogenous body yet it can be anatomically delineated into 3 major subdivisions (Amunts et al. 2005); the LB nuclei, the SF subnuclei and the CM subnuclei (see Figure 7.2.). What's more, evidence for differing

functional response properties among amygdala subnuclei is starting to grow, however they are yet to be clearly understood (LeDoux et al., 1984, 1990a; Aggleton et al., 1980; Romanski and LeDoux, 1993; Ball et al. 2007; Kumar et al. 2012).

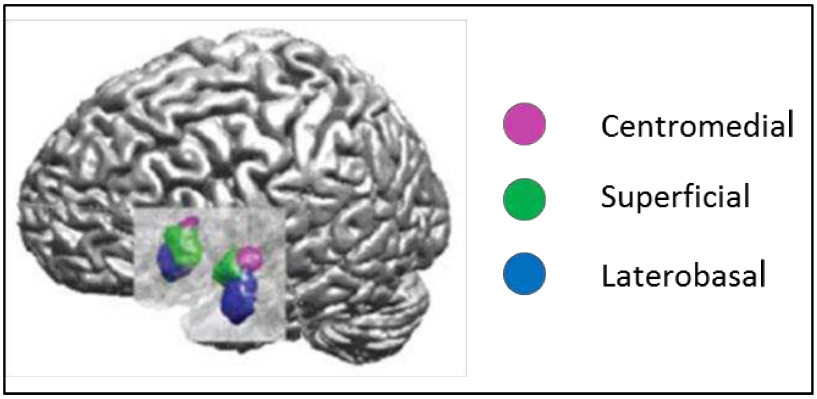


Figure 7.2. Major subnuclei divisions of the amygdala. Schematic adapted from Amunts et al. (2005).

This study investigated how the presence of chronic tinnitus impacts upon emotional processing in older, hearing-impaired adults. Using a novel double-echo imaging sequence for optimal detectability of subcortical activity, an *a priori* approach to investigate the amygdala's response to emotionally valent soundscapes i.e. very pleasant, neutral and very unpleasant sounds was undertaken. The following two hypotheses were tested;

1) Sound clips rated with the highest and lowest levels of emotional valence elicit stronger amygdala activity than neutral sound clips.

2) People with tinnitus have greater amygdala activity in response to emotionally valent sounds (relative to neutral sounds) compared to age and hearing-matched controls.

7.2 METHODS

This study has adapted the experimental protocol used by Irwin et al. (2011) for the purposes of eliciting responses to emotionally evocative sounds in individuals with tinnitus. This protocol has previously been found to produce sound-evoked amygdala and auditory activation (Irwin et al. 2011).

7.2.1 Participants

The same well-matched 23 individuals with and without chronic subjective tinnitus took part (refer to sections 5.2.1. - 5.2.3. for full patient demographics and audiological characteristics).

7.2.2 Sound stimuli

The present study used 84 sound clips derived from a previously published fMRI study (Irwin et al. 2011). This subset of sound clips were chosen to vary among natural and mechanical real-world sound sources and were previously rated as being very pleasant e.g. bird song, very unpleasant e.g. car crash or neutral e.g. footsteps. For a detailed description of the strategy used to rate the sound clips please refer to Irwin et al. (2011). In brief, five participants (aged between 21-40) rated a total of 219 sound clips

using a 9 point visual analogue scale with anchor points at either end e.g. 1 = unpleasant, unhappy and 9 = pleasant, happy. The intensity of all sound clips was matched at 71 dBA by taking a root-mean-square level average over the 7.8 second clip duration. In an effort to preserve ecological validity of listener experience, frequency content was not altered to compensate for participant hearing levels. Their hearing loss could have impaired their perception of sound stimuli. According to Kumar et al. (2008), certain acoustic features of sound such as spectral frequency (in the range of 2.5 kHz and 5.5 kHz) and temporal modulation (in the range of 1 to 16 kHz) may serve as predictors of perceived unpleasantness to sound. This should therefore be considered as a potential confound although we note that both groups were well matched in hearing profile and their hearing thresholds up to 5 kHz was on average far better than the intensity level of the delivered sound stimuli.

Figure 7.3. shows an illustrative example of the sound clip sequence design which participants had to listen to whilst in the MRI scanner. Each sound clip had a 50 ms onset and offset ramp. Sound clips were presented to participants in a pseudo-randomised order, such that the three categories of sound (neutral, very pleasant, and very unpleasant) and silence period occurred within a single block that was repeated 16 times. Within each block two

segments of sound clips of the same category (or silence) were played in quick succession (brief inter-stimulus gap of 450 ms) in order to elicit a maximal response for a given sound category. Each participant therefore listened to each sound category (and silent periods) a total of 32 times. The sequence of sounds was constrained to avoid two sequential blocks of the same sound category. Three different unique orderings of sounds were created (i.e., not similar within or across blocks) and randomised across subjects (refer to Figure 7.3.).

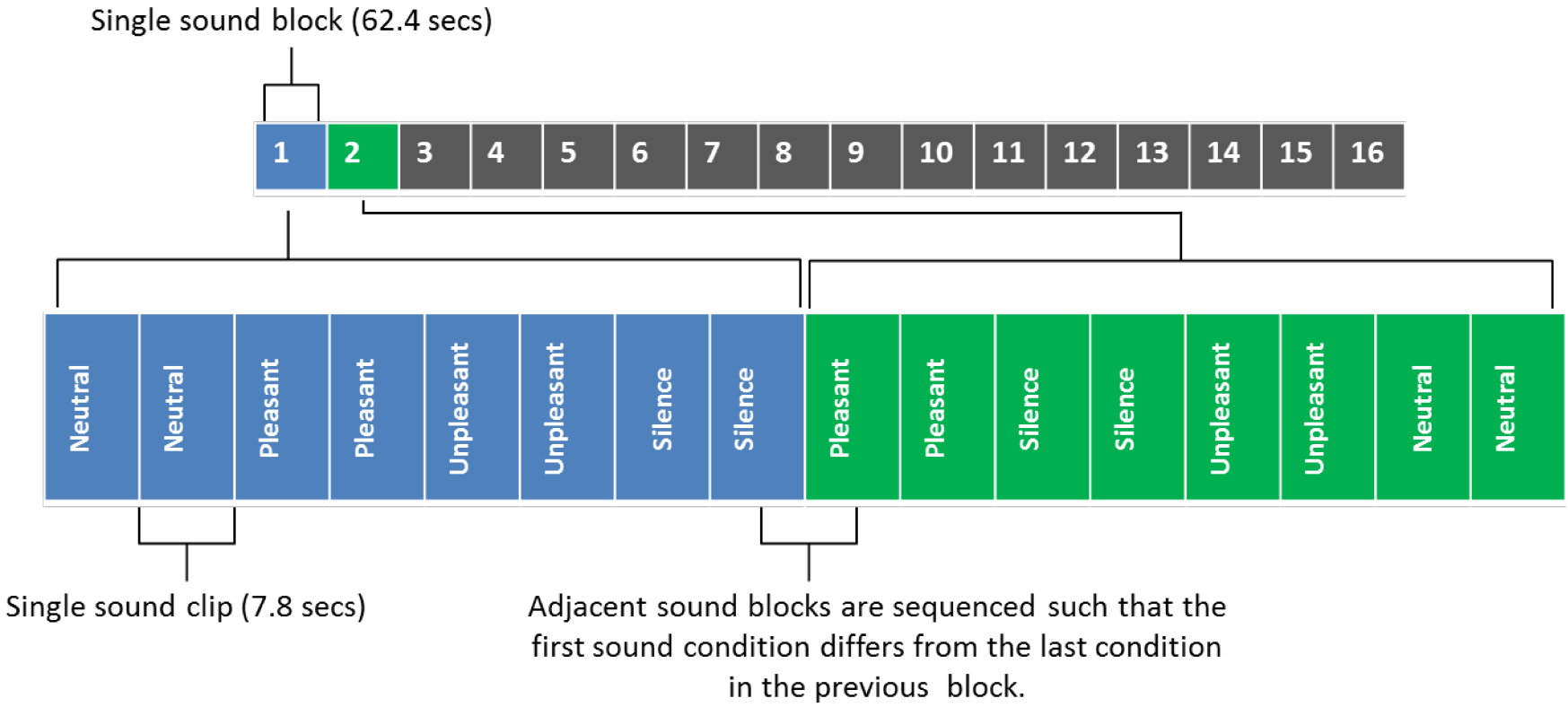


Figure 7.3. Sound clip sequence, with blocks 1 & 2 being broken down into their component parts for illustrative purposes. Each sound block contains 4 different sound conditions / 8 sound clips (each sound clip is repeated in quick succession; with a brief inter-stimulus gap of 450 ms). Total duration of all 16 sounds blocks was 16 minutes 38 seconds.

7.2.3 fMRI acquisition

Data were obtained using a Philips Achieva 3T MR scanner (Philips Medical Systems, The Netherlands) and an 8-channel SENSE receiver head coil. Whole brain functional images were acquired for each participant using the same double-echo imaging sequence as previously for optimal detectability of subcortical activity (Irwin et al. 2012) (echo times: 20, and 45 ms, TR = 8250ms, acquisition time 2420 ms, 36 slices, 0 mm slice gap, FOV = 240 x 240mm along AC-PC line, voxel size 3x3x3 mm, acquisition matrix 80 x 77, 120 volumes, SENSE factor = 2.3, descending slice order). Slice acquisition angle was tilted to capture as much of the brain as possible, with the same negative sloping pitch in the sagittal plane for each subject (see Figure 7.4.).

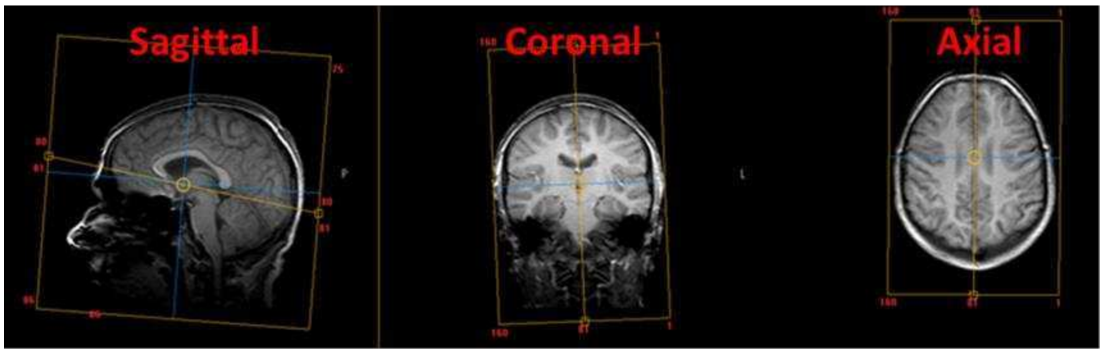


Figure 7.4. Example of anatomical scan showing negative slice acquisition angle (through the sagittal plane) aligned to anterior and posterior commissure.

A sparse sampling sequence was adopted, which gave long periods of no scanner noise (5830 ms) in between acquisitions (Hall et al., 1999). Sound clips were presented as shown in Figure 7.5. A five minute MPRAGE anatomical image was also acquired for each participant (160 slices, FOV = 256, voxel size 1x1x1 mm).

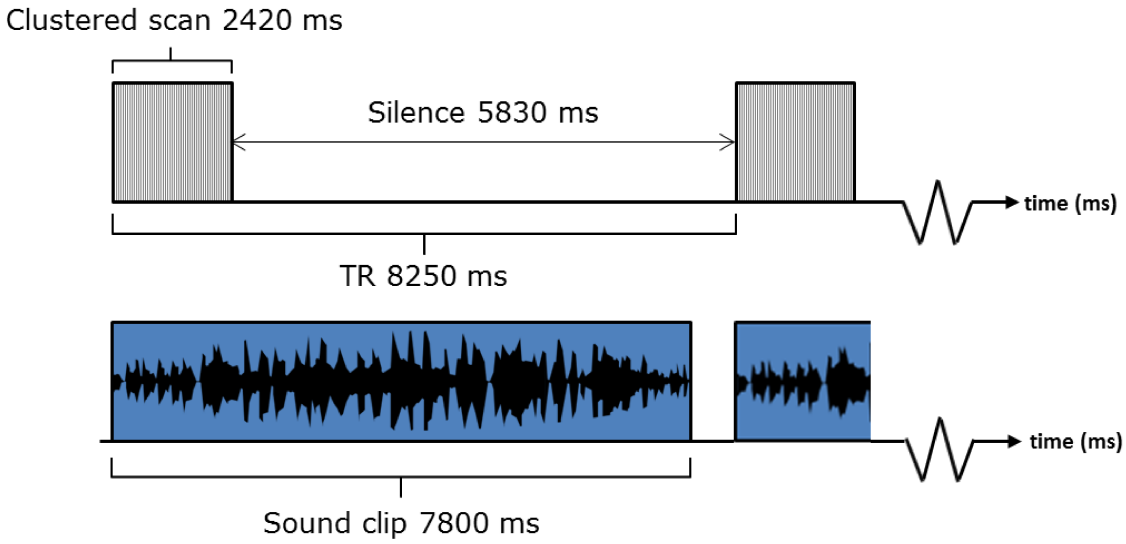


Figure 7.5. fMRI listening task paradigm.

The participants were instructed to keep still with their eyes closed and listen to the sounds. Scanning duration was approximately 16 minutes. Sound stimuli were delivered through customised circum-aural ear defenders which could provide up to 40 dB attenuation. The ear defenders also employed active noise cancellation, helping to reduce scanner noise by up to an additional 35 dB (Hall et al. 2009). The noise reduction procedures were considered critical for

the perception of the sounds, but also to make the scanner environment more suitable for people with tinnitus, whose tinnitus sound could otherwise be masked by the scanner noise or even exacerbated.

7.2.4 Preprocessing steps

Functional MRI data were preprocessed using statistical parametric mapping software SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Images were realigned, co-registered with the participant's high resolution anatomical scan, normalised to the Montreal Neurological Institute (MNI152) template and spatially smoothed (4 mm full-width at half maximum). A 4 mm smoothing kernel was chosen because of the desire to limit signal spread in order to increase discriminability of small activation regions such as the amygdala and inferior colliculus (Morawetz et al. 2007). A double echo sequence was used to image two specific areas of interest: bilateral auditory cortex and amygdala. These data were combined to form a weighted average of both echo images, improving signal to noise ratio prior to further analysis (Posse et al. 1999; Marciani et al. 2000). Refer back to section 5.2.5. for details relating to the double echo imaging sequence.

7.2.5 Analysis approach summary

We adopted a general linear model approach in this analysis. A first level fixed effects analysis was performed on each individual's smoothed data. The following sound contrasts were considered; sound>silence, very pleasant>neutral, very unpleasant>neutral and salient>neutral. Here, 'salient' is defined as the sum of both very pleasant and very unpleasant sound conditions and 'sound' is defined as the sum of all sound conditions. Within group whole brain analysis and between group whole brain t-tests were also conducted. To test our *a priori* hypotheses relating to sound-evoked amygdala activation, a ROI analysis was used. Finally, data from the ROI analysis were assigned on to anatomically defined probabilistic maps of the amygdala in an effort to uncover amygdala response patterns at a subnuclei level.

7.2.6 General effects of sound on brain activity

The first analysis sought to identify brain regions which were significantly responsive to sound in order to confirm that the study was detecting simple sound-related activity in the expected regions of interest. This was achieved by comparing the whole group averaged (n=23) brain response to the sounds versus silence condition. Results were corrected for family wise error and thresholded at $p<0.05$ (see Figure 7.6.).

Beyond the auditory cortex, the main region of interest was the amygdala. Given its modest size and complex make up of multiple inter-connected nuclei, hypotheses regarding its response to emotional stimuli remained unspecific in terms of distinct amygdala circuitry, only making general predictions about overall amygdala response magnitude. However, in light of the previous evidence for differing functional response properties among amygdala subnuclei I felt further exploration at the subdivision-level was warranted.

7.2.7 Measuring amygdala response magnitude to emotionally evocative sounds

To define amygdala activity I used the left and right hemisphere voxel co-ordinates which corresponded to each participant's peak maxima amygdala activity in response to the salient versus neutral sound condition. Here, a single voxel (smoothed to 4 mm full-width at half maximum) has a volume of 64 mm^3 which is approximately 27 times smaller than that of an average human amygdala. However, choosing to define the entire amygdala as an anatomical ROI can bias results towards the null hypothesis as true activations will only make up a small proportion of the ROI (Poldrack and Mumford, 2009). Results were masked ($p<0.05$, uncorrected) using the MNI amygdala template (Amunts et al. 2005) to ensure

that peak activity resided within these predefined anatomical amygdala regions. Beta values derived from each participant's peak amygdala activity were extracted using SPM8 and averaged amongst each participant group, providing an overall estimate of amygdala response magnitude for each sound condition. These data were then submitted to a mixed model analysis of variance (ANOVA), with two within-group factors; hemisphere (left and right) and valence (very pleasant, neutral and very unpleasant) and one between-group factor; (no tinnitus and tinnitus).

7.2.8 Defining the extent of amygdala activation

To better understand the pattern and origin of amygdala activation for each individual, the extent of subnuclei amygdala percentage activation was calculated using the SPM anatomy toolbox v1.8 (http://www.fz-juelich.de/inm/inm-1/DE/Forschung/_docs/SPMAnatomyToolbox/SPMAnatomyToolbox_node.html, Eickhoff et al. 2005). This was achieved by mapping each participant's functional brain response to the salient > neutral sound condition ($p<0.05$, uncorrected) in to stereotaxic space using a pre-defined probabilistic map of the amygdala (Amunts et al. 2005). The number of "activated" voxels which fell within the pre-defined amygdala subnuclei space was then expressed as a percentage of the total number of voxels assigned to that same

space. Incidence maps for each group were also created to visualise the consistency of amygdala response to emotional sounds (see Figure 7.10 and 7.11). This was achieved by first creating a binary image for each individuals response to salience > neutral sound condition (thresholded at $p<0.05$, uncorrected). These binary images were then summated within each group and masked using the same probabilistic map of the amygdala as before (Amunts et al. 2005). Finally, outlines of the amygdala subnuclei (LB, CM, SF) with full extent assignment probability (Amunts et al. 2005) were overlaid on to the incidence maps, aiding visual interpretation.

Unlike other cortical brain areas, the amygdala cannot be mapped via sulcal landmarks. Precise localisation of the amygdala and its subnuclei require microscopic observation. Amunts and colleagues (2005) produced these cytoarchitectonically verified maps of the amygdala based on the observations of 10 post-mortem brains (five males, five females; mean age 64.9 years). Cytoarchitectonic mapping was performed in serial, cell-body stained histological sections. Percentage activation of amygdala subnuclei along with statistical outputs for left and right peak voxel amygdala co-ordinates are presented in Tables 7.1. and 7.2.

7.3 RESULTS

7.3.1 Sound-related activation of ascending auditory pathways

The first analysis sought to detect the presence of sound-related brain activity within the auditory pathways. A one-sample t-test of whole group averaged (n=23) brain response to the sounds versus silence condition ($p<0.05$ FWE corrected) revealed robust sound-evoked activation within the structures of the ascending auditory pathways. Significantly active neural structures included the inferior colliculus, medial geniculate body and the primary auditory cortex, across both brain hemispheres (see Figure 7.6.). A two-sample t-test of the same sound versus silence condition revealed no significant differences between groups ($p>0.05$ FWE corrected).

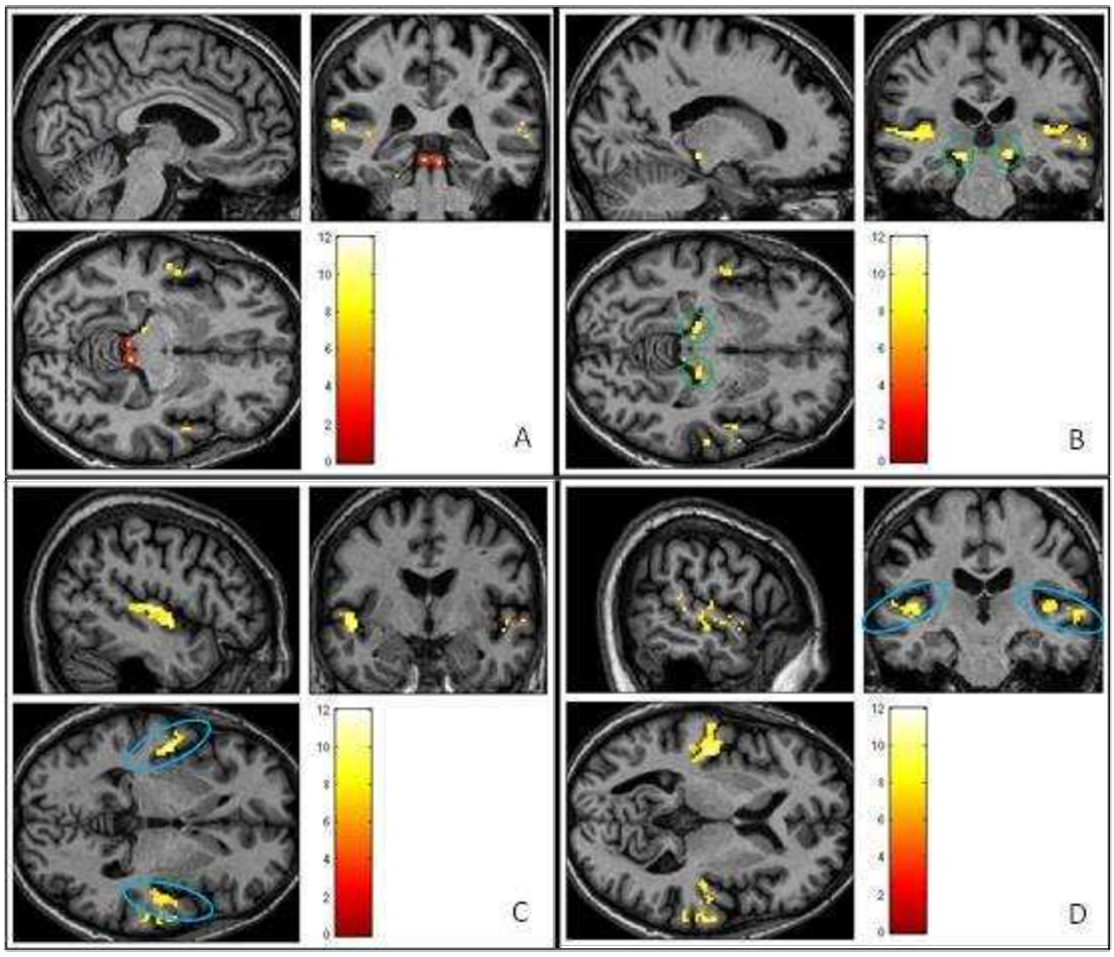


Figure 7.6. Shows group averaged (n=23) activation of ascending auditory structures in response to all sound conditions (very pleasant, neutral and very unpleasant) > silence (p<0.05 FWE corrected). (A) Inferior colliculus circled in red. (B) Medial geniculate body circled in green. (C) Primary auditory cortex circled in blue. (D) Primary auditory cortex circled in blue.

7.3.2 Sound evoked amygdala activity

A one-sample t-test of whole group averaged (n=23) brain response to the salient > neutral sound condition masked by the amygdala template revealed activation of both amygdalae (p<0.05,

uncorrected). This did not survive statistical thresholding after implementing FWE small volume correction.

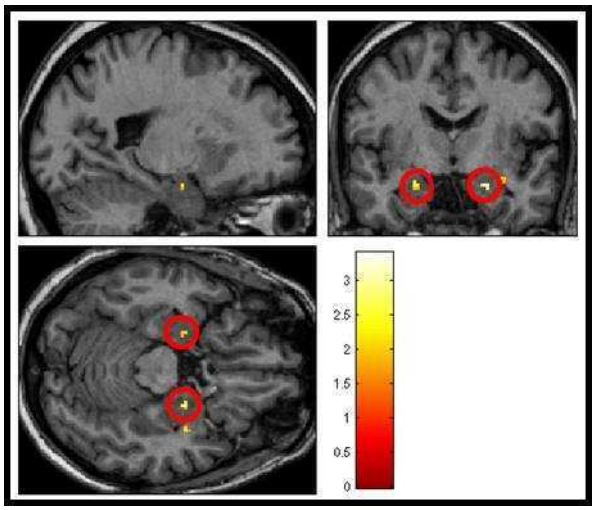


Figure 7.7. Shows group averaged (n=23) activation of amygdala structures (circled in red) in response to salience > neutral sound condition, masked with amygdala template (p<0.05 uncorrected).

This initial finding provided support for our first hypothesis which predicted a stronger amygdala response to emotionally evocative sound stimuli as compared with neutral sounds. To address our second hypothesis which predicted that people with tinnitus have greater amygdala activity in response to emotionally evocative sounds (relative to neutral sounds) compared to age and hearing-matched controls, left and right amygdala response patterns to all sound conditions were contrasted between groups. Group averaged beta values ($p<0.05$, uncorrected) derived from each individual's peak amygdala activity co-ordinates are displayed in Figure 7.8.

7.3.3 Sound evoked amygdala activity: the effects of pleasantness

The U-shaped functions indicated in Figure 7.8. demonstrate a broadly equivalent response in amygdala to both very pleasant and very unpleasant sounds in both brain hemispheres.

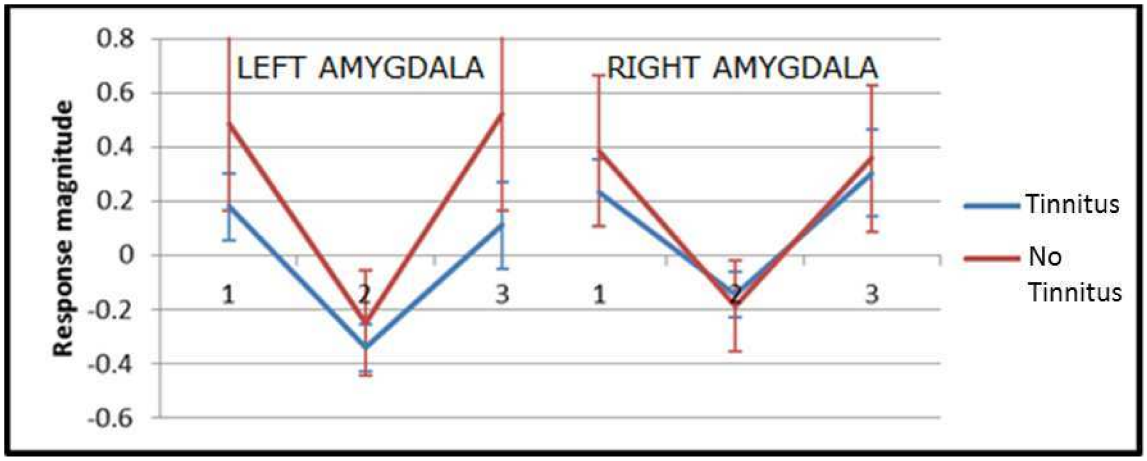


Figure 7.8. Plots of mean response magnitude (beta values p<0.05, uncorrected) for the left and right amygdala across three categories of pleasantness (1) very pleasant (2) neutral (3) very unpleasant. Error bars represent 95% confidence intervals.

Contrary to our second hypothesis, results from the mixed model ANOVA revealed no main between-subject effect of group ($p=0.072$, effect size $r=0.38$) thus indicating that the amygdala's overall response was generally the same between 'tinnitus' and no 'tinnitus' groups (see Figure 7.9.).

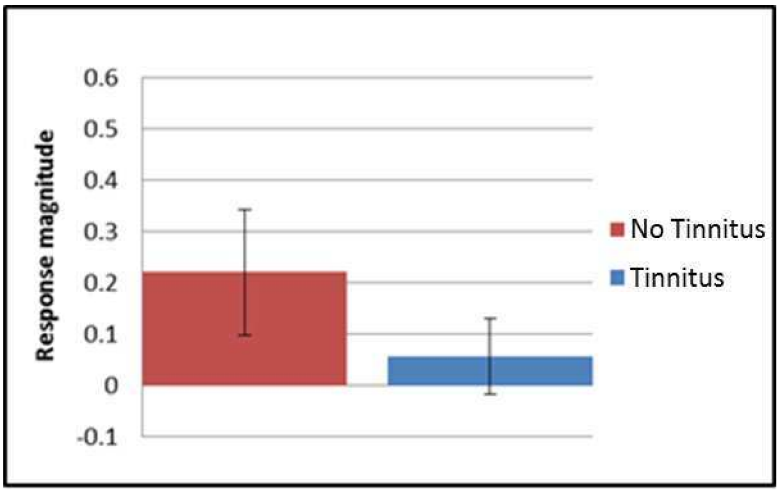


Figure 7.9. Plot of overall mean amygdala response magnitude (beta values) to all sound conditions as a function of group. Error bars represent 95% confidence intervals.

A direct comparison of amygdala response activation between brain hemispheres also revealed no significant differences (p=0.608, effect size *r*=0.11) and there was no interaction between hemisphere and group (p=0.166, effect size *r*=0.29). However as predicted in our first hypothesis, there was a highly significant main effect of valence (p<0.0001, effect size *r*=0.91) with the amygdala showing the greatest response to very pleasant sounds and very unpleasant sounds as compared with neutral sounds. There was also a significant interaction effect between sound valence and group (p=0.035, effect size *r*=0.38). This indicated that the amygdala's response pattern to different sound valences differed across tinnitus and no tinnitus groups. Planned contrasts in

the ANOVA showed that the no tinnitus group had a significantly greater amygdala response to very pleasant > neutral sounds (p=0.024, effect size *r*=0.47) and very unpleasant > neutral sounds (p=0.043, effect size *r*=0.43) compared to the tinnitus group. Direct comparison of the amygdala's response to neutral sounds were not significantly different between groups (p=0.77, effect size *r*=0.06) suggesting that both groups had a similar 'baseline reaction' to neutral sounds.

7.3.4 Amygdala subnuclei activation

Percentage activation of amygdala subnuclei along with associated cluster size and peak voxel statistics (T and Z scores) for the tinnitus and no tinnitus groups are presented below in Tables 7.1. and 7.2. respectively. This assignment of peak activation site to micro-anatomically defined amygdala subnuclei regions in a probabilistic fashion provided additional information as to the extent and location of amygdala subnuclei activation for each individual. However, when interpreting these data it is important to acknowledge our limitations in spatial resolution based on our fMRI parameters e.g. functional voxel size and level of applied smoothing (as will be discussed in section 7.4.3.).

Table 7.1. Tinnitus group: Amygdala response to salient > neutral sound condition (p< 0.05 uncorrected). Statistical outputs are reported for each individual's peak voxel amygdala co-ordinates (across hemispheres). Amygdala subnuclei; SF = superficial, CM = centromedial, LB = laterobasal. n.s = not significant (p>0.05).

	Left Amygdala							**Subnuclei % activation**		
	Peak voxel co-ordinates and associated statistics									
subject no	**x**	**y**	**z**	**T stat**	**Z score**	**T2* intensity**	**cluster size**	**LB**	**SF**	**CM**
1	-24	-14	-8	2.19	2.17	35.07	24	5.3	2.1	6.1
6	-26	-6	-30	2.75	2.7	26.95	7	1	0	0
17	-22	-10	-24	3.01	2.94	59.42	36	6.8	1.7	0
19	-20	-8	-12	2.41	2.38	29.54	10	1.4	3.1	0
24	-22	-6	-16	3.29	3.2	50.14	133	18.3	4.7	0
25	-26	2	-28	2.68	2.63	34.64	71	5.1	0.8	0
29	-26	-6	-24	1.93	1.91	20.62	2	0	1.1	0
30	-30	-2	-18	1.63 n.s	1.63 n.s	57.08	4	probability not assigned		
34	-34	-2	-22	2.4	2.36	40.93	4	0.3	0	0
45	-16	0	-18	2.94	2.87	55.26	9	probability not assigned		
54	-32	-6	-32	2.44	2.39	41.64	16	1.7	0	0
74	-28	-6	-20	3.88	3.72	57.78	134	21.7	23.5	2.3
Average:						**42.42**		**5.6**	**3.36**	**0.76**
S.D:						**13.35**		**7.35**	**6.59**	**1.82**
	Right Amygdala							**Subnuclei % activation**		
	Peak voxel co-ordinates and associated statistics									
subject no	**x**	**y**	**z**	**T stat**	**Z score**	**T2* intensity**	**cluster size**	**LB**	**SF**	**CM**
1	26	-2	-18	2.4	2.37	55.21	17	2.7	1.6	0
6	32	-10	-10	2.55	2.51	55.45	3	0.9	0	0
17	18	-6	-20	2.44	2.4	65.28	17	0	0.4	0
19	28	-14	-8	2.83	2.77	43.75	10	2.3	0	0.6
24	32	-2	-36	3.41	3.31	37.96	42	2.6	0	0
25	30	2	-24	2.95	2.88	57.84	43	4.1	0	0
29	30	4	-32	1.49 n.s	1.49 n.s	0	2	probability not assigned		
30	28	-2	-18	1.84	1.83	69.45	3	0.2	0.1	0
34	30	-4	-22	3.05	2.97	49.25	79	17	5.5	0
45	24	-4	-12	2.47	2.43	60.07	10	0.1	5.4	0
54	20	-10	-12	2.23	2.19	59.98	10	0.2	5.4	0
74	20	-8	-12	2.27	2.23	45	15	0	8.1	0
Average:						**49.93**		**2.74**	**2.41**	**0.05**
S.D:						**18.19**		**4.77**	**2.99**	**0.17**
	(T stat of 1.66 / p = 0.049)									

Table 7.2. No tinnitus group: Amygdala response to salient > neutral sound condition (p< 0.05 uncorrected). Statistical outputs are reported for each individual's peak voxel amygdala co-ordinates (across hemispheres). Amygdala subnuclei; SF = superficial, CM = centromedial, LB = laterobasal. n.s = not significant (p>0.05).

	Left Amygdala							**Subnuclei % activation**		
	Peak voxel co-ordinates and associated statistics									
subject no	**x**	**y**	**z**	**T stat**	**Z score**	**T2* intensity**	**cluster size**	**LB**	**SF**	**CM**
79	-22	-6	-16	2.6	2.54	41.7	23	1.4	7.3	0
80	-22	0	-22	3.18	3.09	137.02	60	9.1	0	0
81	-20	0	-22	4.07	3.88	31.85	53	1.5	0.1	0
82	-22	-8	-20	3.2	3.1	39.82	55	10.4	1.3	0
83	-24	-2	-22	3.08	2.99	53.07	50	4.8	1.4	0
84	-22	-6	-28	2.5	2.45	38.23	12	0.5	0	0
85	-26	2	-26	1.8	1.78	48.41	3	probability not assigned		
86	-20	-4	-10	1.57 n.s	1.57 n.s	30.39	1	probability not assigned		
88	-22	-6	-14	3	2.92	46.41	24	3.6	6.3	0
89	-20	-6	-6	2.89	2.82	22.56	5	0	2.3	0.9
90	-26	-6	-28	2.55	2.5	40.54	23	3.1	0	0
Average:						**48.18**		**3.44**	**1.87**	**0.09**
S.D:						**30.70**		**3.65**	**2.64**	**0.27**
	Right Amygdala							**Subnuclei % activation**		
	Peak voxel co-ordinates and associated statistics									
subject no	**x**	**y**	**z**	**T stat**	**Z score**	**T2* intensity**	**cluster size**	**LB**	**SF**	**CM**
79	20	-6	-12	2.23	2.2	77.17	9	0	5.2	0
80	32	-2	-22	2.5	2.45	62.82	17	2.4	0	0
81	32	0	-20	2.41	2.36	54.44	8	0.3	0	0
82	36	-4	-32	2.7	2.64	39.77	15	0.8	0	0
83	28	-16	-8	2.63	2.57	45.23	6	1	1.2	0.6
84	24	-4	-30	3.21	3.11	35.56	27	0.7	0	0
85	28	2	-26	1.8	1.78	37.39	1	probability not assigned		
86	30	-8	-14	1.88	1.87	35.71	3	0.9	0	0
88	34	-6	-20	2.62	2.57	52.74	14	4	0	0
89	34	2	-26	2.38	2.34	28.96	14	2	0	0
90	30	-2	-20	2.43	2.39	62.67	10	2	0	0
Average:						**48.40**		**1.28**	**0.58**	**0.05**
S.D:						**14.84**		**1.21**	**1.57**	**0.18**
(T stat of 1.66 / p = 0.049)										

Bilateral activation of the amygdala (in at least 1 subnuclei) was found in 9 out of 12 (75 %) tinnitus participants and 9 out of 11 (81.8%) of the no tinnitus controls. Unilateral amygdala activation was found in four participants (3 from the tinnitus group). One participant (subject 85 in the no tinnitus group) showed no amygdala activation in either the left or right hemisphere. Overall, a similar decreasing trend of LB > SF > CM subnuclei extent of activation (%) was observed across left and right brain hemispheres in both groups.

Figure 7.10 and 7.11 show incidence maps for the tinnitus and no tinnitus groups respectively. Here, the distribution of overlapping supra-threshold amygdala activity was sparse, with only four participants in either group sharing activity in the same voxel locations.

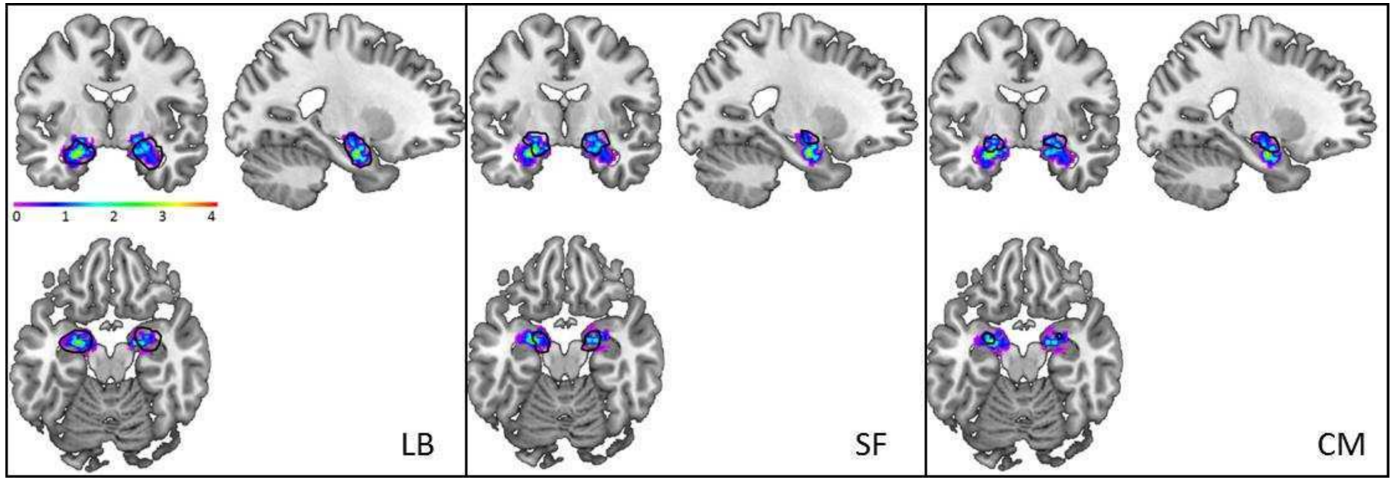


Figure 7.10 Incidence map of tinnitus group. MNI co-ordinates -24 -6 -18 chosen to represent maximum amygdala incidence for this group. Subnuclei outlined in black.

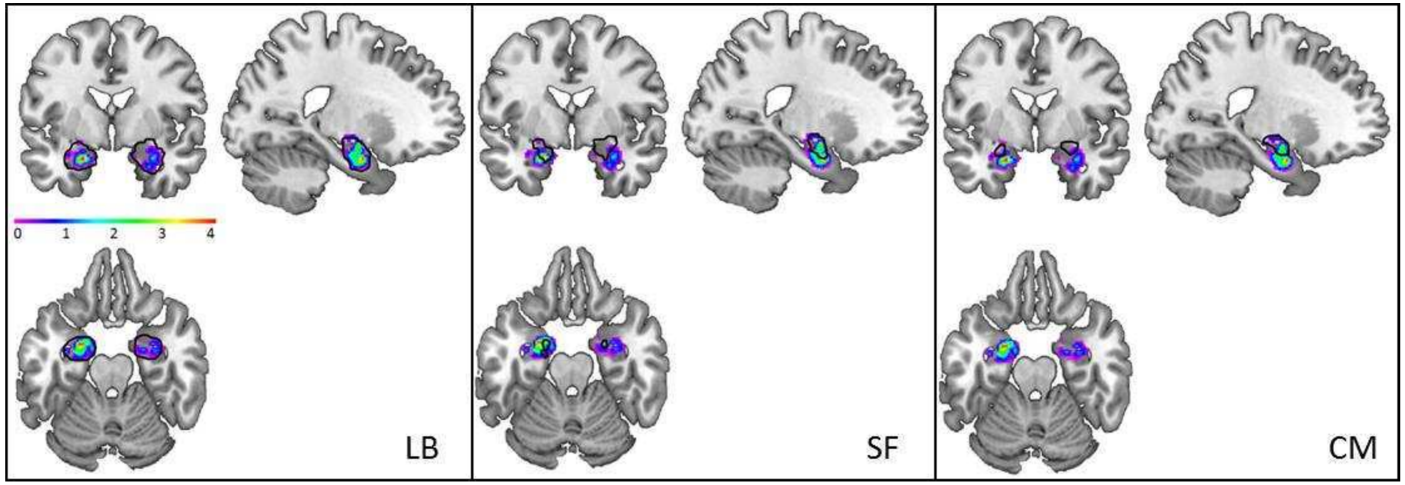


Figure 7.11 Incidence map of no tinnitus group. MNI co-ordinates -22 -2 -22 chosen to represent maximum amygdala incidence for this group. Subnuclei LB, SF and CM outlined in black.

7.4 DISCUSSION

This study examined how the amygdala responds to emotionally evocative sounds in people with and without chronic tinnitus. Using an experimental protocol adapted from a previously published study (Irwin et al. 2011) we were able to successfully measure activation of auditory brain areas and the amygdala in response to emotionally evocative sounds. The main findings of all analyses are discussed below.

7.4.1 Sound-related activation of ascending auditory pathways

Firstly, we found significant sound-related activity in several portions of the ascending auditory pathways including the inferior colliculus, medial geniculate body and the primary auditory cortex, across both brain hemispheres. As expected, this replicates the findings of several earlier sound-evoked studies (Carpenter et al. 2014, Irwin et al. 2011; Husain et al. 2011; Hunter et al. 2010). Upon direct statistical comparison between groups, we found no differences in activation amongst auditory brain regions. This finding mimics that of Carpenter-Thompson et al.'s (2014) study which implemented a similar experimental design and also controlled for hearing loss.

7.4.2 The effects of pleasantness on amygdala activity

In support of my first hypothesis we found that the amygdala's response to sound was significantly modulated by emotional valence. That is, compared with neutral sound clips, the amygdala's response to very pleasant and very unpleasant sound clips was significantly enhanced. This overall quadratic response to pleasantness reflects the same amygdala response pattern found by Irwin et al. (2011) in young adults with normal hearing. Also in agreement with Irwin et al.'s 2011 data, we found no main effect of hemisphere, suggesting a lack of amygdala dominance. Like Irwin et al. (2011), our results did not survive FWE small volume corrections. However, the distinctive amygdala response pattern observed across both studies seems to suggest a genuine neurophysiological difference in amygdala function between sound conditions which cannot be explained by chance alone.

Contrary to our second hypothesis, we found no significant main effect of group, indicating that the amygdala's overall response to emotionally evocative sounds was similar between groups. Surprisingly however, a consistent trend for higher activation in response to salient sounds compared with neutral sounds was observed in the 'no tinnitus group'. Planned contrasts revealed the specific nature of this relationship. Compared to the 'tinnitus group', the 'no tinnitus' group had significantly greater

amygdala response magnitude to both very pleasant and very unpleasant sounds (> neutral sounds). Opposing my original hypothesis, this finding seems to indicate a 'muting' of the amygdala response function amongst individuals with tinnitus. Interestingly, this finding agrees with Carpenter-Thompson et al. (2014) who observed a decreasing trend in amygdala response activation for NH>HL>TIN groups as previously discussed. Here the authors suggested that individuals with tinnitus may re-route their emotionally signalling pathway to avoid the amygdala. Supporting this notion, Domes et al. (2010) found that a group of healthy adults were able to modulate their amygdala activation up or down by increasing or decreasing their emotional response to affective stimuli. It may therefore be plausible that in an effort to reduce one's emotional reaction to tinnitus, affected individuals suppress amygdala activation through self-modulation in an effort to divert attention away from the experience of chronic tinnitus. In doing so, this leaves less available 'resource' for assignment to other emotional stimuli.

7.4.3 Extent of amygdala activation

Amygdala activation was found in the vast majority of participants (22/23). This number is considerably higher than Irwin et al.'s 2011 study from which this experimental protocol was adapted,

where only 3/16 participants demonstrated suprathreshold amygdala activity. This large difference in amygdala detectability between studies may reflect our application of a double echo imaging sequence, which is known to provide wider brain coverage and improved BOLD sensitivity across a range of tissues (Marciani et al., 2006; Posse et al., 1999).

By assigning individual amygdala response patterns onto micro-anatomically defined probabilistic maps (Amunts et al. 2005), we uncovered a distinct decreasing trend in the extent of amygdala subnuclei activation which was common to both groups. This trend saw the greatest % extent activation in the LB nuclei, followed by SF nuclei then the CM subnuclei. Within the animal literature, it is well known that the LB nuclei acts as the 'gateway' for sensory information to the amygdala, receiving input from both the auditory thalamus and from association areas of the auditory cortex (Bordi and Le Doux, 1992). Support for similar involvement of the LB nuclei when processing emotionally evocative auditory stimuli has been presented in more recent human neuroimaging studies (Ball et al. 2007; Kumar et al. 2012). Kumar et al. (2012) found both the LB and the SF nucleus to encode acoustic features necessary for attributing valence. An earlier study by Ball et al. (2007) also found activation of the LB nuclei but in response to both pleasant and unpleasant sounds. Here, the authors thought

this finding may reflect a predominance of auditory inputs to LB subnuclei. In line with this literature, our observed decreasing trend of LB > SF > CM subnuclei activation seems to suggest that the LB nuclei played the most active role in processing the emotional auditory stimuli. However, Ball et al. (2007) discuss an important caveat relevant to the present study, which is the choice of spatial resolution concerning the functional images i.e. 3mm isotropic resolution for each voxel. Given that the centres of the different amygdala nuclei are at most 1 cm apart (Mai et al., 1997), subdivision-level investigation of the human amygdala requires higher spatial resolution of the functional images e.g. 1mm isotropic voxels (Apergis-Schoute and Phelps, 2007).

7.5 CONCLUSION

To summarise, this study used a double echo imaging sequence to measure amygdala response patterns to emotionally evocative sounds in people with tinnitus. Our main results show a strong modulatory effect of emotional valence on the amygdala's response in a smooth U-shaped manner. This pattern of activation was reduced in individuals with tinnitus contrary to our expectations. By using micro-anatomically defined probabilistic maps, we were able to estimate the origins of amygdala peak level activity. In line with

previous research, this found the LB nucleus to be most active when processing emotional auditory stimuli. Based on these findings, the amygdala does appear to provide some useful information which could help in the identification of tinnitus. However, such activation patterns are, up to now, unlikely to be able to differentiate between the true presence or absence of tinnitus on a single subject level. Future studies targeting amygdala function should carefully consider fMRI parameters to ensure sufficient signal quality from the amygdala regions.

8 SUMMARY AND FINAL DISCUSSION

The research undertaken in this thesis was originally centred on a large controlled clinical trial whose primary aim was to assess the benefit of hearing aid provision for the management of tinnitus over a 6 month period. A range of patient-reported clinical measures, as well as methods of fMRI were used to identify clinical and neurophysiological markers of treatment-related change. My first study in Chapter 4 assessed the behavioural effects of hearing aid amplification on tinnitus. Results showed a reduction in tinnitus distress for those individuals who opted to try hearing aids, consistent with previous studies which have assessed hearing aid efficacy for tinnitus management. Tinnitus loudness as well as levels of anxiety, depression and self-reported measures of physical and mental health did not change over time. Given the lack of strong clinical benefit, three further investigations were conducted to identify objective neurophysiological markers associated with the presence of tinnitus. Chapter 5 features a resting-state fMRI study. Here a sub-set of 'tinnitus' (n=12) and 'no tinnitus' (n=11) participants with closely matched demographics were selected. Baseline auditory network activity was compared in an effort to objectively quantify the presence of tinnitus during rest. Despite replicating previously published methods (Kim et al. 2012), we found no between-group differences

in auditory network activity. These results suggested that the presence of chronic tinnitus does not reliably modify patterns of resting-state auditory network brain connectivity. This finding is consistent with other more recent resting-state tinnitus studies (Burton et al. 2012; Wineland et al. 2012; Schmidt et al. 2013).

In Chapter 6, further exploratory analyses were applied to the same resting-state data set with the aim of quantifying hierarchical connectivity relationships between auditory brain regions and the amygdala. Patel's conditional dependence measures (Patel et al. 2006) corroborated our earlier findings of strong but similar auditory network connectivity patterns amongst both participant groups. In addition, between-hemisphere amygdala connectivity was comparable across both groups although contrary to the findings of Kim et al. (2012), auditory brain regions did not engage with either amygdala. My final fMRI study (Chapter 7) revealed a strong modulatory effect of the amygdala in response to emotionally valent sounds. Specifically, the amygdala showed the greatest response to both highly pleasant and highly unpleasant sound clips, replicating the results of Irwin et al. (2012) which featured participants with 'normal' hearing. Between-group comparisons revealed a consistent trend for higher activation in response to both very pleasant and very unpleasant versus neutral sounds in participants without tinnitus. This unexpected result

suggests a 'muting' of the amygdala's emotional response or even a re-routing of emotional signal to avoid the amygdala in participants with tinnitus and therefore disputes my original hypothesis which predicted a hyper-active amygdala response in those with tinnitus.

8.1 CHALLENGES AND RECOMMENDATIONS FOR fMRI TINNITUS RESEARCH

As with any scientific study, the basic principle of careful variable control to ensure reliable and accurate results should be prioritised. Naturally, some areas of research such as laboratory-based studies will permit the application of this principle more easily than others. The study of tinnitus in human beings faces several challenges. The heterogeneous nature of tinnitus and variation in accompanying audiological, psychological and demographic characteristics make this principle of variable control somewhat difficult. Adding to this complexity is the use of functional neuroimaging, a method offering multiple avenues for parameter adjustment and data exploration. Indeed, entire PhD theses may be centred on the development of fMRI methodology alone (e.g. Clare, 1997). This thesis utilised resting-state and sound-evoked fMRI methods in its objective investigation of the tinnitus brain. Having discussed both areas

generally (see sections 2.6, 2.7) and in the context of tinnitus (see sections 5.1, 6.1, 7.1) it is apparent they share similar limitations. These will be discussed along with the challenges relating to the recruitment of individuals with tinnitus.

8.2 PARTICIPANT CHALLENGES

The design of most tinnitus research seeks to isolate tinnitus as the sole experimental variable when contrasting tinnitus participants to healthy controls. To achieve this, many other characteristics should be controlled for.

8.2.1 Age

Most fMRI tinnitus studies and indeed tinnitus studies in the wider context (Plein et al. 2015) have typically recruited participants in their fifth decade of life. This comes as no surprise given that age influences hearing acuity and tinnitus is associated strongly with hearing loss (Nondahl et al. 2011). However, if targeting an older age group one must also consider the potential age-related changes in brain atrophy which have the potential to influence functional connectivity, cognition, fMRI signal quality and functional signal change (see sections 2.5.3. and 7.1) (Wu et al. 2011; Tomasi & Volkow, 2012). An area which needs further attention itself. It is therefore essential to ensure that participants groups are well matched in age (both mean and range).

8.2.2 Gender

Gender should be balanced amongst participant groups. Ruytjens et al. (2007) found gender differences in the primary auditory cortex when processing noise stimuli. A recent study of over 500,000 adults from the UK Biobank dataset found that females were more likely to report bothersome tinnitus than males (4.1% vs. 3.5%) (McCormack et al. 2014). It should be pointed out that this measure of tinnitus distress was based on the following question "How much do these noises worry, annoy or upset you when they are at their worst?" Four response options were given: 'not at all', 'slightly', 'moderately', or 'severely'. Bothersome tinnitus was defined as those who responded 'severely' or 'moderately'. The same study also reported that the prevalence of tinnitus was significantly greater in males (18.4% vs. 14.1%) (McCormack et al. 2014). This difference in tinnitus prevalence has been previously reported (Lockwood et al, 2002) and reflects the general recruitment patterns observed in many tinnitus studies with men making up the majority of participant groups. In a systematic review of 147 tinnitus trials, Plein et al. (2015) found that 62% of participants were men. One should therefore be aware of this male weighted gender imbalance when recruiting tinnitus participants.

8.2.3 Hearing loss

Controlling for the effects of hearing loss in tinnitus research is highly necessary and has been recognised by many tinnitus neuroimaging researchers (Lanting et al. 2009; Adjamian et al. 2009; Husain et al. 2011; Davies et al. 2013). According to Husain et al. (2011), compensatory mechanisms for hearing loss may differ to those of tinnitus, resulting in differences in functional neural responses. In spite of this a number of fMRI resting-state tinnitus studies (see Table 5.2.) continue to compare individuals with hearing loss and tinnitus to normal hearing controls. Within this current body of work, functional MRI data from 12 of the 44 participants with tinnitus and 11 of the 27 participants without tinnitus was used for the fMRI studies featured in Chapter 5, 6, and 7. The decision to prioritise the matching of hearing loss profile across groups at the expense of group size was taken to minimise the confounding effects of hearing loss. This retrospective selection process was somewhat unique to this research given that the data set had already been collected. Future studies are encouraged to measure hearing thresholds across a wide range of frequencies and match participants accordingly in order to rule out the influential effects of hearing loss on any resulting data. Furthermore, consideration about what impact any hearing loss is likely to have on a participant's ability to hear presented stimuli should not be

ignored. Researchers may wish to survey participants post-scan on their listening experience to confirm they have heard the intended stimuli.

8.2.4 Hyperacusis

Hyperacusis can be described as 'unusual tolerance to ordinary environmental sounds' (Vernon, 1987) and can sometimes accompany tinnitus (Baguley, 2003). Although not always considered when recruiting participants for tinnitus research, Gu et al. (2010) found that the presence of hyperacusis was actually the confounding variable mistaken as the neural correlate of tinnitus. That is, sound-evoked activation of the inferior colliculus and medial geniculate body were correlated with hyperacusis not tinnitus. They suggested that this may account for the results in some of the previous tinnitus studies (Lanting et al. 2008; Melcher et al. 2009). Clinical diagnosis of hyperacusis places more emphasis on a thorough patient history rather than through questionnaires such as the Hyperacusis questionnaire (Khalfa et al. 2002) which according to Fackrell et al. (2015) does not accurately assess hypersensitivity to sound in a tinnitus population and is yet to be validated in a UK clinical population. In spite of this, many fMRI tinnitus studies use this questionnaire as a diagnostic indicator of the condition yet ignore the intolerance behaviour

which true hyperacusis participants are likely to show when placed in the noisy MRI scanning environment. The participants selected for the fMRI studies in this thesis showed no behavioural signs of hyperacusis. They tolerated noise levels of the MRI scanning environment and had on average, a HQ score of 14.6 which was comparable to that of the general population (≈15) used by Khalfa et al. (2002). Future studies should combine clinical audiological testing with appropriately validated questionnaires and subjective feedback from participants in order to establish the true presence or absence of hyperacusis.

8.2.5 Tinnitus Characteristics

Tinnitus may be defined by far more than just the presence of phantom sound. As discussed in section 2.1., the perceptual characteristics of tinnitus such as pitch, loudness and laterality not to mention its onset and nature are highly variable between participants. Because of this, it is possible that multiple sub-types of tinnitus may exist. It is therefore suggested that participants with subjective bilateral tinnitus which is constant and chronic (present for > 6 months) in nature should be targeted for recruitment. At the very least, this should filter out cases of objective or unilateral tinnitus. Clinical intuition may suggest that this group is more likely to signify a pathological sub-group rather

than a 'representative' population of individuals with bilateral subjective tinnitus common with hearing loss and advancing age.

Growing interest in tinnitus severity has led to some studies trying to recruit specific sub-sets of tinnitus individuals with high or low levels of tinnitus distress, often quantified through tinnitus questionnaires such as the THI for example (Burton et al. 2012 and Wineland et al. 2012). This seems reasonable providing that direct comparisons are made between low and high distress groups. The resting-state and sound-evoked fMRI studies in this thesis (chapter 5, 6 & 7) use participants with low to moderate distress, reflected by a group average global THQ score of 43.7 out of a possible 100. Thus, one might expect to see alterations in resting-state network activity in brain regions which govern emotion and attention had a high distress tinnitus group been used. The unexpected sound-evoked results reported in section 7.4.2 show a 'muting' of the amygdala's response to emotional sounds in individuals with tinnitus. Given that this group of individuals had mild to moderate tinnitus distress, it is possible that these individuals could suppress amygdala activation through self-modulation in an effort to divert attention away from the experience of chronic tinnitus. Based on this theory, one might expect the opposite from individuals who are highly distressed by their tinnitus. In this instance, a heightened amygdala response during emotional auditory processing and

indeed during resting-state should be observed. As a minimum, tinnitus severity should be measured using a validated tinnitus questionnaire.

8.3 fMRI CHALLENGES

Functional MRI offers spatially resolved insight into cognitive function and perception. However, it is also associated with high acoustic noise levels and a plethora of methodological considerations which have the ability to influence data outcomes. Poldrack et al. (2008) presented some general guidelines for reporting fMRI studies having previously recognised the general lack of methodological detail in published research which could not only hinder one's understanding as a reader or reviewer but also prevent independent replication and meta-analysis. The guidelines recommended providing detailed descriptions of participants, including demographics and inclusion/exclusion criteria as well as detailing what tasks participants were instructed to perform. Authors should clear specify brain space co-ordinates, including the atlas or template that they have matched to. Determination of ROIs should be detailed e.g. were the ROIs functionally or anatomically defined. Statistical testing should account for the multiple testing problem e.g. using FWE or FDR corrections. In short, the guidelines encourage full disclosure of experimental

details and results which could enable independent replication and accurate interpretation of the study.

8.3.1 Group size

As is known throughout scientific research, large group sizes are often needed to make group inferences with adequate statistical power (Friston et al. 1999). Thirion et al. (2007) suggests that 20 subjects or more should be used in functional neuroimaging studies to ensure sufficient reliability. However functional MRI research is often associated with smaller participant numbers. This is due to several contributing factors such as scanning cost, scanning time and MRI compatibility requirements i.e. no implantable devices. Beyond these scanner-related restrictions the aforementioned participant selection criteria variables such as participant age, degree of hearing loss and tinnitus type, will also narrow eligibility for recruitment as was the case in this present research (see section 3.3.1). Importantly then, when concluding results derived from smaller datasets one should avoid making population level inferences. A meta-analysis approach offers potential for pooling results from many fMRI tinnitus studies in an effort to increase power and certainty of effect. Up to now, this has only been carried out in resting-state and sound-evoked tinnitus studies which utilise PET imaging (Song et al. 2012). Compatibility of participant

characteristics and fMRI data across studies are strong limiting factors which are likely to explain the current lack of meta-analyses.

8.3.2 Statistical thresholding

When making statistical inferences about group data, one must bear in mind the possibility of type I and type II error. In the context of fMRI, this issue is common as tens of thousands of voxels which make up the volumetric space in each brain are statistically compared on an individual basis. Consequently, if the conventional p-threshold of 0.05 were to be applied on a voxel-wise level across the whole brain, then purely by chance alone, hundreds if not thousands of voxels may incorrectly be considered active i.e. a false-positive. To restrict such error, it is desirable to employ either familywise error (FWE) or false discovery rate (FDR) corrections. In FWE correction, the error rate is controlled for the whole family, guaranteeing an X% chance (depending on chosen alpha level) of any false positives occurring. However, it also assumes that every active voxel is a true positive despite knowing fMRI data is "noisy" meaning it is reasonable to expect some false positive results. As FWE correction methods adapt to the number of tests being performed (i.e. the number of voxels in neuroimaging) it is advantageous to reduce the volumetric space under

investigation. If there are *a priori* hypotheses about given brain regions, then one may choose to restrict the statistical testing to this specific region. This practice is known as small volume correction. In FDR correction, the rationale is to control the number of possible false positives. For example, setting the FDR level to 0.05 will guarantee that no more than 5% of the active voxels will be false positives. The advantage of this being that it is adaptive depending on the level of the signal present.

Given the high dimensionality of data associated with fMRI, it is essential that future studies apply appropriate statistical corrections when reporting results. Indeed, it may even be the case that some published fMRI tinnitus studies e.g. Kim et al. (2012) may fail to find any significant effects had they been statistically corrected. The application of strict statistical thresholds may reverse the significant effects reported in many published studies.

8.3.3 Imaging the amygdala

As indicated in this thesis and indeed several other tinnitus studies, the amygdala seems to play an important role in tinnitus perception. Consequently, it is often targeted as a region of interest within fMRI tinnitus studies. However, its small size and location close to the sinuses presents some inherent challenges. Sharp boundaries arising from the varying densities of this air-

tissue barrier causes magnetic field inhomogeneities leading to image distortions and signal loss (Deichmann et al., 2002). Several methodological suggestions have been made to mitigate this problem including reducing voxel size, using an axial scan plane and altering echo time to between 40-45 milliseconds (Merboldt et al., 2001; Robinson et al. 2004; Stocker et al, 2006). So whilst it is possible to optimise scanner parameters to maximise signal detection within the amygdala, this will inevitably come at the expense of other brain regions which may also be under investigation. As suggested by Chen et al. (2003), an optimal parameter design would be to use multiple echo times each optimised to the region of interest. This research employed a novel double echo imaging sequence (see section 5.2.5), combining echo times optimised to the detection of auditory and amygdala brain regions. This approach should be considered in future fMRI tinnitus research which seeks to investigate several brain regions.

8.3.4 Region of Interest determination and effects

Region of interest analysis has so far proven to be a popular approach in fMRI tinnitus research. Where *a priori* hypotheses about given brain regions are established, ROI analysis offers targeted investigation and quantification of functional relationships whilst implementing a higher degree of type I statistical control

when compared with other data-driven approaches (see section 2.6 for more information on data analysis approaches). One important aspect of ROI analysis which can influence result outcomes, is defining the ROI (Cole et al., 2010). In this research, ROIs were functionally defined based on peak level activation using a separate localiser scan and then cross checked against an anatomical mask to ensure desired anatomical location. In the author's opinion, this approach seems reasonable however more methodological research in this area would be useful to enable further recommendations.

Functional MRI tinnitus research presents the researcher with multiple avenues of exploration. And whilst the precise effects of any given methodological parameter decision on data outcome may be unclear, it is absolutely necessary to specify such decisions in clear detail as to permit independent replication. Currently, the tinnitus research network TINNET are pioneering a number of new international work streams aimed at driving forward our understanding of tinnitus with a view to developing new treatments. The neuroimaging work stream aims to establish standard operation procedures for data acquisition and analysis development and standardization of innovative data-analysing methods.

8.4 FUTURE RESEARCH DIRECTIONS

Beyond Chapter 4, the studies presented in this thesis were weighted towards the objective investigation of the tinnitus brain using resting-state and sound-evoked methods of fMRI. Whilst this work did reveal a variety of results, perhaps most notable, were differences in the amygdala emotional response function amongst tinnitus and no tinnitus groups. However, conclusions were restricted to the chosen group demographic which had moderate levels of tinnitus distress. Future studies might therefore choose to replicate this work targeting participants with very low and very high levels of tinnitus distress, testing the hypothesis that the amygdala's response to emotionally valent sounds may be proportionate to the individual's perceived levels of tinnitus distress. If so, one would expect to see a hyperactive amygdala response in those with severe tinnitus and a hypo-active response in those with mild or non-bothersome tinnitus.

8.5 CLOSING REMARKS

Tinnitus has been documented in human history for many centuries and in its plainest form describes the phantom perception of sound. Behind its simple definition lies an enigmatic auditory condition which is yet to be fully understood. Modern developments in novel

functional neuroimaging methods have promised to shed light on its underpinning neurophysiology however up to now, research in this field has often created more questions than answers. As a consequence, many clinical treatments tend to target the co-morbid symptoms of tinnitus such as hearing loss and depression with mixed degrees of success. Functional neuroimaging will undoubtedly continue to contribute to our knowledge of tinnitus if we as a research community allow it to. The formation of new international working groups like the TINNET which promote the need for a well-controlled standardised approach to tinnitus research are paramount if a world without troublesome tinnitus is to be realised.

9 APPENDIX A

9.1 A NEW COMBINATION HEARING AID FOR TINNITUS MANAGEMENT: FEASIBILITY OF EVALUATION, USABILITY AND ACCEPTABILITY

This study has been submitted to *Trends in Hearing*. The study took place between August 2013 and April 2014 and was funded by Oticon A/S. The study management group consisted of Dr Magdalena Sereda (chief investigator), Professor Deborah Hall (co-investigator), Mr Michael Nilsson (co-investigator) and Mr Jeff Davies (Audiologist). My role within this study principally involved the clinical assessment and fitting of eight participants with a pre-market version of the Oticon Alta hearing aid with tinnitus sound generator. In line with one of the study aims I was also required to provide clinical feedback on device usability using a specially devised questionnaire. Together with Dr Magdalena Sereda and Professor Deborah Hall, I co-authored the end of study report and the study which is presented here.

INTRODUCTION

In most cases tinnitus is accompanied by some degree of hearing loss (Shargorodsky, Curhan, & Farwell, 2010). Current tinnitus management guidelines (Tunkel et al., 2014) recognise the importance of addressing hearing difficulties, with hearing aids being a common option (Biesinger et al., 2011; Department of Health, 2009; Hoare, Edmondson-Jones, Sereda, Akeroyd, & Hall, 2014; Hoare, Searchfield, El Refaie, & Henry, 2014). Some studies estimate that even up to 90% of people with tinnitus might benefit from the amplification (Johnson, 1998; Schechter & Henry, 2002). Sound therapy, in the form of hearing aids or sound generators, is a core component of many tinnitus management programmes (Hobson, Chisholm, & El Refaie, 2012). Potential mechanisms of benefit include making tinnitus less noticeable, promoting habituation, distracting attention from tinnitus, and promoting neuroplastic changes within the auditory system (Newman & Sandridge, 2012).

Technological improvements in hardware and software have enabled the prescription of open fit, digital hearing aids for people with mild hearing loss and tinnitus. However, hearing aids do not provide sound masking. The two devices cannot be worn at the same time and so combination hearing aids are a preferable option in these situations. Combination devices provide both amplification

and sound generation, and new generations of such devices now offer the same amplification features as their 'standard' digital hearing aid counterparts (Henry, Rheinsburg, & Zaugg, 2004).

Current tinnitus management guidelines lack any clear recommendations about candidature and prescription options for combination hearing aids, including the acoustic features of the masking sound (Department of Health, 2009; Tunkel et al., 2014). Perhaps the only recommendation to explicitly advise on combination hearing aids is the Tinnitus Research Initiative algorithm, where authors suggest using combination hearing aids "for intrusive tinnitus where hearing aids alone are ineffective" (Biesinger et al., 2011). This recommendation is not evidence-based within the guideline, nor does it advise on hearing loss characteristics or device prescription options. Guidelines might even go so far as to take into account patient preferences, since patient acceptability is an important determinant of treatment success (Vernon & Meikle, 2000). The same might also be said for clinical trials (Hoare, Adjamian, Sereda, & Hall, 2013).

Historically sound was used to mask tinnitus, i.e. reduce tinnitus loudness or make tinnitus inaudible (Hoare et al., 2014). However, recently rather than talking about maskers we would rather talk about sound generators as masking of the tinnitus percept is not the only goal and mechanism of action when it

comes to sound therapy. While tinnitus masking might be one of aims to provide relief, relaxation and providing distraction from tinnitus seem to be equally important (Henry et al., 2004; Henry, Zaugg, Myers, & Schechter, 2008). Henry et al. (2004, 2008) applied the definition of tinnitus relief as reduction in annoyance caused by tinnitus, regardless of the mechanism by which it is achieved (masking, partial masking or not masking the tinnitus). However, even the sounds that do not mask tinnitus can provide relief through aiding relaxation (soothing sounds) and providing distraction from tinnitus (interesting sounds; Henry et al., 2008).

With respect to device prescription options, current combination devices offer a wide choice of noise types (Hoare et al., 2013; Hoare et al., 2014). Broadband noise options (white, pink, red, or brown noise) are 'standard' on most of the devices, with additional options to modulate the sound or to apply low- or high-bandpass filtering. Several manufacturers including Phonak and Starkey offer individualised broadband noise options that are shaped according to individual audiogram and/or tinnitus pitch (http://www.phonak.com/com/b2c/en/hearing/tinnitus.html; http://www.starkey.com/hearing-aids/technologies/xino-tinnitus). Here, the concept of acceptability is perhaps more important than effectiveness as a tinnitus masker. Acceptability relates to listening comfort and promotes sustained device usage (Henry et al., 2008;

Hoare et al., 2013). For example, a study by (Terry & Jones, 1986) demonstrated that people with tinnitus rated low-pass noise maskers as more 'annoying' than high-pass noise maskers. A number of manufacturers have developed their own masking sounds as additional options. For example, GN Resound devices currently offer six "soothing nature sounds" (such as 'Shoreline' and 'Beach Surf') in addition to the white noise option (http://www.resoundpro.com/en-US/hearing-aids/linx2-pro). The use of the nature sounds for tinnitus relief has been studied by (Henry et al., 2004). The authors noted that environmental sounds have natural masking properties. They also examined the relative acceptability of environmental sounds as maskers and found that the more dynamic and nature sounds, such as water, were rated as reducing tinnitus annoyance to a greater degree than the less dynamic sounds; perhaps because they were perceived to be relaxing. Use of nature sounds may also enable the application of mental imagery techniques (e.g. imagine sitting on a beach) to enhance the effect of pleasant sounds on tinnitus. A Widex device offers "Zen Therapy" inspired by the relaxing effect of certain types of music. The therapy combines counselling, relaxation, amplification with random chime-like fractal tones with pitch, tempo and volume that can be adjusted to individual preferences (Sweetow & Jeppesen, 2012).

There is a need for trials investigating the clinical efficacy of combination hearing aids compared to usual care (standard hearing aids or sound generators). Only two controlled trials of combination devices have been published recently. Henry et al. (2015) examined the effects on tinnitus of a combination device that provided amplitude- and frequency-modulated masking noise, compared to standard hearing aids. After 6 months of treatment, both groups showed a clinically significant (> 13 point) improvement in the functional impact of tinnitus as measured by the Tinnitus Functional Index (TFI; Meikle et al., 2012). However, there was no significant difference between treatment groups. Another randomised trial (dos Santos et al. 2014) found improvement in Tinnitus Handicap Inventory (THI; scores in both arms: amplification only and combination hearing aids. There was however no difference between groups. It is worth noting that for this study devices developed by Department of Otorhinolaryngology of the University of Sao Paulo were used, which might mean that the results might not be generalizable to other types of devices available on the market. Several other studies have examined Zen tones (Johansen, Skellgard, & Caporali, 2014; Sweetow & Sabes, 2010), but sample size is rather small and results are difficult to interpret. Johansen et al. (2014) investigated effects of fractal tones on tinnitus handicap measured

by the Tinnitus Handicap Inventory (Zachariae et al., 2000). Fractal tones were delivered as a part of a stepped approach; patients first received counselling, later amplification, and later again a sound generator component was enabled. While treatment led to an overall reduction in tinnitus handicap, it is difficult to separate out the specific effects of each step. Sweetow and Sabes (2010) investigated patient preferences for four different fractal tone programmes that differed in pitch, tonality, dynamic range and tempo. The most preferred fractal programmes had slow or medium tempo and a restricted dynamic range. However, preferences were very variable across patients. None of the studies to date have considered acceptability and use of devices in different listening situations.

There is a clear need for a high quality clinical trial looking at all of these important factors; clinical efficacy, acceptability, preferences and usage. However, there are a number challenges with respect to a good trial design. The study presented here was originally designed to evaluate different programmes available within a pre-market version of the Oticon Alta with Tinnitus Sound Generator (thereafter called the 'intervention device'), compared to participants' existing combination device. Our experience in conducting the study provides a rich dataset to retrospectively

address the following feasibility questions, which will inform good trial design:

1. Participant recruitment;
2. Acceptability
3. Programme preferences in different self-nominated listening situations
4. Usability;
5. Compliance;
6. Adverse events.

As an exploratory question, we also examined the patterns emerging across those who had attended different audiology centres, in order to investigate indicative evidence for consistencies in fitting or inconsistencies that might be reflective of clinician-centred approaches to the fitting prescription.

METHODS

Study site/funding

The study was conducted at the National Institute for Health Research (NIHR) Nottingham Hearing Biomedical Research Unit and funded by Oticon A/S. This study received a favourable ethics opinion from the NHS Health Research Authority Nottingham Research Ethics Committee 1 (Reference Number: 13/EM/0269) on 23 July 2013. The study Sponsor was Nottingham University Hospitals NHS Trust.

Inclusion and exclusion criteria

Experienced combination device users only were recruited so that we could make a direct comparison between the patient's current noise options and programmes and those available on the experimental devices. Inclusion criteria are listed in Table 1. Exclusion criteria were: pulsatile tinnitus, Ménière's disease, temporomandibular joint disorder related to tinnitus, intermittent tinnitus, reduced sound level tolerance (score >28 on Hyperacusis questionnaire, (Khalfa et al., 2002), amplification users <6 months or long-term amplification users with audiological adjustments within last 1 month, using Zen tones on the current digital combination device, and taking part in another trial during the last 30 days before study start. Use of Zen tones was an exclusion because this masking sound forms one component of Zen Therapy, including counselling and relaxation. It is not a fair comparator to a standard combination device sound therapy.

Table 1: Original (Protocol v1) and redesigned (Protocol v2) inclusion criteria for the study.

Protocol v1	Substantial protocol amendment: Protocol v2 (15th October 2013) approved by ethics (2nd November 2013)
Target recruitment: n=5	Target recruitment: n=10
Inclusion criteria: • Combination hearing aid device wearer for at least 6 months, with no audiological adjustments within last 1 month. • Wearing the current combination device for at least 6 hours/day. • Audiometric criteria defined a 'mild sloping high frequency hearing loss' as follows: - 250 Hz: 0-40 dB - 1000 Hz: 10-60 dB need to allow normal hearing at 1 kHz - 2000 – 6000 Hz: 30-70 dB - Symmetrical loss: ≤ 10 dB difference between right and left ear, but 15 dB difference at one frequency is accepted. • Score 18-76 on Tinnitus Handicap Inventory (i.e. at least mild tinnitus and not catastrophic tinnitus, (McCombe et al., 2001) • ≥ 18 years. • Willing to wear the experimental device for at least 6 hours/day and try using the different programmes and features • Sufficient command of English language to read, understand and complete the questionnaires. • Able and willing to give informed consent.	• Audiometric criteria redefined as "Perceiving benefit from both amplification and sound generation on current device."

Intervention device

The intervention device was a Pre-Market version of Oticon Alta with a Tinnitus Sound Generator, receiver-in-the-ear (RITE) digital combination hearing aid. Four programmes were available on the intervention device (Table 2) and all four programmes were active. In programme 4, the device offered three novel nature sounds that all resembled the sound of the ocean. Other fitting options included parameters for the masker noise. In particular, the device provided white, pink, and brown broadband masking noise options, with minimum and maximum settings for the masker sound level. Additional parameters for shaping the noise included three options for frequency cut off (high-pass, low-pass, no pass) and several options for the modulation of the masking noise (pre-specified combinations of depth and rate).

Table 2. Programmes available on the intervention device

Programmes	
Programme 1	Amplification Manual volume control for adjusting the level of amplification
Programme 2	Amplification Masking noise (white/pink/brown, unmodulated or modulated, non- filtered or bandpassed) Manual volume control for adjusting
Programme 3	Amplification Masking noise (white/pink/brown, unmodulated or modulated, non-filtered or bandpassed) Automatic level steering for adjusting the level of masking noise
Programme 4	Amplification Ocean sounds (three options) Manual volume control for adjusting the level of the nature sound

The device also contained a "streamer" which was a compact Bluetooth device that acted as a gateway between the combination device and external sound sources. The streamer could also be used as a remote control for adjusting the volume of amplification or masking noise as well as changing programmes on the combination device. Use of the streamer was optional for each participant.

Device fitting

The intervention device was programmed by a qualified audiologist (JD), according to manufacturer's standard clinical protocol and programming software. Training in the device fitting procedure was provided by one of the manufacturer's audiologists. Amplification was matched to the participant's current device using Real Ear Measurements (REM), adhering where possible to the British Society of Audiology (BSA) and British Academy of Audiology guidelines (British Society of Audiology & British Academy of Audiology, 2007). As we did not have access to each participant's computer-based clinical hearing aid settings, this was achieved by first measuring the in-situ 'aided gain' of the participant's current device using a 65 dB modulated speech noise. This measure then became the 'target' response curve to which the intervention device was fine tuned to match. In all cases, we were able to

closely match the aided gain of the intervention device with each participant's own device to within +/- 5 decibels.

Participants selected the standard masker noise (white, pink, brown) that most resembled that of their current device. Loudness was subjectively matched to be similar to their current masker noise. A nature sound was chosen according to preference (I.e. the most pleasant and most resembling an ocean sound).

The audiologist (JD) created and used the Quick Guide (Appendix 1) as a reference to explain the different programmes to participants. Operating instructions for the manual volume control, and automatic level steering (Programme 3) were given. He also carefully went through each option and each step of the fitting, referring the participant to the Quick Guide. He then re-capped at the end, allowing participants to manually select each programme for themselves. As the programmes were all different, several explanations were needed before participants were confident in their familiarity with operating the device.

Each participant received the manufacturer's written instruction guide for the intervention device and a spare set of batteries. Participants were instructed to wear the device for at least 6 hours/day and try the device in all situations that they nominated as those where alleviating their tinnitus was important for them (see: Results: Patient preferences in different self-

nominated listening situations section). Participants were encouraged to contact the audiologist (JD) in case of any problems or further questions. In case of any adverse event, participants were advised to stop using the experimental device, go back to their current device and contact a member of the study team as soon as possible.

Procedure

Figure 1 illustrates the timeline of the study. Although participants kept their current devices for the entire duration of the study, they were encouraged to always use the intervention device for a two-week period. During that time, they were encouraged to try all the four programme options in different listening situations. After two weeks, participants returned the intervention device and went back to using their own device.

Consent, eligibility and baseline measurements	Fitting of the intervention device	Using intervention device at least 6 hours/day	End point assessment
Measures for eligibility: • Audiometry • Tinnitus Handicap Inventory (THI) • Hyperacusis Questionnaire (HQ) • Tinnitus Case History Questionnaire (TCHQ) Baseline measures: • Tinnitus Functional Index • Questions assessing relief from tinnitus when using current device in nominated listening situations (Q. 1.1-1.4)			Assessment measures: • Tinnitus Functional Index • Questions assessing relief from tinnitus when using intervention device in nominated listening situations (Q. 1.5-1.8) • Questions about participant's personal experiences with the new device (Q. 2.1-2.12) • Questions for participant about different aspects of usability of the new device (Q. 3.1-3.5) • Questions for audiologist performing the fitting about different aspects of usability of the new device (Q. 4.1-4.9)
Day 1		2 weeks	Day 14

Figure 1. Timeline of the study. Questions are reported in Appendix 2.

Measures

A number of patient-reported questionnaires were used for data collection. Demographic and tinnitus case history information were collected on the Day1 assessment, using the Tinnitus Case History Questionnaire

(http://www.tinnitusresearch.org/en/consensus/consensusdocuments/en/TINNITUS_SAMPLE_CASE_HISTORY_QUESTIONNAIRE.pdf) Authors' own questionnaires were created to collect information about acceptability and preferences of different masker sound options and patient and audiologist's perspectives of device usability. These comprised a mix of open and closed questions (Appendix 2).

Relevant for this article, 12 questions explored the acceptability in terms of the physical aspects of the device, the programme options (masker sound options), and the listening experience. Questions covered the appearance of the device, its comfort to wear, sound quality, speech intelligibility, listening comfort and overall hearing ability, masker sound options and level steering. These are listed in Appendix 2 (Questions 2.1-2.12). Six questions required a rating judgement on a 5-point Likert scale ('Strongly agree' to 'Strongly disagree'), six required a 'Yes/No' response. All questions invited open text responses for participants to give further details.

Two questions explored patient preferences in the different self-nominated listening situations (see Appendix 2, Questions 1.5 and 1.6). The first asked which programme they preferred to use in which self-nominated situation where alleviating tinnitus was perceived to be important. The second question asked how much

that programme helped with their tinnitus. This required a response on a 5-point Likert scale ('Never' to 'All the time').

To provide information on device usability questions 3.1-3.5 asked about ease of using the device including putting it on and taking it off, changing programmes, changing volume of the noise, changing batteries. This estimate was made using a 5-point Likert scale ('Strongly disagree' to 'Strongly agree').

Another author's-own questionnaire was used to assess the usability of the devices from audiologist's perspective. Nine open and closed questions asked about ease of fitting, flexibility of the device, instructing patients on different options available on the device and choosing the right noise for each patient (4.1-4.9).

Adverse events were reported to a member of the study team and were dealt with according to the Sponsor's Standard Operating Procedure (SOP). An adverse event could be a marked worsening of tinnitus.

To explore differences between clinics we collected data on the clinical practice that had fitted the patient with his/her own current device, on the make and model of that device, side of fitting, number and features of the available programmes and noise option/s. These were all based on information given by the participant, and from our handling of the current devices during the fitting procedure. Information about the noise options was verified

by the audiologist during the fitting by matching the noise on current and intervention devices.

As a measure of compliance participants were asked to confirm that they had used the intervention device for at least 6 hours/day.

RESULTS

Participant recruitment

The study opened on 31st July 2013, with an original recruitment target of 5 enrolled participants. The recruitment target was increased to 10 (Substantial protocol amendment) to account for the increased variability among participants regarding hearing profiles.

A range of advertising sources were targeted. The British Tinnitus Association (BTA) is the largest UK charity supporting people with tinnitus. The BTA support the national event "Tinnitus Awareness Week" and so information about the study was highlighted at various regional events during study set-up (6th-9th February 2013). Subsequently, a short feature was published in their 'Quiet' magazine (Winter 2013), which has a circulation of approximately 5000 readers. The BTA support a national network of patient self-help groups and so the study team used this network across the Midlands region by highlighting the study in the

newsletter of the Birmingham and District Tinnitus Group (February 2014), and at regional events (e.g. self-help groups meetings).

Our research unit holds a large database of over 1,000 people, many of whom have hearing-related problems and have agreed to be contacted about new research studies. The information about the study was sent to 33 participants with tinnitus who indicated that they wear a hearing device and live within the travelling distance from the BRU. A short feature was also published in our unit's quarterly newsletter (Issue no 3, July 2013) and distributed by email to all those on the database, and was posted to a number of regional audiology clinics. Website advertising took the form of short articles on our institutional website (www.hearing.nihr.ac.uk) and the BTA's website (www.tinnitus.org.uk).

Finally, recruitment targeted a number of local audiology sites. The Nottingham Audiology Services at the Sponsor site did not at that time offer combination devices. Hence, the study team contacted 10 NHS audiology clinics to assist in advertising and recruitment. In our experience, a majority of clinics did not fit combination hearing aids and those that did had fitted only a limited number of patients (reported as between 3 and 20). Our recruitment "net" therefore gradually expanded to include NHS audiology sites in the North West and South East of England that were known to offer combination devices. We also made contact

with 5 independent sector hearing aid clinics in the East Midlands area.

Amendment to the inclusion criteria

By 30th September 2013, no participants had been enrolled, despite screening nine potentially eligible successful combination device users. Most failed screening on the audiometric criteria defining a 'mild sloping high frequency hearing loss' (see Table 1). Interestingly, this criterion had been specified according to the manufacturer's expectations of what a 'typical' combination device recipient would be. Two screen fails exceeded the upper limit of hearing level and four screen fails had asymmetric hearing loss (>15dB difference between ears at more than one frequency). An agreement was made with the study Funder and Manufacturer to amend this criterion. To account for increased variability among participants regarding hearing profiles the recruitment target was increased to 10.

Low rate of recruitment, high screen failure rate

By 31st May 2014, 34 participants had been screened and eight of those enrolled onto the study. Reasons for exclusion are listed in Figure 2. A large number of screen fails were from those device users who reported unsatisfactory benefit for their tinnitus (n=7)

and 12 users of current conventional hearing aids users (amplification only) wanted to try a combination device. By 31st May 2014, two months had passed without enrolling a single eligible participant and so a decision was made to terminate the study without meeting the amended recruitment target.

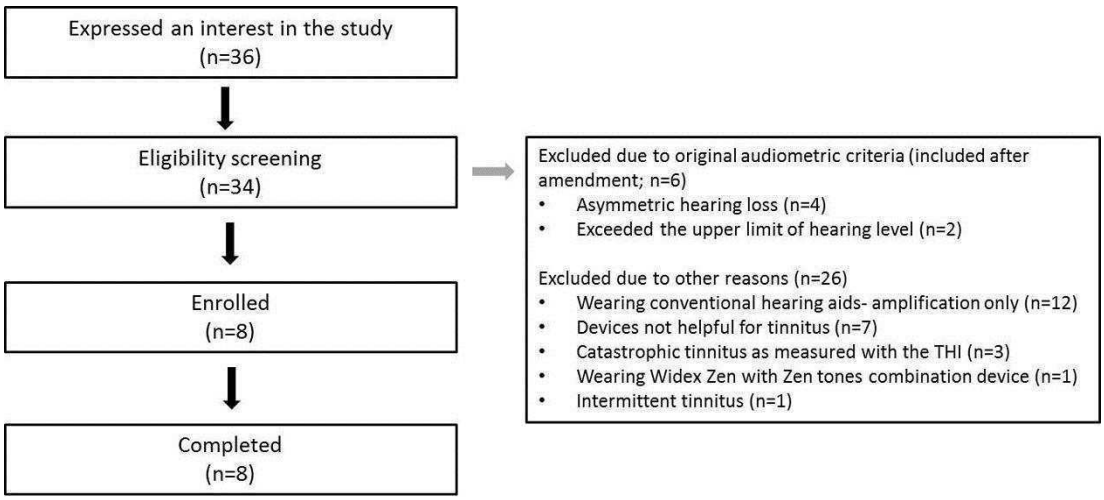


Figure 2. Study flow chart

Characteristics of the eligible participants

Eight males were enrolled onto the study. All had unilateral (n=5) or bilateral (n=3) chronic subjective tinnitus (mean duration = 8.2 years, SD= 6.4). They were aged between 62-72 years (mean age 67.25 years, SD=3.8). Tinnitus severity measured by the THI varied between 24 and 68 points (mean 46, SD=16). Two participants described their tinnitus as whistling, three as hissing,

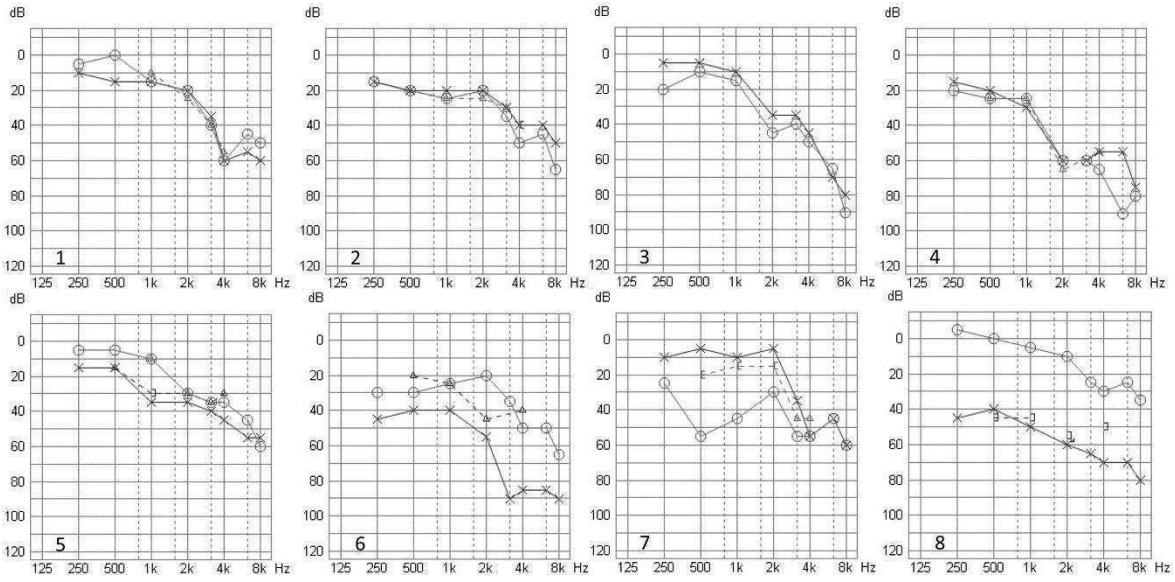
one as buzzing, and two had two sounds (white noise and whistling).

Table 3. Characteristics of the 8 enrolled participants

Participant	Age (years)	Global THI score (0-100)	Tinnitus duration (years)	Tinnitus laterality	Tinnitus description
1	63	66	10	Unilateral, left ear and left side of the head	High-pitched whistle
2	66	58	20	Bilateral, worse in the right ear	Whistling
3	67	42	7	Unilateral, left ear	Hissing
4	71	68	2	Unilateral, right ear	Hissing
5	66	38	7	Unilateral, left ear	Buzzing
6	72	24	3	Bilateral, worse in left ear	Hissing
7	62	36	2	Bilateral, worse in the left ear	White noise (right ear) and high-frequency fluctuating tone (right ear)
8	71	36	14	Unilateral, left ear and left side of the head	White noise and whistling

Participants all had an aidable hearing loss. Five had high-frequency hearing loss in both ears and three had an asymmetric hearing loss, according to national audiometric procedures (British Society of Audiology, 2011, Figure 3). Six received free combination devices through the NHS, and two paid through an independent sector clinic. Characteristics of participants are summarised in the Table 3.

Figure 3. Audiometric profiles of the 8 enrolled participants



Acceptability

Thirteen questions explored acceptability in terms of the physical aspects of the device, the programme options (masker sound options and automatic level steering), and the listening experience.

In general, participants reported the physical aspects of the experimental device to be acceptable. They liked the fact that the device was small and not very noticeable. Participants reported that the device was comfortable and very often they "forgot it was there".

Six participants agreed that the ocean sound was pleasant to listen to. One participant neither agreed nor disagreed and stated that they could not use it in all situations. Only one participant did not find that option helpful at all as he found the modulation of the sound distracting and sometimes irritating. Six participants agreed that the ocean sound sounded like the real ocean and two did not. One participant commented that for him it resembled more 'gusts of wind', another one indicated that for him it did not sound exactly like an ocean but he could understand why it is called that. One participant commented that it sounded similar to their CDs of waves on a beach, which he uses when he goes to bed.

Some participants described why the novel ocean sounds were acceptable: "(…)the sound of waves breaking on the shore, are very calming", "(Ocean sound) does not mask tinnitus but provides the distraction (…) when I wanted to distract myself from listening to my tinnitus", and "It is useful to have a variation from white noise".

Six participants agreed that the broadband masker was pleasant to listen to and two neither agreed nor disagreed. Participants commented that it was "What I am used to" and "What I expected". Seven participants were satisfied with the automatic level steering option and one neither agreed nor disagreed commenting that in particular situation (work, proximity of the head to physical objects) this programme caused a lot of feedback. Participants agreed unanimously that the listening experience provided by the experimental device was acceptable. Compared to their current device, they reported that sound quality was similar (n=3) or better (n=5), speech intelligibility was similar (n=4) or better (n=4), listening comfort was similar (n=3) or better (n=5), and overall hearing ability was similar (n=3) or better (n=5). Six participants reported no feedback when using the experimental device, two reported some feedback issues in particular situations (driving a car, proximity of the head to the physical objects, attempt to wear ear protection over the device). Participants reported that "listening comfort is better that my current device and I found I can wear it for much longer periods because of the better sound quality" and that it "Felt more comfortable with the new device".

Patient preferences in different self-nominated listening situations

A wide range of situations were self-nominated ranging from quiet activities (e.g. reading, gardening, working on a computer, working in office, doing nothing), through one to one conversations or watching TV to very noisy environment and activities (e.g. social situations with a lot of people talking at the same time, pubs and restaurants, travelling on a train, noisy work environment). Each participant nominated both quiet and noisy situations as being important for them to alleviate their tinnitus. Choices were very individual and dependent on the style of living. Despite this variability all participants were able to find an option on the intervention devices that provided satisfactory relief from tinnitus for each of the self-nominated situations (Table 4).

Those programmes (Table 2) with amplification and masking features (2, 3 and 4) were equally preferred over the basic amplification-only programme (1). Programmes 2 and 3 using the 'standard' broadband masker as well as Programme 4 using the nature sound were chosen for the range of situations. What is most striking from these data is that the individual preference for the different programme options varied widely, both across participants and across listening situations. Seven out of the eight participants indicated a preference for one or another programme, depending which one was perceived to help relieve the tinnitus at the time.

Four participants used two different programmes in the same listening situation, depending on which one seemed more comfortable.

All participants reported that they preferred the intervention device to their current device. For a majority, this choice was not due to masking efficacy, but rather due to the availability of choice in different programmes and of different noise options. Patients reported that choice gave them a sense of control over their tinnitus: "It is good to have different noises, I feel more in control". Patients also noted that having an alternative sound to the standard noise option allowed them to 'have a rest' from constantly listening to the 'white noise': "It is nice to have variation from the white noise".

Table 4. Pattern of programme preferences used in different self-nominated situations. For a description of programmes see Table 2.

Programme number (1-4)	**Number of participants (max 8)**	**Situation**
1	1	Going out with family/social situation One to one conversation
2	6	Reading newspaper/book in quiet Working in the garden Concentrating on activity Watching TV Driving One to one conversation Boys Brigade (noisy with a lot of people talking at the same time) Noisy work (construction) Pub
3	5	Household activities when other people are at the house Golf club (~30 people talking) Pub quizzes Reading newspaper Waking up in the morning (1st hour) Concentrating on activity Conversation with one or two people
4	5	Driving Reading/writing in quiet Gardening Concentrating on activity Pub Quiet situation (when occupied or not) On the train

Usability

No concerns regarding usability of the device were reported by the participants. Participants agreed that the device was easy to put on and take off, adjusting the volume and changing programmes was straightforward as well as was changing the batteries. For one participant who used only one programme in all self-nominated

situations it was preference not difficulties managing multiple programmes that determined usability (see previous section).

From the perspective of the audiologist, there were no issues with meeting amplification needs and frequency responses despite the range of hearing losses. The intervention device accommodated the whole range of hearing losses. Although there were no major issues regarding the fitting of intervention device, the fitting took between 1.5 and 2.5 hours for each participant. The most time consuming aspects of fitting were choosing the right type of masking noise and adjusting the level of the noise.

The audiologist commented that the choice of sound options made the fitting process more interactive and engaging. Most participants were able to express their specific requirements, possibly because they were experienced combination devices users already. There were no issues with selecting the right noise/level combinations to meet individual needs.

Explaining the different programmes to participants required careful instructions and referring to the Quick Guide (Appendix 1). None of the participants required any additional explanations after the initial fitting.

Compliance

All participants reported that they used the device at least 6 hours/day for the whole 2 weeks duration and tried the device in all

self-nominated situations. Participants reported that for majority of the self-nominated situations (36 out of 45) they used the intervention device for all the time. Only one participant did not use the device at the end of the study in one of the self-nominated situations (going to the gym) as he was worried about damaging the device.

Adverse events

No adverse events were reported for the current study and none of the participants returned to their current device during the two weeks.

Patterns of practice across audiology centres

Table 5 reports the participants' current device and available options (i.e. number of programmes and noise options offered). The most popular combination device offered was Danalogic iFit (n=5) with Siemens (Pure and Life) being the second choice (n=3). It seems that the choice of the manufacturer might be clinic specific as usually participants recruited from the same clinic used the same type of devices (2 out of 3 from clinic A used Danalogic iFit, one used Siemens but was fitted considerably earlier than two other participants; both participants from clinic B used Danalogic iFit,; both participants from clinic C used Siemens). Different clinics seemed to vary also in the number of programmes offered to the patients. Four participants from clinics B and C and one participant

from clinic D had only one programme available on their current devices which combined amplification with sound generation. All three participants from clinic A had three programmes available on their current devices: i) amplification only; ii) amplification and sound generation; iii) sound generation only.

The laterality of the fitting seemed more consistent across clinics and seemed to depend on both tinnitus and hearing loss laterality. Patients with bilateral tinnitus and bilateral hearing loss were fitted with two combination devices with noise active in both ears (participants 2 and 6; clinic B and C). Participants with unilateral tinnitus were fitted with the combination devices either in one (participants 1 and 3, clinic A) or two ears (participants 4, 5 and 8; clinics B, C and D) depending on the level of hearing loss in non-tinnitus ear. Four out of five participants fitted bilaterally had amplification and sound generation in both ears, regardless of the laterality of tinnitus (2 with uni- and 2 with bilateral tinnitus). Only one participant, who had unilateral tinnitus and bilateral hearing loss, was fitted with two combination hearing aids with noise component active only in the tinnitus ear and amplification only in the non-tinnitus ear (participant 8; clinic D).

No	Current device	No of devices	No of programmes	Current programmes	Matched noise on the intervention device	Tinnitus laterality	Clinic
1	Danalogic iFit, open dome - left	1	3	Left ear: 1: amplification 2: sound generator 3: amplification and sound generator	Pink noise	Unilateral, left ear and left side of the head	A
2	Danalogic iFit, power dome - right, open dome - left	2	1	Both ears: amplification and sound generation	White noise	Bilateral, worse in the right ear	B
3	Danalogic iFit, power dome - left	1	3	Left ear: 1: amplification 2: sound generator 3: amplification and sound generator	Pink noise	Unilateral, left ear	A
4	Siemens Pure, receiver in the canal, Nathos micro NHS hearing aids	2	1	Both ears: Amplification and sound generation Would occasionally put hearing aids if amplification only required	White noise	Unilateral, right ear	C
5	Danalogic iFit, open dome	2	1	Both ears: amplification and sound generation	White noise	Unilateral, left ear	B
6	Siemens Pure, receiver in canal	2	1	Both ears: amplification and sound generation	White noise	Bilateral, worse in left ear	C
7	Siemens Life500, 2107 no vent mould - right	1	3	Right ear: 1: amplification 2: sound generator 3: amplification and sound generator	White noise	Bilateral, worse in the left ear	A
8	Danalogic iFit, open dome – right, power dome - left	2	1	Left ear: amplification and sound generation Right ear: amplification only	Pink noise modulated 'spirited'	Unilateral, left ear and left side of the head	D

Table 5. Characteristics of participants' current devices

All participants regardless of the clinic had only a broadband noise option (white or pink) available on their devices. Only one participant (clinic D) had modulation applied to the broadband noise.

DISCUSSION

The current study retrospectively analysed the data collected to evaluate different programmes available within a combination device to examine the feasibility of conducting a UK-based clinical trial on the clinical efficacy of combination devices for tinnitus. Several feasibility issues around recruitment, acceptability and usability have been identified and a set of recommendations for future studies have been formulated.

Recruitment

Although, recent British Tinnitus Association tinnitus service evaluation shown that 74% UK audiology clinics have an option to offer combination hearing aids (Hoare, Broomhead, Stockdale, & Kennedy, 2015), the challenges that we faced in recruiting existing combination device users suggests that the numbers of wearers are small, certainly too small to support clinical research in which this is an eligibility requirement. This concurs with our previous observation that those NHS clinics contacted for the current study stated that they had fitted between 3 and 20 patients with

combination hearing aids (until May 2014). Moreover, it is possible that many people who obtain benefit for tinnitus with their existing solution would not be willing to risk worsening of their tinnitus symptoms by trying a novel solution.

Recruitment into a UK clinical trial would be more successful if enrolment was extended to include either current conventional hearing aid (amplification only) users with tinnitus or those who do not use any devices to manage their hearing loss and tinnitus. A decision very much depends on the particular research question but feasibility of recruitment should be carefully assessed.

Acceptability

Overall, all participants found the experimental device to be acceptable in terms of its physical aspects, choice of programme options (in particular the ocean sound) and the listening experience provided by the amplification. One important caveat is that we explicitly recruited successful existing combination device users so such high rates of acceptability might not be repeated in clinical research recruiting new users or those there may be a period of adaptation to a new device and that period of adaptation/familiarisation needs to be accounted for in clinical trial design. Acceptability and the role of different sounds in providing tinnitus relief should be investigated alongside clinical efficacy.

Further feasibility work is recommended to better understand these issues.

Patients' preferences regarding different sound options

Preferences for different noise options varied across different listening situations and across participants. Participants in our study also pointed to a different role of the sound options provided by the device. While broadband noise was the most effective tinnitus masker, the sound of the ocean often did not mask tinnitus but rather provided distraction from tinnitus and/or aided relaxation.

Terms 'masking' and 'maskers' are still widely used in the context of sound therapy and this does not reflect different goals that sound therapy for tinnitus might have. While masking of tinnitus is one of these goals, providing distraction from tinnitus sound, aiding relaxation and promoting habituation are at the centre of many management programmes (e.g. Tinnitus Retraining Therapy, Zen Therapy, Jastreboff & Jastreboff, 2006; Sweetow & Jeppesen, 2012). All participants in the current study expected their tinnitus to be masked (i.e. loudness being reduced) by the noise provided on the intervention devices. However, for the ocean sound that was not always the case. Instead the main mechanism of action for the ocean sound was distracting attention or aiding relaxation. It is therefore worth considering adequate counselling of

patients about the rationale behind the sound therapy and role of different types of sound in providing relief from tinnitus.

The above can be a reason for differences between participants in the current study in the choice of the programme that provided largest tinnitus relief. If the same kind of sound had different mechanism of action for different participants it would not be surprising that there was no consistent pattern in the type of sound optimal for particular situations. Therefore it was not possible to determine on the basis of the results of the current study e.g. which sound would be optimal for quiet and which for noisy situations. Another reason for individual differences might be differences in life styles and a range and differences in situations experienced in everyday life and those varied considerably among participants in the current study. This might point to the need of exploring the role and meaning of different sounds individual patient's life as well as lifestyles in order to provide the best and most effective options for tinnitus relief. It is also worth noting that one of the participants did not need additional sound all the time and in some situations (social situations, conversations) they were using the amplification only programme as the most optimal.

Previous studies pointed to the importance of a sense of control in managing long term conditions including tinnitus (Budd & Pugh, 1995; Sirois, Davis, & Morgan, 2006) with people feeling

more in control and cope better with their condition. A recent questionnaire, the Tinnitus Functional Index (TFI; Meikle et al., 2012), also assesses 'sense of control'. For some participants having a choice of different programmes and different sound options rather that better masking properties or higher acceptability of the sounds seemed key to more satisfactory management of their tinnitus.

On the basis of the above findings rather than seeking to limit or restrict 'customised' sound options we would recommend a more pragmatic trial design that allows for patient flexibility, but includes qualitative data to examine which options were effective, for which participants and in what situations.

Usability

Although the participants and audiologist were generally satisfied with device usability, the audiologist observed that fitting appointment took on average 2 hours. Tinnitus consultation in the NHS audiology clinic last on average 1 hour for diagnostic assessment or management, or 1.25 hours for a combined appointment (Hoare, Gander, Collins, Smith, & Hall, 2012). However, those times varied considerably between clinics, with between 15 to 150 minutes for diagnostic assessment and between 45 and 150 minutes for combined appointments (Hoare et al.,

2012). Therefore one should take into consideration a significantly longer appointment time needed for fitting combination hearing aids with multiple programmes if different masking noise options are to be provided. It is also possible that device fitting in first time combination users or those who do not have previous experience with using sound for tinnitus relief might be even more time consuming. There is little manufacturer guidance for selecting optimal masking stimuli in terms of noise type, modulation and intensity. Therefore, future studies should take into consideration the additional time and resources needed.

Variability in current practice

Given the lack of detailed manufacturers' fitting guidelines, many audiology departments develop their own fitting guidelines informed by personal experiences and anecdotal evidence. This results in the fitting protocol varying widely between different audiology clinics, similarly to the findings regarding fitting of hearing aids for tinnitus (Sereda, Hoare, Nicholson, Smith, & Hall, 2015).

Differences between clinics observed in this study included the number of programmes and noise options offered and the brand of devices used. Moreover, the laterality of fitting seemed to depend on a particular combination of tinnitus and hearing loss laterality. While participants with bilateral hearing loss and bilateral

tinnitus were consistently fitted with two combination devices, in those with unilateral tinnitus the laterality of fitting was not consistent across clinics. This is in conflict with the results of our Delphi survey exploring the current practice regarding fitting of the conventional hearing aids for patients with tinnitus, where majority of clinicians agreed that amplification for tinnitus patients should be provided bilaterally, regardless of the tinnitus laterality (Sereda et al., 2015). Exploring common practices and seeking consensus between UK clinics regarding fitting of combination hearing aids is warranted.

CONCLUSIONS

Given that the study protocol would need to be sufficiently flexible to cover individual needs and preferences of patients regarding amplification and tinnitus relief would call for more pragmatic trial. Qualitative data could inform understanding of the utilisation of different options on the devices in the real and what the reasons behind those choices. The current study identified a number of feasibility issues that need to be taken into consideration when designing future studies looking at the effectiveness of combination hearing aids for tinnitus. The following recommendations are proposed:

1. Future studies should consider recruitment of current conventional hearing aid (amplification only) users with

tinnitus or those who do not use any devices to manage their hearing loss and tinnitus. Feasibility of recruitment should be assessed before designing a large scale study.

2. The candidacy criteria and outcome measures should be tailored according to the intended mechanism of action of the sound used.
3. The acceptability and role of different sounds in providing tinnitus relief should be investigated alongside efficacy.
4. The fitting protocol should be sufficiently flexible to accommodate individual needs and preferences.

Service evaluation and exploring common practices and seeking consensus between UK clinics regarding fitting of combination hearing aids as well as reasons and rationale for different practices should be conducted.

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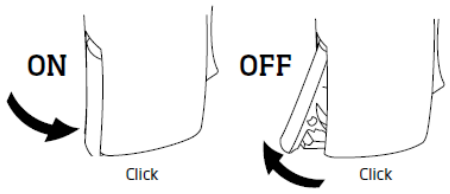
APPENDICES

Appendix 1

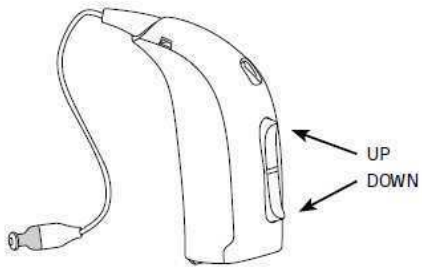
Quick Guide

On / Off



Hearing aid defaults to program 1 when first switched on

Program and volume selection



Volume control

To increase volume, briefly press upper part of button

To decrease volume, briefly press lower part of button

Program selection

Press and hold upper part of button (2 seconds) to move forwards in program cycle e.g. P1 to P2

Press and hold lower part of button (2 seconds) to move backwards in program cycle e.g. P3 to P2

Program 1 *"1beep"*	general amplification (volume control)
Program 2 *"2 beeps"*	general amplification + masking sound (volume control for masking sound only)
Program 3 "3 *beeps"*	general amplification + masking sound (masking sound automatically adjusts) * Avoid touching volume control when in this program *
Program 4 *"4 beeps"*	general amplification + nature sound (volume control for nature sound)

Appendix 2

Questions assessing relief from tinnitus when using current and new device in nominated listening situations.	
1.1	How bothersome is your tinnitus in that situation when you are not wearing your device? 0___N/A 1___Not at all 2___Only a little 3___A moderate amount 4___Quite a lot 5___Very much indeed
1.2	What feature on your current device are you using in that situation? 0___Amplification only 1___Amplification and sound generator 2___Sound generator only
1.3	In this situation, what proportion of the time do you wear your current device? 0___N/A 1___Never/Not at all 2___About ¼ of the time 3___About ½ of the time 4___About ¾ of the time 5___All the time
1.4	In this situation, how much does your current device help with your tinnitus? 0___N/A 1___No help at all 2___Device is some help 3___Device is quite helpful 4___Device is a great help 5___Can not hear my tinnitus
1.5	What feature on the new device did you tend to use in that situation? 0___N/A 1___P1- amplification only 2___P2- amplification with noise and volume control 3___P3- amplification with noise and level steering 4___P4- amplification with ocean sound

1.6	In this situation, what proportion of the time did you wear the new device? 0___N/A 1___Never/Not at all 2___About ¼ of the time 3___About ½ of the time 4___About ¾ of the time 5___All the time
1.7	In this situation, how much did the new device help with your tinnitus? 0___N/A 1___No help at all 2___Device was some help 3___Device was quite helpful 4___Device was a great help 5___Could not hear my tinnitus
1.8	In the above situation which of the two devices would you prefer to use? Current device New device
Questions about participant's personal experiences with the new device.	
2.1	I like the appearance of the device. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
2.2	The device is comfortable to wear. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
2.3	The 'ocean sound' sounds like a real ocean. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
2.4	The 'ocean sound' is pleasant to listen to.

	Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
2.5	The noise sound is pleasant to listen to. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
2.6	I am satisfied with the level steering option in Programme 3. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
2.7	Sound quality is the same with the new and my current device. Yes-No Please explain/give your comments
2.8	Speech intelligibility is the same with the new and my current device. Yes-No Please explain/give your comments
2.9	Listening comfort is the same with the new and my current device. Yes-No Please explain/give your comments
2.10	Loudness is the same with the new and my current device. Yes-No Please explain/give your comments
2.11	Feedback is the same with the new and my current device. Yes-No Please explain/give your comments
2.12	Overall my hearing ability is the same with the new and my current device. Yes-No Please explain/give your comments
2.13	The streamer is as good on the new device as it is on my current device. (Streamer users) The streamer adds value to the new device in comparison to my current device. (Streamer non-users)

	Yes-No Please explain/give your comments
Questions for participant about different aspects of usability of the new device.	
3.1	It is easy to put the device on. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
3.2	It is easy to take the device off. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
3.3	It is easy to change the programmes. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
3.4	It is easy to change the volume of the noise/ocean sound. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
3.5	It is easy to change the batteries. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
3.6	It is easy to use the streamer. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
Questions for audiologist performing the fitting about different aspects of usability of the new device.	
4.1	It is easy to fit the device. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
4.2	The device provides enough flexibility.

	Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
4.3	I did not have any problems to instruct the patient about the use of the single button. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
4.4	I did not have any problems explaining level steering to the patient. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
4.5	I did not have any problems explaining the use of manual volume control to the patient. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
4.6	I did not have any problems to instruct the patient about the use of the streamer. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
4.7	I did not have any problems explaining different programmes to the patient. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
4.8	I did not have any problems choosing the right noise for the patient. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments
4.9	I did not have any problems adjusting the level of the noise for the patient. Strongly agree- Agree- Neutral -Disagree -Strongly disagree Please explain/give your comments

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