CORTICAL OSCILLATIONS IN TINNITUS

Martin Holding

Institute of Hearing Research

School of Medicine

University of Nottingham

A Thesis Submitted for the Degree of Doctor of Philosophy

2018

Abstract

Tinnitus, described as a phantom perception of sound in its absence is a condition that affects millions of people worldwide. In its chronic form it can be associated with increased levels of anxiety and depression and can be highly debilitating in extreme cases. It is commonly held that it is related to deficits in hearing, either as a result of ageing or due to noise exposure. However beyond this there is little else known about the precise mechanisms involved in its generation or maintenance. In particular, little is known about the neural properties of tinnitus. Neural oscillations of various frequencies have been linked to tinnitus, although the evidence for which specific frequencies are involved is somewhat mixed. The main aim of the present thesis was to investigate these neural oscillations further, both in how they relate to the perception of tinnitus and how they can potentially be modulated.

The first study presented is an investigation into the subjective characteristics of tinnitus. The main aim was to investigate the relationship between hearing loss and tinnitus pitch, it was hypothesised that the primary tinnitus pitch would fall within the region of hearing loss. There were also two exploratory aims of the study, the first was to investigate the levels of agreement between two measures of tinnitus loudness one that was measured by a questionnaire (Tinnitus Case History Questionnaire) and the other that was measured as a rating of similarity to an externally presented sound. The second exploratory aim was to investigate the potential relationship between perceived tinnitus loudness and hyperacusis, or auditory hypersensitivity. As these secondary aims were exploratory there were no specific hypotheses made. To investigate the primary aim, the characteristics of each participant's tinnitus were gathered alongside their

audiometric profiles up to 12 kHz. A series of regression models were applied to the audiometric profile in order to determine the edge of hearing loss, slope of hearing loss and the frequency of worst hearing. These variables were then correlated with the dominant tinnitus pitch. The secondary aims were assessed by performing Bland-Altman Limits of Agreement analysis on the two measures of tinnitus loudness, and then performing a Pearson's R correlation between those two measures of tinnitus loudness and participants score on the Hyperacusis Questionnaire. Our results indicated that, as hypothesised, the dominant tinnitus pitch did appear to fall within the region of hearing loss, however this was not confirmed statistically. We also found that the two measures of tinnitus loudness we collected did agree with one another. However, only the questionnaire reported measure of tinnitus loudness correlated with the hyperacusis score, potentially indicating an emotional component inherent in the questionnaire based approach to measuring tinnitus loudness.

The second study presented aimed to investigate the role of delta (1-4 Hz), and alpha (8-12 Hz) oscillations in tinnitus using EEG. The phenomenon of residual inhibition (the temporary quietening of the tinnitus percept following presentation of a masking noise) was utilised to provide a within-subjects design. Oscillatory power in each of the four frequency bands was assessed in a baseline period, before residual inhibition was induced and compared with power after residual inhibition had been induced across two groups, one group that experienced residual inhibition and one group that did not experience any change in their tinnitus loudness. It was hypothesised that we would see significant increases in the alpha band and significant decreases in the delta band in the group that experienced residual inhibition. Exploratory analyses in the theta (5-7 Hz) and the beta (13-20 Hz) bands were also conducted, though no specific hypotheses were made regarding these. An

ANOVA showed significantly higher alpha and beta power in the group that experienced residual inhibition versus the group that did not. There were no significant changes observed between baseline and the residual inhibition period in any of the frequency bands, although significantly higher alpha was observed in the first 5 seconds of the residual inhibition period compared to the last 5 seconds.

The final experiment presented aimed to investigate the effects of transcranial direct stimulation (tDCS) on alpha and delta band oscillations. Both of these oscillatory frequencies have been implicated in the generation and maintenance of tinnitus and being able to modulate them may have effects on the tinnitus perception. A forward masking paradigm was implemented, while normal hearing control subjects underwent anodal tDCS at the same time as having their neural activity recorded via MEG. Cluster based permutation statistics revealed significant decreases in delta band activity, as well as increases in alpha band activity as a result of anodal stimulation. This indicates that tDCS is capable of modulating oscillatory frequency bands associated with tinnitus.

Declarations

I declare that all the work contained herein is my own, except where explicitly stated. I also confirm that this work has not been submitted before for any other degree or professional qualification.

Martin Holding	Date

Acknowledgements

I would like to express my sincere gratitude to both my supervisors, Peyman and Deb, without whose support, encouragement and wisdom this piece of work would not have been possible. I would also like to extend my thanks to Nathan Weisz and Gianpaolo Demarchi for hosting me in their lab in Trento, and whose experience in MEG and fieldtrip was invaluable. Thanks also to all the PhD students at the IHR with me, Carrie, Adam, Alex and above all Ben. Trying times they were, but we got through them all together and even managed to crack a smile or two along the way. Of course, thanks also to my partner throughout all of this, Hilary. Without whose constant support (and forgiveness of my stress based moodiness) I would have quit a hundred times over. Thank you all, for helping me in all the ways it is possible to help someone. Finally, thanks to you, my examiners for joining a select group of people to ever read this document in its entirety before it goes under the dodgy end of the coffee table to stop it wobbling.

List of Abbreviations

Acetylcholine - ACh

Analysis of Covariance - ANCOVA

Analysis of Variance - ANOVA

Brain Derived Neurotrophic Factor - BDNF

Broadband Noise - BBN

Decibels - dB

Dopamine - DA

Dorso-Lateral Prefrontal Cortex - DLPFC

Electroencephalography – EEG

Evoked Response Potentials/Fields - ERP/F

Excitatory PSP - EPSP

Fast Fourier Transforms - FFT

Gamma-Aminobutyric Acid - GABA

Glutamate - GLU

Glutamate - GLU

Hearing Level - HL

Independent Component Analysis - ICA

Inhibitory PSP - IPSP

Linearly Constrained Minimum Variance - LCMV

Long term depression - LTD

Long term potentiation - LTP

Magnetic Resonance Imaging - MRI

Magnetoencephalography – MEG

Minimum masking level - MML

Montreal Neurological Institute - MNI

N-acetylaspartate - NAA

N-methyl-D-aspartate - NMDA

Noradrenaline - NA

Postsynaptic Potentials - PSP

Primary Auditory Cortex – A1

Primary Visual Cortex - v1

Quantile-Quantile - QQ

Residual Excitation - RE

Residual Inhibition – RI

Serotonin - 5-HT

Sound Pressure Level - SPL

Spontaneous Firing Rates - SFR

Statistical Package for the Social Sciences - SPSS

Superconductive Quantum Interference Device - SQUID

Synthetic Aperture Magnetometry - SAM

Time Frequency Representations - TFR

Tinnitus Case History Questionnaire - TCHQ

Tinnitus Functional Index - TFI

Transcranial Alternating Current Stimulation - tACS

Transcranial Direct Current Stimulation – tDCS

Transcranial Magnetic Stimulation - TMS

Tucker Davis Technologies - TDT

Table of Contents

Abstract i

Declarations iv

Acknowledgements v

List of Abbreviations vi

List of Figures 0

List of Tables 2

Chapter 1 – Neurophysiology of Tinnitus 3

1.1 Epidemiology 3

1.2 Causes of Tinnitus 4

1.2.1 Cortical Reorganisation 6

1.2.2 Neural Gain 8

1.2.3 Neural Oscillations 11

1.2.4 An integrative model of tinnitus 15

1.3 Treatments and Therapies 24

1.3.1 Acoustic Maskers 24

1.3.2 Neurostimulation 25

1.4 Conclusion 26

Chapter 2 - An Introduction to Magneto/Electroencephalography 28

2.1 The Neuronal Signal 28

2.1.1 Neurophysiology 28

2.2 EEG and MEG Machinery 32

2.2.1 EEG Machinery 32

2.2.2 MEG Machinery 34

2.3 Using M/EEG in Research 37

2.3.1 Analysis Methods 37

2.4 Conclusion 47

Chapter 3 – Analysis of the Subjective Characteristics of Tinnitus and Associated Conditions. Experiment 1 48

3.1 Introduction 48

3.1.1 Hearing Loss and Tinnitus 48

3.1.2 Subjective Tinnitus Measurements 49

3.1.3 Tinnitus and Hyperacusis 55

3.1.4 Aims and Hypotheses 57

3.2 Methods 58

3.2.1 Ethics 58
3.2.2 Participants 58
3.2.2 Equipment and Apparatus 58
3.2.3 Procedure 64
3.2.4 Data Analysis 65
3.3 Results 67
3.3.1 Relationship between Tinnitus Frequency and Hearing Loss 67
3.3.2 Subjective Tinnitus Ratings 71
3.3.3 Agreement of Loudness Measurements 72
3.3.4 Prevalence of Hyperacusis 73
3.4 Discussion 76
3.4.1 Relationship between Tinnitus Frequency and Hearing Loss 76
3.4.1 Relationship between the two tinnitus measures 78
3.4.2 Relationship between Tinnitus Loudness and Hyperacusis 78
3.4.3 Conclusions and Future Directions 80
Chapter 4 – The Effects of Residual Inhibition on Cortical Oscillations in Tinnitus - Experiment 2 82
4.1 Introduction 82
4.1.1 Background 82
4.1.2 Mechanisms and Properties 83
4.1.3 Using Residual Inhibition to Study Tinnitus 85
4.1.4 Preparatory Review of Published Methods of RI Measurements 87
4.1.5 Aims and Hypotheses 93
4.2 Methods 95
4.2.1 Participants 95
4.2.2 Equipment and Apparatus 95
4.2.3 Experimental Protocol 97
4.2.4 Data Analysis 98
4.3 Results 103
4.3.1 Missing Data 103
4.3.2 Baseline Tinnitus Loudness Ratings 104
4.3.3 Tinnitus Loudness Change ratings 105
4.3.4 EEG Results 113
4.4 Discussion 130
4.4.1 Effects of Residual Inhibition on Oscillatory Power 130
4.4.2 The Returning Tinnitus Perception 132

4.4.3 Repeated Inductions of Residual Inhibition 135
4.4.4 Conclusions and Future Directions 137
Chapter 5 - The Effects of Transcranial Direct Current Stimulation on Auditory Cortical Oscillations Measured By Magnetoencephalography – Experiment 3 139
5.1 Introduction 139
5.1.1 History of Transcranial Direct Current Stimulation 139
5.1.2 Mechanisms of tDCS 141
5.1.3 Aims and Hypotheses 150
5.2 Methods 151
5.2.1 Ethics 151
5.2.1 Participants 151
5.2.2 Equipment and Apparatus 151
5.2.3 Experimental Protocol 154
5.2.4 Data Analysis 156
5.2.4.1 MEG Data Analysis 156
5.3 Results 159
5.3.1 Participants 159
5.3.2 Behavioural Results 160
5.3.3 Effects of stimulation Neural Activity 161
5.3.3.1 Confirmatory Analysis 161
5.3.3.2 Effects of stimulation on Evoked Responses 162
5.2.5 Neural Oscillations 166
5.4 Discussion 173
5.4.1 Behavioural Results 173
5.4.2 Modulation of Evoked Responses 174
5.4.3 Modulations of Oscillations 175
5.4.4 Conclusions and Future Directions 178
Chapter 6 – General Discussion 181
6.1 Summary of Main Findings 181
6.2 Implications of the Present Work 182
6.2.1 The Role of Oscillations in Tinnitus 182
6.2.2 Relationship between Tinnitus and Associated Conditions 184
6.3 Future Work 185
6.4 Conclusions 186
References 188

List of Figures

Figure 1.1: The Homeostatic Gain Mechanism 10
Figure 1.2: The Thalamocortical Dysrhythmia Model 14
Figure 1.3: Proposed Sub-Networks in Tinnitus Generation 17
Figure 2.1: Oscillatory Neural Activity Across Different Neuronal Assemblies 29
Figure 2.2: Simplified Diagram of a Neuron 31
Figure 2.3: Example EEG cap setup and 10-20 System Layout 33
Figure 2.4: Diagram of a SQUID Loop 36
Figure 2.5: Common MEG Coil Setups 37
Figure 2.6: Example Neural Waveform 40
Figure 2.7: Fourier Transform into TFR and Power Spectrum 42
Figure 2.8: Deconstructed 10 Hz Sine Wave 43
Figure 3.1: Audiogram of All Participants 61
Figure 3.2: Experiment 1 Setup 65
Figure 3.3: Median Audiogram and Peak Tinnitus Frequencies for All Participants 67
Figure 3.4: Bland-Altman Plot Of TCHQ and Tinnitus Tester Tinnitus Loudness Ratings 73
Figure 3.5: Correlation between Tinnitus Loudness versus Hyperacusis Questionnaire Score 74
Figure 4.1: Experiment 2 Setup 98
Figure 4.2: Screen Captures of the Rating Scales Used 101
Figure 4.3: Correlation Between Block 1 Tinnitus Loudness Ratings and Global TFI score 105
Figure 4.4: Bland-Altman Plots of Tinnitus Tester Loudness Change Ratings and RI Tester Loudness Change Ratings 107
Figure 4.5: Mean Loudness Ratings for All Participants 109
Figure 4.6: Mean Loudness Change Ratings for All Participants across the Time Points 112
Figure 4.7: Mean Loudness Change Ratings for All Participants across the Blocks 112
Figure 4.8: ERP Plots for the Baseline and Masker Period 114
Figure 4.9: Power Spectra for Each Subject Group, Block, Time Point 117-19

Figure 4.10: Estimated Marginal Means of Power for the Time Point and Change Grouping Interaction……123

Figure 4.11: Estimated Marginal Means of Power for the Block and Change Grouping Interaction……124

Figure 4.12: Estimated Source Locations for the Observed Changes in Oscillatory Power for Each Frequency Band and Time Point Comparison Across All Groups..129

Figure 4.13: Estimated Source Locations of the Observed Changes in Oscillatory Power for Each of the Three Time Points and Four Frequency Bands in the Residual Inhibition Grouping……130

Figure 4.14: Estimated Source Locations of the Observed Changes in Oscillatory Power for Each of the Three Time Points and Four Frequency Bands in the No Change Grouping……131

Figure 4.15: Estimated Source Locations of the Observed Changes in Oscillatory Power for Each of the Three Time Points and Four Frequency Bands in the Residual Excitation Grouping……132

Figure 5.1: tDCS electrode positions presented on an EEG 10-20 system……155

Figure 5.2: Example of a Completed Up/Down Adaptive Staircase for the Masker Threshold……157

Figure 5.3: Experiment 3 Setup……158

Figure 5.4: Visual Representation of the Pre-processed Data and the Data after Beamforming……159

Figure 5.5: Estimated Marginal Mean Stimulus Intensity for Each Time Point and Across Each Stimulation Condition……163

Figure 5.6: Confirmatory Evoked Response and Source Analysis on a Single Subject……164

Figure 5.7: Evoked Responses Fields for the First Second of Each Tone Presentation Condition……167

Figure 5.8: Time Frequency Representations for Each of the Tone Conditions in the Sham Stimulation Condition……170

Figure 5.9: Time Frequency Representations for Each of the Tone Conditions in the Anodal Stimulation Condition……171

Figure 5.10: Time frequency Representations for Each of the Stimulation Conditions, Collapsed over the Tone Presentation Conditions……172

List of Tables

Table 3.1: List of Tinnitus Questionnaires.....52

Table 3.2: Participant Demographics.....60

Table 3.3: Correlation Coefficients for Hearing Profile Characteristics and Peak Tinnitus Frequencies.....70

Table 3.4: Participant Scores for Global TFI, Hyperacusis Score, Tinnitus Tester Loudness Ratings and TCHQ Loudness Ratings.....72

Table 4.1: Methods of RI Measurement Across a Sample of Studies.....91

Table 4.2: Tinnitus Loudness Ratings and Tinnitus Loudness Change Ratings From Our Test and the Tinnitus Tester.....101

Table 4.3: Distribution of Missing Values in Tinnitus Loudness Change Ratings.....102

Table 4.4: Number of Participants in Each Group.....109

Table 5.1: Neurotransmitters Implicated in LTD and LTP.....144

Chapter 1 – Neurophysiology of Tinnitus

1.1 Epidemiology

Tinnitus, the auditory phantom perception of sound, is a condition to affects up to 15% of the population in Europe and the USA (Baguley, McFerran, & Hall, 2013). Prevalence rates vary around the world but remain quite high, ranging between 5 and 18% (Khedr et al., 2010; Lasisi, Abiona, & Gureje, 2010; Michikawa et al., 2010). For many this perception is temporary, such as after listening to loud music at a concert, and will pass after a few minutes or hours but for 8% of the adult population it occurs daily either transiently or constantly throughout the day (Shargorodsky, Curhan, & Farwell, 2010) and can dramatically reduce their quality of life.

The tinnitus percept can manifest itself in many different ways. For most it occurs as a hissing noise or a whistling tone, but can also take the form of distant voices or music (Holmes & Padgham, 2011). The pitch and volume of the tinnitus can also vary between tinnitus patients, as well as the initial onset, with some experiencing a gradual rise in the perception of the tinnitus symptoms and others experiencing a more abrupt onset (Baguley et al., 2013). Further, there exists 2 distinct types of tinnitus, objective and subjective. Objective tinnitus refers to tinnitus with a definable physical

cause, such as middle ear myoclonus (Bhimrao, Masterson, & Baguley, 2012; Ellenstein, Yusuf, & Hallett, 2013), and can frequently be perceived by outside listeners. It is also much rarer, perhaps accounting for as little as 1% of tinnitus cases (Folmer, Martin, & Shi, 2004). Subjective tinnitus, conversely, is only heard by the sufferer and as yet, has no known cause. It is the discovery of potential causes of subjective tinnitus that form the underlying aims of this project.

1.2 Causes of Tinnitus

The precise causes of tinnitus are unclear. One of the primary risk factors for developing tinnitus is hearing loss (Nondahl et al., 2011), however this is not sufficient to explain all cases. Many people with clinically normal hearing experience tinnitus, whilst many with hearing loss do not (Baguley et al., 2013). Nondahl et al (2011) also reported loud working environments, head injuries, ear infections and arthritis as significant risk factors in developing tinnitus. A number of different drugs have also been found to induce tinnitus, including salicylate, quinine, aminoglycosides and antineoplastic agents (Cianfrone et al., 2011). It is often very difficult to pinpoint the exact external cause of someone's tinnitus may be, and this is especially confounded by the fact that tinnitus can manifest itself both gradually over time, and very suddenly, seemingly in response to a particular event. Given the complexities in the external causes of tinnitus, as well as its idiopathic nature, it is necessary to look further into its pathophysiology.

Whether tinnitus originates in the ear or the brain has been a matter of some debate. Evidence for an ear generated tinnitus has mostly come from findings of increased Spontaneous Firing Rates (SFR) within auditory nerve fibres following admission of certain ototoxic drugs, for example high doses of salicylate (Evans, Wilson, & Borerwe, 1981). However, these results are somewhat incongruent as other drugs that are known to cause tinnitus (through animal studies in which the animal is conditioned to indicate tinnitus symptoms) such as quinine and aminoglycosides reduce the SFRs of auditory nerve fibres (Kiang, Moxon, & Levine, 1970; Mulheran, 1999). These changes in SFRs may, however, point to changes in central auditory structures (Eggermont & Roberts, 2004). In addition, various neuroimaging studies have found structural changes in both auditory and non-auditory structures within the brain (Landgrebe et al., 2009) as well as neural activity correlated with tinnitus distress and duration being found in non-auditory areas of the brain (Schecklmann et al., 2013). These findings indicate that the tinnitus sensation is most likely generated and maintained in structures within the brain, rather than the ear, and so it is prudent that research into the underlying mechanisms should focus on the study of the brain.

While the underlying theories of tinnitus generation discussed in the following sections are all fundamentally different, they share some similar mechanisms. For example, all the following theories centre on the auditory cortex as the primary generator of the tinnitus percept. Further, they all propose that the changes observed or theorised, either in oscillations, tonotopy, or cortical networks is initiated by hearing loss. What follows is a

discussion on models of tinnitus generation, beginning with proposed changes to tonotopic reorganisation on the auditory cortex, through to altered neural network activity through the whole brain. All of these theories can be linked by the proposals that the auditory cortex is the root of the tinnitus percept and that some form of hearing loss or damage to peripheral auditory pathway precludes the tinnitus sensation.

1.2.1 Cortical Reorganisation

As hearing loss is one of the primary predictors of developing tinnitus, it is often assumed that tinnitus is a response to neurological rebalance or redistribution following sensory deprivation (Eggermont & Roberts, 2004). According to the cortical reorganisation model, cochlea lesions either from noise trauma or age related hearing loss, result in 'dead' frequency regions which map onto auditory cortex (Rajan, Irvine, Wise, & Heil, 1993). These dead regions are then appropriated by neighbouring frequencies, which decrease their firing thresholds leading to the tinnitus perception (Rauschecker, 1999).

The cortical reorganisation hypothesised by this theory has been observed in animal models (Eggermont & Roberts, 2004). As have changes in the balance of excitatory and inhibitory pathways as a result of salicylate-induced tinnitus (Bauer, Brozoski, Holder, & Caspary, 2000), which may account for the perpetuity of the percept. Specific evidence for this reorganisation in humans, however, remains scant. A magnetoencephalographic study by Mühlnickel et al. (1998) did reveal shifts

in the anticipated cortical region of tinnitus frequencies into neighbouring areas, but beyond this there is no direct evidence for tonotopic reorganisation in tinnitus patients. Although there is evidence that this plasticity is possible. Pantev et al. (1998) found increased cortical representation of piano tones in musicians, demonstrating that cortical reorganisation is possible in the auditory cortex, albeit in the absence of the hearing loss and damage that is typical in tinnitus.

More recent findings have also challenged the theory. A review by Elgoyhen et al. (2015) points out several criticisms of the tonotopic reorganisation model of tinnitus generation. Firstly, tonotopic reorganisation would predict that the edge frequencies, adjacent to the region of hearing loss, will become over represented in the cortex and it would be from these frequencies that the tinnitus percept would arise. However, this has been found to not be the case, with tinnitus frequencies more closely matching the region of hearing loss (Norena, Micheyl, Chéry-Croze, & Collet, 2002; Sereda et al., 2011a; Sereda, Edmondson-Jones, & Hall, 2015). Tinnitus has also been observed in the absence of macroscopic cortical reorganisation (Langers, de Kleine, & van Dijk, 2012), indicating that, while microscopic changes may still be present, it is not to the extent that the model would predict. This may be linked to the third criticism levelled at cortical reorganisation. The model predicts that damaged areas in the auditory cortex are prefaced by damage to the cochlea, resulting in hearing loss. However, tinnitus can occur in the absence of clinical hearing loss (Tang, Ji, & Liu, 2011), and small changes in hearing thresholds do not lead to cortical reorganisation in animals (Rajan,

1998). Taken together, it is more probable that cortical reorganisation reflects hearing loss and damage, rather than being a direct cause of tinnitus (Elgoyhen et al., 2015).

1.2.2 Neural Gain

It is also important to consider why such changes occur, not just how. The cortical reorganisation hypothesis describes how cochlear lesions can cause hyperactivity (through over representation of certain frequencies) in central auditory structures but it does not detail the reasons these changes might occur. The central gain theory proposes that these changes occur as a result of the brain's innate homeostatic plasticity, meaning the brain is hardwired to preserve an average neural activity and coding efficiency when faced with sensory deprivation (Schaette & Kempter, 2006). When sensory deprivation occurs, spontaneous activity and input from the cochlea to central auditory structures is reduced (Liberman & Dodds, 1984), reducing input to central structures. The mechanisms proposed by the central gain theory exist to level out these reduced inputs ensuring a consistent level of input, and also to redistribute the modified cochlea inputs to maintain dynamic range further up the auditory system (Noreña & Farley, 2013). However, because the gain is now increased at a central level the hyperactivity that would normally be confined to the cochlea now occurs in central auditory structures, at the level of perception, causing tinnitus.

As with cortical reorganisation, the central gain theory of tinnitus generation relies upon hearing loss being present in order for the

development of tinnitus. It also relies upon types of hearing loss and deprivation that result in increased central gain, but preserve cochlear nerve firing rates. Such as hearing loss that is driven by damage to outer hair cells, leaving inner hair cells (damage to which spontaneous firing rates are more sensitive too) intact. We would therefore expect, and in fact observe, tinnitus to be present in hearing loss that is the result of outer hair cell loss (Ozimek, Wicher, Szyfter, & Szymiec, 2006), conductive hearing loss (Lima, Sanchez, Bonadia Moraes, Batezati Alves, & Bento) and silence both natural (Knobel & Sanchez, 2008) and caused by blockages to the ear canal in the form of ear wax (Midani, Carels, Marks, & Wall, 2006) and ear plugs (Schaette, Turtle, & Munro, 2012). The specificity of this type of hearing loss may go some way to explaining why tinnitus arises in some cases of hearing loss, but not others.

Evidence for these central gain mechanisms in humans has been presented in the form of wave amplitudes in Auditory Brainstem Responses (ABRs). Significantly lower wave I amplitudes and elevated wave V responses (Figure 1.1), in tinnitus subjects compared with normal hearing controls have been observed (Gu, Herrmann, Levine, & Melcher, 2012; Schaette & McAlpine, 2011). Schaette and McAlpine (2011) attribute this 'rebalancing' of wave amplitudes to the homeostatic central gain mechanisms, while Gu et al. (2012) point to the potential role of the Ventral Cochlea Nucleus (VCN) in this rebalancing. Further, Schaette & McAlpine (2011) used the finding of lowered wave I responses as evidence for a 'hidden hearing loss' (hearing loss that is not found on a standard clinical audiogram up to 8 kHz) exhibited in tinnitus.

The presence of tinnitus in the absence of clinical hearing loss is the central premise of many of the criticisms of current models of tinnitus generation.

More recent work, with larger sample sizes, has either found no relationship between noise exposure and ABR amplitudes (Prendergast et al., 2017) or results that are inconsistent with the predictions made by the

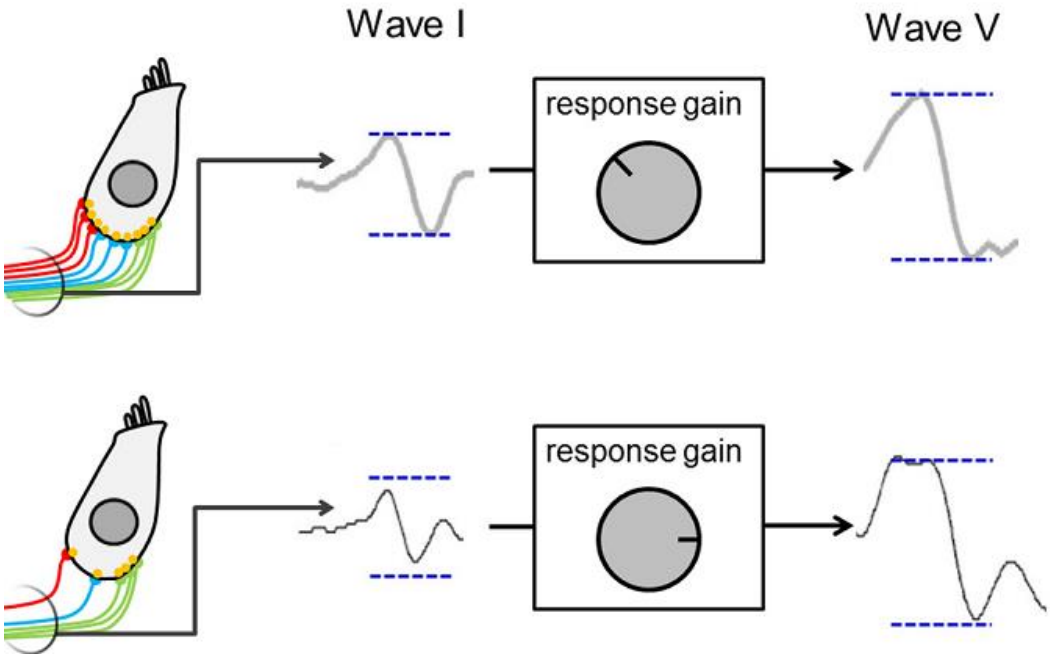


Figure 1.1: Illustration of the homeostatic gain control mechanism proposed by Schaette and McAlpine (2011). The colored lines on the left represent auditory nerve fibers leading into the cochlea (Green = Low threshold fibers, blue = medium threshold fibers, red = high threshold fibers). The top diagram represents a normal hearing individual, who produces a normal wave I response, and with little response gain a normal wave V responses. The bottom diagram represents an individual with hidden hearing loss, who produces a much lower amplitude wave I response. The response gain is much higher as a result, giving the normalized wave V response. Taken without permission from Schaette and McAlpine (2011).

central gain theory (Brotherton, Plack, Schaette, & Munro, 2017). It is worth bearing in mind that neither of these two studies used participants with hearing loss or tinnitus. Prendergast et al (2017) used 127 normal hearing participants and estimated cumulative lifetime noise exposure using a leisure and work noise exposure questionnaire (Lutman, Davis, & Ferguson, 2008) while Brotherton et al. (2017) induced a hearing loss in 28 participants using

noise attenuating earplugs. The types of hearing loss and sensory deprivation that can result in tinnitus and that fit within the theory of central gain, including the use of ear plugs (Schaette et al., 2012) have already been discussed. It is therefore plausible that the discrepancies between this work and the work of Schaette and McAlpine (2011) is a result of an absence of the tinnitus percept. In the original work, Schaette and McAlpine (2011) only tested tinnitus participants and non-tinnitus controls (both with clinically normal hearing) and so the hypothesis that changes in ABR amplitude are the result of tinnitus specifically, and not hearing loss, is untested.

1.2.3 Neural Oscillations

Increases in SFRs as a result of either cortical reorganisation or increases in neural gain carry with them the possibility of increased neural synchrony. Such increases have been observed in various auditory structures in animal models. In cat primary auditory cortex (A1) increases in neural synchrony have been observed after applications of both quinine and salicylate, two drugs that are thought to cause tinnitus (Ochi & Eggermont, 1996, 1997). While it is possible that these increases in neural synchrony are chance artefacts as a result of an increase in SFRs, this is unlikely and there is evidence to support the position that this synchrony is more than just a chance event (Bauer, Turner, Caspary, Myers, & Brozoski, 2008).

In humans, neural synchrony can be considered analogous to neural oscillations. Oscillatory activity in different frequency bands has been used to distinguish pathological states in the past, including schizophrenia

(Weinbruch et al., 2003), memory impairment (Osipova et al., 2006) and brain tumours (Oshino et al., 2007). The thalamocortical dysrhythmia model aims to describe the neural mechanisms that might underlie these changes in oscillatory activity (Llinas, Ribary, Jeanmonod, Kronberg, & Mitra, 1999). The model was originally built on data from a variety of neurological conditions, including depression, Parkinson's disease, neurogenic pain and tinnitus. It proposes that the symptoms of these conditions are intrinsically linked with abnormal low frequency (<10Hz) and high frequency (>30Hz) neural oscillations during resting state. Deafferentation to specific thalamocortical pathways from layer VI thalamus, to layer I cortex cause reduced inputs to both cortical pyramidal neurons and inhibitory cortical interneurons. Deafferentation to a second, non-specific thalamocortical pathway generates temporal coherence via the same mechanism. The disfacilitation caused by this results in an influx of calcium current and a decrease in potassium current (Jahnsen & Llinas, 1984) this leads to increased low frequency oscillations (figure 1.2). The reduced input from the specific and non-specific pathways to the inhibitory cortical interneurons results in an increase in power of high frequency oscillations in neighbouring areas, termed the 'edge effect' (Llinas et al, 1999). According to this theory, the increase in high-frequency oscillations in cortical layers leads, in the case of tinnitus, to its perception.

The idea that tinnitus is somehow linked to increased low and high frequency oscillatory activity is an easily testable hypothesis (Adjamian, Sereda, & Hall, 2009). Increased theta (4-7Hz) activity in the single tinnitus

patient studied was observed in the initial work by Llinas et al (1999) when compared with control subjects. However the hypothesis predicting increases in high frequency activity was not tested. Increased gamma has been observed in the literature since the thalamocortical dysrhythmia was proposed, as well as evidence that it originates in the temporal cortex (Ashton et al., 2007; Weisz, Dohrmann, & Elbert, 2007). Further, van der Loo et al. (2009) reported significant interactions between the intensity of gamma activity and tinnitus loudness. However, more recent work failed to find any increases in gamma as a result of tinnitus or hearing loss (Adjamian, Sereda, Zobay, Hall, & Palmer, 2012). In addition, the model predicts that the

tinnitus pitch will occur on the edges of hearing loss (where the 'edge effect' from deafferentated regions will be strongest), but research has repeatedly shown this is not always the case (Norena et al., 2002; Sereda et al., 2011b).

Increased slow wave activity, in particular around the delta (1-4Hz) range, is a more consistent finding (Adjamian et al., 2012; Kahlbrock & Weisz, 2008; Weisz, Moratti, Meinzer, Dohrmann, & Elbert, 2005). Kahlbrock and Weisz (2008) also reported transient reductions in delta band oscillatory power (1-4 Hz) as a result of residual inhibition (the temporary quietening of the tinnitus percept following a masking noise). A study investigating

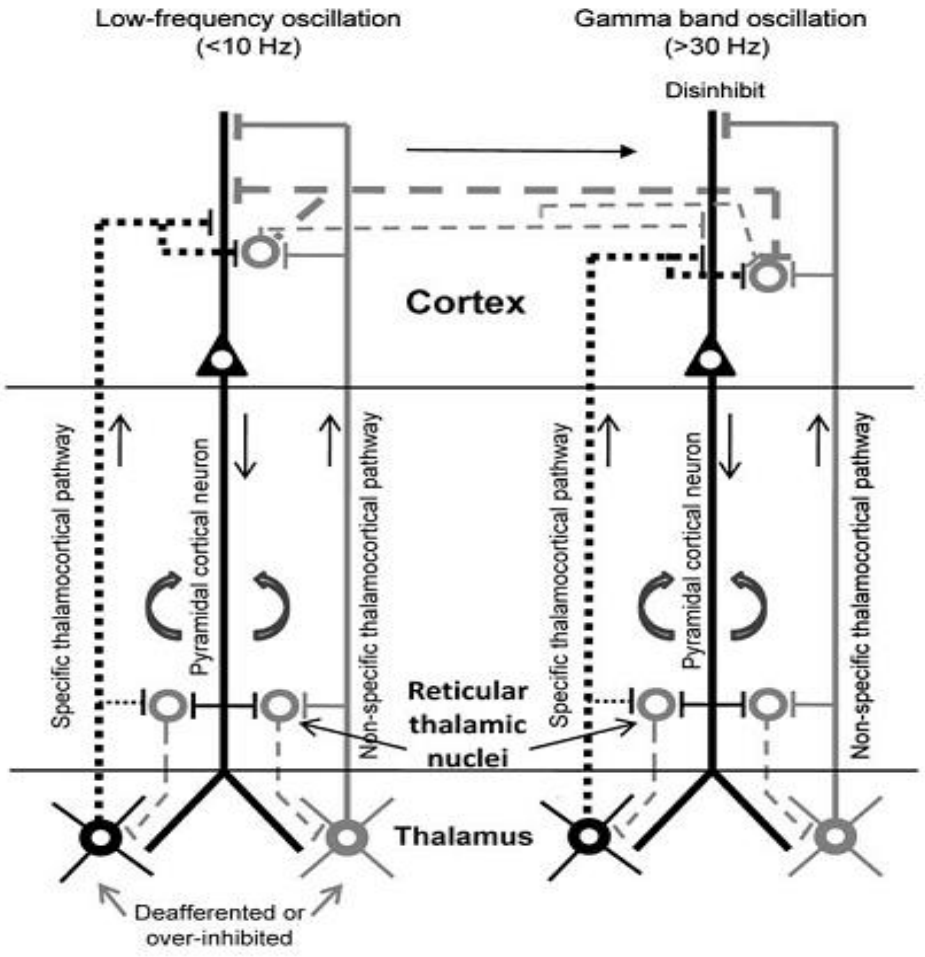


Figure 1.2 Schematic overview of the thalamocortical dysrhythmia model. Deafferentation (due to hearing loss) to thalamic neurons (bottom left black and grey circles) propagate damage up specific and non-specific thalamocortical pathways (black dotted line and solid grey line, respectively). This reduces inputs at cortical synapses to pyramidal cortical neurons (black solid line), and hyperpolarizes calcium channels in the reticular thalamic nuclei, leading to increased slow wave oscillations. Further, lack of input from pyramidal cortical neurons reduces firing of inhibitory cortical inter neurons (dashed grey line), causing increased firing of neighboring high frequency areas. Reproduced without permission from Adjamian et al (2009)

temporary tinnitus experienced by musicians following a band practice found no modulations in delta activity (Ortmann, Muller, Schlee, & Weisz, 2011), suggesting that increased delta activity is the result of more permanent deafferentation and tinnitus. It is worth noting that both the original model, and subsequent reviews of the thalamocortical dysrhythmia model specifically implicate increases in theta band (5-8Hz) power as the instigator of thalamocortical dysrhythmia, and not delta band (De Ridder, Vanneste, Langguth, & Llinas, 2015; Llinás et al, 1999). De Ridder et al (2015) attempts to reconcile this discrepancy by integrating a Bayesian point of view into the model. In short, a Bayesian point of view conceives of a brain that is attempting to always predict and explain its experiences (Friston, 2010). Perceptions are regarded as predictions about the world that are confirmed or denied (the posterior belief) by a combination of sensory evidence and a priori beliefs (memories and experiences of the external world). As such, confirmed perceptions will then become a priori beliefs. The auditory oscillations governing this mechanism have been recently identified, in particular identifying a delta-beta cross coupling in prediction accuracy (Arnal, Doelling, & Poeppel, 2015). As maladaptive prediction accuracy is intrinsic in the permanence of the tinnitus percept, it would stand to reason that these frequencies would be active during tinnitus.

1.2.4 An integrative model of tinnitus

The previously discussed models have all considered tinnitus as a single homogenous condition. Treating it purely as a sound-based phenomenon, with no consideration for its other aspects such as its emotional or cognitive

or behavioural impacts. The tinnitus percept can vary on a number of levels. As previously discussed, tinnitus is typically described as a hissing or tonal sound, but this can vary (Holmes & Padgham, 2011). It also varies in the distress it causes those who have it. It is thought that only 20% of those who perceive tinnitus are distressed by it (Axelsson & Ringdahl, 1989) and within this group tinnitus has further links with anxiety and depression (Gomaa et al., 2014; Loprinzi et al., 2013; Vogel et al., 2014). Further, the perceived location of the tinnitus can vary, with patients reporting unilateral, bilateral and alternating tinnitus. These aspects vary individually within the tinnitus population, and must be considered when developing an accurate model of tinnitus.

The integrative model of tinnitus proposes that tinnitus is a unified percept arising from a number of sub-networks (De Ridder et al., 2014b). These sub-networks individually process different aspects of the tinnitus, and partially overlap with one another. The areas of the brain where these networks overlap are known as hubs and it is through these hubs that communication across the sub-networks occurs. Broadly speaking the model considers four sub-networks, each processing a different aspect of the tinnitus, and one core network, from which the actual tinnitus itself is

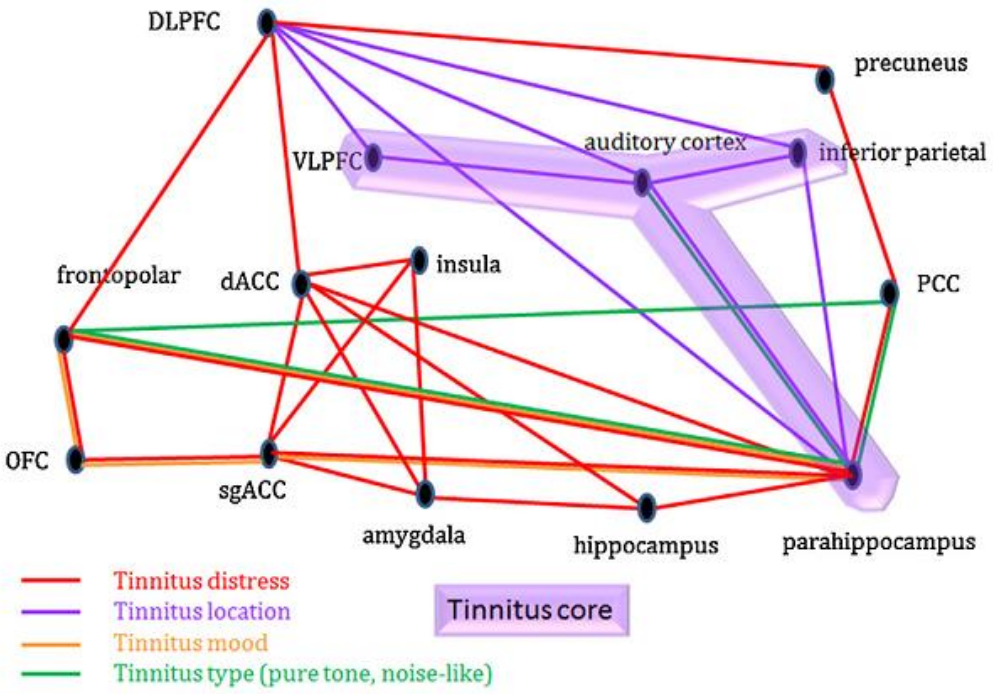


Figure 1.3: The proposed sub-networks governing the tinnitus percept from the integrative model of tinnitus. The core tinnitus network is highlighted in lilac. Lines between the areas do not denote that these areas are neurologically connected, only that they form part of the same sub-network. Those areas that form part of multiple sub-networks are considered as hubs, and are capable of oscillating at multiple frequencies. Communication between the sub-networks is propagated through these hubs. Figure reproduced without permission from De Ridder et al (2014a)

generated (figure 1.3). The four sub-networks comprise of a tinnitus distress

network, a tinnitus location network, a tinnitus mood network, and a tinnitus type network (De Ridder et al., 2014a).

The Core Tinnitus Network

It has been proposed in visual science that activation of V1 cortex is necessary for perception of visual stimuli, but not sufficient (Crick & Koch, 1995) and similar suggestions have been made for the primary auditory cortex (Meyer, 2011). This suggests that there must be a number of other areas in the brain involved in the generation of the tinnitus percept. The core tinnitus network proposed by De Ridder et al. (2014) comprises of the minimal amount of brain areas that, taken together, generate the percept, irrespective of any of its other aspects such as perceived location, loudness, cognitive and emotional distress. These areas (the auditory cortex, inferior parietal area, ventrolateral prefrontal/frontopolar cortex and the parahippocampus) overlap with areas associated with auditory awareness of pitch (Brancucci, Franciotti, D'Anselmo, Della Penna, & Tommasi, 2011) and auditory pitch memory. It is then assumed, that the tinnitus percept is pulled from memory but perceived as an external stimulus (De Ridder et al., 2006). Evidence for this assumption is derived from the observation that the areas involved in auditory pitch memory and external auditory pitch awareness, are less active during sleep. Phantom limb sensations are often not perceived during sleep while dreaming (Alessandria, Vetrugno, Cortelli, & Montagna, 2011; Mulder, Hochstenbach, Dijkstra, & Geertzen, 2008), and it is thought that tinnitus is the same (De Ridder et al., 2014b). As such, reduced activity in these areas during sleep when tinnitus is not perceived, would indicate the

potential role they play in the generation of the tinnitus percept. However, the assumption that tinnitus is not perceived during sleep is based upon unpublished data from Klaps and De Ridder and a full investigation into this does need to be conducted.

Tinnitus Distress and Mood Sub-Networks

It is well known that tinnitus has considerable links with anxiety and depression (Gomaa et al., 2014; Loprinzi et al, 2013; Vogel et al., 2014). It has been assumed in the past that these conditions are a reaction to the tinnitus, however more recent theories suggest that the increased prevalence of depression amongst tinnitus sufferers is due to shared pathophysiological mechanisms (Langguth, Landgrebe, Kleinjung, Sand, & Hajak, 2011; Rauschecker, Leaver, & Muhlau, 2010). Further, there are distinct functional connectivity changes between those who find their tinnitus bothersome and those who do not (Burton et al., 2012; Wineland, Burton, & Piccirillo, 2012). This would indicate a distinct sub-network within the global tinnitus network that, while evidently not necessary for its conscious perception, is nonetheless important in the experience of the tinnitus.

There are a number of overlaps between areas that comprise the salience network (the network of brain areas involved in bringing perceptions to consciousness) and the tinnitus distress and mood sub-network, such as the amygdala, anterior cingulate and the anterior insula (De Ridder, Vanneste, & Congedo, 2011; Joos, Vanneste, & De Ridder, 2012; Vanneste, Plazier, der Loo, et al., 2010). There is also significant overlap with the areas

controlling the autonomic nervous system and limbic system (Critchley, Elliott, Mathias, & Dolan, 2000; Critchley, Melmed, Featherstone, Mathias, & Dolan, 2002; Kraus & Canlon, 2012; Nicotra, Critchley, Mathias, & Dolan, 2006; Ter Horst, Hautvast, De Jongste, & Korf, 1996; Wong, Massé, Kimmerly, Menon, & Shoemaker, 2007). This would indicate a role in the autonomic nervous system, and in particular the sympathetic component of the autonomic nervous system, in bringing the tinnitus to consciousness and also applying an emotional component as described in earlier models of tinnitus generation (Jastreboff, 1990; van der Loo, Congedo, Vanneste, Van De Heyning, & De Ridder, 2011). Further, it was earlier indicated that auditory memory was a component of the core tinnitus network. It has been noted that memory retrieval is improved under the sympathetic nervous system (Murchison, Schutsky, Jin, & Thomas, 2011) which may explain why stress is so associated with tinnitus (Fagelson, 2007; Hinton, Chhean, Pich, Hofmann, & Barlow, 2006).

Tinnitus Location Sub-Network

Much of the evidence for a tinnitus location sub-network is based upon oscillations, particularly gamma, in the auditory cortex. Typically, these results indicate that tinnitus sidedness is determined by increased gamma activity in the auditory cortex contralateral to the perceived tinnitus (De Ridder, van der Loo, et al., 2011; Llinás et al., 1999; Weisz, Muller, et al., 2007). Although this can be debated, as a study by Vanneste et al., (2011) found increased gamma in the primary and secondary auditory cortices irrespective of sidedness or laterality of the tinnitus. The same study also

found that tinnitus sidedness in narrow band tinnitus is related to gamma activity in the contralateral parahippocampal area. Indicating a role in the parahippocampus in determining the sidedness of the tinnitus percept.

Evidence for the involvement of other areas in the tinnitus location sub-network is derived from area differences in people with unilateral and bilateral tinnitus. Increased beta2 (18.5Hz-21Hz) activity in the superior prefrontal gyrus is observed in unilateral tinnitus compared with bilateral tinnitus (Vanneste et al., 2011; Vanneste, Plazier, van der Loo, Van de Heyning, & De Ridder, 2010). Whereas slow wave delta activity is observed in the ventrolateral prefrontal cortex in comparison to unilateral tinnitus (De Ridder et al., 2014a). Further, neuromodulation studies have shown an ability to influence perceived sidedness of the tinnitus percept. When high amplitude Transcranial Magnetic Stimulation (TMS) was applied to the posterior of the superior temporal gyrus the laterality of the tinnitus percept was altered (De Ridder et al., 2007; De Ridder, Vanneste, Kovacs, et al., 2011c).

The tinnitus location sub-network shares almost the entirety of its brain areas with the proposed tinnitus core network. This would make sense, as the mechanisms of tinnitus location have been shown to be related more to changes in patterns of activity, rather than differing locations (De Ridder et al., 2011; Llinás et al, 1999; Vanneste et al., 2011; Weisz et al., 2007). As such, the areas in which tinnitus is initially generated could also determine where it was perceived, by alterations to the oscillatory activity in those areas.

Tinnitus Type Sub-Network

It has been hypothesised that differences between tinnitus types may be related to differences in firing modes of two parallel auditory thalamic pathways. Synchronous hyperactivity along the non-tonotopic extralemniscal pathway was proposed to leads to white noise like tinnitus, whereas synchronous tonic firing along the tonotopic lemniscal pathway results in pure tone tinnitus (De Ridder et al., 2007a). Evidence for this hypothesis stems from neuromodulation studies, which revealed that pure tone and noise like tinnitus respond differently to tonic and burst stimulation for both TMS and implanted electrodes (De Ridder et al., 2007a; De Ridder, Vanneste, Kovacs, et al., 2011; Vanneste, Plazier, Van Der Loo, et al., 2010). This matches the differences in firing mode observed in the two auditory thalamic pathways, with the lemniscal pathway predominantly firing in tonic mode, and extralemniscal pathway firing in burst mode (He & Hu, 2002). However, this only accounts for two types of tinnitus, noise like and pure tone. While these two types of tinnitus are amongst the most common there are still a number of variants such as those whose tinnitus is musical in sound or takes the form of distant voices (Holmes & Padgham, 2011), that are not accounted for by the proposed mechanism.

Integration of Other Models

Discussion of the model so far has focused on the various brain areas associated with the different aspects of tinnitus and little on the actual mechanisms by which the tinnitus is generated. It is proposed that, similar to the models previously described, deafferentation may initially trigger the

responses observed in the tinnitus core network (De Ridder et al., 2014b). This is then maintained by a faulty noise cancellation mechanism, similar to what has been described by Schaette and McAlpine (2011). The core tinnitus network then becomes coupled with more distant cortical areas via low and high frequency oscillations, as has been observed in auditory processing (Doesburg, Green, McDonald, & Ward, 2012). In particular, it has been found that gamma activity integrates information on a local level, while theta integrates information over longer distances (von Stein & Sarnthein, 2000). This would imply an important role in theta and gamma oscillations as carrier waves for the tinnitus information, which has been posited by Llinas et al., (1999).

The number of different areas involved in the complete tinnitus percept (from its initial generation, to its emotional components) would also explain the wide variety of oscillatory frequencies associated with tinnitus (Adjamian et al., 2012; Kahlbrock & Weisz, 2008; Weisz et al., 2007; Weisz et al., 2005). Separate, parallel resting state networks have been shown to be able to communicate with each other using multiple discrete oscillatory frequencies simultaneously (Palva & Palva, 2012), and roles for each of the frequency bands are laid out within the model. The slow wave delta and theta oscillatory bands are supposed to be involved in a maladaptive predictive mechanism, predicting the presence of a sound when it is not present, whereas the higher frequency beta and gamma are involved in the conscious perception of the sound (Arnal & Giraud, 2012; De Ridder et al., 2014a). The alpha activity is suggested to be slowed down into theta activity,

along the same mechanisms as outlined in the thalamocortical dysrhythmia model.

1.3 Treatments and Therapies

At present, there remains no cure for tinnitus that is capable of eliminating the perception permanently (Baguley et al., 2013; Rauschecker et al., 2010). The lack of treatment and universally effective therapy has, in part, been attributed to the large number of potential treatment targets and disagreement about the underlying mechanisms within the brain (Teismann, Okamoto, & Pantev, 2011). The large heterogeneity in the experience of tinnitus is likely also a significant factor in the difficulty in developing a treatment. Difficulties notwithstanding, a number of therapies are available that range in effectiveness (Hoare, Adjamian, Sereda, & Hall, 2013). These therapies can differ in approach, aiming to either manage the tinnitus symptoms or eliminate the percept itself. It is the latter that this section will focus on.

1.3.1 Acoustic Maskers

Amongst the most common forms of current therapy for tinnitus are acoustic masking devices (Hoare, Gander, Collins, Smith, & Hall, 2012). These devices are widely available commercially, and operate by presenting the patient with an acoustic masking noise, typically one that is tailored in some manner to the individual's tinnitus. They are based upon the assumption that by introducing an external sound, the contrast between the tinnitus and the background auditory activity is reduced, which results in a perceived

quietening of the tinnitus (Vernon, 1977). While a recent Cochrane review concluded that the effectiveness of these devices was limited, they also cited a lack of reliable studies in the subject area (Hobson, Chisholm, & El Refaie, 2010). It is also common to combine this therapy with other treatments, such as hearing aids and psychological therapies which may account for the difficulties observed in finding adequate research studies (Hobson et al., 2010). When considered with the therapies that often accompany the commercially available acoustic masker packages (such as Serenade ® by SoundCure, Zen® by Widex and Neuromonics® by Neuromonics), the positive effects of these devices is more promising Hoare et al., 2012). However, in these instances it is difficult to tease out the benefit of the masker specifically from the benefits of the accompanying therapies.

1.3.2 Neurostimulation

The effects of neuromodulator techniques such as transcranial magnetic stimulation (TMS) and transcranial Direct Current Stimulation (tDCS) on tinnitus symptoms are well studied. A review by Song et al. (2012) found a 13.5% mean reduction of tinnitus loudness in 39.5% as a result of tDCS application. Similarly, a large study of 64 tinnitus patients revealed 56% of patients in the active TMS group had a significant reduction in their tinnitus loudness (Folmer et al., 2015). Although, a recent review concluded that while the application of TMS as a therapy in tinnitus was promising, there were still a number of methodological considerations that need to be resolved in current TMS studies (Theodoroff & Folmer, 2013). While these neuromodulators do seem capable of reducing the tinnitus, it is not 100%

effective. Nor does it appear to eliminate the tinnitus entirely. There remains a great deal of research needed in order to build upon the potential of neuromodulators to create a more effective therapeutic solution.

1.4 Conclusion

Tinnitus is a prevalent condition, occurring in up to 15% of the population in Europe and the USA (Baguley et al., 2013). It is associated with a number of psychiatric conditions, such as anxiety and depression (Gomaa et al., 2014; Loprinzi et a.l, 2013; Vogel et al., 2014). The precise mechanisms of tinnitus remain unknown, although recent theories and models postulate that deafferentation due to hearing loss result in changes to the SFRs in the auditory cortex via homeostatic mechanisms designed to maintain a constant input to the auditory cortex (Schaette and McAlpine, 2011). High frequency oscillations that result in this generate the tinnitus percept. Low frequency oscillations then spread the tinnitus information to other brain areas, which give the tinnitus percept its emotional components (De Ridder et al 2014). There remains no effective treatment or therapy for tinnitus. Although a number of commercially available masking devices are available. Neuromodulation devices such as TMS and tDCS are also promising, though neither therapy is 100% effective in all tinnitus patients. It is possible that this is due to the wide heterogeneity of the tinnitus percept. In order to develop a more effective therapy for tinnitus, more research is needed into its core mechanisms, as well as how these mechanisms are altered across different

tinnitus percept. Understanding this, would allow for the development of better targeted treatments and therapies.

Chapter 2 - An Introduction to Magneto/Electroencephalography

2.1 The Neuronal Signal

2.1.1 Neurophysiology

In principle, MEG and electroencephalography EEG measure different aspects of the same neural phenomena. When neurons fire they generate both an electrical current and a magnetic field. The electrical current is measured by EEG and the magnetic field by MEG. While these two aspects (electrical and magnetic) of the firing neuron are very closely related, there are some inherent technological differences in how they are measured.

Electrical and magnetic fields are generated in neurons through both action potentials and Post Synaptic Potentials (PSPs). Action potentials, while generally larger than PSPs in amplitude, are too transient to be measured by M/EEG. Nor do they fire with the synchrony required to produce a strong enough summated signal. PSPs, however, have a much longer time course, which allows for greater synchrony and summation between adjacent neurons. Figure 2.1 shows how different levels of synchrony can affect the neural activity measured by M/EEG. It is a summation of synchronous PSPs (known as local field potentials) that is measured by M/EEG.

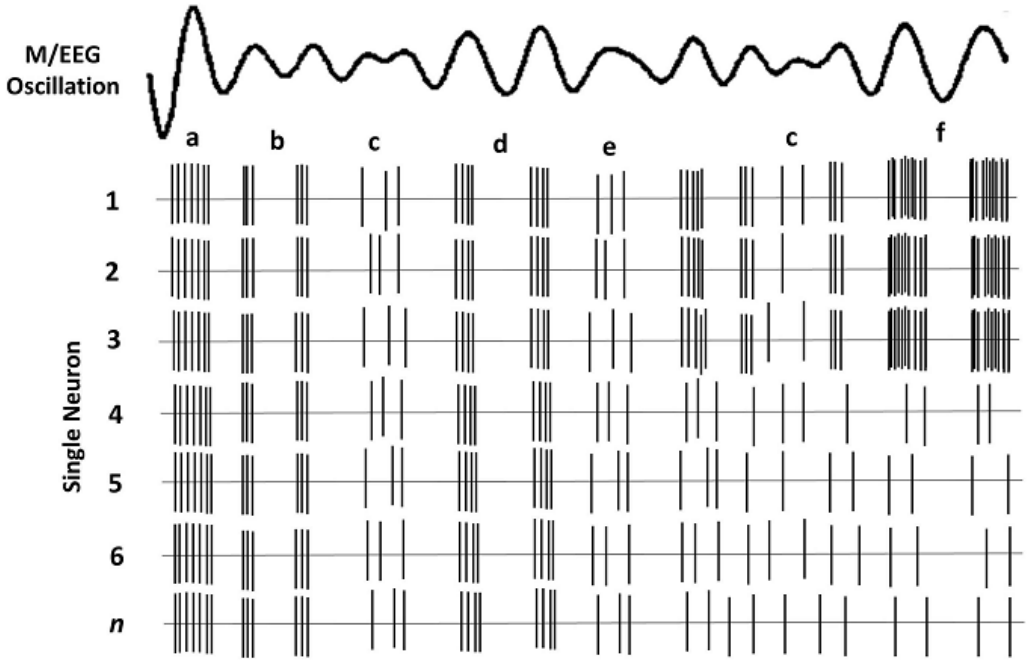


Figure 2.1: Schematic diagram of measured oscillatory activity as a results of different example neuronal assemblies. Each row represents a different neuron, while each column represents a different firing pattern. Higher coherence in firing and firing rate (columns a and f) result in higher local field potential signals. Whereas non-coherent firing (columns c and e) result in much lower local field potentials. Reproduced with the author's permission from Adjamian (2014) through the CC BY License.

PSPs are driven by other neighbouring neurons releasing neurotransmitters into their connecting synapses following their own firing. There are two main types of PSP, inhibitory (IPSP) and excitatory (EPSP). The neurotransmitters themselves are not inherently excitatory or inhibitory, but rather the receptors they bind to dictate the response of the neuron. Neurons have a resting state potential of -70mV (Figure 2.2 a), which is maintained by balancing sodium (Na+) ions on the outside of the cell membrane and potassium (K+) ions on the inside. An IPSP results in the net gain of negative charge resulting in a hyperpolarisation, as the membrane potential moves further from 0. The neuron does not fire if the majority of inputs are inhibitory, as the membrane potential is moving further from its

firing threshold. If an EPSP occurs however, Na+ ion channels open along the membrane, allowing the influx of Na+ ions into the cell. This input causes a depolarisation to the threshold potential (-55mV) when this threshold is reached, Na+ ion channels in the axon hillock are opened. This causes an influx in positive Na+ ions within the axon body, increasing the polarity of the cell and causing a large depolarisation as seen in figure 2.2 b. This increase also causes other points along the axon to reach their threshold potential, opening more Na+ ion channels and propagating the action potential. When the peak positive voltage has been reached the Na+ channels close, and the K+ ion channels open. This allows the K+ ions to leave the cell, beginning the refractory period. The opening of the K+ channels causes a hyperpolarisation of the cell below that of its normal resting state. The Na+ channels then return to their normal state causing the cell to return to its resting state potential. This action potential may then lead the release of further neurotransmitters, which in turn may begin more action potentials in other cells.

Since MEG and EEG are both measures of local field potentials, and each electrode can be recording the summated PSPs of at least 10,000 neurons (Nunez & Srinivasan, 2006) it is important to consider what neural populations the techniques are measuring. Both the orientation and depth of the neural population should be considered when assessing what neural signal EEG and MEG are analysing. MEG is most sensitive when detecting the magnetic fields of neurons that are tangential to the skull. A common belief is that MEG cannot measure fields from radial sources. However this is

incorrect, MEG is less sensitive to radial sources, but can still measure them (Baillet, 2017). Both MEG and EEG are poor at measuring the signals originating in sub-cortical areas. As such the majority of the signal picked up by both MEG and EEG originates in the 3-5mm of cortex that encompasses the cortical surface (Lopes da Silva, 2010).

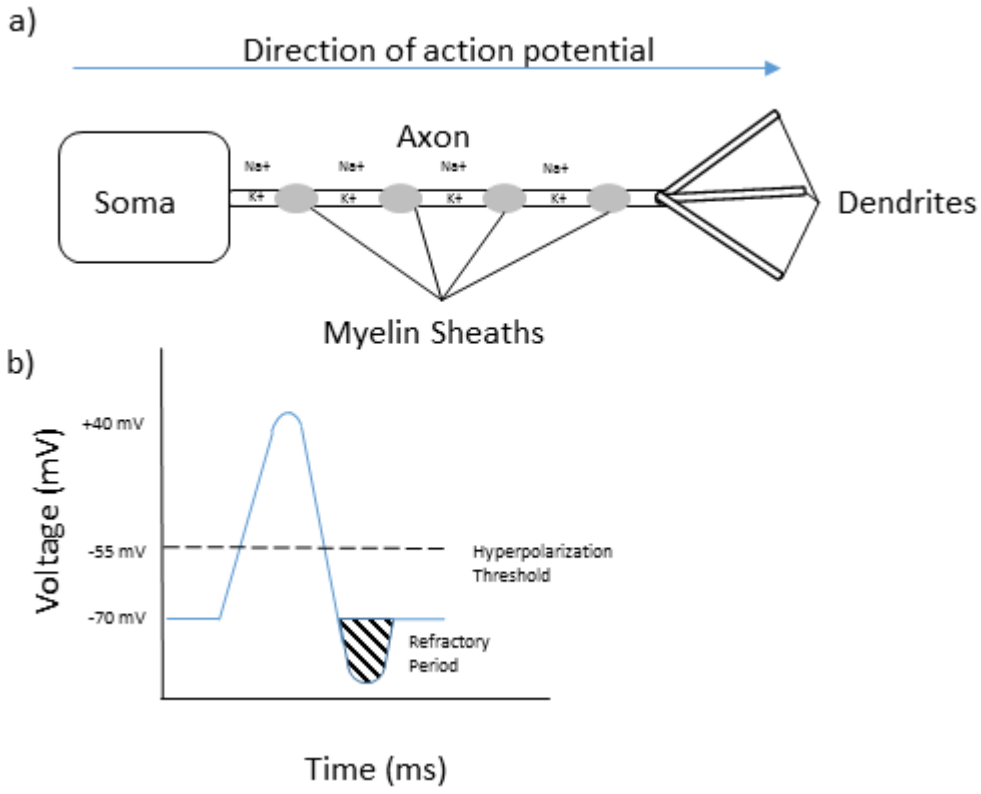


Figure 2.2: a) A simplified diagram of a neuron. As the neuron depolarizes, voltage gated ion channels open, allowing the flow of potassium (K+) ions out of the cell and sodium (Na+) ions into the cell. This movement causes further depolarisation and propagates the action potential down the axon. b) A typical action potential showing how the cell hyperpolarises at the peak of the action potential, flipping from a negative resting potential to a positive peak before dropping rapidly below the resting potential. This period below the resting potential is known as the refractory period. The neuron cannot fire again while it remains in this period.

2.2 EEG and MEG Machinery

2.2.1 EEG Machinery

One of the chief considerations in EEG is being able to generalise across participants and sessions. It is important to know the precise positions of the sensors that are recording the signal and to ensure that sensors are evenly spaced and distributed. This is difficult in EEG as the electrodes in EEG are affixed to the scalp, leaving considerable room for movement in the placement of the electrodes. By using an elasticated cap with electrode clips set up to a standardised layout, such as the EEG 10-20 system (Klem, Luders, Jasper, & Elger, 1958), and then aligning the cap position to a series of points across the head (typically the two auricular points on the ears, and the midway point between the inion and nasion) this consideration can be dealt with effectively. Contact with the scalp is maintained through the application of an electro-conductive paste beneath the electrode. This set up (shown in figure 2.3) allows for a standardised positioning of electrodes both within and across studies.

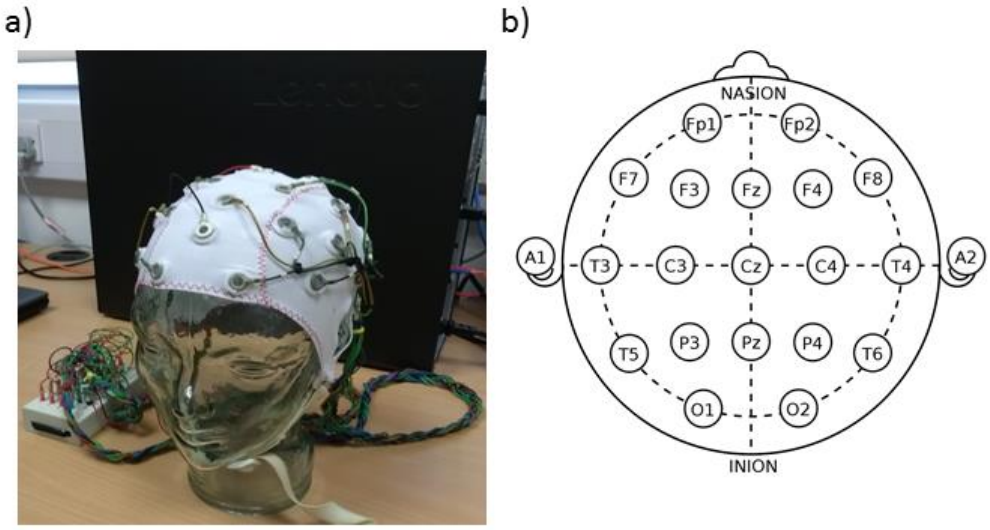


Figure 2.3: a) Example of a 32 channel EEG cap set up, mounted on a glass head. b) A diagram of the EEG 10-20 layout system detailing the arrangement of the EEG electrodes across the cap. Each electrode is evenly spaced from its neighbors.

Signals recorded from the electrodes are first passed through a differential amplifier before being passed through various filters and passed onto the computer for storage. These differential amplifiers record the potential differences between two electrodes. In a typical EEG setup, this difference will be between an 'active electrode' and a 'reference electrode'. Ideally, this reference electrode would be placed at an electro-physiologically silent location. The idea behind this is that the recording electrode should be placed near to the signal generator, whereas the reference electrode should be placed outside the signal field of the generator. Generators of scalp EEG signals consist of multiple gyri spread across the cortex. As such, these regions are often in the order of 10's of centimetres large. Given that head diameters are only in the 20's of centimetres, there is insufficient space on

the head to find a place that is distant enough from a given generator region to be considered silent. However, merely placing the reference electrode at a non-cephalic site is not a catch-all solution to the problem. Non-cephalic reference points, while silent in terms of EEG data, introduce other artefacts; most notably electrocardiographic ones. Furthermore, it is important to note that electrodes that are closer together will cancel out uniform signals across both electrodes, this is particularly true of slow wave activity (Pivik et al., 1993). Owing to the difficulties in both cephalic and non-cephalic reference locations there is no 'perfect' place for reference electrode placement. It is therefore a matter of researcher preference and dependent on the research question being asked, though it has been suggested that there is essentially no difference between a recording electrode and a reference electrode (Nunez & Srinivasan, 2006).

2.2.2 MEG Machinery

The magnetic fields emitted from neural activity are minute, being many magnitudes of scale below even background magnetic fields of the Earth. As a result the equipment needed to measure them is very sensitive and sophisticated. Indeed, because the magnetic fields produced by depolarising neurons are so small, conventional magnetic field detectors, such as microelectromechanical devices, are not sensitive enough to detect them. One way to make such devices sensitive enough is via superconductivity. When certain materials (traditionally Niobium or a lead alloy in MEG sensors) are cooled to a low enough temperature (called the

critical temperature) they lose electrical resistance. Passing a current through a superconductor arranged in a ring or loop will result in that current circulating that loop ad infinitum. An additional property of superconductors is the generation of a shielding current. When an external magnetic field is applied to a superconductor, such as one generated by the brain, a continuous shielding current is generated on the surface of the superconductor. This current generates a magnetic field which exactly matches, and thus cancels out, the external magnetic field being applied. In this way, an indirect measure of the external magnetic field (in this case, the neural activity) is made.

However, difficulties arise when actually trying to measure the magnetic field produced by the shielding current. Ordinary methods of measuring this cannot be applied without ruining the superconductive properties of the material. The device used in MEG scanners is the Superconductive Quantum Interference Device (SQUID). This device utilises a component known as a Josephson Junction which allow for measurement of these fields. These Josephson Junctions are essentially 'weak links' in the SQUID loop that allow for the interference of the current, without the disturbance of the superconductivity. This interference produces a measurable quantity of resistance, from which the changes in magnetic field over time are inferred. Figure 2.4 gives a schematic diagram of a SQUID loop.

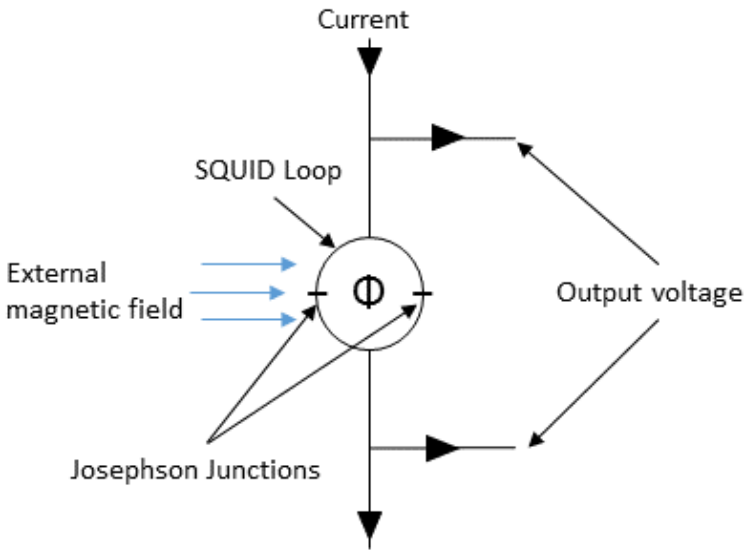


Figure 2.4: Diagram of a SQUID loop. A current is applied and measured before passing through the loop. As the current passes through the loop, an external magnetic field is applied and produces the magnetic flux, Φ. This magnetic flux will alter the resistance produced by the Josephson junctions, and so a flux dependent difference can be determined when the voltage of the current is again measured after the loop.

It is necessary, due to the small size of SQUIDs, to include a flux transformer in MEG sensor setups. This allows current to be drawn from a much larger area then if the SQUID were applied alone. Typically these flux transformers consist of between 1 and 3 additional coils. A pick-up coil which is placed closest to the head, an optional compensation coil and a signal coil which is placed on top of the SQUID itself. Figure 2.5 depicts some of the most common arrangements for flux transformers in MEG systems. It is often beneficial to utilise a compensation coil, as a pick up and sensor coil on their own (such as in the magnetometer configuration) is prone to picking up signals that are not related to brain activity. Introducing a compensation coil

that is wound oppositely to the pick-up coil renders the entire sensor insensitive to distant homogeneous fields as no net shielding current is produced, and so is not coupled to the SQUID. This increases the signal-to-noise ratio significantly.

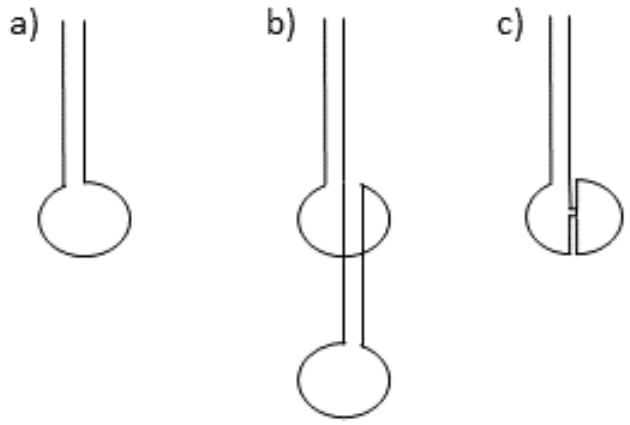


Figure 2.5: The 3 most common set ups for MEG sensor coils. Figure 2.5 a) is a magnetometer. This is the simplest configuration, and while effective, it is sensitive to magnetic fields that are not produced by the brain. Figure 2.5 b) and c) are axial and planar gradiometers, respectively. The addition of a compensation coil that is placed in series to the pick-up coil and wound in the opposite direction allows for the insensitivity of these coils to homogeneous fields produced from more distant sources.

2.3 Using M/EEG in Research

2.3.1 Analysis Methods

When analysing M/EEG data, the aim is often to analyse the measured signals in respect to a given event or stimulus. The voltage fluctuations that occur as a result of the stimulus are referred to as Event-Related Potentials (ERPs). There are two main ways of analyse these ERP's which are discussed here. The first, involves plotting the change in voltage as

a function of time and is referred to as an evoked response. Induced responses (also referred to as oscillations), however are plotted as changes as a function of frequency. Both of these methods are discussed in more detail here.

Evoked Responses

Raw measured signals from M/EEG contain components that are from both the response to the stimulus in question and those that are not invoked from the stimulus (Picton, 2000). Unfortunately, these noise components, which are often greater than the signal being measured, masks the true effect in single trials. One way to overcome this is to average over multiple trials where the stimulus in question is repeated. By time locking to the stimulus the random noise component becomes cancelled out, increasing the signal to noise ratio of the component related to the stimulus. The reason that averaging increases the signal to noise ratio is based upon two assumptions. Firstly, that the latency of the signal does not vary and the signal is of a fixed shape. Secondly, that the noise can be accurately modelled as a zero mean Gaussian, which is not correlated across trials and is not time locked to an event. When both of these assumptions are met it is possible to average out the noise component successfully by repeating the event multiple times.

When an averaged trace has been constructed it is possible to separate out individual components. Typically, when naming these components voltages that are increasing are given the 'P' prefix and voltages

going down are given the 'N' prefix. The number following this relates to either its position in the wave or its latency in milliseconds (Luck, 2014). Figure 2.6 shows an example waveform, along with a number of common components. In this example, the P1 and N1 components occur around 100ms after the stimulus onset, whereas the P2 and N2 responses occur around 200ms after the stimulus onset.

There are a number of different ways to look at specific components, the oldest is simply to look at specific measurement window (such as the one shown in figure 2.6) and pick the biggest value (either positive of negative depending on the component of interest). This value then becomes the value of the components peak. However, this leads to a significant problem. The highest value in the window may not be related to the component of interest. Indeed, in the example given in figure 2.6, the highest value in the measurement window actually represents the slope leading to the P3 response, and not the desired P2 response. A better, and more common, way to analyse components, and the method used for all ERP component analysis in this thesis, is to use a mean amplitude measure. A mean measure simply takes the average voltage value across the measurement window. In this way

one avoids two key issues relating to peak measurements. By not analysing just the highest value, one avoids

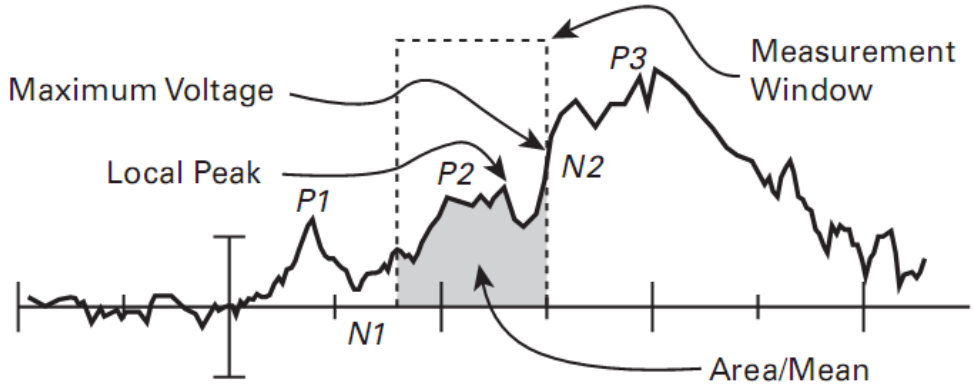


Figure 2.6: Example of an EEG waveform depicting some common components. The dashed line box depicts a measurement window for the P2 response, using this method one can pick the P2 response by looking for the local peak within the window, alternatively the mean voltage of the area under the measurement window can be used to determine the P2 component. Reproduced and adapted without permission from Luck (2014).

arbitrarily selecting a value which may not have anything to do with the component of interest. It also avoids making the assumption that peak of the waveform is the same as the component, which is not always the case (Luck, 2014).

Spontaneous Ongoing Activity

The use of M/EEG allows the recording of long stretches of ongoing activity that is directly related to neural activity in the brain. The long time courses of this data allow us to examine how neural oscillations might change over time in response to a stimulus. There are two principle methods for analysing neural oscillations, Fourier analysis and Time Frequency Representations (TFR). Both of these techniques involve a transformation of ERP waveform data, such as seen in figure 2.6 into frequency data and in fact,

TFR analysis can be considered an extension of Fourier analysis as both involve the same initial steps.

Fourier analysis

Conducting a Fourier analysis of a waveform is relatively straight forward. As mentioned, the initial raw waveform data has to be transformed from the time domain into the frequency domain. This is done through a Fourier transformation. Fourier transformations are based upon the proof that any complex or simple waveform can be recreated by summing together sine waves of various frequency, amplitude and phase. The transform itself can be used to determine what sine waves and of what characteristics, are needed to recreate the waveform provided. As shown in figure 2.7 b) the resulting power spectra show the amplitude of each frequency present in the waveform. Individual amplitude values can then be extracted for each frequency and further analysis conducted.

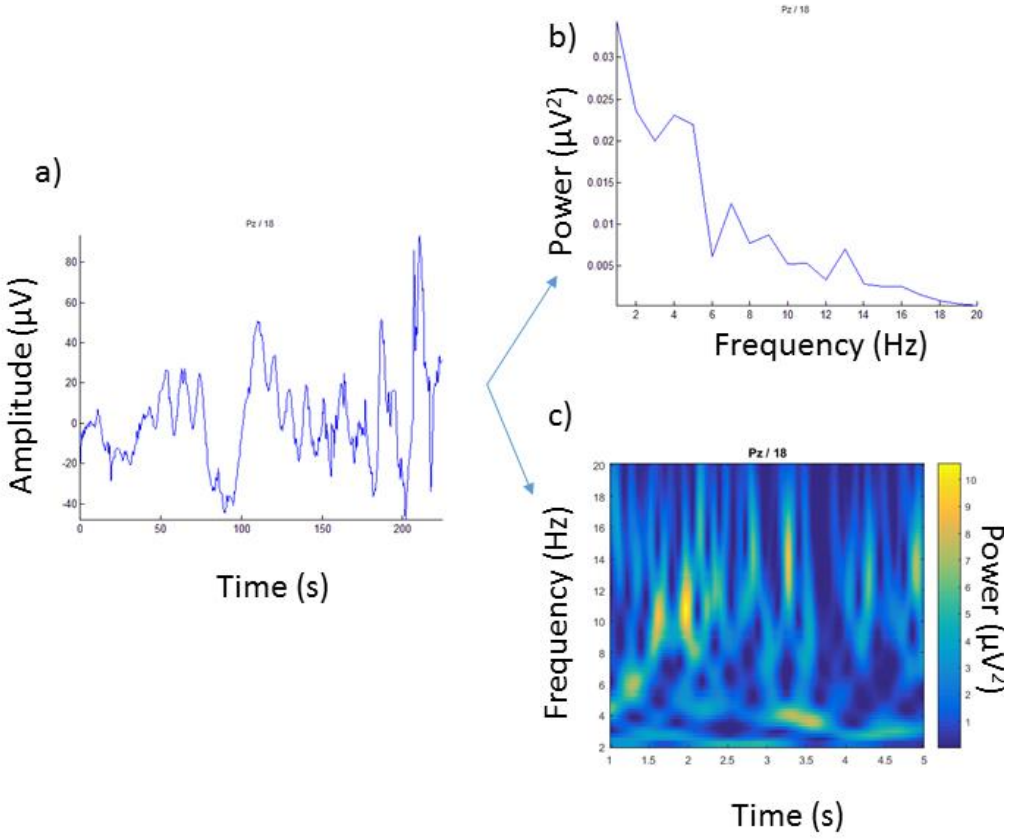


Figure 2.7: Shows the results of a Fourier transformation and analysis from a raw ERP waveform of a single subject, trial and channel recording (a) into a power spectrum (b) and a time frequency representation (c).

Time Frequency Representation Analysis

TFR analysis is more complex. As opposed to Fourier analysis, where the time series data is lost, TFR analysis preserves the time series data as well as transforming the data into the frequency domain. Although there is more than one way to perform a time frequency analysis, this section will focus only on wavelet analysis. This is because by using wavelet analysis (as opposed to, for example, a moving window Fourier analysis) it allows for a higher precision of power values at all frequencies (by using a variable time window) and treats all values within the time window as equal contributors to the overall power value of the time window (Luck, 2014).

The underlying theory of time frequency analysis is based upon the components extractable from a sine wave. EEG data in particular, is often modelled as series of sine waves (Roach & Mathalon, 2008), and as discussed, a Fourier transformation into the frequency domain is based upon the summation of various sine waves of different amplitudes and frequencies. A sine wave can be deconstructed into three components, its frequency, magnitude and phase. Figure 2.8, taken from Roach & Mathalon (2008), shows a 10Hz sine wave (figure 2.8 a) that has been decomposed into its magnitude and phase components (figure 2.8 b). The magnitude and phase

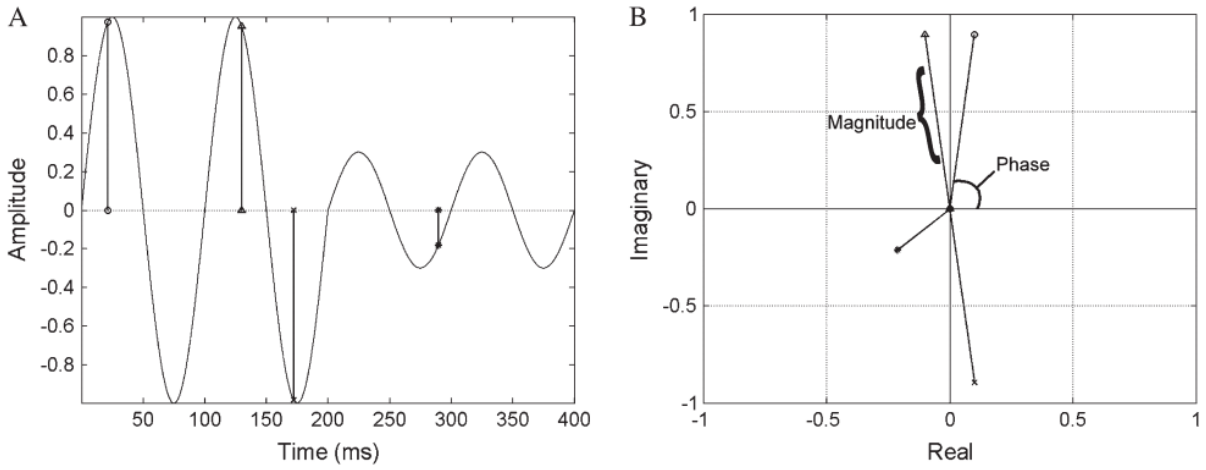


Figure 2.8: Shows 4 cycles of a 10Hz sine wave (a) and four time points that have been deconstructed into their magnitude and phase components (b). Reproduced without permission from Roach & Mathalon (2008)

components of a sine wave refer to the 'height' (or amplitude) of the waves peaks and valleys, and the location of the time points within a wave cycle. Decomposing the sine wave results in a complex number that comprises a real and an imaginary component. These components can be plotted as in figure 2.8 (b), where the imaginary component is plotted on the x axis, and the real component is plotted on the y. The magnitude vector (which relates

to the amplitude of the sine wave) can then be calculated using Pythagorean theorem ($a^2 + b^2 = c^2$) where the real (a) and imaginary (b) components form two legs of a right angle triangle and the magnitude is c. The phase is then equal to the angle between the magnitude and the x axis, between 180^o and -180^o (Roach & Mathalon, 2008). This basic principle can also be applied to an M/EEG waveform. Using convolution (the multiplication of one vector of numbers by another) and a sliding time window, the magnitude and phase components of a wave form can be individually extracted, squared, and then averaged across trials. The vector that is convolved with the waveform is a complex Morlet wavelet, that comprises both real and imaginary components (Roach & Mathalon, 2008). This results in a power value for a given frequency at a given time point. These results can then be plotted in a heat map, such as in figure 2.7 (c).

Source space analysis and the forward and inverse problems

The previously discussed analysis techniques have all taken place at the sensor level. That is to say, the analysis has occurred on the measured signal on the scalp. It is often desirable to study the underlying sources of these signals, to determine where changes in the brain are being generated. In order to do this, it is necessary to reconstruct potential source generators within the brain volume. Reconstructing these generators requires solutions to two problems, the forward problem and the inverse problem. The forward problem refers to finding an accurate model of measured potential at a given electrode, with a given underlying source generator. The inverse problem is, as the name suggests, the inverse of this. It is concerned with finding the

source location of a measured signal at an electrode. It is therefore necessary to find a solution to the forward problem first, as without this information it is not possible to accurately reverse engineer a source model (Hallez et al., 2007).

While the forward problem exists in both EEG and MEG, the electrical, rather than magnetic nature of EEG measurement means that the forward problem is substantially more complex in EEG. Magnetic fields, unlike electrical currents, are not influenced by the intravenous fluid, bone and skin layers of the skull. It is in modelling the head that many of the complexities of finding a solution to the forward problem lie. As such, it is generally assumed that EEG requires a more detailed head model in order to accurately find a solution to the forward problem (Baillet, 2017; Lanfer et al., 2012). In their guidelines Vorwerk et al (2014) suggest it is admissible for MEG head modelling to omit certain aspects on account of its reduced sensitivity to inaccuracies in the head model. Although MEG is not without its inherent biases and problems regarding the forward problem these are considered to be better understood and controlled, and thus less likely to lead to inaccurate models (Baillet, 2017).

While it is possible to accurately solve the forward problem in EEG with simple multi-layer spheroids (Berg & Scherg, 1994), these solutions fail to accurately take into account the shape or inner structures of the head. As a guideline, it has been suggested that at a minimum, an accurate head model should encompass the skin, skull and brain, the cerebrospinal fluid, a

distinction between white and grey matter and, ideally, anisotropic white matter (Vorwerk et al., 2014). However even more advanced head models, which model these components, are prone to making the error that conductivity is equal across the head (Lanfer et al., 2012). The difficulties in modelling the head mean that there is currently no perfect solution for the forward problem in EEG. Although more accurate head models are being created, these often rely on individual subject structural brain scans acquired by magnetic resonance imaging (MRI), which are costly and time expensive procedures.

Once an adequate forward solution has been obtained, a solution to the inverse problem must be found. The chief difficulty in the inverse problem is a lack of information. There are typically ~300 channels on a modern MEG machine and between 32 and 128 on an EEG machine. Additionally, there are many more synaptic connections and configurations that could be giving rise to the measured output. External noise factors also often serve to further confound potential solutions (Vrba, 2002). A common, and highly useful, method for solving the inverse problem is beamforming (Wendel et al., 2009). Beamformers act as spatial filters, essentially attenuating a particular source, and filtering out any other background sources as noise (Van Veen & Buckley, 1988). In this way, an inverse solution can be determined for every point of interest. While this is a useful approach, it is still not perfect at determining accurate solutions to the inverse problem (Wendel et al., 2009).

2.4 Conclusion

Both MEG and EEG are direct measures of neural activity. They both measure summations of PSP's, albeit different aspects of those summations. With EEG measuring the direct electrical activity, and MEG measuring the magnetic field fluctuations caused by the electrical activity. As a result of this, both also have a very fine temporal resolution. The principle advantages and disadvantages to using one over the other relate to cost of use (with EEG being significantly cheaper) and spatial resolution (with MEG having the greater resolution). The lack of perfect solutions to the forward and inverse problems are limitations to the techniques of MEG and EEG. Effective, if imperfect, solutions to these problems do exist which allow for source reconstruction of signals and with analysis techniques that are capable of picking out individual ERP/F's in response to a stimulus to mapping ongoing oscillatory changes M/EEG measurements are capable of providing a great insight into the mechanisms and neural changes associated with tinnitus. The next chapters describe several experiments that utilise both MEG and EEG to aid our understanding of neural oscillations in tinnitus.

Chapter 3 – Analysis of the Subjective Characteristics of Tinnitus and Associated Conditions. Experiment 1

3.1 Introduction

3.1.1 Hearing Loss and Tinnitus

Chapter 1.2 discusses some of the possible causes of tinnitus, including its links to hearing loss. Due to the prevalence of hearing loss within populations with tinnitus (Nondahl et al., 2011), there has been some debate as to what relationship there is between the pitch of the perceived tinnitus, and the audiometric profile. This is in part fuelled by neurophysiological models of tinnitus generation which predict two hypotheses about this relationship (see section 1.2.1 for more details about these models). Tonotopic expansion models such as proposed by Rajan et al., (1993), predict a tinnitus pitch that lies on the edge of normal hearing in a steep-sloping sensorineural hearing loss. This is due to the, now over represented, frequencies that neurons from damaged neighbouring frequencies have returned to. In contrast, neural synchrony models such as Eggermont & Roberts (2004), which propose

synchronous hyperactivity in neurons within the region of hearing loss, predict a tinnitus pitch that lies within this area.

Studies investigating these two predictions have produced mixed results. A number of studies have failed to find any relationship at all between the shape of the hearing loss and the pitch of the tinnitus (Pan et al., 2009; Tyler, Conrad-Armes, & Smith, 1984), others have found a predominant tinnitus pitch at the edge of hearing loss, as predicted by tonotopic expansion models (König, Schaette, Kempter, & Gross, 2006; Penner, 1980) while still others have observed a tinnitus pitch within the region of hearing loss (Henry & Meikle, 1999; Norena, Micheyl, Chéry-Croze, & Collet, 2002; Schecklmann et al., 2012; Sereda et al., 2011). Part of the reason behind this discrepancy is sample sizes and the heterogeneity of the tinnitus percept (Baguley et al., 2013). The tinnitus percept is widely heterogeneous and in studies that involved large, unselected groups it is probably unreasonable to suggest that statistical significance would emerge (Sereda et al., 2015). Similarly, studies that use groups that are too small are also prone to error. A further investigation into the links between the audiometric profile and tinnitus pitch forms one of the aims of the present research.

3.1.2 Subjective Tinnitus Measurements

The perceptual and emotional characteristics of tinnitus render it currently impossible to capture the entire tinnitus percept using purely objective measurements. It is necessary, therefore, to capture these aspects using subjective measures such as questionnaires and psychoacoustic

measurements. These measures can provide useful information as to the effectiveness of interventions and treatments by providing baseline measurements at intake and then further measurements after the intervention, which can then be compared.

Psychoacoustic Measures

A standard battery of four clinically appropriate psychoacoustic measurements of tinnitus has been a recommendation since the early 1980's (Evered & Lawrenson, 1981). These include loudness matching, pitch matching, minimum masking level testing (MML), and residual inhibition (RI). Loudness and pitch matching require asking participants to rate the similarity of their tinnitus in either loudness or pitch to an externally presented sound (in the case of loudness matching, this is most effective when the sound is a 1 kHz pure tone (Meikle, Stewart, Griest, & Henry, 2008)). In MML procedures, participants are asked to increase or decrease the level of a masking noise until their tinnitus is masked, while RI measures the temporary suppression, or in rarer cases facilitation, of tinnitus following a masking stimulus.

All of these methods are easy and quick to administer for a trained professional, and relatively easy to understand for the participant. However, psychoacoustic measures require technical equipment and set ups that may not be available to all clinicians and researchers, most notably sound proofed booths that will allow for the presentation of external stimulus without any interfering environmental noise. Further, there is some debate as to how accurately these methods actually measure a person's tinnitus. While methods, like loudness matching, provide a good, reliable measure of the

loudness of a person's tinnitus (Vernon & Meikle, 2003), this does not bear a consistent relation to the perceived loudness or severity of the tinnitus (Henry & Meikle, 2000). They have also been found to be less reliable and valid than their questionnaire based counterparts (Hall, Mehta, & Fackrell, 2017)

Questionnaires

Questionnaires used to evaluate tinnitus have been in development from the 1980's and 1990's. There are at least nine tinnitus questionnaires encompassing 175 questions regarding various tinnitus characteristics, which are summarised in table 3.1. These questionnaires were developed without the recognition of the importance of responsiveness in questionnaire design, in particular when evaluating treatment-related changes (Meikle et al., 2008). As such, there have been more recent attempts to devise a questionnaire that is sensitive to treatment-related changes, as well as attempts to develop a questionnaire that seeks to address concerns about a lack of consensus of tinnitus measurement at intake and evaluation across clinics. One such questionnaire is known as the Tinnitus Functional Index (TFI, Meikle et al., 2012). This questionnaire is summarised alongside their earlier counterparts in table 3.1.

Questionnaire Title	Authors and Year	Number of Items	Response Format
Tinnitus Questionnaire	Hallam, Jakes and Hinchcliffe (1988)	33	Verbal rating scale with 3 levels: *true, partly true, not true*
Tinnitus Handicap Questionnaire	Kuk, Tyler, Russell and Jordan (1990)	15	Numerical Rating Scale, ranging from 0 (strongly disagree) to 100 (strongly agree)
Tinnitus Severity Scale	Sweetow and Levy (1990)	27	4 levels variable choices between questions
Subjective Tinnitus Severity Scale	Halford and Anderson (1991)	16	2 choice, yes/no response scale
Tinnitus Reaction Questionnaire	Wilson, Henry, Bowen and Haralambous (1991)	5	Verbal rating scale, 5 levels: not at all, a little of the time, some of the time, a good deal of the time and almost all of the time.
Tinnitus Severity Grading	Coles, Lutman, Axelsson and Hazell (1992)	9	5 levels, variable choices between questions
Tinnitus Severity Index	Meikle, Griest, Stewart and Press (1995)	12	5 levels, variable choices between questions
Tinnitus Handicap Inventory	Newman, Jacobson and Spitzer (1996)	25	Verbal rating scale, 3 levels: yes, sometimes and no
Intake Interview for Tinnitus Retraining Therapy	Jastreboff and Jastreboff (1999)	12	Variable choices and levels between questions
Tinnitus Case History Questionnaire	Langguth et al. (2007)	35	Variable between questions
Tinnitus Functional Index	Meikle et al. (2012)	25	Numeric Rating Scale, 10 levels, variable choices between questions

Table 3.1: The 11 tinnitus questionnaires published to date, alongside the number of items they contained and the way in which the responses were coded. Taken and adapted without permission from Meikle et al., (2008).

The TFI in particular has gained significant interest in the years since its release, having being translated into 14 different languages (Henry et al., 2016). Its psychoacoustic properties have been examined both in randomised control trials carried out by the researchers who developed it (Henry et al., 2016; Meikle et al., 2012) and in an independent retrospective analysis (Fackrell, Hall, Barry, & Hoare, 2016), scoring very highly on tests of internal reliability and consistency. Its original purpose of providing a measure of intervention related change (Meikle et al., 2012) , has been called into question however, with recent studies finding it is sub-optimal at measuring treatment related changes in research populations (Fackrell et al., 2016). The same authors did also conclude that the TFI was an adequate measure of the functional impact of tinnitus, and for this reason the TFI is used in this study to gain a measure of the global impact of tinnitus on an individual's life over the previous week and not as a measure of change pre-and post-residual inhibition.

In addition to the TFI, the TCHQ is used in this study to gain a more detailed understanding of the tinnitus percept. The TCHQ was developed as an attempt to increase consistency between research centres by introducing a common questionnaire to evaluate tinnitus characteristics at intake (Langguth et al., 2007). It does not have a scoring mechanism, and unlike the TFI, is not designed to measure intervention related changes nor has it currently been translated into other languages. It does, however, provide the ability to gather more detailed responses regarding the history of the tinnitus, such as its perceived onset and any co-morbidities with conditions

such as temporomandibular disorder which can provide useful background information for a person's tinnitus.

Psychoacoustic vs Self-reported measures of tinnitus loudness

It is important to consider the agreement between different measures of tinnitus loudness. A recent review identified that 14% of clinical studies were using measures of tinnitus loudness as their primary measure of therapeutic effect but there was little consistency in the way that tinnitus loudness was measured (Hall et al., 2016). Given that clinicians are using these different measures of tinnitus loudness, with the view that they are all measuring the same underlying health-related construct and have convergent validity it becomes important to confirm that this is indeed the case. Psychoacoustic measures and self-reported measures of tinnitus have been found to be lacking in convergent validity in the past, as well as significant differences in measurement precision, with psychoacoustic measures being more prone to measurement errors then their questionnaire based counterparts (Hall et al., 2017). This same study, however also noted that while self-reported measures of tinnitus performed better against criteria for validity and reliability, these measures may be being erroneously regarded by the participant as synonymous with tinnitus impact, rather than purely tinnitus loudness.

In this study, we gather tinnitus loudness data from both psychoacoustic and self-reported measures. In light of the importance of finding standardised measures of tinnitus loudness, one of the secondary

aims of this study will be to carry out a brief analysis investigating the levels of agreement between our measures of tinnitus loudness.

3.1.3 Tinnitus and Hyperacusis

Hyperacusis, like tinnitus, is a poorly understood condition. At present, there is not even a standard definition (Tyler et al., 2014). Definitions range from a "heightened awareness of sound" (Phillips & Carr, 1998) to the "consistent exaggeration or inappropriate response to sounds that are neither threatening nor uncomfortably loud to a typical person" (Klein, Armstrong, Greer, & Brown, 1990; Vernon, 1987). A recent review into hyperacusis, advocates separating out its emotional and auditory components into different definitions which should, at their simplest, encapsulate 4 domains: loudness, annoyance, fear and pain (Tyler et al., 2014). Common to all definitions, however, is the negative response to sounds that would ordinarily be perceived as low-intensity. This should be distinguished from misophonia and phonophobia, both of which involve the negative reactions to specific sounds (such as chewing), whereas hyperacusis results in broader intolerance that is not limited to specific sounds and noises (Baguley, 2003).

The prevalence of hyperacusis in people with tinnitus has been estimated as being between 21% and 86% (Anari et al., 1999; Jastreboff & Jastreboff, 2000; Juris, Andersson, Larsen, & Ekselius, 2013). The reason behind this discrepancy has been attributed to the lack of a formal definition (Tyler et al., 2014), with different clinics and research groups being stricter or

looser with their definitions of a person with hyperacusis. It has also been reported that loud noises can worsen a person's tinnitus (Tyler & Baker, 1983) which may be mistaken for a loudness hyperacusis (Tyler et al., 2014). In order to counteract some of this discrepancy, the present study will look at the prevalence of hyperacusis in our own tinnitus sample. Hyperacusis in this instance will be assessed by the Hyperacusis Questionnaire (Khalfa et al., 2002), a 14 item questionnaire which asks participants to rate their agreement (on a 4 point scale: no, yes a little, yes, quite a lot and yes a lot) with a number of statements regarding their emotions and feelings about external noises.

It is also possible that perceived tinnitus loudness may impact on a person's hypersensitivity scores. If a person has some form of auditory hypersensitivity as well as tinnitus, it is plausible to suggest that their perceived tinnitus loudness may be influenced by their sensitivity to sounds. There has been little to no work investigating this link between hypersensitivity and tinnitus loudness. To the authors knowledge, there has been no work to date investigating the relationship between tinnitus loudness and hyperacusis, although there have been a number of prevalence studies suggesting a high rate of comorbidity between tinnitus and hyperacusis (Anari et al., 1999; Jastreboff & Jastreboff, 2000; Jüris, Andersson, Larsen, & Ekselius, 2013). As such we make no specific predictions about the possible relationship between these two variables. An investigation into this forms an exploratory aim of the present study.

3.1.4 Aims and Hypotheses

The main aim of Experiment 1 is to evaluate the links between hearing loss and tinnitus in our sample, according to the methods of Sereda et al., (2011, 2015). As a result of using the same methods of analysis as these previous studies by Sereda et al, we anticipate confirming that tinnitus will lie within the region of hearing loss.

There were also two secondary aims of the present study. Owing to the potential differences in loudness measure between a self-reported measure of tinnitus loudness, and a psychoacoustic measure of tinnitus loudness, the first secondary aim was to analyse the level of agreement between the two measures of tinnitus loudness used in this study. The first measure is question 12 on the TCHQ, Describe the LOUDNESS of your tinnitus using a scale from 1-100. The second measure is a psychoacoustic loudness matching measure, the Tinnitus Tester (Roberts et al., 2008).

An exploratory aim of this study addressed what relationship there is between tinnitus loudness and hyperacusis as assessed by the Hyperacusis Questionnaire (Khalfa et al. 2003).

3.2 Methods

3.2.1 Ethics

Ethics approval for both this study and the follow up EEG study (chapter 4) was granted by the University of Nottingham School Of Medicine Ethics committee.

3.2.2 Participants

Demographics, Tinnitus History and Recruitment

Twenty-nine participants took part in this experiment (17 male, average age = 59.7, standard deviation = 11.59). Participants were recruited through a combination of forum posts to specialist tinnitus help websites and contacting participants from a participant database store at the National Institute of Health Research Nottingham Biomedical Research Centre. All participants had chronic tinnitus (defined as tinnitus that had persisted for over 6 months) and no history of any neurological conditions, precise details of each participant's tinnitus characteristics are given in table 3.2.

3.2.2 Equipment and Apparatus

Audiometry

Pure tone audiometry was used to assess hearing thresholds from 125Hz-12 kHz using a GSI 16 Audiometer, including bone conductance audiometry up to 8 kHz in both ears. All audiometry was conducted according to the British Society of Audiology guidelines (British Society of Audiology, 2012) and involved a 1 up 2 down staircase procedure, in 5 dB Hearing loss (HL) and 10 dB HL increments, respectively. Individual pure tone audiograms

for each ear and the median pure tone audiogram across all subjects and ears is given in figure 3.1. Note that four participants failed to respond to the tone at 12 kHz, at the maximum loudness of 120dB HL, as such a threshold of 120dB for 12 kHz was used for these participants.

Participant Number	Age	Gender	Tinnitus Laterality	Tinnitus Type	Tinnitus Loudness (Tinnitus Tester)	Tinnitus Frequency	Tinnitus Etiology
1	36	F	Bilateral Unilateral	Tonal	13	0.5 kHz	Unknown
2	35	M	Right Unilateral	Tonal	86	4 kHz	Unknown
3	40	F	Right Unilateral	Hissing	80	12 kHz	Change in hearing
4	55	F	Left	Hissing	81	8 kHz	Unknown
5	67	M	Bilateral	Tonal	30	6 kHz	Unknown
6	56	F	Bilateral	Hissing	50	10 kHz	Unknown/Stress
7	72	F	Bilateral	Hissing	30	12 kHz	Unknown
8	49	M	Bilateral	Tonal	36	12 kHz	Unknown
9	68	M	Bilateral	Tonal	56	8 kHz	Loud Blast of Sound
10	64	M	Bilateral Unilateral	Hissing	25	6 kHz	Unknown
11	66	M	Left	Hissing	14	7 kHz	Change in hearing
12	63	F	Bilateral	Tonal	80	6 kHz	Unknown
13	76	M	Bilateral Unilateral	Tonal	8	5 kHz	Unknown
14		F	Left Unilateral	Tonal	70	8 kHz	Unknown
15	62	F	Left Unilateral	Hissing	26	1 kHz	Change in hearing
16	66	M	Left Unilateral	Ringing	61	4 kHz	Change in hearing/stress
17	58	M	Left	Hissing	10	4 kHz	Unknown
18	70	M	Bilateral	Hissing	30	3 kHz	Change in hearing
19	54	M	Bilateral	Tonal	30	10 kHz	Head Trauma
20	61	M	Bilateral	Tonal	37	7 kHz	Unknown
21	65	M	Bilateral	Tonal	30	5 kHz	Loud Blast of Sound
22	61	M	Bilateral	Ringing	61	7 kHz	Unknown
23	67	M	Bilateral	Tonal	20	8 kHz	Loud Blast of Sound
24	69	M	Bilateral	Tonal	91	7 kHz	Loud Blast of Sound
25	47	F	Bilateral	Ringing	40	8 kHz	Loud Blast of Sound
26	71	F	Bilateral	Tonal	92	8 kHz	Unknown
27	51	F	Unilateral	Tonal	80	1 kHz	Loud Blast of Sound
28	80	F	Unilateral	Hissing	30	5 kHz	Change in hearing
29	42	M	Bilateral	Ringing	25	10 kHz	Working in industry

Table 3.2: Participant demographics detailing age, gender, tinnitus laterality, tinnitus loudness (as determined by the Tinnitus Tester (Roberts et al 2008)), peak tinnitus frequency and tinnitus aetiology.

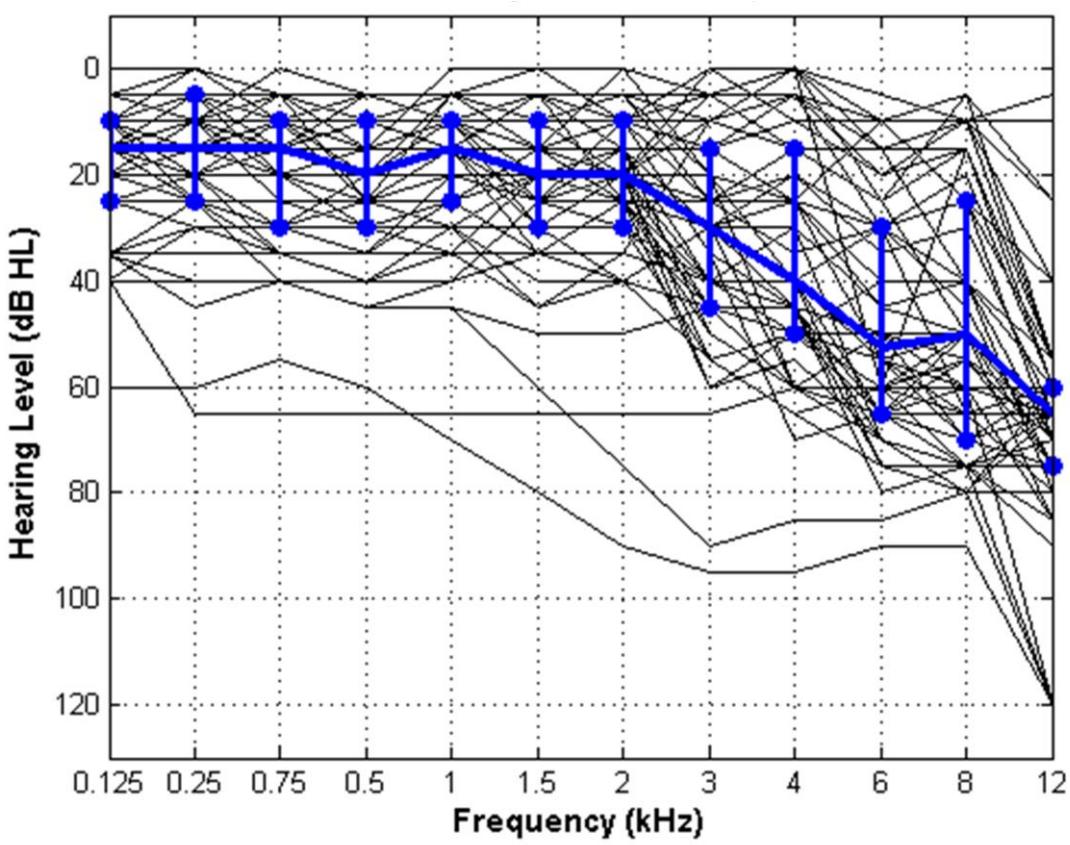


Figure 3.1: Individual audiograms for each ear and all participants. The blue line represents the median audiogram for both ears and all participants, with error bars representing the 25th and 75th percentiles. There were 4 participants who failed to respond to the 12kHz tone at the highest level the audiometer could produce (120dB HL), these participants were registered as having a hearing threshold of 120dB HL for this frequency.

Questionnaires

A total of four questionnaires were administered over the course of the session, the TFI (Meikle et al. 2012), the TCHQ (Langguth et al. 2007), the Hyperacusis Questionnaire (Khalfa et al. 2002) and a general health questionnaire developed in house. The TFI questionnaire is a 25-item questionnaire asking participants to rate their responses to questions of scales of either 0-10 or 0-100% on a number of aspects of their tinnitus and its impact split across eight subscales. Higher total scores on this questionnaire were interpreted as more severe tinnitus impact and distress.

It has a minimum score of 0 and a maximum of 100, after the results have been processed (Meikle et al. 2012). The TCHQ is a 35-item questionnaire designed to gain information about a subject's tinnitus history at intake. There is no specific scoring or interpretation associate with this questionnaire (Langguth et al. 2007). The Hyperacusis Questionnaire is a 14-item questionnaire designed to test for the possible presence of hyperacusis or auditory hypersensitivity. The possible range of values for this questionnaire was 0-45. With higher scores indicating higher auditory hypersensitivity. Khalfa et al., (2002) stated that a score of 28 or more of the hyperacusis questionnaire represented a "strong auditory sensitivity".

Scores were calculated for each of the sub-domains in the TFI, as well as the global score, and the Hyperacusis Questionnaire. Within this study, two measures of tinnitus loudness were gathered, one as part of the TCHQ, in response to the question: "Describe the LOUDNESS of your tinnitus using a scale from 1-100" and the other was a measurement of the Tinnitus Tester on a scale of 1-100. The scores were entered into a computer database on Microsoft Excel, along with relevant information from the TCHQ and general health questionnaire (for example, age, gender, tinnitus aetiology and self-reported tinnitus loudness and pitch).

Tinnitus Tester

The Tinnitus Tester (Roberts et al., 2008) was also administered. Sound stimulus was generated within the program and outputted using 2 Tucker Davis Technologies (TDT) RP5 Sound Processor Units and delivered via

Sennheiser HD280 Pro headphones. All responses were collected using a Griffin Powermate dial and button (Griffin Technologies, Nashville, TN, USA).

The Tinnitus Tester is designed as a more quantitative measure of a person's tinnitus. It begins by determining the laterality of the tinnitus percept, and then goes on to ask the participant to compare the tinnitus to a series of sounds (a pure tone, a hissing noise and a ringing noise) and select which sound their tinnitus most closely resembles. Participants were then played that sound at a number of different frequencies (0.5-12kHz) and asked to rate, on a scale of 0-100 how similar that sound was to their tinnitus. This was repeated three times for each frequency and an average likeness was calculated. The frequency with the highest average likeness was deemed to be the frequency of their tinnitus. Whilst there are some known problems with this method, for example if the participant does not rate any of the tones as being like their tinnitus or produces similar likeness ratings for multiple stimulus, this was not observed in our sample and all participants were able to produce a dominant tinnitus pitch. This is shown in table 3.2. The program also took a measure of tinnitus loudness in a similar manner. The stimulus type selected in the second step was presented at a range of centre frequencies (0.5-12kHz), and the participant was asked to adjust, using the dial, the loudness of the stimulus until it matched their tinnitus loudness. This was repeated twice for each centre frequency and an average was taken. Finally, a measure of residual inhibition was taken. Thresholds for a 1kHz pure tone were taken within the program in dB sound pressure level (SPL), 55 dB SPL was added to this threshold and a white noise was presented at this

adjusted loudness level for 30 seconds. Participants were then asked to rate how their tinnitus had changed for each tinnitus ear, on a scale of -5 (tinnitus had gone) to +5 (tinnitus was much louder than normal), a rating of 0 indicated no change in tinnitus loudness. This procedure was carried out twice and an average was taken as a measure of RI.

3.2.3 Procedure

The experimental procedure was split into three steps. Each step of the experiment was explained to the participant both before the experiment began, and again as each step approached and are depicted graphically in figure 3.2. All three steps were administered by the experimenter from an adjoining room, with a video and audio link, and a glass viewing panel to communicate with the participant. The participant sat in a sound proofed room. Pure tone and bone conductance audiometry was first conducted, followed by the four questionnaires (in no particular order). After participants were done filling out the questionnaire data, the final test, the Tinnitus Tester was administered. As this part of the experiment was controlled by the participant, the experimenter took the time to calculate the test scores from the questionnaires, this also allowed for the checking of any mistakes or missed questions. After the Tinnitus Tester was complete, any missing data from the questionnaires could be filled in. This concluded the experimental session. Participants were invited back for a second session on a different date for the EEG study described in chapter 4.

3.2.4 Data Analysis

Data analysis and plotting was carried out using both Microsoft Excel and IBM SPSS V21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). The slope of hearing loss and the edge of hearing loss was extracted from the audiometric data. In

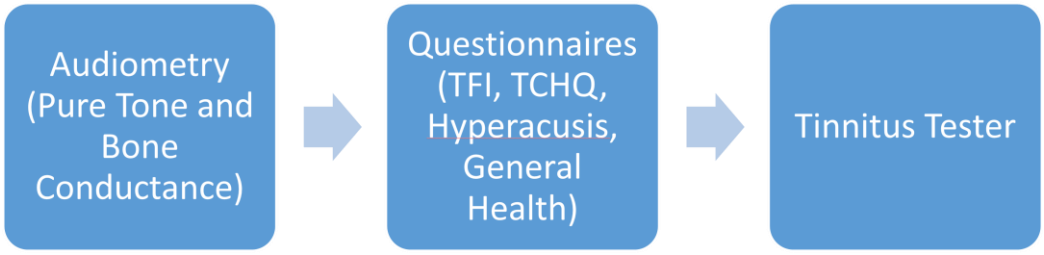


Figure 3.2: Schematic diagram showing the 3 steps of the experiment and the order they were carried out in.

order to improve the estimations of these parameters, a model was fitted to the data using the same procedures and custom Matlab procedure described in Sereda et al. (2011). Three models were applied to the audiometric data of each ear of each participant, a linear regression with 0 breaks, and a 1 and 2 break regression. The number of breaks in the regression referred to the number of times the model changed direction or gradient on a linear slope. A least-squares estimation then assessed whether the 1-break regression provided a better estimate of the hearing profile then the 0-break regression, and if this was so, compared the 2-break regression to the 1-break.

Where 1 and 2 break regressions were found to be the best fit to the data, values corresponding to the edge of hearing loss (the frequency at which the

first break occurred that resulted in the audiogram going below 20 dB) were extracted. Where a linear regression best described the data there was no edge of hearing loss. This analysis also provided details regarding the slope of the hearing loss (the slope of the regression function) and the degree of hearing loss (the area under the regression slope) which was extracted and used in the analysis.

A Bland and Altman levels of agreement test was used to analyse the agreement between the two measures of tinnitus loudness. The level of agreement refers to the test designed by Bland and Altman (1993), which is commonly used to determine the clinical agreement between two measures and the extent to which they are interchangeable.

3.3 Results

3.3.1 Relationship between Tinnitus Frequency and Hearing Loss

We hypothesised that in our sample, the dominant tinnitus frequency would fall within the region of hearing loss. Figure 3.3 plots both the median audiogram for all the participants, as well as the peak tinnitus frequencies (as measured by the Tinnitus Tester) for each participant. A trend can be seen developing, which indicates the large majority of peak tinnitus ratings (26/29) were in frequencies where the median hearing threshold shows a hearing loss (A threshold above 20 dB).

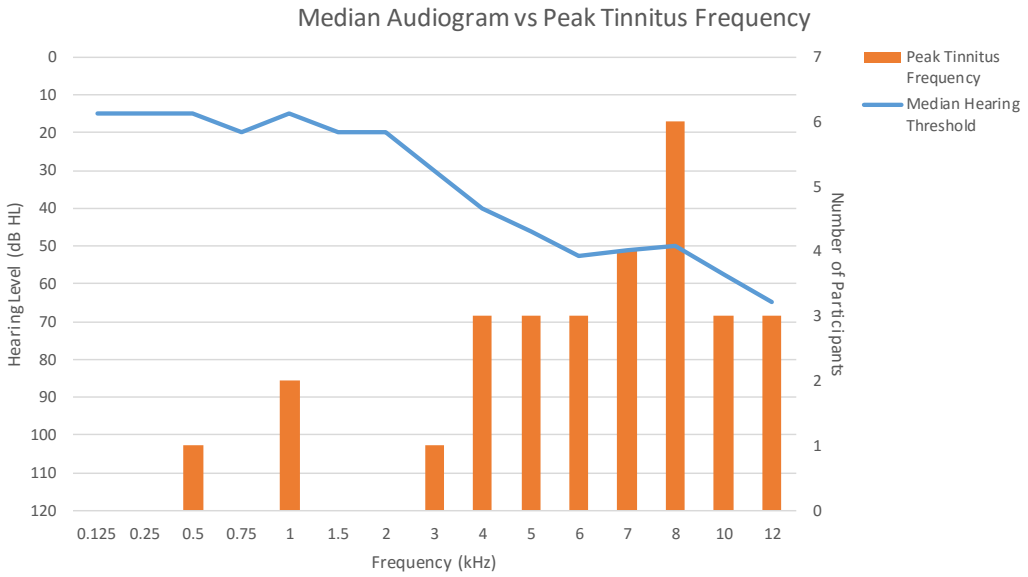


Figure 3.3: Median hearing threshold for all participants plotted alongside the peak tinnitus frequency for each participant. A trend can be observed that the large majority of peak tinnitus ratings occur in frequencies that are in the region of hearing loss.

In order to assess this trend statistically, a broken stick regression was applied to individual participant audiograms, to determine the edge, slope, area and worst frequency of the hearing loss. Each ear was analysed separately, and subsequently categorised into either the “steeper ear” or the

"less steep ear" categories, based upon the slope of the regression. All variables with the exception of edge of hearing loss in the steeper ear, and the frequency of worst hearing in both the steeper and less steep ears were normally distributed. Those variables that were not normally distributed were log10 transformed, which led to their being normally distributed. The resulting values were then correlated, using a Pearson's correlation to the participant's peak tinnitus frequencies.

Descriptive Data

A total of 58 ears (29 participants) were assessed. Across all ears linear regressions described the audiometric profile best in 34 cases. 1 and 2-break regressions described the audiometric profile best in 5 and 19 cases respectively. The range for the edge of hearing loss (in the case of 1 and 2-break fits, where an edge was identified) was quite large, ranging from 0.13 kHz to 3.71 kHz, however the inter-subject variation did not appear to be that high (mean = 1.16, standard deviation = 0.83). The ranges and inter subject variances for both the slope of the hearing loss (range = -7.03 to 23.75, mean = 9.67, standard deviation = 7.24) and the degree of hearing loss (range = 11.41 to 257.13, mean = 58.16, standard deviation = 34.92) were much larger.

When categorised into 29 steep and 29 less steep ears, linear regressions described the audiometric profile best in 13 of the steeper ears and 21 of the less steep ears. The 1-break fits described the profile best in 3 of the steeper ears and 2 of the less steep ears, whilst the 2-break

regressions fitted the data best in 13 of the steeper ears and 6 of the less step ears. In the steeper ear the ranges and inter-subject variability were similar to the general group statistics in the edge of hearing loss (range: 0.13 to 3.71, mean: 1.38, standard deviation: 0.89), slope of hearing loss (range: -7.03:23.75, mean: 12.35, standard deviation: 7.56) and the degree of hearing loss (range: 8:257.13, mean: 62.89, standard deviation: 42.09). The same was true in the less steep ear group for all three measurements, the edge of hearing loss (range: 0.13 to 1.5 mean: 0.71, standard deviation: 0.47) the slope of the hearing loss (range: -3.07 to 20.64, mean: 6.98, standard deviation: 5.76) and the degree of hearing loss (range: -2.13 to 106.73 mean: 53.43 standard deviation: 24.94).

Correlations

Pearson's correlations were performed to assess the relationships between the peak tinnitus frequency and edge of hearing loss, area of hearing loss and the frequency of worst hearing in both the steep and less steep ears. The edge of hearing loss in both categories (steep and less steep), the degree of hearing loss in the steeper ear, and the frequency of worst hearing were all non-normally distributed according to their skewness and kurtosis statistics being double that of their standard error (Coolican, 2009). These variables were transformed using a log10 transformation. This resulted in all the variables being normally distributed to meet the assumptions required of a Pearson's correlation.

Table 3.3 displays the correlation coefficients and *p*-values for the planned correlations. To account for the multiple comparison problem a Bonferroni correction was performed on the alpha level for the tests on each of the three main variables (edge of hearing loss, slope of hearing loss and frequency of worst hearing), leading to a corrected *p*-value of <.025 being necessary to infer statistical significance. The results indicated no significant correlations between the edge of hearing loss and tinnitus pitch in either the ear with steeper hearing loss (r = .37, p = .16) or the less steep ear (r = .10, p = .82).

Variable		**Correlation Coefficient**	***p*-value**
Edge of Hearing Loss	Steeper Ear	.37	.16
	Less Steep Ear	.10	.82
Area of Hearing Loss	Steeper Ear	.01	.95
	Less Steep Ear	.31	.11
Frequency of Worst Hearing	Steeper Ear	.41	.03
	Less Steep Ear	.75	<.01

Table 3.3: Correlation coefficient values for the tested variables, edge of hearing loss, area of hearing loss and frequency of worst hearing against peak tinnitus frequency for both ears individually. Each ear was categorised as being either the ear with the steeper hearing loss (steeper ear) or the one with less steep hearing loss (less steep ear).

Similarly, no significant correlations were observed between tinnitus pitch and the area of hearing loss in the steeper ear (r = .01, p = .95) or the less steep ear (r = .31, p = .11). Significant correlations were observed between

the frequency of worst hearing and the tinnitus pitch in both the steeper ear (r = .41, p = .03) and the less steep ear (r = .75, p = <.01). This would indicate, in our sample, that there is a relationship between the peak tinnitus frequency and the frequency of worst hearing, however this does not extend to the tinnitus pitch being related to the area of hearing loss or the edge of hearing loss.

In summary: We hypothesised that in our sample, as in Sereda et al., (2011), we would see that the peak frequency of tinnitus would fall within the region of hearing loss. This was supported by our data and can be seen in figure 3.5. We did not observe the tinnitus frequency falling at the edge of hearing loss. A correlation was observed between tinnitus frequency and the frequency of worst hearing, although only the less steep ear survived a Bonferroni correction.

3.3.2 Subjective Tinnitus Ratings

The global TFI score, Hyperacusis Questionnaire score and the loudness ratings for both the Tinnitus Tester and the TCHQ are given for each participant in table 3.4. A mean TFI score of 41.6 was found, as well as mean scores of 13.4, 45.6 and 52.9 for the Hyperacusis Questionnaire, the Tinnitus Tester Loudness rating and the TCHQ loudness rating respectively.

Participant	Global TFI	Hyperacusis Questionnaire	Tinnitus Tester Loudness	TCHQ Loudness Scores
1	40	27	13	35
2	66	16	86	75
3	88	20	80	90
4	54	16	81	80
5	26	8	30	35
6	34	10	50	70
7	33	14	30	40
8	40	16	36	50
9	19	13	56	50
10	27	4	25	50
11	5	9	14	15
12	84	19	80	90
13	2	0	8	5
14	51	9	70	80
15	24	6	26	50
16	63	18	61	75
17	9	1	10	20
18	19	9	30	35
19	34	12	30	40
20	29	5	37	40
21	31	13	30	30
22	46	22	61	40
23	69	7	20	20
24	80	19	91	100
25	30	11	40	70
26	96	38	92	95
27	22	18	80	80
28	72	19	30	50
29	15	8	25	25

Table 3.4: Individual participant scores for the Tinnitus Functional Index, Hyperacusis Questionnaire and the two measures of tinnitus loudness from the Tinnitus Tester and the Tinnitus Case History Questionnaire.

3.3.3 Agreement of Loudness Measurements

In order to assess the level of agreement between these two measures of tinnitus a Bland-Altman Limits of Agreement test (Bland & Altman, 1986) was conducted. The results of this analysis are shown in figure 3.4. The vast majority of the values (93%, 27/29) fell within the limits of

agreement (+/- 2 Standard Deviations from the mean), indicating moderate agreement between the two measures.

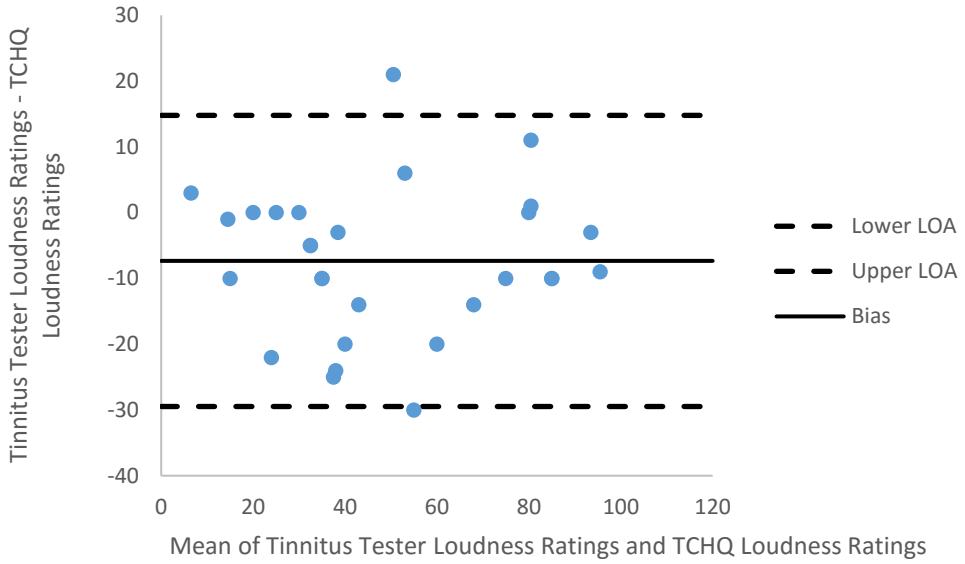


Figure 3.4: Bland-Altman plot for the tinnitus loudness ratings of the TCHQ and the Tinnitus Tester. The upper and lower limits of agreement (LOA) are shown as +/- 2 standard deviations from the mean difference. 93% of the values fell within the limits of agreement, indicating moderate agreement between the two measures. Further, the bias (average difference between the two measures) was quite low further indicating a moderate agreement.

3.3.4 Prevalence of Hyperacusis

Only one participant met the criterion specified by Khalfa et al. (2003) for a possible diagnosis of hyperacusis, and the remaining participants had a large range (range = 0-27) and variance of responses (mean = 13.34, standard deviation = 7.85). The low average score would indicate that the prevalence of hyperacusis in our population of tinnitus participants was quite low.

To determine if initial tinnitus loudness had any relationship with the degree of auditory hypersensitivity, an exploratory Pearson's R Correlation was performed on the tinnitus loudness ratings and the Hyperacusis

Questionnaire scores. Both measures of tinnitus loudness were independently assessed. All data were normally distributed according to the

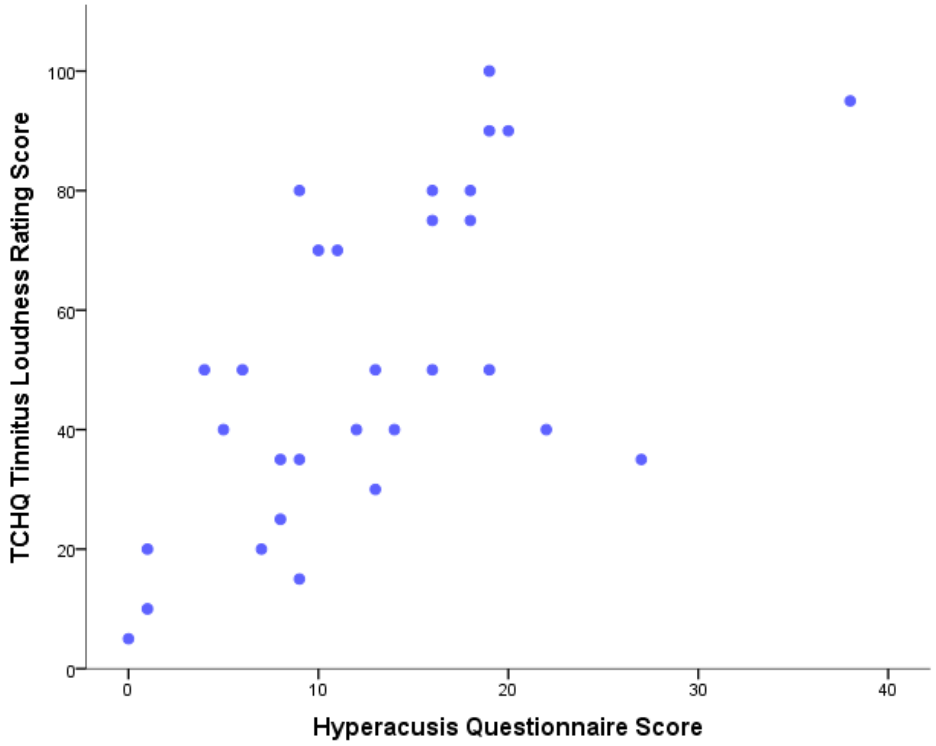


Figure 3.5: Scatterplot showing that louder tinnitus ratings, as assessed by the TCHQ, result in greater auditory hypersensitivity as assessed by the Hyperacusis Questionnaire.

skewness and kurtosis statistics being less that of their standard error (Coolican, 2009). In order to account for the multiple comparisons problem, the significant alpha level was adjusted using a Bonferroni correct. This lead to a *p*-value of <.025 being necessary to infer statistical significance. The test revealed no significant correlation between hyperacusis questionnaire score and tinnitus loudness as assessed by the Tinnitus Tester (r = .180, p = .380) however, a significant positive correlation was found between the hyperacusis questionnaire score and the tinnitus loudness as assessed by the TCHQ. (r = .618, p = <.01). This correlation is depicted graphically in figure 3.5. These findings would indicate that people who rate their tinnitus as being

louder also experience a higher degree of sensitivity to external sounds. It would also potentially indicate a discrepancy in the two measures of tinnitus loudness, as only one measure correlated with the hyperacusis questionnaire scores. However, given that the two measures of tinnitus loudness were found to broadly agree within one another, it is unlikely that this finding is the result of a discrepancy between the two measurements.

3.4 Discussion

3.4.1 Relationship between Tinnitus Frequency and Hearing Loss

We observed, as in Sereda et al., (2011) that tinnitus pitch typically falls within the region of hearing loss rather than at the edge, as suggested by some models. Figure 5.3 clearly shows the majority of participant's tinnitus pitch falling within the median hearing loss region. We did not observe any other relationships between the variables, and as such cannot make any further particular claims as to how hearing loss affects tinnitus frequency. It is possible that we failed to observe these other relationships due to our small sample size. Sereda et al., (2015) points out that relationships between peak tinnitus frequency and area of hearing loss are typically observed in large sample cohort studies with the sample size ranging between 67 (Sereda et al., 2011) to 286 (Schecklmann et al., 2012). Further, the strongest correlations in the original study were in the groups that had been subdivided into tinnitus bandwidth and tonality. This was not done in the present sample due to low group numbers, but it could explain the lack of relationships observed between the variables.

Where the peak tinnitus frequency occurs in relation to hearing loss is currently widely held as an important source of evidence for various models of tinnitus generation. If the peak tinnitus frequency occurs at the edge of hearing loss, it is supposed the tinnitus is derived from an over-represented frequency in accordance with neurophysiological models of tinnitus generation (Rajan et al., 1993). If instead it lies within the region of the

hearing loss, it is taken as support for neural synchrony models of tinnitus generation (Eggermont & Roberts, 2004; Schaette & McAlpine, 2011). We did not observe direct support for either of these two hypotheses, which is in accordance with some studies that have also failed to find a relationship between audiometric profile and tinnitus pitch (Pan et al., 2009; Tyler et al., 1984). However, as previously discussed there are a number of possible reasons for this. While there remains considerable debate surrounding the precise relationship between tinnitus frequency and audiometric profile, the majority of the difference between conflicting studies has been the types of tinnitus and audiometric profile sampled (Sereda et al., 2015). As the cohort used in this study was one that was recruited for a larger study, no specific sampling occurred. This means that we might find support for the previous studies had we been more specific about our tinnitus population. Not finding a statistical relationship between tinnitus frequency and audiometric profile (beyond it being correlated with the frequency of worst hearing) in our sample does not necessarily indicate an opposition for the models of tinnitus generation presented, simply that when all types of tinnitus and audiometric profile are taken together no relationship emerges between the two, or that it simply wasn't detected in our study design. The large heterogeneity of the tinnitus percept (Baguley et al., 2013) mean it is possible that there are multiple pathways to tinnitus generation and different types of tinnitus (tonal, ringing, hissing) may be the result of different reactions in the auditory cortex – either neural hypersynchrony or tonotopic reorganisation or different combinations of both. This may explain why selecting different

types of hearing loss and tinnitus results in different relationships forming. Future research should focus on why these different relationships might be emerging, not just what the relationship is.

3.4.1 Relationship between the two tinnitus measures

In this sample, a moderate level of agreement was found between the two measures of tinnitus loudness (the Tinnitus Tester and the TCHQ). In this instance, it can be concluded that the measurements of tinnitus loudness and from the Tinnitus Tester and the TCHQ have a degree of convergent validity. While the present study only evaluated two measures of tinnitus loudness, this does go some way to alleviate the issue raised by Hall et al. (2016) that there is a high degree of variability in the loudness measures used by clinicians, but little known agreement between them.

3.4.2 Relationship between Tinnitus Loudness and Hyperacusis

We found support for our hypothesis that the two measures of tinnitus loudness (the TCHQ and the Tinnitus Tester) used in this study would agree with each other. However, only the TCHQ loudness rating scores correlated with the hyperacusis scores. This would appear to indicate that there are some differences between the loudness measures. This would be expected, as they are different methods. It is also probable that the difference is due to the cause-and-effect relationship between perceived tinnitus loudness and hyperacusis score. Given that hyperacusis relates to an increased sensitivity to auditory stimuli (Baguley, 2003), a higher level of hyperacusis would lead to higher self-reported tinnitus loudness as the

increased sensitivity to auditory stimuli would be applied to the auditory elements of the tinnitus perception as well. This would explain why there was a difference in how these tinnitus loudness measures were correlated with hyperacusis. The only tangible difference between the two measures was that one was a self-reported measure of tinnitus loudness on a scale of 1-100, whereas the other estimated loudness using a psychophysical matching paradigm. Asking participants to simply rate how loud their tinnitus is, as in the TCHQ, potentially introduces an emotional confound i.e. participants may be confusing how loud their tinnitus is, with how much it bothers them. It is this confound that is being observed in the positive correlation between tinnitus loudness ratings and hyperacusis scores i.e. participants will say their tinnitus is louder, as they find it more annoying on account of increased auditory hypersensitivity. Conversely, asking participants to rate the similarity of their tinnitus loudness to a series of external sounds eliminates this confound, which is why we do not see a correlation between this measure of tinnitus loudness and the hyperacusis scores.

While the Hyperacusis Questionnaire does not diagnose hyperacusis, a score of 28 or greater is regarded as being a "strong auditory hypersensitivity" and is significantly greater than the population mean of 15 (Khalfa et al., 2002). In our sample, only 3% of participants (1/29) scored higher than 28. This is substantially less then what has been reported by other studies investigating the prevalence of hyperacusis in people with tinnitus (Anari et al., 1999; Jastreboff & Jastreboff, 2000; Juris et al., 2013). However, our sample was much smaller than those used in the previous

studies, which could explain why our prevalence was so much lower. The accuracy of the Hyperacusis Questionnaire at measuring hyperacusis in tinnitus populations has also been brought into question (Fackrell, Fearnley, Hoare, & Sereda, 2015), which may also explain why our sample failed to match the expected prevalence levels of hyperacusis.

3.4.3 Conclusions and Future Directions

We did find support for our initial hypotheses that our two measures of tinnitus loudness would agree with one another. The observation that only the purely subjective measure of tinnitus loudness correlated with hyperacusis scores suggests that work is needed to assess any unwanted emotional components loaded into questions within the TCHQ, as it would imply that participants are confusing loudness with annoyance. Arguably, this could extend too many questionnaires that ask participants to directly rate their tinnitus loudness and this is something that should be considered in future work.

Support for our second hypothesis, that tinnitus frequency would lie within the region of hearing loss, was also found. Though there was no particular relationship between the two variables. There were a number of reasons that this may have been the case, mostly related to the smaller, unselected sample population used in the present study. However, due to the differences that can be found in the relationship between audiometric profile and tinnitus frequency by selecting different tinnitus types and shapes of hearing loss, it asks the question of why this might be the case. Therefore,

it is important to ask not only what the relationship between peak tinnitus frequency and audiometric profile is, but also why these differences might occur. This could potentially be a fruitful avenue for future work to focus upon.

Chapter 4 – The Effects of Residual Inhibition on Cortical Oscillations in Tinnitus - Experiment 2

4.1 Introduction

4.1.1 Background

The phenomenon of RI was first referred to in a medical paper by James Spalding in 1903, in which he describes the temporary reduction or complete cessation of the tinnitus percept following prolonged exposure to a tone matching that of the tinnitus, played on a violin or organ (Spalding, 1903), however it was not until the 1970's and 1980's that work researching its characteristics began in earnest. RI is a phenomenon that is exhibited in a subset of people with tinnitus. RI refers to the temporary quietening or, in rarer cases, the temporary cessation of the tinnitus sensation following the offset of a noise or tone that prevents or "masks" the tinnitus from being heard. Prevalence rates vary, though a sample of 1,150 people with tinnitus found 88% were able to experience RI, though typically for less than two minutes (Meikle, Creedon, & Greist, 2004).

4.1.2 Mechanisms and Properties

A number of psychoacoustic properties of RI have been reported. Those masking sounds which are matched in tone and frequency to the perceived tinnitus are usually the most effective in eliciting RI (Feldmann, 1971; Roberts, Moffat, Baumann, Ward, & Bosnyak, 2008; Terry, Jones, Davis, & Slater, 1983). In addition to the type of masker, duration and loudness of the masker are also important. Terry et al (1983) reported that 1-minute of masker noise was the most effective duration at inducing RI and that any durations above this did not yield any further significant benefits. Similar patterns were also found for the loudness of the masker noise, reporting that a sound that was 10dB above the patients' tinnitus tended to elicit the longest periods of RI and of the greatest depth (i.e. the most quietening of the tinnitus percept).

Many of the properties of RI vary greatly between individuals and masker type used to induce it (Roberts et al., 2008; Terry et al., 1983; Tyler, Conrad-Armes, & Smith, 1984). For example, in Tyler et al. (1984)'s sample of 10, they reported two individuals who experienced a complete suppression of tinnitus, one whose tinnitus became worse (sometimes referred to as residual excitation (Sedley et al., 2012)), one who experienced a softer level of tinnitus which then gradually returned to normal levels, and two who did not experience any lasting RI. Such variability both within the tinnitus perception and within the phenomenon of RI make it difficult to design appropriate methodologies that can encompass all possible variations. As such, most studies typically only present a narrow set of maskers that are

rarely tailored to the participant's tinnitus perception despite research demonstrating maskers that are tailored a patient's tinnitus yield better RI (Roberts et al., 2008; Terry et al., 1983). In the past, it has been too time consuming to tailor make maskers to elicit the greatest depth of RI. However, very recent results have demonstrated an online method for RI induction which can produce tailored acoustic pulses and has been shown to be effective for a large majority of tested participants (Fournier et al., 2018). Unfortunately, this method was developed too recently to be used in the present study. A white noise masker, which encompasses all frequencies, has also been found to be effective at eliciting RI (Roberts et al., 2008). Using such a stimulus would eliminate the need to generate tailor made stimulus and also provide consistency of experimental methods between participants.

As with tinnitus, the mechanisms behind RI remain largely unknown. It has been likened with forward suppression (the suppression in perceptibility of tones immediately following a masking sound) exhibited in normal hearing populations (Galazyuk, Voytenko, & Longenecker, 2017). A series of experiments conducted in mice by Galazyuk et al. investigating the effects of forward suppression on the spontaneous firing rates of the inferior colliculus showed a number of similarities between forward suppression and RI. They observed that the duration of firing rate suppression increased with masker duration (Voytenko & Galazyuk, 2010). Further, they observed that the masker stimulus centre frequency was also linked with suppression success. Those masker stimuli that had centre frequencies that were the same as the characteristic frequency of the neuron being stimulated were

much more successful in eliciting forward suppression (Galazyuk et al., 2017). These findings are remarkably similar to the human behavioural findings of Terry et al. (1983) and Roberts et al (2008), indicating that RI may operate on a similar basis. A further finding of note was that repeated induction of forward suppression reduced its effectiveness in future trials (Galazyuk et al., 2017). This finding has also been replicated in the human literature, though only on a single subject (Sedley et al., 2012). It is worth noting, however, that the Galazyuk et al. studies were conducted solely on neurons from the inferior colliculus in mice. Given the widespread nature of tinnitus throughout the auditory pathways it is unlikely that this mechanism accounts for the entirety of the RI phenomenon. The fact that the Galazyuk studies were on animal models, for example, renders it unclear as to whether this suppression lead to any perceptual changes in the animal's tinnitus.

4.1.3 Using Residual Inhibition to Study Tinnitus

Studying RI can provide valuable insight into the neural underpinnings of tinnitus, both in those in whom RI is effective and in those in whom it is not. Studies of RI have been used to support a number of different theories of tinnitus generation. The tonotopic reorganisation theory, (discussed in more detail in Chapter 1.2) for example, stipulates that damage (as a result of hearing loss) to inhibitory inputs leads to increased synchronous activity via lateral pathways. Roberts et al. (2008) suggest that disrupting this synchronous activity is the cause of RI. This is evidenced by their finding that tailoring a noise stimulus to include a patient's tinnitus frequency spectra elicits longer RI. A similar conclusion has also been drawn in the MEG

literature. In a study investigating the effects of RI on oscillatory frequency power, the finding of reduced delta during RI was attributed to a rebalance of inhibitory neural networks (Kahlbrock & Weisz, 2008), providing a neural basis for the hypothesis proposed by Roberts et al. (2008). Studying neural oscillations in tinnitus associated with pre- and post- RI periods within-subjects eliminates many of the problems associated with the more common practice of between-subject comparisons of tinnitus participants with normal hearing controls. Chiefly, that the strong links between hearing loss and tinnitus (Nondahl et al., 2011) render it difficult to determine if the oscillatory changes are the result of tinnitus, or hearing loss (although this can also be addressed by using hearing loss matched control subjects (Adjamian et al., 2012). By comparing oscillatory power during "normal" tinnitus with the power during RI, a more accurate representation of the role of neural oscillations in tinnitus can be gained.

In addition to finding a reduction in delta band oscillations (Kahlbrock & Weisz, 2008), more recent work has also found decreases in gamma band oscillations within the auditory cortex during RI (Sedley et al., 2012). Interestingly, the reverse does not hold. In situations where the tinnitus perception gets worse following the masking procedure (termed "residual excitation (RE)" by Sedley et al., (2012)), there was no modulation in delta band activity, though gamma band activity was increased. It is worth noting here that the analysis carried out by Sedley et al. (2012) was on the individual level and no group-level analysis was performed. Where group-level analysis has been performed, significant decreases in delta-band activity were again

found during RI, however no significant changes were detected in any of the other frequency bands (Adjamian et al., 2012). Increased delta band activity had already been demonstrated in tinnitus participants (Llinas, Ribary, Jeanmonod, Kronberg, & Mitra, 1999; Weisz, Moratti, Meinzer, Dohrmann, & Elbert, 2005), however showing that delta band activity is modulated by RI demonstrates that it could be involved in the generation of the tinnitus percept. Changes in alpha oscillations during RI have also been found. Sedley et al (2015) demonstrated a decrease in alpha during RI. While their analysis was on intracranial recordings of a single subject only, it does demonstrate, alongside earlier work, the RI is capable of modulating oscillations and thus can be useful in discovering the underlying oscillations associated with tinnitus.

It is worth noting, that while there is a previous body of literature discussing the effects of RI on oscillations there is little to no work on the effects of RI on oscillations over time. All the previously cited literature has discussed the relative power changes in the respective frequency as a whole across their respective RI periods. Tracking these changes may reveal information about how the tinnitus perception returns and what oscillations are driving this change.

4.1.4 Preparatory Review of Published Methods of RI Measurements

Introduction

Typically, RI studies utilise a rating system to subjectively assess the participant's tinnitus loudness before and after masking. However, there is

no standard for the rating of tinnitus loudness or tinnitus change in loudness. This can have serious impacts on the outcome of the experiment. Scales that are too sensitive; for example a scale that asked for changes on a scale of 0-100 in terms of depth of RI, may result in noisy measurements with participants selecting multiple values to describe their change in tinnitus loudness, when in fact it had not differed from the previous trial. This is especially salient in instances where the measurement scale is highly sensitive to changes, leading to type I errors. Scales that aren't sensitive enough risk the opposite, resulting in inaccurate ratings which may not be close to what the participant was experiencing. For example, a binary scale that only asked the participant "Has your tinnitus gone" with a yes or no response would be insensitive to the range of changes in tinnitus loudness a participant may experience. In the case of non-numerical scales, such as the binary choice example given earlier, any leading questions may result in placebo effects that are not necessarily the result of RI. A review search restricted to the more recent studies, with a particular emphasis on neuroimaging studies of tinnitus and RI was conducted to investigate what scales have been used.

Methods

Seven studies were identified through PubMed searches using the key terms *residual inhibition and *tinnitus, and individually assessed for suitability to the reviews aims. The criteria for acceptability were that it must be a study involving RI induced by a masker noise and it must look at depth of

RI (and not just duration). The methods were then read and it was noted how the study recorded RI and also if there were any reported differences in RI laterality (i.e. did the change in perception differ in each ear in the case of bilateral tinnitus participants).

Results

Table 4.1 reports the studies how they recorded RI and analysed the reported differences in RI depth between ears.

RI Recording Methods

The rating scales differed between studies, in both numerical values and (in the cases of the non-numerical scales) wording of the anchors and semantic descriptors (Koizumi et al., 2014; Sedley et al., 2012; Terry et al., 1983). In all selected studies, RI was recorded in similar, but different manners. All but three of the studies (Koizumi et al., 2014; Sedley et al., 2012; Terry et al., 1983) used a numerical rating scale. However, within these studies the ranges used differed. One of the five studies used a 10-point scale, with 0 being no tinnitus and 10 being normal tinnitus or maximum tinnitus loudness ever experienced (Kahlbrock & Weisz, 2008) Two more used a 10-point scale ranging from -5 to +5 where -5 meant complete suppression, +5 meant tinnitus is much louder than normal and 0 is normal tinnitus (Roberts, Bosnyak, Bruce, Gander, & Paul, 2015; Roberts et al., 2008). And one used a 4-point scaled ranging from -2 to +2 (Sedley et al., 2015). In those studies that did not use an numerical scale, two measured it on a Likert scale (Koizumi et al., 2014; Sedley et al., 2012) though with differing

descriptions of each category. Koizumi et al (2014) had four response options: ‘disappeared’, ‘reduced’, ‘unchanged’ and ‘increased’. Sedley et al. (2012) opted for five response options describing tinnitus loudness: ‘very low’, ‘low’, ‘normal’, ‘high’ and ‘very high’. Terry et al. (1983) used a semi-circular graphical scale and manual pointer. Around the semi-circle were the

	How was RI recorded	Any differences in RI effectiveness between ears	Duration of RI Period	Measured RI over time
Kahlbrock and Weisz 2008	0-10 scale (0 being no TI, 10 TI is normal)	Not Analysed	25 seconds of MEG recording, but up to 4 minutes for tinnitus normalization	No, 1 rating before stimulus, 1 rating after 25 seconds of MEG recording
Koizumi et al. 2014	Four categories: disappeared, reduced, unchanged, increased	Not Analysed	Undefined: until tinnitus returned to pre masker levels	Continuous measurement
Roberts et al. 2008	10 point scale. 0 being normal -5 being no tinnitus and +5 being tinnitus is much louder	No apparent differences between ears in RI depth in bilateral tinnitus	Until tinnitus returned to normal or a maximum of 45 seconds.	No, 1 rating immediately after stimulus cessation
Roberts et al. 2015	10 point scale, same as Roberts 2008	Not Analysed	60 seconds	No, RI ratings taken before the main experiment
Sedley et al. 2012	5 point scale ranging from very low to very high and a mid-point of normal	Not Analysed	5-15 seconds	No, one rating taken before stimulus and one after
Sedley et al. 2015	Numerical Scale of -2 to +2	Not Analysed	10 seconds	Yes, 4 points where participant rated tinnitus loudness change,
Terry et al 1983	5 point scale containing twice normal loudness, one and a half normal loudness, normal loudness, half normal loudness and zero loudness.	No	1 – 2 minutes after the tinnitus had returned to normal levels.	Yes, participant changed rating as and when the tinnitus loudness changed.

Table 4.1: All the studies sampled for the RI measurement report, including how they measured RI and whether or not they assessed differences between the ears. It also details the duration of the RI period and whether or not a continuous rating of RI over time was taken.

categories. These were 'normal loudness' (at the 90° position on the semi-circle), 'twice normal loudness' (at the 180° position) and 'zero loudness' (at

the 0° position).

Differences between Each Ear

Two of the studies looked at differences in RI between ears, but only one looked at this is the context of RI depth (Roberts et al. 2008). In this study, there were no reported differences between RI depth in each ear in bilateral tinnitus participants.

Discussion

The lack of consistency in measuring RI prevents comparing results of the change in the depth of RI. Only the two studies by Roberts et al. in 2008 and 2015 have used exactly the same rating scale. Though, a 0-10 numerical rating scale has also been used more than once, it was with different semantic descriptors In spite of the differences discussed, all the numerical scales operate in the same way insofar as the participant makes a numerical selection of their tinnitus loudness. The only change is where the participant rates their tinnitus as being “normal”. On a 0-10 scale this would be at 10, and on negative scale, this would be 0. However, in the context of explaining the rating scales to participants it may be easier to use a scale where 0 indicates no change in tinnitus.

One further aspect of these rating scales which pervades multiple studies is the inclusion of a category of louder than normal tinnitus (coined residual excitation by Sedley et al (2012)). This is an important inclusion, as without this question, residual excitation may go unreported and results may then be misconstrued. This category is not possible on a 0-10 scale where 10

is normal tinnitus loudness such as those used by Kahlbrock and Weisz (2008).

In conclusion, there is no consistent method for the measurement of RI depth across studies. A standard is needed to enhance comparability between studies. With this in mind, the present study uses the same scale used by Roberts et al. (2008, 2015) as it provided a simple scale for participants, which also included the possibility to measure residual excitation. This allows direct comparison between previous studies carried out by Roberts et al. and our work, and allows for the possibility of reporting residual excitation.

4.1.5 Aims and Hypotheses

One of the aims of experiment 2 was to explore a number of behavioural characteristics of RI. Based on the previous work of Galazyuk et al (2017) and Sedley et al (2015), we hypothesised a reduction in depth and duration of RI over repeated presentations of a white noise masker. In addition, we aimed to investigate how tinnitus returns to normal during a period of RI and how to this correlates to any observed oscillatory changes in alpha and delta. RI is known to be transitory and so it is of interest to see how the tinnitus perception returns. This type of analysis has not been carried out before so a hypothesis cannot be accurately created, though it is expected that the tinnitus will return to baseline levels before the end of each trial.

To confirm the quality of the EEG recording and data analysis methods, the evoked response to the white noise stimulus will be assessed first. The primary aim of experiment 2 was to thoroughly investigate the effects of RI on different frequency bands (Delta (1-4 Hz), Theta (5-7 Hz), Alpha (8-12 Hz), and Beta (13-20 Hz)) of brain oscillations associated with tinnitus, using sensor and source based analyses for greater spatial precision focused on auditory cortex activity. Building upon previous research this study aimed to analyse how the oscillations change as a result of the RI, and how they changed over the course of a period of time following RI. Based on the previous literature, the primary prediction was that significant reductions in delta band oscillatory activity would be observed across the RI period (Adjamian et al., 2012; Kahlbrock & Weisz, 2008; Sedley et al., 2012, 2015). While it has not been demonstrated in the RI literature so far, we also expected an increase in alpha band oscillations based on the work of Sedley et al. (2015). We then intend to expand the analysis into source space, and analyse the auditory cortex specifically. Further, as alpha band oscillations are associated with inhibitory networks, and based on the hypothesis of Roberts et al (2008) that these inhibitory networks are damaged as a result of tinnitus we expect a stabilisation of these inhibitory networks as a result of RI.

4.2 Methods

4.2.1 Participants

The participants who took part in this experiment were the same as those who took part in the experiment 1. As such their tinnitus histories, characteristics and recruitment information is given in chapter 3, section 2.1.

Demographics

Twenty-nine participants agreed to take part in the full study, including experiment 1 described in chapter 3 (17 male, average age = 59.7, standard deviation = 11.59). Three participants withdrew before completing the EEG component of the experiment in full leaving 26 completed datasets (16 male, average age = 58.6, standard deviation = 11.20). Initially the results from the RI tester component of the TI Tester described in chapter 3 were planned to be used to exclude those who did not experience residual inhibition. However, due to limitations in the number of tinnitus participants the study was able to recruit, it was deemed appropriate to admit all participants. A total of 8 participants who rated no change in tinnitus loudness during the Tinnitus Tester experienced a change in tinnitus loudness (6 suppression and 2 facilitation) in the EEG portion.

4.2.2 Equipment and Apparatus

EEG Data Recording

EEG data was recorded using a 32 channel Brain Vision EEG system (Brain Products, Munich, Germany). The system utilised 33 Ag/Ag/Cl sintered

ring electrodes affixed to an elastic cap and arrayed according to the standard 10-20 system (Easy Cap, Herrsching, Germany) as depicted in figure 2.2.3 b. The signal was then amplified by a Brain Amp DC (Brain Products, Munich, Germany) EEG amplifier. The reference electrode was set at the vertex, CZ, and the ground electrode at the centre of the forehead at AFz. The CZ electrode was centralised on the middle of the head, at the centre point between the inion and nasion and the two auricular points, measured individually for each participant. All data was recorded at a sampling rate of 500 Hz. Data triggers were relayed through a Tucker Davies Technologies (TDT) RP2 Real-time Processor (Tucker Davies Technologies, Alachua, FL, USA).

Gamma oscillations were not analysed due to limitations in the analysis of gamma using EEG discussed in section 4.4.2. These limitations related to the contamination of gamma from artefacts induced by muscle and eye activity, which would require the addition of electromyography and eye tracking data. This data was not collected during the EEG scan, as we did not have access to this equipment in the lab and even with this data there are still significant limitations to the analysis of gamma in EEG.

Auditory Stimuli

A white noise stimulus (0-22kHz) was generated using the TDT RP2 and delivered to participants at 50dB above their threshold for a 1 kHz pure tone using Sennheiser HD280 Pro over ear headphones and a TDT HB7 Headphone Driver. This method was similar to that of Roberts et al. (2008),

whereby they took the threshold of a 1 kHz pure tone via a staircase procedure, then added 65dB. Participants were then asked to adjust the loudness of a masker to match that of the pure tone, which has been shown to be effective in eliciting tinnitus suppression and residual inhibition.

Response collection

Response prompts were displayed on a Samsung SyncMaster Pro P2270 monitor and were generated using a script coded in Matlab (Mathworks Inc, Natick MA, USA). All responses were collected using a Griffin Powermate dial and button (Griffin Technologies, Nashville, TN, USA).

4.2.3 Experimental Protocol

The EEG experiment was split into 3 blocks with each block containing 10 trials. Figure 4.1 is a diagram depicting the layout of a block. At the beginning of each block there was a 60-second baseline measurement. During the baseline measurement period participants were asked to sit still and fixate upon a cross in the centre of the screen. After the baseline recording they were asked to make a tinnitus loudness rating, on a numerical scale of 1 to 10, with 1 being tinnitus is “very quiet” and 10 being tinnitus is “very loud”. After they made the rating the first trial began. This initial loudness rating functioned as their tinnitus loudness rating for the rest of the block, and they were advised that all questions about their tinnitus during this block related to that rating.

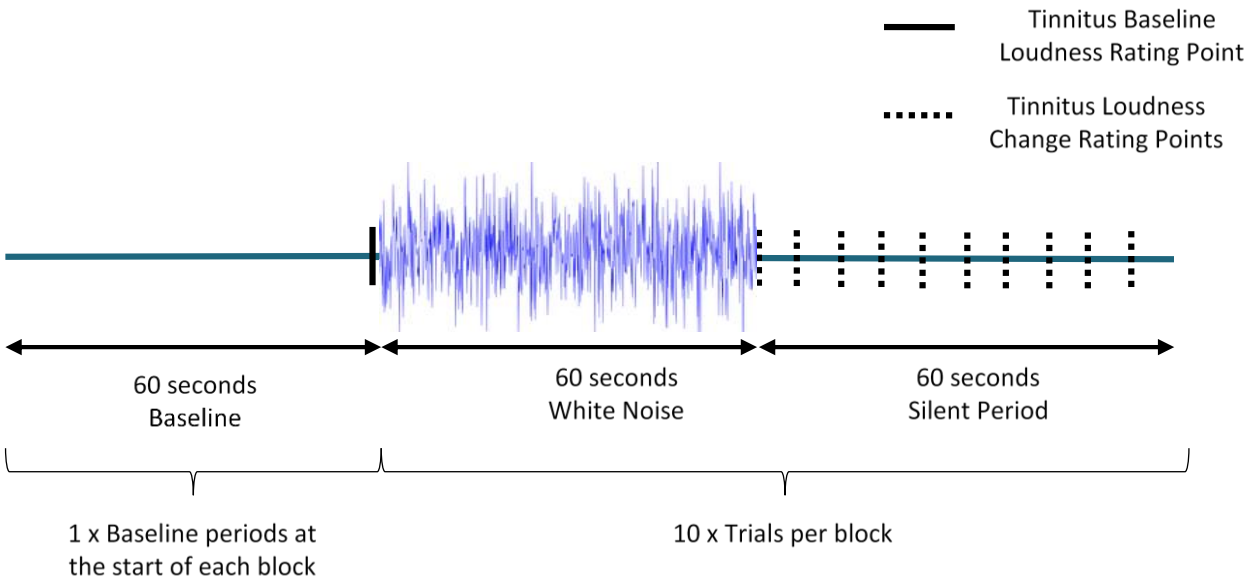


Figure 4.1: Diagram detailing the layout of a single block. At the start of each block a 60 second period of silence was taken as a baseline measurement. Following this, the trials began, first with a 60 second period of white noise and then followed by a 60 second silent period where participants were asked to rate the changes in their tinnitus loudness every 6 seconds. Each 2 minute trial was repeated 10 times in each block, for a total of 30 trials across the experimental session.

On each trial, participants were presented, binaurally, with a 60 second white noise, followed by a 60 second silent period. During this silent period they were asked, once every 6 seconds (for a total of 10 ratings), to rate how their tinnitus had changed compared with the rating they gave at the start of the block. This was done on a discreet scale of -5 ("gone") to +5 ("much louder") with 0 representing no change compared to that initial loudness rating, as in Roberts et al. (2008). Figure 4.2 shows screen capture images of the screens the participant saw when making these ratings.

4.2.4 Data Analysis

EEG signal recordings were processed and analysed using the Fieldtrip toolbox extension for MATLAB (Oostenveld, Fries, Maris, & Schoffelen, 2011). An Independent Component Analysis was performed on all datasets, which separated out temporally independent signals. The waveforms and

topologies of the components were visually inspected to remove muscle and eye movement artefacts. Particular attention was paid to those components that contained a large amount of high-frequency signals, and those that loaded very heavily onto the front sensors, indicating probable eye blinks and saccades. The data was then low pass filtered at 25Hz and re-referenced to the average reference.

The EEG data was segmented first into trials and then into 5-second chunks that corresponded to the periods between the loudness change ratings shown in Figure 4.2. One second of data immediately before the rating trigger was removed in order to account for any movement artefacts incurred as a result of operating the dial to make the rating. Before statistical analysis several preliminary steps were performed. Firstly, the EEG power values were binned according to frequency band. So for each participant/trial/5 second segment combination the data was split into the 4 analysed frequency bands (Delta (1-4Hz), Theta (5-7 Hz), Alpha (8-12Hz), and Beta (13-20 Hz)). An average was then taken across each frequency band, resulting in one value for each participant/trial/segment/band combination. The data was then averaged across trials, resulting in a single power value for each participant/segment/band combination. All statistical analyses were performed using IBM SPSS v21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

Following the statistical analysis of the power spectra, a Dynamic Imaging of Coherent Sources (DICS) beamformer was applied to the dataset.

This beamformer was identical to the ones discussed in chapter 2.3.1. The median frequency from each band (delta = 3Hz, theta = 6Hz, alpha = 10Hz and beta = 15Hz) was beamformed onto a precomputed boundary element method head model (Oostenveld, Stegeman, Praamstra, & van Oosterom, 2003). This allowed for the spatial localisation of changes in oscillatory power across the analysed frequency bands and between the analysed time points.

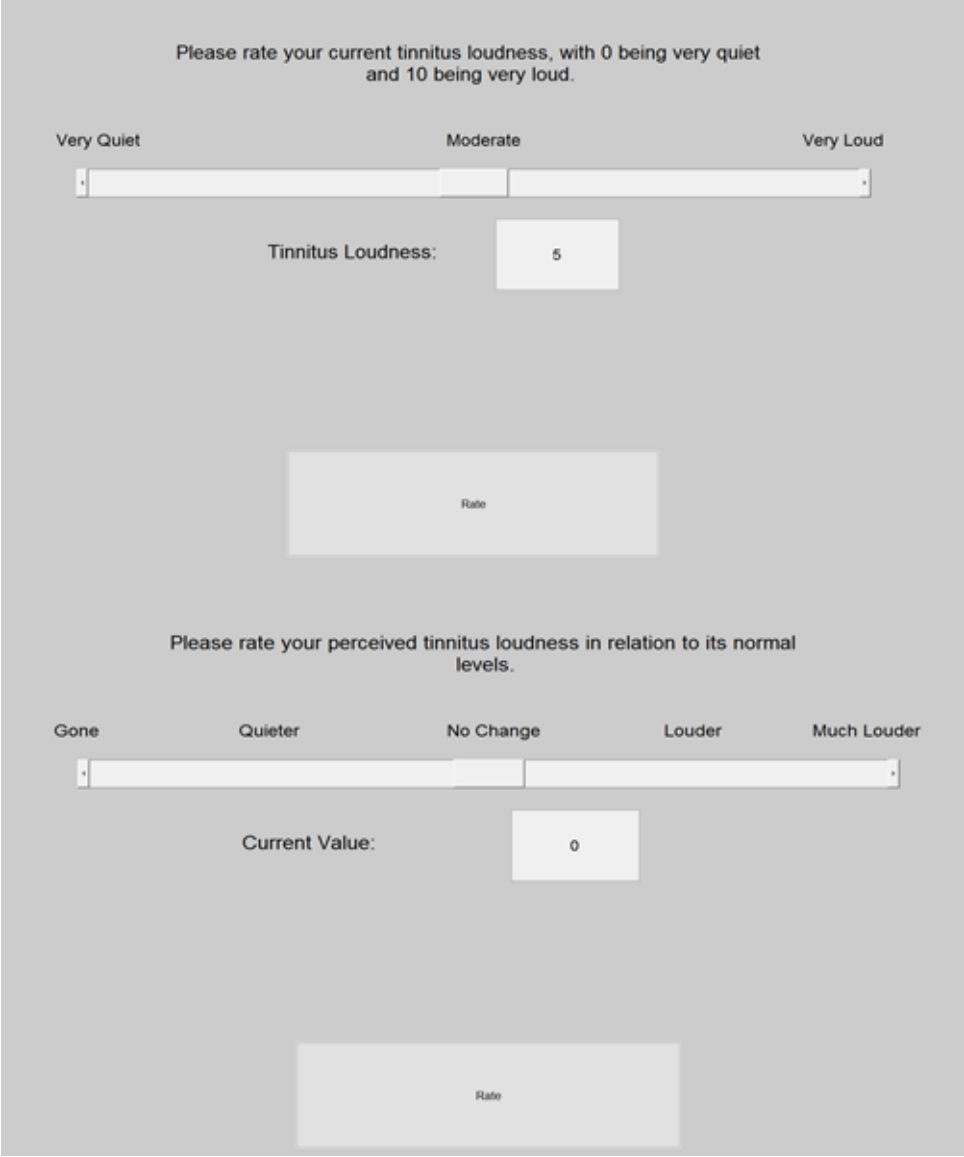


Figure 4.2: Top: Screen capture image of the rating scale participants used to rate their initial tinnitus loudness at the start of each block. Bottom: The rating scale participants used to rate how their tinnitus had changed following the white noise. When a rating was made, the button and scale disappeared. Participants were instructed to make a new rating when the button and scale reappeared.

Table 4.2 shows the loudness rating for each participant for the Tinnitus Tester software completed in Experiment 1 alongside the average tinnitus loudness rating given in Experiment 2. It also shows the average tinnitus loudness change rating from both measurements.

Participant	Tinnitus Tester – Loudness Ratings	EEG - Loudness Ratings	Tinnitus Tester – Loudness Change	EEG – Loudness Change Ratings
1	1.3	5	-2.3	0.71
2	8.6	8	-1.65	1.05
3	8	8	-1.5	-1.07
4	8.1	7	-1.85	-1.69
5	3	4	-1.275	-1.10
6	5	5.6	-1.85	-4.24
7	3.6	5	0	-1.42
8	5.6	4	-5	-0.01
9	2.5	2	0	-2.47
10	1.4	0.6	-0.5	-2.99
11	8	6.6	0	-2.45
12	0.8	4.3	-0.85	-0.92
13	7	6.3	-0.05	-1.62
14	2.6	1.6	-0.7	-0.19
15	6.1	5	-1.95	-0.26
16	1	1	-0.1	-0.33
17	3	4	-0.825	-2.05
18	3.7	6	-1.5	-0.12
19	3	4.3	-3.15	-3.17
20	6.1	6.6	-2.65	-0.26
21	2	2.6	-3.45	0.003
22	9.1	9.3	-0.4	1.78
23	4	4.3	0.1	-0.29
24	9.2	6	-0.275	2.18
25	8	6.6	-1.25	-0.40
26	2.5	3	0	-0.63

Table 4.2: Table showing the tinnitus loudness ratings from both the Tinnitus Tester Software (transformed to fit a 0-10 scale), the EEG Tinnitus Loudness ratings from the present study (an average of the 3 ratings given - 1 for each block), The average tinnitus loudness change rating from the Tinnitus Tester (third column) and the average tinnitus loudness change rating from the present study.

4.3 Results

4.3.1 Missing Data

For the 26 participants who completed the experiment, an inspection of the tinnitus loudness change ratings revealed that a number of the ratings were missing due to unforeseen technical problems. At random points during the experiment, tinnitus loudness change ratings were not registered correctly, and were stored as "NaN" (Not a Number) instead of the numerical value selected. This problem affected a total of 8 out of 26 participants and the distribution across these participants of these missing values is given in table 4.1. A total of 300 data points were collected in total, and so even the highest number of missing values (48) does not represent a significant problem. In order to proceed with the analysis, the missing data was imputed by averaging the data points immediately before and immediately after the missing data point. There were no missing data points from the baseline tinnitus loudness ratings.

Participant Number	**Number of Missing Values**
2	1
4	1
10	48
16	8
17	1
23	3
24	1
26	2
Total	65

Table 4.3: Distribution and total number of missing values across participants values in tinnitus loudness change ratings dataset.

4.3.2 Baseline Tinnitus Loudness Ratings

In order to determine if tinnitus loudness was reset back to normal levels between the three study blocks and also to understand how the tinnitus loudness ratings related to the global TFI score, an Analysis of Covariance (ANCOVA) was conducted investigating the baseline tinnitus loudness ratings at the start of each block with the global TFI score as a covariate of interest. The ANCOVA model therefore consisted of 'block' as the within-subjects factor with 3 levels (Block 1, Block 2 and Block 3) and global TFI score as the covariate. First the data were examined to determine whether they met the assumptions for a standard ANCOVA model. This was done by first assessing the estimates of skewness and kurtosis for each baseline loudness rating the global TFI score (n = 4). The criterion for an acceptable normal distribution was a skewness and kurtosis estimate of less than twice their standard error (Coolican, 2009). All the baseline ratings and the global TFI scores met this criteria and were then assumed to be drawn from a normal distribution. A Mauchly's Test revealed that the variance of the differences in ratings between the blocks was not equal (χ^2 (2) = 12.90, p <.05), i.e. sphericity had been violated. However, given that ε was less than .75 (ε =.70), a Greenhouse-Geisser correction could be performed to correct the F ratio thus reducing the likelihood of falsely rejecting the null hypothesis and allowing a more accurate *p* value. The results show no significant main effect of block on baseline tinnitus loudness ratings, *F* (1.40, 33.60) = .40, p = .60. This indicates that the baseline tinnitus loudness ratings were stable from block to block. In addition, the covariate, global TFI score, had no effect on baseline tinnitus loudness ratings across blocks, *F (*1.40, 33.60) = .138, p = .80. This indicates that baseline tinnitus loudness ratings were consistent across the blocks, irrespective of how highly participants scored on the TFI.

To further explore any relationship between global TFI score and baseline tinnitus loudness ratings, a Pearson's correlation was conducted, separately for each block. This revealed a significant positive correlation for block 1 (R = .72, N = 26, p <.001), block 2 (R = .66, N = 26, p <.001) and block 3 (R = .57, N = 26, p = .002). For illustration, figure 4.3 graphically represents the correlation between block 1 tinnitus loudness ratings and global TFI scores, revealing that higher global TFI scores were matched with higher baseline tinnitus loudness ratings.

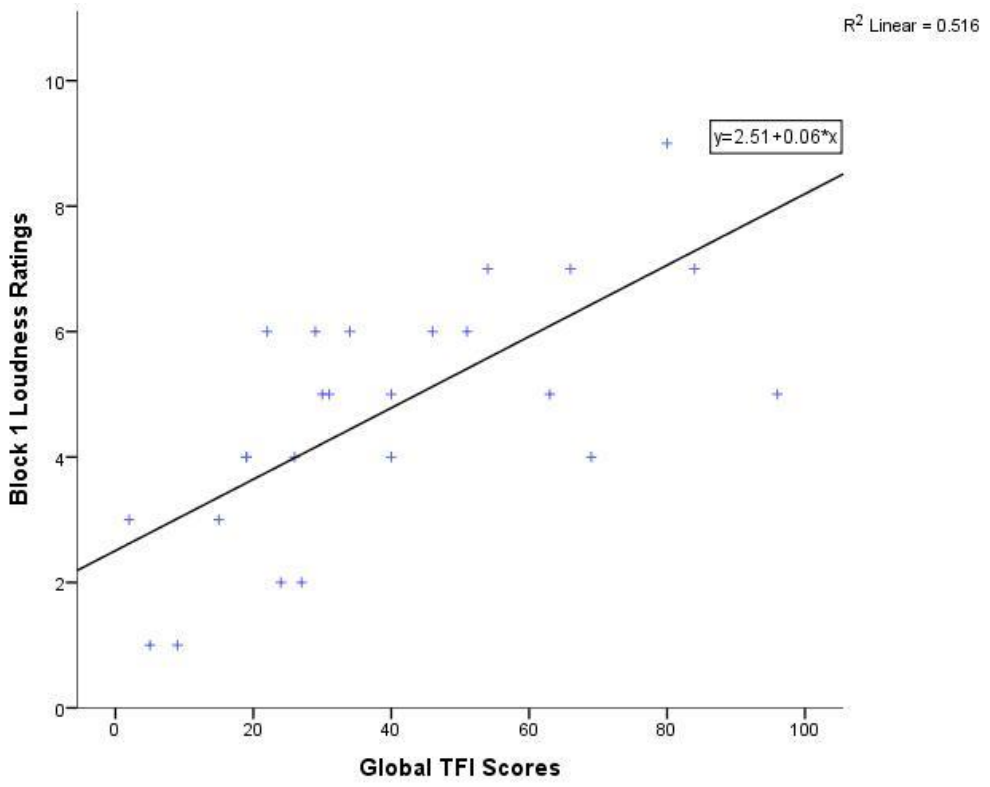


Figure 4.3: Scatterplot showing the significant positive correlation between block 1 tinnitus loudness ratings and global TFI score. Showing that higher global TFI scores were associated with higher tinnitus loudness ratings in block 1 of this experiment.

4.3.3 Tinnitus Loudness Change ratings

We hypothesised a high level of agreement between our measures of tinnitus loudness and tinnitus loudness change and those used by Roberts et al. (2008) in the Tinnitus Tester software. In order to determine the agreement between these measures a Bland-Altman Limits of Agreement

test (Bland & Altman, 1986) was carried out. The resulting plots are shown in figure 4.4 and indicate support for our hypotheses. No values fell outside the upper or lower limits of agreement when the two measures of tinnitus loudness were compared, and only one value out of the 29 fell outside the limits of agreement when the two measures of tinnitus loudness change were compared. This indicates a very high level of agreement between the two measurements.

An analysis was conducted to investigate the pattern of tinnitus loudness change ratings over the course of the experimental session (using SPSS V22). Data were examined for normality of distribution. The estimates of skewness and kurtosis for each separate condition in the study design

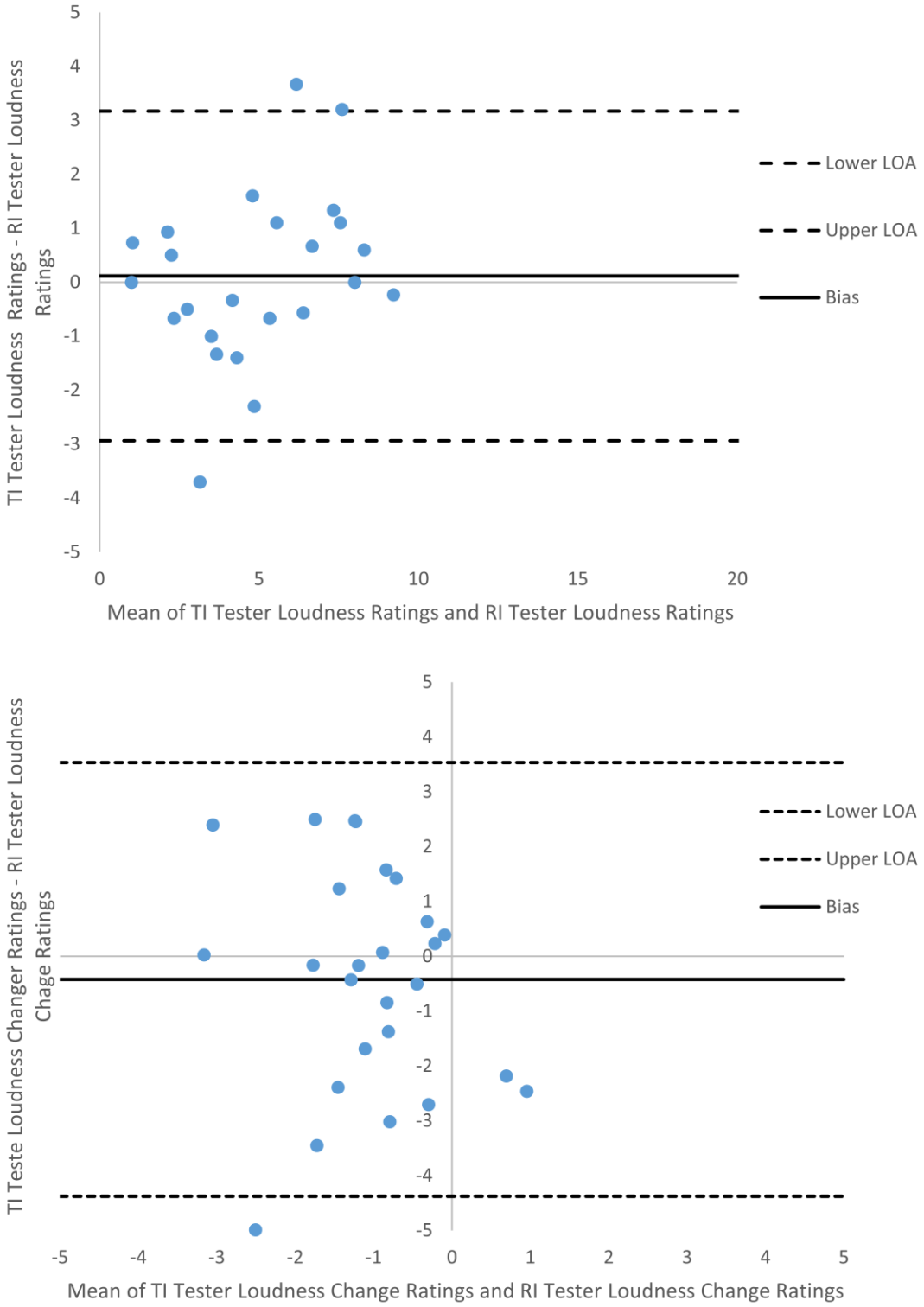


Figure 4.4: Bland-Altman Plots showing the difference between each individuals scores from the TI Tester (Roberts et al., 2008) and our RI Tester against the mean of the two scores. This is plotted for both the baseline loudness ratings (Top plot) and the loudness change ratings (bottom plot). The bias (difference from the expected difference of 0 between the two measures) is seen to be very small in both cases indicating good levels of agreement between the two measures. The upper and lower LOA

(n=300) were calculated. An inspection of the results confirmed that all

conditions met these criteria of an estimate of skewness and kurtosis that was less than twice its standard error. A three-way, repeated measures ANOVA model was specified with two within-subject factors, namely block (3 levels; Block 1, Block 2 and Block 3), trial (10 levels; Trial 1 to Trial 10 within each block) and rating time point (10 levels; Time point 1 to Time point 10 within each trial). A Mauchly's test of sphericity revealed that the variance of the differences in ratings for each of the three factors; block, χ^2 (2) = 30.00, p <.01, trial, χ^2 (44) = 167.54, p <.01, and rating time point, χ^2 (44) = 667.12, p <.01, was not equal thus violating sphericity. However, assumptions were met for the Greenhouse-Geisser correction for each of the three factors; block (ε = .58), trial (ε = .42) and rating time point (ε = .13) and so statistics for the corrected F ratios are reported. There was no significant main effect of block (F (1.17, 29.18) = .285, p = .76), or trials (F (3.75, 93.70) = 1.88, p = .13). However, there was a significant main effect of rating time point (F (1.16, 29.10) = 6.74, p = .01). The mean ratings (adjusted to the other variables in the model) across the 10 rating time points and averaged across all trials, are plotted in figure 4.5. The plot illustrates a consistent increase in tinnitus loudness ratings over the course of a trial. This was confirmed statistically by examining the tests of within-subject contrasts created by the ANOVA model where a significant linear component (F (1, 25) = 7.36, p = .012) was observed but no significant quadratic (F (1, 25) = 2.82, p = .11) or cubic (F (1, 25) = .18, p = .67) components. No significant two-way interactions were observed (p > .05).

Although Figure 4.5 shows that the group average ratings for each time point is that of a reduction in tinnitus loudness, inspection of the raw data revealed that not all participants experienced a reduction in loudness. In order to assess the differences in how participants rated their tinnitus loudness changes, participants were categorised into those who experienced a reduction in loudness, an increase in loudness or no change. Given that in all 3 blocks, the biggest change in loudness occurred in the first rating (see figure 4.5) participants were categorised according to the mean value of the first rating for each trial. If this value was -1 or less they were categorised in a group called suppression, if it was +1 or greater they were categorised in a group called facilitation. Otherwise, they were categorised as having

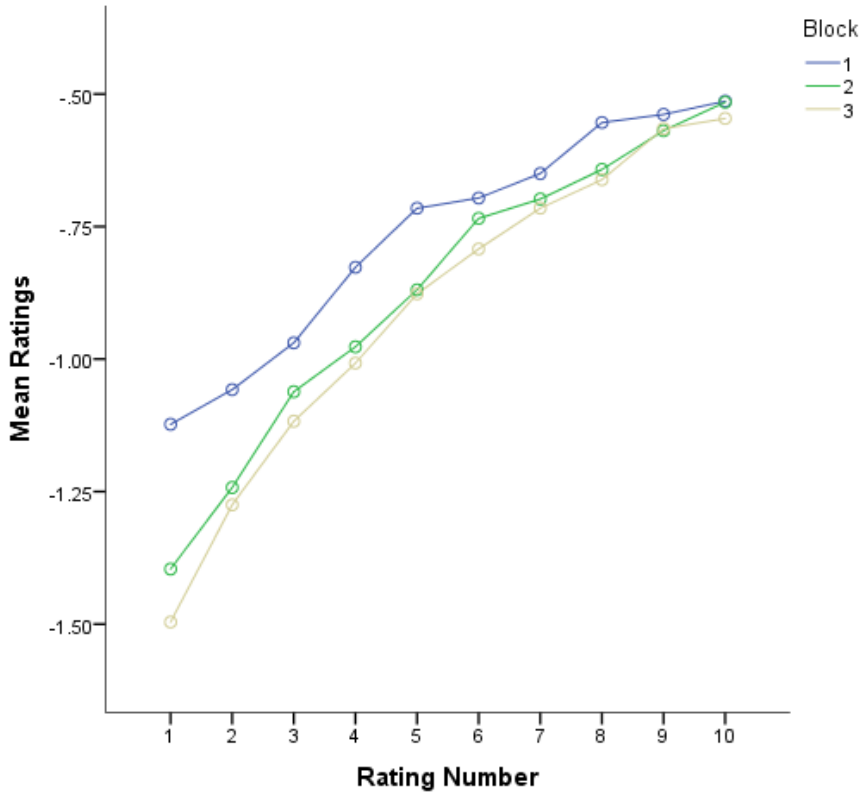


Figure 4.5: Adjusted mean (Estimated marginal means) ratings for each rating time point across all 3 blocks. Note that the x axis reflects at what point in the 1 minute of post masking silence the prompt to make a rating was scheduled to occur.

experienced ‘no change’. Table 4.4 details the number of participants in each group.

Group	Number	Mean at Time Point 1	Standard Deviation
Suppression (Residual Inhibition)	12	-3.2	0.65
No Change	12	-0.13	0.01
Facilitation (Residual Excitation)	2	2.70	0.32

Table 4.4: Number of participants in each group according to whether they experienced a reduction (Suppression), increase (Facilitation) or no change in their tinnitus loudness and the mean and standard deviation for each group at the first loudness change rating time point

To investigate the effect of subject group on the pattern of tinnitus loudness change ratings over the course of the experimental session another ANOVA was carried out. The previous ANOVA model was re-specified but this time adding subject group as a between-subject factor. As before, Mauchly’s test revealed that sphericity had been violated on the block (χ^2 (2) = 19.41, p <.01), trial (χ^2 (4) = 150.80, p <.01), and rating time point (χ^2 (44) = 533.70, p <.01), levels and so the Greenhouse-Geisser corrected statistics are reported (Block ε = .63, trial ε = .43 and rating time point ε = .15). There was no significant main effect of block (F (1.26, 28.99) = 2.92, p = .09), trial (F (3.94, 90.71) = .71, p = .69) or rating time point (F (1.30, 30.01) = .99, p = .45). However, significant two-way interactions between block and ‘subject group’ (F (2.52, 28.99) = 6.20, p <.01) and between rating time point and ‘subject group’ (F (2.60, 30.01) = 9.20, p <.01) were found. No significant interaction effect between trial and ‘subject group’ was observed, F (7.89, 90.72) = 2.04,

p = .051. Post-hoc testing could not be conducted for those interactions that included a within and between subject factor and so instead profile plots for the time point and 'subject group' and the block and 'subject group' interaction are shown in figures 4.6 and 4.7. Figure 4.6 shows for the first few time points the suppression group show a reasonably strong tinnitus suppression (negative rating value) which returns toward baseline over the course of the trial. In contrast the facilitation group shows a reasonably strong effect of tinnitus facilitation (positive rating value) which again returns toward baseline over the course of the trial. The no change group remained around zero for the whole trial. Figure 4.7 plots the average change rating for each of the three groups across the three blocks, and shows a marked increase in tinnitus loudness as the blocks in the facilitation grouping. Similarly, a greater reduction in tinnitus loudness can be observed in the suppression grouping in later blocks.

The findings indicate that the categorisation of the tinnitus loudness change results in a clearly defined difference in tinnitus loudness rating across the 3 subject groups. Overall the suppression group, rated their tinnitus loudness 1.91 points lower than the no change subject group and 4.02 points lower than the facilitation subject group. The facilitation group overall rated their tinnitus as 2.11 points higher than the no change group. Further, the findings show that this categorisation results in marked changes in tinnitus loudness rating across the three blocks with mean increases in tinnitus loudness change rating of 1.81 and 0.004 in the facilitation and no

change groupings, respectively, and a mean decrease in tinnitus loudness change rating of -0.49 in the suppression group.

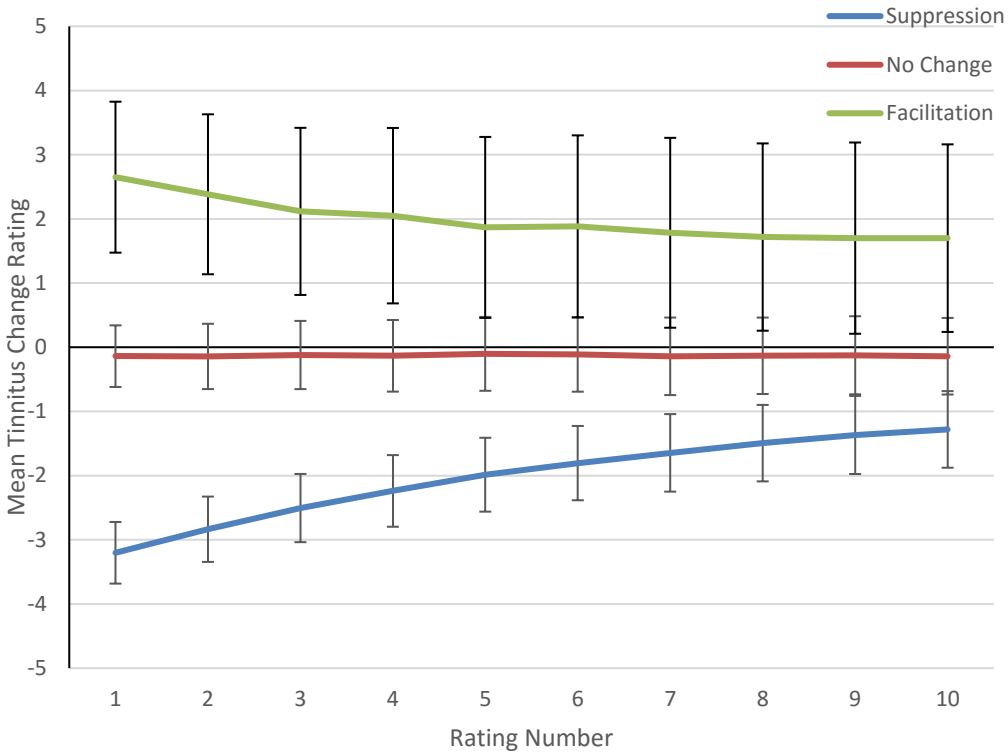


Figure 4.6: Mean ratings of tinnitus loudness change across participants for each 'subject group' and each rating time point with 95% confidence intervals. Shows a linear increase in tinnitus loudness in the suppression group (or decrease in the case of the facilitation group) as the RI period went on.

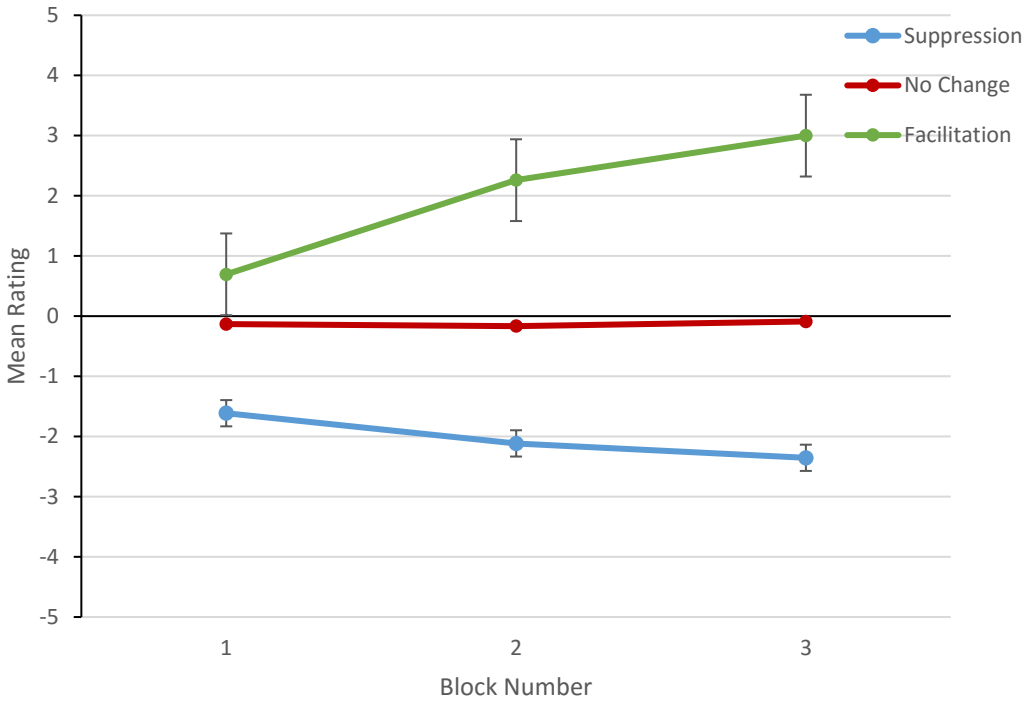


Figure 4.7: Mean ratings of tinnitus loudness change for each subject group across the three blocks in the experiment with standard error bars. This shows a decrease in tinnitus loudness in the suppression group in later blocks and an increase in tinnitus loudness in the facilitation group in the later blocks.

4.3.4 EEG Results

Confirmatory analysis

To determine the validity of our methods, an analysis of the evoked response to the white noise stimulus was conducted. It was expected that an auditory evoked potential would be observed as a result of the onset of the white noise stimulus with a peak at around 100ms corresponding to the N100 response. To determine this deflection, data was time locked to the final second of the baseline silent period and again to the first second of the white noise stimulus. The difference between these two conditions was then beamformed into source space and plotted on a template MRI brain scan. The results are shown in figure 4.8, and depict a clear N100 response during

the first second of the masker noise. The source space analysis revealed that this response originated in the auditory cortex. These results confirm that our initial data acquisition methods and source-based analysis protocols are appropriate.

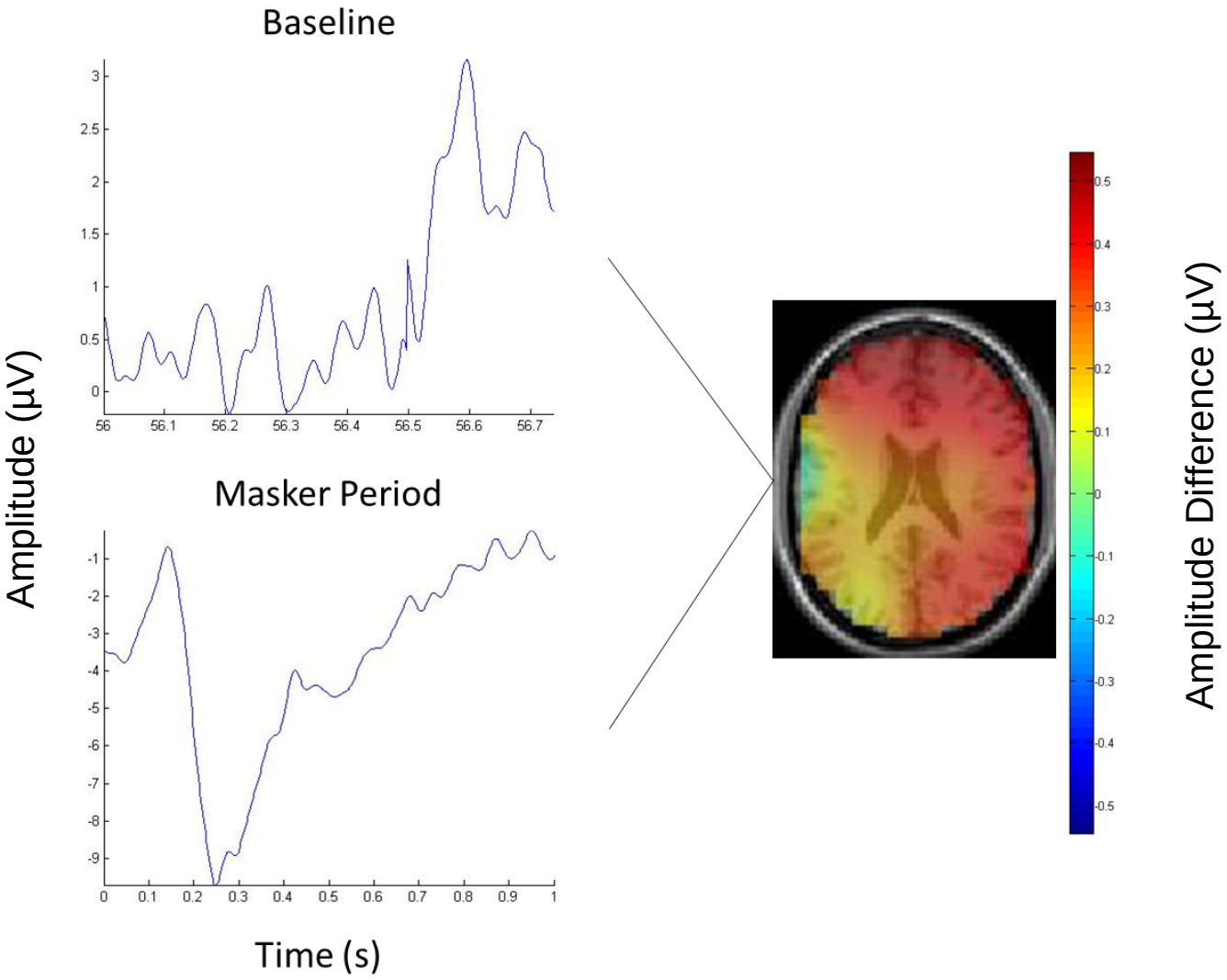


Figure 4.8: Evoked Response plots for the time locked data for both the baseline period and the masker period. Also depicts the source projected data of the difference between the baseline and the masker period.

Data preparation

For the statistical analysis following, only the first 5 second data segment and the last 5 second data segment for each participant was

analysed, alongside the first 5 seconds of their baseline measurement. It was expected that tinnitus would be present during the baseline period, at its most changed (either louder or quieter) during the first 5 seconds post-masker, and to have returned to pre-masker baseline levels during the last 5 second period. Due to the fact that the trial lengths varied between participants, the last 5 second period chosen was the latest 5 second period that was common to all trials and participants, in this instance 120-125s. Owing to the small number of participants who experience facilitation (n=2) they were excluded from this analysis.

Normality of the data set and detection of outliers was performed on the studentised residual values. Any studentised residual values over 3 were deemed as significant outliers, whilst normality was determined, as before, by examining the skewness statistic (Coolican, 2003). Owing to parts of the data being non-normally distributed and outliers being detected in the delta frequency band, the first frequency band analysed (Studentised residual values: 3.04, 3.16, 3.53, 4.36, 4.66 and 4.66) , all data for each frequency band was transformed using a log10 transformation. This resulted in most of the data being normally distributed, with the skewness statistic being less than twice that of their standard errors, and allowed for our planned ANOVA's to be conducted. For the data that was still non-normally distributed, a closer inspection of the QQ plots revealed very little difference in the distributions between the non-normal and the normal data. In addition, while the skewness statistic for the non-normal data was more than double its standard error, it did not exceed this threshold by much (mean

difference = 1.16). Therefore, it was assumed that the ANOVAs would be robust enough to tolerate these violations. The earlier analysis of the behavioural results indicated that block had no significant effect on the ratings given by participants. In order to examine whether this was also the case in the EEG power spectra, a three-way mixed ANOVA with one between-subject factor (Change grouping) with two levels (Residual Inhibition and No Change) and two within-subject factors (Block and Time Point) both with three levels (Block 1, 2 and 3, and Baseline, First 5 seconds and Latest 5 seconds, respectively) was constructed for each frequency band.

The Effects of Residual Inhibition on Oscillatory Power in Sensor Space

Main Analysis: Alpha and Delta

The main hypothesis of this study was that significant reductions in delta and significant increases in alpha band activity would be observed as a result of RI. To investigate this, the main effects of the change grouping factor were studied. As this was a between-subjects factor with only two levels, a Mauchly's Test of Sphericity was not appropriate, and so the reported statistics assume sphericity. Regarding our main hypotheses, significant main effects of change grouping were observed in the alpha (F (1, 22) = 4.49, p = .05) but not the delta (F (1, 22) = .04, p = .85) band. This indicated significant changes in oscillatory power in the alpha as a result of whether the participant experienced RI or experienced no change in their tinnitus loudness. Bonferroni corrected pairwise comparisons on the main effects of alpha revealed that oscillatory power was higher in the RI group

then in the no change group (Mean difference = .18, p = .05) This was consistent across both block and time point as shown in figures 4.9 and 4.10.

A Mauchly's Test of Sphericity revealed sphericity for the block factor was maintained in the delta (χ^2 (2) = 1.62, p = .45) but violated in the alpha (χ^2 (2) = 7.71, p = .02). Sphericity was also violated for the time point factor in both the frequency bands: delta (χ^2 (2) = 12.73, p = <.01), alpha (χ^2 (2) = 8.37, p = .02)). Therefore Greenhouse-Geisser corrected statistics are reported for the change grouping and block interactions for alpha (ε = .77) band and for the change grouping and time point interactions for delta (ε = .93), and alpha bands (ε = .75).

No significant two-way interactions were observed between change grouping and time point in delta (F (1.38, 30.25) = .01, p = .98) or alpha (F (1.51, 33.11) = 1.67, p = .20) bands. Nor were there any two-way interactions observed between change grouping and block in delta (F (2, 44) = 1.20, p = .20) or alpha (F (1.53, 33.65) = .79, p = .43). Finally no significant three- way interactions were observed in delta (F (2.82, 61.93) = .22, p = .88) or alpha bands (F (2.79, 61.30) = .30, p = .81). This indicates that the main effects of change grouping on oscillatory power in alpha were not related to a specific time point or block or any interaction between these factors.

Exploratory Analysis: Theta and Beta

Exploratory analysis was also performed on the theta and beta frequency bands. As before, a Mauchly's test of Sphericity was not appropriate when measuring the effects of change grouping on oscillatory

power and so the reported statistics assume sphericity. Significant main effects of change group were observed in the beta band (F (1, 22) = 6.20, p = .02) but not the theta band (F (1, 22) = .54. p = .47). As with the alpha band oscillations, this indicates significant changes as a result of whether the participant experienced RI or not. A subsequent Bonferroni corrected pairwise comparison on the main effects of beta revealed that oscillatory power was higher in the RI group then in the no change group (Beta: mean difference = .21, p = .02). This was consistent across both block and time point as shown in figure 4.10 and figure 4.11.

In order to carry out the exploratory analysis investigating the effects of block and time point, a Mauchly's Test of Sphericity was conducted for both the block and time point factors. Sphericity was maintained for the theta band block factor (χ^2 (2) = 1.61, p = .45) but violated in the beta band (χ^2 (2) = 7.74, p = .02). For the time point factor, sphericity was violated for the theta band (theta (χ^2 (2) = 10.01, p = .01) but not beta (χ^2 (2) = 4.92, p = .09). Greenhouse-Geisser corrected statistics are presented for the beta change grouping and block interactions beta (ε = .76) and the theta change grouping and time point interactions (ε = .72).

There were no significant two-way interactions in either theta (F (1.45, 31.85) = .01, p = .79) or beta (F (1.53, 33.63) = .49, p = .57) band oscillations between change grouping and time point. Further, no two-way interactions between change grouping and block were observed in these two frequency bands (theta: (F (2, 44) = .24, p = .08), beta: (F (2.81, 61.77) = .70, p

= .60). There was also no significant three-way interactions in the theta (*F* (2.62, 57.53) = .30, *p* = .80) or beta bands (*F* (2.81, 61.77) = .86, *p* = .49). As in the alpha and delta analysis, this shows that the main effects of beta that

were observed were not limited to any specific time point, block or any interaction between the two.

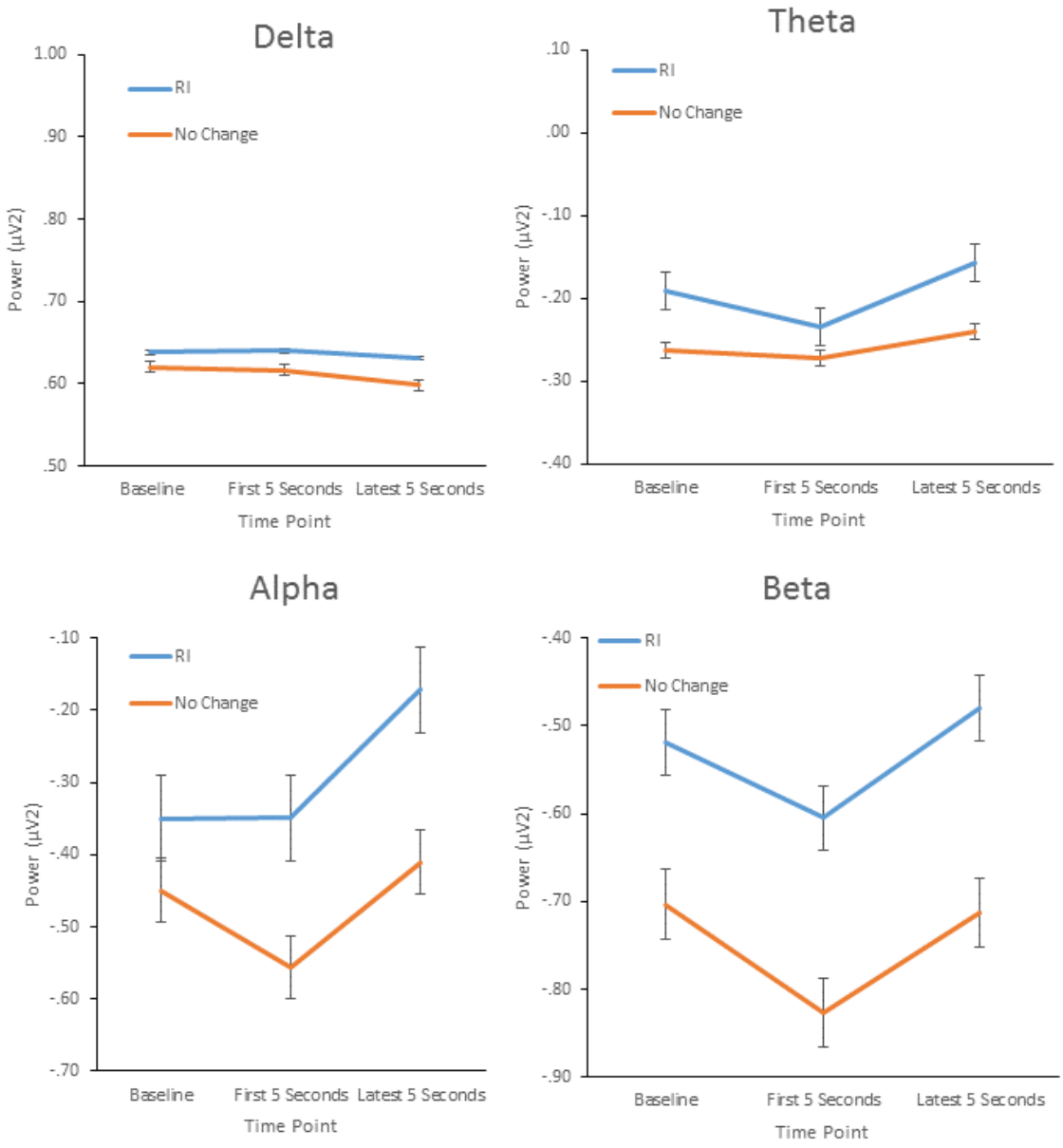


Figure 4.9: Estimated marginal means of power (corrected for all other factors in the model) for the time point and change grouping interaction with standard error bars for each frequency band. The data presented here is the Log10 transformation of the raw data that was passed to the ANOVA model.

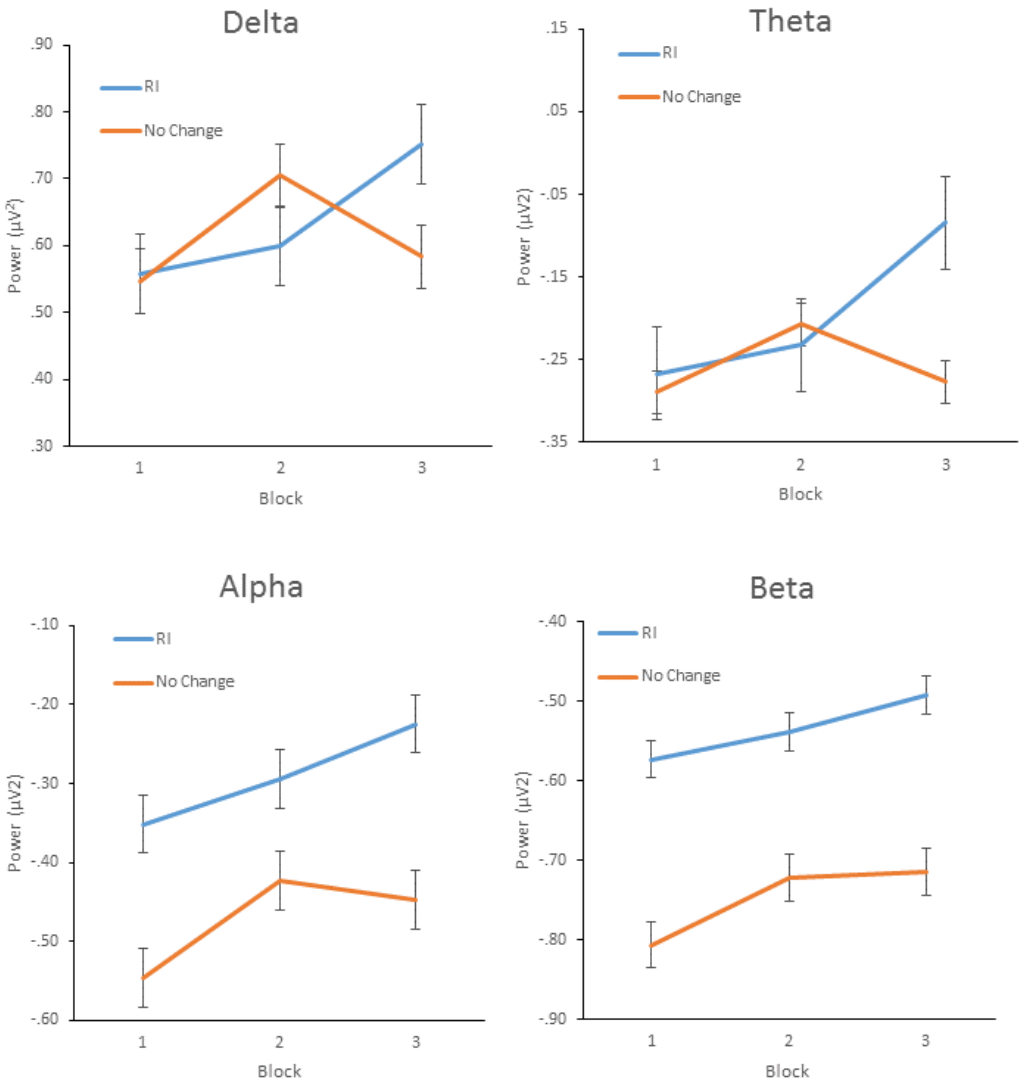


Figure 4.10: Estimated marginal means of power (corrected for all other factors in the model) for the block and change grouping interaction with standard error bars for each frequency band. The data presented here is the Log10 transformation of the raw data that was passed to the ANOVA model.

Changes in Oscillatory Power over Time

Main Analysis: Delta and Alpha

In addition to overall changes in delta and alpha oscillatory power as a result of RI, a secondary hypothesis was that these power changes would

change within a trial, returning to baseline levels as the trial progressed. To this end, the main effects of time point were analysed across frequency bands. Significant main effects of time point were observed in the alpha band (F (1.51, 33.11) = 8.41, p = <.01) but not delta (F (1.38, 30.25) = .03, p = .97).

Post hoc Bonferroni corrected pairwise comparisons on the main effect in the alpha band revealed a significant increase in alpha band power between the first 5 seconds post-masker and the latest 5 seconds (mean difference = -.162, p = <.01), resulting in lower power in alpha during the first 5 seconds time point when compared with the latest 5 seconds time point. As indicated by both the plots in figure 4.10 and the lack of significant two-way interaction between the alpha band and change grouping (F (1.51, 33.11) = 1.67, p = .20), this increase in alpha power across the trial occurred independently of participant experience.

Based upon the behavioural analysis indicating there was no change in tinnitus loudness change ratings across the blocks, we did not anticipate any significant changes in oscillatory power between the blocks in any of the frequency bands. However, it is possible that there were changes in oscillatory power across the blocks that did not manifest themselves as behavioural changes. The main effects of block were analysed across each frequency band and revealed significant main effects in the alpha band (F (1.53, 33.65) = 4.82, p = .01). No significant main effect was observed in the delta band (F (2, 44) = 1.67, p = .20) Profile plots of the estimated marginal means of power for each frequency band are given in figure 4.10.

Bonferroni corrected pairwise comparisons on the block main effects revealed a significant increase in power in the alpha band was also observed between blocks 1 and 2 (mean difference = -.091, p = .03).This shows there was a significantly lower power in alpha frequency oscillations in block 1 compared to block 2.

The main effects observed in both the time point and block factors occurred independently of each other, indicated by the lack of significant two-way interaction between the time point and block factors in either alpha or delta bands (delta: F (2.82, 61.93) = 1.85, p = .13, alpha: F (2.786, 61.30) = 1.15, p = .34). Further the changes were only observed between some of the blocks in alpha, not all of them. Finally, no significant three-way interactions between block, time point and change grouping were observed in either of the frequency bands (delta: F (2.82, 61.93) = .22, p = .88, alpha: F (2.79, 61.30) = .30, p = .81). This indicated there was no impact of block across the other variables in the model. As such, it was deemed that block was not having a reliable impact on oscillatory power.

Exploratory Analysis: Theta and Beta

Our additional exploratory analysis into theta and beta revealed that, as with delta, there were no significant main effects of time point in either theta (F (1.45, 31.85) = .86, p = .40) or beta (F (1.66, 36.40) = 2.72, p = .08).

Significant main effects were observed in the block factor however, in the beta band (F (1.53, 33.63) = 12.76, p = <.01), but not theta (F (2, 44) = 1.98, p = .15). Bonferroni corrected pairwise comparisons of this main effect

revealed a significant decrease in oscillatory power between blocks 1 and 2 (mean difference = .105, p = .01), followed by a significant increase between blocks 2 and 3 (mean difference = -.12, p = <.01).

As in the alpha and delta bands, there were no significant two-way interactions observed in either theta (F (2.62, 57.53) = 1.85, p = .16) or beta (F (2.81, 61.77) = .70, p = .60) which indicated that the main effect of the block factor in the beta band occurred independently of the time point factor. This is further compound by the lack of any significant three-way interactions in either theta (F (2.62, 57.53) = .30, p = .80) or beta (F (2.81, 61.77) = .86, p = .49). This would indicate that, as was the case in alpha and delta, block was not having a reliable impact on the oscillatory power of theta or beta.

Source Space Analysis

The data presented thus far has all been in sensor space. This, while providing useful information, takes into account all sources from across the head and does not reveal where in the brain the changes observed are originating. In order to determine this, a DICS beamformer was applied to the data set, and the percentage change in oscillatory power for each frequency band between the three time points was interpolated onto a template MRI scan. The change between the time points was calculated by taking the power values for each time point and subtracting from it the power values for the time point after. The result was then normalised by dividing them by the power values from the second time point.

Figure 4.12 plots the percentage change in oscillatory power across the whole head. The plots show that the changes in power between the baseline time point and the first and latest 5 seconds post masking noise, were bilateral and mostly observed in the posterior regions of the brain, in the region of the visual cortex. This was particularly evident in the delta and beta frequency bands. Changes between the first 5 and latest 5 seconds were less diffuse but more variable in their precise cortical locations, spread across both temporal lobes. This was to be expected due to the presentation of visual prompts in addition to the masking stimulus during the experiment and during the periods being analysed.

We therefore hypothesised that oscillatory changes relating to RI would occur in the region of the auditory cortex, and as such a region of interest (ROI) analysis was conducted. The temporal cortical regions in the left and right hemisphere were selected, masking all other data. The percentage change between the three time points for each frequency band and all three change groupings are shown in figures 4.13 to 4.15.

The source of the significant difference between the first 5 seconds and the latest 5 seconds post masker observed in the alpha band was estimated to be in the left temporal lobe, in both the residual inhibition and no change groups. However, contrary to what is seen in the marginal mean plots in figure 4.10 the greatest percentage change between these time points is observed in the no change group.

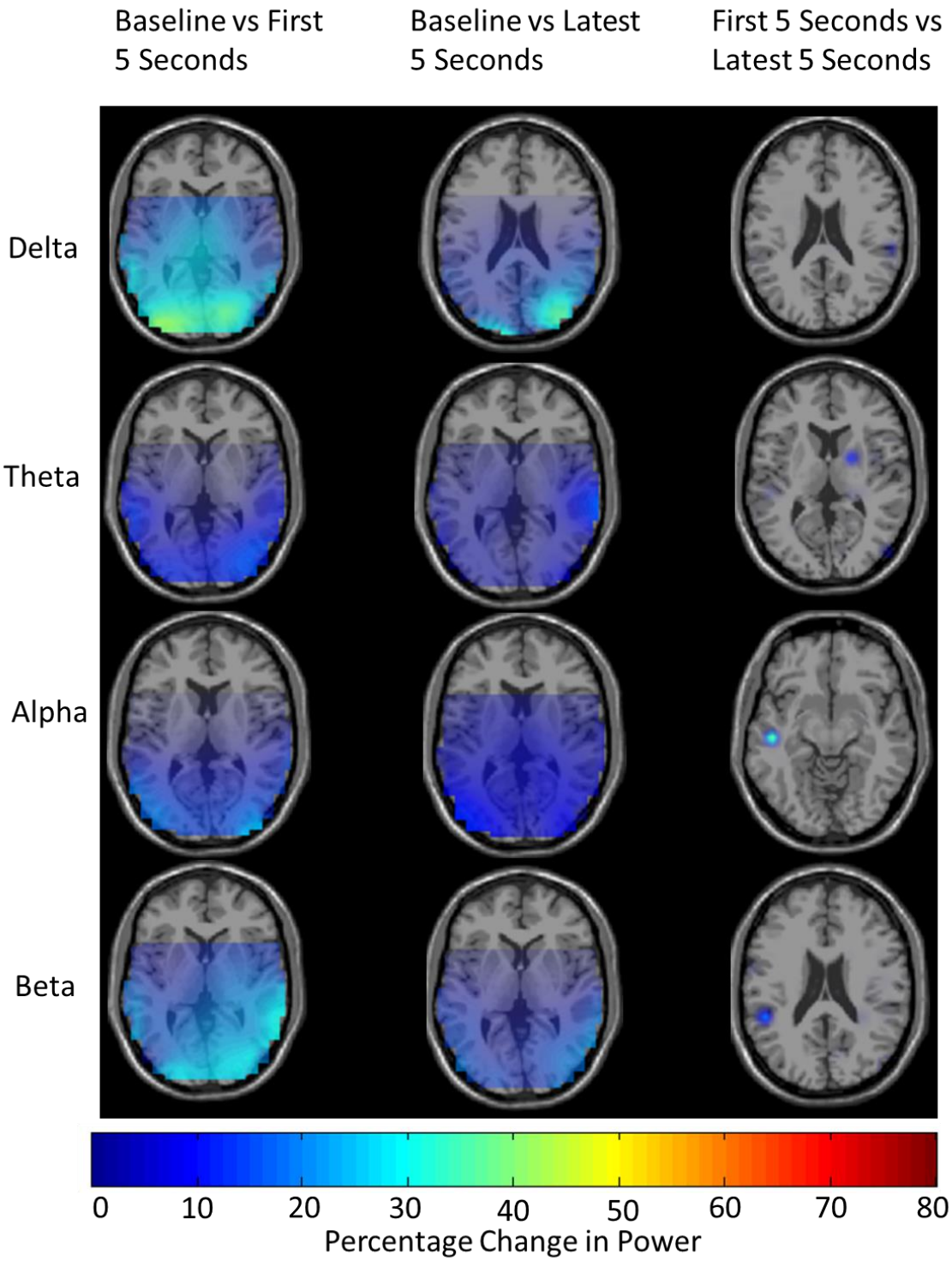


Figure 4.11: Estimated source locations for the observed changes in oscillatory power for each frequency band and time point comparison, collapsed across all the groups. Note the occipital dominance of the power changes. Especially in the lower frequencies and between baseline and the following two time points.

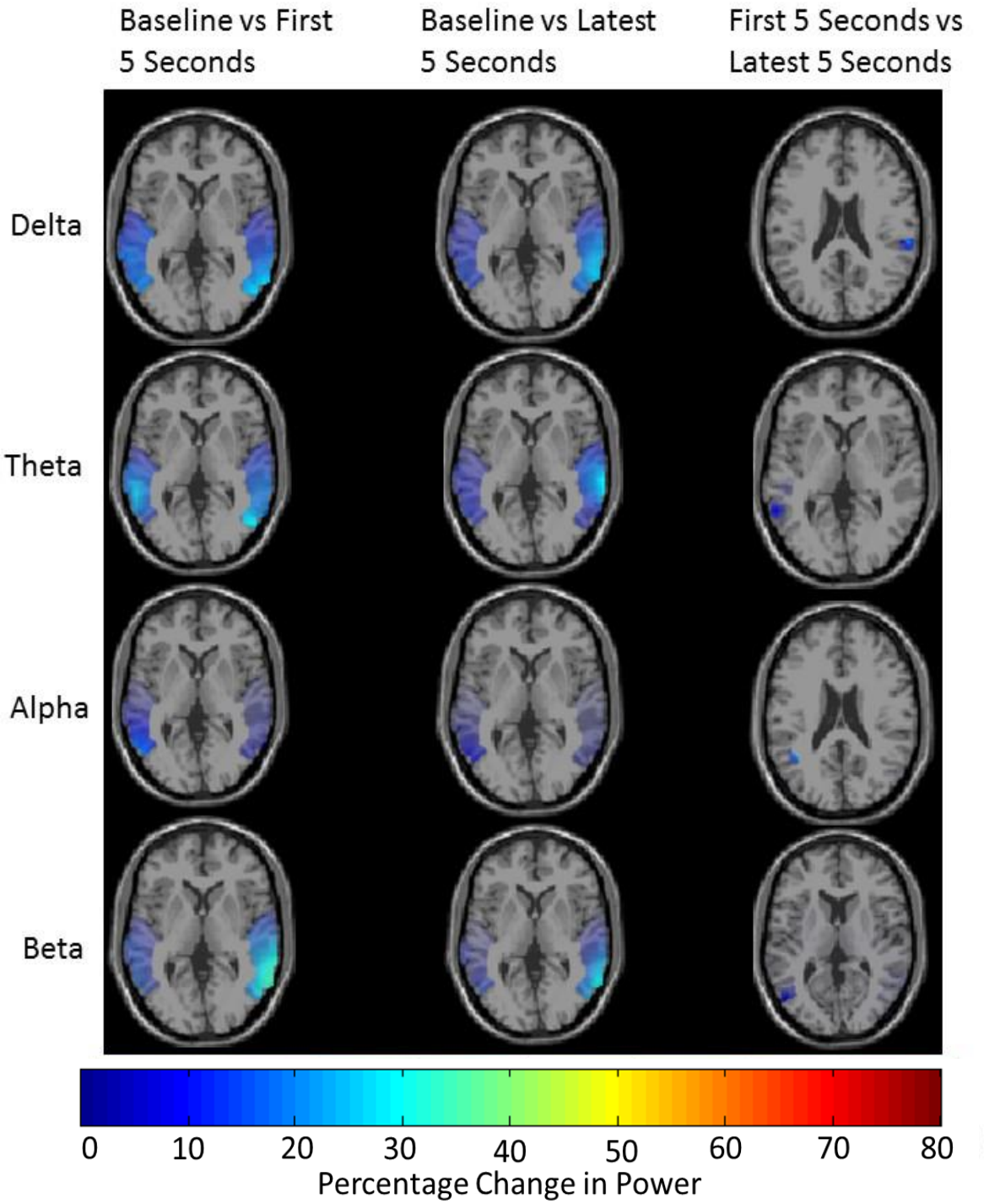


Figure 4.12: Estimated source locations of the observed changes in oscillatory power for each of the 3 time points and 4 frequency bands in the residual inhibition grouping. The analysis was restricted to only depict the changes observed in the temporal lobe, all other information was masked.

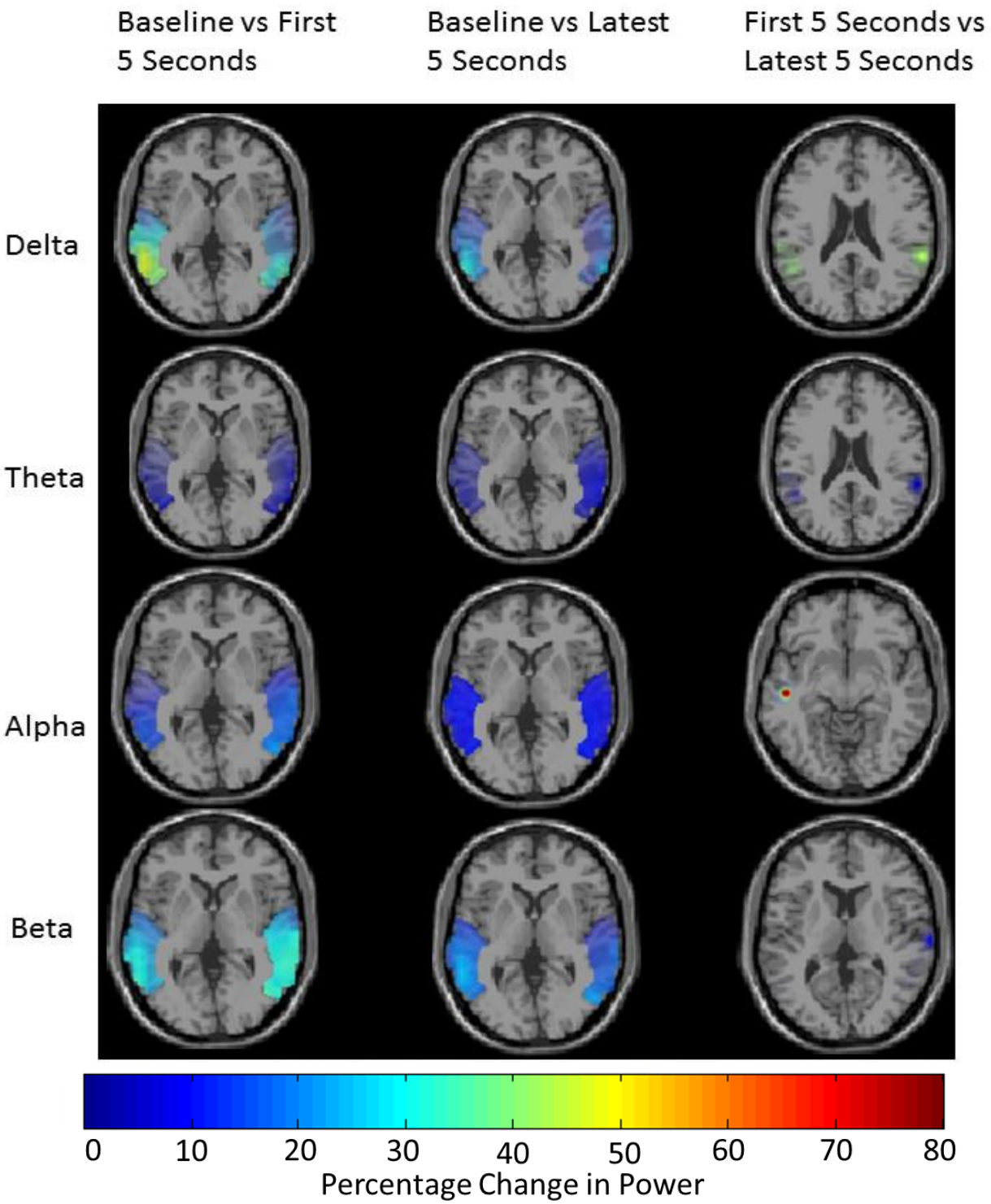


Figure 4.13: Estimated source locations of the observed changes in oscillatory power for each of the 3 time points and 4 frequency bands in the no change grouping. The analysis was restricted to only depict the changes observed in the temporal lobe, all other information was masked.

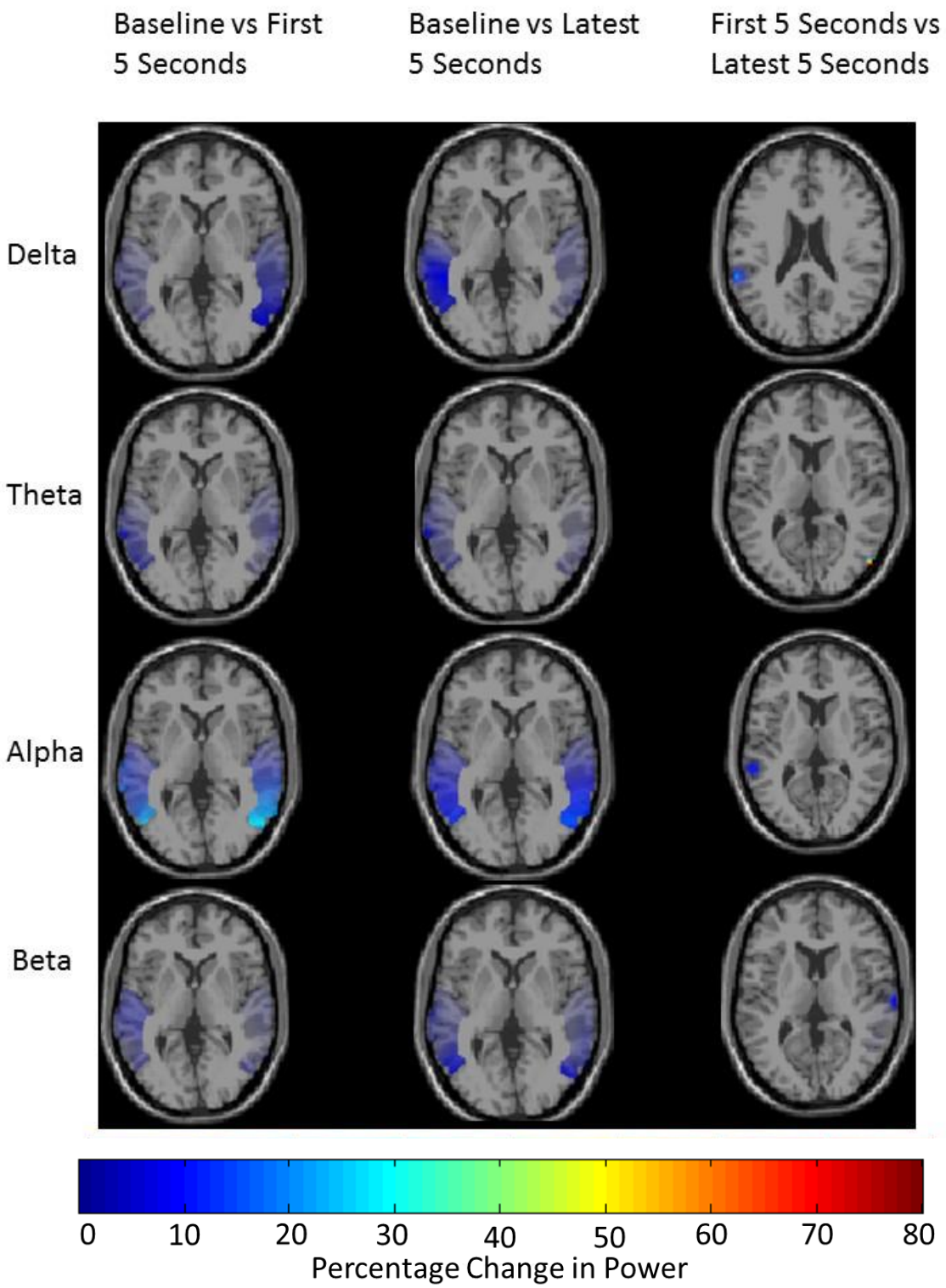


Figure 4.14: Estimated source locations of the observed changes in oscillatory power for each of the 3 time points and 4 frequency bands in the residual excitation grouping. The analysis was restricted to only depict the changes observed in the temporal lobe, all other information was masked.

4.4 Discussion

4.4.1 Effects of Residual Inhibition on Oscillatory Power

It was hypothesised decreased delta activity as result of RI. We also hypothesised an increase in alpha activity during the RI period across the whole head. These two main questions were assessed by a comparison of the baseline time point with the first 5 seconds immediately post-masker where RI was assumed, and later observed, to be the strongest. The observed findings are not in accordance with the previous literature, which has found reductions in delta band activity during the post masking period in participants who experience RI (Kahlbrock & Weisz, 2008; Sedley et al., 2012, 2015). While the power spectra did show trends that appear to be in direct contradiction to the previous literature, it is worth noting that in none of these cases were differences between the time points in the delta frequency band close to approaching significance. It is unclear why our results regarding the RI group did not replicate the previous literature, though it is plausible that it is a statistical anomaly as a result of our larger group sizes. We analysed 12 participants in our RI group, as opposed to 9 in Kahlbrock & Weisz (2008), and the single subject analyses that took place in Sedley et al. (2012, 2015).

We also hypothesised significant increases in alpha in the RI grouping during the post-masking period. We did not observe any significant changes in alpha band oscillatory power between baseline and the first 5 seconds of RI. This is in accordance with previous literature which also failed to find any

alterations in alpha band activity (Kahlbrock & Weisz, 2008), though not the more recent work using intracranial recordings which found reduced alpha (Sedley et al., 2015) in auditory cortical areas where depressed delta and theta activity were also observed.

Interestingly, while we did not observe any changes in alpha power during the RI period, we did see consistently increased alpha in the RI change group compared to the no change group across the whole trial. Higher alpha band power in our RI group could be interpreted as a marker for experiencing tinnitus suppression. In visual attention, alpha power increases when processing to-be-ignored stimulus (Rihs, Michel, & Thut, 2007; Worden, Foxe, Wang, & Simpson, 2000). This attentional processing has also been postulated to occur in auditory cortical alpha (Weisz, Hartmann, Müller, Lorenz, & Obleser, 2011). Potentially the finding here that experience of RI relates to initial higher alpha could relate to differences in attentional processing between the two groups. Speculatively this could imply that, in those who experience RI, the brain is processing tinnitus as a stimulus to be ignored but is unable to fully supress the perception. This would result in the higher alpha observed, generated along the same mechanisms as in the visual cortex (Rihs et al, 2007; Worden, et al, 2000). A hypothesis could be drawn to suggest that individuals who experience RI are better at attentional processing than their counterparts who do not experience a change in tinnitus loudness, and may merit further study.

4.4.2 The Returning Tinnitus Perception

In terms of the tinnitus rating changes, we found a significant linear increase in tinnitus loudness over the course of a trial. This demonstrated a gradual increase in tinnitus loudness ratings as the post masking period went on, as shown in figure 4.2. This was in line with our hypothesis that there would be the return to baseline levels would be gradual and is reflected in both suppression and facilitation groups (figure 4.3). To my knowledge, this is the first time that this has been shown statistically, although a gradual return of tinnitus has been assumed and anecdotally supported in earlier studies of residual inhibition (Feldmann, 1983).

We predicted that the tinnitus would return to baseline levels by the end of the trial. This was shown to not be the case, as if tinnitus had returned to baseline levels the increase in mean ratings would stabilize at 0 (no change on our change rating scale). RI has been found to typically last under two minutes (Meikle, Creedon, & Greist, 2004) and often less than one (Roberts, Moffat, Baumann, Ward, & Bosnyak, 2008). It is peculiar that our ratings did not return to 0 after a minimum of 1 minute of post-masking silence. On the surface this would suggest that tinnitus was not returning to normal over the course of a trial, however no effect of trial was observed indicating that no changes in tinnitus loudness change rating were observed across trials. With this in mind, it is most likely that this result is due to participant error, possibly a misunderstanding on how to rate the tinnitus loudness change correctly or the participant anticipating a change in their tinnitus loudness,

simply because they were asked to rate it, rather than actually experiencing a change.

The gradual return in tinnitus loudness did not appear to be reflected in the oscillatory frequency bands analysed. We anticipated that in these oscillatory frequencies there would be significant changes in power between the first 5 second and the latest 5 second time points. This was only observed in the alpha frequency, however it was not related to whether the participant experienced any tinnitus suppression (RI) or not. There are two possible reasons for this finding. The first is that the RI was not over by the time the last time point sample was taken and tinnitus had not yet returned to normal. The latest 5 second window that was sampled was the one that was common to all participants, therefore it is plausible that in some participants the period of RI lasted much longer than this. However, this would require most participants RI to last over one minute, which is not in accordance with previous literature describing the majority of RI as being less than one minute in duration (Roberts, Moffat, Baumann, Ward, & Bosnyak, 2008). It also does not address the observation that tinnitus in our sample did not return to baseline (see figure 4.3) over the course of a trial, as such it is unlikely that our finding was related to our choice of time point sample.

The second reason is related to the oscillatory frequency bands analysed. Theories of tinnitus generation such as the thalamocortical dysrhythmia model proposed by Llinas et al (1999) and the integrative model of tinnitus by De Ridder (De Ridder et al., 2014) discussed in chapter 1.2

propose that high frequency oscillations are the driver of the tinnitus percept. There is evidence to suggest that gamma oscillations are more involved in the conscious perception of the sound (Arnal & Giraud, 2012; Dirk De Ridder et al., 2014a). As such, it is plausible that changes in oscillatory power in the first 5 seconds post masker and the latest 5 seconds did exist, but in the gamma frequency. Gamma oscillations were not analysed in the present work for several reasons. Analysing gamma oscillatory activity with EEG is notoriously difficult as contaminants can arise from blinks and eye saccades, neck and facial muscles movements and power line noise (Nottage and Hoarder, 2015). All of these produce artefacts in the region of gamma, and in the case of neck and facial muscles, can account for up to 90% of recorded gamma at certain electrode locations (Whitham et al., 2007). Without accounting for these artefacts it is common to misinterpret muscle artefacts as gamma oscillations (Muthukumaraswamy, 2013; Yuval-Greenberg, Tomer, Keren, Nelken, & Deouell, 2008). Increasingly, methods are being developed which can account for these artefacts, including novel ways of subtracting muscle artefacts using EMG and EOG electrodes (Nottage and Hoarder, 2015) which go some way to opening accessibility of gamma measured through EEG. There is, however further work to be done in this regard, these methods require more evaluation to confirm their effectiveness and the analysis pipelines need to be optimised. For these reasons, and also for reasons relating to the technical limitations of the equipment available to us in our lab we chose not to analyse gamma in this study.

4.4.3 Repeated Inductions of Residual Inhibition

A further aim of the present study was to analyse the findings in relation to animal (Galazyuk et al., 2017) and human (Feldmann, 1983; Sedley et al., 2015) research that repeatedly inducing RI would result in a decay in its effectiveness – relating to its duration and depth. We hypothesised significant decreases in RI depth over the course of a block and the experiment. We did not observe any changes in RI depth as a result of trials or blocks when all the participant data was grouped together. This does not support our hypothesis and previous research. However, this analysis was performed on all participants, regardless of whether the participant experienced a suppression, an increase or no change in their tinnitus loudness. When the data was separated into the three groups (Suppression, Facilitation and No Change), interaction effects were observed for the change group and block interaction. Although post hoc tests could not be performed on this data to confirm these observations statistically, figure 4.5 indicates that this change in tinnitus loudness change rating across the three blocks was likely driven by increases in tinnitus loudness change rating in the facilitation group across the blocks. A smaller decrease in tinnitus loudness change rating across the blocks can also be observed in the suppression group. It is also worth noting that, in several participants we observed changes in RI experience between the first session where questionnaire and tinnitus tester data was collected, and the second session where EEG data was collected. In some participants (see table 4.2) this was quite marked, either going from no change in their tinnitus loudness (around 0) to

experiencing RI or vice versa. Part of this variance between the sessions can be explained by the fact that in the EEG testing session there were far more ratings that were averaged over to produce the final result shown in table 4.2. However, it is worth bearing in mind when designing future studies that multiple session studies investigating RI may not be appropriate as there may be changes in RI effectiveness or experience across sessions.

Both Galazyuk et al (2017) and Sedley et al (2015) reported reductions in effectiveness in RI as a result of repeated inductions. Our results do not indicate this. We did not see any alterations in RI depth on the trial level, and the changes we saw on the block level showed an increase in RI depth (i.e. a decrease in loudness change rating). Neither of these two findings corroborate with the previous literature, however there are reasons why this might be the case. The first reason is the Galazyuk et al (2017) work was focused on firing rates in the inferior colliculus of mice. While the similarities between the known psychoacoustic properties of RI in humans and the properties observed by Galazyuk et al.'s lab are clear, it is probably that there are a number of intervening processes between the inferior colliculus and the perception of tinnitus suppression. Therefore, it is unlikely that activity changes in the inferior colliculus accounts for the entirety of the RI phenomenon. It is possible then, that the incongruence between our findings and theirs relates to these unknown mechanisms between the inferior colliculus and conscious perception. Further, the analysis performed on the human subject in Sedley et al. (2015), was a single subject analysis only. In addition, their subject also had epilepsy which could introduce a confound

and a possible reason for the difference in our findings. We also observed a reduction in the effectiveness in certain participants on an individual level, however this effect was lost on the group level. The possibility remains that reduced effectiveness of RI as a result of repeated inductions is a trait that is exhibited on an individual level, and is related to specific properties of an individual's tinnitus. This is something that should be investigated in future work.

4.4.4 Conclusions and Future Directions

In conclusion, while the study failed to support many of our initial hypotheses regarding modulation of specific frequency bands and the effects of repeatedly inducing RI, it did reveal two particularly interesting traits of RI and tinnitus suppression. Firstly, the study statistically confirms the long held assumption and observation that tinnitus gradually returns to "normal" levels following a suppression by a masking noise. The second was that, although alpha band power was not modulated during the period of RI following the white noise masker, it was higher in general in the RI group than in the group that did not experience a change in their tinnitus loudness.

Experiment 2 presents evidence for several new hypotheses that can be tested in future work. Firstly, the finding of increased alpha band power in those that went on to experience suppression of their tinnitus, even before it was suppressed raises the possibility of a marker for those who are more likely to experience RI. In particular it is hypothesised here that being able to experience RI could be related to attentional processes, and future research

could explore this area. Further, future research into this area should focus on modulations in the higher frequency gamma band oscillations, as these are supposed to contain more salient information regarding perceptions.

Chapter 5 - The Effects of Transcranial Direct Current Stimulation on Auditory Cortical Oscillations Measured By Magnetoencephalography – Experiment 3

5.1 Introduction

5.1.1 History of Transcranial Direct Current Stimulation

The idea of using electrical currents, such as in tDCS was reported as early as 40AD when the Roman physician, Scribonius Largos used the currents produced by electric torpedo fish to treat various pains (Jocks, 2013). Its potential for alleviating disorders of the mind was also discovered early on, when in 1804 direct current stimulation was successfully used to treat melancholy (Aldini, 1804). Work into using direct current stimulation for treatment of mental disorders continued for two centuries, but was thereafter slowly abandoned due to its variable effects (Priori, 2003). A brief

resurgence in the field came in the 1960's when evidence for the physiological basis of tDCS emerged. In a brace of papers published in 1966 it was revealed that tDCS can affect brain functions by altering cortical excitability, eliminating or speeding memory consolidation in rats depending on the type of stimulation administered (Albert, 1966b, 1966a). Interest in the clinical applications of tDCS soon waned however, due in part, to the already established and similar field of electro-convulsive therapy and the emerging field of psycho-pharmacology (Priori, 2003). However, systematic studies of the effects of tDCS on behaviour in healthy humans continued into the 1970's, some of which is discussed in the coming sections. Another period of resurgence has occurred recently, and been sustained for the past 16 years. This is perhaps due to an increased understanding of the mechanisms of action of tDCS, in part due to advancements in other non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) as well as neuroimaging (Utz, Dimova, Oppenländer, & Kerkhoff, 2010).

In its most common and current form tDCS is administered using 2, usually rubber, electrodes place at contralateral locations to one another on the scalp. These electrodes function as an anode and cathode and a current (0.5-2 mA) is passed between them. However, one limitation of this is that the electrodes are quite large (20-35 cm^2) and so it can be quite unclear which part of the brain is being stimulated. It is not currently thought that there is a direct current flow through the head from anode to cathode, but the current flow is dependent upon both tissue shape and conductivity as well as the positioning of the electrodes (Neuling, Wagner, Wolters, Zaehle, &

Herrmann, 2012). Spatial specificity has also been somewhat addressed by the invention of high definition tDCS (HD-tDCS), which involves placing the active electrode and then surrounding it by a number of electrodes of the opposite polarity. This ensures that rather than the current passing through the whole brain, the current only passes from the central electrode to the ring around it, stimulating the area between. This technique has been shown to be more spatially specific (Alam, Truong, Khadka, & Bikson, 2016), however the bulk of the current literature and the present experiment, focus upon regular tDCS, which will be discussed further.

5.1.2 Mechanisms of tDCS

Physiological Basis of tDCS

The physiological basis of tDCS is at present not fully understood. Unlike other non-invasive brain stimulation techniques, such as TMS, tDCS does not directly induce neuronal firing or action potentials, but rather biases the cortical excitability (Nitsche & Paulus, 2000). In animal studies from the 1960's it has been shown that anodal stimulation depolarises neural membranes, which leads to the increase in excitability and spontaneous firing rates, while cathodal hyperpolarizes cell membranes decreasing their excitability (Bindman, Lippold & Redfearn, 1962). However, this trend was reversed in the deeper layers of the motor cortex of cat (Creutzfeldt, Fromm, & Kapp, 1962) suggesting that the observed changes in cortical excitability are not just dependent on the polarity of stimulation, but also the type and orientation of the cells being stimulated (Utz et al., 2010). Indeed, further work showed that non pyramidal tract neurons required lower stimulation

intensities than their pyramidal counterparts to elicit the same effects (Pupura & McMurtry, 1965) illustrating that different cell types respond differently to stimulation.

It should be noted that these earlier studies involved the direct, invasive, stimulation of cortical cells, whereas, in humans, tDCS stimulates the brain via the scalp. This does lead to a loss of current reaching the cortical layers, however it is thought that around 45% of the total current reaches the cortex (Rush & Driscoll, 1968). In their study, Nitsche and Paulus (2000) were able to replicate excitability changes of 40% using weak tDCS, equal to what has been exhibited in TMS. These effects were polarity specific, with anodal increasing cortical excitability and cathodal stimulation decreasing it, consistent with the earlier animal models. Further, prolonged excitability changes have been observed, lasting up to 90 minutes after exposure(Nitsche & Paulus, 2001).

It is presently unclear what mechanisms are involved to produce the observed lasting changes due to tDCS. Two proposed mechanisms that are gaining traction in the field are the modulation of Long Term Potentiation (LTP) and Long Term Depression (LTD). LTP and LTD are not new ideas, having been originally proposed as one of the mechanisms of modulation in synaptic plasticity (Stagg & Nitsche, 2011). LTP refers to the gradual strengthening of synapse and signal between two neurons based upon synchronous, and repeating, pre and post synaptic activity, whereas LTD results in long term decrease in synapse strength between neurons (Cooke et al., 2006). Both LTP

and LTD are modulated by neuromodulators, which have little to no effect on base neural activity but boost or reduce responses from other transmitters (Stagg & Nitsche, 2011). Table 5.1 outlines a number of relevant neuromodulators.

Name	Abbreviation	Source
Glutamate	GLU	Throughout the Brain
Noradrenaline	NA	Locus Coreuleus
Dopamine	DA	Ventral Tegmental Area
Acetylcholine	ACh	Nucleus Basalis of Meynert
Serotonin	5-HT	Raphe Nuclei

Table 5.1: *Details the names, abbreviations and sources in the brain of a number of neuromodulators implicated in LTP and LTD. Taken and adapted without permission from Stagg et al, 2011.*

Dopamine is of particular interest as it has been reported to interact with both NMDA and GABAergic neurons (Wang & O'Donnell, 2001). NMDA has been implicated as a mediator of the long term effects of tDCS in a number of studies. For example, dextromethorphane, an NMDA receptor antagonist, has been shown to decrease the long term aftereffects of anodal tDCS (Nitsche et al., 2003). Further, agonising NMDA using the partial agonist, D-Cycloserine prolongs these effects. It has also been suggested that the driving force behind these effects is activity dependent brain-derived

neurotrophic factor (BDNF) (Fritsch et al., 2010). Fritsch et al (2010) suggest anodal tDCS is capable of improving motor function, but only when this BDNF activation is also in place. Recent work has furthered this point, suggesting that anodal tDCS increases expression of a BDNF regulating gene, increasing both BDNF and, subsequently, LTP (Podda et al., 2016). tDCS has also been found to alter the concentrations of GABA within the brain (Stagg et al., 2009). The weight of evidence suggesting changes in NMDA and GABA are the result of tDCS is heavily indicative of LTP and LTD-like plasticity (Dayan, Censor, Buch, Sandrini, & Cohen, 2013). It is likely then that LTP and LTD do have a significant role in the observed changes in neural activity following tDCS. This would mean that tDCS does have therapeutic potential for conditions of the brain that are associated with neuroplasticity (Podda et al., 2016).

tDCS and Neural Oscillations

Not much is known about the mechanism of action involved with tDCS with regards to neural oscillations. While there has been evidence to suggest that tDCS is capable of modulating brain oscillations(Lapenta, Minati, Fregni, & Boggio, 2013) this research has only analysed the Mu (9-11Hz) frequency oscillations, and only following tDCS, not during. As such it is unclear what effects tDCS is having on other frequency oscillations. It is important that in spite of the amount of research investigating the neuronal basis of tDCS in animals that the actual, externally measurable effects on humans are still contested (Horvath, Forte, & Carter, 2015). Therefore it is imperative that work is done that investigates the online effects of tDCS in humans. Recent

studies have investigated the concentrations of metabolites and neurotransmitters during tDCS using magnetic resonance spectroscopy in humans (Hone-Blanchet, Edden, & Fecteau, 2016). Using the common electrode montage of placing the anode over the left Dorso-Lateral Prefrontal Cortex (DLPFC), or F3 on an EEG 10-20 layout, and the cathode over the right DLPFC they found increased concentrations of both glutamate (GLU) and *N*-acetylaspartate. Interestingly, these increases were location specific with the increase in NAA being specific to the left DLPFC and the increase in GLU being in the left striatum only. The paper does not confirm whether anodal or cathodal stimulation was delivered, however given the area of the effect it is likely that only anodal stimulation was given. The increase in glutamate would imply the validity of the previous assertions that anodal stimulation is excitatory in nature. However, it is noted that these increases did not last beyond the period of stimulation, so it is still unclear as to what effects tDCS is having post-stimulation. It is also still unclear what effects tDCS is directly having on neural activity as this study only analysed the concentrations of neurotransmitters. The present research aims to plug this gap by looking at a variety of frequency bands whilst tDCS is being administered using simultaneous acquisition of tDCS and oscillations recorded with MEG.

Simultaneous acquisition of MEG and tDCS

Attempting to acquire MEG data whilst also stimulating using tDCS presents unique challenges. Due to the nature of MEG it is very sensitive to other electrical fields and the electrical fields produced by tDCS are many orders of magnitude greater than those produced by the brain. As result

there are complications caused by artefacts in the data. Work in the area of transcranial Alternating Current Stimulation (tACS) and EEG/MEG provide some insight regarding these challenges. TACS is a very similar electrical stimulation device to tDCS, but rather than provide a constant current that is either positive (anodal) or negative (cathodal) it fluctuates between them at a frequency defined by the operator. Previous attempts to acquire both tACS and EEG/MEG have used a variety of techniques to counteract the electrical artefacts produced when using transcranial electrical stimulation devices. For example, one study utilised an independent/principal component analysis paradigm constructing an artefact template and subtracting this from the actual artefact data (Helfrich et al., 2014). Another subtracted the signal from two reference electrodes from every other electrode and then passed a filter that was notched at the stimulation frequency of the tACS device (Voss et al., 2014). However, it has been noted that by using simple subtraction such used in both Voss et al. (2014) and Helfrich et al. (2014) there is a risk of removing actual data as well as artefactual data if the frequency of interest and the frequency of stimulation happen to align (Neuling et al., 2015). It is also worth noting that both Neuling et al (2015) and Voss (2014) are tACS experiments, and while this is a similar device does present differences to tDCS. It is therefore preferred that another method is used. It is also worth noting that the previous studies were both EEG experiments. Due to the fact that both the tDCS/tACS electrodes and the EEG electrodes need contact with the scalp this creates competition for space meaning less EEG data and lower spatial specificity. Using MEG would allow for the application of tDCS/tACS

electrodes without losing any channels as the SQUID does not actually need contact with the head. Further, beamforming techniques commonly used in MEG analysis can also be used to remove the artefact produced by the stimulation (Neuling et al., 2015; Soekadar et al., 2013). Soekadar et al (2013) used synthetic aperture magnetometry (SAM) to suppress the artefactual activity produced from tDCS originating outside the brain i.e. the electrodes and then reconstruct this data within the brain. Neuling et al (2015) performed a similar analysis routine on their tACS data, only instead of using a SAM beamformer they utilised a linearly constrained minimum variance (LCMV) beamformer. Using these beamformer techniques it is now possible to simultaneously acquire MEG and tDCS datasets allowing for a more in depth analysis of the true effects of tDCS on neurological activity, utilising these methods to investigate the .

Clinical applications of tDCS

The use of tDCS in a clinical setting is on the rise. It has been used in treating a host of conditions such as pain, depression, dementia and tinnitus (Kuo, Paulus, & Nitsche, 2014) and while its effects are contested (Horvath et al., 2015; Yokoi et al., 2015) it continues to be explored as a treatment and therapeutic option. Transcranial direct current stimulation (tDCS) is of interest for tinnitus researchers as it can induce temporary suppression of tinnitus (Sven Vanneste, Walsh, Van De Heyning, & De Ridder, 2013). A review and meta-analysis on the effects of tDCS on tinnitus perception found that 39.5% of tinnitus participants who underwent tDCS treatment responded with a mean tinnitus loudness reduction of 13.5% (Song et al.,

2012), these numbers may seem small initially, but it is important to note that at the time of the study, there were few published articles relating to tDCS effectiveness in tinnitus, and so were the same study conducted again today, the reduction may be greater. Further to this, there is some evidence to suggest that tDCS may be capable of having an effect on RI, with more people exhibiting RI whilst being stimulated, though further work is required to confirm this (Shekhawat, Kobayashi, & Searchfield, 2014). In a study by Shekhawat et al. (2014), tinnitus participants were asked to continuously adapt the minimum masking level (MML, i.e. the minimum sound level at which the tinnitus could no longer be heard above) required to mask their tinnitus for 5 minutes using a broadband noise (BBN) prior to anodal tDCS, 20 minutes during tDCS and 30 minutes after tDCS. Participants were also asked to provide a tinnitus loudness rating both at the start of testing and at the very end. In addition to the MML measurements and the tDCS, RI was also induced by increasing the MML by 10dB for 1 minute. The RI was induced at one of three points, either before tDCS, during tDCS or after tDCS. A tinnitus loudness rating change was calculated by subtracting the baseline loudness rating from the loudness rating given at the end. It was found that in 7 out of 9 cases, there was a rated improvement in tinnitus symptoms when RI was presented at the same time as tDCS. However, this improvement was not found to be statistically significant. There are two possible reasons for this, firstly that the BBN was not loud enough to elicit effective RI. Previous work has found that a more effective volume increase would have been 65dB (Roberts et al., 2008). Further, the length of time between the BBN offset and

the next tinnitus rating may have been too long. In the study, a full 30 minutes elapsed before participants were asked to rate their tinnitus again. As previously mentioned, the RI typically last under 2 minutes in the majority of cases (Meikle et al., 2004) and so there is a quite considerable gap between offset and rating. It is possible, that the authors deemed this appropriate as tDCS has been found to have effects that can last up to 90 minutes following stimulation for a prolonged (above 20 minutes) period (Nitsche & Paulus, 2001).

One of the chief measurements of Shekhawat et al. (2014) was the continuous tracking of the MML. Precisely what lowering the MML means in terms of tinnitus oscillatory activity is unknown as there have been no studies to the author's knowledge which have examined effects of maskers on ongoing oscillations. With this in mind, it is timely to investigate the effects tDCS can have on ongoing neural activity, not only with regards to the relevant brain frequency bands, but also in response to the masker noises used to induce RI. In order to do this, participants will be presented with tDCS in either an active or sham condition whilst being exposed to the masker noises in the MEG scanner. They will also be asked to engage in a simple perceptual task, in order to assess the effects of combined tDCS and masking on auditory processing ability. If tDCS can modulate responses to an external sound, it is quite reasonable to assume it is capable of doing the same to the internally generated sound of tinnitus as these operate on the same auditory pathways. This experiment will concentrate on aiding and understanding the combination of two tinnitus perception modulators, RI and tDCS by focusing

on basic and, as yet, unanswered questions regarding neural activity in non-tinnitus controls in response to masker type sounds. By identifying changes in the ongoing neural oscillatory activity in response to white noise maskers in non-tinnitus controls, we can better understand the neural changes that occur in participants with tinnitus as they experience RI. Neural differences between tinnitus participants related to tinnitus inhibition has the potential to identify subtypes of the tinnitus disorder, for example if consistent differences could be observed in neural activity between those who experience RI compared with those who do not, this could be used to identify a subset of the tinnitus population who are likely to respond to masker therapies. The present work is based upon the previous work investigating this combination carried out by Shekhawat et al., (2014).

5.1.3 Aims and Hypotheses

The main aim of Experiment 3 was to carry out an investigation of the effects of tDCS on auditory cortical oscillations. It aimed to do this by utilising the analysis techniques developed by Neuling et al., (2015), and conducting a concurrent MEG/tDCS experiment. Based upon the findings of Shekhawat et al., (2014) where tDCS in combination with RI was capable of increasing inhibition of tinnitus, we hypothesise an increase in alpha band (8-13Hz) oscillatory power which is associated with inhibitory mechanisms. In line with the findings of Shekhawat et al. (2014) where tDCS was able to influence the length and depth of RI, we also anticipate that tDCS will be capable of modulating the perception of the tone, providing longer periods of masking post-stimulus.

5.2 Methods

5.2.1 Ethics

Informed consent was obtained prior to participation and the study was approved by the local ethics committee at the University of Trento.

5.2.1 Participants

A total of 11 healthy participants took part in the study after having the experimental protocol described to them (6 female, age range: 18-34, mean age: 29 years). Participants were recruited using a Facebook page specifically designed to advertise experiments happening at the university.

5.2.2 Equipment and Apparatus

MEG data was recorded using a 306 channel axial gradiometer Elekta Neuromag magnetoencephalography machine (Elekta Oy, Finland) at a sampling rate of 1000Hz. To localise the head in the scanner and monitor head movement, three fiducial points (nasion, left and right post auricular points), and five Head Position Indicator (HPI) coils were attached to the head before data collection. Moreover, to co-register the MEG data with each person's MRI scan, ~200 head shape points were acquired using a head shape digitiser (Polhemus, Vermont, USA) for each subject before the scanning commenced. The stimulus presentation program was coded using Psychtoolbox for Matlab (Mathworks Inc, Natick MA, USA). Auditory stimulus were presented using a set of etymotic pneumatic stereo ear pieces attached to a Datapixx system (VPixx, Saint Bruno, QC, Canada). All visual stimuli were

also presented using the Datapixx system and were back projected onto a screen place in front of the participant. Responses were collected using a Datapixx Responsepixx system, consisting of two buttons. Electrical stimulation was administered using a Neuroconn DC-Stimulator Plus device (Neuroconn, Ilmenau, Germany), the electrodes were inserted into saline soaked sponges and held in position using a rubber swimming cap. The electrodes were positioned according to the method proscribed by (Shekhawat et al., 2014) and denoted in figure 5.1, with the anode positioned midway between T3 and T5 and the cathode midway between F8 and T4.

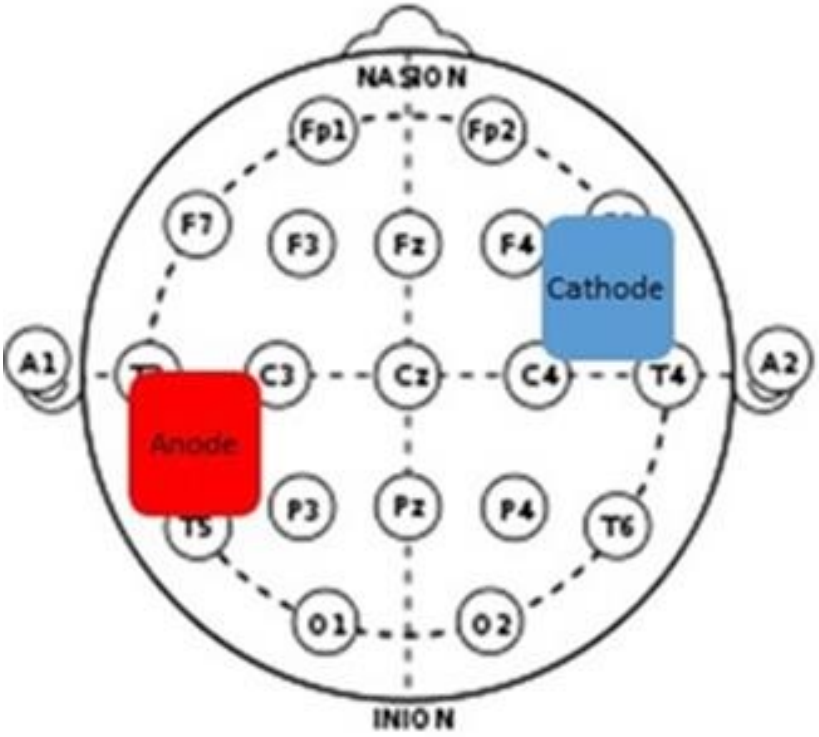


Figure 5.1: The positions of the electrodes of the tDCS device as presented on an example EEG 10-20 system. In our set up, the anode was the active electrode, passing a positive current through brain to the cathode.

Before experiment 3 began participants were required to undergo a simple test to assess the threshold of hearing for a simple white noise (0-22kHz)

generated in Adobe Audition™. This was carried out in the form an adaptive up/down staircase. The staircase procedure was developed using the Palamedes toolbox extension for Matlab and was designed to take the 50% threshold of the masker noise. Participants were played a reference tone and at a random point within 2 seconds were presented with 1 second of white noise. They were then prompted via the program as to whether they heard the white noise or not. If the participant responded that they had heard the noise (i.e. a positive response), the volume level was dropped by an intensity of 0.001, if they responded otherwise the volume was increased by 0.001. The 50% threshold was located by assessing the volume at which the participant was experiencing frequent "reversals" i.e. flipping from a positive to a negative response and vice versa on adjacent trials (see figure 5.2 for an example). This adaptive staircase procedure was similar to that which was used in the main experiment. Further to this, a threshold was obtained for perception of the tDCS stimulation. This was done via verbal feedback. All tDCS following this was administered at the participant's threshold so they could not perceive it.

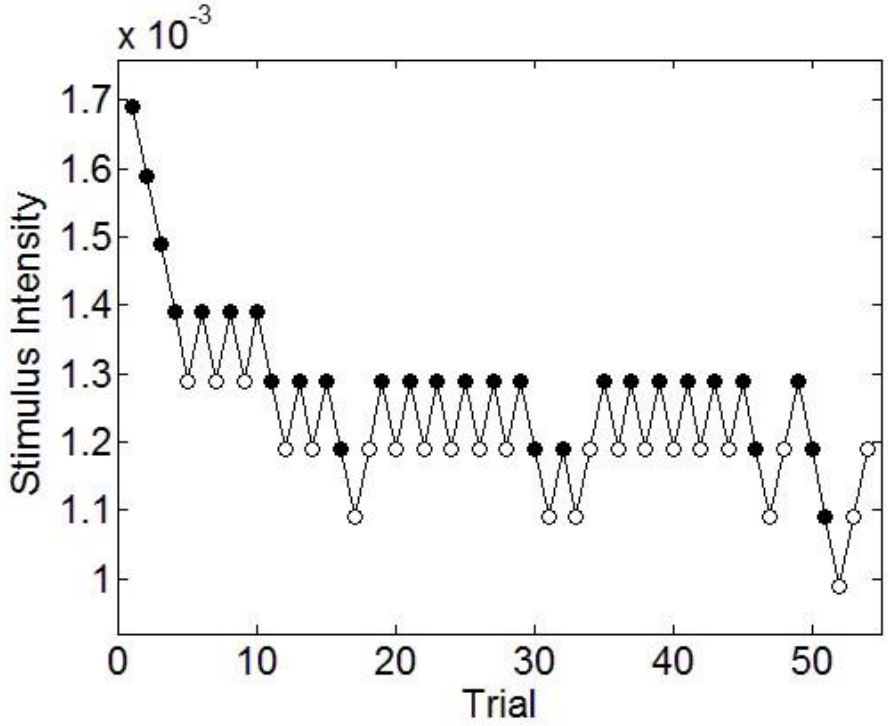


Figure 5.2: An example of a completed up/down adaptive staircase for the masker threshold. In this instance the 50% stimulus perception threshold was assessed (i.e. the participant was required to get 1 positive responses before the intensity was lowered and 1 negative before it was raised. Black dots indicate positive responses, white dots indicate negative. The step size for this test was 0.01.

5.2.3 Experimental Protocol

Figure 5.3 outlines an example of a typical trial in the main experiment. Participants were seated in an upright position in the MEG scanner and instructed to avoid moving during the experiment with the exception of pressing the button. On all 320 trials participants were first exposed to 5 seconds of white noise presented at 50dB above their previously ascertained hearing threshold. Following this, on 50% of the trials (160/320) a 50ms pure tone was presented at 1 of 4 time points – 50ms, 250ms, 450ms or 650ms. Each time point accounted for 25% (40/160) of the trials in the 160 where a tone was played and 12.5% of the total trials in the experiment. In the remaining 50% (160) of trials, there was no tone presented. In both cases, whether a tone was played or not, a 2.5 seconds

(minus the length of the tone if one was played) period of silence followed and participants were then asked whether or not they heard a tone. They were given a further 2 seconds to respond to this question using a ResponsePixx 2 button box.

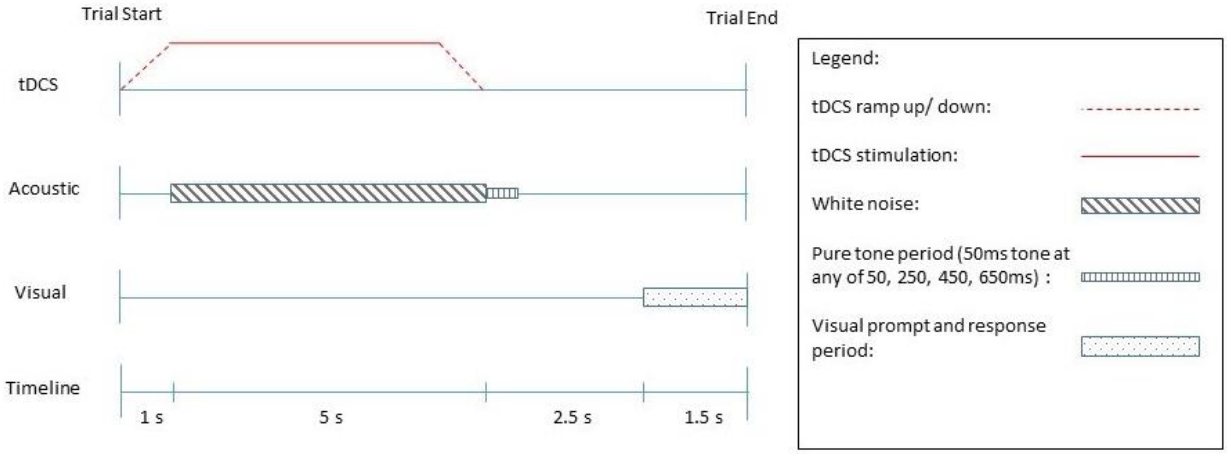


Figure 5.3: Stimulus presentation timetable for a trial involving both a pure tone and anodal stimulation. A tone was presented on 50% of the trials, at one of the 4 time points (50, 250, 450 and 650ms). In both tone and no tone trials, this was followed by a period of 2.5 seconds (minus the 50ms if a tone was played) and then a 2 second period where the participant was required to make a rating. On the sham tDCS trials a very weak stimulation was applied rather than the full anodal stimulation.

If the participant correctly determined that a tone was played when one was played 3 times in a row for each individual time point, then the stimulus intensity of that tone was lowered by .001. If they did not perceive a tone when one was played then the intensity of the corresponding time point was increased by .001. This was in accordance with a 3-up, 1-down adaptive staircase similar to the one proscribed for the masker threshold test but requiring three correct responses in order to lower the intensity, rather than

just one. The intensities were tracked like this for each time point across each stimulation condition i.e. for time points 50, 250, 450 and 650ms in each of the sham and anodal conditions for a total of 8 thresholds.

5.2.4 Data Analysis

5.2.4.1 MEG Data Analysis

Analysing the MEG data presents with a number of challenges that are similar to those encountered by Neuling et al (2015) in their proof-of-concept study investigating simultaneous MEG and tACS. Insofar as the tDCS produced a very large artefact that permeated all the sensors in the MEG scanner and so was impossible to eradicate in sensor space (Figure 5.4, top panel).

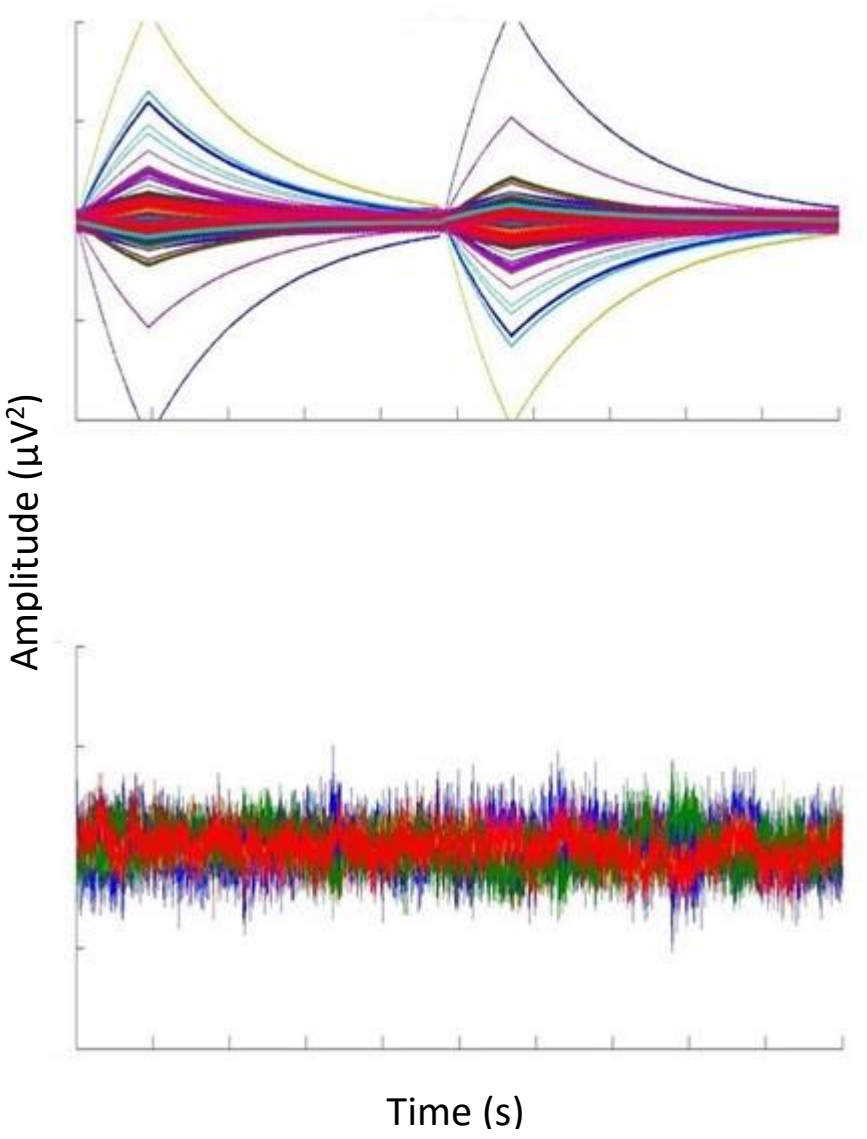


Figure 5.4: Visual Representation of the preprocessed data (top) and the data after beamforming (bottom) for one participant. The tDCS artefact can be clearly seen as the rising and falling pattern in the top plot. Both plots show the data for all sensors across one full trial. Note how the tDCS artefact permeates all the sensors of the MEG scanner.

For analysis, we followed a similar method to the one proscribed in the paper by Neuling et al (2015), in that we avoided sensor space analysis in favour of Linearly Constrained Minimum Variance (LCMV) beamformers (VanVeen, vanDrongelen, Yuchtman, & Suzuki, 1997) to project the data directly into source space. The beamformer itself functions as a spatial filter. Its ability to

reduce noise in the data has been well documented (Adjamian, Hadjipapas, Barnes, Hillebrand, & Holliday, 2008; Hillebrand, Singh, Holliday, Furlong, & Barnes, 2005). In this instance, the spatial filtering properties of the beamformer are what enables it to nullify the tDCS artefact. We constructed an individual beamformer for each point on each individual participants head shape, this enabled us to safely dismiss the tDCS as all the activity from the tDCS would be originating from points outside this grid. Thus the beamformer is able to effectively eliminate the artefact caused by the tDCS (see figure 5.4). The output of the beamformer is a virtual sensor which was applied to 889 points across the brain using the procedure described in Matlab's Fieldtrip Toolbox (R Oostenveld et al., 2011). Each individual point corresponded to one point on a grid of 889 points equally spaced by 1.5cm in Montreal Neurological Institute (MNI) space. This grid was then then warped to each participants individual head shape obtained prior to the experiment. The virtual sensor consisted of a covariance matrix for each trial was obtained which was then averaged across all trials. Using this, the head model obtained from the individuals head shape and the lead field matrix the beamformer filter was constructed. We were then able to continue with the analysis. A time frequency analysis was then conducted. This broke down the averaged signal into its component frequency bands and displayed them over the course of a whole trial, allowing us to ascertain the oscillatory effects of the tDCS over time.

In order to detect any significant changes a cluster based permutation statistical test was employed. Given that we are testing for differences

between many hundreds of channel-time pairings in each condition, if we employed a traditional statistical method we would surely encounter the multiple comparisons problem resulting in a number of false alarms. By using cluster based permutation statistics we can avoid this problem (Maris & Oostenveld, 2007). The test is described in full in Maris and Oostenveld (2007) but a brief description is also given here. The test works by first running t-test statistics on each channel-time pair. Groups of channels in each discrete time point are then clustered together based upon the value of the t-statistic (if it exceeds a defined absolute value). The sum of these absolute t-values is then calculated for each cluster. Following this, the data is permuted i.e. the conditions are randomly swapped in the data and the process is repeated. The sum of the absolute t-values for both the observed clusters and the permuted clusters and then tested to see if they differ significantly. If they do then this is counted as a either a significant positive cluster or a significant negative cluster, depending on the direction of the difference.

5.3 Results

5.3.1 Participants

All 11 participants who were recruited initially (6 female, age range: 18-34, mean age: 29 years) completed the experiment, with no drop outs.

However, one dataset was excluded from the analysis due to technical difficulties in data collection, leaving 10 complete data sets.

5.3.2 Behavioural Results

A number of technical difficulties presented themselves during the collection of the behavioural responses. For certain trials no responses were recorded by the experimental program, and for others it did not update the stimulus intensity levels. These problems are discussed in more detail later, however, enough usable trials were collected from each participant to allow for a statistical analysis.

The Effects of Anodal Stimulation on Tone Perception

We initially hypothesised that anodal tDCS would be capable of extending the period of perceptual suppression following stimulus. In order to test this hypothesis, an ANOVA with two within-subject factors, time point with 4 levels (50, 250, 450 and 650ms post masker), and simulation condition with two levels (anodal and sham) was constructed. There were no significant effects of time point (F (4, 7) = .869, p = .501) or stimulation conditions (F (2, 9) = 1.203, p = .301). Nor was an interaction observed between stimulation and time point (F (4, 7) = .933, p = .474). The difference between the two stimulation conditions is very slight, but a trend can be seen developing in terms of the stimulus intensity across stimulation conditions in figure 5.5, with anodal stimulation resulting in higher stimulus intensity's across all time points, when compared with anodal stimulation. This would appear to indicate anodal stimulation is decreasing perceptual sensitivity to pure tones.

However, the large confidence intervals suggest this observation may not be very robust.

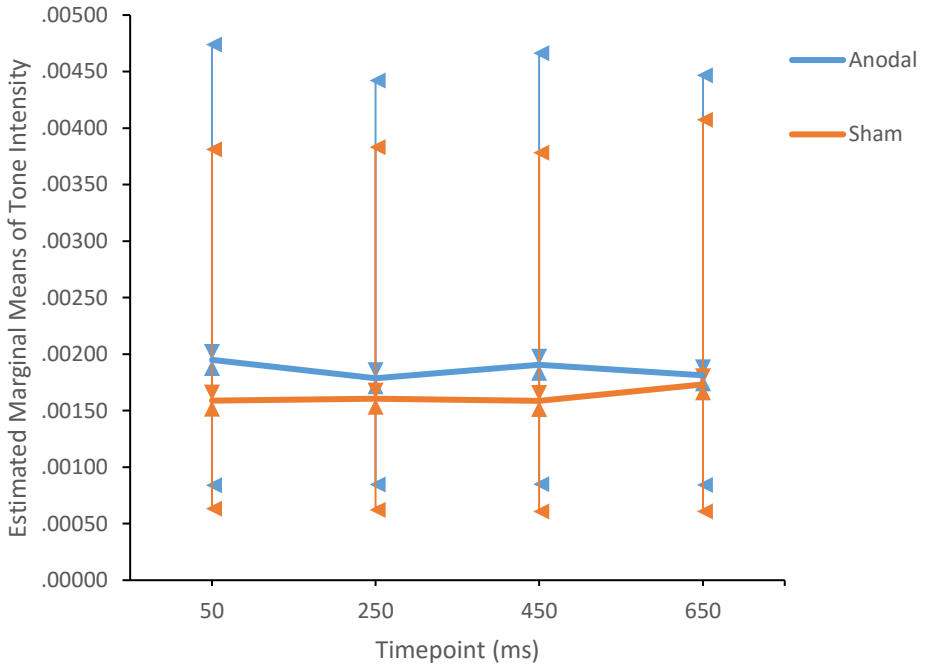


Figure 5.5: The estimated marginal mean stimulus intensity for each time point and across each stimulation condition, with 95% confidence interval error bars that are colour coded to the relevant condition. The plot shows a slight trend developing that anodal stimulation results in tones of a higher intensity being required to elicit perception.

5.3.3 Effects of stimulation Neural Activity

5.3.3.1 Confirmatory Analysis

A confirmatory evoked response and source analysis was conducted on a single participant's data in order to confirm the suitability of our data acquisition and analysis methods. The analysis was performed on the first 100ms immediately after the presentation of the white noise and tDCS stimulus. During this time, a pure tone was presented and as a result of this, it was expected that an auditory evoked response would be observed. This

was found to be the case, confirming our analysis protocol. The resulting evoked response and its localisation to the auditory cortex can be seen in figure 5.6.

5.3.3.2 Effects of stimulation on Evoked Responses

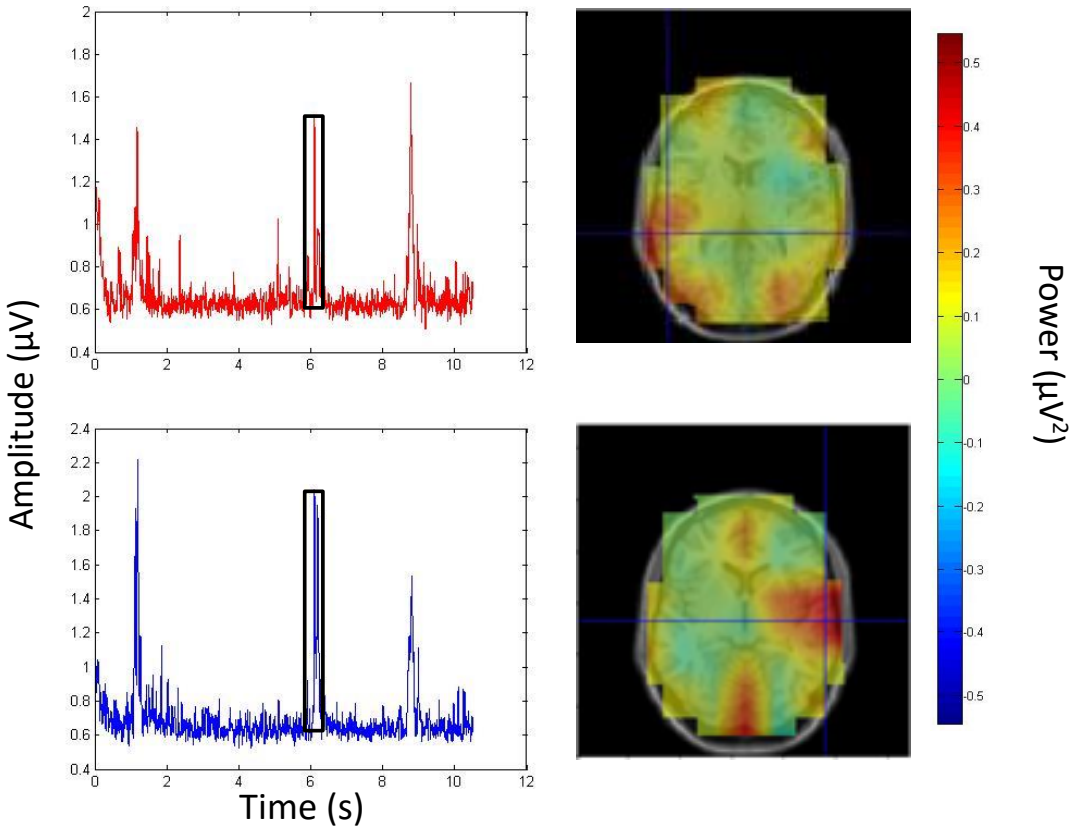


Figure 5.6: Confirmatory evoked response and source analysis on a single subject. The top half of the figure, in red, is the evoked response and source localisation from the anodal condition. The bottom half depicts the evoked response and source localisation from the sham condition.

We did not make any specific hypotheses regarding the effects of anodal stimulation on the evoked responses. However, given we anticipated significant changes to the perception of the tone following stimulation it seemed pertinent to carry out an exploratory investigation into the effects on

the evoked responses. To carry out this analysis, the MEG raw data for each participant was time locked to 1 second before the onset of the masker. This data was then grand averaged across all participants and channels across all tone presentation time point/stimulation pairings. Figure 5.7 show the grand-average Evoked Response Field (ERF) data across all participants and for each tone presentation and stimulation condition pairing. The most notable difference between the sham and anodal conditions is the additional spike in amplitude occurring at 4 seconds in all of the anodal/tone pairings that is absent in the sham data. However, this was assumed to be artefactual in origin, as there was no additional stimulus at this time that could have elicited this response, as such it is not analysed any further. In addition, this artefact was likely due to difficulties in timing the length of the masking stimulus precisely between the two stimulus conditions. As a result of which, it is not pertinent to analyse any of the neural data following the offset of the masker, as across the two conditions, the timings of the trials were no longer matched. The following analysis will therefore concentrate on the analysis of the masker onset and the period during the masker presentation. There appears to be some modulation of the response to onset of the white noise (0-1 seconds), with the anodal condition eliciting responses of lower amplitude. Based up these observations, the evoked responses at 0-1 seconds was chosen to analyse further. A cluster-based permutation approach was chosen to statistically analyse the data in order to compensate for the multiple comparison problem.

Effects of anodal tDCS on the masker onset response

Where each tone presentation condition was analysed separately, significant changes between the amplitude of the evoked response in the anodal and sham stimulation conditions were observed only in the 450ms tone presentation condition. Significant reductions in amplitude between the sham and anodal conditions were found between 0.47-0.50s (p = .03), and again between 0.71-0.76s (p = .02). Similarly, a significant reduction in amplitude was present when the tone conditions were collapsed between 0.42-0.51s (p =<.01). In the conditions where no tone was presented, significant reductions in amplitude were seen between 0.35-0.44s (p = <.01), 0.58-0.66s (p = .01) and 0.79-0.94s (p = <.01). All the significant clusters observed were reductions from sham to anodal stimulation, suggesting that the primary effect of the anodal stimulation was that of reducing amplitude of evoked responses to the onset of sounds.

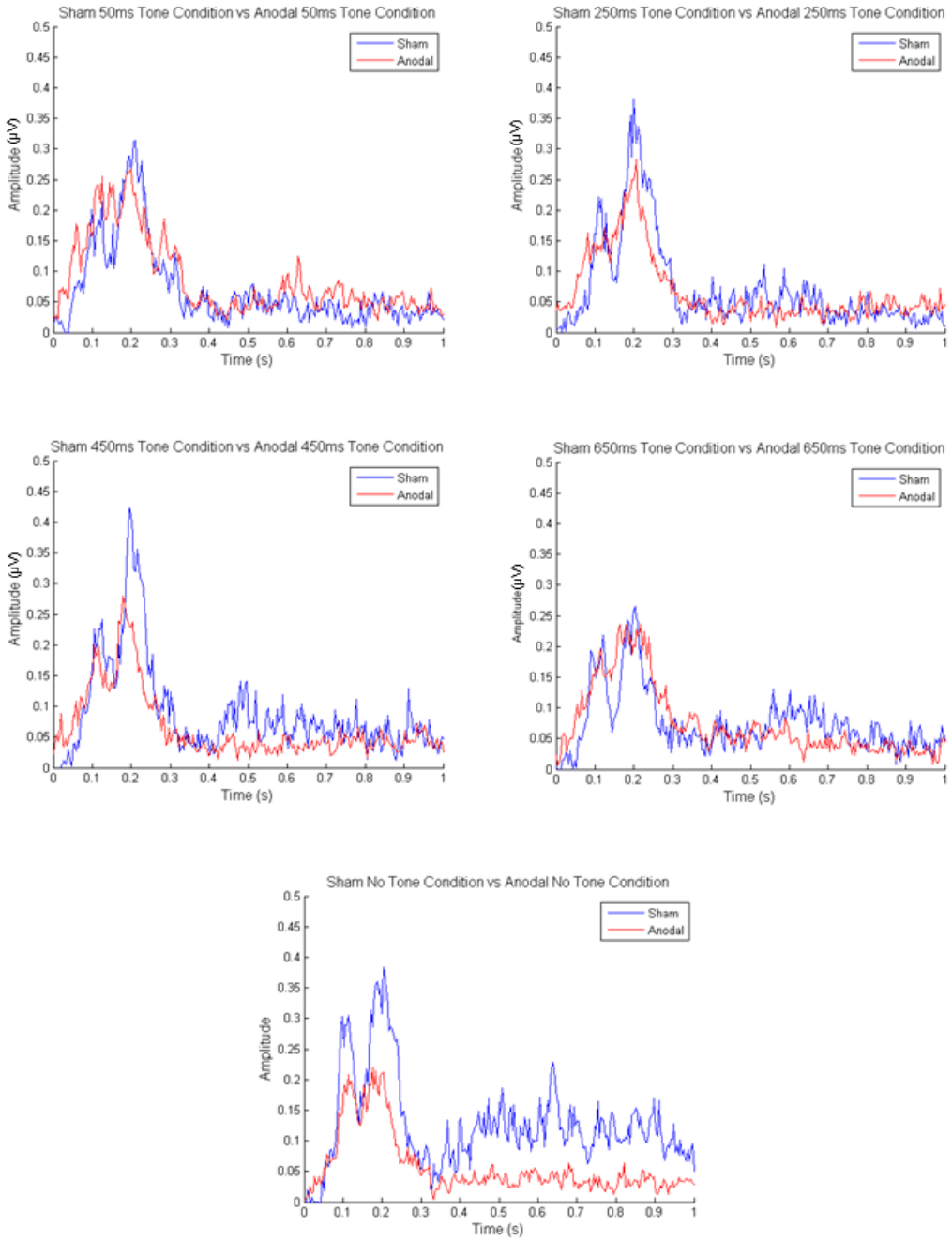


Figure 5.7: Evoked Responses Fields for the first second of each tone presentation condition. The anodal condition (red) is overlaid onto the sham condition (blue). From the top left and working clockwise the conditions are: 50ms Tone Presentation, 250ms Tone Presentation, 450ms Tone Presentation, 650ms Tone Presentation and the No Tone Presentation conditions.

5.2.5 Neural Oscillations

Time frequency analysis was performed on the ongoing data for each participant individually for all channels and also for the grand averaged data of all the participants. Prior to plotting, the data was baseline corrected, using the time window between 0.2 and 0.7 seconds as the baseline. This was performed in order to determine any changes in oscillatory power across the whole trial. The plots for each tone condition are shown in figures 5.8 and 5.9. We then selected a post-stimulation window of 6-8 seconds and two frequency bands, delta (1-4Hz) and alpha (8-13Hz) to investigate statistically. These were selected based upon the observed time-frequency representations and upon our hypotheses.

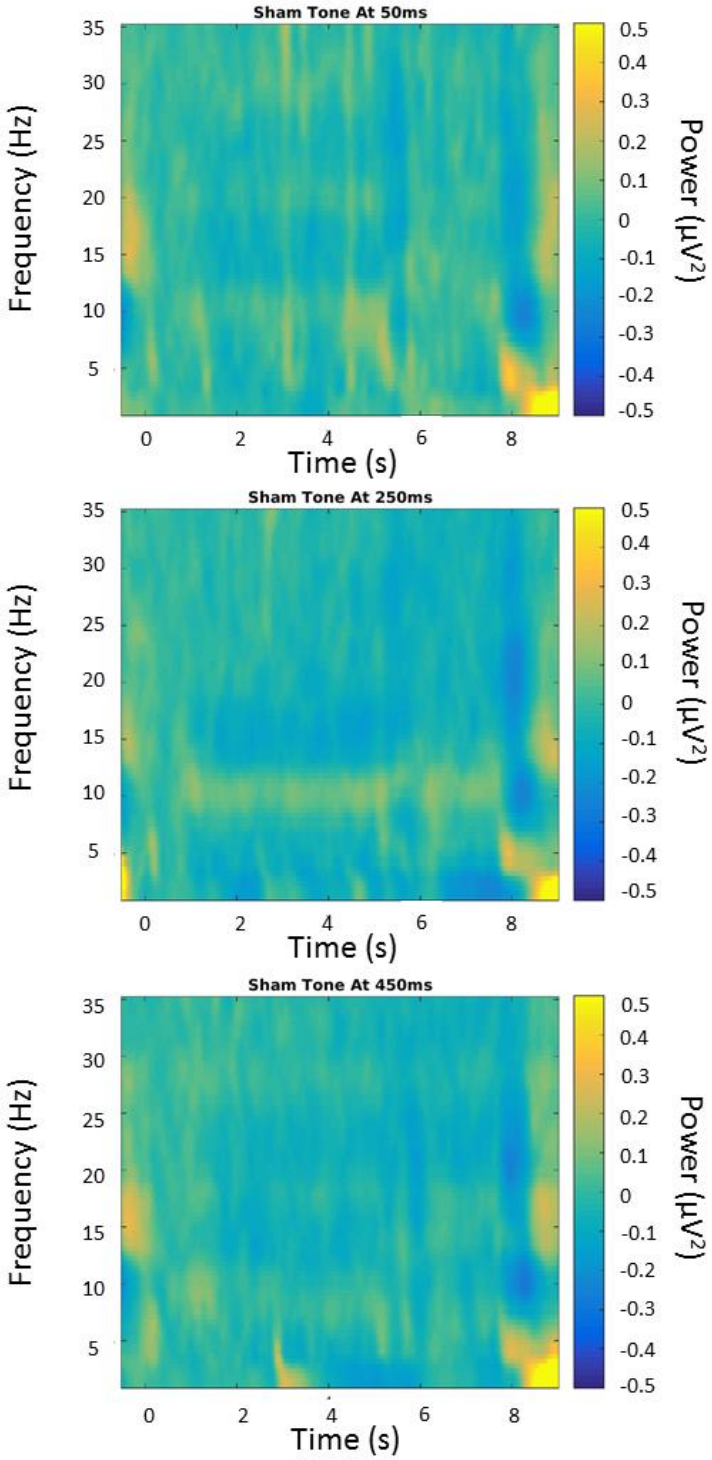
Modulations in delta band activity

Owing to the fact that this study was performed on healthy, normal hearing control subjects, we did not hypothesise any modulations to delta activity. However, a consistent decrease in delta (1-4Hz) power across all the anodal conditions immediately post stimulation (6-8s) when compared with their respective sham conditions can be clearly seen in the time frequency representations shown in figures 5.8 and 5.9. This decrease is also evident when all the tone conditions are collapsed together as shown in figure 5.10. A significant negative cluster was observed in the 50ms tone timing condition between 6.00-6.95s (p = <.01). Significant negative clusters were also observed in the 250ms tone timing condition between 6.00 - 6.35s (p = <.01), in the 450ms condition between 6.00 – 6.25s (p = <.01), and 6.25 – 6.55s (p = .02) and in the 650ms tone presentation condition between 6.00 – 6.35s (p =

.01) and between 6.00 – 6.55s (p = .02). A significant cluster was also observed when all the tones were collapsed, between 6.00–7.70s (p = <.01) and when no tones were played between 6.00 – 6.90s (p = <.01), 6.00 – 6.60s (p = <.01) and 7.30 – 7.90s (p = <.01). All these clusters indicated a negative change in power, meaning that the power of the delta oscillations was significantly lower during this time points in the anodal condition than in the sham condition.

Modulations in alpha band activity

There is also a visible increase in the alpha band (8-13Hz) post stimulation in the anodal no tone condition, though this is not present in any of the individual tone plots or the collapsed tone plots. Cluster-based permutation statistics revealed a significant cluster in the condition where no tone was presented between 7.65 – 8.00s (p = .049). This cluster indicated a positive change, showing an increase in alpha band power during this time.


Sham Tone At 50ms
Frequency (Hz)
Time (s)
Power (μV²)
Sham Tone At 250ms
Frequency (Hz)
Time (s)
Power (μV²)
Sham Tone At 450ms
Frequency (Hz)
Time (s)
Power (μV²)

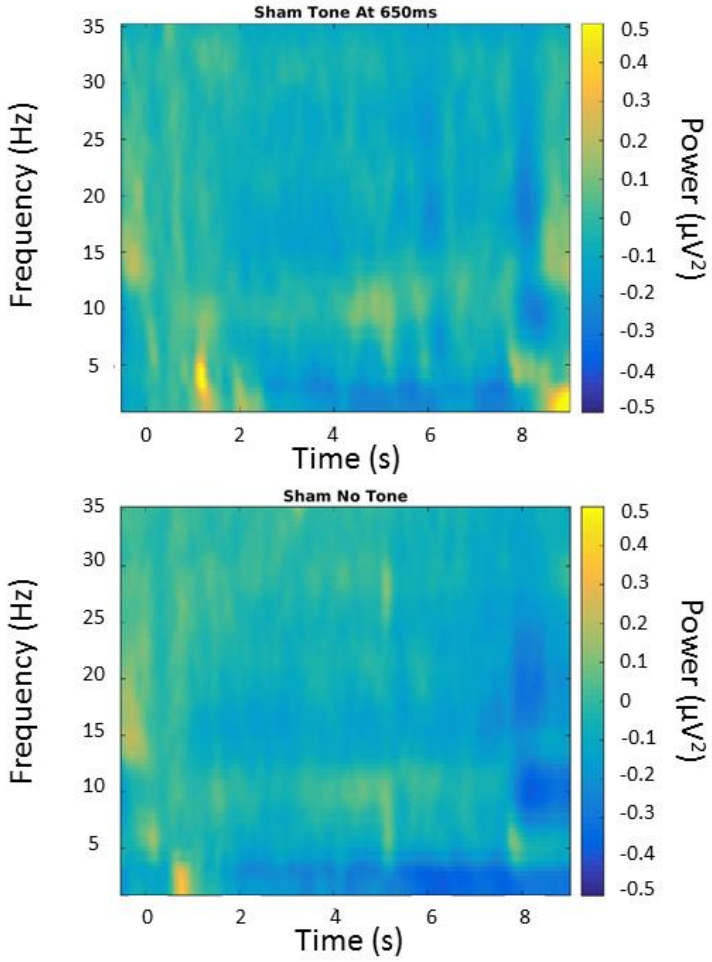
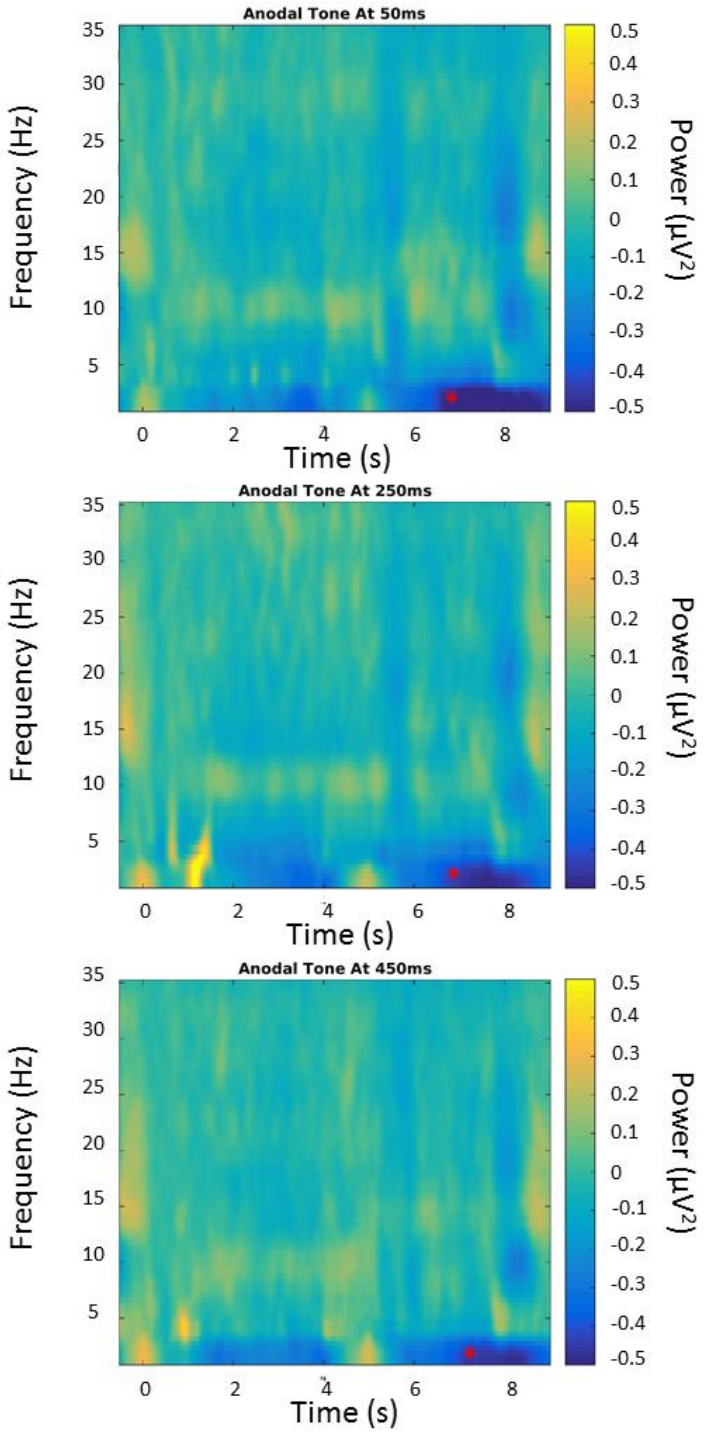


Figure 5.8: Time frequency representations for each of the tone conditions in the sham stimulation condition averaged over all participants and channels.


Anodal Tone At 50ms
Frequency (Hz)
Time (s)
Power (μV²)
Anodal Tone At 250ms
Frequency (Hz)
Time (s)
Power (μV²)
Anodal Tone At 450ms
Frequency (Hz)
Time (s)
Power (μV²)

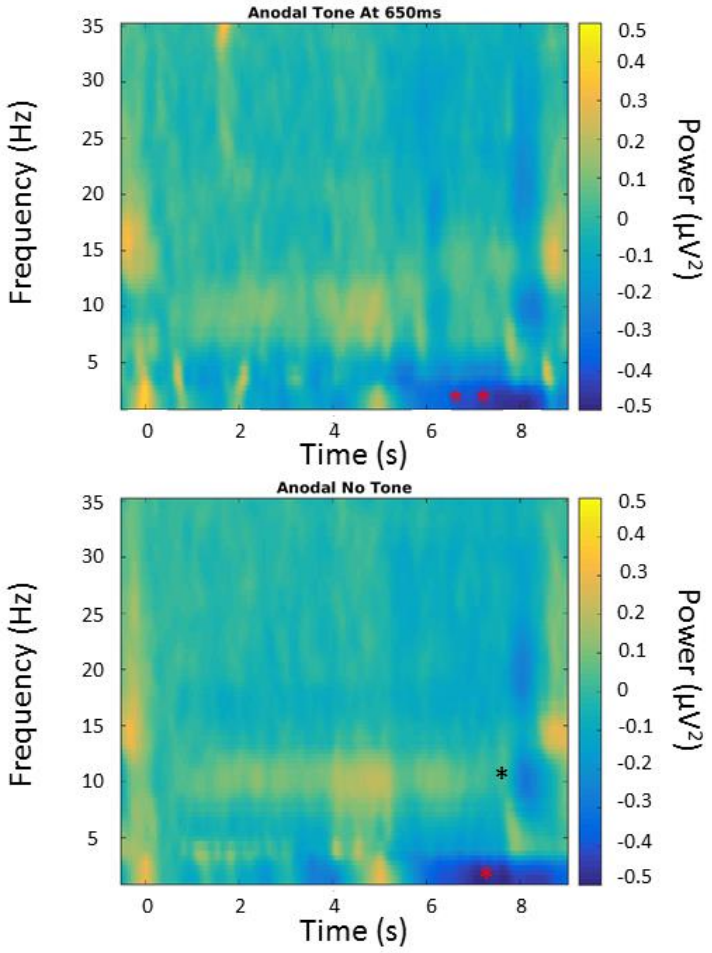
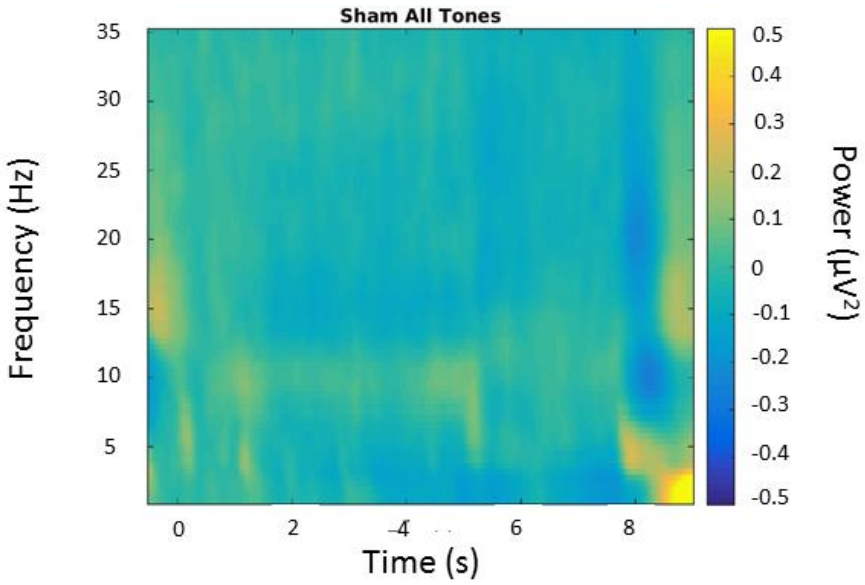


Figure 5.9: Time frequency representations for each of the tone conditions in the anodal stimulation condition averaged over all participants and channels. The red asterisks denote areas where significant reductions in delta (1-4Hz) power occurred compared with the corresponding condition in the sham condition. The black asterisk denotes a positive increase in alpha (8-12Hz) power compared with the corresponding sham condition.



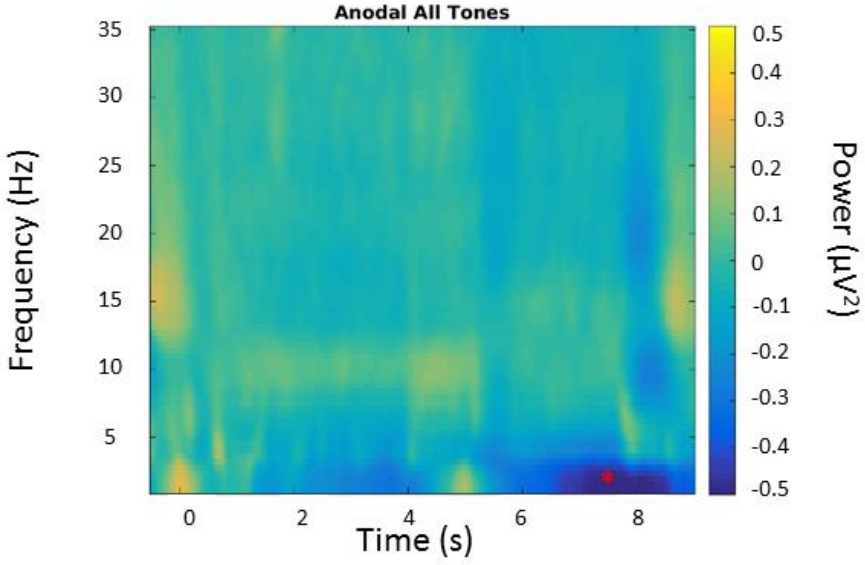


Figure 5.10: Time frequency representations for the sham and anodal conditions collapsed over the tone presentation conditions averaged over all participants and channels. The red asterisk denotes a significant reduction in power between the anodal and sham conditions in the delta (1-4Hz) power band.

5.4 Discussion

5.4.1 Behavioural Results

A slight trend is seen to be emerging with the amplitude of tones presented in conjunction with the anodal stimulation consistently requiring lower stimulus intensities to maintain a 50% detection rate. This would imply that the tDCS is having an effect on perception of tones as well as on oscillations, however these differences were not significant. It should also be noted that there were some technical difficulties with the collection of the behavioural results. A problem with stimulus delivery mean that on some trials where a tone should have been presented, no tone was presented and on others where the amplitude of the tone should have been modulated based on the participant's response no modulation took place. Owing to the difficulties in the collection of the behavioural data and the potential trend observed this particular part of the experiment may warrant further investigation and a repeat study. A number of previous studies have demonstrated and investigated the behavioural effects of tDCS on various auditory tasks (Heimrath, Fiene, Rufener, & Zaehle, 2016). Including finding changes in pitch discrimination (Mathys, Loui, Zheng, & Schlaug, 2010; Matsushita, Andoh, & Zatorre, 2015), pitch memory (Schaal, Williamson, & Banissy, 2013) and random gap detection (Ladeira et al., 2011). However no work to the author's knowledge has been conducted on tone detection such as was done here. This indicates a further gap in the literature which should be addressed in future studies.

5.4.2 Modulation of Evoked Responses

It is interesting to find that there is an effect of tDCS on the onset of the masker, given that at the time points in question are before the tDCS has ramped up to its full output. Of even more interest is the finding that this is somehow linked to the tone time point presentation conditions, as when each time point was analysed individually only 1 (450ms) came out significant. This finding demonstrates that even very low intensity anodal stimulation presented for very short durations is capable of having an immediate effect on neural responses to the onset of a stimulus. The effects of tDCS on auditory evoked responses have been reported previously. Zaehle et al. (2011) reported increased auditory cortical P50 amplitudes in response to a 1kHhz pure tone following anodal stimulation applied over the temporal regions. However, here we report a significant reduction in the amplitude of the evoked response. There are several possible reasons for this difference in findings. Firstly, Zaehle et al. (2011) were looking specifically at the N50 responses 200ms tone. Conversely we examined the amplitude over an extended period (1s) of time and also in response to the onset of an extended (5 second) stimulus. Previous work on visual evoked responses has revealed that there are differing effects of anodal tDCS on evoked potentials of differing latencies. For example anodal stimulation has been found to decrease the amplitude of the P100 visual evoked response (Accornero, Li Voti, La Riccia, & Gregori, 2007) but increase the amplitude of the N70 response (Antal, Kincses, Nitsche, Bartfai, & Paulus, 2004). It is feasible therefore, that the same differences in effect exist within the auditory cortex

and the discrepancy in our finding is the result of a mismatch in the types of evoked potential being analysed. We also found significant decreases in the amplitude of the evoked responses between 8 and 9 seconds. Given the timing of these responses it is likely that this is a visual evoked response to the prompt, asking participants whether or not they heard a tone being played. This decrease is consistent with the previous findings of Acconero et al. (2007) but again not Antal et al. (2004). It is probable therefore, that the evoked potentials observed here are occurring later in the processing stages. This difference in response to tDCS at for different evoked responses has been attributed to a number of mechanisms (Zaehle, Beretta, Jäncke, Herrmann, & Sandmann, 2011). For example it has already been noted that the effects of tDCS are dependent not just on the polarity of stimulation, but also the types and layers of cell being stimulated (Antal et al., 2004; Creutzfeldt et al., 1962; Utz et al., 2010). Antal et al. (2004) and Zaehle et al. (2011) also note the possibility of the effects of "virtual electrodes" which arise in areas adjacent to the stimulation site and are of the opposite polarity. Stimulation in these adjacent areas may influence the generation of certain evoked responses, and since this stimulation is the reverse polarity of the primary stimulation, it may result in some of the diverging effects that are observed.

5.4.3 Modulations of Oscillations

We initially hypothesised that there would be no modulation in delta band activity as a result of the stimulation. The data presented here shows a clear difference between the two stimulation conditions, contradicting our

hypothesis. The reduction in delta band activity observed immediately post stimulation is almost certainly the result of the anodal stimulation as it is only seen in the anodal conditions. What is puzzling, however, is that this effect was a reduction in power. As previously mentioned, several authors have found that the effects of anodal stimulation were to increase cortical excitability and thus enhance firing rates (Bindman et al., 1962; Nitsche & Paulus, 2000; Pupura & McMurtry, 1965). What we have observed is a decrease in firing rates, which would appear to be in disagreement with these findings. It is possible that this decrease is in fact reflecting a large increase in delta band oscillations that occurred during the stimulation window. The data plotted in the TFR's of figures 5.9, 5.10 and 5.11 was calculated as a change in power relative to a baseline. This baseline was taken from the data from 0-2s-0.7s. This was during the 1s ramp up window of the tDCS. It is therefore feasible that there was such a sharp increase in oscillatory power during this window that the resulting decrease when the stimulation stopped resulted in the drop we observed in the data. However, this theory would imply that the effects of the tDCS were not long lasting, and ceased along with the stimulation. It also fails to address why the significant effect did not extend beyond the average of 0.54s if it was indeed a return to pre-stimulation levels. The lack of longer lasting effects could be explained by the short stimulation time of 5s. There has been no work investigating the minimum length of stimulation to elicit a post stimulation effect, but the maximum duration it is safe to stimulated for is less than an hour (Nitsche et al., 2003). Typically, most studies stimulate for somewhere

between 10 and 20 minutes, though there is little evidence for how this de facto standard has emerged. What remains however, is an interesting finding that tDCS can and does modulate delta frequency oscillations which, to the authors knowledge is a novel finding. Whilst previous work has found tDCS to be capable of modulating the, beta and mu oscillations (Hanley, Singh, & McGonigle, 2016; Lapenta et al., 2013) none found any modulation of delta activity.

A limited increase in alpha band oscillation was also reported following tDCS exclusively in the no tone conditions. The positive increase is in line with both our hypothesis that anodal stimulation should increase alpha frequency oscillations. This finding also confirmed the observation of increased alpha as a result of anodal stimulation found in the proof-of-concept study combining MEG and tDCS by Soekadar et al. (2013). However, as found in the delta modulations, the effect was short, lasting only 0.35s. What is also unclear is why the effect should be limited to the no tone trials or why the onset of the effect was delayed following stimulation. The delay in the onset of the effect may be due to the type of cortex being stimulated. While we aimed to stimulate only the auditory cortex, the nature of tDCS is that it is difficult to control where the current actually flows as it travels from electrode to electrode. As such, it is possible that any number of areas are being concurrently stimulated, not just those that lie directly underneath the electrodes. It is possible then, that the reason that there is a delay in the increase in alpha following stimulation is due to this oscillatory change being elicited in the visual cortex, rather than then the auditory. This would appear

to be supported by the significant differences in the amplitude of evoked responses at the same time. These evoked responses are likely elicited from the appearance on screen of the visual prompt, prompting participants to rate if they heard a tone or not. Given that the modulation of alpha band oscillations occurs at this time also, it is feasible that this is a modulation of a visual cortical oscillation. However, this would imply a longer lasting effect then previously described. Within the delta frequency the effect lasted for under a second, however if this hypothesis is true then the effect can last much longer.

5.4.4 Conclusions and Future Directions

This work has presented a number of novel findings. Firstly, it has demonstrated that the methods outlined in Neuling et al. (2015) for the simultaneous collection of MEG and tACS data can also be applied to MEG and tDCS data. This is an interesting finding as it opens out the field of neurostimulation into new avenues. Much of the work to date has focused on offline effects of tDCS; that is to say, participants undergo stimulation first, and then the device is stopped and the effects on neural activity are then measured using MEG or EEG. Using this method it is now possible to collect data concurrently allowing for far greater insight into the effects of tDCS. This is important, as there has been some dissonance in the field as to the precise effects and mechanisms of action of tDCS (Horvath et al., 2015). Being able to measure the online effects of tDCS would go some way in alleviating these concerns and disentangling what tDCS is capable of

achieving both as a clinical tool and as a method of understanding more basic brain processes.

The second chief finding of this work was that tDCS is capable of modulating auditory cortical oscillations and evoked responses. While the effects of tDCS on auditory evoked responses have been reported previously (Zaehle et al., 2011) the finding that auditory cortical oscillations are also affected is, to my knowledge, novel. What is also interesting is that these changes are observed following such short stimulation lengths. TDCS safety guidelines suggest stimulation lengths of no longer than 15 minutes per session (Nitsche et al., 2003) and typically, experiments stimulate for around this length. Such short periods of stimulation have, to the author's knowledge, not been assessed in detail before. Indeed, this finding could have profound impacts on how tDCS experiments are designed in the future as a typical tDCS experiment will also include a sham condition, in which the device is ramped up to a particular current output over the course of several seconds and then switched off. What we demonstrate here is that even such short simulations can have a lasting effect on neural activity, albeit one of very short duration. This means that even the ramp up could potentially have a lasting effect of neural activity meaning sham stimulation may not be as appropriate as originally thought as a control condition.

Further work should therefore focus on the effects of short duration tDCS, as it is also possible that what we see in this data is a cumulative effect of multiple sessions of short burst anodal stimulation presented in quick

succession. It would also be beneficial to address the technical problems experienced within this study and repeat the behavioural part of this experiment to confirm the trends we observe here and truly assess the impact of tDCS on auditory activity and perception and its potential as a modulator of tinnitus.

Chapter 6 – General Discussion

6.1 Summary of Main Findings

The experiments conducted here present a number of novel findings relating to a variety of characteristics of tinnitus. In experiment 1 it was found that, in accordance with the previous literature, the dominant tinnitus pitch fell within the region of hearing loss (see figure 3.3) for the median audiogram. It was also observed that higher scores on the Hyperacusis Questionnaire (Khalfa et al., 2003) were positively correlated with tinnitus loudness. However, this only extended to tinnitus loudness as measured via the TCHQ questionnaire (Langguth et al., 2007), and not the second measure of tinnitus loudness via the Tinnitus Tester (Roberts et al., 2008).

Experiment 2 found significantly higher alpha and beta oscillatory power in the group of people who experienced RI then in those who did not experience a change in their tinnitus loudness. This was not found to be related to a specific time point or block. Indicating that those who went on to experience RI had higher power in alpha and beta frequencies, which was consistent across the whole experiment. It also confirmed statistically the gradual return and linear return of the tinnitus perception to baseline levels in those groups that experienced a change in their tinnitus loudness (be that a suppression or a facilitation).

The final study, experiment 3, found that externally applied electrical currents in the form of tDCS were capable of modulating ongoing neural

oscillations. In particular it found that tDCS was capable of modulating both delta and alpha frequency oscillations. The effect of this was short lived however, and did not extend beyond two seconds post stimulation. Evidence was also observed for a more immediate effect of stimulation, as ERFs were found to be significantly reduced in the anodal condition compared to the sham condition in response to the onset of the masker.

6.2 Implications of the Present Work

6.2.1 The Role of Oscillations in Tinnitus

The main aim of the project was to investigate the role of oscillations in the generation and maintenance of tinnitus. This aim was realised in the studies conducted in experiments 2 and 3. Previous literature had led to the hypothesis that oscillatory power in alpha and delta frequency bands would be the primary biological correlate of the tinnitus percept (Adjamian et al., 2012; Kahlbrock & Weisz, 2008; Sedley et al., 2012). As such, it was hypothesised that both alpha and delta frequency band activity would be modulated by the RI and also by the tDCS. Modulations to delta and alpha band oscillations were not observed as a results of inducing RI, in opposition to the previous research (Adjamian et al., 2012; Kahlbrock & Weisz, 2008; Sedley et al., 2012). Nor were any modulations to theta or beta bands observed in the exploratory analyses. Further, experiment 3 indicated that, while tDCS was capable of modulating both delta and alpha band oscillations, it did not result in significant perceptual changes. The thalamocortical dysrhythmia model proposed by Llinas et al. (1999) suggests that tinnitus is

caused by increased low-frequency oscillations (such as delta and theta) and also increased high-frequency oscillations (in the gamma range >20Hz). The implication of the present work is that the subjective loudness of the tinnitus percept is being borne out in these high frequency oscillations. The dual-observations of experiments 2 and 3 support this hypothesis. Firstly, when a participants perceptions are modulated (such as is the case with RI) no neural oscillatory changes below gamma are observed and secondly that the reverse is true. When neural oscillations below gamma are modulated (via the mechanism of tDCS) no changes in perception are observed. This is not to say that lower frequency oscillations (such as delta and alpha) do not have a role in tinnitus, but the present results do not appear to indicate that they are involved in the auditory perception of the tinnitus.

It should be noted that the presented experiments did not analyse high frequency oscillations, and so it is impossible to determine the accuracy of the hypothesis. However, it is also not entirely unfounded. It has previously been supposed that the perceptual information of tinnitus is carried on high frequency gamma oscillations (Arnal & Giraud, 2012; De Ridder et al., 2014a) and these findings would seem to support this. If this is true, then by modulating the perception of tinnitus we might have expected these changes to be observed out in the gamma oscillations, rather than alpha and delta. This could then suggest that alpha and delta could still have a role to play in the generation or maintenance of tinnitus as suggested by previous work (Adjamian et al., 2012; Kahlbrock & Weisz, 2008; Sedley et al., 2012), just not the perception. This would also imply that RI disrupts only the perceptual

mechanisms of tinnitus, and has little effect on the ongoing maintenance and generation of the tinnitus. This would also mark a distinguishable difference between the mechanisms that govern the perception of tinnitus, and those that govern the maintenance of tinnitus. This could be along the lines of the integrative model of tinnitus postulated by De Ridder et al. (2014a), wherein the perceptual characteristics and mechanisms of tinnitus would be more closely linked with the distress networks, rather than the core tinnitus generation network, as is currently supposed.

6.2.2 Relationship between Tinnitus and Associated Conditions

In addition to gathering data regarding the neural activity involved in tinnitus, data was also gathered about comorbid conditions that may be present alongside tinnitus, such as hearing loss and hyperacusis. It is pertinent, in particular, to closely examine the relationship between hearing loss and tinnitus as finding the underlying components of this relationship would give valuable insight into the origins of the tinnitus percept, including how tinnitus pitch is related to the audiometric profile.

There are two main hypotheses about the relationship between tinnitus and hearing loss which would inform us about the origins of tinnitus which are discussed in detail in chapter 3. However to briefly reiterate, the two hypotheses suppose that the peak tinnitus frequency will lie either in the region of hearing loss (Rajan et al., 1993) or at its audiometric edge i.e. the frequency at which hearing first drops into clinically meaningful hearing loss (Eggermont & Roberts, 2004; Schaette & McAlpine, 2011). We did not find

statistical support for these two hypotheses in our sample, although limited support can be seen by observing the trend in figure 3.6. However, there were a number of reasons why this might have been the case which are discussed in chapter 3. As we did not find a relationship in our sample, it is difficult to ascertain the origins of the neural activity we observed in the later experiments.

6.3 Future Work

The results of this project offer many new avenues for future research to explore. There were also several limitations, which should be rectified for future research. The role of gamma in the perception of tinnitus should be investigated further using residual inhibition. It was not investigated in the present study due to the artefacts that often emerge in EEG that are mistaken for brain gamma oscillations (Nottage & Horder, 2015). However, a future study that used either MEG or was careful in recording and analysing the gamma oscillations and muscle artefacts would be beneficial. This future study could address the previously discussed hypothesis that gamma oscillations reflect the perceptual characteristics of tinnitus and should be noticeably different during RI. Such a study could also utilise a tDCS paradigm, in order to fully determine the effects of tDCS on tinnitus related neural oscillations something experiment 3 could not address directly.

It was also hypothesised that as RI was a perceptual phenomenon suppressing a person's tinnitus it should be that it produced changes primarily in the tinnitus distress sub-network outlined by De Ridder et al.

(2014). A further future study could analyse this via changes in network connectivity after and during RI to reveal the networks involved in the suppression of tinnitus.

6.4 Conclusions

The main aim of the project, to investigate the role of cortical oscillations in tinnitus, was achieved with some measure of success. While the results do not provide complete support for some of our hypotheses and previous literature, we did uncover some novel findings which can be used to further inform us about the role of oscillations in tinnitus. Chiefly, that of the increased alpha in those who experienced residual inhibition versus those who did not. We conclude then, based on our findings, that alpha does have a role to play in the generation of tinnitus as an inhibitory oscillation. However, it remains unclear whether alpha is the generator of the actual perception of tinnitus. We also conclude that tDCS can have an effect on auditory oscillations, specifically in delta. We cannot say whether or not this will translate into any meaningful effect on those with tinnitus, but it could be potentially of benefit to those with tinnitus. Finally, we cannot draw a solid conclusion regarding the relationship between hearing loss and tinnitus based on the methods we used to analyse this. However, we can conclude that there is a need to further analyse questionnaire structure, in particular where questions such as “how loud is your tinnitus” are being asked as there is a possibility that there is a latent emotional component to this question that is disguising the “true” loudness of a participants tinnitus.

A number of limitations and future research possibilities are also discussed here. The project, on the whole, was successful as it not only achieved its aims but also generated a number of future avenues to explore. It will be of great interest in the future to explore these questions and further our understanding on the mechanisms behind the generation and maintenance of tinnitus.

References

Accornero, N., Li Voti, P., La Riccia, M., & Gregori, B. (2007). Visual evoked potentials modulation during direct current cortical polarization. *Experimental Brain Research*, *178*(2), 261–266. http://doi.org/10.1007/s00221-006-0733-y

Adjamian, P., Hadjipapas, A., Barnes, G. R., Hillebrand, A., & Holliday, I. E. (2008). Induced Gamma activity in primary visual cortex is related to luminance and not color contrast: An MEG study. *J Vis*, *8*(7), 7. http://doi.org/10.1167/8.7.4

Adjamian, P., Sereda, M., & Hall, D. A. (2009). The mechanisms of tinnitus: perspectives from human functional neuroimaging. *Hear Res*, *253*(1–2), 15–31. http://doi.org/10.1016/j.heares.2009.04.001

Adjamian, P., Sereda, M., Zobay, O., Hall, D. A., & Palmer, A. R. (2012). Neuromagnetic indicators of tinnitus and tinnitus masking in patients with and without hearing loss. *J Assoc Res Otolaryngol*, *13*(5), 715–731. http://doi.org/10.1007/s10162-012-0340-5

Alam, M., Truong, D. Q., Khadka, N., & Bikson, M. (2016). Spatial and polarity precision of concentric high-definition transcranial direct current stimulation (HD-tDCS). *Physics in Medicine and Biology*, *61*(12), 4506–4521. http://doi.org/10.1088/0031-9155/61/12/4506

Albert, D. J. (1966a). The Effect of Spreading Depression on the Consolidation of Learning. *Neuropsychologia*, *4*.

Albert, D. J. (1966b). The Effects of Polarizing Currents on the Consolidation of Learning. *Neuropsychologia*, *4*, 65–77.

Aldini, G. (1804). Essai theorique et experimental sur le galvanisme. *Paris: Fournier*, *2 Vols*.

Alessandria, M., Vetrugno, R., Cortelli, P., & Montagna, P. (2011). Normal body scheme and absent phantom limb experience in amputees while dreaming. *Consciousness and Cognition*, *20*(4), 1831–1834. http://doi.org/10.1016/J.CONCOG.2011.06.013

Anari, M., Axelsson, A., Eliasson, A., & Magnusson, L. (1999). Hypersensitivity to sound--questionnaire data, audiometry and classification. *Scandinavian Audiology*, *28*(4), 219–30. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10572967

Antal, A., Kincses, T. Z., Nitsche, M. A., Bartfai, O., & Paulus, W. (2004). Excitability Changes Induced in the Human Primary Visual Cortex by Transcranial Direct Current Stimulation: Direct Electrophysiological Evidence. *Investigative Opthalmology & Visual Science*, *45*(2), 702.

http://doi.org/10.1167/iovs.03-0688

Arnal, L. H., Doelling, K. B., & Poeppel, D. (2015). Delta–Beta Coupled Oscillations Underlie Temporal Prediction Accuracy. *Cerebral Cortex*, *25*(9), 3077–3085. http://doi.org/10.1093/cercor/bhu103

Arnal, L. H., & Giraud, A.-L. (2012). Cortical oscillations and sensory predictions. *Trends in Cognitive Sciences*, *16*(7), 390–398. http://doi.org/10.1016/j.tics.2012.05.003

Ashton, H., Reid, K., Marsh, R., Johnson, I., Alter, K., & Griffiths, T. (2007). High frequency localised “hot spots” in temporal lobes of patients with intractable tinnitus: A quantitative electroencephalographic (QEEG) study. *Neurosci Lett*, *426*(1), 23–28. http://doi.org/10.1016/j.neutet.2007.08.034

Axelsson, A., & Ringdahl, A. (1989). Tinnitus--a study of its prevalence and characteristics. *British Journal of Audiology*, *23*(1), 53–62. http://doi.org/10.3109/03005368909077819

Baguley, D. M. (2003). Hyperacusis. *Journal of the Royal Society of Medicine*, *96*(12), 582–585. http://doi.org/10.1258/jrsm.96.12.582

Baguley, D. M., McFerran, D., & Hall, D. (2013). Tinnitus. *Lancet*, *382*, 1600–1607. Retrieved from http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(13)60142-7.pdf

Baillet, S. (2017). Magnetoencephalography for brain electrophysiology and imaging. *Nature Neuroscience*, *20*(3), 327–339. http://doi.org/10.1038/nn.4504

Bauer, C. ., Brozoski, T. ., Holder, T. ., & Caspary, D. . (2000). Effects of chronic salicylate on GABAergic activity in rat inferior colliculus. *Hearing Research*, *147*(1–2), 175–182. http://doi.org/10.1016/S0378-5955(00)00130-1

Bauer, C. A., Turner, J. G., Caspary, D. M., Myers, K. S., & Brozoski, T. J. (2008). Tinnitus and inferior colliculus activity in chinchillas related to three distinct patterns of cochlear trauma. *Journal of Neuroscience Research*, *86*(11), 2564–2578. http://doi.org/10.1002/jnr.21699

Berg, P., & Scherg, M. (1994). A fast method for forward computation of multiple-shell spherical head models. *Electroencephalography and Clinical Neurophysiology*, *90*, 58–64. Retrieved from http://ac.els-cdn.com/0013469494901139/1-s2.0-0013469494901139-main.pdf?_tid=904047d2-5bf8-11e7-9825-00000aab0f01&acdnat=1498651058_ac8612464afca21b7d773c63b36e3f97

Bhimrao, S. K., Masterson, L., & Baguley, D. (2012). Systematic Review of Management Strategies for Middle Ear Myoclonus. *Otolaryngology-*

Head and Neck Surgery, *146*(5), 698–706. http://doi.org/10.1177/0194599811434504

Bindman, L. J., Lippold, O, C, J., & Redfearn, J, W, T. (1962). Long-lasting Changes in the Level of the Electrical Activity of the Cerebral Cortex produced by Polarizing Currents. *Nature*, *196*(4854), 584–585. http://doi.org/10.1038/196584a0

Bland, J. M., & Altman, D. G. (1986). Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*, *1*(8476), 307–10. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2868172

Brancucci, A., Franciotti, R., D'Anselmo, A., Della Penna, S., & Tommasi, L. (2011). The sound of consciousness: neural underpinnings of auditory perception. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *31*(46), 16611–8. http://doi.org/10.1523/JNEUROSCI.3949-11.2011

British Society of Audiology. (2012). Recommended Procedure Pure-tone air-conduction and bone-conduction threshold audiometry with and without masking General foreword. British Society of Audiology. Retrieved from http://www.thebsa.org.uk/wp-content/uploads/2014/04/BSA_RP_PTA_FINAL_24Sept11_MinorAmend06Feb12.pdf

Brotherton, H., Plack, C. J., Schaette, R., & Munro, K. J. (2017). Using acoustic reflex threshold, auditory brainstem response and loudness judgments to investigate changes in neural gain following acute unilateral deprivation in normal hearing adults. *Hearing Research*, *345*, 88–95. http://doi.org/10.1016/j.heares.2017.01.009

Burton, H., Wineland, A., Bhattacharya, M., Nicklaus, J., Garcia, K. S., & Piccirillo, J. F. (2012). Altered networks in bothersome tinnitus: a functional connectivity study. *BMC Neuroscience*, *13*, 3. http://doi.org/10.1186/1471-2202-13-3

Cianfrone, G., Pentangelo, D., Cianfrone, F., Mazzei, F., Turchetta, R., Orlando, M. P., & Altissimi, G. (2011). Pharmacological drugs inducing ototoxicity, vestibular symptoms and tinnitus: a reasoned and updated guide. *European Review for Medical and Pharmacological Sciences*, *15*(6), 601–36. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21796866

Coles, R. R. A., Lutman, M. E., Axelsson, A., & Hazell, J. W. P. (1992). Tinnitus Severity Gradings: Cross-Sectional Studies. In J. M. Aran & R. Dauman (Eds.), *Tinnitus 91: Proceedings of the Fourth International Tinnitus Seminar* (First, pp. 453–455). New York: Kugler.

Cooke, S. F., Bliss, T. V. P., Abel, T., Nguyen, P., Barad, M., Deuel, T., … Ruge, D. (2006). Plasticity in the human central nervous system. *Brain : A*

Journal of Neurology, *129*(Pt 7), 1659–73. http://doi.org/10.1093/brain/awl082

Coolican, H. (2009). *Research Methods and Statistics in Psychology* (5th Editio). London: Hodder Education.

Creutzfeldt, O. D., Fromm, G. H., & Kapp, H. (1962). Influence of transcortical d-c currents on cortical neuronal activity. *Experimental Neurology*, *5*(6), 436–452. http://doi.org/10.1016/0014-4886(62)90056-0

Crick, F., & Koch, C. (1995). Are we aware of neural activity in primary visual cortex? *Nature*, *375*(6527), 121–123. http://doi.org/10.1038/375121a0

Critchley, H. D., Elliott, R., Mathias, C. J., & Dolan, R. J. (2000). Neural activity relating to generation and representation of galvanic skin conductance responses: a functional magnetic resonance imaging study. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *20*(8), 3033–40. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10751455

Critchley, H. D., Melmed, R. N., Featherstone, E., Mathias, C. J., & Dolan, R. J. (2002). Volitional control of autonomic arousal: a functional magnetic resonance study. *NeuroImage*, *16*(4), 909–19. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12202079

Dayan, E., Censor, N., Buch, E. R., Sandrini, M., & Cohen, L. G. (2013). Noninvasive brain stimulation: from physiology to network dynamics and back. *Nature Neuroscience*, *16*(7), 838–844. http://doi.org/10.1038/nn.3422

De Ridder, D., De Mulder, G., Verstraeten, E., Seidman, M., Elisevich, K., Sunaert, S., … Moller, A. (2007). Auditory cortex stimulation for tinnitus. *Acta Neurochirurgica. Supplement*, *97*(Pt 2), 451–62. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17691335

De Ridder, D., Fransen, H., Francois, O., Sunaert, S., Kovacs, S., & Van De Heyning, P. (2006). Amygdalohippocampal involvement in tinnitus and auditory memory. *Acta Oto-Laryngologica*, *126*(sup556), 50–53. http://doi.org/10.1080/03655230600895580

De Ridder, D., van der Loo, E., Van der Kelen, K., Menovsky, T., van de Heyning, P., & Moller, A. (2007). Do tonic and burst TMS modulate the lemniscal and extralemniscal system differentially? *International Journal of Medical Sciences*, *4*(5), 242–6. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17952200

De Ridder, D., van der Loo, E., Vanneste, S., Gais, S., Plazier, M., Kovacs, S., … van de Heyning, P. (2011). Theta-gamma dysrhythmia and auditory phantom perception. *Journal of Neurosurgery*, *114*(4), 912–921. http://doi.org/10.3171/2010.11.JNS10335

De Ridder, D., Vanneste, S., & Congedo, M. (2011). The distressed brain: a

group blind source separation analysis on tinnitus. *PloS One*, *6*(10), e24273. http://doi.org/10.1371/journal.pone.0024273

De Ridder, D., Vanneste, S., Kovacs, S., Sunaert, S., Menovsky, T., van de Heyning, P., & Moller, A. (2011). Transcranial magnetic stimulation and extradural electrodes implanted on secondary auditory cortex for tinnitus suppression. *Journal of Neurosurgery*, *114*(4), 903–911. http://doi.org/10.3171/2010.11.JNS10197

De Ridder, D., Vanneste, S., Langguth, B., & Llinas, R. (2015). Thalamocortical dysrhythmia: A theoretical update in tinnitus. *Frontiers in Neurology*. http://doi.org/10.3389/fneur.2015.00124

De Ridder, D., Vanneste, S., Weisz, N., Londero, A., Schlee, W., Elgoyhen, A. B., & Langguth, B. (2014a). An integrative model of auditory phantom perception: tinnitus as a unified percept of interacting separable subnetworks. *Neuroscience and Biobehavioral Reviews*, *44*, 16–32. http://doi.org/10.1016/j.neubiorev.2013.03.021

De Ridder, D., Vanneste, S., Weisz, N., Londero, A., Schlee, W., Elgoyhen, A. B., & Langguth, B. (2014b). An integrative model of auditory phantom perception: Tinnitus as a unified percept of interacting separable subnetworks. *Neuroscience and Biobehavioral Reviews*, *44*, 16–32. http://doi.org/10.1016/j.neubiorev.2013.03.021

Doesburg, S. M., Green, J. J., McDonald, J. J., & Ward, L. M. (2012). Theta modulation of inter-regional gamma synchronization during auditory attention control. *Brain Research*, *1431*, 77–85. http://doi.org/10.1016/j.brainres.2011.11.005

Eggermont, J. J., & Roberts, L. E. (2004). The neuroscience of tinnitus. *Trends in Neurosciences*, *27*(11), 676–82. http://doi.org/10.1016/j.tins.2004.08.010

Eggermont, J. J., & Roberts, L. E. (2004). The neuroscience of tinnitus. *Trends in Neurosciences*, *27*(11), 676–682. http://doi.org/10.1016/j.tins.2004.08.010

Elgoyhen, A. B., Langguth, B., De Ridder, D., & Vanneste, S. (2015). Tinnitus: perspectives from human neuroimaging. *Nature Reviews: Neuroscience*, *16*(10). http://doi.org/10.1038/nrn4003

Ellenstein, A., Yusuf, N., & Hallett, M. (2013). Middle ear myoclonus: two informative cases and a systematic discussion of myogenic tinnitus. *Tremor and Other Hyperkinetic Movements (New York, N.Y.)*, *3*.

Evans, E. F., Wilson, J. P., & Borerwe, T. A. (1981). Animal models of tinnitus. *Ciba Foundation Symposium*, *85*, 108–138.

Evered, D., & Lawrenson, G. (1981). Appendix II: Guidelines for Recommended Procedures in Tinnitus Testing. In *CIBA Foundation Symposium 85: Tinnitus* (pp. 303–306). Pitman Books, London.

http://doi.org/10.1002/9780470720677.app2

Fackrell, K., Fearnley, C., Hoare, D. J., & Sereda, M. (2015). Hyperacusis Questionnaire as a Tool for Measuring Hypersensitivity to Sound in a Tinnitus Research Population. *BioMed Research International*, *2015*, 1–12. http://doi.org/10.1155/2015/290425

Fackrell, K., Hall, D. A., Barry, J. G., & Hoare, D. J. (2016). Psychometric properties of the Tinnitus Functional Index (TFI): Assessment in a UK research volunteer population. *Hearing Research*, *335*, 220–235. http://doi.org/10.1016/J.HEARES.2015.09.009

Fagelson, M. A. (2007). The Association Between Tinnitus and Posttraumatic Stress Disorder. *American Journal of Audiology*, *16*(2), 107. http://doi.org/10.1044/1059-0889(2007/015)

Feldmann, H. (1971). Homolateral and Contralateral Masking of Tinnitus by Noise-Bands and by Pure Tones. *Audiology*, *10*, 138–144.

Feldmann, H. (1983). Time Patterns and Related Parameters in Masking of Tinnitus. *Acta Otolyngolica*, *95*, 594–598.

Folmer, R. L., Martin, W. H., & Shi, Y. (2004). Tinnitus: questions to reveal the cause, answers to provide relief. *J Fam Pract*, *53*(7), 532–540. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15251092

Folmer, R. L., Theodoroff, S. M., Casiana, L., Shi, Y., Griest, S., & Vachhani, J. (2015). Repetitive Transcranial Magnetic Stimulation Treatment for Chronic Tinnitus. *JAMA Otolaryngology–Head & Neck Surgery*, *141*(8), 716. http://doi.org/10.1001/jamaoto.2015.1219

Fournier, P., Cuvillier, A., Gallego, S., Paolino, F., Quemar, A., Londero, A., & Norena, A. (2018). A New Method for Assessing Masking and Residual Inhibition of Tinnitus. In *11th Tinnitus Research Initiative Coference* (p. 80).

Friston, K. (2010). The free-energy principle: a unified brain theory? *Nature Reviews Neuroscience*, *11*(2), 127–138. http://doi.org/10.1038/nrn2787

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., & Lu, B. (2010). *Direct Current Stimulation Promotes BDNF-Dependent Synaptic Plasticity: Potential Implications for Motor Learning*. *Neuron* (Vol. 66). http://doi.org/10.1016/j.neuron.2010.03.035

Galazyuk, A. V., Voytenko, S. V., & Longenecker, R. J. (2017). Long-Lasting forward Suppression of Spontaneous Firing in Auditory Neurons: Implication to the Residual Inhibition of Tinnitus. *Journal of the Association for Research in Otolaryngology*, *18*(2), 343–353. http://doi.org/10.1007/s10162-016-0601-9

Gomaa, M. A. M., Elmagd, M. H. A., Elbadry, M. M., & Kader, R. M. A. (2014). Depression, Anxiety and Stress Scale in patients with tinnitus and hearing loss. *European Archives of Oto-Rhino-Laryngology*, *271*(8), 2177–

2184. http://doi.org/10.1007/s00405-013-2715-6

Gu, J. W., Herrmann, B. S., Levine, R. A., & Melcher, J. R. (2012). Brainstem auditory evoked potentials suggest a role for the ventral cochlear nucleus in tinnitus. *JARO - Journal of the Association for Research in Otolaryngology*, *13*(6), 819–833. http://doi.org/10.1007/s10162-012-0344-1

Halford, J. B., & Anderson, S. D. (1991). Tinnitus severity measured by a subjective scale, audiometry and clinical judgement. *The Journal of Laryngology and Otology*, *105*(2), 89–93. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2013737

Hall, D. A., Haider, H., Szczepek, A. J., Lau, P., Rabau, S., Jones-Diette, J., … Mazurek, B. (2016). Systematic review of outcome domains and instruments used in clinical trials of tinnitus treatments in adults. *Trials*, *17*(1), 270. http://doi.org/10.1186/s13063-016-1399-9

Hall, D. A., Mehta, R. L., & Fackrell, K. (2017). How to Choose Between Measures of Tinnitus Loudness for Clinical Research? A Report on the Reliability and Validity of an Investigator-Administered Test and a Patient-Reported Measure Using Baseline Data Collected in a Phase IIa Drug Trial. *American Journal of Audiology*, *26*(3), 338. http://doi.org/10.1044/2017_AJA-16-0129

Hallam, R. S., Jakes, S. C., & Hinchcliffe, R. (1988). Cognitive variables in tinnitus annoyance. *The British Journal of Clinical Psychology*, *27 (Pt 3)*, 213–22. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3191301

Hallez, H., Vanrumste, B., Grech, R., Muscat, J., De Clercq, W., Vergult, A., … Lemahieu, I. (2007). Review on solving the forward problem in EEG source analysis. *Journal of Neuroengineering and Rehabilitation*, *4*, 46. http://doi.org/10.1186/1743-0003-4-46

Hanley, C. J., Singh, K. D., & McGonigle, D. J. (2016). Transcranial modulation of brain oscillatory responses: A concurrent tDCS–MEG investigation. *NeuroImage*, *140*, 20–32. http://doi.org/10.1016/j.neuroimage.2015.12.021

He, J., & Hu, B. (2002). Differential distribution of burst and single-spike responses in auditory thalamus. *Journal of Neurophysiology*, *88*(4), 2152–6. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12364537

Heimrath, K., Fiene, M., Rufener, K. S., & Zaehle, T. (2016). Modulating Human Auditory Processing by Transcranial Electrical Stimulation. *Frontiers in Cellular Neuroscience*, *10*, 53. http://doi.org/10.3389/fncel.2016.00053

Helfrich, R. F., Schneider, T. R., Rach, S., Trautmann-Lengsfeld, S. A., Engel, A. K., & Herrmann, C. S. (2014). *Entrainment of Brain Oscillations by Transcranial Alternating Current Stimulation*. *Current Biology* (Vol. 24).

http://doi.org/10.1016/j.cub.2013.12.041

Henry, J. A., Griest, S., Thielman, E., McMillan, G., Kaelin, C., & Carlson, K. F. (2016). Tinnitus Functional Index: Development, validation, outcomes research, and clinical application. *Hearing Research*, *334*, 58–64. http://doi.org/10.1016/j.heares.2015.06.004

Henry, J. A., & Meikle, M. B. (1999). Pulsed versus continuous tones for evaluating the loudness of tinnitus. *Journal of the American Academy of Audiology*, *10*(5), 261–72. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10331618

Henry, J. A., & Meikle, M. B. (2000). Psychoacoustic measures of tinnitus. *Journal of the American Academy of Audiology*, *11*(3), 138–55. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10755810

Hillebrand, A., Singh, K. D., Holliday, I. E., Furlong, P. L., & Barnes, G. R. (2005). A new approach to neuroimaging with magnetoencephalography. *Human Brain Mapping*, *25*(2), 199–211. http://doi.org/10.1002/hbm.20102

Hinton, D. E., Chhean, D., Pich, V., Hofmann, S. G., & Barlow, D. H. (2006). Tinnitus among Cambodian refugees: Relationship to PTSD severity. *Journal of Traumatic Stress*, *19*(4), 541–546. http://doi.org/10.1002/jts.20138

Hoare, D. J., Adjamian, P., Sereda, M., & Hall, D. A. (2013). Recent technological advances in sound-based approaches to tinnitus treatment: A review of efficacy considered against putative physiological mechanisms. *Noise Health*, *15*(63), 107–116. http://doi.org/10.4103/1463-1741.110292

Hoare, D. J., Gander, P. E., Collins, L., Smith, S., & Hall, D. A. (2012). Management of tinnitus in English NHS audiology departments: an evaluation of current practice. *Journal of Evaluation in Clinical Practice*, *18*(2), 326–334. http://doi.org/10.1111/j.1365-2753.2010.01566.x

Hobson, J., Chisholm, E., & El Refaie, A. (2010). Sound therapy (masking) in the management of tinnitus in adults. In J. Hobson (Ed.), *Cochrane Database of Systematic Reviews* (p. CD006371). Chichester, UK: John Wiley & Sons, Ltd. http://doi.org/10.1002/14651858.CD006371.pub2

Holmes, S., & Padgham, N. D. (2011). “Ringing in the Ears”: Narrative Review of Tinnitus and Its Impact. *Biological Research for Nursing*, *13*(1), 97–108. http://doi.org/Doi 10.1177/1099800410382290

Hone-Blanchet, A., Edden, R. A., & Fecteau, S. (2016). Online Effects of Transcranial Direct Current Stimulation in Real Time on Human Prefrontal and Striatal Metabolites. *Biological Psychiatry*, *80*(6), 432–438. http://doi.org/10.1016/j.biopsych.2015.11.008

Horvath, J. C., Forte, J. D., & Carter, O. (2015). Quantitative Review Finds No

Evidence of Cognitive Effects in Healthy Populations From Single-session Transcranial Direct Current Stimulation (tDCS). *Brain Stimulation*, *8*(3), 535–550. http://doi.org/10.1016/j.brs.2015.01.400

Jahnsen, H., & Llinas, R. (1984). Electrophysiological Properties Of Guinea-Pig Thalamic Neurons - An Invitro Study. *Journal of Physiology-London*, *349*(APR), 205-.

Jastreboff, M. M., & Jastreboff, P. J. (1999). Questionnaires for Assessment of the Patients and Treatment Outcome. In J. W. P. Hazell (Ed.), *Proceedings of the Sixth International Tinnitus Seminar* (First, pp. 487–490). London: Tinnitus and Hyperacusis Centre.

Jastreboff, P. J. (1990). Phantom auditory perception (tinnitus): mechanisms of generation and perception. *Neuroscience Research*, *8*(4), 221–54. http://doi.org/10.1016/0168-0102(90)90031-9

Jastreboff, P. J., & Jastreboff, M. M. (2000). Tinnitus Retraining Therapy (TRT) as a Method for Treatment of Tinnitus and Hyperacusis Patients. *J Am Acad Audiol*, *11*, 162–177. Retrieved from https://www.audiology.org/sites/default/files/journal/JAAA_11_03_05.pdf

Jocks, I. T. (2013). *The Compositiones Medicamentorum of Scribonius Largus*. University of Glasgow. Retrieved from http://theses.gla.ac.uk/4892/1/2013jocksmres.pdf

Joos, K., Vanneste, S., & De Ridder, D. (2012). Disentangling Depression and Distress Networks in the Tinnitus Brain. *PLoS ONE*, *7*(7), e40544. http://doi.org/10.1371/journal.pone.0040544

Juris, L., Andersson, G., Larsen, H. C., & Ekselius, L. (2013). Psychiatric comorbidity and personality traits in patients with hyperacusis. *International Journal of Audiology*, *52*(4), 230–235. http://doi.org/10.3109/14992027.2012.743043

Jüris, L., Andersson, G., Larsen, H. C., & Ekselius, L. (2013). Psychiatric comorbidity and personality traits in patients with hyperacusis. *International Journal of Audiology*, *52*(4), 230–235. http://doi.org/10.3109/14992027.2012.743043

Kahlbrock, N., & Weisz, N. (2008). Transient reduction of tinnitus intensity is marked by concomitant reductions of delta band power. *Bmc Biology*, *6*. http://doi.org/10.1186/1741-7007-6-4

Khalfa, S., Dubal, S., Veuillet, E., Perez-Diaz, F., Jouvent, R., & Collet, L. (2002). Psychometric normalization of a hyperacusis questionnaire. *ORL; Journal for Oto-Rhino-Laryngology and Its Related Specialties*, *64*(6), 436–42. http://doi.org/10.1159/000067570

Khedr, E. M., Ahmed, M. A., Shawky, O. A., Mohamed, E. S., El Attar, G. S., & Mohammad, K. A. (2010). Epidemiological Study of Chronic Tinnitus in

Assiut, Egypt. *Neuroepidemiology*, *35*(1), 45–52. http://doi.org/10.1159/000306630

Kiang, N. Y., Moxon, E. C., & Levine, R. A. (1970). Auditory-nerve activity in cats with normal and abnormal cochleas. In: Sensorineural hearing loss. *Ciba Foundation Symposium*, 241–273.

Klein, A. J., Armstrong, B. L., Greer, M. K., & Brown, F. R. (1990). Hyperacusis and otitis media in individuals with Williams syndrome. *The Journal of Speech and Hearing Disorders*, *55*(2), 339–44. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2329796

Klem, G., Luders, H., Jasper, H., & Elger, C. (1958). The ten-twenty electrode system of the International Federation. *Electroencephalography and Clinical Neurophysiology*, *10*(2), 371–375. http://doi.org/10.1016/0013-4694(58)90053-1

Knobel, K. A. B., & Sanchez, T. G. (2008). Influence of silence and attention on tinnitus perception. *Otolaryngology-Head and Neck Surgery*, *138*(1), 18–22. http://doi.org/10.1016/j.otohns.2007.09.023

Koizumi, T., Nishimura, T., Yamashita, A., Yamanaka, T., Imamura, T., & Hosoi, H. (2014). Residual inhibition of tinnitus induced by 30-kHz bone-conducted ultrasound. *Hearing Research*, *310*, 48–53. http://doi.org/10.1016/j.heares.2014.01.011

König, O., Schaette, R., Kempter, R., & Gross, M. (2006). Course of hearing loss and occurrence of tinnitus. *Hearing Research*, *221*(1–2), 59–64. http://doi.org/10.1016/j.heares.2006.07.007

Kraus, K. S., & Canlon, B. (2012). Neuronal connectivity and interactions between the auditory and limbic systems. Effects of noise and tinnitus. *Hear Res*, *288*(1–2), 34–46. http://doi.org/10.1016/j.heares.2012.02.009

Kuk, F. K., Tyler, R. S., Russell, D., & Jordan, H. (1990). The psychometric properties of a tinnitus handicap questionnaire. *Ear and Hearing*, *11*(6), 434–45. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2073977

Kuo, M. F., Paulus, W., & Nitsche, M. A. (2014). Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. *Neuroimage*, *85*, 948–960. http://doi.org/10.1016/j.neuroimage.2013.05.117

Ladeira, A., Fregni, F., Campanhã, C., Valasek, C. A., De Ridder, D., Brunoni, A. R., … Keith, R. (2011). Polarity-Dependent Transcranial Direct Current Stimulation Effects on Central Auditory Processing. *PLoS ONE*, *6*(9), e25399. http://doi.org/10.1371/journal.pone.0025399

Landgrebe, M., Langguth, B., Rosengarth, K., Braun, S., Koch, A., Kleinjung, T., … Hajak, G. (2009). Structural brain changes in tinnitus: Grey matter decrease in auditory and non-auditory brain areas. *Neuroimage*, *46*(1), 213–218. http://doi.org/10.1016/j.neuroimage.2009.01.069

Lanfer, B., Scherg, M., Dannhauer, M., Kn?sche, T. R., Burger, M., & Wolters, C. H. (2012). Influences of skull segmentation inaccuracies on EEG source analysis. *NeuroImage*, *62*(1), 418–431. http://doi.org/10.1016/j.neuroimage.2012.05.006

Langers, D. R. M., de Kleine, E., & van Dijk, P. (2012). Tinnitus does not require macroscopic tonotopic map reorganization. *Frontiers in Systems Neuroscience*, *6*, 2. http://doi.org/10.3389/fnsys.2012.00002

Langguth, B., Goodey, R., Azevedo, A., Bjorne, A., Cacace, A., Crocetti, A., … Vergara, R. (2007). Consensus for tinnitus patient assessment and treatment outcome measurement: Tinnitus Research Initiative meeting, Regensburg, July 2006. *Progress in Brain Research*, *166*, 525–36. http://doi.org/10.1016/S0079-6123(07)66050-6

Langguth, B., Landgrebe, M., Kleinjung, T., Sand, G. P., & Hajak, G. (2011). Tinnitus and depression. *The World Journal of Biological Psychiatry*, *12*(7), 489–500. http://doi.org/10.3109/15622975.2011.575178

Lapenta, O. M., Minati, L., Fregni, F., & Boggio, P. S. (2013). Je pense donc je fais: transcranial direct current stimulation modulates brain oscillations associated with motor imagery and movement observation. *Frontiers in Human Neuroscience*, *7*, 9. http://doi.org/10.3389/fnhum.2013.00256

Lasisi, A. O., Abiona, T., & Gureje, O. (2010). Tinnitus in the elderly: Profile, correlates, and impact in the Nigerian Study of Ageing. *Otolaryngology-Head and Neck Surgery*, *143*(4), 510–515. http://doi.org/10.1016/j.otohns.2010.06.817

Liberman, M. C., & Dodds, L. W. (1984). Single-neuron labeling and chronic cochlear pathology. II. Stereocilia damage and alterations of spontaneous discharge rates. *Hearing Research*, *16*(1), 43–53. http://doi.org/10.1016/0378-5955(84)90024-8

Lima, A. da S., Sanchez, T. G., Bonadia Moraes, M. F., Batezati Alves, S. C., & Bento, R. F. (n.d.). The effect of timpanoplasty on tinnitus in patients with conductive hearing loss: a six month follow-up. *Brazilian Journal of Otorhinolaryngology*, *73*(3), 384–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17684660

Llinás, R. R., Ribary, U., Jeanmonod, D., Kronberg, E., & Mitra, P. P. (1999a). Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(26), 15222–7. http://doi.org/10.1073/pnas.96.26.15222

Llinás, R. R., Ribary, U., Jeanmonod, D., Kronberg, E., & Mitra, P. P. (1999b). Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(26), 15222–7. http://doi.org/10.1073/pnas.96.26.15222

Llinas, R., Ribary, U., Jeanmonod, D., Kronberg, E., & Mitra, P. P. (1999). Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc Natl Acad Sci U S A*, *96*(26), 15222–15227. http://doi.org/10.1073/pnas.96.26.15222

Lopes da Silva, F. H. (2010). Electrophysiological Basis of MEG Signals. In P. C. Hansen, M. L. Kringelbach, & R. Salmelin (Eds.), *MEG: An Introduction to Methods* (First Edit, pp. 1–24). Oxford University Press.

Loprinzi, P. D., Maskalick, S., Brown, K., & Gilham, B. (2013). Association between depression and tinnitus in a nationally representative sample of US older adults. *Aging Ment Health*, *17*(6), 714–717. http://doi.org/10.1080/13607863.2013.775640

Luck, S. J. (2014). *An Introduction To The Event-Related Potential Technique*. (S. J. Luck, Ed.) (2nd ed.). MIT Press.

Lutman, M. E., Davis, A. C., & Ferguson, M. A. (2008). Epidemiological Evidence for the Effectiveness of the Noise at Work Regulations, RR669. Retrieved from https://eprints.soton.ac.uk/65355/

Maris, E., & Oostenveld, R. (2007). Nonparametric statistical testing of EEG- and MEG-data ☹ , ☹☹, *164*, 177–190. http://doi.org/10.1016/j.jneumeth.2007.03.024

Mathys, C., Loui, P., Zheng, X., & Schlaug, G. (2010). Non-Invasive Brain Stimulation Applied to Heschl's Gyrus Modulates Pitch Discrimination. *Frontiers in Psychology*, *1*, 193. http://doi.org/10.3389/fpsyg.2010.00193

Matsushita, R., Andoh, J., & Zatorre, R. J. (2015). Polarity-specific transcranial direct current stimulation disrupts auditory pitch learning. *Frontiers in Neuroscience*, *9*, 174. http://doi.org/10.3389/fnins.2015.00174

Meikle, M. B., Creedon, T. A., & Greist, S. E. (2004). Tinnitus Archive Second Edition. Oregon Hearing Research Center, Department of Otolaryngology, Oregon Health and Science University: <http://www.tinnitusArchive.org/>.

Meikle, M. B., Griest, S. E., Stewart, B. J., & Press, L. S. (1995). Measuring The Negative Impact of Tinnitus: A Brief Severity Index. *Abstracts of the Association for Research in Otolaryngology*, 167.

Meikle, M. B., Henry, J. A., Griest, S. E., Stewart, B. J., Abrams, H. B., McArdle, R., … Vernon, J. A. (2012). The Tinnitus Functional Index. *Ear and Hearing*, *33*(2), 153–176. http://doi.org/10.1097/AUD.0b013e31822f67c0

Meikle, M. B., Stewart, B. J., Griest, S. E., & Henry, J. A. (2008). Tinnitus outcomes assessment. *Trends in Amplification*, *12*(3), 223–35. http://doi.org/10.1177/1084713808319943

Melcher, J. R., Sigalovsky, I. S., Guinan, J. J., & Levine, R. A. (2000). Lateralized tinnitus studied with functional magnetic resonance imaging: Abnormal inferior colliculus activation. *Journal of Neurophysiology*, *83*(2), 1058–1072.

Meyer, K. (2011). Primary sensory cortices, top-down projections and conscious experience. *Progress in Neurobiology*, *94*(4), 408–417. http://doi.org/10.1016/J.PNEUROBIO.2011.05.010

Michikawa, T., Nishiwaki, Y., Kikuchi, Y., Saito, H., Mizutari, K., Okamoto, M., & Takebayashi, T. (2010). Prevalence and Factors Associated with Tinnitus: A Community-Based Study of Japanese Elders. *Journal of Epidemiology*, *20*(4), 271–276. http://doi.org/10.2188/jea.JE20090121

Midani, A., Carels, I., Marks, M., & Wall, M. (2006). Safety and efficacy of Sofenz ceruminolytic solution. *Ear, Nose, & Throat Journal*, *85*(2), 87–8, 90–2. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16579195

Mühlnickel, W., Elbert, T., Taub, E., & Flor, H. (1998). Reorganization of auditory cortex in tinnitus. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(17), 10340–3. http://doi.org/10.1073/PNAS.95.17.10340

Mulder, T., Hochstenbach, J., Dijkstra, P. U., & Geertzen, J. H. B. (2008). Born to adapt, but not in your dreams. *Consciousness and Cognition*, *17*(4), 1266–1271. http://doi.org/10.1016/J.CONCOG.2007.04.001

Mulheran, M. (1999). The effects of quinine on cochlear nerve fibre activity in the guinea pig. *Hear Res*, *134*(1–2), 145–152. http://doi.org/10.1016/s0378-5955(99)00076-3

Murchison, C. F., Schutsky, K., Jin, S.-H., & Thomas, S. A. (2011). Norepinephrine and ß1-adrenergic signaling facilitate activation of hippocampal CA1 pyramidal neurons during contextual memory retrieval. *Neuroscience*, *181*, 109–116. http://doi.org/10.1016/j.neuroscience.2011.02.049

Muthukumaraswamy, S. D. (2013). High-frequency brain activity and muscle artifacts in MEG/EEG: a review and recommendations. *Frontiers in Human Neuroscience*, *7*, 138. http://doi.org/10.3389/fnhum.2013.00138

Neuling, T., Ruhnau, P., Fusca, M., Demarchi, G., Herrmann, C. S., & Weisz, N. (2015). Friends, not foes: Magnetoencephalography as a tool to uncover brain dynamics during transcranial alternating current stimulation. *Neuroimage*, *118*, 406–413. http://doi.org/10.1016/j.neuroimage.2015.06.026

Neuling, T., Wagner, S., Wolters, C. H., Zaehle, T., & Herrmann, C. S. (2012). Finite-Element Model Predicts Current Density Distribution for Clinical Applications of tDCS and tACS. *Frontiers in Psychiatry*, *3*, 83. http://doi.org/10.3389/fpsyt.2012.00083

Newman, C. W., Jacobson, G. P., & Spitzer, J. B. (1996). Development of the Tinnitus Handicap Inventory. *Archives of Otolaryngology--Head & Neck Surgery*, *122*(2), 143–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8630207

Nicotra, A., Critchley, H. D., Mathias, C. J., & Dolan, R. J. (2006). Emotional and autonomic consequences of spinal cord injury explored using functional brain imaging. *Brain*, *129*(3), 718–728. http://doi.org/10.1093/brain/awh699

Nitsche, M. A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., … Paulus, W. (2003). Pharmacological Modulation of Cortical Excitability Shifts Induced by Transcranial Direct Current Stimulation in Humans. *The Journal of Physiology*, *553*(1), 293–301. http://doi.org/10.1113/jphysiol.2003.049916

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology*, *527*(3), 633–639. http://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x

Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*, *57*(10), 1899–1901.

Nitsche, M., Liebetanz, D., Lang, N., Antal, A., Tergau, F., Paulus, W., & Priori, A. (2003). Safety criteria for transcranial direct current stimulation (tDCS) in humans [1] (multiple letters). *Clinical Neurophysiology*, *114*(11), 2220–2223. http://doi.org/10.1016/S1388-2457(03)00235-9

Nondahl, D. M., Cruickshanks, K. J., Huang, G.-H., Klein, B. E. K., Klein, R., Nieto, F. J., & Tweed, T. S. (2011). Tinnitus and its risk factors in the Beaver Dam Offspring Study. *International Journal of Audiology*, *50*(5), 313–320. http://doi.org/10.3109/14992027.2010.551220

Noreña, A. J., & Farley, B. J. (2013). Tinnitus-related neural activity: Theories of generation, propagation, and centralization. *Hearing Research*, *295*, 161–171. http://doi.org/10.1016/j.heares.2012.09.010

Norena, A., Micheyl, C., Chéry-Croze, S., & Collet, L. (2002). Psychoacoustic characterization of the tinnitus spectrum: implications for the underlying mechanisms of tinnitus. *Audiology & Neuro-Otology*, *7*(6), 358–69. http://doi.org/66156

Nottage, J. F., & Horder, J. (2015). State-of-the-Art Analysis of High-Frequency (Gamma Range) Electroencephalography in Humans. *Neuropsychobiology*, *72*(3–4), 219–28. http://doi.org/10.1159/000382023

Nunez, P. L., & Srinivasan, R. (2006). *Electric Fields of the Brain: The Neurophysics of EEG* (Second Edi). Oxford University Press.

Ochi, K., & Eggermont, J. J. (1996). Effects of salicylate on neural activity in cat primary auditory cortex. *Hearing Research*, *95*(1–2), 63–76. http://doi.org/10.1016/0378-5955(96)00019-6

Ochi, K., & Eggermont, J. J. (1997). Effects of quinine on neural activity in cat primary auditory cortex. *Hearing Research*, *105*(1–2), 105–18. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9083808

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J. M. (2011). FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Comput Intell Neurosci*, *2011*, 156869. http://doi.org/10.1155/2011/156869

Oostenveld, R., Stegeman, D. F., Praamstra, P., & van Oosterom, A. (2003). Brain symmetry and topographic analysis of lateralized event-related potentials. *Clinical Neurophysiology*, *114*(7), 1194–1202. http://doi.org/10.1016/S1388-2457(03)00059-2

Ortmann, M., Muller, N., Schlee, W., & Weisz, N. (2011). Rapid increases of gamma power in the auditory cortex following noise trauma in humans. *Eur J Neurosci*, *33*(3), 568–575. http://doi.org/10.1111/j.1460-9568.2010.07542.x

Oshino, S., Kato, A., Wakayama, A., Taniguchi, M., Hirata, M., & Yoshimine, T. (2007). Magnetoencephalographic analysis of cortical oscillatory activity in patients with brain tumors: Synthetic aperture magnetometry (SAM) functional imaging of delta band activity. *NeuroImage*, *34*(3), 957–964. http://doi.org/10.1016/j.neuroimage.2006.08.054

Osipova, D., Rantanen, K., Ahveninen, J., Ylikoski, R., Häppölä, O., Strandberg, T., & Pekkonen, E. (2006). Source estimation of spontaneous MEG oscillations in mild cognitive impairment. *Neuroscience Letters*, *405*(1–2), 57–61. http://doi.org/10.1016/j.neulet.2006.06.045

Ozimek, E., Wicher, A., Szyfter, W., & Szymiec, E. (2006). Distortion product otoacoustic emission (DPOAE) in tinnitus patients. *The Journal of the Acoustical Society of America*, *119*(1), 527–38. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16454306

Palva, S., & Palva, J. M. (2012). Discovering oscillatory interaction networks with M/EEG: challenges and breakthroughs. *Trends in Cognitive Sciences*, *16*(4), 219–230. http://doi.org/10.1016/j.tics.2012.02.004

Pan, T., Tyler, R. S., Ji, H., Coelho, C., Gehringer, A. K., & Gogel, S. A. (2009). The relationship between tinnitus pitch and the audiogram. *International Journal of Audiology*, *48*(5), 277–94. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19842803

Pantev, C., Oostenveld, R., Engelien, A., Ross, B., Roberts, L. E., & Hoke, M. (1998). Increased auditory cortical representation in musicians. *Nature*, *392*(6678), 811–814. http://doi.org/10.1038/33918

Penner, M. J. (1980). Two-tone forward masking patterns and tinnitus. *Journal of Speech and Hearing Research*, *23*(4), 779–86. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7442211

Phillips, D. P., & Carr, M. M. (1998). Disturbances of loudness perception. *Journal of the American Academy of Audiology*, *9*(5), 371–9; quiz 399. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9806411

Picton, T. W. (2000). Guidelines for using human event-related potentials to study cognition: Recording standards and publication criteria. *Psychophysiology*, *37*(2), 127–152. http://doi.org/10.1111/1469-8986.3720127

Pivik, R. ., Broughton, R. ., Coppola, R., Davidson, R. ., Fox, N., & Nuwer, M. . (1993). Guidelines for the recording and quantitative analysis of electroencephalographic activity in research contexts. *Psychophysiology*, *30*, 547–558.

Podda, M. V., Cocco, S., Mastrodonato, A., Fusco, S., Leone, L., Barbati, S. A., … Podda, M. V. (2016). Anodal transcranial direct current stimulation boosts synaptic plasticity and memory in mice via epigenetic regulation of Bdnf expression. *Scientific Reports*, *6*, 22180. http://doi.org/10.1038/srep22180

Prendergast, G., Guest, H., Munro, K. J., Kluk, K., Léger, A., Hall, D. A., … Plack, C. J. (2017). Effects of noise exposure on young adults with normal audiograms I: Electrophysiology. *Hearing Research*, *344*, 68–81. http://doi.org/10.1016/j.heares.2016.10.028

Priori, A. (2003). Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. *Clinical Neurophysiology*, *114*(4), 589–595. http://doi.org/10.1016/S1388-2457(02)00437-6

Pupura, D. P., & McMurtry, J. G. (1965). Intracellular Activities and Evoked Potential Changes During Polarization of Motor Cortex. *Journal of Neurophysiology*, *28*(1), 166–85. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14244793

Rajan, R. (1998). Receptor organ damage causes loss of cortical surround inhibition without topographic map plasticity. *Nature Neuroscience*, *1*(2), 138–43. http://doi.org/10.1038/388

Rajan, R., Irvine, D. R. F., Wise, L. Z., & Heil, P. (1993). Effect of unilateral partial cochlear lesions in adult cats on the representation of lesioned and unlesioned cochleas in primary auditory cortex. *The Journal of Comparative Neurology*, *338*(1), 17–49. http://doi.org/10.1002/cne.903380104

Rauschecker, J. P. (1999). Auditory cortical plasticity: a comparison with other sensory systems. *Trends in Neurosciences*, *22*(2), 74–80. http://doi.org/10.1016/S0166-2236(98)01303-4

Rauschecker, J. P., Leaver, A. M., & Muhlau, M. (2010). Tuning Out the Noise: Limbic-Auditory Interactions in Tinnitus. *Neuron*, *66*(6), 819–826. http://doi.org/10.1016/j.neuron.2010.04.032

Rihs, T. A., Michel, C. M., & Thut, G. (2007). Mechanisms of selective inhibition in visual spatial attention are indexed by ?-band EEG synchronization. *European Journal of Neuroscience*, *25*(2), 603–610. http://doi.org/10.1111/j.1460-9568.2007.05278.x

Roach, B. J., & Mathalon, D. H. (2008). Event-related EEG time-frequency analysis: an overview of measures and an analysis of early gamma band phase locking in schizophrenia. *Schizophrenia Bulletin*, *34*(5), 907–26. http://doi.org/10.1093/schbul/sbn093

Roberts, L. E., Bosnyak, D. J., Bruce, I. C., Gander, P. E., & Paul, B. T. (2015). Evidence for differential modulation of primary and nonprimary auditory cortex by forward masking in tinnitus. *Hearing Research*, *327*, 9–27. http://doi.org/10.1016/j.heares.2015.04.011

Roberts, L. E., Moffat, G., Baumann, M., Ward, L. M., & Bosnyak, D. J. (2008). Residual inhibition functions overlap tinnitus spectra and the region of auditory threshold shift. *Journal of the Association for Research in Otolaryngology : JARO*, *9*(4), 417–35. http://doi.org/10.1007/s10162-008-0136-9

Roberts, L. E., Moffat, G., Baumann, M., Ward, L. M., & Bosnyak, D. J. (2008). Residual inhibition functions overlap tinnitus spectra and the region of auditory threshold shift. *JARO - Journal of the Association for Research in Otolaryngology*, *9*(4), 417–435. http://doi.org/10.1007/s10162-008-0136-9

Roberts, L. E., Moffat, G., Baumann, M., Ward, L. M., & Bosnyak, D. J. (2008). Residual inhibition functions overlap tinnitus spectra and the region of auditory threshold shift. *J Assoc Res Otolaryngol*, *9*(4), 417–435. http://doi.org/10.1007/s10162-008-0136-9

Rush, S., & Driscoll, D. A. (1968). Current distribution in the brain from surface electrodes. *Anesthesia and Analgesia*, *47*(6), 717–23. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/4972743

Schaal, N. K., Williamson, V. J., & Banissy, M. J. (2013). Anodal transcranial direct current stimulation over the supramarginal gyrus facilitates pitch memory. *European Journal of Neuroscience*, *38*(10), 3513–3518. http://doi.org/10.1111/ejn.12344

Schaette, R., & Kempter, R. (2006). Development of tinnitus-related neuronal hyperactivity through homeostatic plasticity after hearing loss: a computational model. *European Journal of Neuroscience*, *23*(11), 3124–3138. http://doi.org/10.1111/j.1460-9568.04774.x

Schaette, R., & McAlpine, D. (2011). Tinnitus with a normal audiogram: physiological evidence for hidden hearing loss and computational

model. *Journal of Neuroscience*, *31*(38), 13452–13457. http://doi.org/10.1523/JNEUROSCI.2156-11.2011

Schaette, R., Turtle, C., & Munro, K. J. (2012). Reversible Induction of Phantom Auditory Sensations through Simulated Unilateral Hearing Loss. *PLoS One*, *7*(6). http://doi.org/ARTN e35238DOI 10.1371/journal.pone.0035238

Schecklmann, M., Landgrebe, M., Poeppl, T. B., Kreuzer, P., Manner, P., Marienhagen, J., … Langguth, B. (2013). Neural correlates of tinnitus duration and Distress: A positron emission tomography study. *Human Brain Mapping*, *34*(1), 233–240. http://doi.org/Doi 10.1002/Hbm.21426

Schecklmann, M., Vielsmeier, V., Steffens, T., Landgrebe, M., Langguth, B., & Kleinjung, T. (2012). Relationship between Audiometric Slope and Tinnitus Pitch in Tinnitus Patients: Insights into the Mechanisms of Tinnitus Generation. *PLoS ONE*, *7*(4), e34878. http://doi.org/10.1371/journal.pone.0034878

Sedley, W., Gander, P. E., Kumar, S., Oya, H., Kovach, C. K., Nourski, K. V., … Griffiths, T. D. (2015). *Intracranial Mapping of a Cortical Tinnitus System using Residual Inhibition*. *Current Biology* (Vol. 25). http://doi.org/10.1016/j.cub.2015.02.075

Sedley, W., Teki, S., Kumar, S., Barnes, G. R., Bamiou, D.-E., & Griffiths, T. D. (2012). Single-subject oscillatory gamma responses in tinnitus. *Brain*, *135*, 3089–3100. http://doi.org/10.1093/brain/aws220

Sereda, M., Edmondson-Jones, M., & Hall, D. A. (2015). Relationship between tinnitus pitch and edge of hearing loss in individuals with a narrow tinnitus bandwidth. *International Journal of Audiology*, *54*(4), 249–56. http://doi.org/10.3109/14992027.2014.979373

Sereda, M., Hall, D. A., Bosnyak, D. J., Edmondson-Jones, M., Roberts, L. E., Adjamian, P., & Palmer, A. R. (2011a). Re-examining the relationship between audiometric profile and tinnitus pitch. *International Journal of Audiology*, *50*(5), 303–312. http://doi.org/10.3109/14992027.2010.551221

Sereda, M., Hall, D. A., Bosnyak, D. J., Edmondson-Jones, M., Roberts, L. E., Adjamian, P., & Palmer, A. R. (2011b). Re-examining the relationship between audiometric profile and tinnitus pitch. *International Journal of Audiology*, *50*(5), 303–312. http://doi.org/10.3109/14992027.2010.551221

Shargorodsky, J., Curhan, G. C., & Farwell, W. R. (2010). Prevalence and Characteristics of Tinnitus among US Adults. *American Journal of Medicine*, *123*(8), 711–718. http://doi.org/10.1016/j.amjmed.2010.02.015

Shekhawat, G. S., Kobayashi, K., & Searchfield, G. D. (2014). Methodology for Studying the Transient Effects of transcranial direct current stimulation

combined with auditory residual inhibition on tinnitus . *Journal of Neuroscience Methods*, *239*, 28–33.

Soekadar, S. R., Witkowski, M., Cossio, E. G., Birbaumer, N., Robinson, S. E., & Cohen, L. G. (2013). In vivo assessment of human brain oscillations during application of transcranial electric currents. *Nature Communications*, *4*. http://doi.org/10.1038/ncomms3032

Song, J. J., Vanneste, S., Van de Heyning, P., & De Ridder, D. (2012). Transcranial Direct Current Stimulation in Tinnitus Patients: A Systemic Review and Meta-Analysis. *Scientific World Journal*, 7. http://doi.org/10.1100/2012/427941

Spalding, J. A. (1903). Tinnitus, with a plea for its more accurate musical notation. *Archives of Otology*, *32*(4), 263–272.

Stagg, C. J., Best, J. G., Stephenson, M. C., O'Shea, J., Wylezinska, M., Kincses, Z. T., … Johansen-Berg, H. (2009). Polarity-Sensitive Modulation of Cortical Neurotransmitters by Transcranial Stimulation. *Journal of Neuroscience*, *29*(16), 5202–5206. http://doi.org/10.1523/JNEUROSCI.4432-08.2009

Stagg, C. J., & Nitsche, M. A. (2011). Physiological Basis of Transcranial Direct Current Stimulation. *The Neuroscientist*, *17*(1). http://doi.org/10.1177/1073858410386614

Sweetow, R. W., & Levy, M. C. (1990). Tinnitus Severity Scaling for Diagnostic/Therapeutic Usage. *Hearing Instruments*, *41*, 44–46.

Tang, J., Ji, B., & Liu, L. (2011). Study of hearing loss in 200 patients with subjective tinnitus. *Journal of Clinical Otorhinolaryngology, Head, and Neck Surgery*, *25*(16), 726–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22070077

Teismann, H., Okamoto, H., & Pantev, C. (2011). Short and Intense Tailor-Made Notched Music Training against Tinnitus: The Tinnitus Frequency Matters. *PLoS One*, *6*(9). http://doi.org/e2468510.1371/journal.pone.0024685

Ter Horst, G. J., Hautvast, R. W., De Jongste, M. J., & Korf, J. (1996). Neuroanatomy of cardiac activity-regulating circuitry: a transneuronal retrograde viral labelling study in the rat. *The European Journal of Neuroscience*, *8*(10), 2029–41. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8921293

Terry, A. M., Jones, D. M., Davis, B. R., & Slater, R. (1983). Parametric studies of tinnitus masking and residual inhibition. *British Journal of Audiology*, *17*(4), 245–256. http://doi.org/10.3109/03005368309081485

Theodoroff, S. M., & Folmer, R. L. (2013). Repetitive Transcranial Magnetic Stimulation as a Treatment for Chronic Tinnitus. *Otology & Neurotology*, *34*(2), 199–208. http://doi.org/10.1097/MAO.0b013e31827b4d46

Tyler, R. S., & Baker, L. J. (1983). Difficulties experienced by tinnitus sufferers. *The Journal of Speech and Hearing Disorders*, *48*(2), 150–4. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/6621006

Tyler, R. S., Conrad-Armes, D., & Smith, P. A. (1984a). Postmasking Effects of Sensorineural Tinnitus: A Preliminary Investigation. . *Journal of Speech and Hearing Research*, *27*, 466–474.

Tyler, R. S., Conrad-Armes, D., & Smith, P. A. (1984b). Postmasking effects of sensorineural tinnitus: a preliminary investigation. *Journal of Speech and Hearing Research*, *27*(3), 466–474.

Tyler, R. S., Pienkowski, M., Roncancio, E. R., Jun, H. J., Brozoski, T., Dauman, N., … Moore, B. C. J. (2014). A Review of Hyperacusis and Future Directions: Part I. Definitions and Manifestations. *American Journal of Audiology*, *23*, 402–419. http://doi.org/10.1044/2014_AJA-14-0010

Utz, K. S., Dimova, V., Oppenländer, K., & Kerkhoff, G. (2010). Electrified minds: Transcranial direct current stimulation (tDCS) and Galvanic Vestibular Stimulation (GVS) as methods of non-invasive brain stimulation in neuropsychology—A review of current data and future implications. *Neuropsychologia*, *48*(10), 2789–2810. http://doi.org/10.1016/j.neuropsychologia.2010.06.002

van der Loo, E., Congedo, M., Vanneste, S., Van De Heyning, P., & De Ridder, D. (2011). Insular lateralization in tinnitus distress. *Autonomic Neuroscience : Basic & Clinical*, *165*(2), 191–4. http://doi.org/10.1016/j.autneu.2011.06.007

van der Loo, E., Gais, S., Congedo, M., Vanneste, S., Plazier, M., Menovsky, T., … De Ridder, D. (2009). Tinnitus intensity dependent gamma oscillations of the contralateral auditory cortex. *PloS One*, *4*(10), e7396. http://doi.org/10.1371/journal.pone.0007396

Van Veen, B. D., & Buckley, K. M. (1988). Beamforming: a versatile approach to spatial filtering. *ASSP Magazine, IEEE*. http://doi.org/10.1109/53.665

Vanneste, S., Heyning, P. Van de, & Ridder, D. De. (2011). Contralateral parahippocampal gamma-band activity determines noise-like tinnitus laterality: a region of interest analysis. *Neuroscience*, *199*, 481–90. http://doi.org/10.1016/j.neuroscience.2011.07.067

Vanneste, S., Plazier, M., der Loo, E. van, de Heyning, P. Van, Congedo, M., & De Ridder, D. (2010). The neural correlates of tinnitus-related distress. *NeuroImage*, *52*(2), 470–80. http://doi.org/10.1016/j.neuroimage.2010.04.029

Vanneste, S., Plazier, M., Van Der Loo, E., Ost, J., Van de Heyning, P., & De Ridder, D. (2010). Burst transcranial magnetic stimulation: which tinnitus characteristics influence the amount of transient tinnitus suppression? *European Journal of Neurology*, *17*(9), 1141–1147. http://doi.org/10.1111/j.1468-1331.2010.02987.x

Vanneste, S., Plazier, M., van der Loo, E., Van de Heyning, P., & De Ridder, D. (2010). The differences in brain activity between narrow band noise and pure tone tinnitus. *PloS One*, *5*(10), e13618. http://doi.org/10.1371/journal.pone.0013618

Vanneste, S., Walsh, V., Van De Heyning, P., & De Ridder, D. (2013). Comparing immediate transient tinnitus suppression using tACS and tDCS: a placebo-controlled study. *Experimental Brain Research*, *226*(1), 25–31. http://doi.org/10.1007/s00221-013-3406-7

VanVeen, B. D., vanDrongelen, W., Yuchtman, M., & Suzuki, A. (1997). Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *Ieee Transactions on Biomedical Engineering*, *44*(9), 867–880. http://doi.org/10.1109/10.623056

Vernon, J. (1977). Attemps to relieve tinnitus. *Journal of the American Audiology Society*, *2*(4), 124–31. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/845067

Vernon, J. A. (1987). Pathophysiology of tinnitus: a special case--hyperacusis and a proposed treatment. *The American Journal of Otology*, *8*(3), 201–2. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3631220

Vernon, J. A., & Meikle, M. B. (2003). Tinnitus: clinical measurement. *Otolaryngologic Clinics of North America*, *36*(2), 293–305, vi. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12856298

Vogel, I., van de Looij-Jansen, P. M., Mieloo, C. L., Burdorf, A., & de Waart, F. (2014). Risky Music Listening, Permanent Tinnitus and Depression, Anxiety, Thoughts about Suicide and Adverse General Health. *PLoS One*, *9*(6). http://doi.org/e9891210.1371/journal.pone.0098912

von Stein, A., & Sarnthein, J. (2000). Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization. *International Journal of Psychophysiology : Official Journal of the International Organization of Psychophysiology*, *38*(3), 301–13. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11102669

Vorwerk, J., Cho, J.-H., Rampp, S., Hamer, H., Kn?sche, T. R., & Wolters, C. H. (2014). A guideline for head volume conductor modeling in EEG and MEG. *NeuroImage*, *100*, 590–607. http://doi.org/10.1016/j.neuroimage.2014.06.040

Voss, U., Holzmann, R., Hobson, A., Paulus, W., Koppehele-Gossel, J., Klimke, A., & Nitsche, M. A. (2014). Induction of self awareness in dreams through frontal low current stimulation of gamma activity. *Nature Neuroscience*, *17*(6), 810–812. http://doi.org/10.1038/nn.3719

Voytenko, S. V., & Galazyuk, A. V. (2010). Suppression of spontaneous firing in inferior colliculus neurons during sound processing. *Neuroscience*, *165*(4), 1490–1500. http://doi.org/10.1016/j.neuroscience.2009.11.070

Vrba, J. (2002). Magnetoencephalography: The art of finding a needle in a haystack. *Physica C: Superconductivity and Its Applications*, *368*(1–4), 1–9. http://doi.org/10.1016/S0921-4534(01)01131-5

Wang, J., & O'Donnell, P. (2001). D(1) dopamine receptors potentiate nmda-mediated excitability increase in layer V prefrontal cortical pyramidal neurons. *Cerebral Cortex (New York, N.Y. : 1991)*, *11*(5), 452–62. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11313297

Weinbruch, C., Moratti, S., Elbert, T., Vogel, U., Fehr, T., Kissler, J., … Rockstroh, B. (2003). Source distribution of neuromagnetic slow wave activity in schizophrenic and depressive patients. *Clinical Neurophysiology*, *114*(11), 2052–2060. http://doi.org/10.1016/S1388-2457(03)00210-4

Weisz, N., Dohrmann, K., & Elbert, T. (2007). The relevance of spontaneous activity for the coding of the tinnitus sensation. *Prog Brain Res*, *166*, 61–70. http://doi.org/10.1016/S0079-6123(07)66006-3

Weisz, N., Hartmann, T., Müller, N., Lorenz, I., & Obleser, J. (2011). Alpha Rhythms in Audition: Cognitive and Clinical Perspectives. *Frontiers in Psychology*, *2*, 73. http://doi.org/10.3389/fpsyg.2011.00073

Weisz, N., Moratti, S., Meinzer, M., Dohrmann, K., & Elbert, T. (2005). Tinnitus perception and distress is related to abnormal spontaneous brain activity as measured by magnetoencephalography. *Plos Medicine*, *2*(6), 546–553. http://doi.org/10.1371/journal.pmed.0020153

Weisz, N., Muller, S., Schlee, W., Dohrmann, K., Hartmann, T., & Elbert, T. (2007). The neural code of auditory phantom perception. *Journal of Neuroscience*, *27*(6), 1479–1484. http://doi.org/10.1523/JNEUROSCI.3711-06.2007

Weisz, N., Müller, S., Schlee, W., Dohrmann, K., Hartmann, T., & Elbert, T. (2007). The neural code of auditory phantom perception. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *27*(6), 1479–84. http://doi.org/10.1523/JNEUROSCI.3711-06.2007

Wendel, K., Väisänen, O., Malmivuo, J., Gencer, N. G., Vanrumste, B., Durka, P., … Grave De Peralta Menendez, R. (2009). EEG/MEG source imaging: Methods, challenges, and open issues. *Computational Intelligence and Neuroscience*, *2009*. http://doi.org/10.1155/2009/656092

Whitham, E. M., Pope, K. J., Fitzgibbon, S. P., Lewis, T., Clark, C. R., Loveless, S., … Willoughby, J. O. (2007). Scalp electrical recording during paralysis: Quantitative evidence that EEG frequencies above 20Hz are contaminated by EMG. *Clinical Neurophysiology*, *118*(8), 1877–1888. http://doi.org/10.1016/j.clinph.2007.04.027

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

197–201. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2008074

Wineland, A. M., Burton, H., & Piccirillo, J. (2012). Functional Connectivity Networks in Nonbothersome Tinnitus. *Otolaryngology-Head and Neck Surgery*, *147*(5), 900–906. http://doi.org/10.1177/0194599812451414

Wong, S. W., Massé, N., Kimmerly, D. S., Menon, R. S., & Shoemaker, J. K. (2007). Ventral medial prefrontal cortex and cardiovagal control in conscious humans. *NeuroImage*, *35*(2), 698–708. http://doi.org/10.1016/j.neuroimage.2006.12.027

Worden, M. S., Foxe, J. J., Wang, N., & Simpson, G. V. (2000). Anticipatory biasing of visuospatial attention indexed by retinotopically specific alpha-band electroencephalography increases over occipital cortex. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *20*(6), RC63. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10704517

Yokoi, Y., Sumiyoshi, T., Alonzo, A., Brassil, J., Taylor, J., Martin, D., … Hamilton, R. (2015). Application of transcranial direct current stimulation to psychiatric disorders: trends and perspectives. *Neuropsychiatric Electrophysiology*, *1*(1), 10. http://doi.org/10.1186/s40810-015-0012-x

Yuval-Greenberg, S., Tomer, O., Keren, A. S., Nelken, I., & Deouell, L. Y. (2008). Transient Induced Gamma-Band Response in EEG as a Manifestation of Miniature Saccades. *Neuron*, *58*(3), 429–441. http://doi.org/10.1016/J.NEURON.2008.03.027

Zaehle, T., Beretta, M., Jäncke, L., Herrmann, C. S., & Sandmann, P. (2011). Excitability changes induced in the human auditory cortex by transcranial direct current stimulation: direct electrophysiological evidence. *Experimental Brain Research*, *215*(2), 135–140. http://doi.org/10.1007/s00221-011-2879-5