NON-INVASIVE BRAIN STIMULATION AND AUDITORY CONNECTIVITY IN TINNITUS

By

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To

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Supervised by Prof. Rosemary Varley, Prof. Giriraj Singh Shekhawat and Prof. Chris Clark

Declarations

I, Tori Elyssa Kok, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Background: This PhD thesis is an evaluation of transcranial direct current stimulation (tDCS) and high-definition tDCS (HD-tDCS) for the management of tinnitus, as well as an investigation of auditory network connectivity in tinnitus. Tinnitus is the perception of a sound without an external source, and it affects around 10% of the adult population. It can be severely debilitating, and therefore effective therapies are needed, but currently there is no cure. Tinnitus mechanisms are not fully understood. TDCS is a non-invasive brain stimulation tool which uses electrodes to administer a small current to the cortex, thereby increasing or decreasing cortical excitability. HD-tDCS is a type of tDCS which uses a cap of micro-electrodes for more focal stimulation. Both have been explored as management options for tinnitus.

Methods: This PhD project aimed to evaluate the efficacy and acceptability of (HD-)tDCS for tinnitus management by conducting a scoping review on the current evidence (Chapter 3) and surveying tinnitus patients' opinions on the technique (n = 272) (Chapter 4). This project also aimed to examine tinnitus auditory connectivity by way of a scoping review (Chapter 5) and by conducting a resting-state functional magnetic resonance imaging study (rs-fMRI) (Chapter 6).

Results and discussion: This thesis found that the evidence-base for the efficacy of tDCS in tinnitus is not robust, and current tDCS trial outcomes are far from delivering the effect sizes required by tinnitus sufferers to render tDCS an acceptable management option. It was also found that tinnitus is associated with alterations to functional connectivity patterns, although exact results are rarely replicated. This thesis found increased functional connectivity between bilateral thalamus and right visual association cortex in tinnitus patients compared to controls, suggesting a role for thalamic hyperactivity in tinnitus. Future research should investigate the role of the thalamus in tinnitus further.

Impact Statement

Tinnitus plagues millions of people every day. The absence of effective treatment leaves some of those people feeling desperate. Tinnitus sufferers around the globe are looking for a cure. However, it is hard to develop a cure or an effective treatment when little is certain about the mechanisms of the condition.

My thesis takes a step in the right direction towards understanding tinnitus mechanisms better. I conducted a functional magnetic resonance imaging study with 84 participants to compare the resting brain activity between individuals with tinnitus and without. Although I didn't replicate some common findings in attentional and emotional networks, I did find increased connectivity between the thalamus and visual association cortex in the tinnitus group compared to the control group. This provides some evidence for thalamic hyperactivity as a potential mechanism involved in tinnitus. The impact for academia is that it provides direction for future studies to focus on the role of thalamus in tinnitus further. The impact outside academia is that continuation of this line of work could potentially find a biomarker for tinnitus which could eventually help in developing an effective treatment.

I also investigated the acceptability of transcranial direct current stimulation (tDCS) as an intervention for tinnitus by conducting an online survey. A total of 272 tinnitus sufferers gave their opinions on tDCS as a management option which led to some interesting insights. Most importantly, if tDCS is found to reduce tinnitus-related distress but not its actual loudness, there is a large subgroup of tinnitus sufferers that would not be satisfied with tDCS as an option. However, a subgroup of tinnitus sufferers might still find this acceptable. Also, current interventions are a long way from reaching the effect sizes that would be considered worthwhile for the tinnitus sufferers in my survey. The impact for academia is that this provides some important guidance to future tDCS intervention trials. They should make it very clear what the therapeutic target is (tinnitus distress, loudness, or both) and select stimulation protocols accordingly. The impact outside academia is that tinnitus sufferers were able to share their view on tDCS for the first time which is a very important step towards tDCS becoming a clinical tool, if proven effective.

In conclusion, this thesis takes a step in the right direction to A) finding a biomarker for tinnitus through brain imaging; and B) evaluating the evidence for tDCS efficacy and acceptability of the method, so that one day tDCS might be clinically available to tinnitus sufferers.

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Rosemary Varley (second author): conception and design, and critically revising the manuscript for important intellectual content
Giriraj Shekhawat (corresponding author): conception and design, and critically revising the manuscript for important intellectual content

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Rosemary Varley: conception and design, and critically revising the manuscript for important intellectual content
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Table of Contents

Abbreviations

ACC – anterior cingulate cortex

AI – anterior insula

ALFF – amplitude of low-frequency fluctuations

BA – Brodmann's area

BDI – Beck depression inventory

BOLD – blood-oxygenation-level-dependent

BSA – British society of audiology

CGI – clinical global improvement

DAN – dorsal attention network

DARTEL - Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra

DLPFC – dorsolateral prefrontal cortex

DMN – default mode network

DTI – diffusion tensor imaging

EEG – electroencephalography

FA – fractional anisotropy

FC – functional connectivity

FEF – frontal eye fields

fMRI – functional magnetic resonance imaging

FP – fronto-parietal

FWHM – full-width at half maximum

GE-EPI – gradient-echo echo-planar imaging

GCA – Granger causality analysis

HADS – Hospital Anxiety and Depression Scale

HD-tDCS – high-definition transcranial direct current stimulation

HG – Heschl's gyrus

HL – hearing loss

HQ – Hyperacusis Questionnaire

IC – inferior colliculus

ICA – independent component analysis

IFG – inferior frontal gyrus

IHC – inner hair cells

IPL – inferior parietal lobule

IPS – intraparietal sulcus

LTA – left temporoparietal area

M1 – primary motor cortex

MFG – middle frontal gyrus

MGB – medial geniculate body

MNI – Montreal neurological institute

MOG – middle occipital gyrus

mPFC – medial prefrontal cortex

MRI – magnetic resonance imaging

MRS – magnetic resonance spectroscopy

MTG – middle temporal gyrus

NAc – nucleus accumbens

NH – normal hearing

NIBS – non-invasive brain stimulation

OFC – orbitofrontal cortex

OHC – outer hair cells

PAC – primary auditory cortex

PCC – posterior cingulate cortex

PST – prolonged spontaneous tinnitus

PTA – pure tone audiometry

ReHo – regional homogeneity

ROI – region of interest

rs-fMRI – resting-state functional magnetic resonance imaging

RSN – resting-state network

SAS – Zung Self-Rating Anxiety Scale

SCA – seed-based correlation analysis

SDS – Zung Self-Rating Depression Scale

SFC – superior frontal cortex

SFG – superior frontal gyrus

SPC – superior parietal cortex

SPM – Statistical Parametric Mapping

SPL – superior parietal lobule

STG - superior temporal gyrus

tACS – transcranial alternating current stimulation

TCD – thalamocortical dysrhythmia

tDCS – transcranial direct current stimulation

TE – echo time

tES – transcranial electrical stimulation

THI – Tinnitus Handicap Inventory

THQ – Tinnitus Handicap Questionnaire

TFI – Tinnitus Functional Index

TMS – transcranial magnetic stimulation

TPJ – temporal-parietal junction

TR – repetition time

tRNS – transcranial random noise stimulation

TQ – Tinnitus Questionnaire

ULL – uncomfortable loudness levels

V1 – primary visual cortex

VAN – ventral attention network

VAS – visual analogue scale

VBM – voxel-based morphometry

VMHC – voxel-mirrored homotopic connectivity

vmPFC – ventral medial prefrontal cortex

WoS CC – Web of Science Core Collection

Chapter 1 Introduction

This project is an investigation of non-invasive brain stimulation and auditory connectivity in tinnitus. Tinnitus is the perception of a sound without an external source, and it affects around 10% of the adult population. It can be severely debilitating, and therefore effective therapies are sought. Examples of non-invasive brain stimulation are transcranial direct current stimulation (tDCS) and high-definition transcranial direct current stimulation (HD-tDCS). Both methods use electrodes placed on the scalp to administer a small electrical current, which reaches the cortex and influences neuronal excitability. The HD-variant results in more focal stimulation, targeting smaller areas, whereas tDCS targets wider distributed brain areas (Datta et al., 2009).

Both tDCS and HD-tDCS have been under investigation as a tinnitus management option. Preliminary results are positive but warrant further investigation (Shekhawat et al., 2015c). This PhD project aims to explore the use of tDCS and HD-tDCS for tinnitus management, as well as investigate functional connectivity networks in tinnitus and the implications of brain imaging research for the use of tDCS and HD-tDCS in the future. The main goal is to provide direction for the future of tDCS and HD-tDCS research in the field of tinnitus, so that one day these tools might be clinically available to tinnitus patients, should they be proven effective.

This project was impacted by COVID-19, which necessitated changes to the original research proposal which had outlined several different HD-tDCS intervention trials for tinnitus. The plans for these trials had to make place for other types of research that were possible during a climate of lockdowns, being two scoping review projects (Chapter 3 and 5) an online survey project (Chapter 4), and a large-scale brain imaging project (Chapter 6).

1.1 Objectives

This thesis was undertaken with the following objectives in mind:

- To present a birds-eye overview of the field of tinnitus research by means of literature review (Chapter 2);
- To investigate the impact of tDCS and HD-tDCS on tinnitus perception by means of a scoping review (Chapter 3);
- To investigate tinnitus patients' opinions on HD-tDCS as a management option by means of an online survey (Chapter 4);
- To investigate changes to resting-state networks in tinnitus as measured by fMRI by means of a scoping review (Chapter 5);
- To investigate changes to functional connectivity in tinnitus further by conducting a resting-state fMRI study (Chapter 6);
- To discuss the implications of the findings from this thesis, particularly with regards to their relevance for the application of (HD-)tDCS in tinnitus (Chapter 7).

Chapter 2 Literature review

2.1 Tinnitus: General

2.1.1 Epidemiology

Hearing sounds, even in silent conditions, is a very common experience. Numerous experiments have shown that people with normal hearing when placed in a sound-proof room can still hear sounds like buzzing, humming, or ringing. The percentage of people who report such symptoms varies widely from 40% (Graham and Newby, 1962) up to 94% (Heller and Bergman, 1953). The perception of sound in silence is called tinnitus, derived from the Latin 'tinnire' (*to ring*). Although many people report tinnitus-like perceptions in a soundproof room, this environment does not resemble everyday listening situations. In reality, there is almost always some background noise present, which might have a masking effect on tinnitus perception. This could account for why the percentage of people that report tinnitus in a soundproof room is much higher than the actual prevalence of tinnitus in daily life (Baguley et al., 2013).

Tinnitus can be classified as subjective or objective. In subjective tinnitus, the noise can only be heard by the affected person and has no physical source, whereas in objective tinnitus the noise can be measured with specialised sound equipment (Esmaili and Renton, 2018). Objective tinnitus is often pulsatile in nature and often has a specific, identifiable cause (Hofmann et al., 2013). In this thesis, unless mentioned otherwise, "tinnitus" will refer to subjective, non-pulsatile tinnitus.

Tinnitus is very prevalent globally, with estimates of prevalence ranging from 8.2% to 30.3% of adults experiencing prolonged tinnitus (Eggermont, 2012). A robust study into the epidemiology of tinnitus was conducted by Davis and El Rafaie (2000) as part of the Medical Research Council's Institute of Hearing Research in the UK. This study randomly sampled 48,313 participants in four cities by means of a postal survey and had a response rate of over 80%. They adhered to the definition of prolonged spontaneous tinnitus (PST) (tinnitus that lasts at least five minutes) and found 10.1% of adults experience PST. A study in the US reported bothersome tinnitus in about 8% of participants (Nondahl et al., 2002), whereas Davis and El Rafaie (2000) found 2.8%

of people in the general population were moderately annoyed by their tinnitus, and in 0.5% of people the tinnitus severely impacted their quality of life. Axelsson and Ringdahl (1989) reported that 2.4% of the total population was plagued by their tinnitus all day.

A recent population-based study in Rotterdam, the Netherlands, surveyed 6098 participants over the age of 50 and found tinnitus was present at least once a week in 21.4% of participants. For one in every ten participants with tinnitus, the tinnitus interfered with their daily life (Oosterloo et al., 2021).

2.1.2 Tinnitus impact

Tinnitus can have a severe, negative emotional impact on the sufferer, including changes in mood, sleeping difficulties and annoyance (Mrena et al., 2002). There is a lot of variability in the experience of tinnitus: the impact of tinnitus can range from no impact to, in the most extreme cases, suicide (Pridmore et al., 2012), although the relationship between tinnitus and suicide is debated (Szibor et al., 2019). Several studies have shown there is a high comorbidity between tinnitus and emotional disorders such as depression and anxiety (Baguley et al., 2013).

The Swedish LifeGene cohort included 7615 participants with tinnitus, 697 (9.2%) of whom had bothersome tinnitus. The cross-sectional survey data showed that bothersome tinnitus, compared to non-bothersome tinnitus, was associated with factors, amongst others of higher age, reduced subjective hearing ability, and depression and anxiety (Basso et al., 2021).

Based on the lower estimate of 0.5% of the UK population severely impacted by tinnitus, over 300,000 people in the UK alone suffer from major consequences on their quality of life. This number is only expected to increase due to an aging population as the prevalence of tinnitus is found to be twice as frequent in older individuals compared to young adults (Wise et al., 2015a, Eggermont, 2012). Therefore, the cost of managing tinnitus that is carried by society is expected to increase. Economic modelling has shown that the total healthcare bill for tinnitus in

the UK sums up to 750 million GBP, or 0.6% of the annual healthcare budget (Stockdale et al., 2017). Similarly, in the Netherlands, the annual health care bill for tinnitus has been estimated at 1.9 billion euros or an average of 1544 euros annually per patient (Maes et al., 2013). In the US, cost per patient has been estimated at 660 dollars per year (Goldstein et al., 2015). The need for effective treatment is urgent, but currently there is no curative treatment available that significantly reduces tinnitus loudness (Langguth et al., 2009).

Tinnitus is popularly thought to interfere with the perception of sound, either because the tinnitus is louder than external stimuli or because the tinnitus is distracting from the external stimuli. However, Zeng et al. (2020) found that tinnitus did not interfere with auditory and speech perception in 45 people with chronic tinnitus compared to 27 controls. They compared performance across 36 measures, including gap detection, frequency and intensity discrimination, masking, temporal modulation detection and speech-in-noise perception tasks. They found 32 measures were unaffected by the tinnitus after correcting for age and hearing loss. In the remaining four measures, tinnitus only worsened performance in one measure, and enhanced performance in the other three, but the differences were very small. The authors interpret the lack of effect of tinnitus on auditory perception as a result of two independent pathways between perception of tinnitus and external sounds.

These results contradict those from widespread self-report of poor speech perception, especially in noise, by tinnitus sufferers (Ivansic et al., 2017). However, previous studies also found little (0 – 2 dB differences in speech reception thresholds) (Gilles et al., 2016) or no deficits (Moon et al., 2015) in hearing for people with tinnitus after controlling for age and hearing loss. There are different explanations for this discrepancy. First, it could be that self-report measures are not completely reliable, i.e., the participant might feel like their speech reception is worsened because of their tinnitus, when in fact it could be attributed to other factors such as hearing loss, age, or attention problems. Second, it could be that the tests used to measure speech reception in a laboratory experiment do not accurately reflect the

real-world conditions of listening in noise that tinnitus sufferers report struggling with. It is difficult to mimic, for example, a noisy pub situation in a laboratory.

2.1.3 Difficulties in tinnitus management

Several management options are available that can be helpful in coping with the tinnitus, such as counselling or sound therapy, but these do not reduce the tinnitus itself and not everyone benefits from them (Probst et al., 2019). In particular, those with tinnitus and deafness or severe-to-profound hearing loss do not benefit from therapies that require normal access to sound (Alzahrani et al., 2022).

Developing effective treatments for tinnitus is problematic because the underlying neuropathology of tinnitus is not fully understood (McFerran et al., 2019). This is partly because the presenting symptoms are heterogeneous (Cederroth et al., 2019): the tinnitus sound can be unilateral, bilateral or centrally in the head; it can be a pure tone or more like noise; and the pitch and the loudness can vary as well (Baguley et al., 2013). The majority of patients match their tinnitus tone to a pitch above 3 kHz. It has been suggested that the pitch of the tinnitus corresponds to the start of measured hearing loss on the audiogram, although this is not the case in all tinnitus patients (Baguley et al., 2013). Descriptions of the tinnitus sound also widely vary, from whistling to hissing, buzzing or ocean waves. Objective measurement of tinnitus is currently not possible, and therefore assessment relies on self-reporting and questionnaires to establish tinnitus severity (McFerran et al., 2019).

Although there is no standardised or fully accepted protocol for tinnitus assessment in research (Henry, 2016), there is clinical guidance available for the measurement of tinnitus from NICE (National Institute for Health and Care Excellence) (https://www.nice.org.uk/guidance/ng155) and the BSA (British Society of Audiology. The NICE guideline recommends using the Tinnitus Functional Index for adults to assess how tinnitus impacts them, or in the case of language issues or cognitive impairment, more accessible measures such as a visual analogue scale should be used (NICE, 2020). They also recommend audiological examination. For individuals with pulsatile tinnitus, imaging is recommended.

The BSA's practice guidance for tinnitus in adults (British Society of Audiology, 2021) (https://www.thebsa.org.uk/resources/practice-guidance-tinnitus-in-adults/) recommends history taking (including determining potential triggers), tinnitus questionnaires (e.g. Tinnitus Functional Index or Tinnitus Handicap Inventory), otoscopic examination, and in cases of pulsatile tinnitus, auscultation to ears, head and neck to exclude a bruit. They also recommend people with bothersome and distressing tinnitus should be referred for audiological assessment.

Both NICE and the BSA recommend against the use of psychoacoustic testing (e.g. pitch and loudness matching) for tinnitus as well as uncomfortable loudness levels tests, as they have not been shown to have a clinical benefit to the individual's tinnitus management. It should be kept in mind clinical guidance on tinnitus testing has different goals than tinnitus testing in research and therefore the assessment procedures used in clinical practice will vary from research. The individual's welfare should always be kept in mind when performing tinnitus tests whether in clinic or research and informed consent should be sought.

2.1.4 Tinnitus and hearing loss

It is estimated that around 70 – 85% of those with tinnitus have hearing loss (Henry et al., 2005, Vernon and Meikle, 2000). Therefore, hearing loss is not seen as a prerequisite for tinnitus, although it has been proposed that a "hidden hearing loss" exists in tinnitus patients with normal audiograms (Schaette and McAlpine, 2011a). Lefeuvre et al. (2019) examined 66 tinnitus patients with normal audiograms on standard pure tone audiometry (PTA) using high-definition audiograms up to 20,000 Hz. They discovered a hearing loss in 81.8% of patients that went undetected on standard audiogram; in controls without tinnitus (n = 24), no hidden hearing losses were detected.

It is unclear why only some people with hearing loss also develop tinnitus, and why there is a small proportion of people with intact hearing who develop tinnitus. One proposition is that tinnitus can be divided in a "top-down" type and a "bottom-up" type: patients with moderate-to-severe hearing loss show a bottom-up tinnitus

driven by sensory deafferentation, and patients with minimal-to-no hearing loss present a top-down tinnitus driven by a failed noise-cancellation system (Vanneste et al., 2019).

Oosterloo et al. (2021) found that participants with hearing impairment (n = 1547) were twice as likely to have tinnitus than participants without hearing impairment (n = 4551) in a population survey. Unlike previous studies, they did not find that the prevalence of tinnitus increased with age (50 – 85 years old, analysed in five-year increments, prevalence was around 20% in each age bracket). This could be because the youngest age group was 50 – 55 years, whereas in other studies, adults from the age of 18 are commonly included. Also, the percentage increase of hearing impairment above the age of 54 was similar in both tinnitus and non-tinnitus groups, suggesting that tinnitus, unlike hearing impairment, is probably not associated with the aging process itself. Therefore, the authors proposed that the frequent co-occurrence of tinnitus and age-related hearing loss is due to the hearing impairment, and not the age-related aspect of the hearing loss.

2.1.5 Comorbidities

A common comorbidity of tinnitus is hyperacusis (Fackrell et al., 2022, Schecklmann et al., 2014). Hyperacusis is a hearing disorder characterised by a reduced tolerance to sound(s) that are perceived as normal to the majority of the population (Adams et al., 2021). Every day sounds can be extremely uncomfortable to someone with hyperacusis, affecting their day-to-day life and relationships.

The prevalence of tinnitus in people with hypersensitivity to sound is much higher than in a general population, with estimates ranging from 40% - 86% (Fackrell et al., 2015). This has implications for research into both tinnitus and hyperacusis, as both may have a significant influence on patterns of auditory activity in response to external sounds which makes it difficult to disentangle their individual contributions. In severe cases of hyperacusis, this can also impact the therapeutic options available to the tinnitus patient if sound therapy becomes less acceptable or comfortable.

Other comorbidities of tinnitus are anxiety and depression (Baguley et al., 2013). Depressive symptoms are common in people with tinnitus and hyperacusis, and tinnitus and depression share common factors such as insomnia and anxiety (Aazh and Moore Brian, 2017). From the tinnitus patient's perspective, the perceived loudness of their tinnitus is an important factor leading to tinnitus distress and in a large app study (*n* = 658), Probst et al. (2016) showed this relationship is mediated by stress.

2.2 Tinnitus models and mechanisms

Multiple models have been developed describing the mechanisms behind tinnitus. It is very likely, however, that no single model will have the power to explain tinnitus in all patients (Baguley, 2002). The majority of tinnitus cases are associated with otological pathology. Specifically, cochlear dysfunction was prevalent amongst the early explanations, such as the idea that discordant damage of inner hair cells (IHC) and outer hair cells (OHC) could be driving the tinnitus percept. This was proposed after observations that intense noise and ototoxic agents do not damage IHC and OHC uniformly, and the subsequent "uneven" damaging in certain regions of the cochlea could result in tinnitus perception (Baguley, 2002). Modern theories acknowledge the potential role of ear-related pathologies in tinnitus, but place more focus on central mechanisms to explain the tinnitus percept. Several prominent tinnitus models will now be discussed below.

2.2.1 Jastreboff's Neurophysiological Model

Early physiological models of tinnitus worked from the premise that tinnitus originates from inner-ear malfunction. The most prominent model was the Jastreboff neurophysiological model, see Figure 2-1 (Jastreboff, 1990). According to this model, cochlear damage causes abnormal activation in the auditory pathway, and subsequent activation of the limbic system and the autonomic nervous system (ANS) consolidates the perception of tinnitus along with its negative associated emotions. The model has been influential in clinical practice and widely applied in Tinnitus Retraining Therapy (TRT), which consists of directive counselling and sound therapy (e.g. wearing a hearing aid or sound generator to enrich background noise) to aid

habituation to the tinnitus (Jastreboff, 2004). See also section 2.4.2 for more information on TRT and other sound-based interventions.

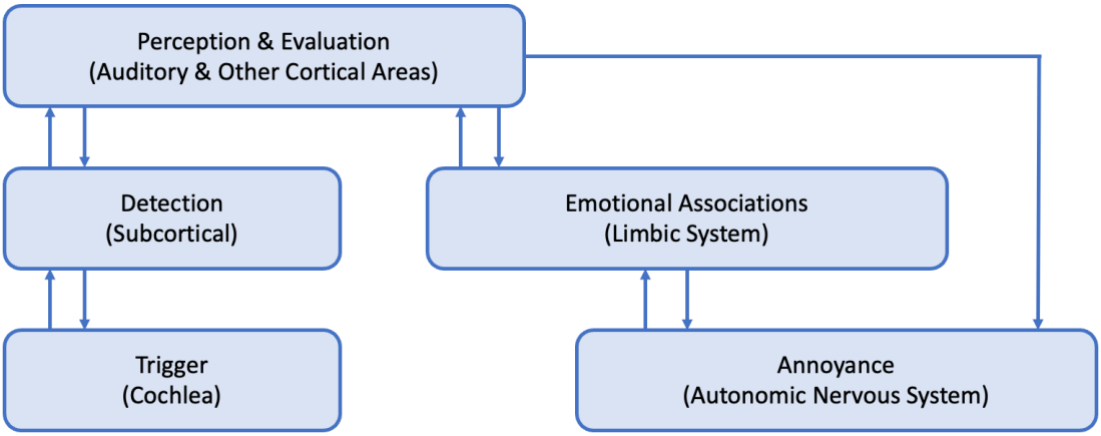

Figure 2-1 Jastreboff's Neurophysiological Model Schematic. Cochlear damage triggers tinnitus detection at the subcortical level and the involvement of limbic system and ANS is responsible for the association of annoyance with tinnitus. Redrawn from Jastreboff et al. (1996), p. 237.

More recently, attention has shifted away from cochlea-focussed accounts in favour of proposals incorporating network models of the central auditory system. Some of these accounts still acknowledge the role of the cochlea, but rather as an ignition point of tinnitus, i.e. events in the cochlea could initially trigger tinnitus but do not sustain it (Baguley et al., 2013). However, it is not enough to just consider what might have initially caused the tinnitus, as it does not explain why tinnitus becomes chronic. Therefore, recent models pay more attention to the promoting mechanisms of central origin to explain mechanisms of tinnitus (Baguley et al., 2013, Baguley, 2002). Sedley et al. (2016a) present an overview of existing tinnitus models and their limitations, which forms the basis of the discussion below.

2.2.2 Hyperactivity models

Subcortical hyperactivity models state that tinnitus is caused by excessive spontaneous neural activity relayed to auditory cortex. Four prominent hyperactivity models are the central gain model, neural synchrony model, frontostriatal gating, and thalamocortical dysrhythmia.

2.2.2.1 *Central gain*

Central gain refers to a compensatory increase in central auditory activity in response to the loss of sensory input (Auerbach et al., 2014). Deafferentation of auditory nerve fibres due to hearing loss results in increased central gain and could lead to tinnitus. This happens because of homeostatic mechanisms which try to stabilise the mean neuronal activity after decreased input from the cochlea (Schaette and Kempter, 2006). In neurons upstream of the auditory nerve, increased excitatory gain is generated, as well as reduced inhibitory control. The result is that neurons become more excitable, amplifying spontaneous activity, leading to hyperactivity (Schaette and McAlpine, 2011a). This hyperactivity could be interpreted as a sound resulting in tinnitus.

2.2.2.2 *Frontostriatal gating*

Frontostriatal circuits are neural pathways that connect frontal regions of the brain to the basal ganglia (or striatum). These circuits act as central gatekeepers, which evaluate the relevance and affective meaning of sensory stimuli such as sounds. They modulate information flows via descending and cortico-cortical pathways. Rauschecker et al. (2015) suggest that in tinnitus, brain changes observed with imaging techniques predominantly occur in frontostriatal circuits including ventromedial prefrontal cortex and nucleus accumbens (see Figure 2.2). They suggested that if the frontostriatal circuit is faulty, there is a lack of suppression of irrelevant sensory information, resulting in tinnitus (Rauschecker et al., 2015).

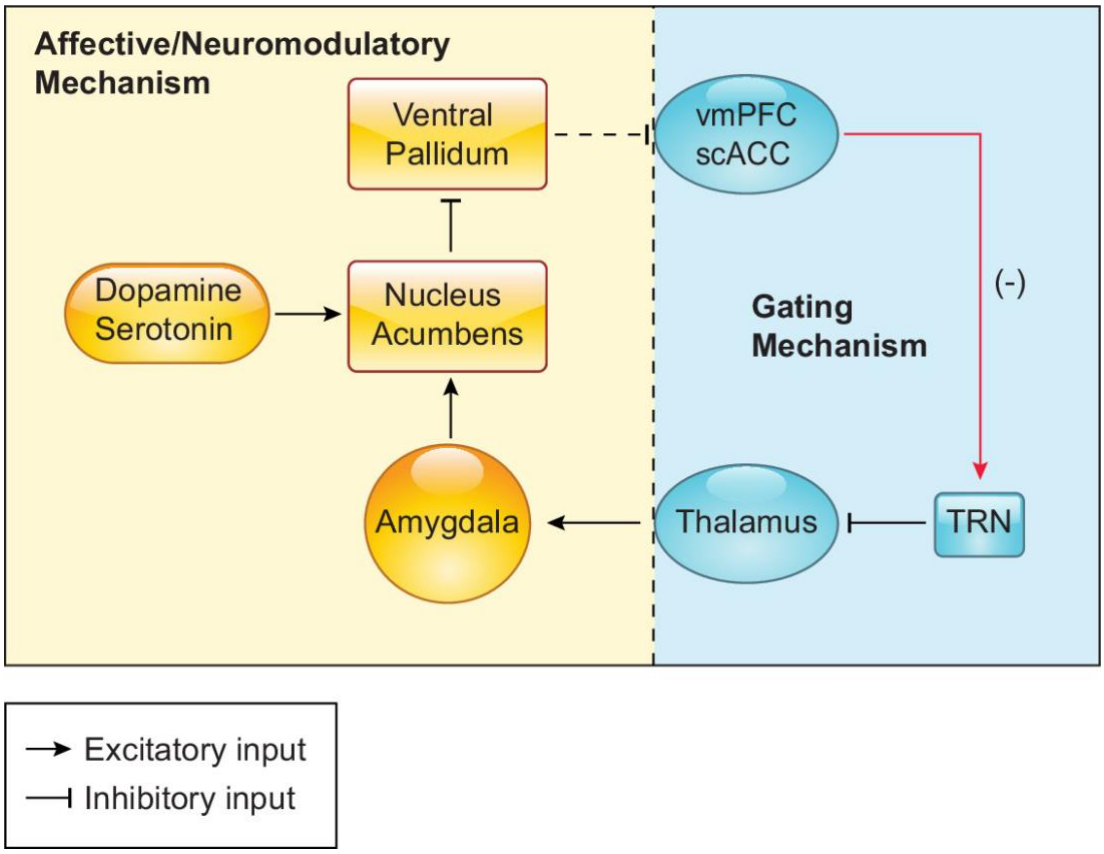

Figure 2-2 Frontostrial Gating model circuit diagram. Reprinted from Henton and Tzounopoulos (2021), pg. 1617, with permission from the American Physiological Society.

2.2.2.3 Thalamocortical dysrhythmia

As described in the central gain model and the frontostriatal gating model, tinnitus might be attributed to a decrease in activity in the auditory nerve, triggering central hyperactivity through homeostatic mechanisms, as well as a failure in cancelling out excessive spontaneous activity, or a failure in the gating system. It is proposed that these two processes alter the auditory thalamocortical signal transmission, leading to thalamocortical dysrhythmia (TCD) (De Ridder et al., 2015, Llinás et al., 1999). It is proposed that deafferentation results in a slowing down of resting-state alpha activity to theta activity, along with an increase in surrounding gamma activity. The theta and gamma activity are coupled, and this coupling allows for theta burst firing to integrate the tinnitus-related gamma activity into consciousness networks (De Ridder et al., 2015).

2.2.3 Filling-in model

The filling-in model states that the tinnitus percept is a consequence of the brain "filling in" the input that is missing at deafferented parts of auditory cortex (Roberts et al., 2013, De Ridder et al., 2015, De Ridder et al., 2014). These cortical regions could receive their input from adjacent frequencies (Robertson and Irvine, 1989). In this case, this tonotopic reorganisation could lead to overrepresentation of adjacent frequencies, resulting in tinnitus corresponding to the "edge" frequency of hearing loss, or where the audiogram shows most change in hearing sensitivity (Moore et al., 2010, Eggermont, 2006b, Rauschecker, 1999).

This hypothesis has been explored by comparing the audiogram of tinnitus patients to the pitch of their tinnitus. The tinnitus pitch is established using a pitch matching procedure, usually by adjusting the frequency of a sinusoid stimulus until the participant reports it matches their tinnitus. Other techniques include forced-choice paradigms between two stimuli of different frequency, to narrow it down to one frequency, or creating a "tinnitus spectrum" by asking participants to rate on a numerical scale the contribution of different frequencies to their tinnitus sensation.

Norena et al. (2002) used the latter method in ten tinnitus participants with high-frequency hearing loss and found that they exhibited a peak in ratings falling within the hearing loss range. König et al. (2006) also found an association between tinnitus pitch and audiogram edge frequency in 24 tone-like tinnitus patients with moderate-to-severe, noise-induced, high-frequency hearing loss. Tinnitus pitch was on average 1.48 ± 0.12 octaves above the audiogram edge frequency, and the two measures were significantly correlated, although the correlation coefficient was small ($r = 0.03$, $p = 0.04$).

On the other hand, Pan et al. (2009) found no association between tinnitus pitch and audiogram characteristics in 195 tinnitus patients with a variety of origin of hearing loss and audiogram configurations. They asked participants to match their tinnitus pitch by presenting stimuli between 125 and 8000 Hz and asking them whether their tinnitus pitch is higher or lower than the presented sound. They repeated the

procedure three times and averaged the scores to reach a pitch match. They reported low within-subject variability between the three scores. The mean edge frequency of the sample was 2237 Hz, whereas the tinnitus pitch was matched at an average of 4968 Hz. The pitch match was significantly higher ($F = 4.11$, $p < 0.01$) for patients with tone-like tinnitus (mean = 5385 Hz) than for patients with noise-like tinnitus (mean = 3266 Hz). Seventy-five out of 195 participants matched their tinnitus pitch to 8000 Hz or higher. Some participants matched their tinnitus pitch close to the edge frequency of their audiogram, but the authors could not find a common characteristic between them.

Moore et al. (2010) tested eleven participants with mild-to-moderate hearing loss and bilateral, tonal tinnitus. They found a very strong correlation between the edge frequency of hearing loss and the tinnitus pitch match ($r = 0.94$, $p < 0.01$). This result is very different from those who reported small (Norena et al. (2002)) or no correlations (Pan et al., 2009). The authors propose this might be because they investigated a very specific sub-group, and they also trained participants to avoid octave errors, which other papers did not do.

Sedley et al. (2016a), in their overview of tinnitus models, note several problems with filling-in models. First, they assume reduced spontaneous subcortical input in deafferented parts of auditory cortex, whereas there is evidence that it is increased. Second, they cannot explain tinnitus in the absence of deafferentation or hearing loss. Third, as they rely on deafferented parts of auditory cortex receiving input from adjacent cortex, they would predict that the tinnitus sound should resemble current or recent familiar input, whereas tinnitus is usually a low-level, unfamiliar percept.

2.2.4 Predictive coding models

2.2.4.1 Sensory precision integrative model

Perception can be described as the process of unconscious inference about the causes of sensations (Helmholtz, 1867). This nineteenth century idea has inspired a plethora of literature on the mechanisms behind such inferences. Predictive coding theory arose from such efforts and can be used to describe how the brain models its

environment and maintains and updates predictions about sensations (Hullfish et al., 2019). Anatomical and physiological evidence for predictive coding has been found predominantly in visual processing systems (Friston, 2018). Under predictive coding, the brain uses a hierarchical model to compare incoming bottom-up sensations to top-down prior beliefs. As such, predictive coding has its grounding in Bayesian inference, and sees the brain as a statistical organ (Friston, 2018). At each level of the hierarchy, the input or "evidence" is compared to the prediction or the "prior". The mismatch between the evidence and the prior, the "prediction error", is the only encoded value, resulting in efficiency in processing complex information (Sedley et al., 2016a). The prediction error at the subordinate level then ascends the hierarchy to the next level and updates the original belief. The prediction error is weighted by its precision, i.e. the confidence in the prior belief and the conditional probability of observing the sensory input under the belief. The idea is that only sufficiently precise prediction errors are allowed to alter the model and affect perception (Hullfish et al., 2019).

As sensory systems are always active, the default is not lack of neural activity, but rather the pattern of imprecise prediction errors that reflect spontaneous activity. In the case of the auditory system, silence is then the inferred cause of this spontaneous activity (Hullfish et al., 2019). The prediction errors reflecting spontaneous activity can act as "tinnitus precursors" if they are awarded too much precision, leading to a rejection of the brain's null hypothesis of silence. The reason for the change of the signal precision may include other models of tinnitus, for example the intensity of the tinnitus precursor being increased because of increased subcortical firing rates (i.e. central gain) (Sedley et al., 2016a). The sensory precision integrative model (see Figure 2-3) describes the above and how the tinnitus precursor can replace the default state of silence, thus leading to the constant perception of a tinnitus sound (Sedley et al., 2016a).

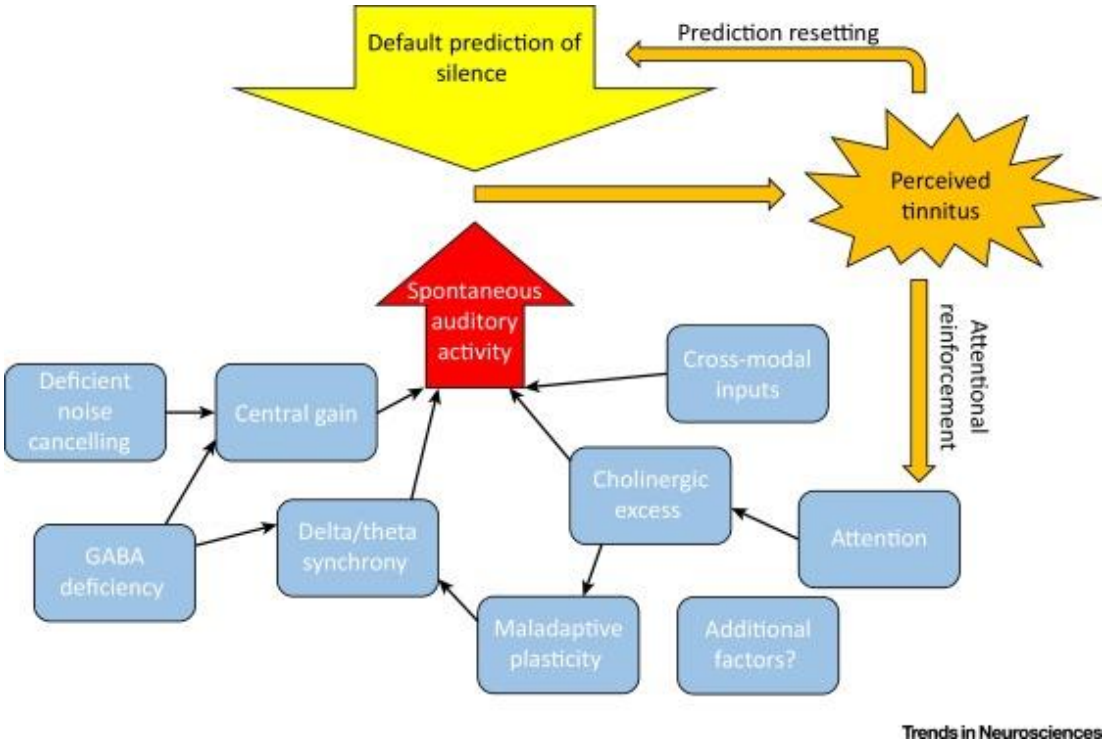

Figure 2-3 Sensory Precision Integrative Model Schematic. Reprinted with permission (open access) from Sedley et al. (2016a), pg. 805.

2.2.4.2 Perception update model

Another predictive coding model is the perception update Model (PU model), see Figure 2-4 (Noda et al., 2018). This model draws a connection to information processing in the computer sciences. Noda et al. (2018) propose that the way the auditory system processes information is analogous to the functioning of a data compression technology called “differential pulse code modulation” or “differential PCM”. This technology compares consecutive inputs and takes the difference between them as the output. The authors propose that sound perception is achieved through integrating sound change, reflected in the auditory N1 response as measured by electroencephalography (EEG). In the case of a hearing loss, there is no registered change in auditory input for those sounds that the cochlea can no longer process. This leads to a state of uncertainty where perception must be predicted based on previous experience, which can lead to the emergence of tinnitus.

The PU model posits that, when there is no registered change in auditory input, perception becomes uncertain and the auditory system infers perception which could

take the shape of phantom perceptions, i.e. tinnitus. Just like the sensory precision model discussed above, the PU model is grounded in predictive coding and assumes that the auditory system is organised hierarchically. The higher levels communicate predictions with the lower levels, and the lower levels communicate the difference between the prediction and the actual input (i.e. the prediction error) to the higher levels.

In short, the PU model sees tinnitus as an error of sound change integration. The auditory N1 is a prominent EEG response to the onset (On-N1) and offset (Off-N1) of an auditory stimulus (Zhang et al., 2016). Another prominent EEG response is the mismatch negativity (MMN), which occurs around 150 – 200 ms after the onset of a change in a regular pattern of auditory stimulation. MMN is usually elicited using an oddball paradigm, which is a series of identical stimuli interrupted by one odd stimulus in no particular order (Näätänen and Picton, 1987, Inui et al., 2010). If tinnitus is the result of sound change integration error, then sound change markers such as the auditory N1 response and the MMN response should differ between tinnitus patients and controls.

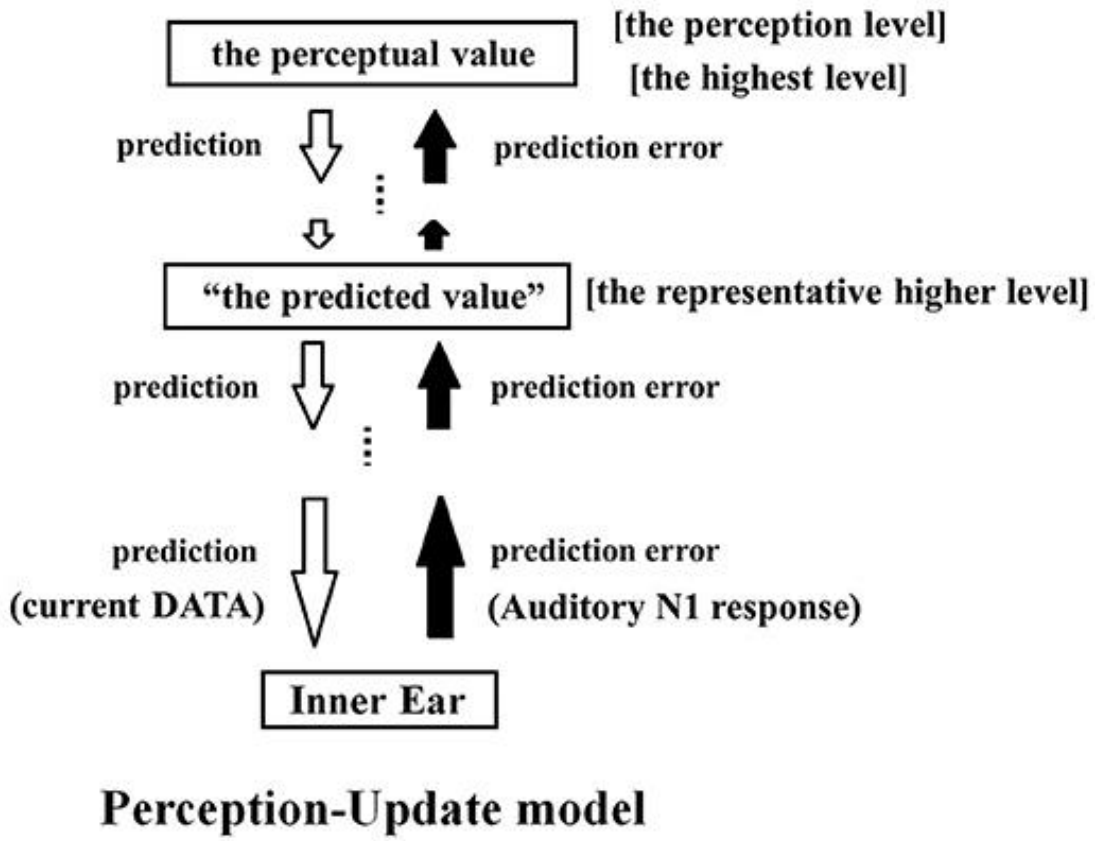

Figure 2-4 Perception-Update model schematic. Reprinted with permission (open access) from Noda et al. (2018), pg. 6.

2.2.4.3 Experimental evidence for predictive coding

One study found that tinnitus patients (*n* = 32) had a significantly decreased amplitude of the N1 potential compared to control participants (*n* = 31), but there was no significant difference in N1 latency between the groups (Jacobson and McCaslin, 2003).

Mohebbi et al. (2019) specifically investigated auditory change detection and sensory memory using MMN considering the predictive coding model. They hypothesised that there would be deficits in a severe tinnitus group compared to mild tinnitus and no tinnitus groups. They found that MMN amplitude and area under the curve for deviants higher than the tinnitus pitch, but not lower, were significantly decreased in the severe tinnitus group compared to the other groups. For silent gap deviants, the severe tinnitus group showed significant decreases in amplitude and area under the curve compared to the no tinnitus group. They did not find any latency differences in

any of the conditions. This is a replication of earlier findings by Mahmoudian et al. (2013) who also found decreased MMN amplitude and area under the curve for deviants of frequency and silent gap in tinnitus patients. They concluded that the MMN differences in severe tinnitus sufferers reflect persistent prediction errors under predictive coding theory: tinnitus is consistently detected as a new signal, preventing habituation.

Electrophysiological measures of auditory change detection, such as the N1 and MMN component, provide an interesting paradigm for comparing unconscious auditory processing in tinnitus sufferers to non-tinnitus sufferers. However, the above studies contain the assumption that, first of all, predictive coding is a correct, proven theory; and second, that EEG components are measures that can reflect predictive coding mechanisms. Although a popular theory of neural function with great explanatory power, it should be noted that predictive coding theory is also debated.

Heilbron and Chait (2018) reviewed the evidence for predictive coding theory in the auditory realm after concerns were raised about certain aspects of predictive coding being untested (Egner and Summerfield, 2013) or even untestable (Kogo and Trengove, 2015). One key prediction of predictive coding theory is that top-down predictions and bottom-up error generation have distinct oscillatory profiles. Sedley et al. (2016b) provided compelling evidence for this through direct recordings of three participants' auditory cortical responses to auditory stimuli whose pitch changed according to specific rules. They found that prediction violations (surprise) were encoded by oscillations in the gamma band, changes to predictions in the beta band, and precision or predictions related to alpha band oscillations. However, Heilbron and Chait (2018) concluded that evidence for distinct oscillatory signatures of prediction and error processing is mixed: only two in six studies confirmed this prediction. They recommend future studies should aim to replicate findings from Sedley et al. (2016b).

2.2.5 Conclusion on tinnitus models

The synopsis of current tinnitus models presented above shows there is no consensus on an explanation of tinnitus. The models are not mutually exclusive, and it could be that different models describe different subtypes of tinnitus. None of the models have the power to account for all experimental evidence available (Sedley et al., 2016a). Predictive coding models potentially have the most explanatory power, as they do not rely on cochlear damage or hearing loss to trigger tinnitus, which makes them useful in accounting for cases of tinnitus without hearing loss. All the models described above focus on neural activity in central (auditory) regions, which have implications for the types of management strategies they would predict are useful. Based on these models, management strategies should aim to reverse the maladaptive changes in neural activity that are thought to underlie the tinnitus percept.

2.3 Tinnitus neurophysiology

2.3.1 Auditory brainstem changes

Accumulating evidence suggests that tinnitus is associated with changes to areas low down the auditory pathway (see Figure 2-5). Bottom-up sound signals travel from the auditory nerve to the brainstem, subdivided into the medulla, pons, and midbrain. In the medulla, sound reaches the cochlear nuclei, which transmit the signal to the opposite side of the brain via the superior olivary nuclei in the pons. Next are the bilateral inferior colliculi in the midbrain, after which the signal exits the brainstem and enters the medial geniculate body in bilateral thalamus. The thalamus is seen as a sensory “relay centre” which has a gating function, providing the signals with access to the auditory cortex (Webster et al., 1992).

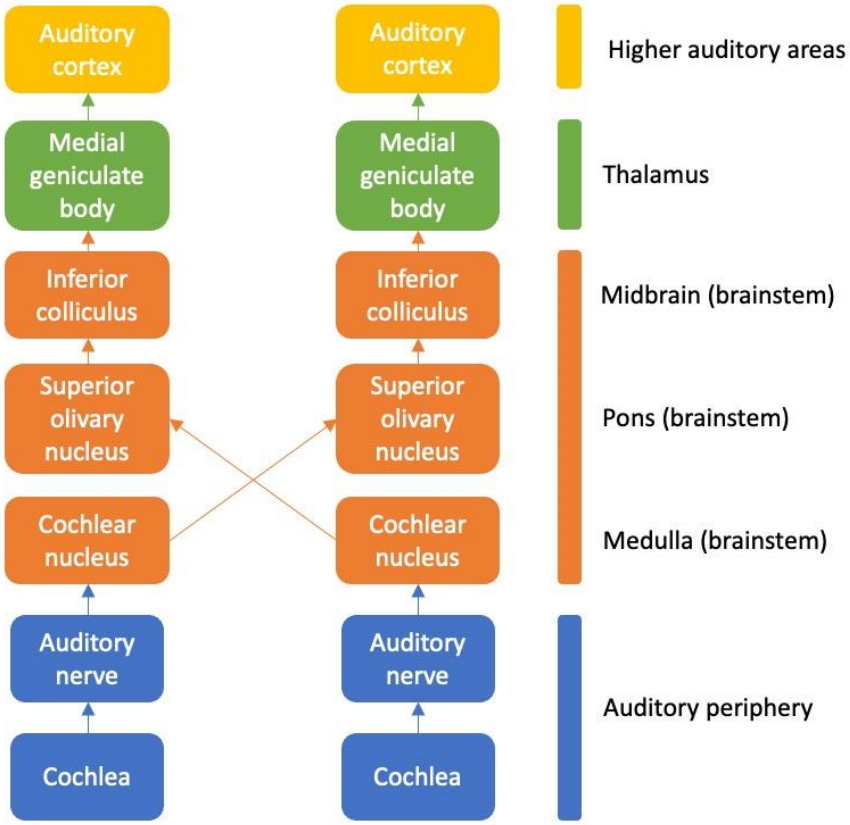

Figure 2-5 Schematic of the ascending auditory pathway

The brainstem has received attention for its potential role in tinnitus generation and modulation (Jacxsens et al., 2022). Animal studies have shown alterations to the spontaneous activity of brainstem auditory nuclei following tinnitus-inducing experiments, including increased spontaneous firing rates and bursting activity (i.e. hyperactivity) and increased neural synchrony (Theodoroff and Kaltenbach, 2019). Hyperactivity in the brainstem has also been found in humans (Melcher et al., 2000, Lanting et al., 2009). On fMRI scans, increased resting-state activity was found in the auditory nuclei of people with somatosensory tinnitus (van Gendt et al., 2012, Lanting et al., 2010), which is characterised by the ability to be modulated via inputs from the somatosensory/somatomotor system, e.g. via eye-gaze or jaw protrusion (Sanchez and Rocha, 2011).

The most common assessment of auditory brain stem function involves auditory evoked potential (AEPs), consisting of short-, middle-, and long-latency responses. Short-latency AEPs, also called auditory brainstem responses (ABRs), are recorded using electrodes on the scalp during the first ten milliseconds following acoustic stimuli, most often a “click” stimulus (Habib and Habib, 2021). The readings consist of seven positive wave peaks, of which wave I, III and V are the most reliably recorded, and are thought to reflect, respectively, activations in the distal auditory nerve, superior olivary nucleus, and the inferior colliculus. ABRs play an important role in the diagnosis of abnormalities along the auditory nerve, as well as in hearing sensitivity testing in populations in which it is difficult to gather behavioural information (e.g. infants) (Young et al., 2021). Middle-latency AEPs are believed to originate from the thalamus and from primary auditory cortex.

Jacxsens et al. (2022) systematically reviewed the evidence for the role of the brainstem in tinnitus generation from studies examining short- and middle-latency AEPs in subjective tinnitus patients compared to controls. They reported results for two sub-groups: tinnitus patients with hearing loss, and tinnitus patients without hearing loss. In the hearing loss group, clinical heterogeneity between studies made statistical pooling impossible, so a best-evidence analysis was performed. Overall, no consistent changes were found in any of the ABR waves in this sub-group.

Meta-analysis was conducted on eleven studies investigating ABRs in tinnitus patients with normal hearing compared to controls. Results showed that the latencies of waves I, III, and V were significantly longer in tinnitus patients than in controls. This was contrary to the authors’ hypothesis that tinnitus-related hyperactivity in the brainstem would be reflected by decreased latency of ABRs. Prolongation of the latency of waves I, III, and V has previously been associated with sensorineural hearing loss, suggesting that the “normal hearing” tinnitus group may have had ultra-high-frequency sensorineural hearing loss undetected by standard pure tone audiometry.

With regards to middle-latency responses, no consistent differences were found in either group. Taken together, there is some evidence for alterations to ABRs in tinnitus patients without visible hearing loss compared to controls, and therefore involvement of the brainstem. However, results are mixed, and limited high-frequency audiometric data make it difficult to conclude these changes are related to the tinnitus percept as they could reflect a "hidden" hearing loss.

2.3.2 Cortical changes

Accumulating evidence from animal studies and brain imaging studies in humans shows that the tinnitus signal is associated with changes to the central nervous system (CNS). As discussed above in section 2.2, tinnitus is no longer considered primarily a cochlear pathology, but rather a pathology of central origin involving auditory as well as non-auditory brain areas and networks. Indeed, various brain imaging methods, including fMRI (see section 2.5), MEG, and EEG, have revealed structural and functional abnormalities across auditory and non-auditory areas. However, these findings contain inconsistencies, some of which can be attributed to study design (Khan et al., 2021, Tarabichi et al., 2018, Yoo et al., 2016).

Tinnitus is a highly heterogeneous disorder, which complicates the identification of the neuronal mechanisms behind it, as the different clinical manifestations are expected to be reflected in these mechanisms (Elgoyhen et al., 2015). The relationships of differential tinnitus characteristics (e.g., loudness, duration, related distress, accompanying hearing loss or hyperacusis) can be explored using correlational analysis of large samples, see for example Schecklmann et al. (2013). These studies show that tinnitus severity and duration are associated with neural correlates of tinnitus, but this association differs between studies significantly.

Several studies have investigated the hyperactivity hypothesis in participants with tinnitus using EEG and MEG (Weisz et al., 2005, Weisz et al., 2007, Moazami-Goudarzi et al., 2010, Balkenhol et al., 2013, Schlee et al., 2014). There is a tendency for these studies to find increased gamma-band activity and decreased alpha-band activity in tinnitus, which is in line with the thalamocortical dysrhythmia hypothesis.

Also in line with the hyperactivity hypothesis are observations of decreases in neuronal inhibition in animal studies, related to alterations in neurotransmitters (Llano et al., 2012, Elgoyhen et al., 2015). Evidence has also been found for neurochemical changes in auditory cortex in people with tinnitus. Using magnetic resonance spectroscopy (MRS) on 14 tinnitus participants with hearing loss and 14 matched controls, Sedley et al. (2015) found that the presence of tinnitus was associated with a reduction in GABA concentration in auditory cortex. GABA is an inhibitory neurotransmitter which has been studied in its relationship to tinnitus in animal models.

A recent study also used MRS on 16 tinnitus patients without hearing loss and 17 matched controls (Isler et al., 2022). They investigated the concentration of an excitatory neurotransmitter, glutamate, as well as the inhibitory neurotransmitter GABA in two bilateral voxel clusters in primary auditory cortex. Under the hyperactivity framework, one would expect increased concentrations of glutamate or decreased concentrations of GABA, or both. The results showed, unexpectedly, a decreased glutamate concentration in the left auditory cortex of the tinnitus group, and this concentration also correlated positively with tinnitus loudness scores. On the other hand, this time consistent with the hypothesis, they did find decreased GABA concentration in the left auditory cortex of the tinnitus group, consistent with Sedley et al. (2015), who also found a decrease in auditory cortex, although it was on the right side.

A clinical trial (https://clinicaltrials.gov/ct2/show/NCT04862572) is currently under way to investigate auditory cortex disinhibition by quantifying GABA concentration using MRS, combined with functional connectivity strength measures using fMRI, in 60 participants (University of Nottingham, 2021). This line of work will be very interesting and could potentially provide a tinnitus biomarker. Efforts are also under way to test pharmacological treatments targeting GABA function, see section 2.4.4.

2.4 Tinnitus treatments

Approaches to treat tinnitus include psychological, pharmacological, surgical, and neurophysiological approaches. Although subgroups of patients report some relief after these interventions, there is no one-size-fits-all approach, and evidence for their efficacy is generally weak to moderate (Eggermont, 2012).

2.4.1 Cognitive Behavioural Therapy

Cognitive Behavioural Therapy (CBT) refers to a group of interventions that are based on the idea that mental disorders and/or psychological distress are maintained by cognitive factors. It proposes that maladaptive cognitions, e.g. general beliefs about the world, the self and the future, maintain emotional distress and give rise to automatic thoughts. CBT aims to revise and challenge these cognitions using therapeutic strategies (Hofmann et al., 2012). A Cochrane review of CBT for tinnitus found low-to-moderate evidence that CBT can reduce the negative impact of tinnitus on quality of life (Fuller et al., 2020). Therefore, CBT is recommended for those who suffer from their tinnitus, although it does not treat the tinnitus symptom itself.

2.4.2 Sound-based approaches

Sound-based approaches are clinically the most common (Del Bo et al., 2011). They can be divided in customised and non-customised strategies. Non-customised strategies include hearing aids, masking therapy, and tinnitus retraining therapy. Customised strategies include tailor-made notched music training, and tinnitus pitch-matched therapy. One review concluded sound-based therapies are effective in some patients, but there is a lack of randomised controlled trials with long-term follow-up (Wang et al., 2020). A recent scoping review found evidence that in 68% of 28 primary research studies hearing aids had a positive effect on tinnitus (Jacquemin et al., 2021). The idea is that restoring some of the missing auditory input using hearing aids, could reverse the maladaptive processes causing the perception of tinnitus. Also, by restoring normal sound input, hearing aids can (partially) mask or distract from the tinnitus percept as the listener has access to more meaningful sounds (Coles and Hallam, 1987). These results are promising, but more work is needed to

investigate which tinnitus sufferers might benefit from hearing aids, and which hearing aid settings are most beneficial.

Tinnitus retraining therapy (TRT) was developed in accordance with Jastreboff's Neurophysiological Model (see Section 2.2.1). TRT aims to remove negative associations with the tinnitus percept, allowing gradual habituation to occur (Jastreboff, 2004). It includes counselling and sound therapy. The counselling focusses on educating the tinnitus patient on the mechanisms of sound and brain function, and sound therapy focuses on enriching the background sound environment to create distractors. A Cochrane review on TRT efficacy could not draw firm conclusions, as it included only one RCT (n = 123) comparing TRT to a masking therapy (Phillips and McFerran, 2010). This one report found that both TRT and masking were effective, but TRT had better effects in the long term (Henry et al., 2006). It is difficult to review the efficacy of TRT as the treatment protocols differ between studies. Furthermore, in the absence of high-fidelity treatment protocols, there is room for variability in the counselling and the sound therapies.

2.4.3 Surgical intervention

Surgical intervention for tinnitus include neurectomies, stapedectomies, tympanosympathectomies, and part or total sectioning of the eighth cranial nerve (vestibulocochlear nerve) (House and Brackmann, 1981). The effects of these invasive surgeries on tinnitus have been explored, often in cases where tinnitus was a secondary complaint and surgery was necessary for other medical reasons (e.g. acoustic neuroma, vertigo). After removal of acoustic tumours with section of the cochlear nerve, tinnitus was improved in 40% of 414 patients. In patients undergoing stapedectomy, hearing improved in most patients, but tinnitus only improved in about half (House and Brackmann, 1981).

One review on the effect of vestibular nerve section identified 18 papers with a total of 1318 patients describing tinnitus status after vestibular nerve section (Baguley et al., 2002). Section of the vestibular nerve is a last resort treatment option, usually performed to treat extreme vertigo or Meniere's disease resistant to other

treatment, and results in a total loss of auditory efferent input. Cochlear fibres are left intact, so while hearing loss is a risk factor of vestibular nerve section, it does not result in deafness. The review showed that results are mixed: tinnitus was exacerbated postoperatively in on average 16.4% of patients (SD = 14.0), tinnitus was unchanged in 38.5% (SD = 15.6), and tinnitus improved in 37.2% (SD = 15.2).

One paper compared section of both vestibular and cochlear nerve to just vestibular nerve section in 110 patients. In both conditions, around half the patients reported improvement of their tinnitus, but vestibular nerve section alone more often worsened tinnitus (Barrs and Brackmann, 1984). Taken together, the mixed evidence for its efficacy and the invasive nature of surgery do not make surgical intervention a desirable option in the majority of tinnitus cases.

2.4.4 Pharmacological treatment

No convincing evidence has yet been found in support of the use of medication for the treatment of tinnitus. Examples of medication that have been trialled for tinnitus are antidepressants, nootropics (“cognitive enhancers”), and anticonvulsants (Elgoyhen et al., 2015). A Cochrane Review of antidepressants for tinnitus (Baldo et al., 2012) included six studies with a total of 610 patients. All but one study had low trial quality. There was not enough evidence to conclude that antidepressants improved tinnitus. Hilton et al. (2013) reviewed the evidence for the use of ginkgo biloba, a nootropic, in a Cochrane review. They included four trials with a total of 1543 participants, all of which had low risk of bias. In three studies, tinnitus was the primary complaint, and no evidence for the efficacy of this drug was found. Furthermore, Hoekstra et al. (2011) reviewed the evidence for the use of anticonvulsants for tinnitus in a Cochrane review. Anticonvulsants are a group of drugs used for epileptic seizures, bipolar disorder, borderline personality disorder, and neuropathic pain. They included seven studies with a total of 453 patients. Risk of bias was deemed high, and the conclusion was that no large positive effects on tinnitus had been demonstrated following anticonvulsant therapy.

As discussed in section 2.3.2, one neurophysiological model of tinnitus proposes that reduced inhibition due to compromised GABAergic mechanisms gives rise to hyperactivity in cortical areas and therefore tinnitus. This leads to the hypothesis that drugs that enhance GABA function (GABAkines) could provide tinnitus relief (Witkin et al., 2022). This hypothesis is being tested in an ongoing clinical trial studying the effects of ketamine on tinnitus at the New York State Psychiatric Institute (2019), as ketamine is known to enhance GABA levels by blocking NMDA glutamate receptors. Forty participants with tinnitus and sensorineural hearing loss are taking part in a randomised, double-blind, cross-over trial with expected completed in 2024. GABA and glutamate levels in auditory cortex will be measured using MRS after administering both the drug and the placebo.

2.4.5 Invasive brain stimulation

Direct stimulation of auditory cortex and deep brain structures has been investigated for the treatment of tinnitus (Eggermont, 2012). In the 1950's, it was discovered that electrical pulses applied to the superior temporal gyrus (STG) in neurosurgical patients could alter or suppress hearing function (Penfield and Rasmussen, 1950, Mullan and Penfield, 1959). Hearing suppression seemed to only occur following stimulation in the auditory belt and parabelt, whereas stimulation of "core" auditory regions (i.e. posterior medial Heschl's gyrus) results in auditory perceptions (Fenoy et al., 2006).

If direct stimulation of STG can "switch off" hearing perception, perhaps it could also switch off tinnitus perception. Direct stimulation can not only occur during neurosurgery, but also via implanted electrodes. De Ridder et al. (2006) implanted electrodes in the auditory cortex of twelve tinnitus patients who demonstrated >50% tinnitus suppression following transcranial magnetic stimulation (see section 2.4.6.1). They found that, for patients with a pure tone tinnitus, direct electrical stimulation through the implant resulted in a 97% tinnitus suppression, and for patients with white noise tinnitus, this was 24%. The mean visual analogue scale scores of tinnitus loudness decreased from 9.5 to 1.5 and from 8.8 to 6.8 respectively. The authors concluded that the stimulation was most effective in patients with unilateral, pure

tone tinnitus. However, there were only two patients with bilateral tinnitus, and they were also the only two patients in the study without hearing loss. The remaining patients had either severe-to-profound hearing loss or deafness.

Smit et al. (2016) retrospectively assessed the outcomes of deep brain stimulation of implants inserted in different locations for a variety of medical reasons. Of the 685 patients approached, 443 participated, of whom 61 reported they had tinnitus at the time of implantation, which was on average four years ago. An age-matched control group of tinnitus patients who did not undergo implantation completed the same retrospective questionnaire, with questions about their tinnitus four years ago compared to their tinnitus in the present. The results showed a significant reduction in average Tinnitus Handicap Inventory score (THI) in the implanted group, from 18.9 to 15.1. No reduction was found on a loudness visual analogue scale (3.9 both pre- and post-operatively). The average THI score in the control group did not change significantly (36.9 to 35.5). The chosen method of statistical analysis should be questioned here: only within-group t-tests were used to compare pre- and post-operative timelines rather than directly comparing the effect of group (implanted vs. control) and time (t0 vs. t1) in one analysis. Therefore, it cannot be concluded that the implanted group benefited significantly compared to the control group. The average change in THI score (3.8) was also very small given that the scale runs from 0 – 100, giving rise to the question how clinically significant the reported reduction was.

One case study reported that complaint of tinnitus improved by 70% after implantation of an electrode in the nucleus accumbens, although the patient noted that the improvement was not in tinnitus loudness, but rather in their ability to cope emotionally with their tinnitus. The authors suggested this could be because the nucleus accumbens plays a role in the emotional gating of tinnitus (Dijkstra et al., 2018).

Combining the evidence above, deep brain stimulation might provide a solution for a specific group of tinnitus patients who fit the criteria and are willing to undergo an

invasive procedure. More research is warranted on the subject. A clinical trial (https://clinicaltrials.gov/ct2/show/NCT03976908) is currently under way to investigate the effect of high-frequency deep brain stimulation of the medial geniculate body, using a randomised, double-blind, cross-over design in six participants (Maastricht University Medical Center, 2021). Another trial (https://clinicaltrials.gov/ct2/show/NCT02630589) started in 2016 and is expected to finish in 2024, and investigates the impact of an auditory brainstem implant in ten patients with severe, unilateral tinnitus and hearing loss in the ipsilateral ear (University Medical Center Groningen, 2016).

2.4.6 Non-invasive brain stimulation

2.4.6.1 Repetitive transcranial magnetic stimulation (rTMS)

Brain stimulation can also be applied non-invasively. One example is repetitive transcranial magnetic stimulation (rTMS), which involves delivering electromagnetic pulses to the head of a patient using an electrical coil. The changing magnetic field is used to induce an electric current in targeted cortical areas. The stimulation can be low- or high-frequency, with research showing that low-frequency stimulation has an inhibitory effect on the underlying neurons, whereas high-frequency stimulation has an excitatory effect (Chen et al., 1997, Kobayashi and Pascual-Leone, 2003).

Given the above, low-frequency rTMS was hypothesised to reduce tinnitus-related hyperactivity (Langguth et al., 2003). Numerous trials have been executed as well as several reviews, but there is no consensus on the efficacy of rTMS for tinnitus (Simoes et al., 2021). A Cochrane review concluded there was very limited support for the use of low-frequency rTMS in patients with tinnitus (Meng et al., 2011). More recently, a systematic review was conducted to investigate whether an optimal rTMS site of stimulation can be identified from the literature (Watson et al., 2022). The review included nineteen studies that were sham-controlled, including eight unique stimulation sites. Tinnitus suppression occurred most often when the site of stimulation was the temporoparietal junction (five out of five studies), whereas suppression occurred in three out of six studies targeting auditory cortex.

2.4.6.2 TRANSCRANIAL DIRECT CURRENT STIMULATION

Another method of non-invasive brain stimulation is transcranial electrical stimulation (tES). TES is an umbrella term, covering techniques that use an alternating current such as transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), or a constant current such as transcranial direct current stimulation (tDCS). All these techniques have been shown to increase cortical excitability in neurotypical subjects (Inukai et al., 2016).

In tDCS, a weak electrical current is administered through two surface electrodes, one anode and one cathode, both placed on the scalp or with one electrode placed away from the head, such as on the upper arm (Thair et al., 2017a). An advantage tDCS has over other brain stimulation methods, is that it can be used effectively in sham-controlled trials (Dinn et al., 2017). In sham stimulation, active tDCS is delivered for just a few seconds before turning off the device, resulting in the same tingling sensations experienced in an active protocol (Fonteneau et al., 2019). In active protocols, stimulation can be either anodal or cathodal, each influencing cortical excitability in a different way. Anodal stimulation typically results in excitatory effects through neural depolarization, whereas cathodal stimulation results in inhibitory effects through neural hyperpolarization (Nitsche and Paulus, 2000a). In one study, the duration of increased excitability after a single treatment of anodal tDCS depended on the duration of stimulation, with five to seven minutes of stimulation resulting in no more than five minutes of after-effects, and nine to thirteen minutes resulting in thirty to ninety minutes of after-effects (Nitsche and Paulus, 2001).

TDCS has been administered to patients with different types of complaints. Lefaucheur (2016) presents a database of published tDCS clinical trials between 2005 and 2016, revealing the effectiveness of tDCS has been investigated for a large number of clinical conditions, amongst which are pain syndromes, depression, post-stroke impairments and dementia. TDCS was administered to tinnitus patients for the first time in 2006 (Fregni et al., 2006). The effects of tDCS are not consistent across studies, possibly because there is no standardised tDCS protocol (Malavera et al., 2015). Important stimulation parameters such as current strength, electrode size,

and duration of stimulation differ considerably across studies (Nitsche et al., 2008). Generally, electrode sizes of 25-35 cm^2 are used, with a current of 1-2 mA for up to 20-40 minutes over multiple sessions (Malavera et al., 2015). Both anodal and cathodal stimulation have been administered to tinnitus patients, with varying degrees of success. As discussed in the overview of tinnitus models, hyperactivity within the auditory pathway has been proposed to play a role in tinnitus. Therefore, one would expect cathodal stimulation to be more effective than anodal stimulation because it should inhibit the hyperactivity, but there is no hard evidence for this (Joos et al., 2014, Pal et al., 2015b).

Different cortical areas have been the target of tDCS, of which three have been examined in tinnitus patients: auditory cortex (AC), dorsolateral prefrontal cortex (DLPFC) and left temporoparietal area (LTA) (Shekhawat et al., 2015c). DLPFC and LTA appear to contribute to tinnitus, but their exact role in tinnitus perception is mostly unknown (Shekhawat et al., 2016). It has been suggested that stimulation of DLPFC and LTA may modulate tinnitus loudness and tinnitus annoyance differently, but tDCS is rather nonfocal, i.e. the electric field also reaches sites other than the target (Shekhawat et al., 2015c).

Song et al. (2012) conducted a systematic review and meta-analysis of tDCS in tinnitus patients. The results showed an overall response rate to tDCS of 39.5%, with a mean tinnitus intensity reduction of 13.5% compared to sham stimulation in the responders group. Results were comparable for stimulation of LTA and DLPFC. However, due to the low number of studies in the systematic review (six) and meta-analysis (two), the efficacy of tDCS in treating tinnitus patients could not be confirmed. Also, the review did not specify what defined a responder and a non-responder.

Another systematic review was conducted by Santos et al. (2018). Contrary to Song et al. (2012), they only included studies that administered more than one session of tDCS per tinnitus patient. They found a lower response rate than in Song et al. (2012) of 14.86%. Santos et al. (2018) suggest this discrepancy is caused by the emergence of new studies which did not show positive responses. They conclude there is still no

firm evidence of a positive therapeutic response to tDCS and they highlight the need for more robust clinical trials using similar methodologies. In the same year, Wang et al. (2018b) also conducted a systematic review and meta-analysis. Their pooled results showed no significant reduction of tinnitus loudness following tDCS, but they did find a significant reduction of tinnitus distress for tDCS compared to sham treatment. To our knowledge, no reviews on the application of HD-tDCS for tinnitus patients have been published. Reviews of tDCS in tinnitus suggest this technique is promising but needs further development and optimisation. It also remains unclear what area of the brain should be stimulated for the most effective tinnitus suppression, and what the effects are of stimulation polarity on tinnitus.

2.4.6.3 High-Definition Transcranial Direct Current Stimulation

Datta et al. (2009) designed a new electrode configuration called high-definition tDCS (HD-tDCS) to increase the focality of stimulation (Datta et al., 2009), allowing for more accurate targeting of specific brain regions (Dmochowski et al., 2011). It uses five microelectrodes most commonly configured in a 4x1 ring, i.e. a central electrode surrounded by four return electrodes (Turski et al., 2017). In addition to increased focality, the effects of HD-tDCS on cortical excitability last at least 30 minutes longer than those of conventional tDCS (Kuo et al., 2013). Chapter 3 will review both the use of tDCS and HD-tDCS for tinnitus in more detail.

2.5 Tinnitus measured by Magnetic Resonance Imaging (MRI)

2.5.1 Structural changes

MRI can be used to visualise brain structure and brain function (See Chapter 6 for an overview of the MRI method). Grey matter structural changes can be assessed through standard T1-weighted imaging. One analysis method is voxel-based morphometry (VBM), which involves a voxel-wise comparison of the local concentration of grey matter between two groups (Ashburner and Friston, 2000). A recent systematic review evaluated structural differences in tinnitus as measured by VBM (Makani et al., 2022). Fifteen studies were included with a total of 423 participants with tinnitus, and 508 controls. The effects of hearing loss were also investigated.

Comparing tinnitus vs. no tinnitus groups in all studies (n = 15 studies) without regarding hearing loss, three significant clusters of decreased grey matter were found in people with tinnitus. These clusters were located in anterior cingulate cortex, medial prefrontal cortex, and left inferior and middle temporal gyri. In individuals with tinnitus and normal hearing compared to hearing-matched controls (n = 7 studies), a statistically significant grey matter reduction was found in the left STG (Hedge's g = -0.59, p = 0.042). Comparing hearing-matched groups of tinnitus patients and controls with hearing loss (n = 7 studies), the tinnitus group showed significantly increased grey matter levels in bilateral lingual gyrus (Hedge's g = 0.49, $p < 0.05$) and the left precuneus (Hedge's g = 0.46, $p < 0.05$).

The results show that hearing levels affect the results: in the absence of hearing loss, tinnitus was associated with a grey matter reduction, whereas in the presence of hearing loss, tinnitus was associated with a grey matter increase. Makani et al. (2022) propose that whereas hearing loss itself is associated with grey matter reductions, the presence of tinnitus in addition to hearing loss preserves grey matter.

Another application of MRI is Diffusion Tensor Imaging or DTI. As opposed to conventional MRI, which relies on tissue relaxation time differences for contrast, DTI relies on the diffusion of water molecules for contrast. This diffusion is measured using nuclear magnetic resonance (NMR) and magnetic field gradient systems (Mori, 2007). Over 90% of the body's protons are located in water molecules, and therefore the MRI signal is dominated by water. DTI can reveal white matter structures with much greater precision than conventional MRI.

In an unstructured space, water molecules diffuse randomly, which is called "isotropic". In a structured space (e.g. brain tissue), diffusion is "anisotropic": constrained in some directions but unconstrained in others. Water molecules diffuse more freely along axons, but are relatively constrained from moving across the axon wall. The diffusivity can be calculated, making it possible to estimate the orientation of axon bundles. The values used are called FA values or fractional anisotropy values (De Erausquin and Alba-Ferrara, 2013), and they are the most commonly used to

study tinnitus using DTI. Other measures are mean diffusivity (general water diffusion in tissue regardless of direction), and fiber tractography, to identify a specific white matter tract of interest (Khan et al., 2021).

DTI has been used to investigate white matter structural differences in tinnitus patients compared to controls, with a wide range of inconsistent findings (Khan et al., 2021). Hearing loss is a potential confound as a systematic review of twenty DTI studies in patients with sensorineural hearing loss found decreased FA values in a range of auditory brain regions, including auditory cortex and inferior colliculus (Tarabichi et al., 2018).

Khan et al. (2021) collected DTI data from 96 participants in four groups: tinnitus with hearing loss (*n* = 43), tinnitus with normal hearing (*n* = 17), controls with hearing loss (*n* = 17) and controls with normal hearing (*n* = 19) to disentangle the effects of tinnitus and hearing loss. Comparing both tinnitus groups to both control groups revealed decreased FA values in the tinnitus group in the right inferior fronto-occipital fasciculus, right superior corona radiata, forceps minor, genu and body of the corpus callosum, left anterior corona radiata, left anterior thalamic radiation, bilateral superior longitudinal fasciculus and left inferior longitudinal fasciculus. To determine whether these results were driven by tinnitus status or hearing status, or both, subgroup analysis was conducted. This showed increased FA values in the tinnitus with normal hearing group compared to the tinnitus with hearing loss group, as well as increased FA values in the control group with hearing loss compared to the tinnitus group with hearing loss. However, when age was added as a covariate of no interest, these differences did not survive multiple comparisons correction. The question remains whether differences seen in white matter are associated with tinnitus, hearing loss, or age. For example, Yoo et al. (2016) concluded that differences in white matter observed in their tinnitus group were hearing loss related, which was in turn age-related.

2.5.2 Functional changes

Functional MRI differences between tinnitus and non-tinnitus patients have been investigated using task-based fMRI. During the scan, the participant is engaged in a task, whilst their brain activity is measured using the BOLD signal (see Section 6.3.2). For example, Hullfish et al. (2018) used a within-subjects design in which they had 75 tinnitus patients listen to blocks of tones matched to their tinnitus frequency, as well as blocks of tones at a control frequency. Under the predictive coding framework, they hypothesised that the tinnitus frequency would evoke less activity in areas related to auditory perception than the control frequency, because the tinnitus frequency is the predicted norm. In emotional areas on the other hand, they expected more activity caused by the tinnitus frequency, reflecting tinnitus-related distress.

First, they conducted a whole-brain analysis using a subtraction design to compare activity in tinnitus and control frequency blocks. During tinnitus frequency blocks, participants exhibited greater activity in regions resembling a network for semantic cognition, involved with the meaning of sound. Second, region-of-interest (ROI) functional connectivity analysis was executed. This showed that the control frequency blocks elicited stronger connectivity between the ROIs than the tinnitus frequency. Therefore, results were mixed and aligned only partly with the hypotheses. What is clear is that tinnitus patients did respond differently to tinnitus-like sounds than control sounds.

Another study used a visual and auditory Stroop task to test differences in behavioural scores and related brain activity tinnitus and control groups. Araneda et al. (2018) found that tinnitus patients' performance was less accurate and less fast on the visual and the auditory Stroop task compared to age-, hearing-, and education-matched controls. These behavioural differences were related to brain activity differences in DLPFC, ventromedial prefrontal cortex and the cingulate gyrus. The authors posit that this could reflect a deficit in top-down cognitive control, and that this deficit could partly explain why the suppression of tinnitus does not occur in chronic tinnitus patients. However, more longitudinal work on cognitive control in

tinnitus patients is needed to determine whether a deficit in top-down control could partly cause tinnitus, or whether it is the tinnitus causing such a deficit. One could ask whether the constant distraction of the tinnitus experience might affect performance on cognitive control tasks.

Another application of fMRI is resting-state fMRI (rs-fMRI). Here, the participant's brain activity is measured when they are not engaged in any task. As tinnitus is a low-level signal that is always present, it has been hypothesised that it is associated with changes to resting-state activity (Eggermont, 2012). Rs-fMRI can be used to study functional networks in the brain, by measuring the temporal dependence of neural activity between regions. Biswal et al. discovered that spontaneous low-frequency oscillations of the BOLD signal were temporally correlated between regions of the motor network when a subject is at rest (Biswal et al., 1995, Biswal et al., 1997). Later work found the same results for other known networks such as the visual network and auditory network (Van den Heuvel and Hulshoff Pol, 2010). These correlations in resting-state BOLD signal between regions are thought to reflect the underlying structural connectivity of the brain (Van den Heuvel et al., 2009). The use of rs-fMRI in tinnitus research will be discussed at length in Chapter 5 and Chapter 6, in a scoping review and a primary research study respectively.

2.6 Conclusion

The discussion of the literature presented above shows that a lot is known about tinnitus, but there are still many questions that remain unanswered. There is no all-encompassing neurophysiological model of tinnitus, likely due to the large variety of tinnitus phenotypes. This makes developing treatments challenging. When treatments are tested, the field struggles to find conclusive evidence on their efficacy due to heterogeneity within the patient groups, small sample sizes, and varying study methodologies. Neuroimaging research is convincingly showing functional changes in the central nervous system of tinnitus patients, but more work is needed to disentangle the contributions of confounders such as hearing loss, aging, and tinnitus characteristics such as cause, distress levels, and duration.

There is consensus on the theory that subjective tinnitus is a pathology of central origin, and that brain plasticity mechanisms can explain the persistence of the tinnitus signal. Neuroimaging research shows tinnitus is a complex phenomenon which involves auditory as well as non-auditory brain regions. This suggests that treatments targeting the aberrant brain activity involved in tinnitus could help alleviate symptoms. However, due to the wide range of findings, it is difficult to select an appropriate target for treatments such as non-invasive brain stimulation. In the next chapters, non-invasive brain stimulation as a treatment option for tinnitus will be explored further. Evidence from brain imaging research will be reviewed and a new brain imaging study will be presented, to unite previous findings and provide guidance for future non-invasive brain stimulation studies.

Chapter 3 Scoping review of the impact of tDCS and HD-tDCS on tinnitus perception

3.1 Preface

3.1.1 Publication

This scoping review was published as a book chapter in *Progress in Brain Research* (Kok et al., 2021) and has been adapted into this thesis chapter with re-use permission from the journal's Copyright Clearance Center (reference: 501773480).

Full published reference:

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3.1.2 What was undertaken?

A scoping review was undertaken as the first step in this project to analyse the current state of evidence for tDCS and HD-tDCS intervention efficacy for tinnitus. In a scoping review, the goal is to map all the available evidence in a research area and to highlight gaps in the existing literature, without excluding studies based on their quality (Arksey and O'Malley, 2005, Mays et al., 2001). One scoping review posed the question whether tDCS modulates tinnitus loudness or tinnitus-related distress (Shekhawat et al., 2015c), but found no conclusive results. The authors suggested that different sites of stimulation might modulate tinnitus in different ways. This hypothesis aligns with the neurophysiology of tinnitus presented in Chapter 2. Here, it was discussed that tinnitus is associated with hyperactivity in auditory cortex and with alterations in emotional networks. Therefore, the question arises whether tDCS of auditory cortex compared to tDCS of DLPFC modulate tinnitus differently.

3.1.3 Why was it needed?

No reviews had analysed HD-tDCS separately from tDCS (Song et al., 2012, Chen et al., 2020, Wang et al., 2018b). As such, the current scoping review grouped studies according to their site of stimulation, and whether the non-invasive brain stimulation method used was tDCS or HD-tDCS.

3.1.4 How does it contribute to the objectives of the PhD?

This study was the first project of the thesis, serving to familiarise myself with the field of tinnitus and tDCS. Another objective of this study was to inform my own tDCS research study which was originally planned. Unfortunately, this line of research could not continue because of the impact of COVID-19 on this project.

3.2 Abstract

Tinnitus is the auditory phantom perception of a sound that severely affects the quality of life of over 300,000 people in the United Kingdom alone. Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation tool, which has been investigated as a potential tinnitus management option since 2006. This study aimed to investigate the impact of tDCS and HD-tDCS on tinnitus perception. A scoping review was undertaken using the framework by Arksey and O'Malley (2005). After consideration of relevance, 38 primary research studies were included in the data charting to examine the impact of (HD-)tDCS on tinnitus. Twenty-two (58%) of the primary research studies reported significant therapeutic effects of (HD)-tDCS on tinnitus perception. However, only eight of these included a sham-control condition. The tDCS protocols in the studies were highly heterogeneous and sample sizes were generally small. More double-blind, sham-controlled trials are needed that use similar protocols and outcome measures before definitive conclusions about the efficacy of (HD-)tDCS for tinnitus can be drawn.

3.3 Introduction

Tinnitus is the conscious perception of a sound without an external source (Eggermont, 2012). It is estimated that about 10% of the UK population experience prolonged tinnitus (Davis and El Rafaie, 2000). Tinnitus can have a severe, negative

emotional impact on the sufferer, including attention difficulties, insomnia and clinically significant levels of depression and anxiety (Axelsson and Sandh, 1985, Crocetti et al., 2009). The need for effective treatment is urgent, but currently there is no curative treatment available for tinnitus (Langguth et al., 2009).

Developing effective treatments for tinnitus is hindered by a lack of objective biomarkers for tinnitus, a lack of robust outcome measures, and large placebo effects in intervention studies (McFerran et al., 2019). Tinnitus phenotypes are highly heterogeneous, and it is likely that different tinnitus subtypes call for different management strategies (Baguley et al., 2013, McFerran et al., 2019).

One relatively new research tool for tinnitus management is non-invasive brain stimulation. It could potentially modulate tinnitus-related activity in the brain (Plewnia, 2011), as tinnitus is thought to arise from abnormal activity due to compensatory mechanisms following cochlear damage (Eggermont, 2012, Eggermont, 2006a). One brain stimulation tool that has received considerable attention over the past two decades not only in tinnitus, but also in other health conditions such as chronic pain and depression, is transcranial direct current stimulation (tDCS) (Lefaucheur, 2016).

TDCS administers a weak electrical current to the brain through two large rectangular pad-electrodes, one anode and one cathode (Thair et al., 2017a), resulting in diffuse or non-focal stimulation (Datta et al., 2009). tDCS is a safe method, with minor side effects such as tingling or itchy sensation and skin redness under the electrodes (Matsumoto and Ugawa, 2017). Contraindications for tDCS are migraines, the use of any stimulators or implants (e.g. cardiac pacemaker or brain implants), epilepsy or history of seizures, and a history of serious head trauma (Arora et al., 2022). Stimulation can be either anodal or cathodal, each influencing cortical excitability in a different way. Anodal stimulation typically results in excitatory effects through neural depolarization, whereas cathodal stimulation results in inhibitory effects through neural hyperpolarization (Nitsche and Paulus, 2000a). These effects typically

last for an hour or more after a single session of sufficient duration (Nitsche and Paulus, 2001).

In 2009, a new electrode configuration called high-definition tDCS (HD-tDCS) was designed to increase the focality of stimulation (Datta et al., 2009), allowing for more accurate targeting of specific brain regions (Dmochowski et al., 2011). It uses five microelectrodes most commonly configured in a 4x1 ring, i.e. a central electrode surrounded by four return electrodes (Turski et al., 2017). In addition to increased focality, the effects of HD-tDCS on cortical excitability last at least 30 minutes longer than those of conventional tDCS (Kuo et al., 2013).

Most work on tDCS and HD-tDCS is exploratory in nature, since the techniques are relatively novel and there are many adjustable parameters related to the stimulation protocols. Example parameters are the current strength, stimulation polarity, electrode size, duration of stimulation, duration of wash-out periods between stimulation sessions, site of stimulation, and number of stimulation sessions (Thair et al., 2017a). Consensus on the most effective stimulation protocols is yet to be reached and indeed the field has been warned about the “chaotic wealth of data” that could result from tDCS research efforts (Lefaucheur et al., 2017).

To maintain order in this research area, it is important to consider all the work cohesively and to disseminate and summarize research findings continuously. Therefore, the aim of the present article was to conduct a scoping review to explore the range of (HD-)tDCS for tinnitus studies. In a scoping review, the goal is to map all the available evidence in a research area and to highlight gaps in the existing literature, without excluding studies based on their quality (Arksey and O'Malley, 2005, Mays et al., 2001). This method was chosen over systematic review, as it was suspected that most research would be of exploratory nature rather than randomised controlled trials (RCT), due to the relative novelty of HD-tDCS.

3.4 Methods

3.4.1 Search strategy

A scoping review was undertaken using the framework proposed by Arksey and O'Malley (2005). The online databases PubMed, Medline, Web of Science (Core Collection) and Embase were searched from inception until the 30th of January 2020 for the following terms: ("tinnitus" AND ("tDCS" OR "transcranial direct current stimulation")). A second search was performed using the following search string: ("tinnitus" AND ("HD-tDCS" OR "high definition transcranial direct current stimulation")). The search was limited to the English language. A search for master/PhD theses was performed by consulting an expert in the field, who suggested two MSc theses for review.

3.4.2 Inclusion criteria

Primary research studies were included which examined the impact of tDCS or HD-tDCS on tinnitus perception. Reviews were excluded. There were no inclusion criteria regarding the presence of a control group. Studies that combined tDCS or HD-tDCS with an additional treatment were included.

3.4.3 Data charting

All references, including abstracts, were exported to EndNote X9 reference manager. Duplicates were removed using EndNote's 'Find Duplicates' functionality. Titles and abstracts were screened for relevance. The remaining records' full-text versions were accessed and divided into three categories: 1) primary research studies of the impact of tDCS or HD-tDCS on tinnitus perception, 2) review studies, and 3) all other reports, i.e. study protocols, reviews, case studies, datasets, commentaries, book chapters, and theoretical discussions. Only the data from the primary research studies were included to investigate the impact of (HD-)tDCS on tinnitus perception.

The included references were taken to the data charting stage. Information was extracted about their study design, electrode configuration, results, and logged in Excel spreadsheets. All data were extracted as mean ± standard deviation unless otherwise specified.

3.4.4 Data analysis

The included references were grouped by their site of stimulation and presented in a table. The table was organized by site of stimulation (from top to bottom, studies that have targeted auditory cortex (AC), dorsolateral prefrontal cortex (DLPFC), or the left temporoparietal area (LTA). Within this order, studies that included sham control were placed first. Studies that used HD-tDCS rather than conventional tDCS were separated by marking them blue. A question mark was noted in cases where the information was unavailable from the full-text version of the reference.

3.5 Results

3.5.1 Search results

A total of 374 records were found in the database search, along with the two MSc theses. Duplicates (*n* = 230) were removed, and the remaining records (*n* = 146) were screened for relevance by title and abstract. Fifty-five records were excluded as their topic was not tinnitus and tDCS, or tinnitus and HD-tDCS. The remaining 91 records were accessed for their full-text versions. A flowchart of study selection is shown in Figure 3-1.

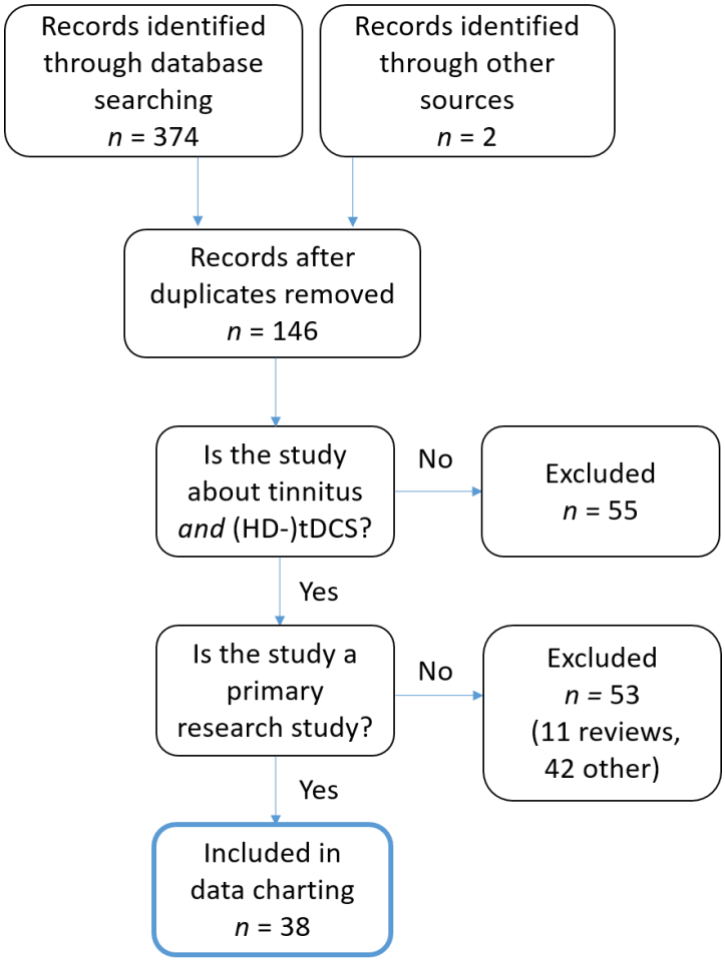

Figure 3-1 Flowchart of study selection

3.5.2 Data charting

Table 3-1 shows an overview of the 38 primary research studies that were found, and Table 3-2 shows the specifics of the stimulation protocol used in each study. Some studies compared the effects of administering tDCS in different ways, in which case the study was split up in two rows to describe the different study arms.

Study	*Site of Stimu-lation*	*Sham Control*	*Sign. Effect*	*Positive Response Rate*	*Primary Outcome Measure*	*n*
Teismann et al. (2014)	AC	Yes	No	Not given	THQ	32

Pal et al. (2015a)	AC	Yes	No	Not given	THI	42
Henin et al. (2016)	AC	Yes	No	14.2%	VAS Loudness	14
Abtahi et al. (2018)	AC	Yes	Yes (anodal)	Not given	Intensity Change -4 to +4 scale	51
Vanneste et al. (2013a)	AC	No	No	Not given	VAS Loudness & VAS Annoyance	36
Joos et al. (2014)	AC	No	Yes (only for 2.0 mA)	Loudness: 17.4%; Annoyance: 11.4%	VAS Loudness & VAS Annoyance	175
Minami et al. (2015)	AC	No	No	TFI: 22%	TFI, TRSw, TSSw, HADS	9
Vanneste and De Ridder (2011)	DLPFC	Yes	Yes	100%	VAS Loudness & VAS Distress	12
Faber et al. (2012a)	DLPFC	Yes	Yes	Not given	VAS Annoyance	15

Vanneste et al. (2013b)	DLPFC	Yes	Yes	Not given	VAS Loudness & VAS Annoyance	24
Cavalcanti et al. (2015)	DLPFC	Yes	No	Not given	THI & VAS Loudness	18
Shekhawat and Vanneste (2018a)	DLPFC	Yes	Yes (loudness only)	Not given	VAS Loudness & VAS Annoyance	13
Hyvarinen et al. (2016) (part 1)	DLPFC	Yes	No	Not given	THI	35
Hyvarinen et al. (2016) (part 2)	LTA	Yes	No	Not given	THI	35
Yadollahpour et al. (2019) (Abstract only)	DLPFC	Yes	Yes	Anodal: 77%, cathodal 70%	THI, VAS Loudness & VAS Annoyance	30
Vanneste et al. (2010)	DLPFC	No	Yes	29.90%	VAS Loudness & VAS Distress	478

Vanneste et al. (2011a)	DLPFC	No	Yes	46.70%	VAS Loudness & VAS Distress	45
Vanneste et al. (2011b)	DLPFC	No	p-value not given	27%	VAS Loudness	153
De Ridder and Vanneste (2012) (part 1)	DLPFC	No	Yes	Distress: 19.2%; Loudness: 22.1%	VAS Loudness & VAS Distress	265
De Ridder and Vanneste (2012) (part 2)	EEG driven location	No	Yes	Distress: 8.2%; Loudness: 12.5%	VAS Loudness & VAS Distress	380
Frank et al. (2010) (Conference abstract)	DLPFC	No	p-value not given	Not given	THI & BDI	20
Frank et al. (2012)	DLPFC	No	Yes, for VAS but not for THI	THI: 15.60%	THI, VAS Loudness & VAS Discomfort	32
Shekhawat et al. (2016) (part 1)	DLPFC	No	Yes	Unclear but >48%	VAS Loudness &	27

					VAS Annoyance	
Shekhawat et al. (2016) (part 2)	LTA	No	Yes	Unclear but >48%	VAS Loudness & VAS Annoyance	27
Rabau et al. (2017)	DLPFC	No	No	Loudness: 26.8-39.1%	TFI, VAS Loudness & HQ	59
To et al. (2017)	DLPFC	No	Yes	Not given	TQ, THI, VAS Loudness	40
Jacquemin et al. (2018) (part 1)	DLPFC	No	Yes, for TFI only	31%	TFI, VAS Loudness, HQ, TQ, HADS	39
Jacquemin et al. (2018) (part 2)	DLPFC / LTA	No	Yes, for TFI only	38% / 27%	TFI, VAS Loudness, HQ, TQ & HADS	78
Shekhawat and Vanneste (2018c)	DLPFC	No	Yes	Not given	VAS Loudness	111
Jacquemin et al. (2019a)	DLPFC	No	Yes	36%	TFI	22

Jacquemin et al. (2019b)	DLPFC	No	Yes, for TFI but not TQ	30%	TFI & TQ	100
Lee et al. (2017)	DLPFC	No	Yes (combined with TMNMT)	Annoyance: 57.5%; Loudness: 28.6%	VAS Loudness & VAS Annoyance	26
Lee (2019)	DLPFC	No	Yes	Not given	THI, BDI & VAS Loudness	14
Fregni et al. (2006)	LTA	Yes	Yes	42%	Tinnitus reduction rating scale 0 - 4	7
Garin et al. (2011)	LTA	Yes	Yes	35%	VAS change scale -4 to +4 (Loudness & Distress)	21
Shekhawat et al. (2015a)	LTA	Yes	No	Not given	VAS Loudness & MML	9
Forogh et al. (2016)	LTA	Yes	No	Not given	THI, VAS Loudness,	22

					VAS Distress & CGI	
Shekhawat et al. (2014a)	LTA	Yes	No (only of hearing aid)	Not given	VAS Loudness, CGI, TFI & MML	40
Mowbray (2016) *MSc thesis*	LTA	Yes	No	64.3%	VAS Loudness & Annoyance	14
Shekhawat et al. (2013)	LTA	No	Yes	56%	VAS Loudness & CGI	25
Cooke (2016) *MSc thesis*	LTA	No	No	Annoyance: 29%; Loudness: 38%	VAS Loudness & Annoyance	13
Artifon et al. (2019) (abstract only)	Not given	No	No	Not given	Rating scale 1-3 (1=no response, 2=mild response, 3=consistent response)	5

Table 3-1 Overview of the included primary research studies. AC = auditory cortex; DLPFC = dorsolateral prefrontal cortex; LTA = left temporoparietal area; THQ = Tinnitus Handicap Questionnaire; THI = Tinnitus Handicap Inventory; VAS = Visual Analogue Scale; TFI = Tinnitus Functional Index; TRSw = Tinnitus Rating scale, 1-week version; TSSw, = Tinnitus Severity Scale, 1-

week version; HADS = Hospital Anxiety and Depression Scale; HQ = Hyperacusis Questionnaire; TQ = Tinnitus Questionnaire; BDI = Beck Depression Inventory; MML = minimum masking level; CGI = Clinical Global Improvement; TMNMT = tailor made notched music training.

Study	*Stimulation*	*Anode*	*Cathode*	*mA*	*Duration*	*Sessions*	*Electrode size (cm2)*
Teismann et al. (2014)	Anodal/cathodal	Left AC/RSO	Left AC/RSO	2.0	30 min	5	A = 35, C = 100
Pal et al. (2015)	Cathodal	PFC (F3-Fz-F4)	Bilateral AC (T3 & T4)	2.0	20 min	5	A = 75, C = 35.75
Henin et al. (2016)	HD-tDCS 2x2	Bilateral AC	Bilateral PFC	2.0	20 min	2	inner radius =6mm, outer =12mm.
Abtahi et al. (2018)	Anodal/cathodal	T3/T4? /contralateral arm	T3/T4? /contralateral arm	2.0	20 min	1?	length: 235 cm (?)
Vanneste et al. (2013a)	Anodal/cathodal	T3 or T4	T3 or T4	1.5	20 min	1	A = 35, C = 35
Joos et al. (2014)	Anodal/cathodal	T3 or T4 + contralateral arm	T3 or T4 + contralateral arm	1.5 or 2.0	20 min	1	A = 35, C = 35

Minami et al. (2015)	Cathodal	left PAC (pSTG)	right PAC (pSTG)	1.0	10 min	1	?
Vanneste and De Ridder (2011)	Bifrontal	F4	F3	1.5	20 min	2	A = 35, C = 35
Faber et al. (2012)	Bifrontal	F3/F4	F3/F4	1.5	20 min	6	A = 35, C = 35
Vanneste et al. (2013b)	Bifrontal	F4	F3	2.0	20 min	1	A = 35, C = 35
Cavalcanti et al. (2015)	Bifrontal	F4	F3	2.0	20 min	5	A = 35, C = 35
Shekhawat and Vanneste (2018a)	Anodal HD-tDCS (4x1)	F4	4x at 3.5cm from anode	2.0	20 min	1	Inner radius = 6mm, outer = 12mm
Hyvarinen et al. (2016) (part 1)	Bifrontal	Left frontal area	Right frontal area	2.0	20 min	10	A = 35, C = 35

Hyvarinen et al. (2016) (part 2)	Anodal	LTA	Right frontal area	2.0	20 min	10	A = 35, C = 50
Yadollahpour et al. (2019)	Bifrontal	F3/F4	F3/F4	2.0	20 min	1	A = 35, C = 35
Vanneste et al. (2010)	Bifrontal	F4	F3	1.5	20 min	1	A = 35, C = 35
Vanneste et al. (2011a)	Bifrontal	F4	F3	1.5	20 min	1	A = 35, C = 35
Vanneste et al. (2011b)	Bifrontal	F4	F3	1.5	20 min	1	A = 35, C = 35
De Ridder and Vanneste (2012) (part 1)	Bifrontal	F4	F3	?	?	?	A = 35, C = 35
De Ridder and Vanneste (2012) (part 2)	Bifrontal	Highest theta band FC based on EEG	Highest gamma band FC based on EEG	?	?	?	A = 35, C = 35

Frank et al. (2010)	Bifrontal	F4	F3	1.0	30 min	6	?
Frank et al. (2012)	Bifrontal	F4	F3	1.5	30 min	6	A = 35, C = 35
Shekhawat et al. (2016) (part 1)	Anodal HD-tDCS (4x1)	F4	4x at 3.5cm from anode	1.0 or 2.0	10 or 20 min	2	Inner radius = 6mm, outer = 12mm
Shekhawat et al. (2016) (part 2)	Anodal HD-tDCS (4x1)	LTA C3<>T5	C5, TP7, CP3, P5	1.0 or 2.0	10 or 20 min	2	Inner radius = 6mm, outer = 12mm
Rabau et al. (2017)	Bifrontal	F4	F3	2.0	20 min	8	A = 35, C = 35
To et al. (2017)	Bifrontal	F4	F3	1.5	20 min	8	A = 35, C = 35
Jacquemin et al. (2018) (part 1)	Anodal HD-tDCS (4x1)	F4	F2, F6, FC4, AF4	2.0	20 min	8	Inner radius = 6mm, outer = 12mm

Jacquemin et al. (2018) (part 2)	Bifrontal / Cathodal	F4 / RSO	F3 / LTA C3 <> T5	2.0	20 min	8	A = 35, C = 35
Shekhawat and Vanneste (2018b)	Bifrontal	F4	F3	1.5 or 2.0	20 or 30 min	2 to 10	A = 35, C = 35
Jacquemin et al. (2019a)	Anodal HD-tDCS (4x1)	F4	F2, F6, FC4, AF4	2.0	20 min	8	Inner radius = 6mm, outer = 12mm
Jacquemin et al. (2019b)	Anodal HD-tDCS (4x1)	F4	?	?	20 min	6	?
Lee (2019)	Bifrontal	F4	F3	1.5	20 min	1 to 6	A = 35, C = 35
Lee et al. (2017)	Bifrontal	F4	F3	1.5	20 min	4	A = 35, C = 35
Fregni et al. (2006)	Anodal	LTA C3<>T5	RSO	1.0	3 min	1	A = 35, C = 35
Garin et al. (2011)	Anodal	LTA C3<>T5	T4<>F8	1.0	20 min	1	A = 35, C = 50

Shekhawat et al. (2015a)	Anodal	LTA C3<>T5	T4<>F8	2.0	20 min	4	A = 35, C = 50
Forogh et al. (2016)	Anodal	LTA C3<>T5	RSO	2.0	20 min	5	A = 35, C = 35
Shekhawat et al. (2014)	Anodal	LTA C3<>T5	T4<>F8	2.0	20 min	5	A = 35, C = 50
Roanna Mowbray MSc thesis (2016)	Anodal HD-tDCS (4x1)	LTA C3<>T5	C5, TP7, CP3, P5 (3.5cm ring) / PO7, CP1, TP9, FC5 (7.0 cm ring)	2.0	20 min	3	Inner radius = 6mm, outer = 12mm
Shekhawat, et al. (2013)	Anodal	LTA C3<>T5	T4<>F8	1.0 or 2.0	10/15/20 min	6	A = 35, C = 50
Christopher Cooke MSc thesis (2016)	Anodal HD-tDCS (4x1)	LTA C3<>T5	C5, TP7, CP3, P5	2.0	20 min	4	Inner radius = 6mm, outer = 12mm
Artifon et al. (2019)	tDCS	Not given	Not given	2.0	30 min	20	Not given

Table 3-2 Stimulation protocol specifics for the included studies. AC = auditory cortex; PFC = prefrontal cortex; RSO = right supraorbital area; PAC = primary auditory cortex; pSTG = posterior superior temporal gyrus; A = anode, C = cathode

3.5.3 Study design

The samples sizes in the included studies ranged from 5 – 479 participants, with a mean of 62.21 participants per study (SD = 97.69). Of these studies, the majority (*n* = 22, 58%) found a therapeutic effect of brain stimulation. Eight of these 22 studies included sham control. On the other hand, there were also ten studies with sham control that did not find any significant benefit following stimulation. The studies were highly heterogeneous, problematizing the formation of a coherent interpretation of the work. Important factors that caused the heterogeneity were the use of different outcome measures to assess therapeutic impact, the use of different stimulation protocols, and differing tinnitus profiles within and between studies. For example, some studies included only participants with unilateral tinnitus, whereas other studies include both unilateral and bilateral tinnitus. Some studies described results in terms of "responders" and "non-responders" to the treatment, but it is unclear which tinnitus characteristics are associated with being a "responder".

The outcome measures that were used the most were Visual Analogue Scales (VAS) (*n* = 26), the Tinnitus Handicap Inventory (THI) (*n* = 9) and the Tinnitus Functional Index (TFI) (*n* = 6). The data charting showed a trend for studies targeting DLPFC to use VAS as the primary outcome measure, whereas studies targeting AC and LTA showed a more diverse pattern. It is important to consider the impact of the outcome measures used in each study, as they might differ in their sensitivity to detect (transient) changes in tinnitus perception. For example, the TFI was developed with the goal of detecting treatment-induced changes, with a 10-point response scale for each item to make it sensitive to small changes and less susceptible to ceiling effects (Meikle et al., 2012a, Jacquemin et al., 2019b), in comparison to questionnaires using coarser scales like the THI. On visual analogue scales, participants are asked to rate separately the loudness of their tinnitus and the annoyance they experience because of their tinnitus on a scale of 0 to 10. It is an easily applicable scale, which may be particularly sensitive for detecting transient change in tinnitus perceptions, but it covers fewer aspects than a questionnaire (Figueiredo et al., 2009).

The studies discussed here all involved different time scales: some studies administered only one session of brain stimulation, whereas others administered multiple sessions across several weeks. This could have motivated the choice of a certain outcome measure, as the immediate impact of a single session of tDCS is probably best captured using a VAS, whereas long-term change is better captured using a questionnaire. The effect of tDCS on tinnitus perception will now be discussed below, organized by site of stimulation.

3.5.4 tDCS of auditory cortex

Six studies were found targeting auditory cortex (AC) in tinnitus patients. Out of these, two studies (Joos et al., 2014, Abtahi et al., 2018) showed a significant improvement on their primary outcome measure, a rating scale, following tDCS treatment. Interestingly, these studies are the only two studies that placed the reference electrode on the contralateral arm. The effect of placing the reference electrode away from the head is currently unclear, but this observation suggests an extracephalic placement could be more effective when stimulating auditory cortex for tinnitus relief. Abtahi et al. (2018) included a sham control group, whereas Joos et al. (2014) did not. However, Abtahi et al. (2018) did not provide details about how the sham protocol was implemented, and from the imprecise description given it can be questioned whether the control group "[given] electrical stimulation" (p. 95) received an effective sham procedure.

Teismann et al. (2014) and Pal et al. (2015b) were double-blind, sham-controlled studies that administered five tDCS sessions instead of a single or double session. Teismann et al. (2014) also combined tDCS with tailor-made notched music training (TMNMT), which was administered at the same time. The combined treatment significantly improved THQ scores, but the type of tDCS (sham, anodal or cathodal) did not significantly affect the improvement, suggesting the positive effect was due to the TMNMT or an unspecific placebo effect from the TMNMT. Pal et al. (2015b) administered cathodal tDCS on five consecutive days and concluded the protocol was safe, but did not significantly improve tinnitus on THI scores or secondary outcome measures such as VAS.

There is little consensus regarding what type of stimulation, anodal or cathodal, is optimal for modulating tinnitus perception through AC stimulation. All AC studies included cathodal stimulation, and some studies also compared this to anodal stimulation. The rationale for using cathodal stimulation for AC is that it should inhibit the hyperactivity observed in AC in tinnitus patients (Pal et al., 2015a, Joos et al., 2014). However, just one study found a therapeutic effect for cathodal stimulation, and this was smaller than for the anodal condition (Joos et al., 2014). Heimrath et al. (2016) suggested that polarity specific changes of non-invasive brain stimulation depend on the participant's current excitation/inhibition balance and thus do not straightforwardly result in a certain behavioural effect.

In summary, few studies have targeted auditory cortex and their protocols are largely heterogeneous. From the limited data, it is advisable to model the electric field distributions of the above protocols to inform the optimal electrode configuration. A comparison of extracephalic and bicephalic electrode placements, as well as anodal and cathodal stimulation, would be warranted for auditory cortex stimulation.

3.5.5 tDCS of dorsolateral prefrontal cortex

Eighteen studies were found targeting DLPFC in tinnitus patients. Twelve of these did not include a sham condition in their design. However, out of the six studies that did include sham control, four found significant improvements after active tDCS compared to sham tDCS. This suggests that the positive results found in fourteen DLPFC studies without sham control could also be real treatment effects rather than placebo effects. Interestingly, the four sham-controlled studies that found a significant improvement all used VAS as their primary outcome measure, and only one of the four (Yadollahpour et al., 2019) also found a significant improvement on TFI. With regards to the number of sessions administered in these studies, no clear pattern arises as Vanneste et al. (2013b) and Yadollahpour et al. (2019) administered a single session, whereas Vanneste and De Ridder (2011) and Faber et al. (2012a) administered two and six sessions respectively.

The majority of DLPFC studies used similar tDCS protocols. The most frequent protocol was bifrontal stimulation, with the anode over the right DLPFC (placed over T4 according to the international 10/20 EEG system), and the cathode over the left DLPFC (placed over T3), which was used in seven studies. Most commonly, the current strength was either 1.5 mA or 2.0 mA and stimulation duration was twenty minutes.

Shekhawat and Vanneste (2018c) conducted a dose-response study of tDCS of DLPFC stimulation. Participants received two, four, six, eight or ten sessions (two sessions a week) of either 1.5 or 2.0 mA, for either twenty or thirty minutes. The results showed that the stimulation significantly reduced tinnitus loudness, regardless of the current strength or stimulation duration used. However, effects plateaued after six sessions. The authors therefore suggested that the optimized settings for tDCS of DLPFC were the following: six sessions, with a three-to-four-day washout period, 1.5 mA current strength, and twenty minutes stimulation duration.

Hyvarinen et al. (2016) examined the efficacy of self-administered domiciliary tDCS but found no significant treatment effect. The electrode set-up in this study was reversed compared to other studies targeting DLPFC: the anode was placed on the left hemisphere and the cathode on the right. Faber et al. (2012a) directly compared the left and right anode montages for DLPFC and found a significant improvement on VAS annoyance scores for both. Therefore, it is currently unclear what effect (if any) reversing the anode and cathode in a bifrontal montage has on tinnitus perception.

To summarise, tDCS of DLPFC with the anode over the right and cathode over the left hemisphere is a well-studied montage, with the majority of studies showing therapeutic effects. These promising results warrant further investigation of this DLPFC protocol.

3.5.6 tDCS of left temporoparietal area

Eight studies were found targeting LTA in tinnitus patients. Studies targeting LTA have almost exclusively administered anodal stimulation, with the anode placed halfway

in between C3 and T5 according to the international 10/20 EEG system and the cathode placed on the right supraorbital area, generally defined as halfway between T4 and F8.

Six out of eight studies included sham control, and only two of these found a significant result of an active tDCS protocol compared to sham tDCS. Whereas DLPFC studies seemed more likely to find significant effects if they used VAS as the primary outcome measure, no such pattern was evident in LTA studies. The first study to administer tDCS to LTA was also the first study ever in tinnitus patients. Fregni et al. (2006) set out to replicate the finding that repetitive transcranial magnetic stimulation (rTMS) of LTA can induce tinnitus suppression and determine whether such an effect can also be achieved by tDCS . In a within-participant design, they compared six different types of stimulation in a randomized order: 10-Hz rTMS of LTA, 10-Hz rTMS of mesial parietal cortex, sham rTMS, anodal tDCS of LTA, cathodal tDCS of LTA and sham tDCS. They found a main effect of stimulation type, and follow-up tests revealed that only 10-Hz rTMS and anodal tDCS of LTA resulted in a significant tinnitus suppression as measured by a tinnitus change rating scale of 0 – 4. Interestingly, the three participants that showed a tinnitus reduction after rTMS also showed a reduction after tDCS, so none of the participants responded selectively to either rTMS only or tDCS only.

The study by Fregni et al. (2006) differs from later studies in that it administered a smaller current (1.0 mA instead of 1.5/2.0 mA) for only a short period (three minutes instead of twenty to thirty minutes). Shekhawat et al. (2013) conducted a dose-response study, testing six combinations of tDCS intensity and duration on 25 participants with chronic tinnitus in incremental order: 1.0 mA for ten minutes, fifteen minutes and twenty minutes, followed by 2.0 mA for ten, fifteen and twenty minutes. Tinnitus loudness was rated on a VAS before and after each round of stimulation, with suppression defined as at least a one-point-decrease on the VAS score. Fourteen out of 25 participants experienced tinnitus suppression following tDCS, and suppression was greatest after twenty minutes of 2.0 mA stimulation. However, because of the incremental nature of the stimulation and the short

washout period of ten minutes between rounds of stimulation, the cumulative impact of the sessions cannot be ruled out as an explanation. Also, Hyvarinen et al. (2016), Forogh et al. (2016) and Shekhawat et al. (2015a) tested these stimulation settings (2.0 mA for twenty minutes) in sham-controlled designs and found no significant tinnitus reduction for active stimulation compared to sham stimulation. Therefore, it cannot be ruled out that the tinnitus reduction found in LTA studies reflects a placebo effect.

3.5.7 HD-tDCS

Eight studies investigated HD-tDCS instead of conventional tDCS, marked in blue in Table 3-1 and 3-2. All but one administered multiple sessions of HD-tDCS. The most common electrode configuration was a 4x1 ring, with one central anode and four surrounding cathodes. However, one study targeted auditory cortex using a 2x2 electrode set-up (Henin et al., 2016), with two anodal electrodes placed over primary auditory areas, and two cathodal electrodes placed over prefrontal cortex. They combined the HD-tDCS treatment with compensatory auditory stimulation (CAS) in a crossover design so that each participant received four treatments (CAS only, HD-tDCS only, combined CAS and HD-tDCS, and sham treatment) divided over two sessions. The CAS consisted of sound exposure similar to daily living (20-minute sound-track of a TV show), which was adapted with compressive gain to compensate for deficits in each participant's audiogram. Even though trends towards a reduction of tinnitus were observed, none of the stimulation paradigms had a significant effect on tinnitus, which according to the authors may have been attributable to the small sample size (n = 14).

Five studies administered anodal HD-tDCS to right DLPFC, all finding significant improvements on both VAS and TFI measurements. However, only one study (Shekhawat and Vanneste, 2018a) included a sham arm. In this double-blind, randomized trial, thirteen participants received sham stimulation and active stimulation with a one-week washout period in between. The results showed a significant improvement on tinnitus loudness, but not on tinnitus annoyance for active stimulation compared to sham stimulation.

Three HD-tDCS studies targeted LTA, of which two studies were (unpublished) masters' theses (Mowbray, 2016, Cooke, 2016). Shekhawat et al. (2016) used a within-participant design to compare different stimulation intensity, duration and location of HD-tDCS, without sham control. The different locations, LTA and DLPFC, were stimulated in two different sessions with a one-week washout period in between. Participants were randomly allocated to receive either LTA or DLPFC stimulation first. In each of these two sessions, four different stimulation parameters were used: 1.0 mA for ten minutes, 1.0 mA for twenty minutes, 2.0 mA for ten minutes and 2.0 mA for twenty minutes. The results showed a significant reduction in tinnitus intensity and annoyance, with a high positive response rate of 77.78%. Higher current intensity of 2.0 mA was significantly more effective than 1.0 mA, and twenty minutes of stimulation was significantly more effective than ten minutes, but it did not matter whether LTA or DLPFC was stimulated. The authors suggest that the relatively high positive response rate (PRR) found in their study could be due to the more focal stimulation pattern of HD-tDCS compared to conventional tDCS.

Cooke (2016) and Mowbray (2016), in their masters' theses, also both administered HD-tDCS of LTA to thirteen and fourteen tinnitus patients respectively. Neither used sham control; both found improvements in tinnitus loudness, which was significant in Mowbray (2016), but not in Cooke (2016). Overall, HD-tDCS seems to be a promising research tool for managing tinnitus. Five out of eight studies reported a significant improvement on their tinnitus outcome measure. However, only three studies included sham control, of which just one found a significant improvement compared to the sham condition. The results call for more sham-controlled, randomised trials, to disentangle placebo effects from treatment effects in HD-tDCS research.

3.6 Discussion

TDCS and HD-tDCS are safe and well-tolerated techniques that can be used to induce a transient suppression of tinnitus. The most common side effects for tDCS and HD-tDCS were tingling sensation, itchiness, mild scalp burn and scalp pain. These effects were brief and mainly at the onset of stimulation (Matsumoto and Ugawa, 2017,

Shekhawat et al., 2016). In the majority of studies, the stimulation resulted in a transient suppression of tinnitus loudness and/or distress. However, the wide variety of tDCS protocols used in research makes it difficult to draw firm conclusions on its efficacy. The short-term efficacy of stimulation of DLPFC seems to be fairly well established, but little evidence was found for the efficacy of stimulation protocols that target auditory cortex or LTA. In support of this observation, in a review of the therapeutic efficacy of tDCS for a range of disorders, Lefaucheur et al. (2017) concluded there is fair evidence that anodal tDCS of LTA is not effective for tinnitus relief. Concerning stimulation of DLPFC, they concluded the evidence remained too preliminary to make any recommendation.

The rationale behind stimulating DLPFC for tinnitus relief is based on tinnitus models, such as the frontostriatal gating model, that postulate a role for frontal areas in tinnitus. Indeed, neuroimaging studies show involvement of frontal areas in the pathophysiology of tinnitus (Vanneste and De Ridder, 2011). Stimulation of DLPFC has resulted in a clinical benefit in the treatment of depression, which is a frequent comorbid disorder of tinnitus (Langguth et al., 2011). Therefore, it may be possible that stimulation of DLPFC might be more effective at modulating tinnitus-related distress than the tinnitus loudness. However, the evidence here is mixed, as one of the sham-controlled studies targeting DLPFC did find a significant reduction in tinnitus annoyance, but not in tinnitus loudness (Faber et al., 2012a), whereas another found a significant reduction in tinnitus loudness, but not in distress (Shekhawat and Vanneste, 2018a). The view that stimulation of different areas modulates loudness and annoyance differently is still under debate (Shekhawat et al., 2015b). It would be useful for future research to elucidate this, potentially by using HD-tDCS for more focal targeting of specific areas, as was also suggested by Shekhawat et al. (2015b).

Not only is the role between stimulation location and tinnitus modulation unclear, there also is little understanding of the role stimulation polarity plays in tDCS protocols for tinnitus. Current neurophysiological models of tinnitus suggest that inhibiting tinnitus-related neural hyperactivity using cathodal stimulation could be an

effective option for tinnitus relief (Pal et al., 2015a, Joos et al., 2014). However, the evidence suggests anodal stimulation could be more effective than cathodal stimulation. More groundwork is needed on polarity-specific effects of tDCS in tinnitus patients to help shine light on this matter.

Finally, it should be mentioned that we are far from understanding individual response patterns to tDCS treatment. As discussed in section 2.1.3, tinnitus is a heterogeneous symptom with varying laterality, sound type, loudness, distress levels and degree of hearing loss, amongst others. Only few studies have attempted to match study groups based on these differing tinnitus phenotypes. It is common practice to obtain audiograms and psychoacoustic tinnitus measurements, but tDCS studies have not yet endeavoured to explore how these relate to treatment outcomes. De Ridder and Vanneste (2012) tried to tailor tDCS to the individual, comparing EEG-driven tDCS (*n* = 380) to bifrontal tDCS (*n* = 265) of DLPFC. In the EEG-driven group, they used tinnitus-related gamma band functional connectivity to decide where to place the anode and the cathode. However, although both groups improved significantly compared to a waiting list control group, the group that received 'blind' bifrontal tDCS showed greater tinnitus relief than the EEG-driven group. As a potential explanation, the authors suggest the exactness of the electrode positioning might have been compromised in the EEG-driven group. The study did not use neuronavigation because of technical reasons, and gamma band activity is usually only present in a small focal area. Further exploration of HD-tDCS as a tool for tinnitus management might prove useful in this, as it is more focal and would allow for more accurate targeting of specific regions tailored to the individual.

One last topic to be touched upon is the potential of combining tDCS with other interventions. Examples of interventions that have been combined with tDCS are tailor-made notched music training (TMNMT) (Lee et al., 2017, Teismann et al., 2014), compensatory auditory stimulation (Henin et al., 2016), auditory residual inhibition (Shekhawat et al., 2015a, Cooke, 2016) and hearing aids (Shekhawat et al., 2014a). In most studies, improvement in tinnitus seems independent of the tDCS condition when combining it with a standard behavioural treatment (Heimrath et al., 2016).

However, it is difficult to pick apart the individual contributions of tDCS and the combination treatment in these studies for methodological reasons. Further studies that are designed to separate effects might shine further light on this matter.

3.7 Consultation Exercise

The sixth stage of the scoping review involved consulting experts in the field about the findings of the review. Five tinnitus experts with neuromodulation experience were invited to share their opinions, of whom three replied with their input. Overall, the consensus was that the findings were consistent with the view they held of the field. The following points summarise recommendations for future studies based on the review and the experience of the consulted experts:

1. Adhere to the "gold standard" of randomised controlled trials wherever possible to establish multi-centre replicability of results, i.e. performing *a priori* power analyses and reporting them, using appropriate randomisation, using double-blind sham procedures, and including relevant outcome measures for tinnitus loudness, as well as psychoacoustic tinnitus measures such as minimum masking levels;
2. Focus on stimulation target optimisation:
    a. Explore multiple target stimulation, for example stimulating DLPFC and LTA at the same time;
    b. Adjust the stimulation to pathophysiology of tinnitus, for example differences between tinnitus with and without hearing loss;
    c. Use modelling of electric field distributions to inform target selection.
3. Combine tDCS/HD-tDCS with behavioural interventions such as auditory stimulation.

3.8 Conclusions

TDCS has been shown to transiently reduce tinnitus loudness and distress, predominantly using a bifrontal set-up targeting DLPFC. However, this result is not robust, as there is a lack of "gold standard" trials using similar protocols and outcome measures. Especially HD-tDCS warrants further investigation because of its increased

focality and potentially longer lasting effects compared to conventional tDCS. In addition, more groundwork is needed on the neurophysiological mechanisms behind tinnitus modulation using (HD-)tDCS. The goal for future studies is to develop rigorously tested stimulation protocols that are suitable for individual tinnitus patient's needs.

Chapter 4 Survey of tinnitus patients' acceptance of HD-tDCS

4.1 Preface

4.1.1 Publication

This survey was published in *International Journal of Audiology (Kok et al., 2022b)* and has been adapted into this thesis chapter. Re-use permission from Taylor & Francis is free for theses and dissertations, so no re-use permission was required.

Full published reference:

Kok, T. E., Varley, R. & Shekhawat, G. S. 2022. Survey of tinnitus patients' acceptance of high-definition transcranial direct current stimulation as a management option. *Int J Audiol*, 61, 507-514. https://doi.org/10.1080/14992027.2021.1933622

4.1.2 What was undertaken?

An online survey was undertaken to gather tinnitus patient perspectives on non-invasive brain stimulation (NIBS) techniques as a management option for tinnitus. 272 participants responded and the majority considered NIBS an acceptable form of management.

4.1.3 Why was it needed?

Chapter 3 showed promise for tDCS as a management option for tinnitus. However, for non-invasive brain stimulation to advance from a research tool to a clinical intervention, it is important to gather patient perspectives on the technique. Therefore, this stage of the project aimed to investigate the acceptability of NIBS, and HD-tDCS in particular, for the management of tinnitus. Tinnitus patient surveys had not previously investigated the acceptability of NIBS.

4.1.4 How does it contribute to the objectives of the PhD?

When researching management option for tinnitus, the main goal is for these tools to become available as treatment one day should they be proven effective. However, some forms of treatment are more acceptable than others. This study therefore

provides direction to future research as the patient perspectives are what matters the most.

4.2 Abstract

This study aimed to investigate the acceptance of non-invasive brain stimulation (NIBS) as a management option for tinnitus. Participants (*n* = 272) completed an online version of the Tinnitus Functional Index (TFI). They recorded their satisfaction ratings with hypothetical intervention outcomes on a 10-point rating scale using Opinio survey software. Participants were English-speaking and the majority had moderate-to-severe tinnitus as measured by the TFI. The survey showed that NIBS was considered an acceptable form of tinnitus management, and that the satisfaction ratings depended significantly on a number of factors: 1) the size of the tinnitus reduction following the intervention ($p < 0.001$); 2) the duration of the intervention ($p < 0.001$); and 3) whether the intervention modulates the actual tinnitus loudness or the tinnitus-related distress ($p < 0.001$). Respondents rated their satisfaction with the intervention 10/10 only if it eliminated tinnitus loudness, although reductions of 50-80% were also rated highly acceptable. No association was found between tinnitus severity and acceptability ratings. These findings are important for future NIBS trials for tinnitus, as they demonstrate the need to optimise stimulation protocols to increase effect sizes and decrease time spent on the treatment.

4.3 Introduction

As discussed in Chapter 2, the prevalence of tinnitus is expected to increase due to an aging population (Wise et al., 2015b) as tinnitus is twice as common in elderly individuals (Eggermont, 2012). There is currently no cure for tinnitus, but this is highly sought after by the tinnitus community. Therefore, the need for effective tinnitus management is urgent. One option under investigation is non-invasive brain stimulation (NIBS). Examples are transcranial direct current stimulation (tDCS) and its high-definition variant (HD-tDCS), which have been used as research tools to modify tinnitus loudness and tinnitus-related distress. In tDCS and HD-tDCS, electrodes are placed over the scalp, and a small electrical current is administered (Thair et al., 2017b). Depending on the placement of the positive and negative electrode,

stimulation can be anodal or cathodal. Anodal stimulation is thought to result in excitatory effects on underlying neurons through neural depolarization, whereas cathodal stimulation results in inhibitory effects through neural hyperpolarization (Nitsche and Paulus, 2000b).

Research efforts regarding tDCS have been ongoing since 2006 (Fregni et al., 2006), and reviews of its efficacy for tinnitus show positive results. Four systematic reviews with meta-analysis, as well as several scoping reviews, have been conducted. In a meta-analysis, Labree et al. (2022) included 6 papers using THI as the primary outcome measure, and found a statistically significant effect favouring active tDCS over sham (MD= −11.62, 95% CI= −18.94 to −4.31, p = 0.002). This included electrode set-ups of both LTA and DLPFC.

Wang et al. (2018a) included eight studies in their review and six in the meta-analysis and found that tDCS had a beneficial effect on tinnitus-related distress, but not on tinnitus loudness. By contrast, Song et al. (2012) included six studies in their systematic review and two in the meta-analysis, and they reported a significant effect of tDCS on tinnitus loudness (mean reduction 13.5%), with 39.5% of participants showing a reduction in tinnitus loudness.

Shekhawat et al. (2015b) in a scoping review posed the question whether tDCS modulates tinnitus loudness or tinnitus-related distress. They included fifteen studies and found that tDCS resulted in a transient suppression of tinnitus loudness as well as tinnitus-related distress, and suggested the site of stimulation might affect these differentially. In a later scoping review, Kok et al. (2021) grouped 38 tDCS studies according to three sites of stimulation to explore this hypothesis further (see Chapter 3). The three sites of stimulation used in tDCS research, in order of most often targeted to least often, were DLPFC, LTA, and auditory cortex. However, no evidence was found in this scoping review that a different site of stimulation affected tinnitus loudness or distress differentially.

In a later systematic review, Martins et al. (2022) included fourteen papers (six used LTA as a target, six DLPFC, and two used both) with a total of 1031 participants and found an over-all positive effect of tDCS on tinnitus loudness (SMD=-0.35; 95%CI=-0.62 to -0.08, $p = 0.01$) and distress (SMD=-0.50, 95%CI=-0.91 to -0.10, $p = 0.02$). Subgroup analysis showed that tDCS of LTA, but not DLPFC, significantly decreased tinnitus loudness (SMD = -0.46, 95% CI = -0.80 to -0.12, $p = 0.009$).

The possibility that tDCS modulates affective dimensions of tinnitus rather than tinnitus loudness is consistent with studies reporting effects of tDCS on other conditions with affective dimensions, such as depression and chronic pain (Lefaucheur et al., 2017). Most notably, stimulation of DLPFC has resulted in clinical benefits in the treatment of depression (Langguth et al., 2011), suggesting DLPFC might be most effective in altering affective dimensions of tinnitus rather than its loudness. The scoping review in Chapter 3 found opposing results in this regard, of which two studies will be discussed (Kok et al., 2021).

Shekhawat and Vanneste (2018b) evaluated HD-tDCS of DLPFC for tinnitus in a double-blind, randomized controlled trial of thirteen participants. Using a cross-over design, they found that active HD-tDCS significantly improved tinnitus loudness, but not tinnitus-related distress, compared to sham HD-tDCS. By contrast, Faber et al. (2012b) administered conventional tDCS of DLPFC to fifteen tinnitus sufferers, and found a significant improvement in tinnitus-related distress, but not loudness when comparing active and sham protocols.

An important question that has remained unaddressed, is: what do tinnitus sufferers think about non-invasive brain stimulation as a potential management option, and do opinions differ depending on whether the intervention modulates tinnitus loudness or tinnitus-related distress? The two concepts do not have a straightforward relationship: the distress of tinnitus appears to be related more to the level of hearing loss, and the presence of hyperacusis or depression, than to its actual loudness (Eggermont, 2012). For non-invasive brain stimulation to become a clinical management tool, it is important to investigate its acceptability for tinnitus patients.

No patient surveys have been undertaken aimed at this goal as far as I know. A literature search in PubMed and Web of Science Core Collection from inception to 18 May 2020 found no such survey. However, several surveys were found that have looked at the acceptability of *invasive* brain stimulation and other types of tinnitus treatment. For example, Tyler (2012) asked 197 self-help group attendees to rate *how willing* they were to undergo a certain treatment on a scale of 0 (not acceptable) to 100 (fully acceptable). In the analysis, an "acceptable" response was characterised as a rating between 91 and 100. Thirty percent of respondents rated external devices (similar to a hearing aid but producing sound or music) as acceptable if they reduced tinnitus loudness and tinnitus-related distress by half, and this increased to 42% if the reduction was complete. For pharmacological interventions, the respective percentages were 52% and 62%; for intracranial implants on the brain surface 13% and 21%; and for implants within the brain 13% and 19%. Tyler (2012) also reported a significant positive correlation between the individual's tinnitus severity and their willingness to accept a treatment.

Engineer et al. (2013) looked more deeply into the acceptability of tinnitus treatments and replicated Tyler's findings. They conducted an online survey with 439 respondents. They analysed how willing patients would be to receive a treatment on a scale of 1 to 4 (1 = not willing at all; 2 = somewhat willing; 3 = willing; 4 = absolutely willing). They compared different therapies, with a focus on vagus nerve stimulation (VNS), in the scenario that the treatment reduced tinnitus-related distress by half, or eliminated tinnitus. The study showed 58.5% of the participants were willing to have a VNS device permanently implanted if it reduced their tinnitus by half, and this percentage increased to 82.4% if the elimination of tinnitus was complete. This study also replicated Tyler's finding that a daily pill was the most acceptable form of intervention. It was again shown that patients who had very loud tinnitus were more likely to accept invasive treatments than patients with soft tinnitus.

Recently, Smit et al. (2018) extended these findings by asking 415 respondents to consider the potential side effects of three invasive procedures (cochlear implantation, deep brain stimulation and cortical stimulation), and with chances of

the treatment being successful at either 50% or 100%. Participants rated their acceptance of these interventions on a scale of 0 – 10. Responses were grouped into three categories: “no acceptance” (0-4), “reasonable acceptance” (5-7), and “full acceptance” (8-10). The survey showed around 20% of participants were reasonably willing to undergo invasive treatment, and a further 20% were fully willing. They also found that people were more willing to undergo an invasive treatment if the chance of a cure was 100% instead of 50%. Smit et al. (2018) also showed that mild side effects (e.g. temporary, non-bothersome) were acceptable to most patients, and severe side effects (e.g. chronic, bothersome) to almost half. However, deafness and death due to the invasive treatment as side effects were acceptable to only a small number of patients. Once again, a small but significant positive correlation was found between acceptance ratings and tinnitus characteristics such as loudness, burden and awareness of tinnitus.

Synthesising the evidence presented above, a variety of invasive treatment methods were judged as acceptable by tinnitus sufferers, and people with severe tinnitus were the likeliest to accept invasive treatments. The success rate of the treatment and the potential side effects played a role in acceptability rating, as well as the strength of the reduction (half or complete) of tinnitus. However, no survey sought opinions on non-invasive brain stimulation as a management option. The surveys also did not compare possible outcomes beyond “reduce tinnitus by half” or “eliminate tinnitus completely”.

The current survey included multiple possible outcomes from HD-tDCS, as a range of effect sizes is observed in intervention trials (Wang et al., 2018a, Song et al., 2012). We also investigated the importance of whether tinnitus loudness is reduced following intervention, or the related distress. Furthermore, we examined the importance of the number of sessions necessary to establish the effect. As such, the current survey was undertaken to evaluate the acceptance of HD-tDCS. Respondents were asked to take into account the following factors: 1) the strength of the tinnitus reduction; 2) the importance of whether tinnitus loudness or tinnitus-related distress is reduced following intervention; and 3) the intervention duration.

4.4 Methods

This survey was an evaluation of the acceptance of HD-tDCS as a potential management option for tinnitus, involving prospective analysis of data collected from May to June 2020. The survey was fully anonymous and therefore individual consent was not sought. Nevertheless, approval by the UCL Research Ethics Committee was obtained to ensure compliance with research ethics (project reference number: 17601/001).

4.4.1 Survey development

The survey was created in Opinio, a web-based survey tool from University College London. A blank copy of the full survey is available in the Supplementary Material of this thesis. Only people with chronic tinnitus (i.e. more than 6 months) were asked to participate. The introduction page of the survey said: "You are invited to take part only if you yourself have experienced tinnitus or a "ringing in the ears" for six months or more. Please do not fill in the survey if you do not have tinnitus." The survey consisted of three parts. Part one was a copy of the Tinnitus Functional Index (25 items) (Meikle et al., 2012b), to score the participant's tinnitus severity. The TFI consists of rating scales of 0 – 10, or 0% - 100%. Part 2 consisted of hypothetical intervention scenarios and outcomes, and participants gave satisfaction ratings for each scenario (twenty items). This part opened with an explanation of what HD-tDCS is suitable for a lay reader. Participants were told HD-tDCS involves placing a cap on their head with small electrodes in it, which administers a small current to the brain. This could feel itchy or tingly. The recipient sits and relaxes during the stimulation, but they have to travel to a location (such as the university that carries out the research, or a treatment clinic) on multiple occasions to receive the stimulation. Satisfaction ratings were probed on a scale of 0 (Not satisfied at all) to 10 (Extremely satisfied). An example question is:

> "Imagine you had to come in two times a week, for THREE WEEKS in a row, so SIX sessions in total. How satisfied would you be if your tinnitus LOUDNESS decreased by 30%?"

Part two was divided across two survey pages, with the first page detailing a scenario in which intervention duration was six sessions total (twenty mins/session, two times/week, for three weeks). The second page detailed a scenario in which the intervention duration was ten sessions total (twenty mins/session, two times/week, for five weeks). Within these two survey pages, the scenarios in the questions varied in two ways. Firstly, in half of the scenarios, the brain stimulation was said to have an effect on tinnitus loudness, and in the other half only on tinnitus-related distress but not loudness. Secondly, five hypothetical strengths of the reduction of tinnitus loudness and tinnitus-related distress were used (10%/30%/50%/80%/100%).

In part three, open-ended questions were posed:

1. What do you think the direction of tinnitus research in the future should be?
2. What are your expectations for HD-tDCS as a tinnitus management option in the future?
3. What else (if anything) would you like us to know?

The open questions were analysed using a category system. The responses were analysed for common themes, resulting in a selection of categories, and subsequently assigned to these categories.

4.4.2 Survey distribution

The survey was open to responses for exactly one month in May – June 2020. The British Tinnitus Association (BTA) created a post on their website about the survey and circulated the link via their social media networks. The BTA is the largest charity for tinnitus sufferers in the UK (https://tinnitus.org.uk/). The survey link was also posted on Tinnitus Hub's (https://www.tinnitushub.com/) "Tinnitus Talk" forum, a worldwide charity where tinnitus sufferers have an open forum for discussion.

4.4.3 Data management

Survey responses that were labelled as unfinished attempts in Opinio were deleted prior to data export. No questions were made obligatory in the survey, and therefore

blanks were possible. For the overall TFI score to be valid, no more than seven items could be omitted. Therefore, contributions that were missing more than seven items of the 25 TFI questions were excluded (*n* = 2).

4.4.4 Data analysis

The TFI scores were analysed in Excel. The overall TFI score was calculated per participant by summing up all the valid answers (max. possible score = 250), dividing this number by the number of questions with a valid answer, and then multiplying by ten (creating an overall TFI score between 0 – 100).

The satisfaction ratings were analysed in IBM SPSS Version 25. The primary outcome measure was the satisfaction rating on a scale of 0 – 10. Data were presented as means and standard deviations. Visual inspection of the data as well as the Shapiro-Wilks test indicated the data were not normally distributed. Therefore, non-parametric analyses were undertaken. The Friedman test was used for comparison between multiple repeated measures, and where significance was identified, this was followed up by a post-hoc two-tailed Wilcoxon signed-rank test. Spearman rank-order correlations were calculated for the relationship between satisfaction ratings and the respondent's tinnitus severity. Correlation strength was defined as weak (0.1 – 0.4), moderate (0.4 – 0.7) and strong (0.7 – 1) (Akoglu, 2018). Bonferroni corrections were applied to $\alpha = 0.05$ for multiple comparisons.

Open questions in part three were analysed using a code system for different types of responses and labelling the responses in Excel according to this code system.

4.5 Results

A total of 274 responses were exported from Opinio. Two responses were deleted because >7 items from the TFI were left blank, leaving 272 responses included in the analysis. The mean overall TFI score amongst the respondents was 55.59 (SD = 18.44). Table 4-1 shows the distribution of TFI scores across five categories (Henry et al., 2016) with the respective frequencies in our survey sample.

TFI score range	*Interpretation*	*Frequency in sample*
0 – 17	Not a problem	*n* = 7
18 – 31	Small problem	*n* = 28
32 – 53	Moderate problem	*n* = 76
54 – 72	Big problem	*n* = 121
73 – 100	Very big problem	*n* = 40

Table 4-1 TFI scores in survey sample

For the descriptive analysis, satisfaction ratings were classified into three categories based on Smit et al. (2018): 0 – 4: “Low satisfaction”; 5 – 7: “Moderate satisfaction”; 8 – 10: “High satisfaction”. For this analysis, results are presented by the strength of the hypothetical therapeutic effect. For each strength, the mean rating per participant for all survey questions was collated (e.g. mean satisfaction for a 10% reduction in either loudness or tinnitus-related distress following either three or five weeks intervention).

Figure 4-1 shows the percentage of respondents in each satisfaction category. High satisfaction (8 – 10) was found for 17% of respondents in the case of a 10% reduction, 24.1% for 30% reduction, 42.4% for 50% reduction, 68.8% for 80% reduction, and 79.6% for complete reduction.

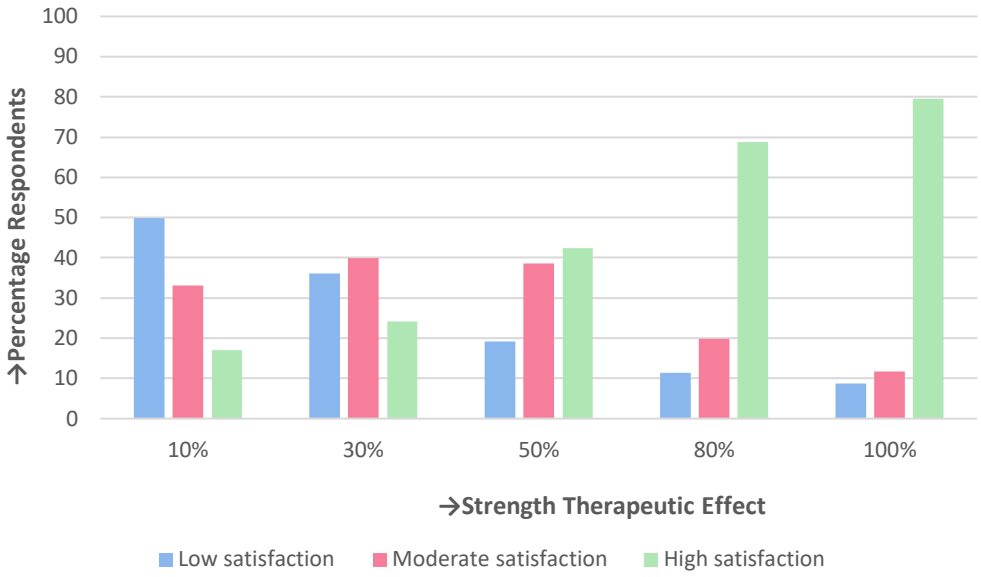

Figure 4-1 Percentage of respondents with low, moderate or high satisfaction by strength of therapeutic effect

For the quantitative analysis, satisfaction ratings were split in two ways. First, the three weeks versus five weeks intervention distinction was omitted, to only compare tinnitus-related distress and loudness modulation (see Figure 4-2). Then, the tinnitus-related distress and loudness distinction was omitted, to compare the effect of the duration of intervention (see Figure 4-3). The exact values (mean (SD)), and Z-scores with p-values, are presented in Table 4-2.

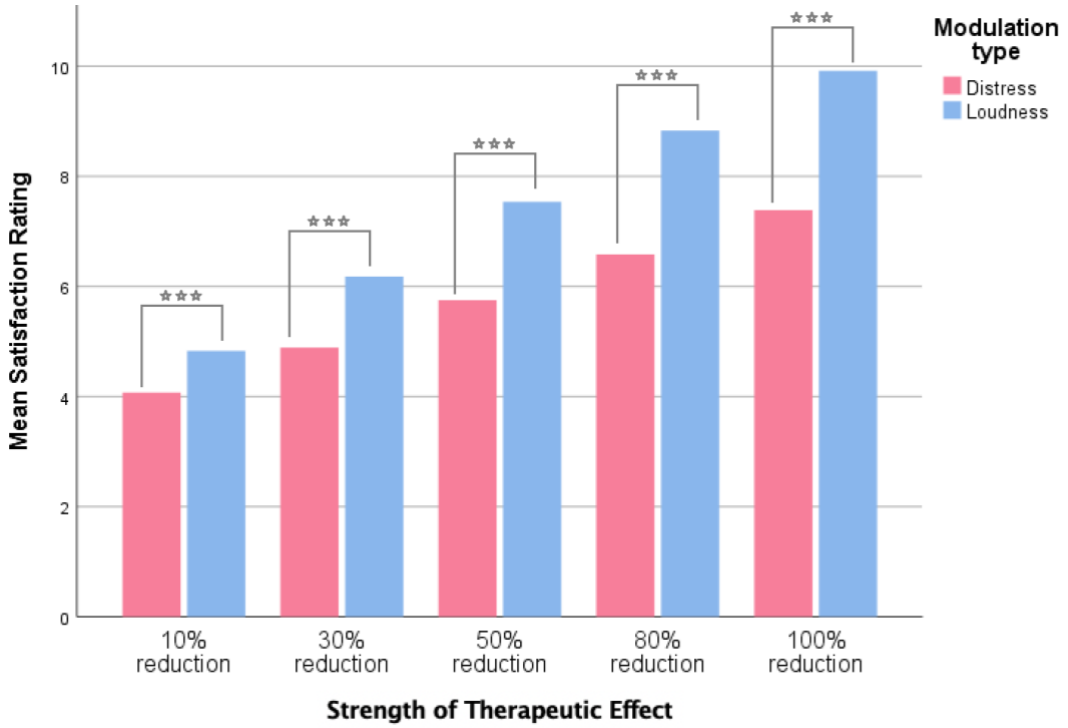

Figure 4-2 Mean satisfaction ratings by strength of therapeutic effect for loudness vs. distress reduction. Asterisks indicate a significant difference between loudness vs. distress reduction mean satisfaction ratings ($p < 0.001$, Bonferonni corrected $\alpha = 0.005$) calculated with the Wilcoxon signed rank test (see Table 4-2 for exact values). The Friedman test showed a significant difference in mean satisfaction ratings between all effect strengths for loudness and distress (not indicated in graph, see Table 4-2).

In the scenarios where HD-tDCS reduced tinnitus loudness, the Friedman test showed a significant difference in satisfaction ratings depending on the strength of the effect ($\chi^2(4) = 901.078$, $p < 0.001$). The post-hoc Wilcoxon tests showed a significant difference between all effect strengths (see Table 4-3).

In the scenarios where HD-tDCS reduced tinnitus-related distress, the Friedman test showed a significant difference in satisfaction ratings depending on the strength of the effect ($\chi^2(4) = 771.384$, $p < 0.001$). The post-hoc Wilcoxon test showed a significant difference between all effect strengths (see Table 4-3).

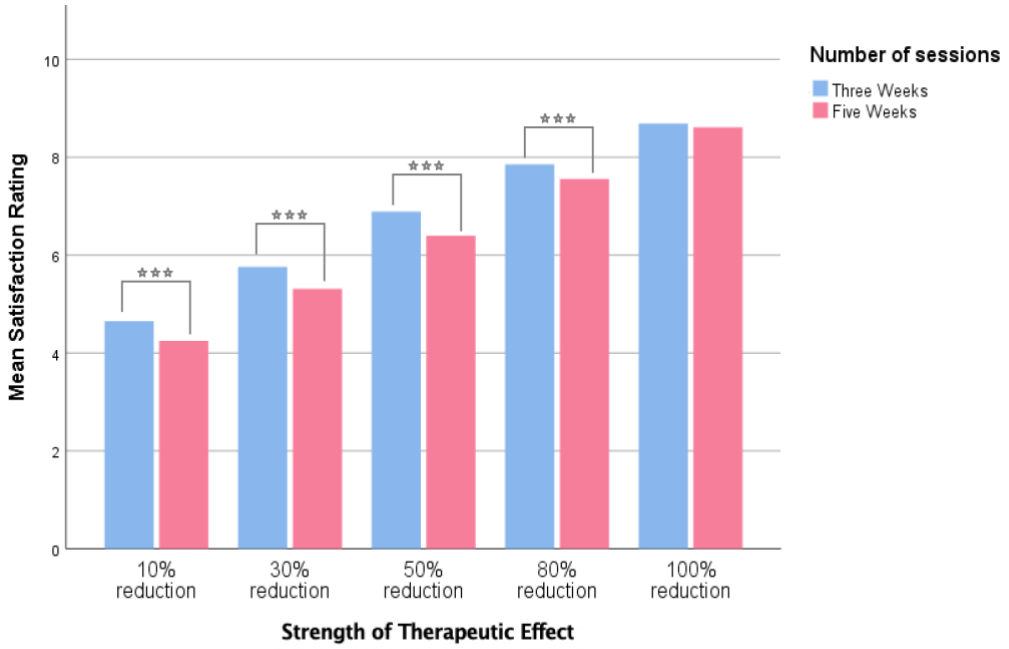

Figure 4-3 Mean satisfaction ratings by strength of therapeutic effect for 3 weeks vs. 5 weeks of stimulation. Asterisks indicate a significant difference between 3 weeks and 5 weeks stimulation mean ratings ($p < 0.001$, Bonferonni corrected $\alpha = 0.005$) calculated with the Wilcoxon signed-rank test (see Table S1 for exact values). The Friedman test showed a significant difference in mean satisfaction ratings between all effect strengths for 3 weeks and 5 weeks (not indicated in graph, see Table 4-2).

With intervention duration of three weeks, the Friedman test showed a significant difference in satisfaction rating depending on the strength of the effect ($\chi^2(4) = 906.555$, $p < 0.001$). The post-hoc Wilcoxon tests showed a significant difference between all effect strengths (see Table 4-3).

With intervention duration of five weeks, the Friedman test showed a significant difference in satisfaction rating depending on the strength of the effect ($\chi^2(4) = 931.555$, $p < 0.001$). The post-hoc Wilcoxon tests showed a significant difference between all effect strengths (see Table 4-3).

Strength of therapeutic effect	***Type of Modulation***			***Duration of Intervention***		
	Loudness	***Distress***	***p-value***	***3 weeks***	***5 weeks***	***p-value***
10%	4.83 (2.90)	4.06 (2.93)	Z = -6.695; p < 0.001	4.65 (2.74)	4.26 (2.92)	Z = -6.381; p < 0.001
30%	6.18 (2.47)	4.89 (2.89)	Z = -9.701; p < 0.001	5.76 (2.44)	5.31 (2.69)	Z = -7.176; p < 0.001
50%	7.54 (1.89)	5.74 (2.88)	Z = -11.204, ; p < 0.001	6.90 (2.14)	6.38 (2.32)	Z = -8.163; p < 0.001
80%	8.83 (1.23)	6.57 (2.97)	Z = -11.795; p < 0.001	7.85 (1.83)	7.57 (1.97)	Z = -5.861; p < 0.001
100%	9.91 (0.59)	7.40 (3.11)	Z = 11.163; p < 0.001	8.69 (1.63)	8.61 (1.68)	Z = -2.480; p = 0.013

Table 4-2 Mean (SD) satisfaction ratings by strength of therapeutic effect, type of modulation, and duration of intervention. The Wilcoxon signed-rank test was used with a Bonferroni-adjusted alpha level of 0.005 ($\alpha = 0.05/10$)

Strength of therapeutic effect	***Loudness modulation***	***Distress modulation***	***3 Weeks Intervention***	***5 Weeks Intervention***
10% vs 30%	Z = -12.904 p < 0.001	Z = -11.564 p < 0.001	Z = -12.693 p < 0.001	Z = -12.654 p < 0.001
30% vs 50%	Z = -12.977 p < 0.001	Z = -11.923 p < 0.001	Z = -13.039 p < 0.001	Z = -13.002 p < 0.001
50% vs 80%	Z = -12.730 p < 0.001	Z = -11.381 p < 0.001	%: Z = -12.385 p < 0.001	Z = -12.896 p < 0.001
80% vs 100%	Z = -11.896 p < 0.001	Z = -10.788 p < 0.001	Z = -12.072 p < 0.001	Z = -12.171 p < 0.001

Table 4-3 Results of post-hoc Wilcoxon signed-rank tests comparing mean satisfaction ratings. A Bonferroni-adjusted alpha level of .003 was used (α = 0.05/16)

To analyse whether the respondent's tinnitus severity was associated with their satisfaction ratings, Spearman's rho-correlation coefficients were calculated. Table 4-4 shows Spearman's ρ, indicating no to weak correlations. Correlation strength was defined as weak (0.1 – 0.4), moderate (0.4 – 0.7) and strong (0.7 – 1) (Akoglu, 2018). There appeared to be a small significant correlation between tinnitus severity and the satisfaction rating in the case of a complete elimination of tinnitus loudness. Further examination of this correlation shows that satisfaction was almost unanimously 10/10 for complete elimination of tinnitus loudness, with a very small

trend for respondents with less severe tinnitus to be less satisfied with complete elimination.

A post-hoc Spearman's correlation was calculated to investigate whether satisfaction with reduction in loudness might be correlated to the individual's tinnitus loudness rating rather than the total TFI score. One question in the TFI is: "Over the past week, on a scale of 0 to 10, how strong or loud was your tinnitus?" The correlations between responses to this question only and responses to questions about loudness reduction were weak and non-significant after Bonferroni adjustment.

Participant tinnitus severity

Participant satisfaction	***Hypothetical scenario***		***Spearman's ρ***
	Loudness reduction	10%	0.076
		30%	0.035
		50%	0.026
		80%	0.002
		100%	0.185*
	Distress reduction	10%	0.063
		30%	0.068
		50%	0.046
		80%	0.049
		100%	0.081
	3 weeks intervention	10%	0.066
		30%	0.031
		50%	0.03
		80%	0.04
		100%	0.08
	5 weeks intervention	10%	0.083
		30%	0.066
		50%	0.048
		80%	0.065
		100%	0.105

Table 4-4 Spearman rho-correlation coefficients of the relationship between satisfaction ratings of the hypothetical intervention outcomes and respondent's tinnitus severity. An asterisk * indicates $p < 0.0025$ according to Bonferroni adjustment ($\alpha = 0.05/20$). Correlation strength is defined as weak (0.1 – 0.4), moderate (0.4 – 0.7) and strong (0.7 – 1) (Akoglu, 2018).

Regarding the third part of the survey, the open-ended question on the future direction of tinnitus research resulted in 245 responses. The responses were coded into six different types of answers shown in Figure 4-4. The majority of participants replied they expected future research to focus on finding a complete cure for tinnitus (31%). Others responded that research should aim to reduce the loudness (14%), or should simply find anything that can manage tinnitus (10%).

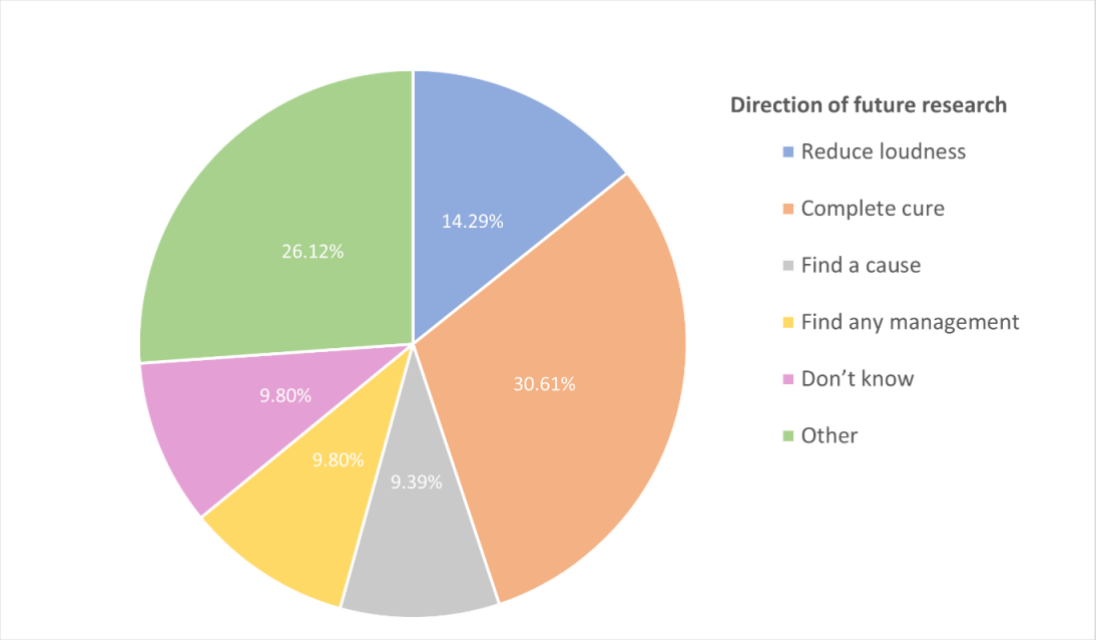

Figure 4-4 Types of answers to the question: "What do you think the direction of tinnitus research in the future should be?"

The second question was about expectations of HD-tDCS as a future management option. The question was answered by 247 respondents and responses were coded in Figure 4-5. Most respondents were optimistic (31%) or open-minded (28%) towards trying it. People who were sceptical or hopeful with caution (12%) mentioned they were concerned with how it could become widely available in healthcare services.

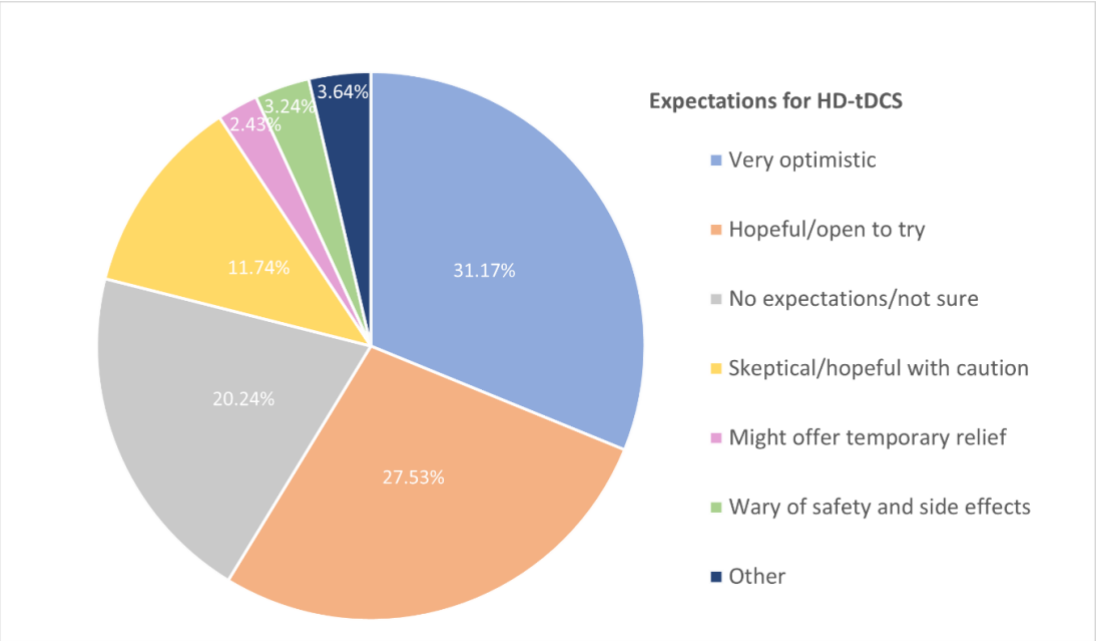

Figure 4-5 Types of answers to the question: "What are your expectations for HD-tDCS as a tinnitus management option in the future?"

The final question was: "Is there anything else you would like us to know?" A total of 145 responses were given to this question, coded in Figure 4-6. Most people (38%) used this free space to share more information about their personal situation and experience of tinnitus, or what they believed caused it. Ten percent of respondents also expressed interest in participating in an HD-tDCS trial.

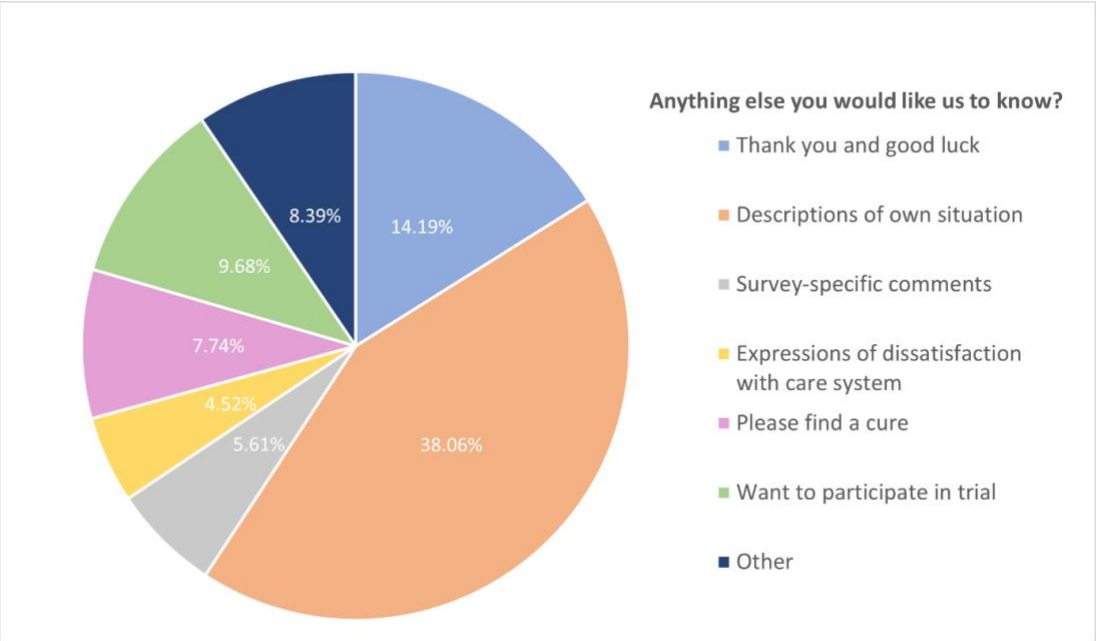

Figure 4-6 Types of answers to the question: “Is there anything else you would like us to know?”

4.6 Discussion

This survey investigated the acceptability of HD-tDCS as a management option for tinnitus. The results showed that most tinnitus sufferers consider HD-tDCS an acceptable management option. Unsurprisingly, the acceptability was shown to be strongly influenced by the strength of tinnitus reduction following stimulation, with average satisfaction ratings reaching high levels (score of 8 – 10) when the hypothetical reduction was 80% or more. Moderate satisfaction (5 – 7) was found for reductions of 30% or more.

Satisfaction ratings were also influenced by whether the intervention affected tinnitus loudness or tinnitus-related distress. Respondents reported higher satisfaction if the tinnitus loudness was reduced following intervention rather than the tinnitus-related distress. This survey showed that, even if the distress reduction was 100%, mean satisfaction ratings were below 8/10 and as such could still not be classified as high (8 – 10). This is an important finding as a number of intervention studies using tDCS for tinnitus found only an effect on tinnitus-related distress (Kok et al., 2021). One systematic review with meta-analysis also found only an effect on tinnitus-related distress but not loudness (Wang et al., 2018a). Therefore, it is key for

future tinnitus intervention research to focus on reducing the tinnitus loudness rather than related distress. This finding also illustrates the need to include a variety of tinnitus loudness measurements. Besides Visual Analogue Scales (VAS), also psychoacoustic measurements such as minimum masking levels (MML) and tinnitus loudness and pitch matching tasks should be considered. This is important because VAS loudness measurements rely on self-reporting and are correlated to self-reported VAS distress measurements, whereas psychoacoustic loudness measurements are not, raising the concern that VAS loudness measurements reflect reactions to the tinnitus rather than its pure loudness perception (Henry, 2016, Hall et al., 2017, Manning et al., 2019).

Another factor that affected satisfaction ratings was the proposed time spent on the stimulation sessions. Participants were more satisfied overall if the intervention duration was six sessions rather than ten sessions. However, if the stimulation could eliminate the tinnitus, this significant difference disappeared, suggesting respondents would be just as open to attending ten sessions in this case.

Interestingly, the present survey did not find an effect of tinnitus severity on satisfaction ratings. Previous surveys looking at invasive brain stimulation (Engineer et al., 2013, Smit et al., 2018, Tyler, 2012) consistently found that people with very severe tinnitus were more likely to accept invasive treatments than people with milder tinnitus. In the present survey, there was no evidence for a correlation between Tinnitus Functional Index scores and the mean satisfaction ratings for all reduction strengths, whether tinnitus loudness or tinnitus-related distress was modulated or whether the intervention was three or five weeks. The one exception was a small but significant correlation between satisfaction ratings in the case of a 100% reduction of tinnitus loudness, in which case it was shown that a higher tinnitus severity score was associated with a higher satisfaction rating. This could reflect that people with severe tinnitus are more eager for a “total cure” than people with mild tinnitus.

Three explanations can be offered for the lack of association between tinnitus severity and acceptability ratings in this survey compared to the aforementioned surveys. It could be due to the invasive nature of the treatments described in the other surveys. People with less severe tinnitus might be less willing to undergo invasive treatments than people with severe tinnitus, but this difference might disappear for non-invasive treatments as people with mild tinnitus might be just as willing. A second factor might be the way questions were framed in the surveys. This survey posed a different question, focusing on *how satisfied* tinnitus sufferers would be with a certain outcome rather than *how willing* they would be to undergo the treatment. It might be that satisfaction with the treatment outcome is not correlated to tinnitus severity in the same way. Finally, it could be that the present survey did not identify a correlation between tinnitus severity and satisfaction ratings because the sample's tinnitus severity was heavily centred around moderate-to-severe tinnitus. The lack of a range of different tinnitus severities could mean a lack of different responses which would make it difficult to detect any correlation.

The reason for framing the question around satisfaction was because generally, tinnitus sufferers are highly motivated to try anything that could help them. This "open to anything" approach may apply less to invasive treatments, but it could apply to HD-tDCS, which is considered safe with minor, transient side effects such as tingling and in few occasions mild scalp burns. This survey only mentioned tingling or itching under the electrodes, although it would have been preferable to have given more information on side effects. Using satisfaction ratings was an attempt to avoid finding relatively high ratings due to "I will try anything" approaches. However, this makes it more difficult to directly compare our results to other acceptability surveys.

Nevertheless, some comparisons can be made, and the results reveal commonalities with previous surveys. For example, Engineer et al. (2013) reported that over half of the tinnitus sufferers in their survey were willing to have a vagus nerve stimulator (VNS) permanently implanted in their body, even if it only reduced their tinnitus by half. The present survey also found that a half-reduction of tinnitus was highly satisfactory for 42.4% of respondents.

It should be mentioned that tinnitus reductions in either loudness or distress of 50% or more are not currently found on a consistent basis in non-invasive brain stimulation trials. Effect sizes tend to be smaller, and the systematic review and meta-analysis reported by Song et al. (2012) found a mean loudness reduction of 13.5%. The present survey showed that for a 10% reduction, 49.9% of participants would not be satisfied, 33.1% would be moderately satisfied, and 17% would be highly satisfied (as demonstrated in Figure 4-1). Therefore, it is important to manage expectations of participants in trials appropriately, while in parallel researchers work on optimising therapeutic effects, if any.

The open-ended questions confirmed the aspiration for large loudness reductions found in the satisfaction ratings analysis. Fourteen percent of respondents said research should focus on finding treatments that can reduce loudness, and 31% wanted a complete cure. With regard specifically to HD-tDCS, over half of the respondents said they were optimistic or willing to try it.

On a final note, the present survey has a number of limitations. First, one might argue that the questions were presented in a suggestive way. By having the questions presented in a cumulative fashion running up from 10% to 100% reduction, people might have been inclined to adjust their ratings in similar linear fashion. It may have been beneficial to either randomise the order of these questions, or to present the questions on separate survey pages rather than immediately below each other, to make this incline in reduction less obvious. However, it is still fair to assume that the strength of the therapeutic effect of the intervention is important to the tinnitus sufferer's satisfaction.

Also, the divide between effects on tinnitus loudness and distress in the questions could be considered leading. In the questions about distress, the question read "distress but not loudness", whereas in the questions about loudness, the question did not read "loudness but not distress" and instead simply read "loudness". It could also be argued that this separation is slightly artificial as in the eyes of respondents, the two are likely intertwined and related.

Second, because this survey was conducted anonymously, no sample characteristics were obtained. It would have been preferable to have had information about age, sex, duration of tinnitus, laterality of tinnitus, and accompanying hearing loss. However, Smit et al. (2018) showed that correlations between these characteristics and acceptability were either weak or absent.

Third, it would have been useful to include a question in the survey about people's previous experiences with non-invasive brain stimulation to understand their prior perceptions about this management option. Future surveys investigating the acceptability of HD-tDCS would also benefit from including a direct comparison with other intervention strategies such as different non-invasive brain stimulation techniques or a daily pill.

4.7 Conclusions

The present survey found that tinnitus sufferers consider HD-tDCS an acceptable management option. Mean satisfaction ratings could be classified as high when the strength of tinnitus loudness reduction following intervention was >80%. However, subgroups of respondents also reported high satisfaction starting from 10% reduction. Currently, there is a gap between the outcomes of tDCS trials and what might be a meaningful improvement for tinnitus patients. The review of tDCS efficacy in Chapter 3 showed that tDCS possibly affects tinnitus distress and not loudness (potentially dependent on stimulation target). Also, pooled effect sizes in meta-analysis (i.e. 13.5% reduction in Song et al. (2012)) are not in line with the desired effect sizes found in the present survey. As such, future HD-tDCS studies should focus on reducing tinnitus loudness following stimulation, to align better with the expectations of tinnitus patients. Alternatively, if tinnitus distress is chosen as a therapy target this should be made clear upfront as this survey showed there are subgroups of tinnitus patients for whom this could be acceptable as well.

Chapter 5 Scoping review of resting-state networks in tinnitus

5.1 Preface

5.1.1 Publication

This study was published open access in *Clinical Neuroradiology* (Kok et al., 2022a) and adapted for this thesis chapter.

Full published reference:

Kok, T. E., Domingo, D., Hassan, J., Vuong, A., Hordacre, B., Clark, C., Katrakazas, P. & Shekhawat, G. S. 2022. Resting-state Networks in Tinnitus. *Clinical Neuroradiology,* 32, 903-922. https://doi.org/10.1007/s00062-022-01170-1

5.1.2 What was undertaken?

A scoping review was undertaken of 29 resting-state functional connectivity studies to investigate resting-state networks in tinnitus. The results are discussed according to the changes found in each network.

5.1.3 Why was it needed?

In Chapter 2, several tinnitus models were discussed. All these models are grounded in the proposal that tinnitus pathology is of central origin. Hence, non-invasive brain stimulation (NIBS) has been trialled for tinnitus relief by targeting this aberrant central activity. The outcomes of these trials were discussed in a scoping review in Chapter 3. This scoping review established that the most targeted regions in tDCS and tinnitus research were DLPFC and LTA. Most studies included in the review found that tDCS intervention reduced either tinnitus loudness or distress, but there was a wide variety of stimulation protocols. The neurophysiological rationale given in studies for choosing one site of stimulation over another was generally absent or weak. DLPFC and LTA, amongst many other cortical and subcortical regions, have been implicated in tinnitus brain imaging studies (Eggermont, 2012), but DLPFC and LTA are not awarded any special status in any of the tinnitus models discussed in Chapter 2. Therefore, this study was needed to establish what knowledge is currently available on the neurophysiology of tinnitus as measured by resting-state fMRI, and how this might inform future tDCS intervention studies.

5.1.4 How does it contribute to the objectives of the PhD?

Neurophysiological rationale is very important to consider when it comes to assessing evidence for non-invasive brain stimulation techniques. This could help create an understanding why an intervention may work or not, and for whom. This study also formed the theoretical basis for the design of the resting-state fMRI study in Chapter 6.

5.2 Abstract

Chronic subjective tinnitus is the constant perception of a sound that has no physical source. Brain imaging studies investigating tinnitus neurophysiology show alterations in tinnitus patients' resting-state networks (RSNs). This scoping review aimed to provide an overview of resting-state fMRI studies in tinnitus, and to evaluate the evidence for changes in different RSNs. Twenty-nine studies were included; 26 of which found alterations in networks such as the auditory network, default mode network, attention networks, and visual network. However, there is a lack of reproducibility in the field which can be attributed to the use of different regions of interest and analytical methods per study, and tinnitus heterogeneity. Future studies should focus on replication by using the same regions of interest in their analysis of resting-state data, and by controlling adequately for potential confounds. These efforts could potentially lead to the identification of a biomarker for tinnitus, and should be used to inform target selection in future tinnitus intervention studies. Additionally, the outcomes of this study formed the basis for the design of the rs-fMRI study presented in Chapter 6.

5.3 Introduction

Tinnitus is the phantom perception of sound without an external source, and is commonly described as a ringing, hissing, whining, pure tone, or "cricket noise" (Henry et al., 2020, Seydell-Greenwald et al., 2012). Tinnitus affects 10-15% of the adult population (Henry et al., 2020) and can have a profoundly negative effect on sleep, attention and overall quality of life (Baguley et al., 2012). Tinnitus can be classified as subjective or objective, pulsatile or non-pulsatile, and chronic (> 6 months) or recent onset (<6 months) (Henry et al., 2020, Sindhusake et al., 2003,

Baguley et al., 2012). In subjective tinnitus, the noise can only be heard by the affected person, whereas in objective tinnitus the noise can be measured with specialised sound equipment (Esmaili and Renton, 2018). Pulsatile tinnitus is almost always objective and has a specific, identifiable cause (Hofmann et al., 2013). This review will only consider chronic, subjective tinnitus, as this type is hypothesised to be of central origin, but its exact mechanisms are unclear.

Despite increasing research into the field of tinnitus, the exact pathophysiology of tinnitus remains unclear (Baguley et al., 2012). Observations that the tinnitus pitch is correlated to the frequency of maximum hearing loss in tinnitus patients (Schecklmann et al., 2012) have led to the idea that deafferentation (e.g. due to hearing loss) could lead to adaptive neuroplasticity in an attempt to return neural activity to its usual homeostatic state (Langers et al., 2012, Schaette and Kempter, 2006). Neurons could become more susceptible to firing in response to spontaneous activity in the case of homeostatic strengthening of excitatory synapses or weakening of inhibitory synapses, referred to as increased gain (see section 2.2.2.1). This firing could be interpreted as a sound, i.e. tinnitus (Langers et al., 2012). However, not everyone with tinnitus has a visible hearing loss on standard audiometry, although a "hidden hearing loss" in the form of reduced neural output from the cochlea may be present in those cases (Schaette and McAlpine, 2011b).

Animal research has supported the plastic reorganisation theory of tinnitus. Yang et al. (2011) stated that plastic reorganisation in the central auditory system and down-regulation of inhibitory synapses were observed in high frequency-specific neurons in rats that showed behavioural characteristics of high frequency tinnitus. However, tinnitus does not consistently arise under conditions that would be expected to create a tinnitus signal – not everyone with a hearing loss also develops tinnitus.

In a review on gain mechanisms and tinnitus, Sedley (2019) concluded increased gain can be induced by peripheral auditory insults, but might not be sufficient to cause tinnitus. Rauschecker et al. (2010) also postulated in their frontostriatal gating model of tinnitus (see section 2.2.2.2) that auditory lesion is not sufficient for tinnitus to

arise. According to their model, tinnitus only occurs if the “noise-cancellation” system, consisting of limbic-auditory connections mediated by the thalamus, breaks down. Tinnitus is also often accompanied by anxiety and depression (Andersson et al., 2003a), and attention networks play a role in tinnitus awareness (Trevis et al., 2017), suggesting that the underlying mechanisms of tinnitus likely consist of multiple neural networks.

One method used to study neural networks is functional magnetic resonance imaging (fMRI). In fMRI, neural activity is not measured directly, but through the blood-oxygen-level-dependent (BOLD) signal (Attwell and Iadecola, 2002, Ogawa et al., 1990). It is based on the observation that local blood flow increases with neural activity (Roy and Sherrington, 1890). The unique fluctuations in BOLD responses are frequently used to compare patient groups with neurological conditions to neurotypical controls. BOLD fMRI has previously been utilised to demonstrate differences in functional networks in people with various neurological and psychiatric disorders (e.g. dementia (Rombouts et al., 2009), Alzheimer’s disease (Greicius et al., 2004, Lee et al., 2013, Sorg et al., 2015), depression (Greicius et al., 2007), and schizophrenia (Van den Heuvel and Hulshoff Pol, 2010)).

A frequent method for the study of functional networks is resting-state fMRI (rs-fMRI). Rs-fMRI quantifies the temporal dependence of neural activity patterns between anatomically separated regions when the subject is not engaged in any task. BOLD signal fluctuations that are correlated in anatomically separated regions can be used to infer functional connectivity between those regions (Van den Heuvel and Hulshoff Pol, 2010). Early work in this field revealed a high correlation between spontaneous neural activation patterns in the motor network (Biswal et al., 1995, Biswal et al., 1997), with later studies replicating this for other networks such as the primary visual network and the auditory network (Van den Heuvel and Hulshoff Pol, 2010). Rs-fMRI investigates low frequency oscillations (~0.01-0.1Hz) of the fMRI time-series, which may be confounded by cardiac and respiratory oscillations. However, it is generally accepted that these resting-state fMRI patterns have a neuronal basis as

they reflect the traditional known systems such as the motor and visual systems (Van den Heuvel and Hulshoff Pol, 2010, Biswal et al., 1995, Biswal et al., 1997).

Rs-fMRI research has given rise to the identification of several prominent "resting-state networks" (RSN) which are consistently identified, regardless of different subject groups, methods of analysis and scanning protocols. These are the sensorimotor network, visual and extra-striate visual network, insular-temporal/ACC (saliency) network, left and right lateralised frontoparietal networks (attention), DMN, and a frontal executive function network (Van den Heuvel and Hulshoff Pol, 2010).

The RSN that has received the most attention in research into cognitive dysfunction is the default mode network (DMN), which is characterised by being more active at rest than during task-state. It comprises posterior cingulate cortex (PCC), precuneus, medial prefrontal cortex (mPFC), and inferior parietal cortical regions (Damoiseaux et al., 2006, Beckmann et al., 2005, Van den Heuvel et al., 2008). As tinnitus is mainly experienced during rest, it has been hypothesized that alterations in the DMN could be associated with tinnitus (Chen et al., 2018a, Husain and Schmidt, 2014).

RSNs have been identified beyond the eight listed above. Most notably of relevance here is the auditory RSN. Cordes et al. (2000) asked participants to perform an auditory text-listening task, and compared the activity map derived from the task-based fMRI scan to an activity map created using rs-fMRI using the auditory cortex as a region of interest. They found the distribution of the auditory task activity was very similar to the resting-state functional connectivity network in auditory regions. Evidence taken together suggests characteristics of functional connectivity maps reflect how networks appear during the relevant active tasks (Cordes et al., 2000).

Other networks that are often described are the dorsal attention network (DAN) and ventral attention network (VAN), which can be confused with the lateralized frontoparietal (FP) networks. Data-driven clustering of networks shows an overlap in some individuals between the FP networks and DAN, but generally they can be

distinguished by the FP covering prefrontal cortex and intraparietal sulcus and the DAN covering a dorsal premotor strip and frontal eye fields (Gratton et al., 2018).

Husain and Schmidt (2014) reviewed six studies on tinnitus and rs-fMRI focusing on the DMN, visual RSN, auditory RSN, the DAN and the limbic network. They found that the DMN-limbic and the auditory-limbic functional connectivity was increased in tinnitus and may be correlated with tinnitus-related distress. New evidence on RSNs in tinnitus has been gathered since the review of Husain and Schmidt (2014) and therefore a comprehensive review is needed to bring together current evidence from rs-fMRI in tinnitus patients. This scoping review aims to present an overview of the research in this area and to answer the question: What has rs-fMRI revealed about resting-state networks in tinnitus patients?

5.4 Methods

5.4.1 Search strategy

A scoping review was undertaken using the framework proposed by Arksey and O'Malley (2005). In a scoping review, the goal is to map all the available evidence in a research area and to highlight gaps in the existing literature, without excluding studies based on their quality (Arksey and O'Malley, 2005, Mays et al., 2001). An optional step in a scoping review is to conduct a consultation with several experts in the field, which was included in this review. The online databases PubMed, Embase, and Web of Science Core Collection (WoS CC) were searched from inception until 22/01/2021 using the following search term:

(“fmri”[tiab] OR “mri”[tiab] OR “magnetic resonance imaging” [tiab] OR “functional connectivity”[tiab] OR “resting state”[tiab]) AND “tinnitus”[ti]

5.4.2 Inclusion criteria

To be included, studies had to be primary research studies, in which participants with chronic (>6 months), subjective tinnitus underwent resting-state fMRI scanning. All

participants had to be adults (>18 years old). Only studies written in English were included. Studies were excluded if they were case studies, review studies, brain imaging studies that did not use rs-fMRI, treatment studies, studies in which participants had pulsatile tinnitus, animal studies, studies with children, and hospital diagnostic studies. Studies that used rs-fMRI combined with other types of MRI were included. There were no inclusion criteria regarding the presence of a control group.

All papers were screened for inclusion by two independent reviewers (T. Kok and D. Domingo) in both abstract stage and full-text stage. Any clashes between the two reviewers were resolved through a discussion between the two reviewers.

5.4.3 Data charting

The included papers were taken to the data charting stage. Information was extracted about the study design, participant characteristics, results, and MRI scanning protocols and logged in Excel spreadsheets. All data were extracted as mean ± standard deviation unless otherwise specified.

5.4.4 Data analysis

Papers were grouped by their method of analysing the resting-state data and summarised in tables. Then, papers were also grouped by which networks were implicated in their findings. A brain template was created with the most important regions for each relevant resting-state network depicted on it (Figure 5-2). These regions were selected based on the RSN literature. To summarise the findings from seed-based functional connectivity studies, if at least one study found an increased or decreased connection between two regions included on the brain template, a solid or dotted line was drawn between the regions. Findings related to any other regions were not presented on the figure, but are available in the results tables, as the number of different regions implicated in total was too high to include all of them in one figure.

For auditory findings specifically, a second figure was created by tallying how often an increased or decreased connection was found with an auditory region-of-interest (Figure 5-3).

5.5 Results

5.5.1 Search results

There were 386 hits in PubMed, 461 hits in Embase, and 352 hits in World of Science Core Collection. All records were exported to the EndNote X9 reference management software. Figure 5-1 shows the flowchart for study selection.

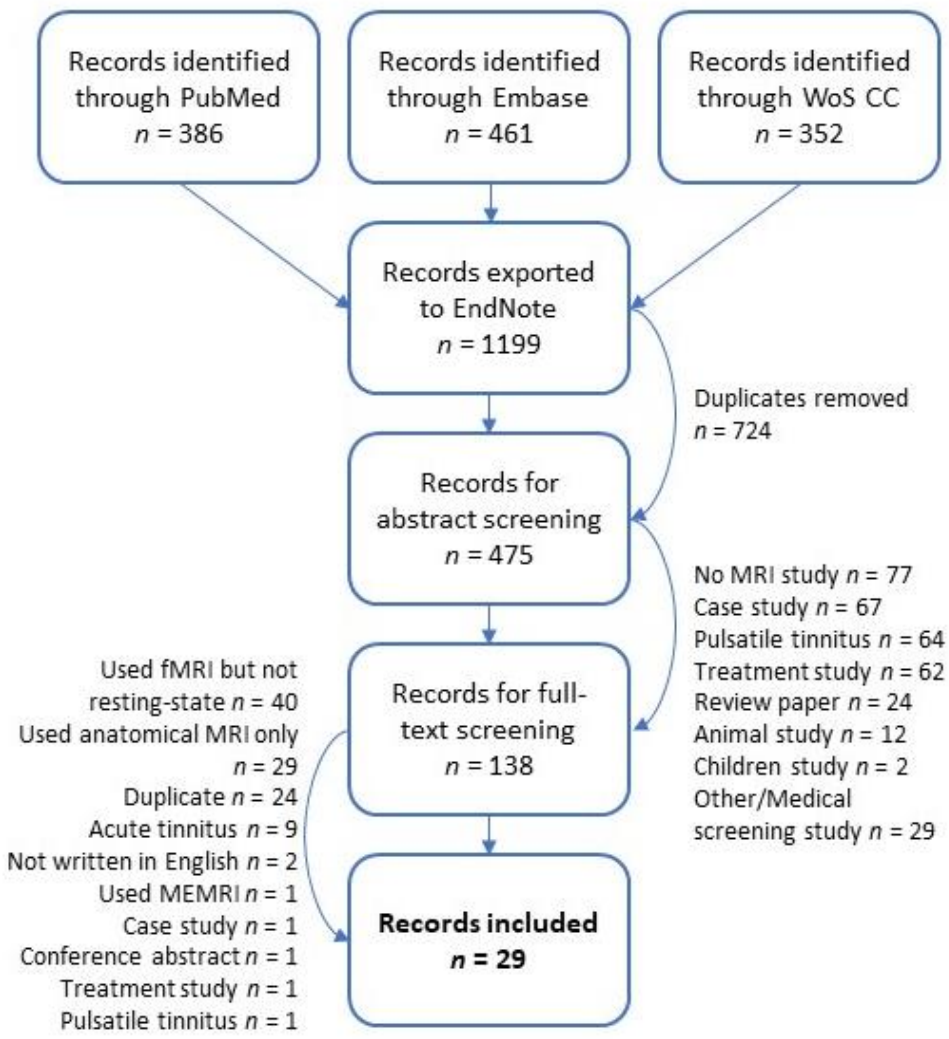

Figure 5-1 Flowchart of study selection. Abbreviations: WoS CC = Web of Science Core Collection, MEMRI = manganese-enhanced MRI

5.5.2 Study design

The 29 studies had total sample sizes ranging from 12 – 105 participants (50.69 ± 22.37), with sample sizes for tinnitus groups ranging from 6 – 50 participants (23.47 ± 10.25), and control groups ranging from 6 – 55 participants (23.48 ± 11.81). Of 29 studies, 25 studies defined chronic status of subjective tinnitus as at least six months (confirmed either within the manuscript or through confirmation via email with the authors), three studies defined chronic as at least one year, and one study defined chronic tinnitus as greater than two years.

Different methods to analyse the rs-fMRI data were found in the included studies. The most common method for analysing functional connectivity was seed-based correlation analysis (SCA). In SCA, the linear correlation is calculated between the time series of a seed region/voxel (an a priori specified "region of interest"), and every other voxel in the brain. Eighteen out of 29 or 62% studies used SCA to analyse functional connectivity patterns. Three studies used Granger causality analysis, which is also a seed-based method, but deploys a statistical method from the field of economics to assess directional aspects of connectivity (Granger, 1969, Chen et al., 2016).

Three studies used regional homogeneity (ReHo) analysis, which can be used to quantify local synchronization in neighbouring voxels, and is a measure of local neural activity coherence during resting-state (Zang et al., 2004). Increased ReHo values reflect increased local synchrony, which could be interpreted as increased coherence of spontaneous neural activity (Zang et al., 2004).

Four studies used amplitude of low-frequency fluctuation calculations (ALFF) to examine resting-state fMRI data. ALFF is an algorithm used to measure the intensity of intrinsic brain activity at a regional level. Resting state ALFF could reflect abnormal changes in activity in various neurological disorders (Chen et al., 2014). ALFF examines brain activity in specific frequency bands rather than across a broad, low-frequency band between 0.01 and 0.1 Hz, as is predominantly used in resting-state fMRI (Chen et al., 2015b).

One study used voxel-mirrored homotopic connectivity (VMHC), which measures synchrony between a voxel in one hemisphere and its mirrored counterpart in the opposite hemisphere, and it can be used to study interhemispheric functional connectivity (Chen et al., 2015a).

Three studies used Independent Component Analysis, which is a data-driven method in which it is not necessary to define a region of interest in advance (Meszlényi et al., 2017). ICA is a mathematical technique to separate a set of data into "components"

based on statistical independence. This data-driven technique can be applied to rs-fMRI data to identify spatially distinct resting-state networks (Lee et al., 2013). The analyst has to determine the number of components to create which can have an effect on the results ((Jouan-Rimbaud Bouveresse et al., 2012).

A final proof-of-concept study used cyclicity analysis, which studies leader-follower relationships between two signals in a time series (Zimmerman et al., 2019).

5.5.3 Study findings

5.5.3.1 Seed-based Correlation Analysis: non-directional

Fifteen studies used non-directional SCA to analyse the resting-state patterns in tinnitus patients. Regions of interest (ROI) were predefined in these studies, and the correlations between the rs-fMRI time series of these ROIs and all other voxels in the brain were calculated. The resulting functional connectivity map of the chosen seed regions was then compared between tinnitus and control groups.

A wide range of ROIs were investigated, consisting of auditory and non-auditory seed regions. Non-auditory seed regions were often located in a known resting-state network, such as the default mode network (DMN), dorsal attention network (DAN), ventral attention network (VAN), visual network, sensorimotor network, or cognitive/control network. ROIs were selected in different ways, most often using WFU_Pickatlas software. Figure 5-2 shows an overview of the findings of SCA studies.

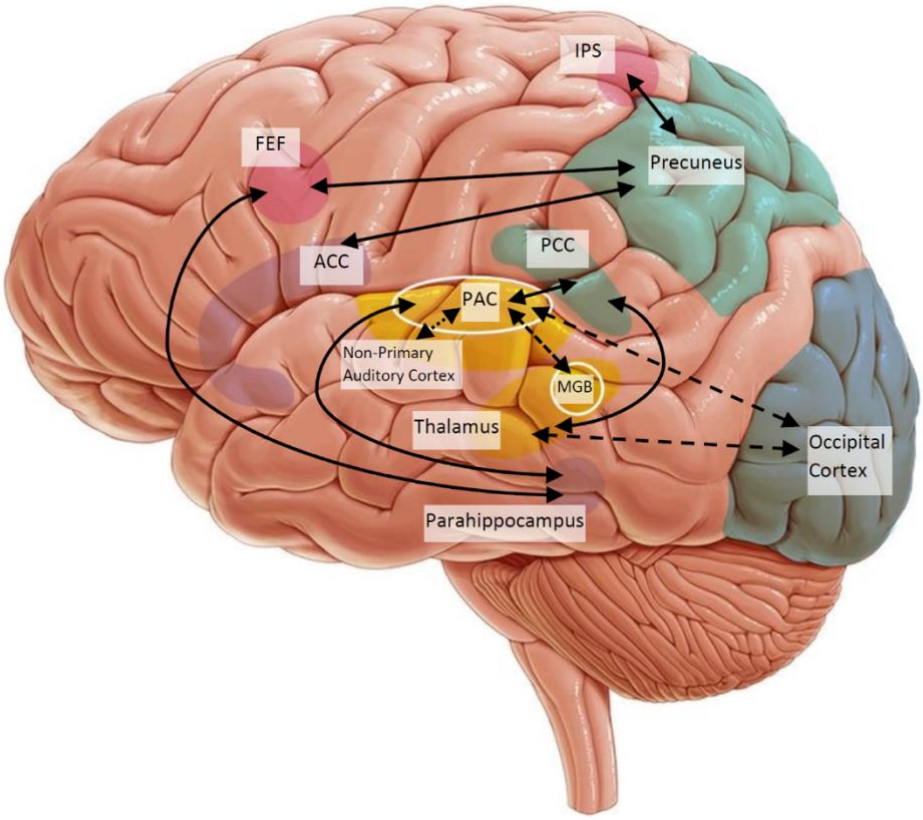

Figure 5-2 Schematic of findings of seed-based studies. Solid lines represent increased functional connectivity between regions, whereas dotted lines represent decreased functional connectivity in tinnitus groups compared to control groups. A line was drawn between two regions if at least one paper found this increased/decreased connection. Only the results relevant to the regions on the template are presented in this overview. Yellow = auditory network, aqua = default mode network, pink = dorsal attention network, purple = limbic system, blue = visual network. Please note some of the presented structures are internal to the brain and their location is therefore an approximation on this schematic IPS = Intraparietal Sulcus, FEF = Frontal Eye Fields, ACC = Anterior Cingulate Cortex, PCC = Posterior Cingulate Cortex, MGB = Medial Geniculate Body. Image template copyright: Kenhub GmbH, illustrator: Paul Kim (Ocran, 2021) (Permission for use granted)

To investigate auditory connectivity specifically, Figure 5-3 shows findings of SCA studies that used auditory regions of interest (ROI). The thickness of red ribbons

reflect how many times increased connectivity was found for the given ROI. For green ribbons, this is decreased connectivity.

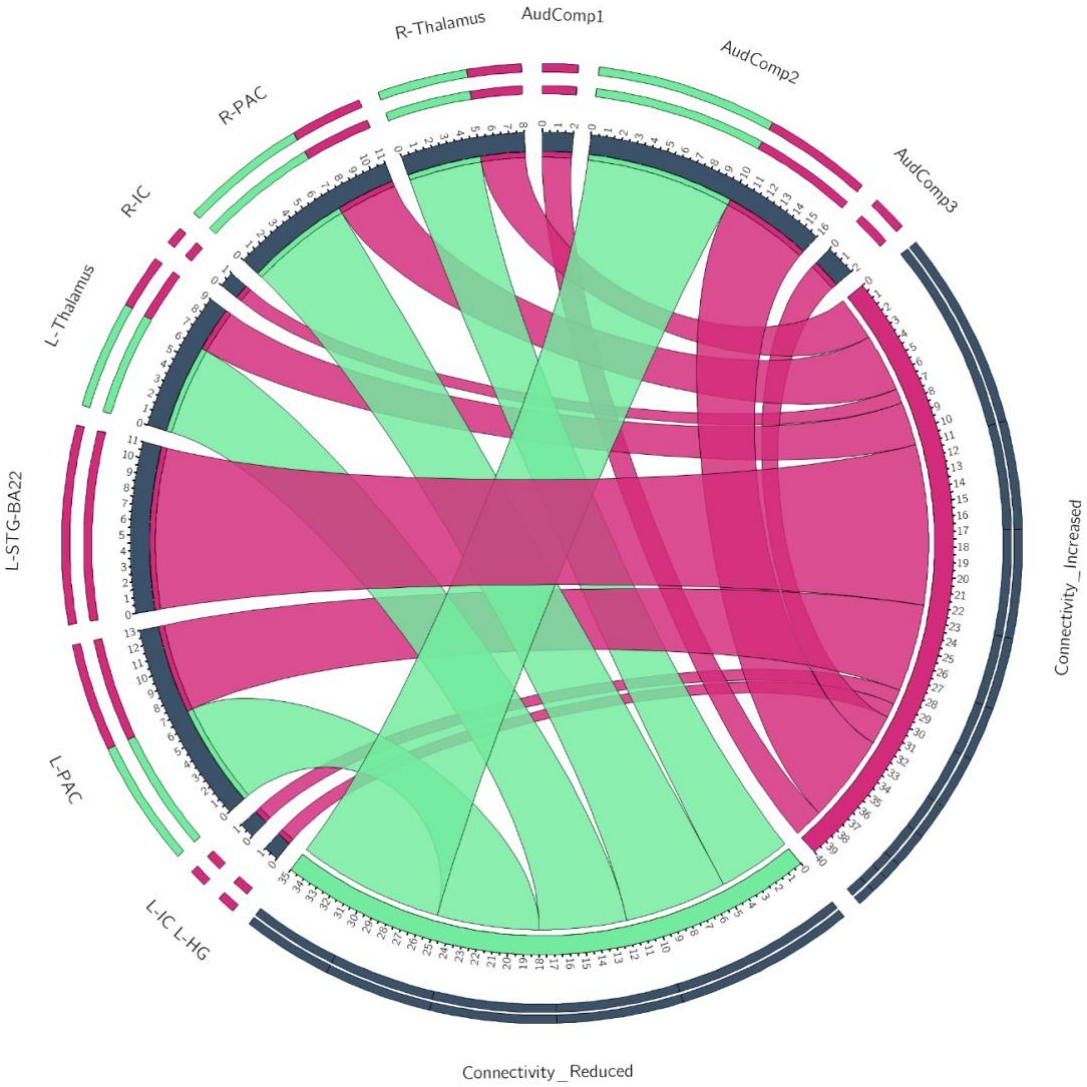

Figure 5-3 Findings of increased or decreased auditory connectivity in tinnitus patients compared to controls. Labels reflect regions-of-interest (ROI) used in the papers. Red indicates increased connectivity, and green indicates decreased connectivity. The thickness of the ribbons reflects the number of identified increased or decreased connections for that region. Abbreviations: L-HG = Left Heschl's Gyrus, L-IC = Left Inferior Colliculus, L-PAC = Left Primary Auditory Cortex, L-STG-BA22 = Left Superior Temporal Gyrus (BA22), R-IC = Right Inferior Colliculus, R-PAC = Right Primary Auditory Cortex, AudComp1 = Auditory Component consisting of Bilateral Auditory Cortex & Bilateral Non-Primary Auditory Cortex, AudComp2 = Bilateral Transverse Temporal Gyrus, Bilateral Superior Temporal Gyrus & Bilateral Insula, AudComp3 = Auditory Component consisting of Bilateral Primary Auditory Cortex

Table 5-1 shows an overview of the studies' findings; Table S1 in the supplementary materials presents detailed information on all included studies and their methods. All included studies have been numbered in these tables for clarity, as there are some publications with similar authors and years of publication. All but two studies [12, 15] showed altered functional connectivity networks in tinnitus patients.

Study	*Sample size*	*Hearing loss*	*Control Matching*	*ROI/seed*	*Findings of increased ↑ or decreased ↓ FC (tinnitus vs. control)*	*Networks implicated*
Berlot et al. (2020) [1]	Tinnitus n=6 Control n=6	Yes, matched	Age Sex Hearing thresholds Handedness	PAC, Non-PAC, MGB, IC	↓ PAC <> non-PAC ↓ PAC <> MGB	Auditory
Chen et al. (2017a) [2]	Tinnitus n=40 (20 depressive) Control n=23	Normal audiogram	Age Sex Hearing thresholds Years of education SAS & SDS scores	L Amygdala, R Amygdala	Tinnitus (depressed + non-depressed) vs. controls: ↑ L+R Amygdala <> L PoCG ↓ L+R Amygdala <> L STG ↓ L Amygdala <> L MFG ↓ L Amygdala <> R PCC ↓ R Amygdala <> R MFG ↓ R Amygdala <> R SFG See Table S1 for other group comparisons.	Prefrontal-cingulate-temporal circuit DMN Attention Somatosensory Visual

Study	*Sample size*	*Hearing loss*	*Control Matching*	*ROI/seed*	*Findings of increased ↑ or decreased ↓ FC (tinnitus vs. control)*	*Networks implicated*
Chen et al. (2018a) [3]	Tinnitus n=40 Control n=41	Normal audiogram	Age Sex Hearing thresholds Years of education Handedness	ACC, PCC	↑ ACC <> L Precuneus* ↑ PCC <> R mPFC** * positively correlated with tinnitus duration (r=0.451, p=0.007) ** positively correlated with tinnitus distress (r=0.411, p=0.014)	DMN
Chen et al. (2018b) [4]	Tinnitus n=31 Control n=40	Normal audiogram	Age Sex Years of education Hearing thresholds SDS & SAS scores	Rostral ACC, dorsal ACC	↑ rACC <> L Precuneus* ↑ rACC <> R PoCG ↑ rACC <> R Putamen ↑ dACC <> R STG ↑ dACC <> R IPL** ↑ dACC <> R OFC ↑ dACC <> R mPFC ↓ rACC <> L Calcarine cortex ↓ dACC <> R Fusiform gyrus	Auditory DMN Visual Executive functions Somatosensory

Study	*Sample size*	*Hearing loss*	*Control Matching*	*ROI/seed*	*Findings of increased ↑ or decreased ↓ FC (tinnitus vs. control)*	*Networks implicated*
			Brain parenchyma volume Handedness		* positively correlated with tinnitus severity (r=0.507, p=0.008). ** positively correlated with tinnitus severity (r=0.447, p=0.022)	
Chen et al. (2018c) [5]	Tinnitus n=35 Control n=50	Normal audiogram	Age Sex Years of education Hearing thresholds SDS & SAS scores Brain parenchyma volume	PCC	↑ PCC <> R mPFC* * Correlated with the poorer Trail Making Test-B scores (r=0.474, P=0.008) but not with tinnitus diagnostics.	DMN

Study	*Sample size*	*Hearing loss*	*Control Matching*	*ROI/seed*	*Findings of increased ↑ or decreased ↓ FC (tinnitus vs. control)*	*Networks implicated*
			Grey and white matter volume Handedness			
Feng et al. (2018) [6]	Tinnitus n=28 Control n=29	Normal audiogram	Age Sex Years of education Hearing thresholds Brain parenchyma volume Grey and white	Cerebellum (9 seeds)	↑ L Crus I <> L PHG ↑ R Crus I <> R IOG ↑ R Crus II <> R IOG ↑ L Lobule VIIb <> R STG* ↑ R Lobule VIIb <> L PCG ↑ Vermis <> R STG** * positively correlated with THQ scores (r = 0.577, p = 0.004). ** positively correlated with the THQ score (r = 0.432, p = 0.039).	Auditory Limbic system Visual

Study	*Sample size*	*Hearing loss*	*Control Matching*	*ROI/seed*	*Findings of increased ↑ or decreased ↓ FC (tinnitus vs. control)*	*Networks implicated*
			matter volume Handedness			
Henderson-Sabes et al. (2019) [7]	Tinnitus n=15 Control n=15	Unilateral deafness, matched	Age Sex Handedness Hearing thresholds Duration of deafness	L+R HG, L+R caudate nucleus	↑ L caudate nucleus <> L HG ↑ L caudate nucleus <> R SMA	Auditory Limbic system Motor DMN Visual DAN
Hinkley et al. (2015) [8]	Tinnitus n=15 Control n=15	Yes, not matched, hearing loss included as	Age Sex	L+R PAC, L+R dorsal striatum, L+R caudate head, L+R NAc	↑ L PAC <> R STG ↑ L PAC <> L MTG ↑ L PAC <> SFG ↑ L PAC <> posterior cerebellum ↑ L PAC <> PHG	Auditory Limbic system Visual DMN DAN

Study	*Sample size*	*Hearing loss*	*Control Matching*	*ROI/seed*	*Findings of increased ↑ or decreased ↓ FC (tinnitus vs. control)*	*Networks implicated*
		covariate in analysis			↑ L PAC <> L lingual gyrus ↑ R PAC <> L MTG ↑ R PAC <> L SFG ↑ R PAC <> L MOG ↑ R PAC <> R PoCG ↑ Striatal ROIs <> frontal, temporal & occipital regions (See Table S1) ↓ L+R dorsal striatum <> L+R lingual gyrus ↓ L dorsal striatum <> L culmen ↓ R caudate head <> L culmen ↓ R caudate head <> R lingual gyrus ↓ L NAc <> R STG ↓ L NAc <> R culmen ↓ L NAc <> L lingual gyrus ↓ L NAc <> L IPL	

Study	*Sample size*	*Hearing loss*	*Control Matching*	*ROI/seed*	*Findings of increased ↑ or decreased ↓ FC (tinnitus vs. control)*	*Networks implicated*
Job et al. (2020) [9]	Tinnitus n=19 Control n=19	Yes, not matched, hearing loss included as covariate in analysis	Age Sex	L+R HG, L+R MGB, L+R IC, n=5 operculum ROIs, n=7 whole-brain RSNs	↑L HG <> PCC ↑ L&R IC <> R SPL ↑ R operculum <> R SFG ↑ Posterior R operculum <> L SFG ↑ Posterior R operculum <> L IPL Whole brain RSN analysis found enhanced FC with sensorimotor-auditory network & frontoparietal network.	Auditory DMN Sensorimotor-auditory Frontoparietal
Zhang et al. (2015) [10]	Tinnitus n=31 Control n=33	Normal audiogram	Age Sex Hearing thresholds Years of education Handedness	L+R thalamus	↑ L thalamus <> R angular gyrus ↑ L thalamus <> R MCC ↑ L thalamus <> L CPL ↑ R thalamus <> L PCC ↑ R thalamus <> L+R CPL ↓ L thalamus <> R MTG* ↓ L thalamus <> R MOC	Auditory Visual DMN

Study	*Sample size*	*Hearing loss*	*Control Matching*	*ROI/seed*	*Findings of increased ↑ or decreased ↓ FC (tinnitus vs. control)*	*Networks implicated*
					↓ L thalamus <> L MFG ↓ L thalamus <> R PCG ↓ L thalamus <> L+R calcarine cortex ↓ R thalamus <> L STG** ↓ R thalamus <> L amygdala ↓ R thalamus <> R SFG ↓ R thalamus <> L PCG ↓ R thalamus <> L MOG *Negatively correlated with THQ score (r = −0.482, p = 0.011). **Negatively correlated with tinnitus duration (r = −0.454, p = 0.017).	
Schmidt et al. (2017) [11]	MRTIN n=13 MLTIN_1 n=12	Yes, matched	Age Sex Hearing thresholds	L+R PAC, DMN (combined: mPFC, PCC), DAN	For all tinnitus groups vs. controls or long- vs. short-term tinnitus: ↑ DAN <> precuneus	DMN DAN

Study	*Sample size*	*Hearing loss*	*Control Matching*	*ROI/seed*	*Findings of increased ↑ or decreased ↓ FC (tinnitus vs. control)*	*Networks implicated*
	MLTIN_2 n=17 BLTIN n=15 Controls NH n=15 Controls HL n=13		(in the case of the HL control group)	(combined: L+R IPS, L+R FEF)	↑ DAN <> region near L PCG (unspecified); ↓ DMN <> precuneus ↓ DMN <> FMC ↓ DMN <> & lateral SOC No differences were found between mild and bothersome tinnitus subgroups.	
Wineland et al. (2012) [12]	Tinnitus n=18 Controls n=23	Yes, not matched	Sex	58 spherical seed-regions to reflect 7 networks: DAN, VAN, DMN, auditory, cognitive, visual, somatosensory	None found	None found

Study	*Sample size*	*Hearing loss*	*Control Matching*	*ROI/seed*	*Findings of increased ↑ or decreased ↓ FC (tinnitus vs. control)*	*Networks implicated*
Burton et al. (2012) [13]	Tinnitus n=17 Controls n=17	Yes, not matched	Age	Auditory (L+R PAC), Visual (R V1, L cuneus), Somatosensory (R PoCG, L PO), DAN (L+R IPS, L FEF, R VIS), VAN (R TPJ, R STS), Attention control (R MFG, R AI, L+R IFG)	↑ L IFG <> R AI ↓ L+R PAC <> occipital pole ↓ L+R PAC <> L POS ↓ L+R PAC <> calcarine sulcus ↓ L+R PAC <> cuneus ↓ L+R PAC <> lingual gyri ↓ R V1 <> L STF ↓ R V1 <> L sulcal AC ↓ R V1 <> L rostral insula ↓ R V1 <> L IFG ↓ R AI <> L+R mOC ↓ R AI <> L+R lOC ↓ L IFG <> mOC	Auditory Visual Attention control
Minami et al. (2018) [14]	Tinnitus HL n=18	Yes, not matched	Not given	HG, planum temporale, planum	ROI names and statistics are not legible in figures due to poor image quality.	Auditory

Study	*Sample size*	*Hearing loss*	*Control Matching*	*ROI/seed*	*Findings of increased ↑ or decreased ↓ FC (tinnitus vs. control)*	*Networks implicated*
	Tinnitus NH n=11 Control n=19			polare, operculum, insular cortex, STG	According to authors FC in auditory ROIs was weakened in tinnitus.	
Lee et al. (2012) [15]	Tinnitus n=16 Control n=0	Yes	Intra-subject comparison	58 spherical seed regions in 7 networks: DMN, DAN, VAN, cognitive/control, auditory, visual, somatosensory	Participants modulated their tinnitus using orofacial manoeuvers and served as their own baseline, but no differences were found.	None found

Table 5-1 Main findings of non-directional seed-based studies. Abbreviations: <> = functional connectivity, **↑ = increased functional connectivity, ↓ = decreased functional connectivity,** ROI = Region of Interest, PAC = Primary Auditory Cortex, MGB = Medial Geniculate Body, IC = Inferior Colliculus, FC = Functional Connectivity, L = Left, R = Right, DMN = Default Mode Network, ACC = Anterior Cingulate Cortex, PCC = Posterior Cingulate Cortex, mPFC = medial Prefrontal Cortex, IPL = Inferior Parietal Lobule, STG = Superior Temporal Gyrus, HG = Heschl's Gyrus, SMA = Supplementary Motor Area, DAN = Dorsal Attention Network, NA = Nucleus Accumbens, THI = Tinnitus Handicap Inventory, rs = resting-state, SFG = Superior Frontal Gyrus, MCC = Middle Cingulate Cortex, CPL = Cerebellar Posterior Lobe, MOC = Middle Orbitofrontal Cortex, PCG = Precentral Gyrus, MRTIN = mild recent tinnitus, MLTIN = mild long-term tinnitus, BLTIN = bothersome long-term tinnitus, NH = No hearing loss, HL = hearing loss, IPS = Intraparietal Sulcus, FEF = Frontal Eye Field, FMC = Frontal Medial Cortex, SOC = Superior Occipital Cortex, VAN = Ventral Attention Network, V1 = Primary Visual Cortex, PO

= Parietal Operculum, VIS = Ventral Intraparietal Sulcus, TPJ = Temporoparietal Junction, STS = Superior Temporal Sulcus, AI = Anterior Insula, POS = Parietal Occipital Sulcus, mOC = medial Occipital Cortex, lOC = lateral Occipital Cortex

5.5.3.2 *Seed-based Correlation Analysis: directional (Granger Causality Analysis)*

Three studies used Granger Causality Analysis (GCA) to investigate directional connectivity in tinnitus patients. One study [16] selected ROIs based on Degree Centrality (a graph theory based, data-driven method), whereas the other two studies [17, 18] selected ROIs manually. Table 5-2 presents an overview of GCA findings.

Study	*Sample size*	*Hearing loss*	*Control Matching*	*ROI/seed*	*Findings of increased ↑ or decreased ↓ FC (tinnitus vs. control)*	*Networks implicated*
Chen et al. (2016) [16]	Tinnitus n=24 Control n=22	Normal audiogram	Age Sex Hearing thresholds Years of education	L+R SFG	↑L SFG → L OFC* ↑L SFG → L PCG ↑L SFG → L PLC ↑L SFG → R MOG ↑R SFG → R SMA** * Positively correlated with THQ scores (r = 0.504, p = 0.020). ** Positively correlated with THQ scores (r = 0.526, p = 0.014).	Motor Visual Frontal Somatosensory
Chen et al. (2017b) [17]	Tinnitus n=26 Control n=23	Normal audiogram	Age Sex Hearing thresholds Handedness Years of education	L+R amygdala, L+R hippocampus	↑ L amygdala → L STG* ↑ L+R amygdala → L ACC ↑ L amygdala → R angular gyrus ↑ L amygdala → L precuneus ↑ L amygdala ← R MFG ↑ L+R amygdala ← L MTG ↑ L amygdala ← L IFG	Auditory Limbic system DMN DAN Executive control of attention

Study	*Sample size*	*Hearing loss*	*Control Matching*	*ROI/seed*	*Findings of increased ↑ or decreased ↓ FC (tinnitus vs. control)*	*Networks implicated*
					↑ L amygdala ← L PoCG	
					↑ R amygdala → R MFG	
					↑ R amygdala → R STG**	
					↑ R amygdala → R SMG	
					↑ R amygdala ← L MTG	
					↑ R amygdala ← R PoCG	
					↑ L Hippocampus → L MTG	
					↑ L Hippocampus → L PoCG	
					↑ L Hippocampus ← R SFG	
					↑ L Hippocampus ← L Parahippocampal gyrus	
					↑ L Hippocampus ← L Insula	
					↑ R hippocampus → L TTG***	
					↑ R hippocampus → R MTG	
					↑ R hippocampus → R PoCG	
					↑ R hippocampus ← L MTG	

Study	*Sample size*	*Hearing loss*	*Control Matching*	*ROI/seed*	*Findings of increased ↑ or decreased ↓ FC (tinnitus vs. control)*	*Networks implicated*
					↑ R hippocampus ← L+R MFG ↑ R hippocampus ← L angular gyrus ↓ L amygdala → L PLC ↓ R amygdala → R PLC ↓ L hippocampus → L MOG ↓ R hippocampus → R MOG * positively correlated with THQ scores (r = 0.570, p = 0.005). ** positively correlated with THQ scores (r = 0.487, p = 0.018). *** positively correlated with tinnitus duration (r = 0.452, p = 0 .030).	
Xu et al. (2019) [18]	Tinnitus n=50	Normal audiogram	Age Sex	L+R NAc	↑L NAc → L IFG ↑ L NAc ← R MFG* ↑ L Nac ← R MTG.	Frontostriatal circuit Limbic system

Study	*Sample size*	*Hearing loss*	*Control Matching*	*ROI/seed*	*Findings of increased ↑ or decreased ↓ FC (tinnitus vs. control)*	*Networks implicated*
	Control n=55		Hearing thresholds Years of education		↑ R NAc ⟶ L MFG** ↑ R NAc ⟶ R OFC*** ↑ R NAc ⟵ R IFG ↑ R NAc ⟵ R MTG ↓ L NAc ⟶ L Cuneus ↓ R NAc ⟶ R Cuneus * Positively correlated with THQ scores (r = 0.626, p < 0.001). **Positively correlated with THQ scores (r = 0.357, p = 0.015). *** Positively correlated with tinnitus duration (r = 0.599, p < 0.001).	

Table 5-2 Main findings of directional seed-based studies. Abbreviations: <> = functional connectivity, **↑ = increased functional connectivity, ↓ = decreased functional connectivity,** ROI = region of interest, L = left, R = right, SFG = Superior Frontal Gyrus, OFC = Orbitofrontal Cortex, PCG = Precentral Gyrus, PLC = Posterior lobe of cerebellum, MOG = Middle Occipital Gyrus, SMA = Supplementary Motor Area, THQ = Tinnitus Handicap Questionnaire, DMN = Default Mode Network, DAN = Dorsal Attention Network, STG = Superior Temporal Gyrus, TTS = Transverse Temporal Gyrus, NAc = Nucleus Accumbens, IFG = Inferior Frontal Gyrus, MFG = Middle Frontal Gyrus, MTG = Middle Temporal Gyrus

5.5.3.3 NON-SEED-BASED STUDIES

Eight studies used alternative methods of analysis, including amplitude of low-frequency fluctuations (ALFF), regional homogeneity (ReHo), voxel-mirrored homotopic connectivity (VMHC), and cyclicity analysis. Table 5-3 shows the main findings of these studies.

Study	*Sample size*	*Hearing loss*	*Control Matching*	*Analysis*	*Findings of increased ↑ or decreased ↓ values/FC (tinnitus vs. control)*	*Networks implicated*
Cai et al. (2019) [19]	Tinnitus n=16 Control n=15	Normal audiogram	Age Sex Years of education	smALFF & seed-based FC	↑ smALFF values in L HAC, which was positively correlated with tinnitus duration (r = 0.778, p > 0.001), Tinnitus Handicap Inventory Score (r = 0.682, p = 0.004), and Self-Rating Depression Score (r = 0.694, p = 0.003); ↑L HAC <> a wide range of regions (see Table S1); ↑ smALFF value in R Inferior Colliculus, not correlated to any clinical characteristics.	Auditory Motor DAN Executive control Emotion
Chen et al. (2014) [20]	Tinnitus n=31 Control n=32	Normal audiogram	Age Sex Hearing thresholds Handedness	ALFF	↑ ALFF values in R MTG, R SFG, and R angular gyrus. ↓ ALFF values in L cuneus, R MOG, and L+R thalamus.	Auditory DMN Visual

			Years of education			
Chen et al. (2015b) [21]	Tinnitus n=39 Control n=41	Normal audiogram	Age Sex Hearing thresholds Years of education	ALFF/fALFF	↑ ALFF values in R SFG*, R MTG, R angular gyrus, L IFG, and R SMG ↓ ALFF values in L+R MOG ↑ fALFF values in L SFG** and R SMG ↓ fALFF values in L+R MOG. *Positively correlated with THQ score (r = 0.446, p = 0.007) and tinnitus duration (r = 0.544, p = 0.001). ** Positively correlated with THQ score (r = 0.466, p = 0.005) and tinnitus duration (r = 0.526, p = 0.001).	Auditory DMN Visual
Han et al. (2018) [22]	Tinnitus n=25 Control n=25	Normal audiogram	Age Sex Hearing thresholds	ReHo, fALFF & seed-based FC	↑ ReHo values in R MTG & R cuneus ↓ ReHo values in R MFG & Cerebellar anterior lobe ↑ fALFF values in R MTG ↓ R MTG <> R MFG*	Auditory DMN Visual

			Years of education HQ score		↓ R MTG <> R lingual gyrus ↓ R MTG <> R cerebellar posterior lobe ↓ R cuneus <> R MTG * Positively correlated with Tinnitus Handicap Inventory score (r = 0.675, p = 0.001).	
Chen et al. (2015c) [23]	Tinnitus n=29 Control n=30	Normal audiogram	Age Sex Hearing thresholds Years of education	ReHo & seed-based FC	↑ ReHo values in L+R AI, L IFG and R SMG ↓ ReHo values in L cuneus ↑ L AI <> L MFG* ↑ L AI <> R ITG ↑ L AI <> R precuneus ↑ R AI <> R MFG** ↑ R AI <> R STG ↑ R AI <> L precuneus ↑ R AI <> L PCC ↑ L IFG <> R MFG	Attention DMN Visual

					↑ L IFG <> R ITG ↑ L IFG <> R ACC ↑R SMG <> L IFG ↑R SMG <> R OFC. * Positively correlated with THQ score (r = 0.459, p = 0.012). ** Positively correlated with THQ score (r = 0.479, p = 0.009).	
Gentil et al. (2019) [24]	Tinnitus n=19 Control n=16	Yes, mild, not matched	Age Handedness Years of education	ReHo & corelation analysis	↓ ReHo values in cluster between STG/MTG overlapping auditory cortex Significant correlations between tinnitus clinical characteristics and several brain regions (see Table S1 for specifics).	Auditory
Chen et al. (2015a) [25]	Tinnitus n=28 Control n=30	Normal audiogram	Age Sex Hearing thresholds	VMHC & correlation analysis	↑ VMHC values in bilateral MTG, MFG & SOG	Auditory Visual Motor DMN

			Years of education		Significant positive correlation between VMHC values in tinnitus patients and clinical characteristics: THQ score & TTG (auditory cortex) (r = 0.63775); THQ score & STP (r = 0.71195); THQ score & PCG (r = 0.64225); THQ score & CC (r = 0.65234); Uncus & tinnitus duration (r = 0.62026).	Limbic system
Zimmerman et al. (2019) [26]	Tinnitus n=32 Control n=15	Mild-moderate high frequency hearing loss	Age BDI and BAI scores	Cyclicity analysis	Cyclicity analysis was able to differentiate between tinnitus and control groups with 58-67% accuracy. Temporal patterns in rs-fMRI data were less consistent in tinnitus patients than in controls. Twenty regions contributed the most towards distinguishing the tinnitus and	Auditory DMN DAN VAN Attention control Limbic system

		controls groups using machine learning classification methods (see Table S1 for specifics).

Table 5-3 Main findings of non-seed-based studies. Abbreviations: <> = functional connectivity, **↑ = increased functional connectivity, ↓ = decreased functional connectivity,** smALFF = smoothed mean amplitude of low-frequency fluctuations, HAC = Higher Auditory Cortex, DAN = Dorsal Attention Network, FC = functional connectivity, ALFF = amplitude of low-frequency fluctuations, MTG = Middle Temporal Gyrus, SFG = Superior Frontal Gyrus, MOG = Middle Occipital Gyrus, DMN = Default Mode Network, fALFF = fractional amplitude of low-frequency fluctuations, IFG = Inferior Frontal Gyrus, SMG = Supramarginal Gyrus, ReHo = Regional Homogeneity, MFG = Middle Frontal Gyrus, AI = Anterior Insular Cortex, ITG = Inferior Temporal Gyrus, STG = Superior Temporal Gyrus, PCC = Posterior Cingulate Cortex, ACC = Anterior Cingulate Cortex, VMHC = voxel-mirrored homotopic connectivity, SOG = Superior Occipital Gyrus, TTG = Transverse Temporal Gyrus, STP = Superior Temporal Pole, PCG = Precentral Gyrus, CC = Calcarine Cortex, HQ = Hyperacusis Questionnaire, BDI = Beck's Depression Inventory, BAI = Beck's Anxiety Inventory

5.5.3.4 Data-driven studies: Independent Component Analysis

Three studies used Independent Component Analysis (ICA) followed by seed-based FC analysis. The studies below visually selected the auditory component based on the ICA outcome, and used this as a region of interest in the seed-based FC analysis. The main findings are presented in Table 5-4.

Study	*Sample size*	*Hearing loss*	*Control Matching*	*Analysis*	*Main finding (tinnitus vs. control)*	*Network implicated*
Davies et al. (2014) [27]	Tinnitus n=12 Control n=11	Mild-moderate high-frequency hearing loss	Age Sex Hearing thresholds BDI & BAI scores	ICA + seed-based FC Total number of components created: 23	None found (result did not survive multiple comparison correction)	None found
Maudoux et al. (2012) [28]	Tinnitus n=13 Control n=15	Mild-to-severe hearing loss, not matched	Age Sex	ICA + seed-based FC Total number of components created: 30 Auditory component:	↑ Auditory component <> L+R PHG ↑ Auditory component <> L+R brainstem/cerebellum ↑ Auditory component <> L PCG ↑ Auditory component <> L STG ↑ Auditory component <> L IFG ↑ Auditory component <> R basal ganglia ↑ Auditory component <> R PFC	Auditory Attention Emotion Memory Visual

				L+R Heschl's Gyrus, L+R STG, and L+R Insula	↑ Auditory component <> L PoCG ↑ Auditory component <> R OFC ↑ Auditory component <> R IPL ↓ Auditory component <> L SFG ↓ Auditory component <> L Fusiform gyrus ↓ Auditory component <> R STG ↓ Auditory component <> L+R Occipital cortex ↓ Auditory component <> L PFC.	
Schmidt et al. (2013) [29]	Tinnitus n=12 NH control n=15 HL control n=13	Moderate-severe high-frequency HL	Age Sex Hearing thresholds (for HL control group)	ICA + seed-based FC Total n components created: 30	↑ Auditory component <> L Lingual Gyrus (TIN>NH) ↑ Auditory component <> L Parahippocampus (TIN>NH) ↑ DAN <> R Parahippocampus (TIN>HL) ↑ DMN <> R Fusiform Gyrus (TIN>HL) ↑ DMN <> R Lingual Gyrus (TIN>HL)	Auditory DAN DMN Motor Limbic system

	Auditory component: PAC	L+R	↓ DAN <> R SMG (HL>TIN) ↓ DMN <> L Precuneus (HL>TIN) ↓ DMN <> L PCG (HL>TIN) ↓ DMN <> L Cerebellum (HL>TIN) ↓ DMN <> L Cerebellar Vermis (HL>TIN) ↓ DMN <> and R Precuneus (NH>TIN)

Table 5-4 Main findings of studies using Independent Component Analysis. Abbreviations: **↑ = increased functional connectivity, ↓ = decreased functional connectivity,** BDI = Beck's Depression Inventory, BAI = Beck's Anxiety Inventory, ICA = Independent Component Analysis, FC = functional connectivity, L = left, R = right, STG = Superior Temporal Gyrus, PHG = Parahippocampal Gyrus, PCG = Precentral Gyrus, IFG = Inferior Frontal Gyrus, PFC = Prefrontal Cortex, PoCG = Postcentral Gyrus, OFC = Orbitofrontal Cortex, IPL = Inferior Parietal Lobule, SFG = Superior Frontal Gyrus, NH = normal hearing, HL = hearing loss, PAC = Primary Auditory Cortex, DAN = Dorsal Attention Network

5.6 Discussion

This scoping review identified 29 primary research studies that investigated resting-state networks in tinnitus patients. The majority of these studies (*n* = 26) found that resting-state networks as measured with fMRI were altered in tinnitus patients when compared to controls. Alterations were found in a variety of resting-state networks, most notably the auditory network (*n* = 19), the default mode network (DMN) (*n* = 17), visual network (*n* = 14), the attention networks: dorsal attention network (*n* = 7), ventral attention network (*n* = 1), attention/executive control network (*n* = 9), and the limbic system (*n* = 8). It is important to note that the frequency of these findings depends largely on the chosen region of interest in the papers. The next paragraphs present a narrative discussion of the findings for these networks.

5.6.1 Functional changes in tinnitus

5.6.1.1 Auditory network in tinnitus

Tinnitus is an auditory perception, leading to the proposal that the auditory network in tinnitus patients is altered compared to controls. To investigate auditory network changes in tinnitus, several studies placed seeds in primary auditory cortex (PAC) or Heschl's Gyrus (HG), or lower on the auditory pathway. Figure 5-3 presented the findings of SCA studies that used auditory regions of interest in their analysis. Overall, there were more findings of increased connectivity using auditory seeds than there were of decreased connectivity. However, findings of altered connectivity were not consistently in one direction. For bilateral thalamus and PAC, both increased and decreased functional connectivity were found in tinnitus compared to controls.

Berlot et al. (2020) used a high resolution 7 Tesla MRI scanner to investigate frequency-specific responses in subcortical regions of the auditory pathway such as the inferior colliculus (IC) and the medial geniculate body (MGB) in six tinnitus patients compared to six hearing-matched controls. They first used task-based fMRI to build tonotopic maps, but they did not find any differences in tonotopic organization between tinnitus patients and controls. Furthermore, they did not find evidence for an overrepresentation of tinnitus pitch at any level of the auditory hierarchy. Placing seeds in PAC, they did find decreased functional connectivity (FC)

with non-primary auditory cortex. They also found decreased FC between PAC and the MGB. These reductions were seen not only in voxels responsive to the tinnitus frequency, but also in “control” voxels.

Zhang et al. (2015) investigated thalamocortical functional connectivity in tinnitus patients with normal hearing (*n* = 31) compared to matched controls (*n* = 33). They placed seeds in bilateral thalamus and found decreased FC between right thalamus and left superior temporal gyrus (STG) or BA 42, which is part of non-primary AC. The thalamic FC with STG was negatively correlated with tinnitus duration ($r = -0.454$, $p = 0.017$). They also found decreased FC between left thalamus and left MTG or BA 21, which is also part of non-primary auditory cortex, which was negatively correlated with tinnitus severity score ($r = -0.482$, $p = 0.011$). The observed reduced coupling between thalamus and auditory areas is in line with findings from Berlot et al. (2020).

Hyperactivity models of tinnitus such as thalamocortical dysrhythmia (TCD) and the frontostriatal gating model place a central role on MGB. The TCD hypothesis suggests hyperpolarization of the MGB results in an MGB firing mode-switch (Llinás et al., 1999). The frontostriatal gating hypothesis (Rauschecker et al., 2010) suggests tinnitus arises due to a break-down of limbic-auditory interactions at the level of the thalamus, or more specifically from a thalamic reticular nucleus based release of MGB inhibition. Based on the assumption of hyperactivity in auditory regions, one might expect increased PAC-MGB connectivity, rather than decreased connectivity, as was observed in Berlot et al. (2020). However, it could also be argued that decreased connectivity reflects the absence of gating activity.

Several studies have found increased auditory connectivity in tinnitus. Hinkley et al. (2015) found increased FC between bilateral PAC and non-primary auditory cortex, as did Cai et al. (2019). Job et al. (2020) placed seeds in bilateral HG, bilateral IC, and bilateral MGB. They did not observe any altered connectivity with the MGB in patients with non-bothersome tinnitus following acoustic trauma (*n* = 19) compared to controls (*n* = 19), as opposed to Berlot et al. (2020). However, they did observe increased FC between left HG and posterior cingulate cortex (PCC), an important

region of the DMN (discussed in section 5.6.1.2). Next to that, they observed increased FC between bilateral IC and right superior parietal lobule (SPL). The IC is known for its role in auditory integration (Yang et al., 2020), and the SPL is thought to be involved with cognitive control (Esterman et al., 2009), so one explanation for a disturbed link between IC and SPL could be the difficulty of filtering out the tinnitus signal.

Evidence in support of the hyperactivity model of tinnitus was present in studies that used amplitude of low-frequency fluctuations (ALFF) analysis. The four studies using ALFF all found increased ALFF values in auditory regions (Cai et al., 2019, Chen et al., 2014, Chen et al., 2015b, Han et al., 2018), indicating stronger intensity of regional neuronal activity in AC in tinnitus patients.

In summary, altered FC as well as increased ALFF have been found in auditory regions in tinnitus patients compared to controls. However, there is inconsistency between studies finding increased FC and those finding decreased FC along the auditory pathway. Potentially, this dichotomy could be explained by tinnitus heterogeneity, as participants were different with respect to the presence of hearing loss, the laterality of tinnitus, the duration of tinnitus, and tinnitus severity. Alternatively, as studies were small-scale, the contradictory results could also reflect false positives.

5.6.1.2 Default mode network in tinnitus

The DMN consists of ventral medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), precuneus, inferior parietal lobule (IPL), lateral temporal cortex, dorsal medial prefrontal cortex, and the hippocampal formation. It is active when individuals are not performing any external task, but are engaged in internal cognitive processes such as mind-wandering or thinking about the future (Buckner et al., 2008). As tinnitus is mainly experienced at rest, which is when the DMN is most active, it has been hypothesised that aberrant functioning of the DMN may be implicated in tinnitus pathophysiology. The continuous awareness of a sound might put the tinnitus patient in a task-state, therefore disrupting the DMN. Aberrant connectivity

of the DMN was found in several studies included in this review, but studies did not agree on whether the connectivity was increased or decreased.

The precuneus is a hub of the DMN (Utevsky et al., 2014) which was implicated in several studies in this review. Chen et al. (2018a) and Chen et al. (2018b) found increased FC between anterior cingulate cortex (ACC) and left precuneus, which was positively correlated with tinnitus severity ($r = 0.507$, $p = 0.008$) and tinnitus duration ($r = 0.451$, $p = 0.007$). Chen et al. (2018a) also found increased FC between PCC and right mPFC, both regions within the DMN, which was positively correlated with tinnitus distress ($r = 0.411$, $p = 0.014$). Another study by the same group (Chen et al., 2018c) again found increased FC between PCC and right mPFC, this time correlated with poorer performance on a cognitive test (Trail Making Test B) ($r = 0.474$, $p = 0.008$), suggesting increased FC within the DMN in tinnitus patients could be related to executive dysfunction. It is unclear whether this could be related to a failure of a top-down noise-cancellation mechanism proposed by Vanneste et al. (2019), which was discussed in section 2.1.4.

Zhang et al. (2015) found increased FC between right thalamus and left PCC but did not observe any correlations with tinnitus characteristics. Finally, Job et al. (2020) found increased FC between left HG and PCC in a group of non-bothersome tinnitus patients.

In contrast to these studies that found increased FC with DMN, Schmidt et al. (2017), found decreased FC between precuneus and the rest of the DMN. They placed seeds in bilateral PAC, in the DMN, and in the DAN, and compared connectivity across tinnitus subgroups of mild, recent tinnitus ($n = 13$), mild, long-term tinnitus ($n = 29$), and bothersome long-term tinnitus ($n = 15$). They also included a normal hearing control group ($n = 15$) and a hearing loss-matched control group ($n = 13$). No differences were found when comparing the mild and bothersome tinnitus groups. However, when comparing tinnitus groups (?) to controls, or long-term tinnitus to recent tinnitus, they found decreased FC between seeds in the DMN and the precuneus, as well as increased FC between seeds in the DAN and the precuneus. This

opposite pattern of increased/decreased connectivity of precuneus with respectively DAN and DMN could be related to the anticorrelation observed between the DAN and DMN in neurotypical participants at rest, as the DAN is seen as a "task-positive" network and the DMN as a "task-negative" network (Fox et al., 2005).

Considering the evidence above, it is unclear what aberrant connectivity of the DMN in tinnitus might reflect. It could be the awareness of a constant sound disrupting the resting-state, although this is difficult to reconcile with findings of increased FC within the DMN, which were the most common.

5.6.1.3 Attention networks in tinnitus

This section will discuss findings relevant to attention networks, including the DAN, VAN and executive control networks. There is some confusion around the nomenclature of attention networks (Gratton et al., 2018) as mentioned in the introduction, thus it was decided to discuss them together. Van den Heuvel and Hulshoff Pol (2010), in their review of resting-state fMRI, presented findings in support of two lateralised frontoparietal networks consisting of left and right superior parietal and superior frontal regions. These two networks are thought to be involved with processing of attention and memory. A third frontal network consisting of bilateral medial frontal cortex involved with executive control was also reported.

Other resting-state studies have discussed attention networks as consisting of a ventral and a dorsal stream also in frontoparietal regions (Fox et al., 2006). The dorsal attention network (DAN) is bilateral and consists of intraparietal sulcus (IPS) and the frontal eye fields (FEF). The ventral attention network (VAN) is right-lateralised and involves right temporal-parietal junction (TPJ) and right ventral frontal cortex. In tinnitus studies, some papers have used the frontoparietal definition for attention networks, whereas other papers used the dorsal/ventral distinction. Many papers have also distinguished a frontal executive control or attention control network.

Job et al. (2020) defined a seed at the node of the frontoparietal network based on the Human Connectome Project (*www.humanconnectome.org*). They found increased FC between this seed and the right middle frontal gyrus (MFG), thought to

be involved with cognitive control, in patients with non-bothersome tinnitus compared to controls. Job et al. (2020) suggest that this could be a reflection of the cognitive load tinnitus places on the sufferer either in constantly maintaining tinnitus awareness, or in trying to filter out the tinnitus percept. They also placed a seed in the DAN, but they did not find any changes in FC with this seed, possibly due to the non-bothersome nature of the tinnitus in their participants.

Burton et al. (2012) on the other hand investigated a cohort of seventeen patients reporting bothersome tinnitus. They placed seeds in six networks, one being the attention control network (MFG, anterior insula (AI) & IFG). Compared to controls, they exhibited increased FC between left IFG and right AI. The alteration in this network could reflect the increase in cognitive resources required in bothersome tinnitus because of the ongoing effort of ignoring the tinnitus. Seeds were also selected in the DAN and VAN, but no altered connectivity was found. The controls were not matched to the tinnitus group on hearing thresholds, and therefore it cannot be ruled out that the presence of high-frequency hearing loss in the tinnitus group is associated with the findings rather than the tinnitus itself.

Chen et al. (2015c) also found increased FC within the attention control network. They chose their seed regions based on regional homogeneity (ReHo) analysis, which showed increased ReHo values in bilateral AI, amongst other regions (see Table S1 for details). Using bilateral AI as ROIs, they found increased FC between left AI and left MFG, and right AI and right MFG in normal-hearing tinnitus patients compared to controls. These findings were positively correlated with tinnitus severity scores ($r = 0.459$, $p = 0.012$ and $r = 0.479$, $p = 0.009$, respectively). These findings suggest that increased FC within the attention control network is linked to tinnitus severity and it might reflect an increased effort to maintain attention away from the tinnitus.

An ICA study also showed altered FC in attention networks, this time in the DAN in tinnitus patients with high-frequency hearing loss ($n = 12$) compared to matched hearing loss controls ($n = 13$). Schmidt et al. (2013) created two DAN components using bilateral IPS seeds for DAN_1 and bilateral FEF seeds for DAN_2. They found

that DAN_2 showed increased FC with parahippocampus, whereas DAN_1 showed decreased FC with right SMG. The authors suggest the increased FC with parahippocampus "could be a compensatory attempt to manage the phantom stimulus, delegating that process to non-attention processing regions, such those of the limbic system" (Schmidt et al., 2013, pg. 9). This is a good example of the difficulty encountered in post-hoc interpretation of findings in the field. This difficulty is partly caused by non-specific hypotheses such as "we hypothesise altered FC in limbic regions". Also, it is difficult to interpret differences in FC and how they relate to specific cognitive outcomes as the results are correlational and not causal. These are recurring themes which will be discussed more in-depth in the thesis main discussion, Chapter 7.

The results presented here suggest a complex relationship with attention and tinnitus, which is likely linked to tinnitus severity. However, there is one major potential confound not addressed in the studies on attention networks, which is that tinnitus patients participating in a tinnitus brain imaging study, are likely attending to some extent to their tinnitus or the auditory modality in general during the scan, whereas controls are far less likely to attend in that way (Sedley, 2019). Therefore, it is difficult to say if the results reflect increased attentional state in general in the tinnitus group during the experiment, or if the changes are due to the tinnitus itself.

5.6.1.4 LIMBIC SYSTEM IN TINNITUS

The limbic system is one of the evolutionarily older brain systems and is involved with emotional processing. Core regions are the (para)hippocampus, amygdala, nucleus accumbens (NAc), medial prefrontal cortex (mPFC) and ACC (Morgane et al., 2005). It is thought that the limbic system is involved with emotional reactions to tinnitus (Jastreboff and Jastreboff, 2000), and the parahippocampal gyrus (PHG) establishes the auditory memory of tinnitus and therefore prevents habituation (i.e. the process of adaptation where tinnitus becomes non-bothersome) to tinnitus (Vanneste et al., 2011c).

This review found evidence of alterations in the limbic system in chronic tinnitus patients. Chen et al. (2017a) investigated amygdala FC in normal hearing, depressed tinnitus patients compared to non-depressed tinnitus patients and compared to controls. They found decreased FC between amygdala and SFG and MFG. FC between amygdala and SFG was also decreased for non-depressed tinnitus patients compared to controls. The prefrontal cortex is engaged with emotional processing and executive functions and the authors suggested the altered connections between amygdala and prefrontal cortex may play a role in the attribution of negative emotional reactions to tinnitus.

In another study using Granger causality analysis (GCA), Chen et al. (2017b) investigated FC of limbic structures (amygdala and hippocampus) in tinnitus patients (n = 26) with normal hearing compared to controls with normal hearing (n = 23). They did not replicate the finding of decreased amygdala-prefrontal FC. Instead, they found increased FC from right MFG and left IFG to left amygdala, as well as increased FC from right amygdala to right MFG, and from left MFG and right IFG to right amygdala. The tinnitus patients in both studies had similar tinnitus severity scores (mean THQ between 50 and 60 for all groups) and similar tinnitus duration (means between 40 and 55 months), and all tinnitus sufferers had normal audiograms, so it is unclear why amygdala-prefrontal FC was increased in one group and decreased in the other.

The frontostriatal gating model discussed in section 2.2.2.2 involves limbic structures (Rauschecker et al., 2010). The theory poses that a frontostriatal network including vmPFC, NAc and ACC evaluates the relevance and emotional value of sensory stimuli and controls the flow of information through interaction with auditory thalamic regions. Xu et al. (2019) investigated the frontostriatal circuit in tinnitus patients without hearing loss (n = 50) compared with well-matched controls (n = 55). They used GCA to investigate directional connectivity with bilateral NAc. They found increased FC between NAc and regions in prefrontal cortex which was positively correlated with THQ scores ($r = 0.626$, $p < 0.001$) and with tinnitus duration ($r = 0.599$,

$p < 0.001$). Therefore, the findings showed alterations in the limbic system in tinnitus patients which were associated with tinnitus severity and duration.

When considering evidence for the frontostriatal gating model generated by resting-state fMRI research, it is important to separate the theory into two types of gating: One where the tinnitus signal is persistently permitted to pass through the thalamus to the cortex, which could explain how tinnitus occurs at all, compared to a limbic-driven system that decides moment-to-moment whether tinnitus enters conscious awareness or not. The nature of resting-state fMRI is such that any changes in the limbic systems in tinnitus patients might reflect this latter system of the tinnitus reaching conscious awareness rather than the "hard problem" of tinnitus generation itself.

5.6.1.5 Visual network in tinnitus

Changes in FC with visual regions were commonly found in the studies in this review. For example, Burton et al. (2012) placed seeds in primary visual cortex and in primary auditory cortex in tinnitus patients with hearing loss (*n* = 17) and compared to normal hearing controls (*n* = 17). They found a phase reversal in resting-state activity between the two systems characterised by negative correlations. When BOLD signal increased in one system, it decreased in the other. The authors suggest this finding could reflect inhibitory circuits between the two systems, where activation of one sensory system inhibits activation of the other, "non-relevant" sensory system. In tinnitus patients, this would mean the constant activation of the auditory modality because of the perception of a phantom sound, decreases the activation of visual regions through inhibitory circuits.

Using ICA, Maudoux et al. (2012) investigated connectivity of the auditory network in tinnitus patients with mild-to-severe hearing loss (*n* = 13) compared to age-matched but not hearing-matched controls (*n* = 15). They selected fourteen seed regions in an automated way to create the auditory component, and one finding was decreased connectivity with occipital cortex. They also found increased FC with pre- and postcentral gyrus. The authors suggested the links between the auditory system and

visual and sensory-motor network in tinnitus patients could have something to do with clinical observations of tinnitus sufferers who are able to modify their tinnitus perception using eye movements or head- and neck movements.

The studies above did not control for hearing loss, but other studies that found alterations in visual networks in tinnitus patients did. Zhang et al. (2015) found decreased FC between right thalamus and left MOG (visual association cortex), and decreased FC between left thalamus and bilateral calcarine cortex (primary visual) in normal-hearing tinnitus patients (*n* = 31) compared to matched controls (*n* = 33).

One study found decreased ALFF values in right MOG (Chen et al., 2014) which they attributed to the tinnitus salience decreasing spontaneous activity in the visual areas through auditory-visual connections. The same group replicated this result in Chen et al. (2015b) where they again found decreased ALFF values this time in bilateral MOG. No studies regarded alterations in the visual network as a cause of tinnitus; all studies saw these alterations as effects of the tinnitus.

5.6.2 Methodological challenges

The papers included in this review all demonstrated variations in methodology and study design. The most popular analysis method was seed-based whole brain FC analysis. However, the requirement of selecting a priori regions of interest in this analysis method poses problems for reproducibility of results. Only a few studies chose the exact same ROIs to investigate, and therefore the field is lacking reproducibility. Also, some studies used an “eyes open” paradigm for the resting state acquisition, whereas others used an “eyes closed” paradigm, which could explain some of the heterogeneity in findings, as the choice of paradigm was previously shown to affect visual and auditory connectivity (Agcaoglu et al., 2019).

Another concern is the heterogeneity of tinnitus groups. Tinnitus can be characterised in a lot of different ways and therefore careful selection of participants is required. Fifteen of 29 studies included only tinnitus sufferers and controls without a hearing loss visible on a standard audiogram, which makes hearing loss controlled

for as a covariate. However, a concern would be that the results of these studies are not generalisable to the tinnitus community at large, as up to 80% of tinnitus patients are estimated to have hearing loss (Henry et al., 2005, Vernon and Meikle, 2000).

Another source of variation between reports could come from fMRI data preprocessing decisions. These largely depend on the software package used. As most studies in this review used a version of SPM, preprocessing pipelines were similar. Some differences were found in the use of band-pass filtering to extract the resting-state data, where the frequencies of the filter ranged from 0.008 – 0.08 Hz to 0.01 – 0.1 Hz. This is common practice in rs-fMRI research, but concerns have been raised that limiting the data to this frequency band might lose valuable information, as RSNs such as the DMN have been identified in higher frequency bands as well (Boubela et al., 2013).

One concern is whether FC differences should be considered a cause or an effect of tinnitus, which cannot be inferred based on correlational resting-state data. It is difficult to determine what the altered FC reflects, as tinnitus involves many different cognitive components. Alterations in the visual network are usually considered an effect of the tinnitus. It is less clear how to interpret changes in the DMN and attention networks. A concern is how many of these findings are not only not a cause of tinnitus, but also not specific to tinnitus. It is likely that many of the changes in brain states observed in resting-state fMRI are common to all chronic symptomatic conditions that can cause distress and affect attentional states (e.g. chronic pain), and are therefore not specific to tinnitus.

A potential major confound in tinnitus resting-state research is attentional deployment (Sedley, 2019). The instructions for participants in an MRI scanner for the resting-state task is usually “relax and do not think of anything in particular”. However, one might expect that tinnitus patients participating in such an experiment will spend some time focussing attention on their tinnitus, whereas the controls without tinnitus have no such focussed attention.

5.6.3 Consultation stage

The final stage of the scoping review framework was to conduct a consultation to gather insight from experts in the field. Six experts were invited to read the manuscript before submission and give their opinion about the findings and potential future directions. Three questions were asked:

1. Do the findings in the scoping review overlap with the impression of the field you currently hold?
2. What do you think the future direction should be for tinnitus and brain imaging/fMRI research?
3. Are there any important points worth addressing in the review that you think we missed?

Five experts replied with their views. Their overall opinion was the findings aligned with their impression of the field. Several experts noted the problem of multiple comparisons in the resting-state fMRI literature. Seed-based functional connectivity studies often test a large number of different ROIs, and often it is unclear how correction for multiple comparisons was applied as there is no standard in the field on how to implement this. Therefore, the field likely suffers from false positives, which could explain why findings are divergent and sometimes directly opposing.

The need to focus on how this research could help patient care in the future was also pointed out. In order to move forward, tinnitus subtyping, along with controlling carefully for confounds will be necessary. Also, future studies should focus on the "hard problem" of tinnitus, which is how it is generated in the first place, rather than secondary effects of the tinnitus. The complexity here is that the tinnitus generation itself is likely a very subtle alteration, which has smaller impact on distributed brain activity than its far-reaching consequences on attention and distress, which are reflected in the significant correlations between tinnitus distress/severity scores and tinnitus duration with resting-state patterns.

5.6.4 Future directions

It would be interesting for future studies to use a longitudinal design, to address the issue of making inferences about causality by studying tinnitus at onset and across several timepoints afterwards. Ideally, participants would be scanned before the tinnitus arises, although there is an obvious practical difficulty with this. It is also difficult to find tinnitus patients with recent onset tinnitus, as by the time most people with recent onset tinnitus are seen by the health services, it is probably already too late for measuring a true "baseline" state. An alternative would be to use non-invasive brain stimulation and to use rs-fMRI before and after the intervention, provided these interventions reach a state in the future where they reliably alter the tinnitus percept.

Future research could also combine rs-fMRI with methods such as Diffusion Tensor Imaging to see whether changes in functional connectivity are reflected in white matter tracts. Van den Heuvel et al. (2009) successfully used DTI to show that RSNs reflect the underlying anatomy of white matter tracts. Future research could investigate this in tinnitus, and determine if there is a link with tinnitus duration.

Besides these novel approaches, future studies should focus on replicating previous findings by selecting the same ROIs and using the same methodology, to increase replicability of findings in the field. These studies should exclude participants with a history of neurological or psychiatric disorders, as this is known to affect functional connectivity. This review included studies that did not explicitly state whether they included or excluded these participants, but rather lists each study's exclusion criteria in supplementary table S1, which is a limitation of this review.

Future studies could also evaluate differences within the tinnitus populations, such as laterality, cause, pitch, presence of hearing loss, and duration. They could also try to control for differences in attentional deployment in the scanner between tinnitus patients and controls. A first step towards this could be to ask participants after their scan if they were able to hear their tinnitus during the scan. It is likely that some people can still hear their tinnitus in the MRI scanner and others cannot, depending

on the maskability of their tinnitus. Controlling for sound stimulation is a known limitation of fMRI studies in the field, which future studies might want to address by comparing a traditional resting-state paradigm to a task such as “try to listen to your tinnitus” in a within-subjects design. This would not give a pure insight into what brain activity constitutes tinnitus, but it could give some insight into attentional mechanisms and what happens when someone attends to their tinnitus.

Future studies should also be more hypothesis-driven to avoid post-hoc interpretations of findings. They should aim to prove or disprove established tinnitus theoretical models. Next to providing crucial insights into the neurophysiology of tinnitus, the direction of research outlined above could potentially lead to the identification of a biomarker for tinnitus. This could then be used in the development of new management strategies, or as an objective tool to track efficacy of interventions.

5.7 Conclusion

This scoping review included 29 primary research papers investigating resting-state functional connectivity in tinnitus patients. Alterations were found in widely distributed brain networks, including the auditory network, DMN, attention networks, limbic system and visual network. The results show that tinnitus is a complex condition involving multiple overlapping networks, but it is unclear which changes are primary and which are secondary to tinnitus. Future studies should focus on replicating findings and subtyping tinnitus groups, and testing a priori hypotheses and theoretical models of tinnitus. This could potentially lead to the identification of a biomarker for tinnitus and it could inform future tDCS and HD-tDCS studies.

5.8 Acknowledgements

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Chapter 6 Resting-state fMRI

6.1 Preface

6.1.1 Publication

As this was the final project of the PhD, priority was given to writing up the contents in traditional thesis format rather than publication format. As such, the style is slightly different to the previous chapters which were based on published manuscripts. A manuscript based on this chapter is currently being prepared for submission.

6.1.2 What was undertaken?

A large-scale resting-state fMRI study was undertaken including 84 participants. Testing included audiometric assessment, psychoacoustic tinnitus assessment, and a battery of questionnaires.

6.1.3 Why was it needed?

The scoping review in Chapter 5 mapped all the available evidence regarding resting-state fMRI research and tinnitus. The results showed uncertainty regarding changes in the auditory network in tinnitus patients. Some studies showed increased connectivity with auditory regions of interest, and other studies showed decreased connectivity. In Chapter 2, multiple tinnitus models were discussed that rely on the premise of hyperactivity in auditory regions to explain the tinnitus percept (section 2.2.2), or very generally the idea that tinnitus is caused by aberrant spontaneous activity in the central nervous system. This line of thought led researchers to trial tDCS as a management option for tinnitus, to alter the proposed aberrant activity. These research efforts were reviewed in Chapter 3. The site of stimulation chosen most often for the stimulation was DLPFC, but this site was not specifically mentioned in tinnitus models or brain imaging research.

The present chapter conducted a brain imaging study in tinnitus patients to investigate resting-state connectivity of the known resting-state networks (including auditory network). Additionally, resting-state functional connectivity with DLPFC in tinnitus patients compared to controls was explored for the first time, as a first effort to provide a link between tDCS and rs-fMRI research.

6.1.4 How does it contribute to the objectives of the PhD?

The findings of this study might provide a neurophysiological rationale for future tDCS studies in selecting the site of stimulation. As such, this study contributes to the overall objectives of providing insight into the use of tDCS for tinnitus and informing the direction of future research. Additionally, this study also fulfils the objective of encouraging replicability in the tinnitus field by aiming to replicate previous rs-fMRI studies.

6.2 Abstract

Tinnitus is thought to be associated with aberrant spontaneous activity in the central nervous system. Previous resting-state fMRI findings support this hypothesis and have shown a variety of alterations in brain activity in people with tinnitus compared to people without tinnitus. However, there is little replication of findings. Therefore, the current study aimed to replicate previous findings by investigating common resting-state networks, including auditory regions. Additionally, functional connectivity with DLPFC was investigated as this region is most often used as a stimulation target in tDCS and tinnitus research. The results showed that tinnitus patients (n = 46) had increased functional connectivity between bilateral thalamus and right visual association cortex compared to control participants (n = 36). No differences were found with any of the other resting-state networks, or with DLPFC seeds.

6.3 Introduction

As seen in previous chapters, the exact mechanisms behind tinnitus are unclear. Several prominent tinnitus models were discussed, including hyperactivity models. In these models, it is postulated that tinnitus is caused by excessive spontaneous activity in the auditory pathway which is interpreted as a sound (Schaette and Kempter, 2006). If tinnitus is characterised by hyperactivity in auditory areas, one would expect this hyperactivity to be detectable by brain imaging methods such as fMRI.

Indeed, numerous studies have examined brain activity at rest using rs-fMRI in people with and without tinnitus. Chapter 5 reviewed these studies and found that although there is little consistency between studies, the majority does observe alterations in functional connectivity in people with tinnitus compared to without. This distinct lack of replicability of findings is problematic and likely caused, in part, by the large range of methodological decisions that need to be made when collecting and analysing fMRI data. As such, this chapter will first discuss the basics of fMRI data collection and analysis which will help contextualise the difficulties encountered in replicating study findings.

6.3.1 MRI basics

Magnetic Resonance Imaging (MRI) is an imaging method widely used in scientific and clinical settings. It involves placing a person into a static magnetic field (B_0), usually 1.5 or 3.0 Tesla, where 1 Tesla is roughly equal to 20.000 times the strength of the earth's magnetic field. The magnetic field is created by superconducting magnet coils cooled down to almost absolute zero by (very expensive) cryogenic liquid helium. MR also uses gradient coils which superimpose a magnetic field on top of B_0 in either x-, y-, or z-direction, resulting in a change in magnetic field strength along the direction of the applied gradient field. This allows for spatial encoding of the MR signal. Furthermore, there are radiofrequency (RF) coils, which emit a RF pulse to create a change in the energy states of protons in hydrogen atoms in water (Currie et al., 2013).

Hydrogen nuclei are the most abundant nuclei in the human body (Nierhaus, 2012). They consist of a single proton with positive electrical charge which constantly spins, generating an electrical current which, in turn, generates a magnetic moment. The orientation of this magnetic moment is random, but when placed in a magnetic field, protons start to spin mostly parallel to the magnetic field. This type of spin is called precession, and its frequency of rotation is called the Larmor frequency. It is determined by the Larmor equation:

$$\omega_0 = \gamma B_0$$

The Larmor equation takes a constant *y* depending on nuclear species (in this case hydrogen), and B_0 is the strength of the magnetic field. Protons precessing in parallel to B_0 create a sum magnetisation vector M which is known as longitudinal magnetisation. To measure the magnetic field created by the protons, they need to be knocked out of synchronisation with B_0. This is achieved by emitting a RF pulse at exactly the Larmor frequency (called "resonance", hence magnetic "resonance" imaging), inducing an additional magnetic field B_1 that flips M perpendicular to B_0. This transverse magnetisation vector rotates at the Larmor frequency creating an electrical current which can be measured by a receiver coil. This is what constitutes the MR signal. Turning off the RF pulse results in the relaxation of protons back to their original state in B_0. This can be broken up into two relaxation times: T1 which is a time constant of the recovery rate of longitudinal magnetisation, and T2 which is a time constant of transverse magnetisation decay to about 37% of its initial value. The chosen type of relaxation determines the type of image (i.e. T1-weighted image or T2-weighted image). A third contrast, T2*, describes the actual rate of transversal magnetisation decay, as it takes into account the loss of spin coherence due to magnetic field inhomogeneities (Currie et al., 2013). Different types of biological tissue have different T1, T2, and T2* values, which is the source of contrast in an MR image.

6.3.2 Functional MRI

Functional Magnetic Resonance Imaging (fMRI) has been used to study the neurophysiology of tinnitus. The technique was developed in the early 1990s. PubMed was searched on 10/08/2022 with the following search term to get a global impression of the history of fMRI research into tinnitus:

> (tinnitus[Title]) AND ((fmri[Title/Abstract]) OR (functional magnetic resonance imaging[Title/Abstract]) OR (functional MRI[Title/Abstract]))

This search resulted in 160 results, the earliest dating back to 1999. Figure 6-1 shows a histogram of the number of papers published per year since 1999 according to this search.

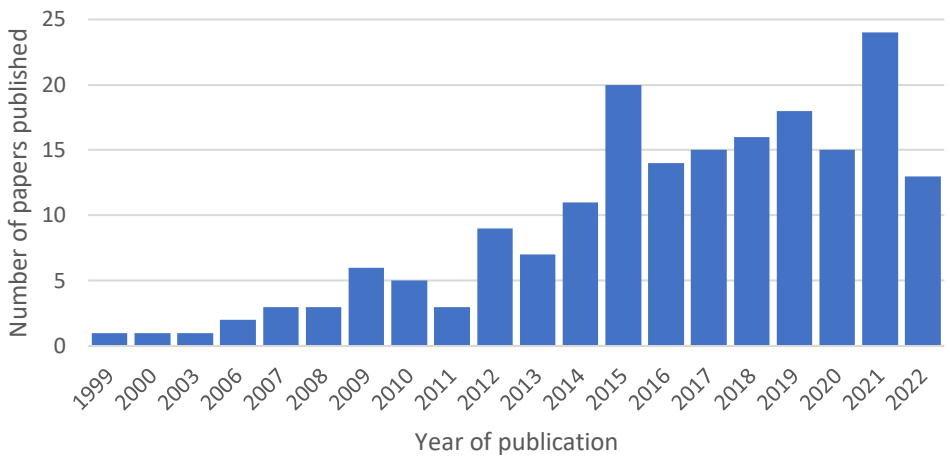

Figure 6-1 Histogram of search results for tinnitus and fMRI studies

There is a general trend for increasing publications each year. This is in line with the number of papers on fMRI in general growing each year, due to MRI's ability to safely and non-invasively measure brain activity with very good spatial resolution (Poldrack et al., 2011a).

The most common method of fMRI relies on the blood oxygen level dependent signal, or BOLD in short. This is a measure of haemoglobin oxygenation level in the blood. The technique relies on the known phenomenon of blood flow increasing to parts in the brain that are neuronally active (Friedland and Iadecola, 1991, Villringer and Dirnagl, 1995). Interestingly, more blood is sent to active regions than needed to sustain the cells' oxygen needs, resulting in a surplus in local blood oxygen. This oxygenation level is measured and referred to as the BOLD signal and was discovered by Ogawa et al. (1990).

The oxygenation level depends on the amount of oxygenated haemoglobin ([oxy-Hb]) and deoxygenated haemoglobin ([deoxy-Hb]) in the blood. The magnetic properties of the two molecules are different, [oxy-Hb] being diamagnetic, and [deoxy-Hb] being paramagnetic. Therefore, [deoxy-Hb] causes local inhomogeneities in the magnetic field, leading to a dephasing of local transversal magnetization and a reduction in T2 relaxation time. Changes in [deoxy-Hb] concentration can be measured ("the BOLD

contrast") in T2-weighted images as an indirect measure of brain activity due to the aforementioned overshoot in oxygenated blood in active regions (Nierhaus, 2012).

6.3.3 Resting-state fMRI

Resting-state fMRI (rs-fMRI) is a type of functional MRI which was discussed briefly in section 2.5.2. In rs-fMRI, participants are asked to lie still in the MRI scanner and think about nothing in particular. The participant is not engaged in any specific task during rs-fMRI. As tinnitus is always audible, and for most people predominantly interferes with their relaxation time, it has been hypothesised that it is associated with changes to resting-state activity (Eggermont, 2012). Rs-fMRI can be used to study functional networks in the brain, by measuring the temporal dependence of neural activity between regions. Biswal et al. discovered that spontaneous low-frequency oscillations of the BOLD signal were temporally correlated between regions of the motor network when a subject is at rest (Biswal et al., 1995, Biswal et al., 1997). Later work found the same results for other known networks such as the visual network and auditory network (Van den Heuvel and Hulshoff Pol, 2010). These correlations in resting-state BOLD signal between regions are thought to reflect the underlying structural connectivity of the brain (Van den Heuvel et al., 2009).

6.3.4 FMRI data preprocessing and analysis

The following paragraphs present an overview of the different steps commonly taken in the preprocessing of fMRI data. Reference is made to the studies included in the review in Chapter 5 and how the majority of these studies handled preprocessing. Readers are referred to supplementary table S1, which contains the details of fMRI data preprocessing for each study included in Chapter 5. This information formed the basis of the preprocessing pipeline chosen for the fMRI study presented in this chapter.

6.3.4.1 Distortion correction

Preprocessing of fMRI data is necessary to transform the data into a usable state for statistical analysis. Poldrack et al. (2011b) present a standard fMRI preprocessing stream, which in order includes the following steps: distortion correction, motion

correction, slice-timing correction, and spatial smoothing. GE-EPI sequences suffer from artifacts at air-tissue interfaces due to the inhomogeneity of the main magnetic field, which can somewhat be corrected for using distortion correction, either by collecting field map images or negative phase-encoded images and using these for correcting distortion.

6.3.4.2 Software packages

Preprocessing of fMRI data varies between software packages (Poldrack et al., 2011b). Almost all studies included in Chapter 5 used either Statistical Parametric Mapping (SPM) version 8 or version 12 (http://www.fil.ion.ucl.ac.uk/spm/). Alongside this, a variety of add-on toolboxes is used in tinnitus fMRI research, such as the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012) or REST toolbox (http://www.restfmri.net/).

6.3.4.3 Motion correction

All studies included in Chapter 5 applied motion correction and excluded participants if they moved their head too much in the MRI scanner (>2.0 degrees rotation or >2.0mm translation). Motion correction usually involves realignment of the images using rigid body transformations, but the number of parameters used for the realignment differed between studies.

6.3.4.4 Slice-timing correction

Slice-timing correction can be applied to correct for the systematically different times of slice acquisition due to the two-dimensional nature of most fMRI data acquisition. The MRI scanner acquires one slice at a time, either in ascending, descending or interleaved order. For event-related paradigms where timing in a task is of the essence, this mismatch between slice-timing acquisition can be a problem. However, there has been a move away from applying slice-timing correction, because when using short repetition times (≤2.0 seconds) and interleaved acquisition, analysis can withstand the slice-timing problems (Poldrack et al., 2011b). Nonetheless, the majority of studies included in the Chapter 5 review (79% or 23/29) still applied slice-timing correction to their data.

6.3.4.5 *Spatial smoothing*

Spatial smoothing is a way of blurring the functional images that removes high-frequency information. Smoothing increases the signal-to-noise ratio which results in signal gain for larger areas. This is beneficial when expecting to find activation across many voxels. Smoothing can also help eliminate some noise, and it helps to minimize the effects of spatial variability in brain anatomy between individuals (Poldrack et al., 2011b).

All the studies included in Chapter 5 used spatial smoothing by means of a Gaussian kernel. The size of the kernel is described by the full-width at half maximum (FWHM) and determines the amount of smoothing. Kernel sizes ranged from 1.5mm to 10mm at FWHM, but was most often 6mm (45% or 13/29 studies).

6.3.4.6 *Spatial normalization*

In order to compare fMRI data from different individuals, the data needs to be transformed into a standard head space. This reduces variability between individuals' brain anatomy and makes comparison more meaningful. The most commonly used templates are those from the Montreal Neurological Institute, i.e. MNI templates. The fMRI images can also be registered to the Talairach and Tournoux (1988) standard anatomical space. This brain atlas is based on anatomical landmarks and played an important part in the development of neuroimaging, but is now seen as less effective than automated registration to a template such as MNI (Poldrack et al., 2011c). Twenty-three of 29 or 79% of studies in Chapter 5 registered images to the MNI template.

6.3.4.7 *Frequency-band Selection*

For resting-state fMRI data, a final step includes filtering the timeseries data to include only the resting-state frequency band. The majority of studies included in the review in Chapter 5 applied such band-pass filtering at low frequencies to remove nuisance variables. Most often, the filter was applied over 0.01 - 0.08 Hz frequencies. Other bandwidths observed were 0.008 – 0.09 Hz, 0.008 – 0.08 Hz, 0.01 – 0.1 Hz, and 0 – 0.1 Hz.

6.3.5 Previous research

As shown in Chapter 5, 29 studies investigated resting-state networks in tinnitus patients compared to controls. A large variety of study protocols was found. The most common analysis method was seed-based functional connectivity analysis, in which the BOLD time-series of a set of a priori defined regions of interest (ROI) is correlated with all other brain voxels to find areas with significant functional connectivity. A large number of different ROIs was reported in Chapter 5, with little replication of studies. Most often, the ROIs were seeds placed in one or more of the well-known resting-state networks as discussed in section 5.2.

The results showed alterations to several resting-state networks in tinnitus patients compared to controls, including but not limited to the auditory network, default mode network (DMN), attention networks, visual network, and limbic system. Chapter 3 showed that DLPFC was the most used stimulation target for tDCS in tinnitus research. However, no studies were found in Chapter 5 that specifically investigated functional connectivity with DLPFC. Therefore, the present study aimed to collect rs-fMRI data from a large number of participants and run seed-based functional connectivity analysis with the most popular resting-state network seeds. Additionally, DLPFC was used as a seed, in an effort to provide neurophysiological support for the use of this region as a target for tDCS research.

6.3.6 Hypotheses

The first hypothesis was to find altered (i.e. either increased or decreased) functional connectivity between thalamus and primary auditory cortex (PAC)/Heschl's gyrus in the tinnitus group compared to the control group, as well as altered functional connectivity between PAC and secondary auditory cortices. Based on the assumption of hyperactivity in auditory regions, one might predict increased auditory connectivity, rather than decreased connectivity, as was observed in Berlot et al. (2020). However, it could also be argued that decreased connectivity reflects the absence of gating activity. Moreover, as shown in Chapter 5, studies have found both increased and decreased FC with auditory regions in tinnitus patients. Therefore, at

this point it is not possible to predict whether any altered FC will be increased or decreased.

Additionally, the second hypothesis was to find alterations to other resting-state networks such as the dorsal attention network and default mode network, based on findings in Chapter 5. Finally, no a priori hypothesis was held regarding DLPFC functional connectivity as this region has not been used as a seed in previous research.

6.4 Methods

6.4.1 Participants

The study was approved by the Research Ethics Committee of University College London, study ID: 17601/001. All participants gave written informed consent.

Participants with tinnitus were recruited through two charities, the British Tinnitus Association and Tinnitus Hub. Recruitment flyers were sent out through their social media and newsletters. Control participants were recruited by asking the tinnitus participants to bring a partner/friend/colleague with them to their appointment, where possible. Control participants were also recruited through the UCL psychology volunteer's portal, and through referrals from colleagues.

Exclusion criteria for all participants were: non-chronic tinnitus (< 6 months' duration), pulsatile tinnitus, hyperacusis, claustrophobia, deafness in one or both ears, profound hearing loss, Meniere's disease, epilepsy, severe smoking/alcoholism/drug abuse, history of brain surgery or trauma (e.g. stroke), dementia or other neurogenerative disease, neurological or psychiatric conditions (e.g. bipolar disorder, schizophrenia, autism, ADHD), diagnosed major depression or anxiety, systemic disease (e.g. diabetes), brain or auditory tumours, history of heart surgery, head surgery or any metal implants (e.g. pacemakers, aneurysm clips), cochlear implants, history of spinal surgery, any metal in the body as a result of an accident, any injury to the eyes with a metallic object, permanent make-up, irremovable piercings, and pregnancy. Control participants should not have

experienced frequent or chronic tinnitus, but occasional experience for short periods (e.g. after a concert) was acceptable.

6.4.2 Questionnaire assessments

All participants completed the following questionnaire assessments on a laptop: Zung Self-Rating Depression Scale (SDS) (Zung, 1965), Zung Self-Rating Anxiety Scale (SAS) (Zung, 1971), and the Hyperacusis Questionnaire (HQ) (Khalfa et al., 2002). Tinnitus participants also completed the Tinnitus Handicap Inventory (THI) (McCombe et al., 2001) and the Tinnitus Functional Index (TFI) (Meikle et al., 2012a). Total scores for each questionnaire were calculated in Microsoft Excel.

6.4.3 Hearing assessment and tinnitus psychoacoustic measures

6.4.3.1 Pure tone audiometry

Pure tone audiometry was performed to record air conduction thresholds following BSA guidelines (British Society of Audiology, 2018) (https://www.thebsa.org.uk/resources/pure-tone-air-bone-conduction-threshold-audiometry-without-masking/), with the addition of 6000 Hz and 12000 Hz probes. Participants were asked if they thought they had a better hearing ear. If so, testing started in the better ear. The order of testing was 1000 – 2000 – 4000 – 6000 – 8000 – 12000 – 500 – 250 – 1000 Hz in both ears. If there was more than a 5 dB difference between the first test of 1000 Hz and its repeat, this difference was investigated and the participant reinstructed if necessary.

6.4.3.2 Uncomfortable loudness levels

Uncomfortable loudness levels (ULLs) were also tested following BSA guidelines. ULLs were tested in both ears separately, at 500 Hz and 4000 Hz, using a pure tone stimulus. The standard protocol dictates starting with presentation at 60 dB. However, due to tinnitus sufferers potentially being more sensitive, as tinnitus often co-occurs with hyperacusis, presentation was started at 40 dB. Stimuli were increased in loudness in 5 dB steps for 1 second, until the participant raised their hand to indicate discomfort. Extra care was taken at 100 dB, and 100 dB was never exceeded, and, if the participant did not report discomfort a ULL of >100 was noted.

6.4.3.3 TINNITUS PITCH MATCHING

Psychoacoustic measures were conducted for the tinnitus group only, and included tinnitus pitch matching, tinnitus loudness matching, and minimum masking levels (MMLs). Procedures for all three measures were based on Shekhawat et al. (2014b). The pitch-matching procedure was conducted using a two-alternative forced-choice task. Pure tones were presented at a loudness of 10 dB in the ear without tinnitus or with less loud tinnitus. If the participant had bilateral tinnitus equal in both ears, pure tones were presented in the better hearing ear. Participants were asked to compare two sounds to their tinnitus and indicate whether the first or second sound was closest to their tinnitus. They were informed the match did not have to be exact, but to select the best match.

First, two tones were presented consecutively for two seconds each, at 1000 Hz and 4000 Hz. The participant was asked to indicate which of the two tones sounded most like their tinnitus. If the lower bound was chosen, the next duo of tones presented was the lower bound (1000 Hz) and half its frequency (500 Hz). If the higher bound was chosen, the next duo was the higher bound (4000 Hz) and double its frequency (8000 Hz). If the lower bound was chosen again, presentation went lower again: 500 Hz vs. 250 Hz. If the higher bound was chosen, presentation went in between: 500 Hz and 750 Hz. Eventually, the forced-choice task settles on one frequency of best match. At that point, two final duos were presented to check for octave confusion, by presenting the chosen pitch along with one octave above it, and along with one octave below it. If octave confusion occurred, the procedure was started over. Order of presentation (e.g. 1000 > 4000 or 4000 > 1000) was randomly chosen by the experimenter.

6.4.3.4 TINNITUS LOUDNESS MATCHING

To determine the loudness of tinnitus, using the best match tone we established previously, participants were asked to listen to the sound as it slowly increased in loudness, and raise their hand when the tone became as loud as their tinnitus. First,

the air conduction threshold at the best match pitch was re-established using 2 dB increments instead of 5. Then, the tone was presented below the threshold and increased in 2 dB increments until the participant raised their hand. The procedure was repeated twice and the average of the three measurements was recorded as the absolute loudness match. The loudness match in sensation level was calculated by subtracting the precise (2 dB increment) hearing threshold from the absolute loudness match.

6.4.3.5 Minimum masking levels

For minimum masking level (MML) testing, participants were instructed they were going to hear a hissing sound, which would become gradually louder. They were asked to indicate when the hissing sound became loud enough that they could no longer hear their tinnitus. Narrow-band noise was used at the established tinnitus pitch for the procedure. First, the air conduction threshold was measured in the ear(s) with tinnitus using narrow-band noise at tinnitus pitch in 2 dB increments. Then, the narrow-band noise was presented in the ear with tinnitus or in both ears at the same time for bilateral tinnitus/tinnitus in the head. Its loudness was increased in 5 dB increments until the participant reported their tinnitus was no longer audible, or until the loudness caused discomfort. The procedure was repeated twice and the average of the three measurements was recorded as the absolute MML. The MML in sensation level was calculated by subtracting the precise hearing threshold from the absolute MML.

6.4.4 MRI data acquisition

Scanning was conducted on a 3T Siemens Magnetom Prisma scanner with a 64-channel head coil at the Great Ormond Street Hospital in London, United Kingdom. MRI acquisition consisted of a T1-weighted MPRAGE anatomical image (duration = 5 minutes, 21 seconds) with a voxel size of 1.0 x 1.0 x 1.0 mm. Other scanning parameters were repetition time (TR) = 2300 ms, echo time (TE) = 2.74 ms, inversion time (TI) = 909 ms, flip angle = 8 degrees, in-plane matrix resolution = 256 x 256 mm, field of view = 256 x 256 mm, GRAPPA acceleration factor = 2.

This was followed by an interleaved resting-state fMRI acquisition (duration = 6 minutes, 18 seconds) using a T2*-weighted echo-planar pulse imaging (EPI) sequence with a voxel size of 2.5 x 2.5 x 2.5 mm. Other scanning parameters were TR = 1240 ms, TE = 26 ms, flip angle = 75 degrees, 40 slices of 2.5 mm thick, in-plane matrix resolution = 80 x 80 mm, field-of-view = 200 x 200 mm, 300 volumes, and a multi-band acceleration factor = 2.

During the resting-state sequence, participants were instructed to look at a cross on the screen (white cross on a black background), stay awake, relax, and think of nothing in particular. During the T1-weighted participants had the option of watching or listening to anything they liked online.

6.4.5 MRI data preprocessing

DICOM images were converted to NifTi format using MRtrix3 (https://www.mrtrix.org/). NEGPE images were collected as part of the MRI sequence, resulting in pairs of images with distortions in opposite directions. We applied FSL (Jenkinson et al., 2012) "topup" to the images to estimate the susceptibility-induced off-resonance field, and to combine the two images into a single corrected image (Andersson et al., 2003b, Smith et al., 2004). The raw images and new, corrected image were inspected side by side in FSLeyes (McCarthy, 2022). Dummy removal included removing the first four volumes of the resting-state acquisition.

Next, the data was preprocessed in SPM12 software (Statistical Parametric Mapping) (Friston et al., 2007) in the following order: motion correction through realignment of the functional images to a single reference image (the middle image was chosen as the reference image following recommendation in Poldrack et al. (2011b)); coregistration of the structural image with the mean functional image; normalisation to MNI-152 standard space; and spatial smoothing with a Gaussian kernel of FWHM = 6 mm^3. Normalisation was achieved by warping the individual anatomical and functional images into standard space using the DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) toolbox in SPM (Ashburner, 2007).

This required first segmenting the structural images to extract grey matter, white matter and cerebrospinal fluid images, and saving the DARTEL compatible native tissue images for each participant. All resulting warped images were inspected along with the MNI-152 template image to verify the accuracy of spatial normalisation. Participants with more than 2.0 mm or 2.0 degrees displacements in the functional scans were excluded from analysis.

Next, the scans were imported to CONN software (RRID:SCR_009550) (Whitfield-Gabrieli and Nieto-Castanon, 2012). The functional data were de-noised in individual time series in MNI space. Eroded white matter and cerebrospinal fluid masks were used to regress out physiological noise from white matter and cerebrospinal fluid using CompCor (Behzadi et al., 2007), to ensure full perseveration of grey matter signal. The Artefact Rejection Toolbox (ART) in CONN was used to detect functional outliers for scrubbing. Then, linear regression of the following confounds was applied: motion (12 realignment parameters based on SPM12 preprocessing), physiological (comprising 5 WM and 5 CSF parameters), and scrubbing (for removal of outlier volumes identified with ART (range = 0 – 50 volumes).

The results of de-noising were inspected in CONN for each participant. Before de-noising, a histogram of the distribution of voxel-to-voxel connectivity values was skewed to the right and varied between participants. After de-noising, all histograms were centred around zero, with reduced inter-subject variability, indicating de-noising results were in line with expectation.

Finally, linear de-trending and a band-pass filter of 0.008 to 0.09 Hz (CONN default) was applied to the time series, to select the resting-state frequency band. The remaining fMRI signal was used for whole-brain seed-to-voxel functional connectivity analysis in CONN.

6.4.6 Seed definition for functional connectivity analysis

To investigate resting-state networks (RSN) in tinnitus, the representative seeds for each RSN loaded into CONN were selected. These seeds are based on the FSL

Harvard-Oxford atlas, and they included the following: DMN (*n* = 4 seeds), sensorimotor network (*n* = 3 seeds), visual network (*n* = 4 seeds), salience network (*n* = 7 seeds), DAN (*n* = 4 seeds), frontoparietal network (*n* = 4 seeds), and language network (*n* = 4 seeds).

To investigate auditory connectivity in tinnitus, four seeds were defined along the auditory pathway, based on the Harvard-Oxford atlas: left thalamus, right thalamus, left Heschl's Gyrus and right Heschl's Gyrus. To investigate DLPFC connectivity in tinnitus, the left and right DLPFC seeds from the CONN frontoparietal network were used. See Table 6-1 for detailed information on all seeds used in the analysis.

Resting-state network	***Seed***	***MNI Coordinates***
Auditory network	**Left thalamus**	-9, -17, 6
	Right thalamus	10, -19, 6
	Left primary auditory cortex	-52, -19, 7
	Right primary auditory cortex	50, -21, 7
Default mode network	mPFC (anterior node)	1, 55, -3
	Left angular gyrus	-39, -77, 33
	Right angular gyrus	47, -67, 29
	PCC-precuneus (posterior node)	1, -61, 38
Sensorimotor network	Left premotor/supplementary motor area	-55, -12, 29
	Right premotor/supplementary motor area	56, -10, 29
	Primary motor area	0, -31, 67
Visual network	Primary visual area	2, -79, 12
	Secondary visual area	0, -93, -4
	Left visual association cortex	-37, -79, 10
	Right visual association cortex	38, -72, 13
Salience network	ACC	0, 22, 35
	Left anterior insula	-44, 13, 1
	Right anterior insula	47, 14, 0
	Left anterior PFC	-32, 45, 27
	Right anterior PFC	32, 46, 27
	Left supramarginal gyrus	-60, -39, 31
	Right supramarginal gyrus	62, -35, 32
Dorsal attention network	Left FEF	-27, -9, 64
	Right FEF	30, -6, 64
	Left IPS	-39, -43, 52
	Right IPS	39, -42, 54

Frontoparietal network	**Left dlPFC**	-43, 33, 28
	Right dlPFC	41, 38, 30
	Left posterior parietal cortex	-46, -58, 49
	Right posterior parietal cortex	52, -52, 45
Language network	Left IFG	-51, 26, 2
	Right IFG	54, 28, 1
	Left pSTG	-57, -47, 15
	Right pSTG	59, -42, 13

Table 6-1 Seed definition for functional connectivity analysis. mPFC = medial prefrontal cortex; PCC = posterior cingulate cortex; ACC = anterior cingulate cortex; PFC = prefrontal cortex; FEF = frontal eye field; IPS = intraparietal sulcus; dlPFC = dorsolateral prefrontal cortex; IFG = inferior frontal gyrus; pSTG = posterior superior temporal gyrus. Seeds in bold were investigated separately; the other seeds were combined in a network analysis (see 6.4.7.2) to reduce the number of individual analyses run.

6.4.7 Statistical analysis of seed-based functional connectivity

6.4.7.1 Within-group analysis

For all participants and seeds of interest, a seed-to-voxel connectivity map was calculated in CONN. The resulting connectivity maps were visually inspected. Within-group analysis of auditory connectivity consisted of a one-sample t-test, while regressing for hearing loss as a covariate of no interest, for each of the four auditory seeds to find areas with significant functional connectivity to these seeds. A p-FDR corrected cluster threshold of $p < 0.05$ was used and a p-uncorrected voxel threshold of $p < 0.001$, which is the recommended default setting in CONN.

6.4.7.2 Between-group analysis

To compare auditory and DLPFC connectivity between the tinnitus and control group, whilst including hearing loss as a covariate of no interest, differential connectivity was calculated using a one-way ANCOVA with the contrasts [1 -1 0] and [-1 1 0], for increased connectivity in tinnitus vs. control participants and decreased connectivity in tinnitus vs. control participants, respectively. A two-sample t-test was also run with the contrasts [1 -1] and [-1 1] to investigate auditory FC without controlling for hearing loss. Analyses were run for each seed in bold separately as indicated in Table 6-1.

For the networks analysis, a single analysis was run per network by selecting all the seeds in the network to investigate regions functionally connected to any of the seeds (i.e. between-sources contrast has an "OR" structure, for example [0 1; 1 0]). The between-subjects contrasts used were [1 -1 0] and [-1 1 0] (with hearing loss as a covariate) and [1 -1] and [-1 1] (without hearing loss as a covariate), as in the auditory connectivity analysis. A p-FDR corrected cluster threshold of $p < 0.05$ was used in all analyses as well as a p-uncorrected voxel threshold of $p < 0.001$, which is the recommended default setting in CONN.

6.4.7.3 Correlation analysis

To investigate any potential relationship between functional connectivity and clinical characteristics of tinnitus patients, the mean z-values for each tinnitus participant were extracted for regions showing significant differences between the tinnitus and the control group. These z-values were exported to SPSS 27.0 for Pearson correlation analysis with the following clinical characteristics: tinnitus duration (in months), THI score, TFI score, HQ score, SDS score, SAS score, tinnitus loudness match in absolute and sensation level, and mean hearing threshold for both ears combined. Partial correlations were calculated with age and years of education as controlling variables. Bonferroni correction was applied to correct for multiple comparisons in the correlation analysis.

6.5 Results

6.5.1 Participants' characteristics

6.5.1.1 Demographics

A total of 84 participants was recruited (48 tinnitus participants and 36 control participants). Two participants from the tinnitus group (both male) were excluded because they exceeded the motion thresholds in their MRI scan. As such, the final control group consisted of 36 participants (19 female) and the final tinnitus group of 46 participants (19 female). Table 6-2 shows the participant demographics. Age was not significantly different between groups: Control (mean = 52.11, SD = 15.16); Tinnitus (mean = 51.72, SD = 11.62), ($t = 0.133$, $p = 0.894$). There were more males in the tinnitus group than in the control group, but this difference was not significant

according to a chi-square test ($\chi 2$ = 1.069, p = 0.301). There was no significant difference in the average years of education between the control and tinnitus groups (16.89 and 17.28 respectively, t = -0.548, p = 0.585).

Group	*Statistics*	*Age*	*Years of education*	*Sex*
Control	Mean	52.11	16.89	17 male/19 female
n = 36	SD	15.16	3.55	-
	Min	23	6	-
	Max	83	25	-
Tinnitus	Mean	51.72	17.28	27 male/19 female
n = 46	SD	11.62	2.95	-
	Min	24	12	-
	Max	72	27	-
Difference	t-/ χ2 statistic	0.133	-0.548	1.069
	sig (2-tailed)	0.894	0.585	0.301

Table 6-2 Demographics of participants. T-statistics are from independent samples t-tests with equality of variance assumed (Levene's test: all p's > 0.05).

6.5.1.2 TINNITUS CHARACTERISTICS

Tinnitus participants had tinnitus for an average of 8.7 years (SD = 10.22 years). The minimum duration was 8 months and the maximum duration was 46 years. The median tinnitus duration was 3.75 years. Participants reported a variety of tinnitus sounds: ringing (n = 25), hissing (n = 25), whistling (n = 13), buzzing (n = 8), static noise (n = 7), humming (n = 4), chirping (n = 1), ocean waves (n = 1). Thirty-nine participants reported their tinnitus is constant throughout the day, and seven reported it fluctuates. Tinnitus laterality was reported in both ears (n = 30), centre of the head (n = 8), left ear (n = 3), right ear (n = 3), and back of the head (n = 2).

Tinnitus pitch matching showed most participants matched their tinnitus to a high-frequency sound. Table 6-3 shows the results of tinnitus pitch matching. Eighty percent of the participants matched their tinnitus pitch to 4000 Hz or higher. Interestingly, 4000 Hz is also where the average hearing thresholds start to drop below the normal hearing range in the tinnitus group (see Figure 6-2). Loudness matching showed the mean absolute tinnitus loudness was 40.48 dB (SD = 20.03) and

the mean tinnitus loudness in sensation level was 10.5 dB (SD = 7.85). The mean absolute minimum masking level was 47.26 dB (SD = 17.9) and the mean minimum masking level in sensation level was 29.46 dB (SD = 16.64) (see Table 6-4).

Pitch match	*Frequency*	*Percentage of total*
250	1	2.2%
500	1	2.2%
750	1	2.2%
1000	2	4.3%
2000	3	6.5%
3000	1	2.2%
4000	7	15.2%
6000	10	21.7%
8000	7	15.2%
12000	13	28.3%

Table 6-3 Tinnitus pitch matching

Statistic	*Loudness match*	*Loudness match SL*	*MML*	*MML SL*
Mean	40.48	10.5	47.26	29.46
SD	20.03	7.85	17.9	16.64
Min	1	1	10	3
Max	96	33	82	78

Table 6-4 Loudness matching and MML in decibels. MML = minimum masking level; SL = sensation level.

6.5.1.3 HEARING STATUS

Table 6-5 shows the mean pure tone audiometry thresholds for both groups. Figures 6-2 and 6-3 show the average audiograms of both groups. Figure 6-4 shows the difference between the groups for both ears combined.

Group	*Ear*	*Statistics*	*250 Hz*	*500 Hz*	*1000 Hz*	*2000 Hz*	*4000 Hz*	*6000 Hz*	*8000 Hz*	*12000 Hz*
Control	Left	Mean	10.14	8.75	8.19	11.94	13.61	20.42	24.31	60.42
n = 36		SD	11.24	12.03	11.22	13.05	16.42	19.91	27.86	27.34
	Right	Mean	10	7.92	7.78	11.81	14.03	17.64	27.08	61.11
		SD	10.21	10.78	10.17	10.83	17.92	21.1	26.09	27.88
Tinnitus	Left	Mean	11.85	10.11	10.43	16.96	26.63	31.63	36.96	69.24
n = 46		SD	9.96	10.67	9.94	14.2	16.83	20.11	21.33	27.06
	Right	Mean	9.89	8.91	9.89	17.07	23.91	27.28	34.02	68.91
		SD	8.6	10.11	10.14	14.05	17.87	21.54	23.59	28.34
	Left	t-statistic	-0.728	-0.541	-0.957	-1.643	-3.514	-2.517	-2.33	-1.458
	Right		0.052	-0.43	-0.935	-1.855	-2.474	-2.03	-1.262	-1.246
	Left	sig (2-tailed)	0.468	0.59	0.341	0.104	0.000731**	0.014*	0.022*	0.149
	Right		0.958	0.668	0.352	0.067	0.015*	0.046*	0.211	0.216

Table 6-5 Pure tone audiometry thresholds. * = p < 0.05; ** = p < 0.001. Equal variances assumed (Levene's test all *p*'s > 0.05).

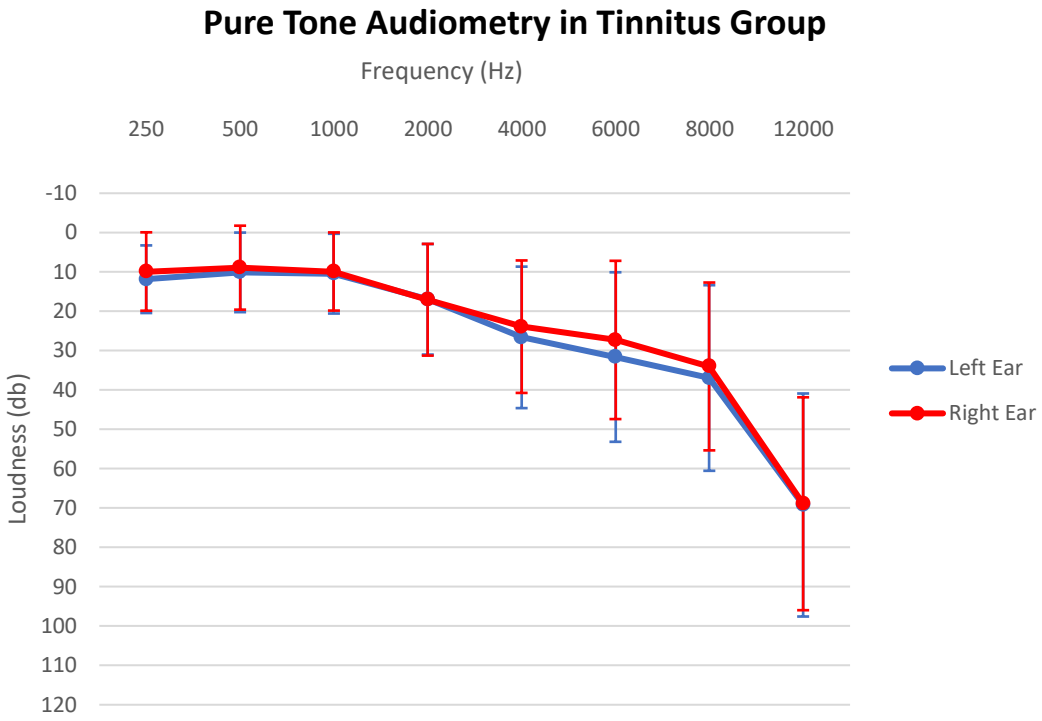

Figure 6-2 Average pure tone thresholds in tinnitus group. Error bars represent ±1 SD.

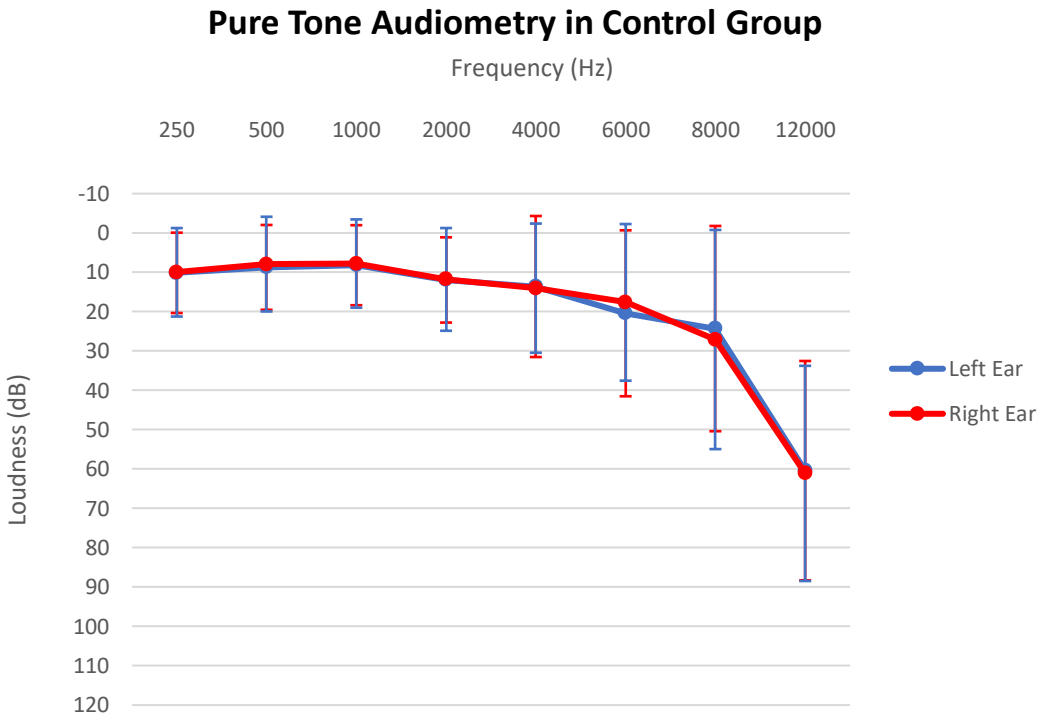

Figure 6-3 Average pure tone thresholds in control group. Error bars represent ±1 SD.

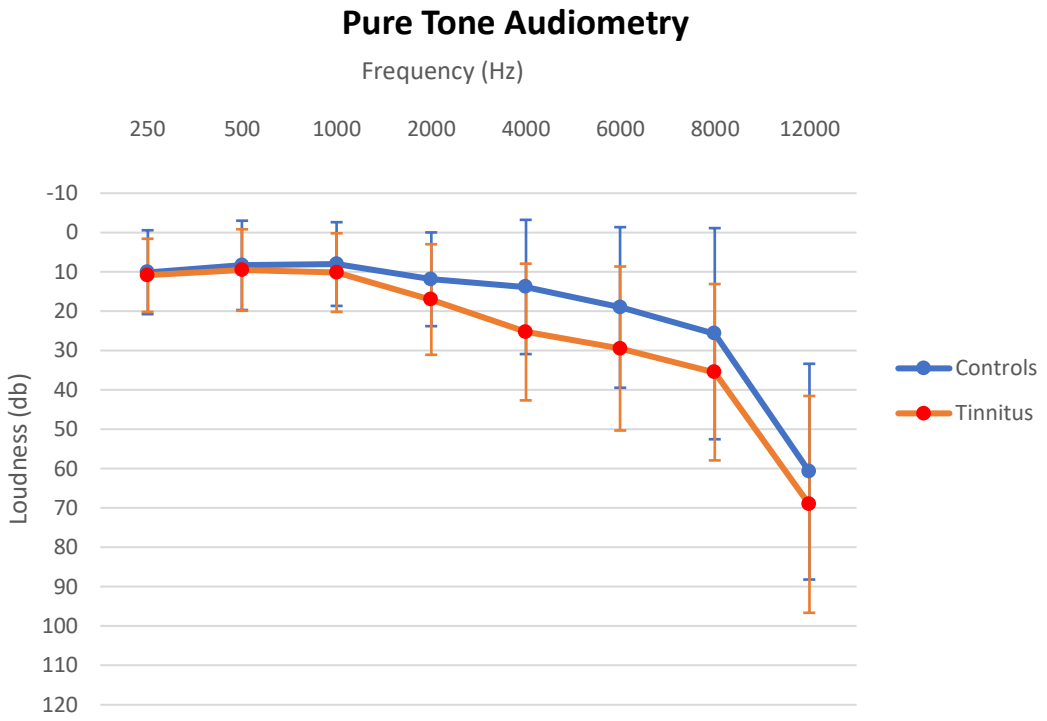

Figure 6-4 Average pure tone thresholds of both ears combined, comparing tinnitus and control groups. Difference between groups is significant for 4000 (L+R), 6000 (L+R), and 8000 (L) Hz (see Table 6-1). Error bars represent ± 1 SD.

There was no difference in mean hearing thresholds between the groups at 250, 500, 1000, 2000, and 12000 Hz. At 4000, 6000, and 8000 Hz, the tinnitus group had significantly higher pure tone thresholds on average than the control group (see Table 6-5). However, the difference was small; around 10 dB on average.

Disregarding the 12000 Hz thresholds (standard clinical practice for hearing loss diagnosis tests up to 8000 Hz), for 14 control participants (39%) all hearing thresholds were under 25 dB, indicating normal hearing at all frequencies. Only 2 participants with tinnitus (4%) had normal hearing at all frequencies. The average hearing threshold (disregarding 12000 Hz) was under 25 dB for 32 control participants (89%) and for 36 tinnitus participants (78%). Interestingly, only 16 participants with tinnitus (35%) reported having a diagnosed hearing loss prior to testing, whereas in 44 participants with tinnitus some degree of hearing loss was present in their audiograms. Hearing loss in both groups followed the pattern of age-related, high-frequency hearing loss, which was mild-to-moderate in most participants. As to be

expected, average pure tone thresholds correlated strongly to age in both groups, see Figure 6-5 and Figure 6-6. In the tinnitus group, the Pearson correlation coefficient was 0.766 ($p < 0.001$), and in the control group, it was 0.729 ($p < 0.001$), indicating strong correlations.

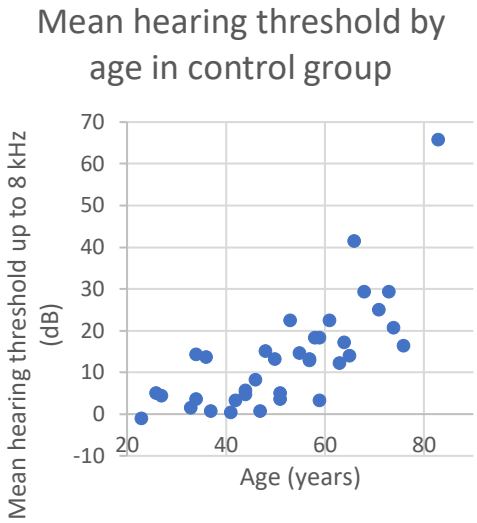

Figure 6-5 Mean hearing threshold displayed by age in the control group.

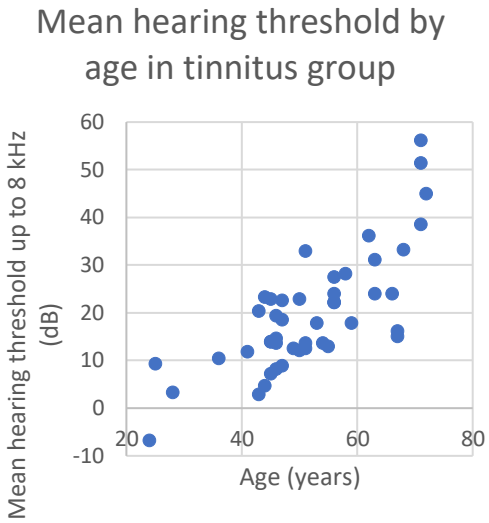

Figure 6-6 Mean hearing threshold displayed by age in the tinnitus group.

Mean uncomfortable loudness levels did not significantly differ between the two groups. The tinnitus group showed ULL averages of 86.04 dB (SD = 10.90) and 86.15 dB (SD = 13.12) on low- and high-frequency stimuli, respectively. The control group showed averages of 86.94 dB (SD = 11.38) and 85.00 dB (SD = 12.58).

6.5.1.4 QUESTIONNAIRES

Table 6-6 shows the results of the questionnaire measures taken for both groups. The tinnitus group had a significantly higher mean SAS and HQ score than the control group (p = 0.027 and p = 0.01, respectively). However, the mean difference in SAS was only 3.11 points on an 80-point scale and both mean scores are within the normal range. Similarly for the HQ, the mean difference was 3.6 points on a 42-point scale and both mean scores were within normal range (0 – 28) (Baguley, 2007). There was no difference in SDS score.

The tinnitus group's tinnitus severity was mild-to-moderate on average. More detail on TFI and THI scores is presented in Figures 6-7 and 6-8 respectively.

Group	*Statistics*	*SDS*	*SAS*	*HQ*	*THI*	*TFI*
Control	Mean	32.33	27.69	8.44	-	-
n = 36	SD	7.13	5.21	5.36	-	-
	Min	20	20	0	-	-
	Max	45	39	20	-	-
Tinnitus	Mean	34	30.8	12.04	30.65	35.73
n = 46	SD	8.56	6.85	6.6	19.59	22.77
	Min	21	20	3	0	2.8
	Max	57	53	30	80	81.2
Difference	t-statistic	-0.94	-2.26	-2.66	-	-
	sig (2-tailed)	0.35	0.027*	0.01*	-	-

Table 6-6 Descriptive statistics for questionnaire measures. * = $p < 0.05$. SDS = Zung Self-Rating Depression Scale; SAS = Zung Self-Rating Anxiety Scale; HQ = Hyperacusis Questionnaire; THI = Tinnitus Handicap Inventory; TFI = Tinnitus Functional Index.

Figure 6-7 Frequency distribution of TFI scores. TFI = tinnitus functional index. Grades: 1 = not a problem (0 – 17); 2 = small problem (18 – 31); 3 = moderate problem (32 – 53); 4 = big problem (54 – 72); 5 = very big problem (73 – 100).

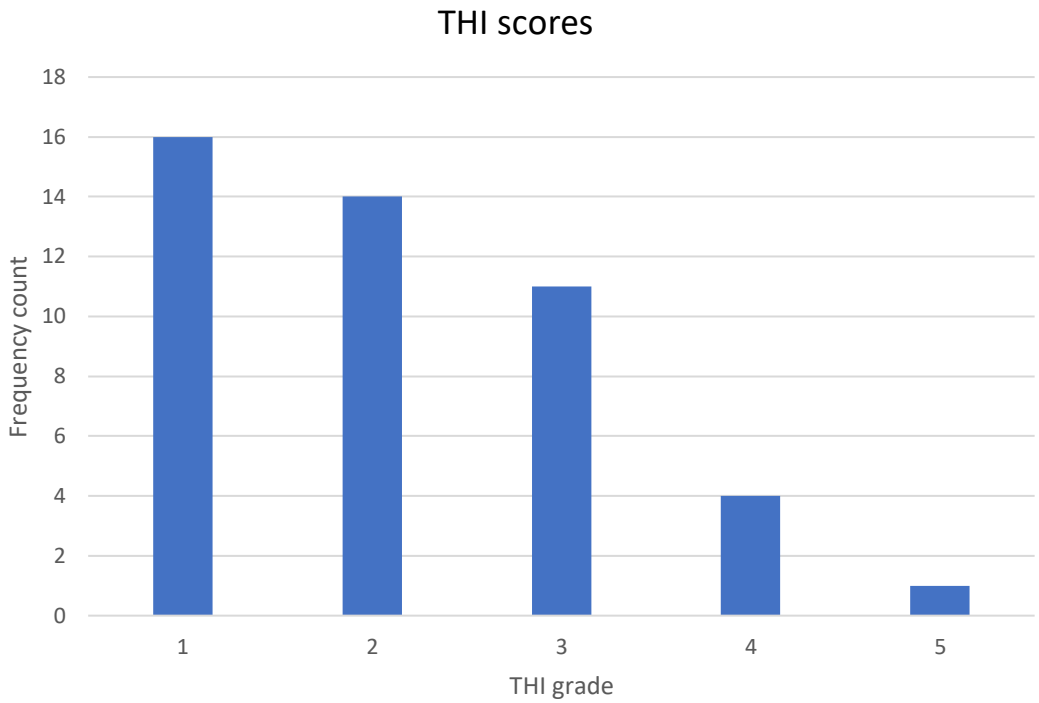

Figure 6-8 Frequency distribution of THI scores. THI = tinnitus handicap inventory. Grades: 1 = slight (0 – 16); 2 = mild (18 – 36); 3 = moderate (38 – 56); 4 = severe (58 – 76); 5 = catastrophic (78 – 100).

6.5.2 Functional connectivity results

6.5.2.1 WITHIN-GROUP ANALYSIS

The results of the within-group analysis using bilateral Heschl's gyrus and bilateral thalamus are depicted in Figure 6-9 and Figure 6-10A, respectively. In both groups, within-group analysis with Heschl's gyri showed widespread bilateral functional connectivity with auditory regions, pre- and postcentral gyrus, cingulate gyrus, precuneus, and insular cortex, amongst others. For thalamus seeds, both groups showed widespread bilateral functional connectivity with precuneus, cingulate gyrus, pre- and post-central gyrus, paracingulate gyrus, and insular cortex, amongst others.

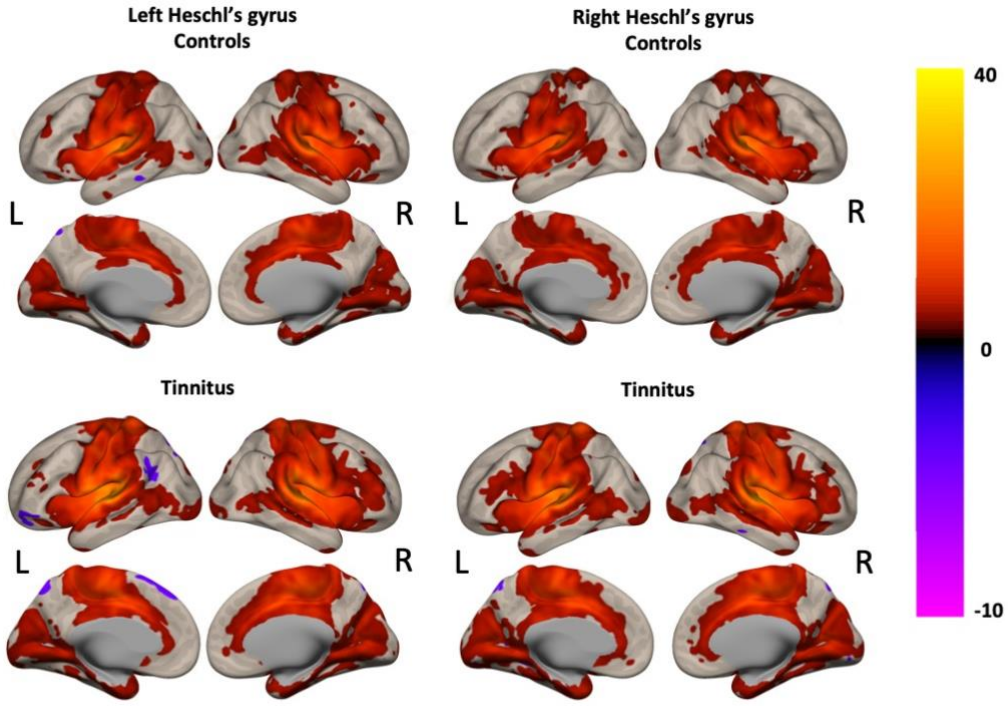

Figure 6-9 Within-group functional connectivity analysis using left Heschl's gyrus and right Heschl's gyrus as seeds for the control group (top) and tinnitus group (bottom). L = left hemisphere view, R = right hemisphere view.

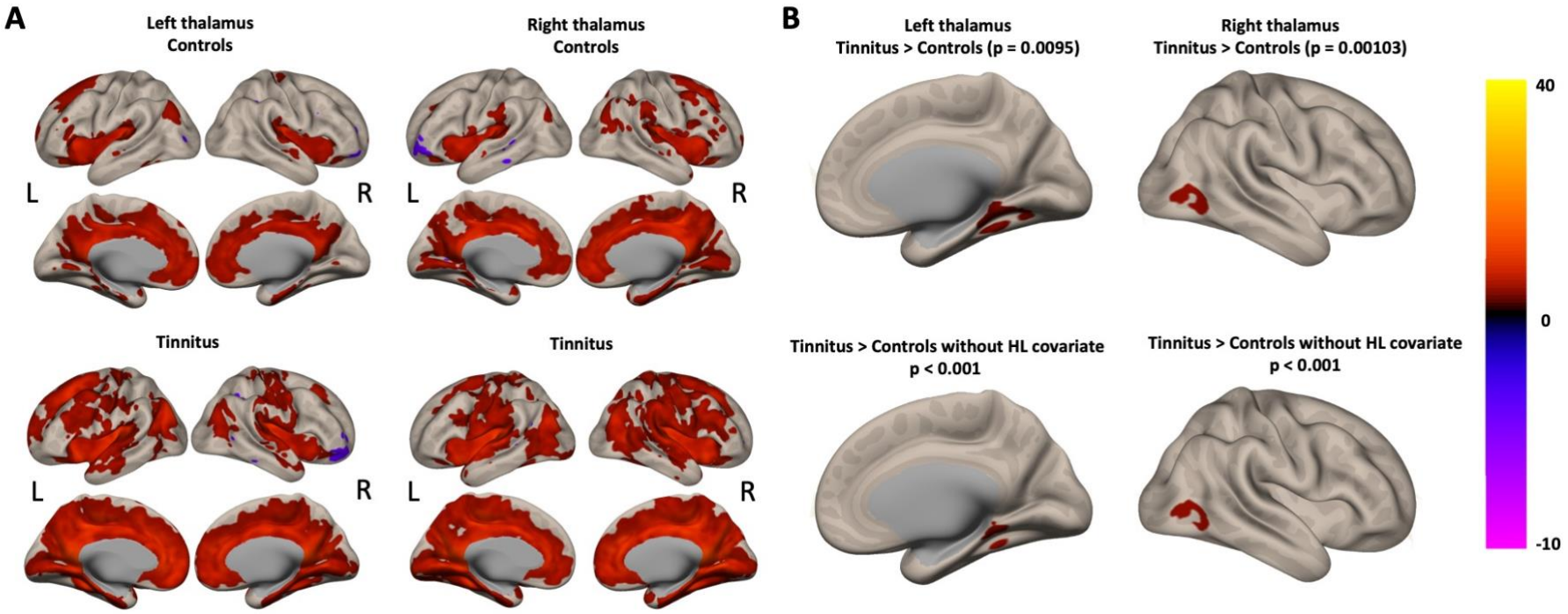

Figure 6-10 **A:** Within-group functional connectivity analysis using left thalamus and right thalamus as seeds for control group (top) and tinnitus group (bottom). **B:** Between-group analysis comparing tinnitus and control group using left and right thalamus as seeds with controlling for hearing loss (top) and without controlling for hearing loss (bottom). L = left hemisphere view, R = right hemisphere view. The p-value refers to the p-uncorrected voxel threshold used in the statistical analysis.

6.5.2.2 BETWEEN-GROUP ANALYSIS

The differential FC analysis between the tinnitus and the control groups (Tinnitus > Control) found increased FC with left thalamus and right thalamus. Figure 6-10B and Table 6-7 show this result. When hearing loss was not included as a covariate in the analysis, left thalamus showed significantly increased FC with a cluster in right visual association cortex in the tinnitus group in comparison to the control group. Similarly, right thalamus also showed significantly increased FC with a cluster in right visual association cortex in the tinnitus group compared to the control group.

Seed	***Brain regions***	***BA***	***MNI coordinates cluster peak***	***t-value, p-value***	***Extent***
Left thalamus (-9, -17, 6)	Right visual association cortex	19	+18, -46, -10	t = 4.06, p < 0.001	137 voxels
Right thalamus (10, -19, 6)	Right visual association cortex	19	+58, -68, +06	t = 3.76, p < 0.001	154 voxels

Table 6-7 Results from Tinnitus > Controls (contrast: [1 -1]) functional connectivity analysis with left thalamus and right thalamus as seeds in tinnitus patients compared to controls without hearing loss as a covariate.

When hearing loss was included as a covariate, these significant clusters did not survive the p-uncorrected threshold of $p < 0.001$. However, the result could be recovered by making the threshold more lenient (also see Figure 6-10B): $p < 0.0095$ for left thalamus seed, and $p < 0.00103$ for right thalamus seed. This could mean the difference in thalamic FC with right visual association cortex in tinnitus patients compared to controls is related at least partly to the tinnitus patients' having higher

hearing thresholds. However, the result is still borderline significant after controlling for hearing loss, suggesting the difference is at least in part driven by the Tinnitus vs. Control contrast.

No differences in FC were found between the groups using bilateral Heschl's gyrus or bilateral DLPFC as seeds, or using any of the combined network seeds as shown in Table 6-1, whether hearing loss was included as a covariate or not. Also, no decreased connectivity was found in the tinnitus group using the [-1 1] (Control > Tinnitus) contrast.

6.5.2.3 CORRELATION ANALYSIS

The z-values for significant clusters in the between-group analysis were extracted for each tinnitus participant to investigate any relationship with tinnitus clinical characteristics. The z-values for FC between left thalamus and right visual association cortex, as well as between right thalamus and right visual association cortex, were not significantly correlated to any of the clinical measures, with or without Bonferroni correction. Table 6-8 shows the results of the Spearman correlation analysis.

		R Thalamus – R VAC	***L Thalamus – R VAC***
HQ score	Correlation	0.018	-0.054
	Significance (2-tailed)	0.908	0.729
SDS	Correlation	0.083	-0.018
	Significance (2-tailed)	0.591	0.908
SAS	Correlation	-0.013	0.076
	Significance (2-tailed)	0.934	0.622
THI score	Correlation	0.188	0.02
	Significance (2-tailed)	0.221	0.898
TFI score	Correlation	0.124	-0.077
	Significance (2-tailed)	0.422	0.621
Tinnitus duration (in months)	Correlation	0.06	0.041
	Significance (2-tailed)	0.701	0.793
Mean hearing threshold (without 12 kHz)	Correlation	-0.115	-0.025
	Significance (2-tailed)	0.458	0.874

Mean hearing threshold (with 12 kHz)	Correlation	-0.109	-0.059
	Significance (2-tailed)	0.479	0.702
Loudness match absolute (in dB)	Correlation	0.038	0.113
	Significance (2-tailed)	0.807	0.466
Loudness match sensation level (in dB)	Correlation	0.013	0.086
	Significance (2-tailed)	0.932	0.579

Table 6-8 Correlation coefficients between thalamortical functional connectivity z-value in tinnitus group and tinnitus clinical measures. Correlations were corrected for age and years of education. R = right, L = left, VAC = visual association cortex, HQ = Hyperacusis Questionnaire, SDS = Zung Self-Rating Depression Scale, SAS = Zung Self-Rating Anxiety Scale, THI = Tinnitus Handicap Inventory, TFI = Tinnitus Functional Index).

6.6 Discussion

This study aimed to replicate the finding in Chapter 5 that tinnitus patients have altered functional connectivity in resting-state networks compared to non-tinnitus participants. Using seeds in the most common resting-state networks provided with CONN, this study found no evidence for widespread alterations to resting-state networks. Comparing the results of within-group functional connectivity analysis visually, it looked as if FC was more widespread in the tinnitus group. However, this was not replicated by the between-group analysis. The exception was a finding of increased functional connectivity between bilateral thalamus and right visual association cortex in the tinnitus group compared to the control group, matched for age, sex, and years of education. This finding was not associated with any clinical tinnitus characteristics, as shown in the correlation analysis. The finding was dependent on hearing status: when controlling for hearing status by including hearing loss as a covariate in the analysis, the finding became only borderline significant, whereas it was significant when uncontrolled for hearing loss.

This raises the question whether the finding is explicable by hearing differences between the groups, by the presence of tinnitus, or both. This study did not exclude participants with hearing loss, contrary to many previous studies. It is estimated that

around 70 – 85% of those with tinnitus have hearing loss (Henry et al., 2005, Vernon and Meikle, 2000). Therefore, excluding this group would not be representative of the tinnitus community at large. However, this does present the issue of controlling for hearing loss in the data. Every effort was made to match the tinnitus and control groups on hearing status, but despite matching the average age of participants, the tinnitus participants' hearing thresholds on high-frequency tones were ±10 dB higher than those of the control participants.

As the result was still borderline significant after controlling for hearing status, and the correlation analysis found no association between hearing status and the functional connectivity strength (z-scores) in the tinnitus group, it is fair to assume the result is not entirely driven by the 10 dB average difference in hearing status between the groups. However, the question remains what is driving the difference, as no association was found with any of the other clinical tinnitus characteristics either. Altered functional connectivity between thalamus and visual areas in tinnitus participants is not a novel finding. Indeed, several other studies have observed differences between these regions.

Zhang et al. (2015) used left thalamus and right thalamus as seeds in their analysis of thalamocortical functional connectivity in 31 tinnitus patients and 33 controls matched for age, sex, education, and all had normal hearing. They found decreased functional connectivity between right thalamus and left middle occipital gyrus, the peak MNI coordinates (-48, -72, 15) corresponding to visual association cortex. This is opposite to the finding of increased FC between right thalamus and visual association cortex found in the present study. Also similarly, Zhang et al. (2015) did not find an association with clinical tinnitus characteristics and their result. However, they observed other alterations in FC beyond this finding that were correlated to tinnitus measures. Right thalamus showed decreased FC with left superior temporal gyrus (auditory cortex), which was negatively correlated with tinnitus duration ($r = -0.454$, $p = 0.017$). Left thalamus showed decreased FC with right middle temporal gyrus (secondary auditory cortex), which was negatively correlated with Tinnitus Handicap Questionnaire total score ($r = -0.482$, p – 0.011).

Job et al. (2020) investigated functional connectivity in 19 tinnitus patients and 19 age-matched controls. Similar to the present study, tinnitus participants had slightly elevated hearing thresholds in the high-frequency range compared to the control participants. Placing seeds in bilateral Heschl's gyrus (HG), and sub-regions of the thalamus (the inferior colliculus (IC) and medial geniculate body (MGB)), they found increased FC between bilateral IC and right superior posterior lobule (SPL), as well as increased FC between left HG and posterior cingulate cortex. The authors proposed the connection between IC and SPL could be due to the SPL's role in cognitive control (Esterman et al., 2009) and is a reflection of the cognitive resources required early along the auditory pathway for filtering out the tinnitus percept.

Finally, Berlot et al. (2020) used high-resolution fMRI at 7 Tesla to examine resting-state FC between IC and MGB, MGB and PAC, and PAC and secondary AC in five tinnitus patients and five age-, sex-, and hearing loss-matched controls. They found decreased FC between MGB and PAC, and PAC and secondary AC. As they did not use whole-brain seed-to-voxel analysis, no other regions were examined in their relationship with the thalamus.

To my knowledge, no other studies have used thalamus or subparts of thalamus seeds in functional connectivity analysis. One study did find decreased amplitude of low-frequency fluctuations (ALFF) values in bilateral thalamus and in visual areas (Chen et al., 2014). The authors speculated this could be related to the decreased FC between auditory and visual areas observed in other studies (Burton et al., 2012, Maudoux et al., 2012). The evidence taken together indicates that thalamocortical functional connectivity was decreased in tinnitus participants compared to control participants in Berlot et al. (2020) and Zhang et al. (2015), but increased in Job et al. (2020) and in the current study. One possible explanation is the hearing status of participants, as in the former reports, participants had normal hearing or very minor hearing loss, whereas in the latter participants with mild-to-moderate high-frequency hearing loss were included.

The thalamus regulates the flow of sensory information to and from the auditory cortex and plays an important role in tinnitus models such as the frontostriatal gating model (see section 2.2.2.2) of Rauschecker et al. (2010). According to this model, the thalamus mediates a noise-cancellation system consisting of limbic-auditory connections, and a failure of this mechanism results in tinnitus. Other models such as the thalamocortical dysrhythmia model (see section 2.2.2.3) also propose that alterations to signal transmission at the level of the thalamus cause tinnitus. Based on these theories, one would predict altered FC between thalamus and other auditory regions or between thalamus and limbic regions. The current study hypothesised such changes, but only found changes between thalamus and visual regions. Therefore, this study found evidence in support of a role for the thalamus in tinnitus perception, although this did not align exactly with any specific predictions made by tinnitus models discussed in section 2.2.

As discussed in section 5.6.1.5, changes to the visual resting-state network in tinnitus were observed in several studies, all of which considered these changes as secondary effects to tinnitus rather than something that could be driving the tinnitus percept itself. Due to the correlational nature of functional connectivity analysis no claims on causality can be made. One explanation is that of anti-correlation between the visual and auditory modality: activation in one system suppresses that in the other (Burton et al., 2012). However, the present study found a positive correlation between the two, and not negative, negating this explanation. As such, it is unclear what the singular finding presented in this study could reflect. There is the possibility that the finding is a false positive, although this seems unlikely as the recommended corrected thresholds for statistical significance in CONN were used. Also, it would seem too coincidental that both left and right thalamus separately would show significant increased FC with right visual association cortex if they were both false positives.

This study also aimed to investigate resting-state connectivity with DLPFC, the most chosen site of stimulation in tDCS research (see Chapter 3). No differences were found in functional connectivity between tinnitus and control groups using DLPFC as a seed. To my knowledge, this was the first study to investigate DLPFC specifically.

However, one study has investigated the functional connectivity of the frontoparietal resting-state network, which DLPFC is a part of. Job et al. (2020) used the frontoparietal network seeds in CONN, similar to the present study, consisting of bilateral DLPFC and bilateral posterior parietal cortex. They found increased FC between the frontoparietal network and the right middle frontal gyrus, but it is not clear which seed in the frontoparietal network was driving the result from their reporting. Therefore, currently there is no evidence available from rs-fMRI research in favour of DLPFC as a region of special interest in tinnitus. As such, the present study failed to provide neurophysiological evidence for the DLPFC as a region involved in tinnitus. Therefore, it seems likely that positive results found in tDCS trials for tinnitus using DLPFC as a target might be unspecific to tinnitus, but rather share commonality with other conditions affecting emotional systems. Indeed, tDCS of DLPFC has been used in the treatment of depression and pain disorders with some positive results as well (Lefaucheur, 2016).

6.7 Conclusion

The present study found increased functional connectivity between bilateral thalamus and right visual association cortex in tinnitus patients compared to controls. No alterations were found in the other resting-state networks, such as the default mode network and the dorsal attention network. No differences in functional connectivity were found with DLPFC either. Taken together, the increased FC with thalamus is in line with tinnitus models that postulate a role for thalamic hyperactivity in tinnitus perception. Additionally, no neurophysiological support was found for a specific role of DLPFC in tinnitus perception.

Chapter 7 Discussion

7.1 General discussion

This thesis explored tDCS and HD-tDCS for tinnitus management as well as tinnitus neurophysiology as measured by resting-state fMRI. The main goal was to provide direction for the future of tDCS and HD-tDCS research in the field of tinnitus, so that one day these tools might be clinically available to tinnitus patients, should they be proven effective. As such, the original plans for this PhD project included several randomised controlled trials testing the effects of HD-tDCS in tinnitus sufferers. The impact of COVID-19 meant that these research plans were replaced with other lines of work, including two scoping reviews (Chapters 3 and 5), an online survey (Chapter 4) and an fMRI study (Chapter 6).

The major findings of this thesis were:

- Although tDCS is considered an acceptable management option by most tinnitus sufferers (Chapter 4), current trial outcomes are far from delivering the effect sizes desired by most tinnitus sufferers to make undergoing the stimulation worthwhile, and the evidence-base for the efficacy of tDCS in tinnitus is not robust (Chapter 3).
- Tinnitus is accompanied by alterations in brain activity (Chapter 5 and 6), which is the foundation for tDCS as a management option. However, fMRI research seems to be picking up on wide-spread changes to brain activity in tinnitus patients caused by the emotional and attentional effects that tinnitus has, rather than the primary cause of tinnitus or the phantom sound generation mechanism itself.
- There is a gap between the knowledge generated by tDCS research and brain imaging research as the cortical areas of interest do not overlap in both fields of research.

As such, the goals of this closing chapter are 1) to discuss the implications of the scoping review in Chapter 3 and the survey work presented in Chapter 4 for the future of (HD-)tDCS research; and 2) to explore how key insights from tDCS and fMRI research in tinnitus might inform and supplement each other.

Chapter 3 of this thesis presented the findings from a scoping review of 38 studies investigating the use of tDCS and HD-tDCS for the management of tinnitus. This was the first study to review outcomes of HD-tDCS in tinnitus research separately from tDCS. The included studies were highly heterogeneous, and there was little consensus on the optimal stimulation protocol. The three cortical targets identified in studies were DLPFC, LTA and auditory cortex. There was some evidence present for the use of tDCS of DLPFC for modulating tinnitus-related distress, although this was not robust.

It remained unclear whether tDCS modulates tinnitus loudness or only tinnitus-related distress. This question is especially relevant since the most convincing evidence is found for DLPFC stimulation, which is also used as a target in, for example, depression research (Lefaucheur et al., 2017), leading to the question whether tDCS of DLPFC might affect emotional dimensions of tinnitus rather than the loudness. Further research is needed to determine the optimal protocol for tDCS, including the duration and frequency of stimulation, the target cortical areas, and the stimulation polarity. In addition, more groundwork is needed on the neurophysiological mechanisms behind tinnitus modulation using (HD-)tDCS, which could help us understand its effects better. One option is to conduct a trial using HD-tDCS which includes pre- and post-intervention fMRI scans. This will be discussed in further detail in the Future Research section.

Chapter 4 of this thesis investigated the acceptability of (HD-)tDCS as a tinnitus management option by surveying 272 tinnitus sufferers' opinions. It is important to understand the acceptability of (HD-)tDCS among tinnitus sufferers before it can be considered a viable management option. This survey was the first to seek tinnitus sufferers' opinions on (HD-)tDCS. Other surveys (Tyler, 2012, Engineer et al., 2013, Smit et al., 2018) have investigated the acceptability of invasive treatments such as cochlear implantation and deep brain stimulation. In these, it was found that the individual's tinnitus severity played a role in the acceptability of invasive treatment, as well as the success rate of the treatment and the potential side effects. These surveys did not compare treatment outcomes beyond "reduce tinnitus by half" and "eliminate tinnitus completely", which are not currently realistic outcomes in tinnitus

trials. As such, the survey of HD-tDCS acceptability that was conducted, also investigated the effect of the strength of the tinnitus reduction following intervention on a scale ranging from 10%-100% reduction. Also considered was whether the intervention would affect tinnitus loudness or on tinnitus-related distress, the duration of the intervention and the effect of the individual's own tinnitus severity.

The survey found that tinnitus sufferers considered (HD-)tDCS an acceptable management option. However, high satisfaction was only found for tinnitus loudness reductions of 80% or above. There were also subgroups of respondents who reported high potential satisfaction with (HD-)tDCS outcomes starting from 10% reduction of tinnitus loudness. The survey also found that satisfaction ratings were influenced by whether the intervention affected tinnitus loudness or tinnitus-related distress: on average, the survey respondents rated satisfaction as high for 100% loudness reduction, whereas only moderate satisfaction was reported even for 100% tinnitus-related distress reduction.

The duration of the intervention (three vs. five weeks) only had a small effect on the satisfaction ratings, and for 100% reduction in tinnitus loudness or distress the difference disappeared completely, indicating that for complete elimination of tinnitus complaint the duration of the intervention would be of less importance. Contrary to previous surveys on invasive tinnitus interventions, this survey did not find an effect of tinnitus severity on the satisfaction ratings. This could be because (HD-)tDCS is non-invasive, so perhaps even those with mild and moderate tinnitus would be open to it, whereas they would not be open to an invasive method.

The most important finding of the survey was that the respondents would never be highly satisfied with the intervention if it minimises the distress, but not the loudness. As mentioned above, DLPFC is most often chosen as the cortical target for (HD-)tDCS intervention, and this target is also used in depression research (Lefaucheur et al., 2017). There is no conclusive evidence if different sites of stimulation affect tinnitus perception or emotion differently (Shekhawat et al., 2015c). As a result, future (HD-)tDCS studies should define clearly whether the proposed therapy target is tinnitus

loudness or tinnitus distress, or both, and choose their outcome measures accordingly. The tinnitus community understandably seems to have a strong preference for tDCS research to focus on optimising tinnitus loudness reduction following stimulation. If tinnitus distress is proposed as a therapy target, this should be made clear upfronting informed consent, as this survey showed that there are subgroups of tinnitus patients for whom this could be acceptable as well.

Chapter 5 presented a review of 29 studies that explored resting-state functional connectivity in tinnitus patients. The studies revealed alterations in widely distributed brain networks, including the auditory network, default mode network, attention networks, limbic system, and visual network. These findings confirm that tinnitus is a complex condition that involves multiple overlapping networks. However, it remains unclear which changes are primary and which are secondary to tinnitus. Changes observed in the visual network for example were considered secondary effects of tinnitus, where the overactivation of the auditory network would lead to differences in functional connectivity with the visual network through inhibitory circuits between the two (Burton et al., 2012).

For other networks, interpretations of the results are less consistent. For example, the attention or executive control networks: could changes in these networks be causes of tinnitus, effects of tinnitus, or even both? It could be argued that the experience of tinnitus itself is distracting and would therefore have an impact on the ability to attend to other stimuli, which could cause changes to attention networks in the long term.

A key question is how large or strong the fMRI signal reflecting the “primary” footprint of tinnitus would be compared to the footprint of the far-reaching emotional affects tinnitus can have. An interesting avenue that could be explored in this direction could be the use of sound stimulation paradigms combined with fMRI. Advanced tinnitus pitch-matching methods could be used to get as close as possible to what the tinnitus perception is for the participant, and this sound could be presented in the scanner compared to a sound that does not sound like the tinnitus.

Compared between tinnitus and non-tinnitus sufferers, the difference in activation between the groups and sound conditions could potentially give a clue as to how strong the actual tinnitus signal could be.

Chapter 5 also highlighted the need for replication in the field by using well-documented methods. A variety of scanning procotols and analysis methods were found. Most importantly, the regions of interest chosen in different studies were lacking replication, causing a wide variety of findings that was difficult to compare to each other. Therefore, the aim of the final project of this thesis was to conduct a large-scale rs-fMRI study using the most common regions of interest and analysis methods from Chapter 5.

As such, in Chapter 6, this thesis aimed to replicate previous fMRI research suggesting that tinnitus patients exhibit altered functional connectivity in resting-state networks compared to non-tinnitus participants. A study was conducted with 46 tinnitus participants and 36 non-tinnitus controls using various seeds in the most common resting-state networks provided with CONN to investigate functional connectivity patterns. Also included were seeds in the DLPFC, which is the most common cortical target in (HD-)tDCS research in tinnitus. The analysis methods in this study were chosen with replicability in mind by executing the pre-processing steps in a way that was aligned with the majority of fMRI studies in the tinnitus field. One of the key issues with fMRI replication is that highly technical choices are made during the acquisition and analysis of the study. Although often justifiable, this wealth of different analysis methods can make direct comparison across studies difficult.

The fMRI study found no evidence for widespread alterations to resting-state networks. Neither did the study find any evidence to support a specific role for DLPFC in tinnitus perception. This is notable as DLPFC is the most chosen site of stimulation in tDCS research for tinnitus treatment. The study's failure to provide evidence for DLPFC's role in tinnitus perception suggests that positive results found in tDCS trials using DLPFC as a target might be non-specific to tinnitus and might be common to other conditions affecting emotional systems, as was also suggested by the scoping

review in Chapter 3. However, another potential explanation for the lack of any findings regarding DLPFC or any other area related to emotional systems in this study could be the underrepresentation of tinnitus participants with severe-to-catastrophic tinnitus in the study sample. Only 28% of the tinnitus participants in the study had TFI scores classified as a big or very big problem, whereas 72% of participants scored a moderate problem or less. The same pattern was visible in THI scores, with 34% of participants scoring the lowest severity grade and only 11% scoring a severe or catastrophic severity score, and the remained scoring mild-to-moderate. Moreover, it should be kept in mind that these are just findings from one study, particularly for the DLPFC region-of-interest. As such, they should be taken with a grain of salt as many factors could potentially influence a non-result, including tinnitus heterogeneity. Future studies could include DLPFC as a region-of-interest to investigate further in a subgroup such as high-severity tinnitus sufferers.

The study did find increased functional connectivity between bilateral thalamus and right visual association cortex in tinnitus participants compared to controls. This finding is in line with tinnitus models that postulate a role for thalamic hyperactivity in tinnitus perception. However, the study found the change in thalamic hyperactivity with visual areas and not auditory areas, which is unexpected as tinnitus is an auditory disorder.

The thalamus is the main sensory relay hub for auditory signal processing. As such, it has been the focus of several tinnitus models discussed in Chapter 2. Most notably in this respect, the frontostriatal gating model proposes that the thalamus "gates" auditory perception and a fault in this system results in a lack of suppression of irrelevant sensory information, resulting in tinnitus (Rauschecker et al., 2015). Furthermore, the review in Chapter 5, as well as the clinical findings presented in Chapter 6, both found evidence for thalamic involvement in tinnitus perception. Therefore, it would be interesting to investigate the effect of brain stimulation targeting thalamus in tinnitus patients. The nature of tDCS is as such, that the stimulation only reaches superficial cortical areas and is not likely to penetrate as far as subcortical areas like the thalamus. As such any stimulation of thalamus would be

invasive. For the most severe tinnitus cases, invasive brain stimulation could be an acceptable form of management, as discussed in Chapter 4. A clinical trial is currently under way to investigate the effect of high-frequency deep brain stimulation of the medial geniculate body (part of the thalamus) using a randomised, double-blind, cross-over design in six participants (Maastricht University Medical Center, 2021). Although of small sample size, the results from this trial will be valuable in testing whether aberrant thalamic signalling has a role in tinnitus perception.

Interestingly, only 16 participants with tinnitus (35%) in the study reported having a diagnosed hearing loss prior to testing, whereas in 44 participants with tinnitus some degree of hearing loss was present in their audiograms. This is important for future studies to keep in mind when recruiting research volunteers, especially if they are looking to recruit tinnitus volunteers with normal hearing only for example.

7.2 Future research

This thesis has raised several questions which would be interesting for future research to address. First and foremost, the efficacy of non-invasive brain stimulation for tinnitus has not been established conclusively and it is recommended that future research examines the efficacy of (HD-)tDCS for tinnitus further. This was part of the original scope of this thesis, but unfortunately the work was impacted by the COVID-19 pandemic and experimental protocols involving working within two metres of a participant were not possible. Nonetheless, the results of the review in Chapter 3 show that tinnitus sufferers could benefit from (HD-)tDCS interventions. In an effort to help researchers navigate the plethora of options available when designing a future (HD-)tDCS study, recommendations are presented below based on the findings of this thesis.

The first recommendation is to explore HD-tDCS further in a sham-controlled trial as the results in the limited number of studies that used HD-tDCS were promising but lacked placebo control. At present, it is difficult to formulate advice on what the stimulation target should be based on either previous HD-tDCS trials or resting-state fMRI research. Therefore, it would be interesting for a future trial to compare sham

HD-tDCS to active HD-TDCS of different cortical targets, such as DLPFC and auditory cortex. A priori power analysis with G*Power (effect size=0.25 (medium), alpha=0.05, power=0.95, correlation among repeated measures=0.5) indicates that a sample size of at least 66 participants (22 per group) is needed to find a significant difference in treatment effect between LTA, DLPFC or sham stimulation. Half of the participants could undergo six sessions spread out over three weeks, and the other half could continue for an additional four sessions to receive ten sessions across five weeks. Chapter 4's survey should satisfaction ratings for both three and five weeks of intervention were acceptable, so it would be worth investigating if there is a difference in effect. Table 7-1 shows a schematic overview of a potential design of such a trial.

Group	Baseline assessment	Non-invasive brain stimulation (HD-tDCS)					Follow-up assessment
	Wk 0	Wk 1	Wk 2	Wk3	Wk 4*	Wk 5*	Wk 6/9/13/17
Group A Auditory Cortex	TQ, THI, TFI, TSNS, Psychoacoustic Tinnitus measures, hearing assessment (PTA), BDI, HADS, VAS, CGI	2 HD-tDCS sessions VAS + CGI	2 HD-tDCS sessions VAS + CGI	2 HD-tDCS sessions VAS + CGI	2 HD-tDCS sessions VAS + CGI	2 HD-tDCS sessions VAS + CGI	TQ, THI, TFI, TSNS, Psychoacoustic Tinnitus measures, BDI, HADS, VAS, CGI
Group B DLPFC		2 HD-tDCS sessions VAS + CGI	2 HD-tDCS sessions VAS + CGI	2 HD-tDCS sessions VAS + CGI	2 HD-tDCS sessions VAS + CGI	2 HD-tDCS sessions VAS + CGI	
Group C Sham (50/50 AC and DLPFC)		2 HD-tDCS sessions VAS + CGI	2 HD-tDCS sessions VAS + CGI	2 HD-tDCS sessions VAS + CGI	2 HD-tDCS sessions VAS + CGI	2 HD-tDCS sessions VAS + CGI	

Table 7-1 Schematic of recommended HD-tDCS study. Abbreviations: TQ = Tinnitus Questionnaire, THI = Tinnitus Handicap Inventory, TFI = Tinnitus Functional Index, TSNS = Tinnitus Severity Numeric Scale, PTA = Pure Tone Audiometry, BDI = Beck Depression Inventory, HADS = Hospital Anxiety and Depression Scale, VAS = Visual Analogue Scale, CGI = Clinical Global Improvement scale, AC = Auditory Cortex.

* Week 4 and Week 5 stimulation should only be administered to half of the participants in each group on a randomised basis to compare efficacy of 3 wks vs 5 wks stimulation.

A trial as outlined in Table 7-1 could potentially inform which target is more effective, auditory cortex or DLPFC, and if three or five weeks of stimulation is better. These parameters could then feed into a next trial which includes measuring changes with fMRI, as outlined in Table 7-2. This study could investigate the efficacy of the optimised HD-tDCS protocol compared to sham stimulation in a double-blind

manner. The effect of the HD-tDCS protocol on the neural networks of tinnitus could be investigated using resting-state fMRI to look at functional connectivity changes pre- to post-intervention. Participants would undergo rs-fMRI scanning before and immediately after the final session of stimulation. Table 7-2 shows a possible design of such a study, with the assumption that the proposed study from Table 7-1 finds that ten sessions (five weeks) are optimal for tinnitus relief.

A priori power analysis with G*Power (effect size=0.25 (medium), alpha=0.05, power=0.95, correlation among repeated measures=0.5) indicates that a sample size of at least 54 participants is needed to find a significant treatment effect for this trial set-up.

Group	Baseline assessment	Non-invasive brain stimulation (HD-tDCS)					Immediate follow up
	Wk 0	Wk 1	Wk 2	Wk3	Wk 4	Wk 5	Wk 5
Group A Optimised HD-tDCS protocol (MESP)	TQ, THI, TFI, TSNS, Psychoacoustic Tinnitus measures, hearing assessment (PTA), BDI, HADS, VAS, CGI, pre-intervention rs-fMRI scan	2 HD-tDCS sessions VAS + CGI	2 HD-tDCS sessions VAS + CGI	2 HD-tDCS sessions VAS + CGI	2 HD-tDCS sessions VAS + CGI	2 HD-tDCS sessions VAS + CGI	TQ, THI, TFI, TSNS, Psychoacoustic Tinnitus measures, BDI, HADS, VAS, CGI, post-intervention rs-fMRI scan
Group B Sham stimulation protocol		2 sham sessions VAS + CGI	2 sham sessions VAS + CGI	2 sham sessions VAS + CGI	2 sham sessions VAS + CGI	2 sham sessions VAS + CGI	

Table 7-2 Schematic of recommended HD-tDCS + fMRI trial. Abbreviations: MESP = most effective stimulation paradigm according to study in Table 7-1 TQ = Tinnitus Questionnaire, THI = Tinnitus Handicap Inventory, TFI = Tinnitus Functional Index, TSNS = Tinnitus Severity Numeric Scale, PTA = Pure Tone Auditometry, BDI = Beck Depression Inventory, HADS = Hospital Anxiety and Depression Scale, VAS = Visual Analogue Scale, CGI = Clinical Global Improvement scale

In addition to cortical targets, another key question is whether stimulation polarity should be anodal or cathodal. Whilst anodal stimulation is generally considered to have an excitatory effect on underlying neurons, and cathodal an inhibitory effect, there are factors beyond the electrode polarity that can influence the "net effect" of the stimulation, e.g. the positioning of the electrodes, orientation of the neurons and axons, degree of current conduction or impedance, duration and intensity of stimulation, initial neural activation state of affected areas, and individual differences in skull thickness, gyral structure, and other anatomical features (Garnett et al.,

2015). This is especially true for HD-tDCS due to its expanded range of configuration options through the use of multiple HD electrodes. Therefore, it is strongly advised that researchers use modelling software, for example HD-Targets (https://soterixmedical.com/research/software/hd-targets) or HD-Explore (https://soterixmedical.com/research/support/products?software=hdexplore) to find the optimal electrode configuration for their intended cortical target (Garnett et al., 2015).

It Is surprising given the amount of research that proposes tinnitus is associated with hyperactivity in auditory regions that (HD-)tDCS research has focussed so little on A) stimulation of auditory areas, and B) cathodal (i.e. "inhibitory") stimulation to suppress this hyperactivity. As seen in Chapter 3, two sham-controlled studies administered five sessions of cathodal stimulation to auditory cortex, and neither found a tinnitus improvement compared to the sham condition (Teismann et al., 2014, Pal et al., 2015b). This could potentially explain the lack of further trials with these parameters. However, Teismann et al. (2014) combined tDCS with tailor-made notched music training, and therefore it was not a "pure" tDCS trial. Pal et al. (2015a) on the other hand, did not combine the tDCS with another treatment, but administered five sessions on consecutive days. Other studies such as Shekhawat and Vanneste (2018c) recommend a wash-out period between stimulation sessions of three-to-four days.

Furthermore, Joos et al. (2014), although not sham-controlled, found an improvement in tinnitus loudness and distress following both cathodal and anodal stimulation of AC with the reference electrode on the contralateral arm. Therefore, given the low number of multi-session studies (n = 2) with sham control that administered cathodal tDCS to auditory cortex, and the absence of such a HD-tDCS study, a final recommendation could be to run a tDCS or HD-tDCS study with three arms: one with cathodal, one with anodal, and one with sham stimulation of auditory cortex. There is value in directly comparing anodal and cathodal stimulation in one study. Firstly, Chapter 5 showed findings of increased connectivity in tinnitus participants compared to controls were slightly more common for auditory ROIs (see

Figure 5-3) than findings of decreased connectivity. The research study presented in Chapter 6 also found only increased functional connectivity between thalamus and visual areas. However, this trend is not strong enough to be conclusive. Secondly, even if there was conclusive evidence for hyperactivity in a specific area or network in tinnitus sufferers, it would remain unclear if the intuition that cathodal stimulation suppresses it best would hold up to experimental testing.

With regards to other stimulation parameters, it is recommend that future trials should administer six sessions, spaced apart three-to-four days, with a duration of twenty minutes per session, and an intensity of 1.5 mA, following the advice from the tDCS dose-response study executed by Shekhawat and Vanneste (2018c). These trials could potentially be delivered remotely, with self-administration.

A key question raised in this thesis is whether (HD-)tDCS could modulate tinnitus loudness or tinnitus-related distress. This is an area where brain stimulation and brain imaging could supplement each other. Future trials are advised to make it clear what the intended therapeutic target of the stimulation is, and to use insights from brain imaging research to motivate the choice of cortical target for stimulation. As shown in Chapter 4, there are subgroups of tinnitus sufferers for whom distress reduction without actual loudness reduction following stimulation is acceptable. However, this is not the case for all tinnitus sufferers and there is a strong need for research to focus on loudness reduction. Future brain imaging studies in tinnitus should focus on finding whether specific areas or connections between areas play an important role in tinnitus generation. This thesis found increased functional connectivity between bilateral thalamus and right visual association cortex in tinnitus participants compared to controls. It would be interesting for future research to investigate thalamic functional connectivity further.

Some limitations to this thesis should be mentioned. Firstly, the loudness vs. distress approach could be critiqued. To measure different complaints associated with tinnitus, such as loudness or distress, visual analogue scales are most often used. Concerns have been raised that there is little evidence demonstrating the

psychometric adequacy for differentiating levels of tinnitus severity between individuals and quantifying clinically significant change on the VAS following tinnitus intervention (Fackrell, 2016, Adamchic et al., 2012). More research is needed to validate the separate measurement of tinnitus loudness and distress complaints using VAS. In the meantime, it is highly recommended to use validated tinnitus questionnaires such as the TFI and THI as primary outcome measures (British Society of Audiology, 2021).

Secondly, the design of the survey questions in Chapter 4 could have received more careful consideration and review rounds. It would have been preferable to ask a panel of tinnitus sufferers to fill in the survey and give their opinions on the questions and wording. This would have been a good exercise in the light of patient involvement, and it would also have strengthened the survey's findings.

Lastly, the fMRI study would have benefited from additional control measures. For example, it would have been preferable to include a post-fMRI survey to ask participants about their scan experience. An eyes-open paradigm was chosen for the scanning to avoid participants falling asleep as a confound (some elderly participants struggled to stay awake during hearing testing for example), but it was not possible to see if a participant had their eyes open or closed during the scan as no monitoring was installed. As the most important finding in the fMRI study related to visual areas, a critic could argue that there was no proper control for visual activation during our eyes-open task and it should have been monitored if participants had their eyes open the whole time or if they experienced any difficulties fixating on the cross.

A final note should be made about an interesting avenue of (HD-)tDCS that is being explored, which is remotely-supervised tDCS (rs-tDCS). In rs-tDCS, a live video connection is used to supervise a participant administering tDCS themselves. Recently, a study analysed over 6000 sessions of rs-tDCS and found that extended and repeated applications were feasible and tolerable using this method (Pilloni et al., 2022). The scoping review in Chapter 5 included one study in tinnitus that used this domiciliary approach (Hyvarinen et al., 2016). Rs-tDCS could facilitate

intervention trials of longer duration and investigate whether repeated tDCS over a longer period of time could improve the longevity of its effects. Rs-tDCS could also be used in conjunction with other interventions such as Cognitive Behavioural Therapy or sound therapy delivered at home. These are interesting options for the future as it would make tDCS more accessible to a wider audience unable to travel into a clinic frequently.

7.3 Conclusions

This thesis found that, although (HD-)tDCS is considered an acceptable management option by most tinnitus sufferers, current (HD-)tDCS trial outcomes are far from delivering the effect sizes desired by most tinnitus sufferers to make undergoing the stimulation worthwhile, and the evidence-base for the efficacy of (HD-)tDCS in tinnitus is not robust. It was also found that tinnitus is associated with alterations to functional connectivity patterns, although results are generally varied and rarely replicated. This thesis' main experimental work found increased functional connectivity between bilateral thalamus and right visual association cortex in tinnitus patients compared to controls, suggesting a role for thalamic hyperactivity in tinnitus. Future research should investigate further the role of the thalamus in tinnitus generation and aim to investigate further the effects of (HD-)tDCS on tinnitus.

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Supplementary material

Chapter 4 Survey

PAGE 1

Welcome to this survey on tinnitus and non-invasive brain stimulation.

Please read the following information carefully.

We would like to know your opinion about non-invasive brain stimulation as a potential management option for tinnitus. You do not need to know what brain stimulation is or how it works. We will explain this later on.

You are invited to take part only if you yourself have experienced tinnitus or a "ringing in the ears" for 6 months or more. You also have to be 18 years or older to participate in this survey. Please forward the link of this survey to anyone you know who has tinnitus. Please do NOT fill out this survey if you do NOT have tinnitus.

This survey consists of three parts. The whole survey takes about 10 to 15 minutes. The first part will ask you 25 questions about your tinnitus. The second part will ask you to rate how satisfied you would be with different outcomes of non-invasive brain stimulation if you were to receive it. The third part will ask you a few more open-ended questions about your view on tinnitus and research.

This survey is 100% anonymous. No one will know who you are by filling out this survey. Please do not fill in any personal information that could identify you in the open questions, as this would compromise your anonymity.

You can stop this survey any time you want. However, if you do not finish all the questions, your contribution will be deleted.

Thank you for participating in this survey. If you have any questions, feel free to contact the primary investigator:

[Details redacted]

PAGE 2

Welcome to the first section of the survey.

We will ask you 25 questions about your tinnitus. This part of the survey takes about 5 minutes.

Over the PAST WEEK ...

Question 1

What percentage of your time awake were you AWARE OF your tinnitus?

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Never aware Always aware

Question 2

How STRONG or LOUD was your tinnitus?

0 1 2 3 4 5 6 7 8 9 10

Not at all strong or loud Extremely strong or loud

Question 3

What percentage of your time awake were you ANNOYED by your tinnitus?

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

None of the time All the time

Over the PAST WEEK...

Question 4

Did you feel IN CONTROL in regard to your tinnitus?

0 1 2 3 4 5 6 7 8 9 10

Very much in control Never in control

Question 5

How easy was it for you to COPE with your tinnitus?

0 1 2 3 4 5 6 7 8 9 10

Very easy to cope Impossible to cope

Question 6

How easy was it for you to IGNORE your tinnitus?

0 1 2 3 4 5 6 7 8 9 10

Very easy to ignore Impossible to ignore

PAGE 3

Over the PAST WEEK, did your tinnitus interfere with...

Question 7

Your ability to CONCENTRATE?

0 1 2 3 4 5 6 7 8 9 10

Did not interfere Completely interfered

Question 8

Your ability to THINK CLEARLY?

0 1 2 3 4 5 6 7 8 9 10

Did not interfere Completely interfered

Question 9

Your ability to FOCUS ATTENTION on other things besides your tinnitus?

0 1 2 3 4 5 6 7 8 9 10

Did not interfere Completely interfered

Over the PAST WEEK ...

Question 10

How often did your tinnitus make it difficult to FALL ASLEEP or STAY ASLEEP?

0 1 2 3 4 5 6 7 8 9 10

Never had difficulty Always had difficulty

Question 11

How often did your tinnitus cause you difficulty in getting AS MUCH SLEEP as you needed?

0 1 2 3 4 5 6 7 8 9 10

Never had difficulty Always had difficulty

Question 12

How much of the time did your tinnitus keep you from SLEEPING as DEEPLY or as PEACEFULLY as you would have liked?

0 1 2 3 4 5 6 7 8 9 10

None of the time All of the time

PAGE 4

Over the PAST WEEK, how much has your tinnitus interfered with...

Question 13

Your ability to HEAR CLEARLY?

0 1 2 3 4 5 6 7 8 9 10

Did not interfere Completely interfered

Question 14

Your ability to UNDERSTAND PEOPLE who are talking?

0 1 2 3 4 5 6 7 8 9 10

Did not interfere Completely interfered

Question 15

Your ability to FOLLOW CONVERSATIONS in a group or at meetings?

0 1 2 3 4 5 6 7 8 9 10

Did not interfere Completely interfered

Over the PAST WEEK , how much has your tinnitus interfered with...

Question 16

Your QUIET RESTING ACTIVITIES?

0 1 2 3 4 5 6 7 8 9 10

Did not interfere Completely interfered

Question 17

Your ability to RELAX?

0 1 2 3 4 5 6 7 8 9 10

Did not interfere Completely interfered

Question 18

Your ability to enjoy " PEACE and QUIET "?

0 1 2 3 4 5 6 7 8 9 10

Did not interfere Completely interfered

PAGE 5

Over the PAST WEEK, how much has your tinnitus interfered with...

Question 19

Your enjoyment of SOCIAL ACTIVITIES?

0 1 2 3 4 5 6 7 8 9 10

Did not interfere Completely interfered

Question 20

Your ENJOYMENT OF LIFE?

0 1 2 3 4 5 6 7 8 9 10

Did not interfere Completely interfered

Question 21

Your RELATIONSHIPS with family, friends and other people?

0 1 2 3 4 5 6 7 8 9 10

Did not interfere Completely interfered

Over the PAST WEEK ...

Question 22

How often did your tinnitus cause you to have difficulty performing your WORK or OTHER TASKS, such as home maintenance, school work, or caring for children or others?

0 1 2 3 4 5 6 7 8 9 10

Never had difficulty Always had difficulty

Over the PAST WEEK ...

Question 23

How ANXIOUS or WORRIED has your tinnitus made you feel?

0 1 2 3 4 5 6 7 8 9 10

Not at all anxious or worried Extremely anxious or worried

Question 24

How BOTHERED or UPSET have you been because of your tinnitus?

0 1 2 3 4 5 6 7 8 9 10

Not at all bothered or upset Extremely bothered or upset

Question 25

How DEPRESSED were you because of your tinnitus?

0 1 2 3 4 5 6 7 8 9 10

Not at all depressed Extremely depressed

PAGE 6

Part 2: Non-invasive Brain Stimulation

This is the second part of the survey.

Non-invasive brain stimulation is a research tool that is being investigated as a potential management option for tinnitus. We would like to know how much effect it should have on your tinnitus for you to be satisfied.

The specific technique we are interested in is called "High-definition transcranial direct current stimulation" or "HD-tDCS". Previous research has shown that multiple sessions of stimulation are more effective than just a single session. Imagine you were to receive HD-tDCS for your tinnitus in a scientific study. This means you would have to go to a location (for example University College London) on multiple occasions. Each stimulation session takes 20 minutes. It involves placing a cap on your head with small electrodes in it, which will administer a small current to your brain. This could feel itchy or tingly. You just sit and relax for 20 minutes during the stimulation.

We will now give you certain scenarios below. Please indicate how satisfied you would be in each scenario.

Imagine you had to come in two times a week, for THREE WEEKS in a row, so SIX sessions in total.

How satisfied would you be if...

Question 26

Your tinnitus LOUDNESS decreased by 10%?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

Question 27

Your tinnitus LOUDNESS decreased by 30%?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

Question 28

Your tinnitus LOUDNESS decreased by 50%?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

Question 29

Your tinnitus LOUDNESS decreased by 80%?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

Question 30

Your tinnitus LOUDNESS completely disappeared?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

How satisfied would you be if...

Question 31

Your tinnitus-related DISTRESS but not loudness decreased by 10%?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

Question 32

Your tinnitus-related DISTRESS but not loudness decreased by 30%?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

Question 33

Your tinnitus-related DISTRESS but not loudness decreased by 50%?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

Question 34

Your tinnitus-related DISTRESS but not loudness decreased by 80%?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

Question 35

Your tinnitus-related DISTRESS but not loudness completely disappeared?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

PAGE 7

Now imagine you had to come in two times a week, for FIVE WEEKS in a row, so TEN sessions in total.

How satisfied would you be if...

Question 36

Your tinnitus LOUDNESS decreased by 10%?

Your tinnitus-related DISTRESS but not loudness completely disappeared?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

Question 37

Your tinnitus LOUDNESS decreased by 30%?

Your tinnitus-related DISTRESS but not loudness completely disappeared?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

Question 38

Your tinnitus LOUDNESS decreased by 50%?

Your tinnitus-related DISTRESS but not loudness completely disappeared?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

Question 39

Your tinnitus LOUDNESS decreased by 80%?

Your tinnitus-related DISTRESS but not loudness completely disappeared?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

Question 40

Your tinnitus LOUDNESS completely disappeared?

Your tinnitus-related DISTRESS but not loudness completely disappeared?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

How satisfied would you be if...

Question 41

Your tinnitus-related DISTRESS but not loudness decreased by 10%?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

Question 42

Your tinnitus-related DISTRESS but not loudness decreased by 30%?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

Question 43

Your tinnitus-related DISTRESS but not loudness decreased by 50%?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

Question 44

Your tinnitus-related DISTRESS but not loudness decreased by 80%?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

Question 45

Your tinnitus-related DISTRESS but not loudness completely disappeared?

0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Extremely satisfied

PAGE 8

Part 3: open questions

This is the last part of the survey. We will ask you some open-ended questions about the future of tinnitus research. We would like your input so we can design our future studies with the wishes of tinnitus sufferers in mind. This place is also meant as an opportunity for you to share your mind with a team of UCL tinnitus researchers.

Question 46

Is your tinnitus influenced by the COVID-19 pandemic? (Please explain why or why not)

Question 47

What do you think the direction of tinnitus research in the future should be?

Question 48

What are your expectations for non-invasive brain stimulation as a tinnitus management option in the future?

Question 49

What else (if anything) would you like us to know?

FINISH

Chapter 5 Supplementary Table S1

Resting-state fMRI studies using seed-based functional connectivity analysis

Non-directional connectivity studies

Nr	Study	Study information	Tinnitus group(s) information:	Control group(s) information:	Scanning information	Data pre-processing	Seed regions (ROIs)	Regions showing increased connectivity in tinnitus compared to controls	Regions showing decreased connectivity in tinnitus compared to controls	Additional findings	Networks associated with the altered connectivity in chronic tinnitus
1	Berlot et al., 2020 A 7 Tesla fMRI investigation of human tinnitus percept in cortical and subcortical auditory areas	**Aim:** To investigate the frequency-specific processing in sub-cortical and cortical regions in tinnitus patients compared to controls **Inclusion Criteria:** unilateral tinnitus (2 left and 4 right), chronic (>6 months), subjective tinnitus, note: all right-handed **Exclusion Criteria:** Decreased sound tolerance,	**Sample Size:** n=-6 **Sex:** 4 F/2 M **Age:** 45.4 ± 12.4 **Tinnitus Duration:** Not given **Tinnitus Lateralisation:** All unilateral 2 L/4 R **Tinnitus Severity:** Not given **Tinnitus Pitch:** Patients experienced tinnitus pitch at the following frequencies:	**Sample size:** n=-6 **Hearing:** no or mild symmetrical HL **Sex:** 4 F/2 M **Age:** 44.8 ± 12.3 **Matched to tinnitus group for:** Age Sex Hearing thresholds Handedness	**Scanner Strength:** 7T **Voxel Size:** Anatomical: 0.6x0.6x0.6 mm^3 Functional: 1.5x1.5x1.5 mm^3 **Image Acquisition:** TR: 2000 ms TE: 19 ms **Instructions in Scanner:** Participants were asked to lie still and fixate on a white cross presented on a black background for ten minutes.	**Distortion Correction** Geometric distortion correction (with FSL's distortion correction tool pop-up (estimating the voxels; displacement based on data collected with the opposite phase encoding polarities) temporal high-pass filtering (removing drifts of four cycles or fewer per run) **Software Used:** Brain voyager QX (Brian Innovations, Maastricht) + custom MATLAB scripts **Motion Correction:** 3D motion correction (with	**Auditory (n=4)** - Primary auditory cortex - Non-primary auditory cortex - Medial geniculate body - Inferior colliculus	None found	PAC - Non-primary auditory cortex PAC - Medial geniculate body	The reduced connectivity between MGB and PAC was not specific to tinnitus pitch	Auditory network

		phonophobia, misophonia, cochlear dead regions (tested by threshold-equalising noise (TEN) test, hearing loss in pure tone over 50dB HL for both ears, a diff in average hearing threshold of more than 10dB b/w right and left ear, history of neurological / psychiatric disorders **Study Location:** Maastricht	205, 2660, 4470, 5600, 6000 and 8000 Hz. **Tinnitus Sound:** Not given **Hearing Information:** Participants were excluded if hearing loss in pure tone over 50dB HL for both ears, a diff in average hearing threshold of more than 10dB b/w right and left ear **Reported Comorbidities:** None			trilinear / sinc interpolation and aligning each volume to the first volume of functional run 1) **Slice timing Correction:** Yes, slice-can-time correction (with sinc interpolation) **Spatial Smoothing:** Temporal smoothing **Spatial Normalisation:** Talairach space					
2	Chen et al., 2017 Amygdala functional disconnection with the prefrontal-cingulate-temporal circuit in chronic tinnitus patients with depressive mood	**Aim:** To investigate the disrupted amygdala-cortical FC in chronic tinnitus with depressive mood using resting-state fMRI **Inclusion Criteria:** Chronic tinnitus (>6 months) **Exclusion Criteria:** Hyperacusis, Meniere's diseases, objective tinnitus, a past history of;	**Sample Size:** n=40 (Depressive: n=20; Non-depressive: n = 20) **Sex:** 25 F/15 M (Depressive: 12 F/8 M; Non-depressive: 13 F / 7 M) **Age:** Depressive: 49.75 ± 11.73 years Non-depressive: 53.60 ± 10.03 years	**Sample size:** n=23 **Hearing:** normal on PTA **Sex:** 13 F/10 M **Age:** 47.13 ± 12.17 years **Matched to tinnitus group for:** Age Sex Hearing thresholds Years of education SAS/SDS scores	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1x1x1 mm^3 Resting state: 3.75x3.75x4.0 mm^3 **Image Acquisition:** TR: 2000 ms TE: 30 ms **Instructions in Scanner:** Rest quietly with eyes closed but remain awake and avoid thinking of anything in particular.	**Distortion Correction** Detrending and filtering (0.01–0.08Hz) **Software Used:** REST **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, Gaussian kernel, 6 mm FWHM **Spatial Normalisation:** MNI template	**Auditory (n=0)** **Non-auditory (n=2)** - L amygdala - R amygdala	**All tinnitus vs. healthy controls:** L amygdala - L postcentral gyrus R amygdala - L postcentral gyrus **Depressive tinnitus vs non-depressive tinnitus:** L amygdala - L postcentral gyrus R amygdala - R lingual gyrus - R postcentral gyrus	**All tinnitus vs. healthy controls:** L amygdala - L superior temporal gyrus - L middle frontal gyrus - R posterior cingulate cortex R amygdala: - L superior temporal gyrus - R superior frontal gyrus - R middle frontal gyrus **Depressive tinnitus vs. non-**	No significant correlation found between the altered amygdala FC in depressed/non-depressed tinnitus patients and Self-rating Depression Scale scores	- Prefrontal-cingulate-temporal circuit - Executive control of attention network - Default mode network - Somatosensory network - Visual network

		severe alcoholism, smoking, head injury, stroke, Alzheimer's disease, Parkinson's disease, epilepsy, major depression or other neurological or psychiatric illness, major medical illness, MRI contraindications or severe visual loss. **Study Location:** Nanjing, China	**Tinnitus Duration:** Depressive: 44.10 ± 40.14 months Non-depressive: 51.60 ± 36.49 months **Tinnitus Lateralisation:** Bilateral/in the head: n=13. Unilateral: n=27 (15 L/12 R) **Tinnitus Severity:** Depressive: 56.78 ± 12.98 Non-depressive: 51.17 ± 13.75 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Normal hearing on PTA **Reported Comorbidities:** Depression based on Self-Rating Depression Scale SDS					**Non-depressive tinnitus vs. healthy controls:** L amygdala - L postcentral gyrus R amygdala - L postcentral gyrus **Depressive tinnitus vs. healthy controls:** L amygdala - L lingual gyrus R amygdala - R postcentral gyrus	**depressive tinnitus:** L amygdala: - L superior frontal gyrus - L middle frontal gyrus R amygdala: - L middle frontal gyrus - L anterior cingulate cortex **Non-depressive tinnitus vs. healthy controls:** L amygdala - L superior frontal gyrus - R posterior cingulate cortex R amygdala: - R superior frontal gyrus **Depressive tinnitus vs. healthy controls:** L amygdala - L middle temporal gyrus - L posterior cingulate cortex R amygdala - L superior temporal gyrus - L superior frontal gyrus		

									- L anterior cingulate cortex		
3	Chen et al., 2018 Tinnitus distress is associated with enhanced resting-state functional connectivity within the default mode network	**Aim:** To determine whether tinnitus disrupted FC patterns within the DMN as measured by using rs-fMRI. **Inclusion Criteria:** Chronic tinnitus (>6 months) **Exclusion Criteria:** pulsatile tinnitus, hyperacusis, Meniere's diseases, or had a past history of otologic surgery, ototoxic drug therapy, noise exposure, or hearing aid use, severe smoking, stroke, alcoholism, brain injury, Parkinson's disease, Alzheimer's disease, epilepsy, major depression, neurological or psychiatric disorders that could affect cognitive function, major medical illness, MRI	**Sample Size:** n=40 **Sex:** 21 F/19 M **Age:** 53.6 ± 12.5 years **Tinnitus Duration:** 41.9 ± 34.5 months **Tinnitus Lateralisation:** All bilateral (n=40) **Tinnitus Severity:** THQ: 52.1 ± 15.9 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Normal hearing on PTA **Reported Comorbidities:** Mild depression and mild anxiety were present in some members of both the tinnitus and the control group.	**Sample size:** n=41 **Hearing:** Normal on PTA **Sex:** 25 F/16 M **Age:** 49.5 ± 10.5 years **Matched to tinnitus group for:** Age Sex Hearing thresholds Years of education Handedness	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1x1x1 mm^3 Resting state: 3.75x3.75x4.0 mm^3 **Image Acquisition:** TR: 2000 ms TE: 30 ms **Instructions in Scanner:** Lie quietly with eyes closed without falling asleep, do not think of anything in particular, and avoid any head motion during the scan. Ear plugs with 32 dB noise attenuation were worn.	**Distortion Correction** Detrending and Filtering (0.01- 0.08 Hz) **Software Used:** Data Processing Assistant for Resting State fMRI (DPARSF) programs based on SPM12, and REST **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 6mm **Spatial Normalisation:** MNI Template	**Auditory (n=0)** **Non-auditory (n=2)** - Anterior cingulate cortex - Posterior cingulate cortex	Anterior cingulate cortex - L precuneus Posterior cingulate cortex - R medial prefrontal cortex	None found	- Enhanced FC between ACC and L precuneus was positively correlated with tinnitus duration (r=0.451, p=0.007) - Enhanced FC between PCC and R mPFC was positively correlated with tinnitus distress (r=0.411, p=0.014)	Default mode network

		contraindications, or severe visual loss. **Study Location:** Nanjing Medical University, China									
4	Chen et al., 2018 Abnormal Resting-State Functional Connectivity of the Anterior Cingulate Cortex in Unilateral Chronic Tinnitus Patients	**Aim:** To illuminate the functional connectivity (FC) network of the ACC subregions in chronic tinnitus patients using resting state fMRI **Inclusion Criteria:** Unilateral chronic tinnitus (>6 months) **Exclusion Criteria:** Meniere's diseases, pulsatile tinnitus, or hyperacusis, or if they had a past history of severe alcoholism, smoking, head injury, stroke, Alzheimer's disease, Parkinson's disease, epilepsy, major depression, or other neurological or psychiatric illness, major medical illness,	**Sample Size:** n=31 **Sex:** 17 F/14 M **Age:** 51.4 ± 13.3 years **Tinnitus Duration:** 40.6 ± 35.5 months **Tinnitus Lateralisation:** All unilateral, left sided (n=31) **Tinnitus Severity:** THQ: 51.7 ± 15.8 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Normal hearing on PTA **Reported Comorbidities:** No depression or anxiety according to SDS/SAS scores.	**Sample size:** n=40 **Hearing:** Normal on PTA **Sex:** 21 F/19 M **Age:** 48.2 ± 14.2 years **Matched to tinnitus group for:** Age Sex Years of education Hearing thresholds SDS & SAS scores Brain parenchyma volume Handedness	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1x1x1 mm^3 Resting state: 3.75x3.75x4.0 mm^3 **Image Acquisition:** TR: 2000 ms TE: 30 ms **Instructions in Scanner:** Lie quietly with eyes closed without falling asleep, do not think of anything in particular, and avoid any head motion during the scan. Ear plugs with 32 dB noise attenuation were worn.	**Distortion Correction** Detrending and filtering (0.01–0.08Hz) **Software Used:** Data Processing Assistant for Resting State fMRI (DPARSF) programs based on SPM8, and REST **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Gaussian kernel FWHM = 6mm **Spatial Normalisation:** MNI template	**Auditory (n=0)** **Non auditory (n= 2)** - Rostral Anterior Cingulate Cortex - Dorsal Anterior Cingulate Cortex	Rostral Anterior Cingulate Cortex - L Precuneus - R Postcentral Gyrus - R Putamen Dorsal Anterior Cingulate Cortex - R Superior Temporal Gyrus - R Inferior Parietal Lobule - R Orbitofrontal Cortex - R Medial Prefrontal Gyrus	Rostral Anterior Cingulate Cortex - L Calcarine Cortex Dorsal Anterior Cingulate Cortex - R Fusiform Gyrus	- Enhanced FC between rostral ACC and L precuneus was positively correlated with tinnitus severity (r=0.507, p=0.008) - Enhanced FC between dorsal ACC and r IPL was positively correlated with tinnitus severity (r=0.447, p=0.022)	- Auditory network - Default mode network - Visual network - Executive functions/frontal network Somatosensory network

		MRI contraindications, and severe visual loss. **Study Location:** Nanjing Medical University, China									
5	Chen et al., 2018 Alterations of the default mode network and cognitive impairment in patients with unilateral chronic tinnitus	To investigate the intrinsic functional connectivity pattern within the default mode network and its associations with cognitive impairment in tinnitus patients using a resting-state fMRI **Inclusion Criteria:** Right-sided chronic tinnitus (>6 months) **Exclusion Criteria:** Meniere's diseases, pulsatile tinnitus, or hyperacusis, or if they had a past history of severe alcoholism, smoking, head injury, stroke, Alzheimer's disease, Parkinson's disease, epilepsy, major depression, or other	**Sample Size:** n=35 **Sex:** 20 F/15 M **Age:** 49.94 ± 13.73 years **Tinnitus Duration:** 37.71 ± 34.58 months **Tinnitus Lateralisation:** All unilateral, right sided (n=35) **Tinnitus Severity:** THQ: 52.22 ± 15.08 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Normal hearing on PTA **Reported Comorbidities:** Mean SAS and SAD was under	**Sample size:** n=50 **Hearing:** Normal on PTA **Sex:** 30 F/20 M **Age:** 45.16 ± 14.35 years **Matched to tinnitus group for:** Age Sex Years of education Hearing thresholds SDS & SAS scores Brain parenchyma volume Grey and white matter volume Handedness	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1x1x1 mm^3 Resting state: 3.75x3.75x4.0 mm^3 **Image Acquisition:** TR: 2000 ms TE: 30 ms **Instructions in Scanner:** Lie quietly with eyes closed without falling asleep, do not think of anything in particular, and avoid any head motion during the scan. Ear plugs with 32 dB noise attenuation were worn.	**Distortion Correction** Detrending and filtering (0.01–0.08Hz) **Software Used:** Data Processing & Analysis for (Resting-State) Brain Imaging (DPABI_ V2.3_170105) **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Gaussian kernel FWHM = 6mm, then detrending, then filtering (0.01-0.08 Hz) **Spatial Normalisation:** MNI template	**Auditory (n=0)** **Non auditory (n=1)** - Posterior Cingulate Cortex	Posterior cingulate cortex - R medial prefrontal cortex	None	Enhanced FC between the PCC and right mPFC was correlated with the poorer Trail Making Test-B scores (r=0.474, P=0.008) but not with any of the other cognitive tests or with tinnitus performance	Default mode network

		neurological or psychiatric illness, major medical illness, MRI contraindications, and severe visual loss. **Study Location:** Nanjing Medical University, China	50 but given the SD some participants might have classified as having mild anxiety/depression								
6	Feng et al., 2018 Increased Resting-State Cerebellar-Cerebral Functional Connectivity Underlying Chronic Tinnitus	**Aim:** To illuminate the functional connectivity network of the cerebellar regions in chronic tinnitus patients and controls using resting state fMRI **Inclusion Criteria:** Chronic tinnitus >6 months **Exclusion Criteria:** Meniere's disease, pulsatile tinnitus or hyperacusis, or if they had a history of severe alcoholism, smoking, head injury, stroke, Alzheimer's disease, Parkinson's disease, epilepsy, major depression,	**Sample Size:** n=28 **Sex:** 19 F/9 M **Age:** 50.2 ± 12.8 years **Tinnitus Duration:** 47.8 ± 40.0 months **Tinnitus Lateralisation:** Bilateral/central (n=8) Unilateral (n=20, 13 L/7 R) **Tinnitus Severity:** THQ: 50.8 ± 16.3 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Normal hearing on PTA	**Sample size:** n=29 **Hearing:** Normal on PTA **Sex:** 19 F/10 M **Age:** 44.3 ± 14.6 years **Matched to tinnitus group for:** Age Sex Years of education Hearing thresholds Brain parenchyma volume Grey and white matter volume Handedness	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1x1x1 mm^3 Resting state: 3.75x3.75x4.0 mm^3 **Image Acquisition:** TR: 2000 ms TE: 30 ms **Instructions in Scanner:** Lie quietly with eyes closed, do not fall asleep, do not think of anything special, and avoid head motion. Ear plugs with 32 dB noise attenuation were worn.	**Distortion Correction** Detrending and filtering (0.01–0.08Hz) **Software Used:** Data Processing Assistant for Resting State fMRI (DPARSF) programs based on SPM8, and REST **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Gaussian kernel FWHM = 6mm, then detrending, then filtering (0.01-0.08 Hz) **Spatial Normalisation:** MNI template	**Auditory (n=0)** **Non auditory (n=9)** - Cerebellum L Crus I - Cerebellum R Crus I - Cerebellum L Crus II - Cerebellum R Crus II - Cerebellum L Lobule VI - Cerebellum R Lobule VI - Cerebellum L Lobule VIIb - Cerebellum R Lobule VIIb - Cerebellum Vermis	L Crus I - L parahippocampal gyrus R Crus I - R inferior occipital gyrus R Crus II - R Inferior occipital gyrus L Lobule VIIb - R superior temporal gyrus R Lobule VIIb - L Precentral Gyrus Vermis - R Superior temporal gyrus	None found	- The increased functional connectivity between L cerebellar Lobule VIIb and R STG was positively correlated with Tinnitus Handicap Questionnaires (THQ) scores (r = 0.577, p = 0.004). - The increased functional connectivity between the cerebellar vermis and the right STG was also associated with the THQ score (r = 0.432, p = 0.039).	- Auditory network - Limbic system - Visual network

		other neurological or psychiatric illness, major medical illnesses, MRI contraindications, and/or severe vision loss. **Study Location:** Nanjing Medical University, China	**Reported Comorbidities:** No depression or anxiety according to SDS/SAS.								
7	Henderson et al., 2019 Corticostriatal functional connectivity of bothersome tinnitus in single-sided deafness	**Aim:** To define whole-brain connectivity patterns of the caudate nucleus and auditory cortex in a single sided deaf cohort with bothersome tinnitus compared to a single sided deaf cohort with no or non-bothersome tinnitus using resting-state fMRI **Inclusion Criteria:** Chronic tinnitus (≥1 year), constant, non-pulsatile, normal hearing in one ear and severe or profound hearing loss in the other	**Sample Size:** n = 15 **Sex:** 6 F /9 M **Age:** 51.1 ± 8.52 years **Tinnitus Duration:** All >1 year (exact duration not given) **Tinnitus Lateralisation:** All unilateral, in deaf ear (n=15, 7 L/8 R) **Tinnitus Severity:** TFI: 41.7 ± 27.89 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:**	**Sample size:** n = 15 **Hearing:** Single-sided deafness **Sex:** 6 F /9 M **Age:** 47.2 ± 17.43 years **Matched to tinnitus group for:** Age Sex Handedness Hearing thresholds Duration of deafness	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 0.5x0.5x1.5 mm^3 Resting state: 1.88x1.88x3.0 mm^3 **Image Acquisition:** TR: 2000 ms TE: 28 ms **Instructions in Scanner:** Ear plugs that attenuate noise by 32 dB were worn.	**Distortion Correction** Temporal bandpass filtering (0.008Hz-0.09Hz) **Software Used:** CONN Toolbox **Motion Correction:** Functional realignment & unwarping **Slice timing Correction:** N/A **Spatial Smoothing:** Gaussian kernel FWHM = 8mm. **Spatial Normalisation:** MNI template	**Auditory (n=2)** - L Heschl's gyrus - R Heschl's gyrus **Non auditory (n=2)** - L caudate nucleus - R caudate nucleus	L Caudate Nucleus - L Heschl's Gyrus - R supplementary motor area	None found	Within the tinnitus group, connectivity strength between the R caudate nucleus and: - cuneus was positively correlated with TFI subscale "relax" (R^2=0.67, p<0.05); - superior lateral occipital cortex was positively correlated with TFI subscale "control" (R^2=0.82, p<0.05); - anterior supramarginal gyrus was positively correlated with TFI subscale "control"	- Auditory network - Limbic system - Motor network - Default mode network - Visual network - Dorsal attention network

		Exclusion Criteria: Not given **Study Location:** San Francisco, University of California, USA.	Non-congenital, single-sided deafness **Reported Comorbidities:** Some had vestibular schwannoma							(R^2=0.78, p<0.05).	
8	Hinkley et al., 2015 Increased striatal functional connectivity with auditory cortex in tinnitus	**Aim:** To test the "striatal gating model" of tinnitus by comparing rs-fMRI patterns of the striatum and auditory regions in tinnitus patients and controls **Inclusion Criteria:** Chronic tinnitus (>1 year) **Exclusion Criteria:** Not given **Study Location:** University of California at San Francisco, USA	**Sample Size:** n = 15 **Sex:** 3 F/12 M **Age:** 53.5 ± 13 years **Tinnitus Duration:** Not given **Tinnitus Lateralisation:** Bilateral (n=9) Unilateral (n=6 3 L/3 R) **Tinnitus Severity:** THI: 39 ± 20.33 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Tinnitus group: wide range from mild to severe hearing loss. **Reported Comorbidities:** Not given	**Sample size:** n = 15 **Hearing:** Normal on PTA **Sex:** Not given **Age:** 57 ± 12 years **Matched to tinnitus group for:** Age Sex Not matched for hearing thresholds	**Scanner Strength:** 3T **Voxel Size:** Anatomical: Slice thickness = 1mm; FOV = 256mm; matrix size = not given Resting state: 3x3x3mm^3 **Image Acquisition:** TR: 2000 ms TE: 28 ms **Instructions in Scanner:** Eyes closed	**Distortion Correction** Linearly detrended and bandpass filtered (second-order Butterworth; 0.01–0.08 Hz) **Software Used:** SPM8 **Motion Correction:** Realignment **Slice timing Correction:** No **Spatial Smoothing:** Gaussian kernel FWHM = 8mm. **Spatial Normalisation:** MNI template	**Auditory (n=2)** - L Primary Auditory Cortex - R Primary Auditory Cortex **Non auditory (n=6)** - L Caudate Dorsal Striatum - R Caudate Dorsal Striatum - L Caudate Head - R Caudate Head - L Nucleus Accumbens - R Nucleus Accumbens	L Primary Auditory Cortex - R anterior superior temporal gyrus - L middle temporal gyrus - L superior frontal gyrus - L posterior cerebellum - R parahippocampal gyrus - L Lingual Gyrus R Primary Auditory Cortex - L middle temporal gyrus - L superior frontal gyrus - R middle occipital gyrus - R post central gyrus L Caudate Dorsal Striatum - L middle temporal gyrus R Caudate Dorsal Striatum	L Caudate Dorsal Striatum - L lingual gyrus - L culmen R Caudate Dorsal Striatum - L lingual gyrus - R lingual gyrus R Caudate Head - L culmen - R lingual gyrus L Nucleus Accumbens - R superior temporal gyrus - R culmen - L lingual gyrus - R lingual gyrus - L inferior parietal lobe	Voxelwise correlations with THI scores in the tinnitus cohort were insignificant when corrected for multiple comparisons.	- Auditory network - Visual network - Default mode network - Dorsal attention network - Limbic system

								- R superior temporal gyrus - R middle occipital gyrus - R post central gyrus L Caudate Head - R Putamen - R middle frontal gyrus - R cingulate - R inferior parietal lobe R Caudate Head - L superior frontal gyrus - R inferior parietal lobe R Nucleus Accumbens - L middle temporal gyrus - L superior frontal gyrus - L posterior cerebellum - L lingual gyrus - L inferior parietal lobe			
9	Job et al., 2020 Functional Connectivity in Chronic Nonbothersome Tinnitus Following Acoustic Trauma: A Seed-Based Resting-State Functional Magnetic	**Aim:** To investigate whole-brain functional connectivity in non-bothersome tinnitus following acoustic trauma, including the role of right	**Sample Size:** n = 19 **Sex:** 0 F/19 M **Age:** 42.5 ± 12 years **Tinnitus Duration:** 12.2 ± 7.3 years	**Sample size:** n = 19 **Hearing:** Normal on PTA **Sex:** 0 F/19 M **Age:** 42.5 ± 11.9 years	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 0.9x0.9x1.2 mm^3 Resting state: 3x3x3.5mm^3 **Image Acquisition:** TR: 2000 ms	**Distortion Correction** Band-pass filtering (0.008 to 0.08H) **Software Used:** SPM12 and CONN toolbox **Motion Correction:** Realignment using DARTEL	**Auditory (n=6)** - L inferior colliculus - R inferior colliculus - L medial geniculate body - R medial geniculate body - L Heschl's gyrus - R Heschl's gyrus **Non auditory (n=5)** - R Operculum 3 - L Operculum 3	L Heschl's Gyrus - Posterior Cingulate Cortex L Inferior Colliculus - R Superior Parietal Lobule R Inferior Colliculus	None found	N/A	- Auditory network - Default mode network - Sensorimotor-auditory network - Frontoparietal network

	Resonance Imaging Study	parietal operculum 3 (OP3). **Inclusion Criteria:** Chronic non-bothersome tinnitus due to acoustic trauma (duration > 6 months) **Exclusion Criteria:** Not given **Study Location:** France	**Tinnitus Lateralisation:** Bilateral (n=13) Unilateral (n=6 3 L/3 R) **Tinnitus Severity:** THI: 16.2 ± 10.5 (slight to moderate) **Tinnitus Pitch:** Not given **Tinnitus Sound:** high-pitched whistling (n=18) medium high-pitched sizzling (n=1) **Hearing Information:** hearing loss at frequencies > 4kHz **Reported Comorbidities:** No anxiety or depression.	**Matched to tinnitus group for:** Age Sex Not matched for hearing thresholds	TE: 32 ms **Instructions in Scanner:** Lie with eyes open and let the mind wander without focusing on anything in particular. A gray background image with a small white cross in the center was displayed.	**Slice timing Correction:** Yes **Spatial Smoothing:** Smoothed with a small kernel (1.5mm^3 isotropic) **Spatial Normalisation:** MNI template	- Anterior to R Operculum 3 - Posterior to R Operculum 3 - Whole R Operculum 3 **Whole networks (n=7)** Based on Human Connectome Project, seeds defined using CONN toolbox - DMN - Visual - Sensorimotor-auditory - Saliency - Language - Frontoparietal - Dorsal attentional	- R Superior Parietal Lobule R Operculum 3 - R Superior Frontal gyrus Posterior to R Operculum 3 - L Superior Frontal Gyrus - L Inferior Parietal Lobule Sensorimotor–auditory network - R paracingulate network - R posterior middle temporal gyrus - L inferior precentral gyrus Frontoparietal network - R middle frontal gyrus			
10	Zhang et al., 2015 Impairments of thalamic resting-state functional connectivity in patients with chronic tinnitus	**Aim:** To compare the degree of thalamocortical functional connectivity in chronic tinnitus patients and controls using resting-state fMRI. **Inclusion Criteria:**	**Sample Size:** n=31 **Sex:** 13 F/18 M **Age:** 40.8 ± 13.2) years **Tinnitus Duration:** 42.6 ± 41.1 months	**Sample size:** n=33 **Hearing:** Normal on PTA **Sex:** 15 F /18 M **Age:** 45.2 ± 11.9 years	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1x1x1 mm^3 Resting state: 3,75x3,75x4 mm^3 **Image Acquisition:** TR: 2000 ms TE: 25 ms	**Distortion Correction** Detrending and filtering (0.01–0.08 Hz) **Software Used:** SBM8, REST, Data Processing Assistant for Resting-State fMRI, WFU_Pickatlas software, VBM8 Toolbox	**Auditory (n=2)** - L Thalamus - R Thalamus **Non auditory (n=0)**	L Thalamus - R angular gyrus - R middle cingulate cortex - L cerebellar posterior lobe R Thalamus - L Posterior Cingulate Cortex	L Thalamus - R Middle Temporal Gyrus - R Middle Orbitofrontal Cortex - L Middle Frontal Gyrus - R Precentral Gyrus - L Calcarine Cortex	- In tinnitus patients, the functional connectivity between the left thalamus and right MTG was negatively correlated with the THQ total score (r = −0.482, p = 0.011).	- Auditory network - Visual network - Default mode network

		Chronic tinnitus (>6 months) **Exclusion Criteria:** Hyperacusis, pulsatile tinnitus, Meniere's disease, history of heavy smoking, stroke, alcoholism, epilepsy, major depression, neurological or psychiatric disorders, brain injury, Parkinson's, Alzheimer's, major medical illness, severe visual impairment or MRI contraindications. **Study Location:** Hospital Southeast University, China	**Tinnitus Lateralisation:** Bilateral/central (n=7) Unilateral (n=24, 14 L/10 R) **Tinnitus Severity:** THQ = 41.4 ± 19.7 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Normal hearing on PTA **Reported Comorbidities:** No depression or anxiety according to SDS/SAS	**Matched to tinnitus group for:** Age Sex Hearing thresholds Years of education Handedness	**Instructions in Scanner:** Keep your eyes closed but remain awake and avoid specific thoughts. Ear plugs with 32 dB attenuation were worn.	**Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 4mm. **Spatial Normalisation:** MNI template		- L Cerebellar Posterior Lobe - R Cerebellar Posterior Lobe	- R Calcarine Cortex R Thalamus - L Superior temporal Gyrus - L Amygdala - R Superior Frontal Gyrus - L Precentral Gyrus - L Middle Occipital Gyrus	- The functional connectivity between the right thalamus and left STG was negatively correlated with tinnitus duration (r = −0.454, p = 0.017).	
11	Schmidt et al., 2017 Connectivity of precuneus to the default mode and dorsal attention networks: A possible invariant marker of long-term tinnitus	**Aim:** The aim was to identify resting state functional connectivity alterations that consistently appear across tinnitus subgroups. We examined two sources of variability in the subgroups: tinnitus severity	M=Mild, B=Bothersome, L=Long-term, R=Recent **Sample Size:** MRTIN: n=13 MLTIN_1: n=12 MLTIN_2: n=17 BLTIN: n=15 **Sex:** MRTIN: 8 F/5 M MLTIN_1: 3 F/9 M MLTIN_2: 4	**Sample size:** NH: n=15 HL: n=13 **Hearing:** NH: Normal on PTA HL: mild to moderate **Sex:** NH: 9 M/6 F HL: 5 M/8 F **Age:**	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1.0x1.0x1.2 mm^3 (scanner 1 & 2) Resting state: 3.4x3.4x4.0 mm^3 (scanner 1) 2.5x2.5x3.0 mm^3 (scanner 2) **Image Acquisition:**	**Distortion Correction** None given **Software Used:** SPM8 **Motion Correction:** Six-parameter rigid body transformation **Slice timing Correction:** Yes **Spatial Smoothing:**	**Auditory (n=2)** - L Primary Auditory Cortex - R Primary Auditory Cortex **DMN (n=2) combined** - Medial Prefrontal Cortex - Posterior Cingulate Cortex **DAN (n=4) combined** - L Posterior Intraparietal Sulcus	Auditory network: None found Dorsal attention network: - Precuneus - Region near L precentral gyrus (unspecified)	Default mode network: - Precuneus - Frontal medial cortex - Lateral superior occipital cortex	No differences were found in any analyses between tinnitus severity subgroups; the differences described are between controls vs. tinnitus groups or between long-term vs. short-term tinnitus groups	- Default mode network - Dorsal attention network

		and tinnitus duration. **Inclusion Criteria:** Between 30 and 70 years old. **Exclusion Criteria:** No hyperacusis. Neurological disorders; Meniere's disease, TMJ, depression or anxiety; chronic physical disease, currently undergoing tinnitus treatment. **Study Location:** Illinois, University of Illinois Urbana-Champaign, USA	F/13 M BLTIN: 7 F/8 M **Age:** MRTIN 48.38 (± 12.15) MLTIN_1 55 (± 6.97) MLTIN_2 51.65 (± 11.79) BLTIN 50.07 (± 10.23) **Tinnitus Duration:** MRTIN: between 6 and 12 months Others: >12 months **Tinnitus Lateralisation:** MRTIN: bilateral (n-=3), unilateral (n=1), unknowns (n=9) MLTIN_1: bilateral (n=8), unilateral left (n=2), unknown (n=2) MLTIN_2: bilateral (n=15), unilateral left (n=1), unknown (n=1) BLTIN: bilateral (n=13), unilateral right (n=1), unknown (n=1) **Tinnitus Severity:** MRTIN: mild (THI: 16.46 ± 4.63) MLTIN_1: mild (THI: 8.33 ±	NH: 53 (SD 8.73) HL: 57.62 (SD 9.39) **Matched to tinnitus group for:** Age Sex Hearing thresholds (in the case of the HL control group)	**TR:** 2000 ms **TE:** 30 ms (scanner 1) and 25 ms (scanner 2) **Instructions in Scanner:** Subjects were instructed to lay still and fixate on a cross for the duration of the scan. They wore ear plugs and headphones.	Yes, Gaussian kernel FWHM = 10mm. **Spatial Normalisation:** MNI Template	- R Posterior Intraparietal Sulcus - L Frontal Eye Field - R Frontal Eye Field				

			6.76) MLTIN_2: mild (THI: 9.41 ± 4.73) BLTIN: mild – moderate (THI: 29.47 ± 10.89) **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Mean PTAs are mild to moderate hearing loss, some participants likely had no hearing loss and others a mild/moderate one. It is unclear if HL was unilateral or bilateral **Reported Comorbidities:** BDI and BAI scores were all minimal or mild.								
12	Wineland et al., 2012 Functional Connectivity Networks in Nonbothersome Tinnitus	**Aim:** To assess functional connectivity in cortical networks in patients with nonbothersome tinnitus compared with a normal healthy nontinnitus	**Sample Size:** n = 18 **Sex:** 6 F/12 M **Age:** Median = 54 (IQR = 52-57) **Tinnitus Duration:**	**Sample size:** n = 23 **Hearing:** Normal on PTA **Sex:** 11 F/12 M **Age:** Median = 46 (IQR = 39-54)	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1x1x1.25 mm^3 Resting state 4x4x4 mm^3 **Image Acquisition:** TR: 2200 ms TE: 27 ms	**Distortion Correction** Band-pass filtering to remove nuisance variables and whole-brain signal normalization to mode 1000 **Software Used:** FreeSurfer **Motion Correction:**	58 spherical seed regions were defined to reflect the following networks: - Dorsal attention network - Ventral attention network - Cognitive network - Default mode network - Auditory network - Visual network	None found	None found	N/A	None found

		control group using rs-fMRI. **Inclusion Criteria:** Non-bothersome, idiopathic subjective tinnitus for at least 6 months. **Exclusion Criteria:** Anyone with (1) an active diagnosis of any acute or chronic brain-related neurological conditions; (2) history of head trauma, seizure, or stroke; (3) a retrocochlear lesion or anatomic/structural lesion of the brain, skull base, temporal bone, or ear; or (4) active depression or anxiety disorder or who had recently began taking medications to treat depression or anxiety. **Study Location:** Missouri, USA	Median = 9 years (IQR = not given) **Tinnitus Lateralisation:** Bilateral (n=12) Unilateral (n=6) **Tinnitus Severity:** Median THI score = 8 (IQR 4-14) **Tinnitus Pitch:** Not given **Tinnitus Sound:** Ringing (14), hum (2), hissing (2), high-tension wire (4), buzzing (2), whistle (1), clear tone (2), cicadas (1), transformer noise (1), clicking (1), crickets (2), **Hearing Information:** From mild to severe hearing loss **Reported Comorbidities:** None	**Matched to tinnitus group for;** Sex Not matched for age Not matched for hearing thresholds	**Instructions in Scanner:** Participants were awake, performed no task, and kept their eyes closed in a darkened room	12 parameter affine transformations **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, spatially smoothed (6 mm FWHM Gaussian kernel) **Spatial Normalisation:** Talairach standard space	- Somatosensory network				
13	Burton et al., 2012 Altered networks in bothersome tinnitus: a	**Aim:** To examine functional connectivity linked to the auditory system in patients with	**Sample size:** n = 17 **Sex:** 12 M/5 F **Age:**	**Sample size:** n=17 **Hearing:** Normal on PTA **Sex:**	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1x1x1.25 mm^3	**Distortion Correction** Band-pass filter for low frequencies, and to remove nuisance variables & Whole brain mean signal	**Auditory network (n=2)** - R Primary Auditory Cortex - L Primary Auditory Cortex	L Inferior Frontal Gyrus - R Anterior Insula	R Primary Auditory Cortex - Occipital Pole - L Parietal Occipital Sulcus	N/A	- Auditory network - Visual network - Attention control network

	functional connectivity study	chronic bothersome tinnitus **Inclusion Criteria:** Bothersome tinnitus (based on THI >38) **Exclusion Criteria:** Hyperacusis **Study Location:** Missouri, USA	53.5 ± 3.6 years **Tinnitus Duration:** 8.3 ± 1.9 years **Tinnitus Lateralisation:** Bilateral (n=11), unilateral (n=5, 4 R / 1 L) **Tinnitus Severity:** 53.5 ± 3.6 (THI) Moderate n=10, severe n=7 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Minimal hearing loss for 1- 3 kHz and > 40dB for 8 kHz in 12 / 17 participants **Reported Comorbidities:** None	7 M/10 F **Age:** 53.5 ± 3.6 years 53.6 **Matched to tinnitus group for:** Age Not matched for hearing thresholds	Resting state: 4x4x4 mm^3 **Image Acquisition:** TR: 2200 ms, TE: 27 ms **Instructions in Scanner:** Participants were awake, performed no task and kept their eyes closed in a darkened room	intensity normalized to mode 1000 across EPI runs **Software Packages:** Analyze (Mayo Research Foundation, Rochester, MN **Motion Correction:** rigid body correction for inter-frame head motion; resliced to 2mm3 by 12 parameter affine transformations **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, with 6 mm FWHM Gaussian kernel **Spatial Normalisation:** Talairach standard space	**Visual network (n=2)** - R Primary Visual - L Cuneus **Somatosensory network (n=2)** - R Postcentral Gyrus - L Parietal Operculum **Dorsal attention network (n=5)** - L Posterior Intraparietal Sulcus - R Posterior Intraparietal Sulcus - L Frontal Eye Fields - R Ventral Intraparietal Sulcus **Ventral attention network (n=2)** - R Temporoparietal Junction - R Superior Temporal Sulcus **Attention control network (n=4)** - R Middle Frontal Gyrus - R Anterior Insula - L Inferior Frontal Gyrus - R Inferior Frontal Gyrus		- Calcarine Sulcus - Cuneus - Lingual Gyri L Primary Auditory Cortex - Occipital Pole - L Parietal Occipital Sulcus - Calcarine Sulcus - Cuneus - Lingual Gyri R Primary Visual Cortex - L Superior Temporal Gyrus - L Sulcal Auditory Cortex - L Rostral Insula - L Inferior Frontal Gyrus R Anterior Insula - L Medial Occipital Cortex - R Medial Occipital Cortex - L Lateral Occipital Cortex - R Lateral Occipital Cortex L Inferior Frontal Gyrus - Medial occipital cortex		

14	Minami et al., 2018 Auditory Related Resting State fMRI Functional Connectivity in Tinnitus Patients: Tinnitus Diagnosis Performance	**Aim:** To investigate functional connectivity in tinnitus patients with and without hearing loss and to design the tinnitus diagnosis performance by resting state functional magnetic resonance imaging (rs-fMRI). **Inclusion Criteria:** Chronic tinnitus > 6 months **Exclusion Criteria:** Not given **Study Location:** Tokyo, Japan	**Sample Size:** With hearing loss: n=18 Without hearing loss: n=11 **Sex:** Not given **Age:** With HL median = 60 Without HL median = 37 years **Tinnitus Duration:** Not given **Tinnitus Lateralisation:** Not given **Tinnitus Severity:** With HL: TFI = 50 (± 21) Without HL: TFI = 39 ± 26 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Mild HL: n=12 Moderate HL n=2 Severe HL: n=4 **Reported Comorbidities:** Not given	**Sample size:** n = 19 **Hearing:** Normal on PTA **Sex:** Not given **Age:** Median = 35 years **Matched to tinnitus group for:** Not given Not matched for hearing thresholds	**Scanner Strength:** 1.5T **Voxel Size:** Anatomical: 0.72x0.72x4 mm^3 Resting state: 3.44×3.44x4 mm^3 **Image Acquisition:** TR: 2500 ms TE: 40 ms **Instructions in Scanner:** Subjects were asked to lie motionless with their eyes open during the rs-fMRI acquisition.	**Distortion Correction** Band-pass filtering (0.008 - 0.09 Hz) **Software Used:** SPM8 & CONN toolbox **Motion Correction:** Realignment **Slice timing Correction:** Not given **Spatial Smoothing:** Yes, specifics not given **Spatial Normalisation:** Atlas not given	**Auditory (n=6)** - Heschl's Gyrus - Planum temporale - Planum polare - Operculum - Insular cortex - Superior temporal gyrus **Non auditory (n=0*)**	None? / ROI names and statistics are not legible in figures	None? / ROI names and statistics are not legible in figures	Associations within auditory ROIs were weakened in tinnitus patients according to authors, but exact ROIs and statistics are not legible due to poor image quality	Auditory network
15	Lee et al., 2012	**Aim:**	**Sample Size:** n = 16	No control group -	**Scanner Strength:** 3T	**Distortion Correction**	58 spherical seed regions with a	None found	None found	N/A	None found

	Functional Connectivity during Modulation of Tinnitus with Orofacial Manoeuvres	To determine changes in cortical neural networks as defined by rs-fMRI during voluntary modulation of tinnitus with orofacial manoeuvres. **Inclusion Criteria:** Idiopathic, subjective, unilateral or bilateral, and chronic, non-pulsatile tinnitus + reproducible, voluntary control over their tinnitus, whether through attention redirection or an orofacial manoeuvre compatible with MRI's motion sensitivity **Exclusion Criteria:** History of hyperacusis, misophonia, or neurological injury or illness **Study Location:** Missouri, USA	**Sex:** 6 F/10 M **Age:** 53.7 ± 10.4 years **Tinnitus Duration:** 20.5 ± 18 years **Tinnitus Lateralisation:** Bilateral (n=10) Unilateral (n=6 3 L/3 R) **Tinnitus Severity:** THI = 32.1 ± 25.6 (0- 78), loudness rating = 5.4 ± 2.4 (scale of 0-10 of loudness) **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Ranging from mild to severe HL **Reported Comorbidities:** Not given	participants served as their own baseline by comparing their resting-state data to their functional data during orofacial manoeuvres	**Voxel Size:** Not given **Image Acquisition:** TR/TE: Not given **Instructions in Scanner:** During the first 2 scans, tinnitus patients performed their tinnitus-altering manoeuvre, and during the last 2 scans, patients remained at rest with their eyes closed.	Whole-brain signal intensity normalisation to a mode of 1000 Temporal band-pass filtering for frequencies <0.1 Hz **Software Used:** Analyze (Mayo Research Foundation, Rochester, Minnesota) **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, 6 mm FWHM Gaussian kernel **Spatial Normalisation:** Atlas derived from 12 healthy adults https://pubmed.ncbi.nlm.nih.gov/16172003/	diameter of 10mm were determined using Talairach coordinates in the following networks: - Default mode network - Dorsal attention network - Ventral attention network - Cognitive/control network - Auditory network - Visual network - Somatosensory network				

Resting-state fMRI studies using seed-based functional connectivity analysis

Directional Connectivity Studies

Nr	Study	Study information	Tinnitus group(s) information:	Control group(s) information:	Scanning info	Data pre-processing	Data Analysis Information	Regions showing increased connectivity in tinnitus compared to controls	Regions showing decreased connectivity in tinnitus compared to controls	Additional findings	Networks associated with the altered connectivity in chronic tinnitus
16	Chen et al., 2016 Disrupted Brain Functional Network Architecture in Chronic Tinnitus Patients	**Aim:** To identify aberrant brain network architecture involved in chronic tinnitus, through comparing the resting-state fMRI (rs-fMRI) patterns of tinnitus patients and healthy controls. **Inclusion Criteria:** Chronic tinnitus (>6 months) **Exclusion Criteria:** Hyperacusis, pulsatile tinnitus or Meniere's diseases, or if they had a past	**Sample Size:** n = 24 **Sex:** 15 F/9 M **Age:** 50.8 ± 12.4 years **Tinnitus Duration:** 46.5 ± 39.1 (6–120) months **Tinnitus Lateralisation:** Bilateral/in the head (n=8) Unilateral (n=16, 10 L/6 R) **Tinnitus Severity:** THQ: 49.5 ± 15.5 **Tinnitus Pitch:** Not given	**Sample size:** n = 22 **Hearing:** Normal on PTA **Sex:** 13 F/9 M **Age:** 44.7 ± 15.4 years **Matched to tinnitus group for:** Age Sex Hearing thresholds Years of education	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1x1x1 mm^3 Resting state: 3.75x3.75x4.0 mm^3 **Image Acquisition:** TR: 2000 ms TE: 30 ms **Instructions in Scanner:** Subjects were instructed to lie quietly with their eyes closed without falling asleep, not think of anything in particular, and avoid any head motion during the scan. They wore	**Distortion Correction** Detrending and filtering (0.01–0.08Hz) **Software Used:** Data Processing Assistant for Resting State fMRI (DPARSF) programs based on SPM8, and REST **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 6mm. **Spatial Normalisation:** MNI template	**Type of Analysis:** Degree centrality of the whole-brain network (data-driven method for selecting ROIs) and Granger Causality Analysis for directional connectivity **Region(s) of Interest:** **Auditory (n=0)** **Non-auditory (n=2)** - L Superior Frontal Gyrus - R Superior Frontal Gyrus	L Superior Frontal Gyrus → L Orbitofrontal Cortex → L Precentral gyrus → L Posterior lobe of cerebellum → R Middle Occipital Gyrus R Superior Frontal Gyrus → R Supplementary motor area	None found	THQ scores positively correlated with the increased effective connectivity from the left SFG to left OFC (r = 0.504, p = 0.020), and from the right SFG to right SMA (r = 0.526, p = 0.014).	- Motor network - Visual network - Frontal network - Somatosensory network

		history of severe smoking, stroke, alcoholism, brain injury, Parkinson's disease, AD, epilepsy, major depression, neurological or psychiatric disorders that could affect cognitive function, major medical illness (e.g., anemia, thyroid dysfunction and cancer), MRI contraindications (e.g., cochlear implants, pacemakers, cerebral aneurysm clips, prosthetic valves, a history of intraocular metal fragments, and claustrophobia), or severe visual loss. **Study Location:** Nanjing Medical University, China	**Tinnitus Sound:** Not given **Hearing Information:** Normal on PTA **Reported Comorbidities:** No depression or anxiety according to SDS/SAS.		ear plugs with 32 dB noise attenuation.						
17	Chen et al., 2017 Tinnitus Distress is Linked to Enhanced Resting-State Functional Connectivity	**Aim:** To identify aberrant effective connectivity of the amygdala and hippocampus in tinnitus patients and to	**Sample Size:** 26 **Sex:** 17 F/9 M **Age:** 50.2 ± 13.0 years	**Sample size:** 23 **Hearing:** Normal on PTA **Sex:** 14 F/9 M **Age:**	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1x1x1 mm^3 Resting state: 3.75x3.75x4.0 mm^3	**Distortion Correction** Detrending and filtering (0.01–0.08Hz) **Software Used:** Data Processing Assistant for Resting State fMRI (DPARSF)	**Type of Analysis:** Granger Causality Analysis **Region(s) of Interest:** **Auditory (n=0)** **Non auditory (n=4)** - L Amygdala	L Amygdala → L Superior Temporal Gyrus → L Anterior Cingulate Cortex → R Angular Gyrus → L Precuneus	L Amygdala → L Cerebellum Posterior Lobe R Amygdala → R Cerebellum Posterior Lobe	- THQ scores were positively correlated with increased connectivity from the left amygdala to left superior	- Limbic system - Auditory network - Default mode network - Dorsal attention network - Executive control of attention network

	from the Limbic System to the Auditory Cortex	determine the relationship with tinnitus characteristics. **Inclusion Criteria:** Chronic tinnitus (>6 months) **Exclusion Criteria:** Pulsatile tinnitus, hyperacusis or Meniere'sdiseases or if they had a past history of severe alcoholism,smoking, head injury, stroke, Alzheimer's disease, Parkinson's disease, epilepsy, major depression, or other neurological or psychiatric illness, major medical illness (e.g.,cancer, anemia, and thyroid dysfunction), MRI contraindications or severe visual loss. **Study Location:** Nanjing Medical University, China	**Tinnitus Duration:** 44.1 ± 38.5 months **Tinnitus Lateralisation:** Bilateral/in the head (n=8) Unilateral (n=18, 12 L/6 R) **Tinnitus Severity:** THQ: 50.0 ± 16.0 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Normal on PTA **Reported Comorbidities:** No depression or anxiety according to SDS/SAS.	44.4 ± 15.1 years **Matched to tinnitus group for:** Age Sex Hearing thresholds Handedness Years of education	**Image Acquisition:** TR: 2000 ms TE: 30 ms **Instructions in Scanner:** Subjects were instructed to lie quietly with their eyes closed without falling asleep, not think of anything in particular, and avoid any head motion during the scan. They wore ear plugs with 32 dB noise attenuation.	programs based on SPM8, and REST **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 4mm. **Spatial Normalisation:** MNI template	- R Amygdala - L Hippocampus - R Hippocampus	← R Middle Frontal Gyrus ← L Middle Temporal Gyrus ← L Inferior Frontal Gyrus ← L Postcentral Gyrus R Amygdala → R Superior Temporal Gyrus → R Anterior Cingulate Cortex → R Middle Frontal Gyrus → R Supramarginal Gyrus ← L Middle Temporal Gyrus ← L Middle Frontal Gyrus ← L Anterior Cingulate Cortex ← R Inferior Frontal Gyrus ← R Postcentral Gyrus L Hippocampus → L Middle Temporal Gyrus → L Postcentral Gyrus ← R Superior Frontal Gyrus ← L Parahippocampal gyrus ← L Insula R Hippocampus → L Transverse Temporal Gyrus → R Middle Temporal Gyrus	L Hippocampus → L Middle Occipital Gyrus R Hippocampus → R Middle Occipital Gyrus	temporal gyrus (r = 0.570, p = 0.005), and from the right amygdala to right superior temporal gyrus (r = 0.487, p = 0.018). - Tinnitus duration was positively correlated with increased connectivity from the right hippocampus to the left transverse temporal gyrus (r = 0.452, p = 0.030).	- Somatosensory network - Motor network

								→ R Postcentral Gyrus ← L Middle Temporal Gyrus ← L+R Middle Frontal Gyrus ← L Angular Gyrus			
18	Xu et al., 2019 Chronic Tinnitus Exhibits Bidirectional Functional Dysconnectivity in Frontostriatal Circuit	**Aim:** To investigate directional connectivity of the nucleus accumbens (NAc) in chronic tinnitus and to ascertain the relationship between this connectivity and tinnitus characteristics. **Inclusion Criteria:** Chronic tinnitus >6 months, confirmed with authors via email **Exclusion Criteria:** Meniere's disease, pulsatile tinnitus or hyperacusis, a history of severe alcoholism, smoking, head injury, stroke, Alzheimer's disease, Parkinson's disease, epilepsy, major	**Sample Size:** n = 50 **Sex:** 32 F/18 M **Age:** 50.20 ± 11.19 years **Tinnitus Duration:** 37.42 ± 36.93 (months) **Tinnitus Lateralisation:** Right: 16; left: 18; bilateral or in the head: 16 **Tinnitus Severity:** THQ: 52.19 ± 14.23 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Normal on PTA **Reported Comorbidities:** No depression or anxiety	**Sample size:** n = 55 **Hearing:** Normal on PTA **Sex:** 34 F/21 M **Age:** 46.82 ± 11.99 years **Matched to tinnitus group for:** Age Sex Hearing thresholds Years of education	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1x1x1 mm^3 Resting state: 3.75x3.75x4.0 mm^3 **Image Acquisition:** TR: 2000 ms TE: 30 ms **Instructions in Scanner:** Participants were instructed to remain awake, keep their eyes closed, and stay motionless without thinking of anything in particular during scanning. They wore ear plugs with 32 dB noise attenuation.	**Distortion Correction** Detrending and filtering (0.01–0.08Hz) **Software Used:** Data Processing Assistant for Resting State fMRI (DPARSF) programs **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 6mm **Spatial Normalisation:** MNI template	**Type of Analysis:** Granger Causality Analysis **Region(s) of Interest:** **Auditory (n=0)** **Non auditory (n=2)** - L Nucleus Accumbens - R Nucleus Accumbens	L NAc → L Inferior Frontal Gyrus ← R Middle Frontal Gyrus ← R Middle Temporal Gyrus R NAc → L Middle Frontal Gyrus → R Orbitofrontal Cortex ← R Inferior Frontal Gyrus ← R Middle Temporal Gyrus	L NAc → L Cuneus R NAc → R Cuneus	- THQ scores were positively correlated with the increased directional connectivity from the right NAc to the left MFG ($r = 0.357$, $p = 0.015$) and from the right MFG to the left NAc ($r = 0.626$, $p < 0.001$). - Tinnitus duration was positively correlated with the increased directional connectivity from right NAc to right OFC ($r = 0.599$, $p < 0.001$).	- Frontostriatal circuit - Limbic system

		depression, other neurological or psychiatric illness, major medical illnesses (e.g., cancer, anemia and thyroid dysfunction), MRI contraindications, and/or severe vision loss. **Study Location:** Nanjing Medical University, China	according to SDS/SAS.								

Non-seed-based resting-state fMRI studies (ALFF, ReHo, FMHC, cyclicity analysis)									
Nr	**Study**	**Study Information**	**Tinnitus Group(s) Information:**	**Control Group(s) Information:**	**Scanning information**	**Data pre-processing**	**Data Analysis Information**	**Findings in tinnitus group compared to control group**	**Networks associated with the altered connectivity in chronic tinnitus**
19	Cai et al., 2019 Abnormal Spontaneous Neural Activity of the Central Auditory System Changes the Functional Connectivity in the Tinnitus Brain: A Resting-State Functional MRI Study	**Aim:** To investigate abnormal functional connections between aberrant spontaneous activity in the central auditory system and the whole brain in tinnitus patients **Inclusion Criteria:** Tinnitus with normal hearing **Exclusion Criteria:** Meniere disease, conductive deafness, alternative hearing level, cognitive or mental disorders, serious systemic diseases, such as heart failure or diabetes, epilepsy, alcoholism or use of psychiatric drugs, pregnancy, acoustic neuroma, brain stem, or inferior colliculi diseases, hyperacusis, smoking, history of stroke, brain injury, Alzheimer's disease, or Parkinson's disease **Study Location:**	**Sample size:** n = 16 **Sex:** 10 F/6 M **Age:** 35.33 ± 10.70 years **Tinnitus Duration:** 36.58 ± 18.03 months **Tinnitus Lateralisation:** Unilateral, right side (n=16) **Tinnitus Severity:** THI score: 55.33 ± 11.03 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Normal on PTA **Reported Comorbidities:** No depression and anxiety	**Sample size:** n = 15 **Hearing:** Normal on PTA **Sex:** 10 F/5 M **Age:** 35.00 ± 10.10 years **Matched to tinnitus group for:** Age Sex Years of educatio	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1x1x1 mm^3 Resting state: 3.125x3.125x3 mm^3 **Image Acquisition:** TR: 2000 ms TE: 30 ms **Instructions in Scanner:** All subjects were asked to remain relaxed with their eyes closed and to avoid serious thought for approximately 20 min.	**Distortion Correction** Global signal regression & Temporal filtering (0.01–0.1 Hz) on all time-series, except for ALFF. **Software Packages:** DPAESF (Data Processing Assistant for Resting-state fMRI) toolbox in SPM **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 8mm **Spatial Normalisation:** MNI template	**Type of Analysis:** Smoothed mean amplitude of low-frequency fluctations (smALFF) + seed-based **Region(s) of Interest:** (based on ALFF outcome) **Auditory (n=1)** - L Higher Auditory Cortex (superior temporal gyrus, BA 22)	**Increased smALFF:** L Higher Auditory Cortex (HAC) - Positively correlated with tinnitus duration (r = 0.778, p > 0.001), Tinnitus Handicap Inventory Score (r = 0.682, p = 0.004), and Self-Rating Depression Score (r = 0.694, p = 0.003). **Decreased smALFF:** R Inferior Colliculus - Not correlated with any clinical characteristics. Enhanced FC with HAC: - L+R Heschl's Gyrus - L+R Superior Temporal Gyrus - R Middle Temporal Gyrus - R Inferior Colliculus - L Cerebellum 4,5 - L Cerebellum 8 - L Hippocampus - L Amygdala - R Supramarginal Gyrus - R Insula - L+R Supplementary Motor Area Decreased FC with L HAC: None found Enhanced/decreased FC with IC: None found	- Auditory network - Motor network - Dorsal attention network - Executive control network - Emotional network

		Guangzhou, China							
20	Chen et al., 2014 Aberrant spontaneous brain activity in chronic tinnitus patients revealed by resting-state functional MRI	**Aim:** To investigate whether aberrant spontaneous brain activity exists in chronic tinnitus patients using resting-state functional magnetic resonance imaging (fMRI) technique. **Inclusion Criteria:** Chronic tinnitus >6 months **Exclusion Criteria:** Hyperacusis, Meniere's disease, objective tinnitus, pulsatile tinnitus, severe smoking/alcoholism, stroke, brain injury, Alzheimer's disease, Parkinson's disease, epilepsy, major depression, psychiatric disorder, major medical illness e.g. cancer, severe visual impairment, MRI contraindications **Study Location:** Zhongda Hospital Southeast University, China	**Sample Size:** n = 31 **Sex:** 14 F/17 M **Age:** 41.9 ± 10.8 years **Tinnitus Duration:** 41.0 ± 36.2 months **Tinnitus Lateralisation:** Bilateral/central (n=12), unilateral (n=19, 6 R/13 L) **Tinnitus Severity:** THQ: 100.6 ± 73.4 (range: 17.41–278.15) **Tinnitus Pitch:** NA **Tinnitus Sound:** NA **Hearing Information:** No hearing loss **Reported Comorbidities:** No included participants had accompanied symptoms such as depression and anxiety according to the Self-Rating Depression Scale (SDS) and Self Rating Anxiety Scale (SAS) (overall scores	**Sample size:** n = 32 **Hearing:** Normal on PTA **Sex:** 15 F/17 M **Age:** 46.5 ± 12.6 years **Matched to tinnitus group for:** Age Sex Hearing thresholds Handedness Years of education	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1x1x1x mm^3 Resting state: 3.75x3.75x4.0 mm^3 **Image Acquisition:** TR: 2000 ms TE: 25 ms **Instructions in Scanner:** Subjects were asked to rest quietly with their eyes closed but to remain awake and avoid thinking of anything particular. Subjects wore ear plugs with 32 dB attenuation	**Distortion Correction** Detrending and filtering (0.01 - 0.08 Hz) **Software Packages:** SPM8, REST **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 4 mm **Spatial Normalisation:** MNI template	**Type of Analysis:** Amplitude of low-frequency fluctuations (ALFF)	**Increased ALFF:** - R Middle Temporal Gyrus - R Superior Frontal Gyrus - R Angular Gyrus **Decreased ALFF:** - L Cuneus - R Middle Occipital Gyrus - L+R Thalamus The ALFF value in right SFG was positively correlated with tinnitus duration and tinnitus handicap questionnaire (THQ) score, respectively (r = 0.464, p = 0.010; r = 0.557, p = 0.007). The ALFF value in right MTG was also positively correlated with the THQ score (r = 0.504, p = 0.004). However, no significant correlations survived after Bonferroni correction.	- Auditory network - Default mode network - Visual network

			below 50, respectively)						
21	Chen et al, 2015 Frequency-specific alternations in the amplitude of low-frequency fluctuations in chronic tinnitus	**Aim:** To investigate the role of frequency-specific components of low-frequency oscillations in tinnitus using amplitude of low-frequency fluctuation (ALFF) and fractional ALFF (fALFF) in two different frequency bands (slow-4: 0.027-0.073 Hz and slow-5: 0.01-0.027 Hz). **Inclusion Criteria:** Chronic tinnitus (>6 months) **Exclusion Criteria:** Pulsatile tinnitus, hyperacusis or Meniere's diseases, a past history of severe smoking, alcoholism, brain injury, stroke, Alzheimer's disease, Parkinson's disease, epilepsy, major depression, or other neurological or psychiatric disorders that could affect cognitive function, major medical illness (e.g., anaemia, thyroid dysfunction and cancer), MRI contraindications, or severe visual loss. **Study Location:**	**Sample Size:** n = 39 **Sex:** 15 F/24 M **Age:** 41.5 ± 14.6 years **Tinnitus Duration:** 36.9 ± 36.4 months **Tinnitus Lateralisation:** Bilateral (n=10) Unilateral (n=29, 16 L/13 R) **Tinnitus Severity:** THQ = 43.5 ± 21.3 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Normal on PTA **Reported Comorbidities:** None reported	**Sample size:** n = 41 **Hearing:** Normal on PTA **Sex:** 20 F/21 M **Age:** 46.0 ± 12.2 years **Matched to tinnitus group for;** Age Sex Hearing thresholds Years of education	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 0.977x0.977x1 mm^3 Resting state: 3,75x3,75x4 mm^3 **Image Acquisition:** TR: 2000 ms TE: 25 ms **Instructions in Scanner:** Subjects were instructed to lie quietly with their eyes closed without falling asleep, not think of anything in particular, and avoid any head motion during the scan	**Distortion Correction** Detrending and filtering (0.01 - 0.08 Hz) **Software Used:** Data Processing Assistant for Resting State fMRI (DPARSF) programs based on SPM8, and REST **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 6 mm **Spatial Normalisation:** MNI template	**Type of Analysis:** Amplitude of low-frequency fluctuation (ALFF) and fractional ALFF (fALFF)	**Increased ALFF:** - R Superior Frontal Gyrus - R Middle Temporal Gyrus - R Angular Gyrus - L Inferior Frontal Gyrus - R Supramarginal Gyrus **Decreased ALFF:** - L+R Middle Occipital Gyrus **Increased fALFF:** - L Superior Frontal Gyrus - R Supramarginal Gyrus **Decreased fALFF:** - L+R Middle Occipital Gyrus Slow-4 ALFF values in R SFG and fALFF values in L SFG were positively correlated with THQ scores (respectively, r = 0.446, p = 0.007; r = 0.466, p = 0.005). Slow-5 ALFF values in R SFG and fALFF values in L SFG were positively correlated with tinnitus duration (respectively, r = 0.544, p = 0.001; r = 0.526, p = 0.001).	- Auditory network - Default mode network - Visual network

		Zhongda Hospital of Southeast University, China							
22	Han et al, 2018 Disrupted local neural activity and functional connectivity in subjective tinnitus patients: evidence from resting-state fMRI study	**Aim:** To investigate the abnormal alterations of both the intra-regional brain activity and inter-regional functional connectivity (FC) in patients with subjective tinnitus using resting-state functional MRI (rs-fMRI) methods. **Inclusion Criteria:** Chronic subjective tinnitus (> 6 months) **Exclusion Criteria:** Hyperacusis or Meniere's disease, neurological or psychiatric disorders, and any contraindication for MRI scans. **Study Location:** Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, China	**Sample Size:** n = 25 **Sex:** 15 F/10 M **Age:** 44.64 ± 8.91 years **Tinnitus Duration:** Median = 14.00 (8.50–54.00) months **Tinnitus Lateralisation:** All unilateral (8 L/17 R) **Tinnitus Severity:** THI: 47.16 ± 24.95 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Normal on PTA **Reported Comorbidities:** Not given	**Sample size:** n = 25 **Hearing:** Normal on PTA **Sex:** 15 F/10 M **Age:** 43.96 ± 8.92 years **Matched to tinnitus group for:** Age Sex Hearing thresholds Years of education Hyperacusis questionnaire score	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1x1x1 mm^3 Resting state: 3×3×3 mm^3 **Image Acquisition:** TR: 2000 ms TE: 30 ms **Instructions in Scanner:** Subjects were asked to keep their eyes closed but remain awake, rest quietly, and avoid thinking of anything in particular	**Distortion Correction** Nuisance covariates regression Band-pass filtering (0.01 - 0.08 Hz) **Software Used:** Data Processing & Analysis for Brain Imaging (DPABI) based on Matrix Laboratory and SPM8 **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 4mm **Spatial Normalisation:** MNI template	**Type of Analysis:** Regional homogeneity (ReHo), fALFF, seed-based FC **Seed-based ROIs:** (selected based on ReHo & fALFF results) - R Middle Temporal Gyrus - R Cuneus - R Middle Frontal Gyrus - L Cerebellar Anterior Lobe	**Increased ReHo** - R Middle Temporal Gyrus - R Cuneus **Decreased ReHo:** - R Middle Frontal Gyrus - L Cerebellar Anterior Lobe **Increased fALFF:** - R Middle Temporal Gyrus **Decreased fALFF:** None found **Increased FC:** None found **Decreased FC:** R Middle Temporal Gyrus - R Middle Frontal Gyrus* - R Lingual Gyrus - R Cerebellar Posterior Lobe R Cuneus - R MTG * Positively correlated with Tinnitus Handicap Inventory score (r = 0.675, p = 0.001).	- Auditory network - Default mode network - Visual network
23	Chen et al, 2015 Altered intra- and interregional synchronization in resting-state cerebral networks	**Aim:** To identify aberrant neural networks involved in chronic tinnitus, by comparing the resting-state functional magnetic resonance	**Sample Size:** n = 29 **Sex:** 13 F/16 M **Age:** 40.9 ± 10.5 years	**Sample size:** n = 30 **Hearing:** Normal on PTA **Sex:** 15 F/15 M **Age:**	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 0,98x0,98x1 mm^3 Resting state: 0,98x0,98x1 mm^3	**Distortion Correction** Detrending and filtering (0.01–0.08Hz) **Software Used:** Data Processing Assistant for Resting State fMRI	**Type of Analysis:** Regional homogeneity (ReHo) + seed-based FC **Seed-based ROIs:** (selected based on ReHo results) **Auditory (n=0)**	**Increased ReHo:** - L Anterior Insular Cortex - R Anterior Insular Cortex - L Inferior Frontal Gyrus - R Supramarginal Gyrus **Decreased ReHo:** - L Cuneus **Increased FC:**	- Executive control of attention network - Default mode network - Visual network

	associated with chronic tinnitus	imaging (fMRI) patterns of tinnitus patients and healthy controls. **Inclusion Criteria:** Chronic tinnitus (>6 months), confirmed with authors via email **Exclusion Criteria:** Hyperacusis, pulsatile tinnitus, or Meniere's diseases or a past history of severe smoking, stroke, alcoholism, brain injury, Parkinson's disease, Alzheimer's disease, epilepsy, major depression, neurological or psychiatric disorders that could affect cognitive function, major medical illness (e.g., anemia, thyroid dysfunction, and cancer), MRI contraindications, or severe visual loss. **Study Location:** Zhongda Hospital Southeast University, China	**Tinnitus Duration:** 39.5 ± 33.7 months **Tinnitus Lateralisation:** Bilateral/in the head (n=11) Unilateral (n=18, 12 L/6 R) **Tinnitus Severity:** THQ: 103.5 ± 74.4 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Normal on PTA **Reported Comorbidities:** No depression or anxiety according to SDS/SAS.	46.2 ± 11.9 years **Matched to tinnitus group for;** Age Sex Hearing thresholds Years of education	**Image Acquisition:** TR: 2000 ms TE: 25 ms **Instructions in Scanner:** Subjects were instructed to lie quietly with their eyes closed without falling asleep, not think of anything in particular, and avoid any head motion during the scan. They wore ear plugs with 32 dB noise attenuation.	(DPARSF) programs based on SPM8, and REST **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 4mm **Spatial Normalisation:** MNI template	**Non auditory (n=4)** - L Anterior Insular Cortex - R Anterior Insular Cortex - L Inferior Frontal Gyrus - R Supramarginal Gyrus	L Anterior Insular Cortex - L Middle Frontal Gyrus* - R Inferior Temporal Gyrus - R Precuneus R Anterior Insular Cortex - R Middle Frontal Gyrus** - R Superior Temporal Gyrus - L Precuneus - L Posterior Cingulate Cortex L Inferior Frontal Gyrus - R Middle Frontal Gyrus - R Inferior Temporal Gyrus - R Anterior Cingulated Cortex R Supramarginal Gyrus - L Inferior Frontal Gyrus - R Orbitofrontal Cortex **Decreased FC:** None found * Positively correlated with THQ score (r = 0.459, p = 0.012). ** Positively correlated with THQ score (r = 0.479, p = 0.009).	
24	Gentil et al, 2019 Alterations in Regional Homogeneity in Patients With Unilateral Chronic Tinnitus	**Aim:** To identify differences in cerebral ReHo in patients with unilateral tinnitus compared with non-tinnitus control subjects in a resting state. Our second objective is to highlight lateralized	**Sample Size:** n = 19 **Sex:** 5 F/14 M **Age:** 63 ± 10 years **Tinnitus Duration:** 12 ± 13 years	**Sample size:** n = 16 **Hearing:** Average hearing thresholds in PTA are in normal range **Sex:** 9 F/7 M	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1x1x1 mm^3 Functional: 3.8 × 3.8 × 3 mm^3 Resting state: 2.39 x 2.39 x 3 mm^3	**Distortion Correction** Field map correction Detrending and filtering (0.01–0.08Hz) **Software Used:** SPM 12, REST	**Type of Analysis:** Regional homogeneity (ReHo) + correlation analysis	**Increased ReHo:** None found **Decreased ReHo:** - Cluster between STG/MTG (auditory cortex), contralateral to tinnitus ear **Correlation between ReHo values in brain regions and clinical characteristics (p<0.005):** - STG/MTG (contralateral) & Visual Analogue Scale for tinnitus loudness (r = -0.6156); THI score (r = -0.6336)	- Auditory network

		differences related to tinnitus lateralization. **Inclusion Criteria:** Chronic tinnitus, >1 year **Exclusion Criteria:** Neurological disorders, Meniere's disease, temporo-mandibular joint disorders, and other neurological issues or chronic physical diseases **Study Location:** Montpellier University Hospital, France.	**Tinnitus Lateralisation:** unilateral 10 right, 9 left **Tinnitus Severity:** THI = 36 ± 13 **Tinnitus Pitch:** 4 kHz n=9 6 kHz, n=10 **Tinnitus Sound:** Not given **Hearing Information:** Average PTA hearing thresholds were in the normal range for the control group whereas the thresholds were moderately elevated in the tinnitus group for 4 & 6 kHz (above 6 kHz not tested). **Reported Comorbidities:** Not given; Presence/absence of hyperacusis not mentioned.	**Age:** 59 ± 11 (range 39–78) years **Matched to tinnitus group for:** Age Handedness Years of education Not matched for sex Not matched for hearing thresholds >4 kHz	**Image Acquisition:** TR: 2400 ms TE: 30 ms **Instructions in Scanner:** Keep eyes closed, think about nothing in particular, and do not fall asleep	**Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 6mm **Spatial Normalisation:** MNI template		- Lingual Gyrus (contralateral) & Visual Analogue Scale for tinnitus loudness (r = -0.5806) - Precentral Gyrus (ipsilateral) & THI score (r = -0.5537) - Middle Temporal Gyrus (ipsilateral) & HHTP (hearing threshold at tinnitus pitch) (r = 0.83704) - Supramarginal/angular Gyrus (ipsilateral) & HTTP (r = 0.7739); tinnitus duration (r = 0.7344) - Lingual Gyrus (ipsilateral) & tinnitus duration (r = 0.7974) - Superior Frontal Lobe (ipsilateral) & tinnitus duration (r = 0.7898)	
25	Chen et al, 2015 Altered interhemispheric functional coordination in chronic tinnitus patients	**Aim:** To examine the resting-state interhemispheric functional connectivity and its relationships with clinical characteristics in chronic tinnitus patients using a novel method,	**Sample Size:** n = 28 **Sex:** 12 F/16 M **Age:** 40.5 ± 13.2 years **Tinnitus Duration:**	**Sample size:** n = 30 **Hearing:** Normal on PTA **Sex:** 15 F/15 M **Age:** 46.2 ± 11.9 years	**Scanner Strength:** 3T **Voxel Size:** 0,98x0,98x1 mm^3 3,75x3,75x4 mm^3 **Image Acquisition:** TR: 2000 ms TE: 25 ms	**Distortion Correction** Detrending and filtering (0.01–0.08Hz) **Software Used:** Data Processing Assistant for Resting State fMRI (DPARSF) programs	**Type of Analysis:** Voxel-mirrored homotopic connectivity (VMHC) + correlation analysis **Region(s) of Interest:** **Auditory (n=0)**	**Increased VMHC:** - Middle Temporal Gyrus - Middle Frontal Gyrus - Superior Occipital Gyrus **Decreased VMHC:** None found **Correlation between VMHC values in brain regions and clinical characteristics (p<0.05):** - L+R Uncus & tinnitus duration (r = 0.62026)	- Auditory network - Visual network - Motor network - Default mode network - Limbic system

		voxel-mirrored homotopic connectivity (VMHC). **Inclusion Criteria:** Chronic tinnitus (>6 months) **Exclusion Criteria:** Hyperacusis, pulsatile tinnitus, or Meniere's diseases or a past history of severe smoking, stroke, alcoholism, brain injury, Parkinson's disease, Alzheimer's disease, epilepsy, major depression, neurological or psychiatric disorders that could affect cognitive function, major medical illness (e.g., anemia, thyroid dysfunction, and cancer), MRI contraindications, or severe visual loss. **Study Location:** Zhongda Hospital Southeast University, China	34.3 ± 34.2 months **Tinnitus Lateralisation:** Bilateral or in the head (n=7) Unilateral (n=21, 9 R/12 L) **Tinnitus Severity:** THQ: 41.3 ± 18.2 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** **No hearing loss** Normal on PTA **Reported Comorbidities:** No depression or anxiety according to SDS/SAS.	**Matched to tinnitus group for;** Age Sex Hearing thresholds Years of education	**Scanner instructions:** Subjects were instructed to lie quietly with their eyes closed without falling asleep, not think of anything in particular, and avoid any head motion during the scan. They wore ear plugs with 32 dB noise attenuation.	based on SPM8, and REST **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 6mm. **Spatial Normalisation:** MNI template	**Non auditory (n=1)** - Interhemispheric connections and the corpus Collosum	- L+R Transverse Temporal Gyrus (BA 42, secondary auditory cortex) & THQ score (r = 0.63775) - L+R Superior Temporal Pole & THQ score (r = 0.71195) - L+R Precentral Gyrus & THQ score (r = 0.64225) - L+R Calcarine Cortex & THQ score (r = 0.65234)	
26	Zimmerman et al, 2019 Dissociating tinnitus patients from healthy controls using resting-state cyclicity analysis and clustering	**Aim:** To explore leader-follower patterns in the temporal ordering of resting-state fMRI data using a novel analysis method, cyclicity analysis, and to explore different machine learning classification methods to	**Sample Size:** n = 32 **Sex:** 14 F/18 M **Age:** 51.15 ± 10.73 years **Tinnitus Duration:** Not given	**Sample size:** n = 15 **Hearing:** PTA average thresholds up to 8 kHz in normal range, thresholds slightly elevated above 8 kHz. **Sex:** 10 F/5 M	**Scanner Strength:** 3T **Voxel Size:** **Anatomical:** 0.9x0.9x0.9 mm^3 **Resting state:** 2.5x2.5x3.0 mm^3 **Image Acquisition:** TR: 2000 ms TE: 25 ms	**Distortion Correction** Not given **Software Used:** SPM12 **Motion Correction:** six-parameter rigid body transformation for head motion correction	**Type of Analysis:** Cyclicity Analysis **Region(s) of Interest:** **Auditory (n=2)** - R primary auditory cortex - L primary auditory cortex **Non auditory (n=31)** - L amygdala	Cyclicity analysis was able to differentiate between TIN and Control groups with 58-67% accuracy. In the controls, there were consistent temporal patterns across frontal, parietal, and limbic regions and amygdalar activity, whereas in tinnitus subjects, this pattern was much more variable. The 20 ROI pairs that helped most to distinguish between tinnitus and control participants were: 1. Precuneus 2. L Posterior Intraparietal Sulcus	- Auditory network - Default mode network - Dorsal attention network - Visual network - Attention control network - Ventral attention network - Limbic system

		differentiate between tinnitus and control populations. **Inclusion Criteria:** Chronic tinnitus, >6 months, confirmed via email **Exclusion Criteria:** Not given **Study Location:** Illinois, University of Illinois Urbana-Champaign, USA	**Tinnitus Lateralisation:** Not given **Tinnitus Severity:** TFI: 23.44 ± 17.78 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Mild to moderate bilateral high-frequency hearing loss **Reported Comorbidities:** BDI: no to minimal depression	**Age:** 47.27 (SD 11.71) years **Matched to tinnitus group for;** Age BDI and BAI scores Not matched for sex Not matched for hearing thresholds >3kHz	**Instructions in Scanner:** Lie still with eyes open fixated on a cross, do not think about anything in particular	**Slice timing Correction:** Yes **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 8mm. **Spatial Normalisation:** MNI template	- L anterior insula - L cuneus - L frontal eye field - L inferior frontal lobe - L inferior parietal lobe - L mid frontal gyrus - L parahippocampus - L posterior intraparietal sulcus - L primary visual cortex - L superior occipital lobe - L superior temporal junction - L superior temporal sulcus - L ventral intraparietal sulcus - Medial prefrontal cortex - Posterior cingulate cortex - Precuneus - R amygdala - R anterior insula - R cuneus - R frontal eye field - R inferior frontal lobe - R inferior parietal lobe - R mid frontal gyrus - R parahippocampus - R posterior intraparietal sulcus - R primary visual cortex - R superior occipital lobe	3. R Postrior Intraparietal Sulcus 4. R Ventral Intraparietal Sulcus 5. L Inferior Parietal Lobule 6. L Superior Occipital Lobe 7. R Superior Occipital Lobe 8. R Primary Visual Cortex 9. L Frontal Eye Field 10. R Frontal Eye Field 11. L Middle Frontal Gyrus 12. R Middle Frontal Gyrus 13. Medial Prefrontal Cortex 14. L Primary Auditory Cortex 15. L Superior Temporal Junction 16. R Superior Temporal Junction 17. Posterior Cingulate Cortex 18. L Parahippocampus 19. R Parahippocampus 20. L Amygdala	

							- R superior temporal junction - R superior temporal sulcus R ventral intraparietal sulcus		

Data-driven resting-state fMRI studies: Independent Component Analysis										
Nr	**Study**	**Study Information**	**Tinnitus Group(s) Information:**	**Control Group(s) Information:**	**Scanning Information**	**Data Pre-processing**	**Data Analysis Information**	**Regions showing increased connectivity in tinnitus compared to controls**	**Regions showing decreased connectivity in tinnitus compared to controls**	**Networks associated with the altered connectivity in chronic tinnitus**

27	Davies et al, 2014 Auditory network connectivity in tinnitus patients: A resting-state fMRI study	**Aim:** To investigate auditory network connectivity, adopting and extending previously used analyses methods to provide an independent evaluation of replicability. **Inclusion Criteria:** Tinnitus duration >2 years **Exclusion Criteria:** Unilateral/asymmetrical hearing loss; hyperacusis **Study Location:** Queen' s Medical Centre, Nottingham, UK	**Sample Size:** n = 12 **Sex:** 5 F/7 M **Age:** 65.8 (range: 49-73) years, SD not given **Tinnitus Duration:** 15.5 ± 20.4 years **Tinnitus Lateralisation:** Bilateral (n=7) Central (n=3) Unilateral (n=2, 1 L/1 R) **Tinnitus Severity:** THQ: 43.7 ± 18.32 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Mild to moderately severe sloping hearing loss, typical of presbyacusis.	**Sample size:** n = 11 **Hearing:** **Sex:** 3 F/8 M **Age:** 68.5 years (range 58-75). SD not given **Matched to tinnitus group for:** Age Sex Hearing thresholds BAI & BDI scores	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1x1x1 mm^3 Resting state: 3.75x3.75x4.0 mm^3 **Image Acquisition:** TR: 2700 ms TE: 20, 45 ms (two echo pulses) **Instructions in Scanner:** Keep still and alert with your eyes closed. Participant wore ear plugs as well as circum-aural active noise cancelling headphones.	**Distortion Correction:** Not given **Software Used:** SPM8 **Motion Correction:** Realignment **Slice timing Correction:** No **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 4mm **Spatial Normalisation:** MNI template	**Type of Analysis:** Independent Component Analysis (ICA) + seed-based FC **Total *n* components created:** 23 **Region(s) of Interest:** (selected based on ICA) **Auditory (n=4)** Concatenated to form one "Auditory Component": - L Primary Auditory Cortex - R Primary Auditory Cortex - L Secondary Auditory Cortex - R Secondary Auditory Cortex **Non-auditory (n=0)**	None found: result below did not survive after correcting for multiple comparisons. Auditory component - R Supramarginal Gyrus - L Posterior Middle Temporal Gyrus	None found	None found

			Reported Comorbidities: No depression or anxiety according to BDI and BAI.							

28	Maudoux et al, 2012 Auditory Resting-State Network Connectivity in Tinnitus: A Functional MRI Study	**Aim:** The aim of this study was to test if functional MRI resting-state connectivity patterns in the auditory network differ between tinnitus patients and normal controls. **Inclusion Criteria:** Chronic tinnitus present either constantly or intermittently for at least 1 year. **Exclusion Criteria:** Major neurological, neurosurgical or psychiatric history, hyperacusis, phonophobia. **Study Location:** University of Liege, Belgium	**Sample Size:** n = 13 **Sex:** 6 F/7 M **Age:** 52 ± 11 years **Tinnitus Duration:** 8 ± 9 years **Tinnitus Lateralisation:** Bilateral (n=3) Unilateral (n=10, 6 L/4 R) **Tinnitus Severity:** Slight to catastrophic THI/TQ: 43.5/31.9. **Tinnitus Pitch:** M = 4846 Hz (SD = 2276), ranging from 1500 Hz - 8000 Hz **Tinnitus Sound:** Not given **Hearing Information:** 4 patients had normal hearing; the rest ranged from mild to	**Sample size:** n = 27 Control1: 12 (for auditory component selection) Control2: 15 (for comparing to tinnitus group) **Hearing:** Control1: not tested Control2: not given **Sex:** Control1: 4 F/8 M Control2: 6 F/9 M **Age:** Control1: 21 ± 3 Control2: 51 ± 13 **Matched to tinnitus group for;** Control1 not matched Control2 matched for age and sex; Not matched for hearing thresholds.	**Scanner Strength:** 3T **Voxel Size:** Tinnitus: 3.0x3.0x3.75 mm^3 Control: 3.4x3.4x3.0 mm^3 **Image Acquisition:** Tinnitus TR: 2000 ms TE: 30 ms Control TR: 2460ms TE: 40ms **Instructions in Scanner:** Not given	**Distortion Correction** Filtering out low frequencies of up to 0.005 Hz and linear trend removal **Software Used:** Brain Voyager **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 8mm **Spatial Normalisation:** Talairach and Tournoux (1988) standard anatomical space	**Type of Analysis:** Independent Component Analysis + seed-based FC **Total *n* components created:** 30 **Region(s) of Interest:** (selected based on ICA) **Auditory (n=14)** Combined into one "Auditory Component" - 3x R Transverse Temporal Gyrus - 3x L Transverse Temporal Gyrus - 3x R Superior Temporal Gyrus - 3x L Superior Temporal Gyrus - R Insula - L Insula	Auditory Component - L+R Parahippocampal Gyrus - L+R Brainstem/Cerebellum - L Precentral Gyrus - L Superior Temporal Gyrus - L Inferior Frontal Gyrus - R Basal Ganglia/Nucleus Accumbens - R Prefrontal cortex - L Postcentral Cyrus - R Orbitofrontal Cortex - R Inferior Parietal Lobe	Auditory Component - L Superior Frontal Gyrus - L Fusiform Gyrus - R Superior Temporal Gyrus - R Occipital Cortex - L Occipital Cortex - L Prefrontal Cortex	- Auditory network - Attentional network - Memory network - Emotional network - Visual network

			severe hearing loss (n=9). **Reported Comorbidities:** Not given. Anxiety/depression not tested.							

29	Schmidt et al, 2013 Default mode, dorsal attention and auditory resting state networks exhibit differential functional connectivity in tinnitus and hearing loss	**Aim:** To investigate auditory, dorsal attention, and default mode networks in adults with tinnitus and hearing loss in a resting state functional connectivity study. **Inclusion Criteria:** Not given **Exclusion Criteria:** Not given **Study Location:** Illinois, USA	**Sample Size:** n = 12 **Sex:** 3 F/9 M **Age:** 55.00 ± 6.97 **Tinnitus Duration:** Not given **Tinnitus Lateralisation:** Not given **Tinnitus Severity:** THI = 8.33 ± 6.76 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Hearing loss was minimal from 250-2000 Hz and moderate to moderate-severe (threshold ≥ 35 dB) for 3-8 kHz **Reported Comorbidities:** No hyperacusis	**Sample size:** NH controls: n=15 HL controls: n=13 **Hearing:** NH: normal on PTA HL: minimal from 250-2000 Hz and moderate to moderate-severe (threshold ≥ 35 dB) for 3-8 kHz **Sex:** NH: 6 F/9M HL: 8 F/5M **Age:** NH: 52.93 ± 8.64 HL: 57.62 ± 9.39 **Matched to tinnitus group for:** NH: Age Sex HLs: Age Sex Hearing thresholds	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1.0×1.0×1.2 mm^3 Resting state: 3.4×3.4×4.0 mm^3 **Image Acquisition:** TR: 2000 ms TE: 30 ms **Instructions in Scanner:** Subjects were instructed to lay still and look at a fixation cross.	**Distortion Correction** Band-pass filtering (0.008 – 0.08 Hz) **Software Used:** SPM8, CONN, GIFT software **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 10mm **Spatial Normalisation:** MNI template	**Type of Analysis:** Independent Component Analysis + seed-based FC **Total *n* components created:** 30 **Region(s) of Interest:** **Auditory component (n=2)** - L Primary Auditory Cortex - R Primary Auditory Cortex **Dorsal Attention Network component #1 (n=2)** - L Posterior Intraparietal Sulcus - R Posterior Intraparietal Sulcus **Dorsal Attention Network component #2 (n=2)** - L Frontal Eye Field - R Frontal Eye Field **Default Mode Network component (n=2)**	Auditory component - L Lingual Gyrus (TIN>NH) - L Parahippocampus (TIN>NH) DAN #2 component - R Parahippocampus (TIN>HL) DMN component - R Fusiform Gyrus (TIN>HL) - R Lingual Gyrus (TIN>HL)	DAN #1 component - R Supramarginal Gyrus (HL>TIN) DMN component - L Precuneus (HL>TIN) - L Precentral Gyrus (HL>TIN) - L Cerebellum (HL>TIN) - L Cerebellar Vermis (HL>TIN) - R Precuneus (NH>TIN)	- Auditory network - Dorsal attention network - Default mode network - Motor network - Limbic system

							- Medial Prefrontal Cortex - Posterior Cingulate Cortex			

Data-driven resting-state fMRI studies: Independent Component Analysis										
Nr	**Study**	**Study Information**	**Tinnitus Group(s) Information:**	**Control Group(s) Information:**	**Scanning Information**	**Data Pre-processing**	**Data Analysis Information**	**Regions showing increased connectivity in tinnitus compared to controls**	**Regions showing decreased connectivity in tinnitus compared to controls**	**Networks associated with the altered connectivity in chronic tinnitus**

27	Davies et al, 2014 Auditory network connectivity in tinnitus patients: A resting-state fMRI study	**Aim:** To investigate auditory network connectivity, adopting and extending previously used analyses methods to provide an independent evaluation of replicability. **Inclusion Criteria:** Tinnitus duration >2 years **Exclusion Criteria:** Unilateral/asymmetrical hearing loss; hyperacusis **Study Location:** Queen' s Medical Centre, Nottingham, UK	**Sample Size:** n = 12 **Sex:** 5 F/7 M **Age:** 65.8 (range: 49-73) years, SD not given **Tinnitus Duration:** 15.5 ± 20.4 years **Tinnitus Lateralisation:** Bilateral (n=7) Central (n=3) Unilateral (n=2, 1 L/1 R) **Tinnitus Severity:** THQ: 43.7 ± 18.32 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Mild to moderately severe sloping hearing loss, typical of presbyacusis.	**Sample size:** n = 11 **Hearing:** **Sex:** 3 F/8 M **Age:** 68.5 years (range 58-75). SD not given **Matched to tinnitus group for:** Age Sex Hearing thresholds BAI & BDI scores	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1x1x1 mm^3 Resting state: 3.75x3.75x4.0 mm^3 **Image Acquisition:** TR: 2700 ms TE: 20, 45 ms (two echo pulses) **Instructions in Scanner:** Keep still and alert with your eyes closed. Participant wore ear plugs as well as circum-aural active noise cancelling headphones.	**Distortion Correction:** Not given **Software Used:** SPM8 **Motion Correction:** Realignment **Slice timing Correction:** No **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 4mm **Spatial Normalisation:** MNI template	**Type of Analysis:** Independent Component Analysis (ICA) + seed-based FC **Total *n* components created:** 23 **Region(s) of Interest:** (selected based on ICA) **Auditory (n=4)** Concatenated to form one "Auditory Component": - L Primary Auditory Cortex - R Primary Auditory Cortex - L Secondary Auditory Cortex - R Secondary Auditory Cortex **Non-auditory (n=0)**	None found: result below did not survive after correcting for multiple comparisons. Auditory component - R Supramarginal Gyrus - L Posterior Middle Temporal Gyrus	None found	None found

			Reported Comorbidities: No depression or anxiety according to BDI and BAI.							

28	Maudoux et al, 2012 Auditory Resting-State Network Connectivity in Tinnitus: A Functional MRI Study	**Aim:** The aim of this study was to test if functional MRI resting-state connectivity patterns in the auditory network differ between tinnitus patients and normal controls. **Inclusion Criteria:** Chronic tinnitus present either constantly or intermittently for at least 1 year. **Exclusion Criteria:** Major neurological, neurosurgical or psychiatric history, hyperacusis, phonophobia. **Study Location:** University of Liege, Belgium	**Sample Size:** n = 13 **Sex:** 6 F/7 M **Age:** 52 ± 11 years **Tinnitus Duration:** 8 ± 9 years **Tinnitus Lateralisation:** Bilateral (n=3) Unilateral (n=10, 6 L/4 R) **Tinnitus Severity:** Slight to catastrophic THI/TQ: 43.5/31.9. **Tinnitus Pitch:** M = 4846 Hz (SD = 2276), ranging from 1500 Hz - 8000 Hz **Tinnitus Sound:** Not given **Hearing Information:** 4 patients had normal hearing; the rest ranged from mild to	**Sample size:** n = 27 Control1: 12 (for auditory component selection) Control2: 15 (for comparing to tinnitus group) **Hearing:** Control1: not tested Control2: not given **Sex:** Control1: 4 F/8 M Control2: 6 F/9 M **Age:** Control1: 21 ± 3 Control2: 51 ± 13 **Matched to tinnitus group for;** Control1 not matched Control2 matched for age and sex; Not matched for hearing thresholds.	**Scanner Strength:** 3T **Voxel Size:** Tinnitus: 3.0x3.0x3.75 mm^3 Control: 3.4x3.4x3.0 mm^3 **Image Acquisition:** Tinnitus TR: 2000 ms TE: 30 ms Control TR: 2460ms TE: 40ms **Instructions in Scanner:** Not given	**Distortion Correction** Filtering out low frequencies of up to 0.005 Hz and linear trend removal **Software Used:** Brain Voyager **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 8mm **Spatial Normalisation:** Talairach and Tournoux (1988) standard anatomical space	**Type of Analysis:** Independent Component Analysis + seed-based FC **Total *n* components created:** 30 **Region(s) of Interest:** (selected based on ICA) **Auditory (n=14)** Combined into one "Auditory Component" - 3x R Transverse Temporal Gyrus - 3x L Transverse Temporal Gyrus - 3x R Superior Temporal Gyrus - 3x L Superior Temporal Gyrus - R Insula - L Insula	Auditory Component - L+R Parahippocampal Gyrus - L+R Brainstem/Cerebellum - L Precentral Gyrus - L Superior Temporal Gyrus - L Inferior Frontal Gyrus - R Basal Ganglia/Nucleus Accumbens - R Prefrontal cortex - L Postcentral Cyrus - R Orbitofrontal Cortex - R Inferior Parietal Lobe	Auditory Component - L Superior Frontal Gyrus - L Fusiform Gyrus - R Superior Temporal Gyrus - R Occipital Cortex - L Occipital Cortex - L Prefrontal Cortex	- Auditory network - Attentional network - Memory network - Emotional network - Visual network

			severe hearing loss (n=9). **Reported Comorbidities:** Not given. Anxiety/depression not tested.							

29	Schmidt et al, 2013 Default mode, dorsal attention and auditory resting state networks exhibit differential functional connectivity in tinnitus and hearing loss	**Aim:** To investigate auditory, dorsal attention, and default mode networks in adults with tinnitus and hearing loss in a resting state functional connectivity study. **Inclusion Criteria:** Not given **Exclusion Criteria:** Not given **Study Location:** Illinois, USA	**Sample Size:** n = 12 **Sex:** 3 F/9 M **Age:** 55.00 ± 6.97 **Tinnitus Duration:** Not given **Tinnitus Lateralisation:** Not given **Tinnitus Severity:** THI = 8.33 ± 6.76 **Tinnitus Pitch:** Not given **Tinnitus Sound:** Not given **Hearing Information:** Hearing loss was minimal from 250-2000 Hz and moderate to moderate-severe (threshold ≥ 35 dB) for 3-8 kHz **Reported Comorbidities:** No hyperacusis	**Sample size:** NH controls: n=15 HL controls: n=13 **Hearing:** NH: normal on PTA HL: minimal from 250-2000 Hz and moderate to moderate-severe (threshold ≥ 35 dB) for 3-8 kHz **Sex:** NH: 6 F/9M HL: 8 F/5M **Age:** NH: 52.93 ± 8.64 HL: 57.62 ± 9.39 **Matched to tinnitus group for:** NH: Age Sex HLs: Age Sex Hearing thresholds	**Scanner Strength:** 3T **Voxel Size:** Anatomical: 1.0×1.0×1.2 mm^3 Resting state: 3.4×3.4×4.0 mm^3 **Image Acquisition:** TR: 2000 ms TE: 30 ms **Instructions in Scanner:** Subjects were instructed to lay still and look at a fixation cross.	**Distortion Correction** Band-pass filtering (0.008 – 0.08 Hz) **Software Used:** SPM8, CONN, GIFT software **Motion Correction:** Realignment **Slice timing Correction:** Yes **Spatial Smoothing:** Yes, Gaussian kernel FWHM = 10mm **Spatial Normalisation:** MNI template	**Type of Analysis:** Independent Component Analysis + seed-based FC **Total *n* components created:** 30 **Region(s) of Interest:** **Auditory component (n=2)** - L Primary Auditory Cortex - R Primary Auditory Cortex **Dorsal Attention Network component #1 (n=2)** - L Posterior Intraparietal Sulcus - R Posterior Intraparietal Sulcus **Dorsal Attention Network component #2 (n=2)** - L Frontal Eye Field - R Frontal Eye Field **Default Mode Network component (n=2)**	Auditory component - L Lingual Gyrus (TIN>NH) - L Parahippocampus (TIN>NH) DAN #2 component - R Parahippocampus (TIN>HL) DMN component - R Fusiform Gyrus (TIN>HL) - R Lingual Gyrus (TIN>HL)	DAN #1 component - R Supramarginal Gyrus (HL>TIN) DMN component - L Precuneus (HL>TIN) - L Precentral Gyrus (HL>TIN) - L Cerebellum (HL>TIN) - L Cerebellar Vermis (HL>TIN) - R Precuneus (NH>TIN)	- Auditory network - Dorsal attention network - Default mode network - Motor network - Limbic system

							- Medial Prefrontal Cortex - Posterior Cingulate Cortex			