Study Title: Functional impact of tinnitus in adults who use cochlear implants and short-term effect of sound textures

Short Title: Sound textures developed for cochlear implants (STCIs)

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1. SYNOPSIS

Study Title	Functional impact of tinnitus in adults who use cochlear implants and short-term effect of sound textures
Abstract	Tinnitus, the perception of a sound in the absence of a sound source, is present in 70% of adults cochlear-implant users, and it is a serious concern for approximately 13% of adult users of cochlear implants (CIs) (Gomersall et al, 2018). The mechanisms of tinnitus are currently not fully understood, but recently an Integrative Model (Sedley et al, 2016) has been proposed that interprets tinnitus in the framework of predictive coding. Predictive coding assumes that the brain continuously makes predictions about the environment. In this process, inputs to the system are compared to predictions, and “prediction errors” are generated. For hearing, the default prediction is silence. However, spontaneous activity in the auditory cortex might become a precursor of tinnitus. If tinnitus is amplified, by virtue of different mechanisms including focusing attention, it may become the default prediction, instead of silence. Based on the Integrative Model: (1) The mismatch negativity response (MMN), which indexes prediction error, should have different patterns across individuals with and without tinnitus; (2) Stimuli with a certain temporal pattern, such as fluctuating sounds, can lead to changes in the prediction of sensory systems as they induce entrainment ("temporal alignment of the sensory system with its environment" as defined by Sameiro-Barbosa & Geiser, 2016). A change in predictions may reduce tinnitus loudness, or even suppress tinnitus. This study will test these hypotheses by: (1) Comparing MMN responses from two groups of adult cochlear-implant users, one with tinnitus and another one without tinnitus (Part A); (2) Quantifying the effect of using sound textures on the reduction of tinnitus loudness/annoyance and on MMN, loudness rating, and annoyance ratings (part B). A control condition will be included where unmodulated filtered white noise will be used. It has also been suggested that, at least for acoustic hearing (i.e. for people with hearing loss but who do not wear a cochlear implant) listening effort as measured using pupillometry is greater in patients with tinnitus than in those without (Juul Jensen et al, 2018). We will explore the relationship between tinnitus, speech recognition, listening effort, and pupillometry.
Inclusion Criteria	Adult (aged 18+ years, with no upper limit) users of unilateral cochlear implants who are fluent in English, attend the Emmeline Centre for Auditory Implants and have had their cochlear implants switched on for at least one year.

Exclusion Criteria	Bilateral cochlear implantation. Aged less than 18 years. Severe visual impairment. Severe mental-health condition. Severe general-health condition. Currently having medication that affects tinnitus or the recording of evoked potentials. Currently receiving other treatments for tinnitus apart from tinnitus management therapy.
Planned sample size	62 participants (31 with tinnitus and 31 with moderate tinnitus). Please note that in order to recruit 62 participants meeting the inclusion criteria, it is likely that a greater number of participants is tested until these two groups are completed with the required sample size.
Aims and objectives	The aim of the present study is to determine the effect of sound textures (Gomersall et al, 2016) on reduction of tinnitus loudness and annoyance. This has applications for the implementation of sound therapies for tinnitus relief. Outcomes will be measured in terms of the psychoacoustic properties of tinnitus (loudness and annoyance) and MMN (brain responses). A secondary aim is to establish what the functional impact of tinnitus is in the population of adults who wear cochlear implants. It has been previously established that 75% of users of cochlear implants experience tinnitus and that nearly a third of the users ranked tinnitus as an area of significant concern (Gomersall et al., 2018). This study will extend this knowledge by obtaining a functional characterisation of tinnitus in the same population using a validated questionnaire and a custom questionnaire. Characterising the type of tinnitus may help us understand the mechanisms behind its generation. Additionally, the relationship between tinnitus, speech recognition outcomes, and listening effort will be investigated.
Research questions	Main question: In cases of moderate or severe tinnitus, do 'sound textures' reduce tinnitus loudness/annoyance for adult cochlear-implant users? Secondary questions: 1) Are there any differences in MMN between the tinnitus group and the no-tinnitus group? If a difference is found, MMN can be used as objective markers of tinnitus. 2) What are the functional impact and characteristics of tinnitus are in adult users of cochlear implants? This is a secondary question that will be addressed using a custom questionnaire, measuring speech recognition outcomes, and listening effort using pupillometry.

	3) In cases of moderate or severe tinnitus: a) Does the MMN change after stimulation with sound textures compared to white noise filtered to match their long-term spectrum? b) Are any changes in the objective measures MMN correlated with the reduction of tinnitus loudness/annoyance?
Changes from previous version	• The power calculations and analysis sections were revised to maximise power and increase feasibility. • The electrophysiological measures are limited to MMN due to new evidence supporting MMN as a tinnitus marker. Reducing the number of electrophysiological measures increases the feasibility of the study. • After PPI consultation and due to carrying out only one electrophysiological measure, the division between a Part A and Part B of the study, which described successive phases of the same study, has been suppressed in order to reduce the number of visits to the centre. • After PPI consultation, the Tinnitus Functional Index, a questionnaire used in the study, and a new questionnaire, the HISQUI-19 (please see below), were implemented online and participants will be offered to complete these online (with help from the researcher via video appointment if needed) or in person during their visit. • The Adapted Cochlear Implant Tinnitus Questionnaire was abbreviated and re-worded as needed after PPI consultation. • We have changed where we store the information of the study as the Specialist Research Audiologist is now employed by the Trust. It is safer and easier to store the data in NHS computers. • We have added one questionnaire, HISQUI-19, to explore sound quality across groups with and without tinnitus. • We have introduced changes to the PIS as a result of consultation with a PPI group of patients with hearing loss, some of them users of cochlear implants. • Extension to 31/12/2023

2. ABBREVIATIONS

ACC	Auditory Change Complex
ASSR	Auditory Steady State Response
CI	Cochlear Implant
HISQUI-19	Hearing Implant Sound Quality Index
MMN	Mismatch Negativity
ROC	Receiver Operating Characteristic
TFI	Tinnitus Functional Index

3. BACKGROUND AND RATIONALE

Tinnitus

Tinnitus is commonly defined as the perception of sound in the absence of an external sound source (Moore, 2012). The sound perceived can be a tone or a noise (hissing, buzzing, ringing, etc). The prevalence of tinnitus is high: one in ten adults in the UK has tinnitus, and two thirds of people who have tinnitus also have a hearing loss (Action on Hearing Loss, 2018). But although tinnitus is a common ailment, only 5% find it moderately or severely annoying and 0.5% report it to be debilitating (Davis & Rafaie, 2000).

The mechanisms of tinnitus are not fully understood. As tinnitus is commonly associated with hearing loss, it was initially thought that tinnitus originated from the damage to the sensory receptors for hearing placed in the cochlea (inner ear). An origin of tinnitus at higher levels of the auditory system was proposed, attributing tinnitus to plastic changes in the neural auditory system due to damage to the system and/or sensory deprivation induced by hearing loss (Noreña, 2012). The nature of these changes is unclear, and while there are many theories about tinnitus mechanisms, no theory or group of theories can account for the tinnitus phenomenology known through several decades of research. This was pointed out by Sedley et al (2016), who developed a framework to explain the origin of tinnitus, the 'Integrative Model', based on predictive coding (Rao & Ballard, 1999).

Predictive coding is a theoretical model to account for the way the brain represents the environment. The model describes a series of hierarchically ordered levels, which contain state units (neurons) that generate predictions about the level below. At this level, the difference between the expected state and the prediction from the level above is encoded as prediction error. Prediction errors are sent to the level above to improve predictions about the level below (Sedley et al., 2016). The state units encode 'posterior beliefs' based on sensory input ('likelihood') and a 'prior' from the level above. Beliefs entail a probability distribution over a perceptual dimension (for example tinnitus loudness). The inverse variance of that distribution is termed 'precision' (post-synaptic gain), which is the confidence placed on a belief. Prediction errors are weighted by precision, and the weighted mean of the prior and the likelihood is the posterior expectation, which encodes the most likely value for the perceptual dimension. According to this model, spontaneous activity in the subcortical auditory pathway is a precursor of tinnitus, which is normally ignored. However, if the intensity of this precursor (i.e. the intensity of tinnitus) or its precision is increased by different contributory mechanisms (Sedley et al., 2016), tinnitus perception arises. Focused attention can lead to further increases in precision and to tinnitus becoming the default prediction (Sedley et al., 2016).

Tinnitus and cochlear implants

The study of tinnitus in cochlear implantation may help to better understand tinnitus in general, which is helpful to the whole community of patients affected by tinnitus, not only to those using cochlear implants. Cochlear-implant users are often affected by tinnitus. In most cases tinnitus predates the time of the surgery, but there is a small number of cases where tinnitus worsens or first appears after surgery (Quaranta et al, 2004). Cochlear implants have been successfully used as a treatment for tinnitus when tinnitus is associated with severe or profound hearing loss (Ruckenstein et al, 2001), including cases of unilateral hearing loss (Van de Heyning et al, 2008; Buechner et al, 2010). Suppression or reduction of the tinnitus loudness after cochlear implantation has been reported both with the cochlear implant switched on and off, and for both the implanted ear and the contralateral ear (Quaranta et al,

2008; Ito & Sakakihara, 1994; Souliere et al, 1992; McKerrow et al, 1991; Yonehara et al, 2006; Greenberg et al, 2016).

In spite of the overall reduction of tinnitus after cochlear implantation, tinnitus is a primary concern for around 13% of cochlear-implant users (Gomersall et al., 2018) and it continues to be an issue for some cochlear-implant users at sleeping hours, presumably because the external components of the implant are usually removed (Pierzycki et al, 2016). Cochlear-implant users may still need active interventions to alleviate tinnitus.

Sound therapy and cochlear implants

One of the most commonly used therapies for tinnitus reduction is sound therapy, which consists of using sound exposure in order to alleviate tinnitus. It is still not well understood whether sound therapy acts by masking tinnitus, by interfering with its mechanisms of production (Noreña, 2012), or through both mechanisms. The clinical effects of sound therapy have been assessed by several clinical trials, although studies including cochlear-implant users are scarce. Additionally, studies differ in design, outcome measures, and mechanisms of bias control.

Recently, Hobson et al (2012) systematically reviewed reports of prospective randomised controlled trials in which adults with persistent, distressing, subjective tinnitus of all aetiologies took part and where management included maskers, noise-generating devices, and/or hearing aids used alone or in combination with other treatments such as counselling/tinnitus management therapy. They identified six studies that matched these inclusion criteria (Davis et al, 2007; Dineen et al, 1999; Henry et al, 2006; Goebel et al, 1999; Hazell et al, 1985; Mehlum et al, 1984) and performed meta-analysis in order to assess the clinical effectiveness of sound therapy. Outcomes were evaluated in terms of tinnitus loudness reduction or impact on quality of life. The bias risk of these studies was moderate to high. No significant effects of sound therapy were found, but because of the limited data, the authors pointed out that the lack of conclusive evidence should not be interpreted as indicative of inefficiency of the treatment. Further research with appropriate design is needed.

To our knowledge, there has been little research evaluating the effect of sound therapy in cochlear-implant users. The signal processing used by cochlear implants strongly modifies the stimuli, and it is important to evaluate these therapies in cochlear implant users. Recently, Tyler et al (2018) used a sound-therapy intervention based on an ‘app’ initially developed for users with acoustic hearing. First, each participant chose their favourite sound from a list of options. Ten participants used the app for two weeks and then completed an online questionnaire and rated the effectiveness of the treatment. Outcomes varied across participants, but for most, the loudness of tinnitus had decreased at the time of responding to the questionnaire. Only three out of ten participants rated the effectiveness of therapy “70% or higher”. These outcomes are hard to interpret as there was no control group or condition. A laboratory trial was also conducted with thirteen participants. Rain, music, and wave sounds were chosen more often within a list of fifteen options including white noise, wind, and crickets, among others. Although no acoustic analysis of the stimuli used by Tyler et al. (2018) was presented, it is likely that these sounds are characterised by a wide-dynamic range given by temporal fluctuations in amplitude (i.e. amplitude modulation). Research conducted by Henry et al. (2004) indicates that customised sounds for tinnitus relief are more effective if they have large dynamic changes due to short-term amplitude modulations. The authors suggested, based on previous work of Feldman (1983), that ‘residual inhibition’ (temporary suppression of tinnitus) could occur due to forward masking when sounds such

as sequences of very brief sounds ('trains of pulses'): tinnitus was not perceived in between the pulses. Forward masking is a phenomenon that is characterised by the decrease in sensitivity to a sound immediately after the presentation of another sound (Henry et al., 2004). However, more recently an alternative explanation was suggested. Residual inhibition could be mediated by the production of sustained neural synchrony in the central auditory pathway that occurs when amplitude-modulated sounds (or other predictable sounds) are presented (Reavis et al, 2012) due to sensory entrainment. Sensory entrainment is the "temporal alignment of the sensory system with its environment" (Sameiro-Barbosa & Geiser, 2016)(Sameiro-Barbosa and Geiser, 2016). Entrainment occurs when predictable stimuli are delivered. Predictability can be based on periodicity or on other regularities of sound (Rimmele et al, 2018). For example, speech contains quasi-periodic and aperiodic irregularities.

Modulated sounds could lead to entrainment as they are predictable. A number of recent studies performed with participants with acoustic hearing (i.e. who were not users of a cochlear implant) have compared modulated and unmodulated sounds and found trends for the that modulated pure-tones, especially those matching the frequency of the tinnitus (Reavis et al, 2012; Neff et al, 2017), to lead to greater residual inhibition than white noise (Reavis et al, 2012; Tyler et al, 2014) or pink noise, amplitude-modulated filtered music (Neff et al., 2017), and unmodulated pure-tones (Neff et al, 2019).

The interpretation of previous studies is complicated by the choice of stimuli to compare. For example, Neff et al. (2017) and Neff et al. (2019) compared the effects of modulated pure tones and unmodulated pure tones. Additionally Neff et al. (2017) used unmodulated and modulated stimuli other than pure tones. For the pure-tone stimuli the unmodulated and modulated sounds were identical apart from amplitude modulation. Thus, it is possible that the outcomes are obscured by confounds. Similarly, Tyler et al. (2014) and Reavis et al. (2012) compared the effect of using modulated pure tones to unmodulated broadband noise, but no comparisons between modulated and unmodulated noise were carried out.

Many of these studies have used stimuli that were pitch-matched to the tinnitus frequency. However, pitch-matching may be difficult to carry out (Hoare et al, 2014), and even when pitch-matching can be performed, the reproducibility of the matches across sessions is limited to sessions that were close in time, which can complicate the prescription of sound therapy based on pitch matching (Hoare et al., 2014). If stimulation at the tinnitus frequency is critical to reduce tinnitus loudness, a broadband stimuli increases the likelihood of success. It is of interest to know whether modulated sounds which are relatively broad in bandwidth can be effective to relieve tinnitus.

In the present study, we will use 'sound textures' created based on the work of Gomersall et al. (2016). Sound textures are stimuli differ in their statistical properties (their slow changes over time, their relative amplitude, or the correlation between them). Based on these properties, normal-hearing listeners can identify sound textures as environmental sounds such as fire, or rain, etc. One issue when using sound therapy for cochlear-implant users could be that the sounds used as stimuli are degraded by the processing of the cochlear implant (Carlyon et al, 2010). This leads to the sounds being less discriminable. Here we will use sound textures that have previously been studied by Gomersall et al. (2016), who examined sound textures that were still distinguishable when processed through a cochlear implant. Two discriminable textures with the same long-term spectrum but with markedly different temporal fluctuations will be used.

Tinnitus and auditory event-related potentials

There have been several attempts to objectively measure tinnitus, as this could contribute to a better understanding of tinnitus mechanisms (see Jackson et al., 2019, for a review). Among these objective measures, auditory electrophysiology has been used to explore different levels of the auditory system. Upon reviewing the literature about auditory brainstem responses, mid- and long-latency evoked potentials, we have identified some event-related auditory evoked potentials that have been suggested as possibly sensitive to tinnitus. These are the Mismatch Negativity (MMN) (Joos et al, 2014; Mahmoudian et al, 2013; Yang et al, 2013; Mahmoudian et al, 2015; Holdefer et al, 2013; Li et al, 2016), the N1-P2 (Houdayer et al, 2015; dos Santos Filha & Matas, 2010; Hong et al, 2016; Paul et al, 2014), the acoustic change complex (ACC) (Han et al, 2017), and the P300 component (dos Santos Filha & Matas, 2010; Gabr et al, 2011; Hong et al, 2016), and the Auditory Steady State Response (ASSR) (Paul et al., 2014). Additionally, the auditory MMN has been shown to be sensitive to tinnitus therapy outcomes (Mahmoudian et al., 2015, El-Minawi et al., 2018).

The MMN and P300 responses are thought to be indicators of pre-attentional and attentional processing. All ACC, MMN, and P300 indicate neural processing to acoustic changes, but they are likely to reflect different processes (Yau et al, 2017; Martin et al, 2012). According to Joos et al. (2014), N1-P2 represent the late phase of sensory gating, and MMN is induced by the violation of expectations about the sensory input, representing a prediction error signal which induces the update of prior representations of the environment, generating the P300 component. Sedley et al. (2016)'s model of tinnitus provides a framework to interpret the distinct characteristics of these event-related responses in people with and without tinnitus. The visual MMN has been interpreted as "a prediction error signal to visual input that does not match probabilistic representations of the predicted (external causes of) input" in the framework of predictive coding (Stefanics et al, 2014).

To our knowledge, no tinnitus studies where participants were users of cochlear implants have used these electrophysiological measures. All of these measures have been recorded from cochlear-implant users with purposes other than tinnitus research. When recording auditory evoked potentials from cochlear-implants users one important issue is the measurement artefact. We will use signal processing techniques to reduce the artefact as much as possible.

In version 1 of this protocol, we intended to measure ASSR, ACC, P300, and MMN from our study sample. The study was then haltered by COVID-19 and therefore, no data has been yet collected. At present, there is new evidence available supporting that MMN could be a biomarker of tinnitus (Mohebbi et al, 2019; Sedley et al, 2019; Sendesen et al, 2021). MMN is also the only measure that has been investigated as a marker for therapy effects. Thus, we decided to limit our investigations to MMN, increasing the feasibility of the study (Mahmoudian et al, 2015; El-Minawi et al, 2018).

Tinnitus and Pupillometry

It has been shown that, for acoustic hearing (i.e. for people with hearing loss but who do not wear a cochlear implant), listening effort as measured using pupillometry is greater in patients with tinnitus than in those without (Juul Jensen et al., 2018). The same authors reported no correlation between tinnitus severity and pupillary response. We know of no studies about listening effort across groups of cochlear-implant users with and without tinnitus.

4. AIMS AND OBJECTIVES

The aim of the present study is to evaluate the effect of sound textures on tinnitus loudness and annoyance. This has applications for the implementation of sound therapies for tinnitus relief. Outcomes will be measured in terms of the psychoacoustic properties of tinnitus (loudness and annoyance), and MMN.

A secondary aim is to establish what the functional impact of tinnitus is in the population of deaf adults who wear cochlear implants. It has been previously established that 75% of users of cochlear implants experience tinnitus and that nearly a third of the users ranked tinnitus as an area of significant concern (Gomersall et al., 2018). This study will extend this knowledge by obtaining a functional characterisation of tinnitus in the same population using a validated questionnaire, and measuring speech recognition outcomes and listening effort using pupillometry.

5. RESEARCH QUESTIONS

The main question is: In cases of moderate or severe tinnitus, do 'sound textures' reduce tinnitus loudness/annoyance for adult cochlear-implant users?

The secondary questions are:

4) Are there any differences in the MMN between the tinnitus group and the no-tinnitus group? If a difference is found, MMN can be used as objective markers of tinnitus.
5) What are the functional impact and characteristics of tinnitus are in adult users of cochlear implants? This secondary question will be addressed using a custom questionnaire, and measuring speech recognition outcomes and listening effort with pupillometry.

6) In cases of moderate or severe tinnitus:
    a. Does the auditory MMN change after stimulation with sound textures compared to white noise filtered to match their long-term spectrum?
    b. Are any changes in MMN correlated with the reduction of tinnitus loudness/annoyance?

6. PARTICIPANTS

6.1 Setting

The study will be carried out at the Emmeline Centre for Auditory Implants (Addenbrooke's Hospital).

6.2 Overall Description of Participants

The participants will be adults (aged 18 years or older) users of unilateral cochlear implants.

6.3 Eligibility Criteria

Inclusion Criteria

The participant must meet ALL of the following criteria to be considered eligible:

Aged 18 years or above (with no upper age limit) who attends the Emmeline Centre for Auditory Implants.
Current user of one cochlear implant for at least one year since activation ('switch-on').
Fluent in English.

Additionally, for the tinnitus group:

Tinnitus present even when cochlear implant is switched on.
Scored 32 or higher in the Tinnitus Functional Index (TFI) questionnaire.

Exclusion Criteria

The participant may not be included if ANY of the following apply:

Bilateral cochlear implantation
Severe visual impairment
Severe mental-health condition
Severe general-health condition that renders participation a burden on the volunteer
Currently receiving any tinnitus treatment other than tinnitus management therapy.

7. SAMPLING

Potential participants will be identified by the clinicians at the Emmeline Centre for Hearing Implants as patients come into the clinic.

7.1 Sample Size Calculations

Comparison of tinnitus and no tinnitus group: Power analysis using G*Power3 (Faul et al, 2007) indicated that the number of patients in order to obtain $1-\beta=0.8$, detecting a moderate effect (partial $\eta^2 = 0.09$) at the significance level of $\alpha=0.05$ performing a between factors ANOVA with two groups and two repetitions (two measurements taken each time), is 62 participants.

Sound textures

Power analysis performed using G*Power3 (Faul et al., 2007) indicated that 24 patients should be tested in order to obtain $1-\beta=0.8$, detecting a moderate effect (partial $\eta^2 = 0.09$) at the significance level of $\alpha=0.05$ using a within-subject repeated-measurements design with two types of sound stimuli (factor sound stimuli), measuring before and after presenting the sound texture (factor time). All measurements to be performed twice.

If there are drop outs or data loss, new participants will be invited in order to achieve the target sample size. We will offer testing to all 31 participants with tinnitus recruited but the minimum sample will be 24 complete datasets.

8. PARTICIPANT INVOLVEMENT

8.1 Recruitment

Potential participants will be given information about the study by their clinical care team at the Emmeline Centre. They may also contact the researchers themselves if they see the advert of the study at the Hospital. Adult users of cochlear implants who attend the Emmeline Centre for Auditory Implants will be informed about the study by their audiologists. If patients show interest, they will be given an invitation pack containing an invitation letter and a Participant Information Sheet, and a pre-paid envelope and form in order for them to contact the Specialist Research Audiologist who will meet them online or in person to discuss the information and ask for consent.

Each invitation pack contains the study Participant Information Sheet and contact information for the potential participants to contact the researchers if they wish to take part. If a potential participant contacts the researchers, the information of the study will be discussed and consent will be obtained before starting the conduct of research.

If any potential participant approaches the researchers as a result of having seen posters, they will be posted an information pack at their request and they will be invited to discuss the information with the researchers.

8.2 Screening and Enrolment

Potential participants who respond to the invitation by contacting Dr Marina Salorio-Corbetto will be contacted in order to arrange for a research appointment at the Emmeline Centre. During this appointment, the information contained in the Participant Information Sheet will be discussed and the potential participant will have the chance of asking any questions about it. If the potential participant wishes to take part in the study, the conditions of taking part will be explained as listed in the Consent Form, and any questions will be answered. Consent will be obtained in written form (by asking the potential participant to sign the consent form).

Participants will be initially interviewed in order to determine whether or not they have tinnitus. If a participant does not report tinnitus, they will be included in the ‘No-tinnitus group’. If a participant reports tinnitus, they will be asked to complete the Tinnitus Handicap Index (THI) and a bespoke questionnaire which is designed to explore the features of their tinnitus. Participant who obtain a score of 32 points or higher on the THI will be included in the ‘Tinnitus group’.

Screening will stop when 31 participants have been recruited in each group.

8.3 Randomisation

For the tinnitus group, when sound textures are used, the initial sound that the participants are stimulated with will be subjected to randomisation. Randomisation will be done using MATLAB, sampling without replacement. One participant will be assigned a random condition (1 or 2) and the next participant will be assigned the other condition. Then the next pair will have a new random order. This will be done so that there is an equal number of participants in each group.

In Part A the groups are determined by the tinnitus status of the participants.

8.4 Risks and Benefits of Participation

Identified risks:

In general, participants may get tired if sessions are long. Breaks and refreshments have been included in planning in order to reduce this burden as much as possible.

Focusing on tinnitus in order to reply to the questionnaires could make the participant more aware of their tinnitus. This means that their tinnitus may appear louder or they may notice it more frequently. This effect does not occur for most people, and when it does, it is usually temporary.

Additionally, sounds used to relieve tinnitus can sometimes increase tinnitus loudness, but this is more frequent when sounds are loud (as similarly, it is common for tinnitus to be worse after being in noisy places). We will check with the participant the loudness level of any sounds presented to them to make sure that no loud/uncomfortable sounds are presented during the study. Participants will be made aware that they can ask us to interrupt what we are doing any time if they feel uncomfortable.

Identified benefits:

In general, taking part in research can help participants better to understand their condition. Participants who listen to sound textures within the study could find that one or more sounds used in the study help them to relieve tinnitus.

8.5 Process for Participant Withdrawal from Study

Participants will be made aware of the fact that their participation is voluntary, and that they can withdraw from the study at any time, without this affecting their medical care. If a participant decides to withdraw from the study, we will not contact them any further about the study, but we will still use any anonymised research data collected up to the date of withdrawal.

9. DATA COLLECTION

Data will be collected by Dr Marina Salorio-Corbetto in maximum of two sessions lasting up to 3 hours each. Participants will be offered short breaks during each session, as well as a longer break half-way through the session.

In the first session, participants will be asked if they have tinnitus or not.

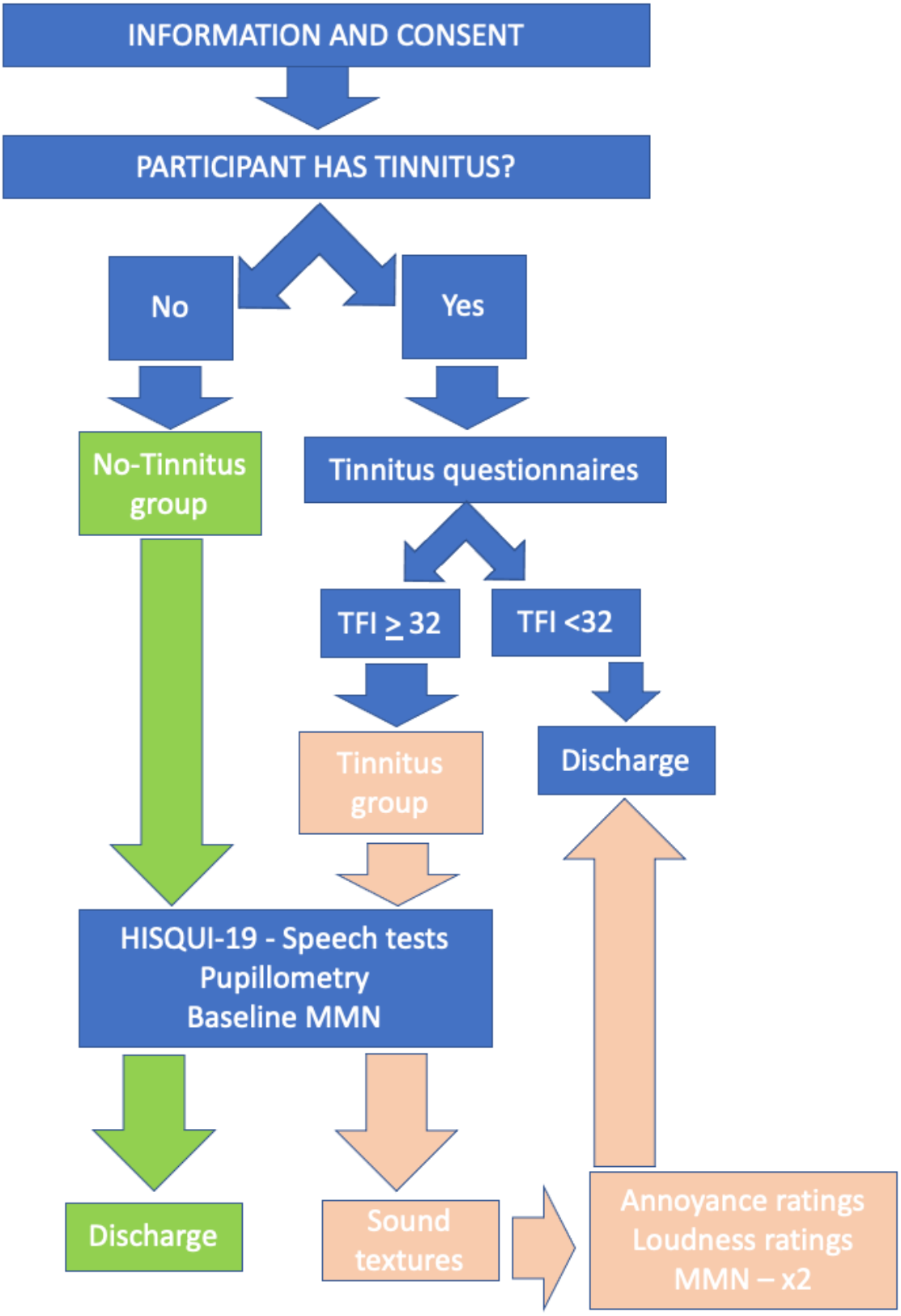
- If a participant reports that they have no tinnitus, they will be included in the 'No-tinnitus group'.
- If a participant reports that they they have tinnitus, they will be asked to fill in the TFI questionnaire, as well as the Adapted Cochlear Implant Tinnitus Questionnaire, which is an extended version of the questionnaire used by Greenberg et al. (2016) (please see Appendix 3). If the participant scores 32 or higher in the TFI questionnaire, they will be included in the 'Tinnitus group'.

Next, pupillometry will be carried out before and during a speech-intelligibility task where the participant will be asked to listen to sentences in the presence of background noise and repeat as many words of the sentences as they can. Participants will be asked to complete the HISQUI-19 questionnaire (Amann & Anderson, 2014) in order to provide information about the sound quality of their implant in everyday life. This will be done for participants in both the 'No-tinnitus' and the 'Tinnitus group'.

After this, the MMN will be recorded using a BioSemi device (two repetitions). This device uses a cap with recording electrodes that sit on the skin. The stimuli to evoke the neural responses will be delivered via the cochlear implant, i.e., will be electrically evoked. The MMN is an evoked potential generated in response to the presentation of a sound stimuli (this is termed the standard stimulus) which is occasionally interleaved with another sound that differs from the standard stimulus in one aspect such as intensity or frequency (this is called the deviant stimulus). It is possible to explore different features in about 30 minutes when testing users of cochlear implants (Näätänen et al, 2017). This will be done for participants in both the 'No-tinnitus' and the 'Tinnitus group'. **Participants who have no tinnitus will end their participation at the end of session 1.**

Participants in the 'Tinnitus group' will be asked to listen to a sound for 10 minutes. During this time, they will provide ratings of tinnitus loudness and annoyance. A new recording of MMN will be done after they hear the sound (two repetitions).

After this is done, participants in the 'Tinnitus group' will be invited to attend for a second session, where they will listen to a different sound for 10 minutes, having had their MMN recorded before and after the presentation of the sound. As in session 1, they will provide ratings of tinnitus loudness and annoyance while listening to the sound. **After this, participation will end.**


INFORMATION AND CONSENT
PARTICIPANT HAS TINNITUS?
No
Yes
No-Tinnitus group
Tinnitus questionnaires
TFI ≥ 32
TFI <32
Tinnitus group
Discharge
HISQUI-19 - Speech tests
Pupillometry
Baseline MMN
Discharge
Sound textures
Annoyance ratings
Loudness ratings
MMN – x2

10. DATA HANDLING AND RECORD KEEPING

10.1 Data Handling

- A pseudo anonymised ID code will be given to each participant. This code will be randomly generated four-digit number followed by randomly chosen letter. A random sequence of codes made of four-digit numbers and a letter will be generated using MATLAB and codes will be assigned to participants as they join the study. For example, a participant could be assigned the ID code 4924H. Dr Marina Salorio-Corbetto will keep a record of the pseudo anonymised ID codes linked to the names and hospital numbers of the participants, together with the contact details provided by the participants for the purposes of arranging for study-related appointments. This record will be saved in an NHS computer.

- The responses of the participants will be stored using their pseudo anonymised ID code and not their name. Evoked-potential data will be originally stored in the computer attached to the BioSemi device, but copies of the output files will be obtained by Dr Marina Salorio-Corbetto in order to analyse the responses. These copies will be stored in a password-protected work laptop. Analysis will be completed either in her work laptop or in laboratory computers, all password protected. It is important to point out that no identifiable data will be included.
- Responses to questionnaires will be recorded originally on paper or via the online interface Gorilla, where the participant will be identified by their pseudo anonymised ID code. No identifiable data will be included. Outcomes will be processed by Dr Marina Salorio-Corbetto.
    - Gorilla is a cloud software platform specifically for the behavioural sciences. Here are some key facts about their data security:
    - **Cyber Essentials**: Certificate of Assurance - IASME-CE-004228
    - **Hosting:** Gorilla is hosted on Microsoft Azure within the EU (Republic of Ireland) which is compliant with ISO/IEC 27001:2005
    - **Traffic Encryption:** All traffic to and from Gorilla is encrypted (TLS/SSL)
    - **Database Encryption:** The database is encrypted using industry-standard cryptography
    - **Data Ownership:** The experiment owner owns the research data that has been collected using Gorilla and has complete control over it
    - **Data Protection:** Gorilla is fully compliant with data protection legislation
    - **BPS:** Gorilla is fully compliant with BPS guidelines.
    - **GDPR:** Gorilla is fully compliant with GDPR.
    - **IP Address:** IP addresses are not provided in the data download unless specifically included.

- The relevant data (scores of the Tinnitus Functional Index, data descriptive of the participant's tinnitus) will be transcribed for further analysis to either Dr Marina Salorio-Corbetto's laptop or a laboratory computer, which are password protected.
- Back-up procedures: The plan also includes backing up non-identifiable research data to an encrypted hard drive.
- No identifiable data will be shared with other researchers/organisations.

10.2 Data Management

- Data entry procedures and personnel: Data will be entered for analysis by Marina Salorio-Corbetto using automated procedures (MATLAB scripts or functions that extract the relevant data and save it in an appropriate format for statistical analysis such as Excel sheets) whenever possible.
- Periodic reports format: Reports will be prepared every month for discussion within the research group. Reports will address progress and preliminary outcomes with a descriptive character.

10.3 Data Monitoring

Monitoring for this study will be conducted through University and Trust standard research policies. All research active persons involved will hold up to date GCP certificates.

We will not have a Data Monitoring Committee in place for this study. We will be continuously monitoring our patients and any adverse events will be reported to the REC in a timely manner.

Any new information that may be relevant to patients during the study will be made available to them at their next visit to the hospital with the researcher or their clinical team within the Emmeline Centre.

The research will be stopped if consistent adverse effects occur affecting the participants.

There is no indication that we will need to close this study prematurely. However, if this situation occurs, the authorising REC will be informed by our PI and patient's data will no longer be captured.

11. DATA ANALYSIS

Analysis will include a flow chart detailing: 1) The number of adult users of cochlear implants seen at the Emmeline Centre; 2) number of patients invited to take part; 3) The number of patients who responded to the invitation; 4) The number of participants who consented to take part and therefore were enrolled in the study; 6) The number of participants withdrawn (and reasons for withdrawal if known); 7) The number of participants lost to follow-up; 8) The number of patients with data not 'up to standard' for analysis; 9) The number of participants with data for analysis.

Additionally, data will be analysed in order to respond to the research questions.

Questionnaire data

The analysis of questionnaire data will be descriptive. Simple context analysis will be used to extract "topics" for future research or interventions from the open text responses of the Adapted Cochlear Implant Tinnitus Questionnaire (Gomersall et al, 2018). Correlations between outcomes of these questionnaires and speech recognition outcomes will be computed.

Comparison of MMN and pupillometry data across groups (tinnitus and no-tinnitus)

MMN, pupillometry, and speech-recognition outcomes will be compared across groups with and without tinnitus. Where the assumptions of ANOVA are met, parametric tests will be performed. If assumptions are seriously violated and data transformations are not successful, appropriate non-parametric tests will be carried out. The diagnostic efficiency of the MMN will be calculated by obtaining receiver operating characteristic (ROC) curves (McNicol, 2004) and calculating the area under the curve to determine whether this measure is sensitive to tinnitus.

Loudness and annoyance ratings and MMN before and after exposure to sound textures

Loudness and annoyance ratings, and the MMN amplitude (if tested) will be compared over time using separate repeated-measures designs (with repeated factor 'time', i.e., before and after exposure to the sound texture).

12. ETHICS

12.1 Participant Confidentiality

Data collection and confidentiality will be achieved adhering to the General Data Protection Regulation 2018 and the Data Protection Principles and the Caldicott Principles, complying with the Trust's Confidentiality Code of Conduct and the General Data Protection Regulation 2018. The Principal Investigator and the Research Associate have received training about confidentiality and General Data Protection Regulation 2018.

Data confidentiality will be achieved by:

- Not disclosing the status of any individual as participant in the research without written

consent from the participant. (For example, the participant's GP will be informed about individual participation, but this will be done with consent.)
- Using pseudo anonymised codes for the data collected and keeping the key to the codes inly accessible to the PI in an encrypted file.
- Keeping any written or printed records locked in a filing cabinet in the laboratory.

The following data will be collected:

- Age
- Cause of deafness
- Duration of hearing-aid use
- Duration of cochlear implantation
- Responses to the questionnaires presented during the course of research
- Electrophysiological responses
- Visual-analogue scale ratings
- Any feedback that the participant gives about their participation in the research.

Where personal data is collected, participants have the right to access their data and can do so by requesting access to the Principal Investigator.
As explained above, some data will be stored in computers and backed up to hard drives. Questionnaires in paper format will be safely stored and scanned to produce digital copies that can be backed up.

The Principal Investigator and the Specialist Research Audiologist could access the participant's clinical record to obtain information relevant to the analysis of results. For example, information about the participant's deafness or cochlear implantation. Information of interest can be added by these members of the research team to the pseudo anonymised record of the participant for analysis together with the rest of the data, in the context of the research project in order to respond to the research questions.

On completion of the study all documents will be archived off site for five years as per Trust policy in a dedicated archiving facility Endex archives.

The data will be used by the research team to respond to the research questions and to plan and design future research.
The outcomes of research, including an anonymised summary of the data and perhaps an anonymised dataset, will be published in international journals.

12.2 Other Ethical Considerations

No participants unable to consent will be included. Travel expenses will not be covered, but each participant will be paid 30 pounds per visit.

Ethical concerns arising of the research design:

1) TFI and tinnitus questionnaires will be performed with each participant who

reports tinnitus, but testing of the sound textures will be offered only to those whose tinnitus is moderate or more severe.
To mitigate the risk of not responding to a clinical need detected, a Tinnitus Management Therapy session at the Emmeline Centre for Auditory Implants, with Senior Audiologist Gemma Crundwell. Respondents to the invitation to take part in the study who 1) Had tinnitus but chose not to take part in research; 2) Responded to the questionnaires and score 31 or lower in the TFI; 3) Were enrolled in other tinnitus treatments and therefore could not take part in the experiments will be invited to attend the tinnitus therapy session immediately after their willingness or suitability for participation in the experiments is ruled out. All other participants who take part in any of the experiments will be invited to the tinnitus therapy session on completion of these experiments or in the event of premature withdrawal.

2) It is possible that sounds used for stimulation lead to an increase in tinnitus annoyance. If this occurs, stimulation will stop.

3) It is possible that the participants find any of the sounds (or both) relieve them from their tinnitus. If participants wish to continue using the sounds for tinnitus relieve, they will be offered to have the sounds loaded on their mobile phones or on other devices that they can use to stream sounds through their cochlear implants (such as an i-Pod). Instructions for use of the sounds will be given in the tinnitus therapy session offered at the end of participation. If participants wish to use the sounds as sound therapy after the study is completed, they will be asked to complete baseline measures of the loudness ratings and TFI at the start of therapy, and any sensitive electrophysiological measures and to repeat all these measurements one month later.

13. PATIENT PUBLIC INVOLVEMENT (PPI)

Following the PPI information provided on the INVOLVE website (www.invo.org.uk), initial versions of the Invitation Letter, Participant Information Sheet (A and B), consent forms, letter to the GP, and custom questionnaire were sent to the Cambridge University Hospital PPI (CUH PPI) group for feedback, which was used to further develop these documents into their form at the time of the original application. After consultation, some changes were made to the wording of the documents and changes were made to the experimental desing in the interest of patient comfort. We eliminated one test condition in order to make the task shorter and we decided to have two shorter sessions over two different days for data collection instead of just one day. In a similar way, we have decided to give the participants a pre-paid envelope for their “Adapted Cochlear-Implant Tinnitus Questionnaire”, so that they have several days to complete the questionnaire.
Ongoing consultation with the PPI group will guide the researchers about ways to engage the general public with our research and ways of disseminating the outcomes of the study. We are currently organising the creation of a hearing-loss specific PPI group.

For this new version of the protocol, after consultation with the ‘Cambridge Hearing PPI’ group within the Emmeline Centre, we have created a new short title to be used

in patient-facing documents, we have re-worded the patient-facing documents, as well as included optional online administration of the questionnaires, and made changes to the experimental design to reduce the number of visits to the hospital.

14. FINANCING

The study is funded by the Addenbrooke's Charitable Trust (ACT). Travel expenses of the participants and any consumables publication fees and costs associated with the dissemination of outcomes will be covered with such funding. The funding also covered Dr Marina Salorio-Corbetto's salary in the initial phases of study design and ethical approval. The laboratory is already equipped with the electrophysiology devices required for conducting the research. Dr Salorio-Corbetto recently obtained additional funding to acquire a pupillometry headset. The funding was awarded by ACT.

14.1 Sponsorship

The study will be jointly sponsored by Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge. The contact on behalf of the sponsor is Mr Stephen Kelleher, based at Addenbrooke's Hospital, Hills Rd, Cambridge, CB2 0QQ, telephone number 01223217418, email research@addenbrookes.nhs.uk

15. TIMETABLE

Recruitment should commence as soon as possible after Ethical Approval and HRA approval amendment are granted. The date for completion of the project is 19th July 2023. However, the actual timing for completion will depend on recruitment flow and participant availability, and there may be interruptions due to conference presentations, training, or contingency. If issues arise, we will apply for an extension.

16. RESOURCES, EQUIPMENT AND PHYSICAL FACILITIES

Resources and equipment:

Evoked potentials will be carried out using a 32-channel BioSemi EEG system and/or an Interacoustics Eclipse device.

Pupillometry will be carried out with an eye-tracking camera which will be acquired for the purpose of the study.

The speech intelligibility task will be carried out using a laptop computer with a MATLAB interface, an external sound card, a Tucker-Davis Technologies (TDT) PA4 programmable

attenuator and a TDT SM3 mixer, and two loudspeakers for the delivery of the speech and the background noise, respectively, or a similar setup in place.

The sound textures will be prepared using a laptop computer running MATLAB.

Physical Facilities:

Participants will be seen at the Emmeline Centre for Hearing Implants. The contact for this site is:

Emmeline Centre, Ms Sophie McKenny, Senior Otology Research Nurse, The Emmeline Centre for Hearing Implants, Level 1, Addenbrooke's Hospital, Cambridge, CB2 0QQ, 01223586625, email sophie.mckenny@addenbrookes.nhs.uk.

Tinnitus management therapy sessions will take place at the Emmeline Centre for Hearing Implants, and audiologist Gemma Crundwell will be in charge of delivering such sessions.

17. INSURANCE STATEMENT

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

18. REFERENCES

Action on Hearing Loss, 2018. *Understanding tinnitus* Version 2., London: Action on Hearing Loss. Available at: file:///C:/Users/ms878/Downloads/Understanding%20tinnitus%20leaflet.pdf.

Amann, E., Anderson, I., 2014. Development and validation of a questionnaire for hearing implant users to self-assess their auditory abilities in everyday communication situations: the Hearing Implant Sound Quality Index (HISQUI19). *Acta oto-laryngologica*, 134(9), p.915–923.

Buechner, A., Brendel, M., Lesinski-Schiedat, A., Wenzel, G., Frohne-Buechner, C., et al, 2010. Cochlear implantation in unilateral deaf subjects associated with ipsilateral tinnitus. *Otology & Neurotology*, 31(9), p.1381–1385. Available at: https://journals.lww.com/otology-neurotology/Fulltext/2010/12000/Cochlear_Implantation_in_Unilateral_Deaf_Subjects.5.aspx.

Carlyon, R.P., Macherey, O., Frijns, J.H., Axon, P.R., Kalkman, R.K., et al, 2010. Pitch comparisons between electrical stimulation of a cochlear implant and acoustic stimuli presented to a normal-hearing contralateral ear. *Journal of the Association for Research in Otolaryngology*, 11(4), p.625–640. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20526727.

Davis, A.C., Rafaie, E.A., 2000. Epidemiology of tinnitus. In R. S. Tyler, ed. *Tinnitus Handbook*. San Diego, CA: Singular, pp. 1–24.

Davis, P.B., Paki, B., Hanley, P.J., 2007. Neuromonics Tinnitus Treatment: third clinical trial. *Ear and Hearing*, 28(2), p.242–259. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17496674.

Dineen, R., Doyle, J., Bench, J., Perry, A., 1999. The influence of training on tinnitus perception: an evaluation 12 months after tinnitus management training. *British journal of audiology*, 33(1), p.29–51.

El-Minawi, M.S., Dabbous, A.O., Hamdy, M.M., Sheta, S.M., 2018. Does changes in mismatch negativity after tinnitus retraining therapy using tinnitus pitch as deviant stimulus, reflect subjective improvement in tinnitus handicap? *Hearing, Balance and Communication*, 16(3), p.182–196. Available at: https://doi.org/10.1080/21695717.2018.1500003.

Faul, F., Erdfelder, E., Lang, A.-G., Buchner, A., 2007. G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior research methods*, 39(2), p.175–191.

Feldman, H., 1983. Time patterns and related parameters in masking of tinnitus. *Acta Oto-Laryngologica*, 95(5–6), p.594–598. Available at: https://doi.org/10.3109/00016488309139449.

Gabr, T.A., El-Hay, M.A., Badawy, A., 2011. Electrophysiological and psychological studies in tinnitus. *Auris Nasus Larynx*, 38(6), p.678–683. Available at: http://www.sciencedirect.com/science/article/pii/S0385814611000460.

Goebel, G., Rübler, D., Stepputat, F., Hiller, W., Heuser, J., et al, 1999. Controlled prospective study of tinnitus retraining therapy compared to tinnitus coping therapy and broad-band noise generator therapy. In International Tinnitus Seminar. Citeseer, pp. 302–306.

Gomersall, P.A., Baguley, D.M., Carlyon, R.P., 2018. A cross-sectional questionnaire study of tinnitus awareness and impact in a population of adult cochlear implant users.

Gomersall, P.A., Turner, R.E., Baguley, D.M., Deeks, J.M., Gockel, H.E., et al, 2016. Perception of stochastic envelopes by normal-hearing and cochlear-implant listeners. *Hearing research*, 333, p.8–24.

Greenberg, D., Meerton, L., Graham, J., Vickers, D., 2016. Developing an assessment approach for perceptual changes to tinnitus sound characteristics for adult cochlear implant recipients. *International Journal of Audiology*, 55(7), p.392–404.

Han, J.-H., Won, J.Y., Hong, S.K., Kim, J.H., Kim, E.S., et al, 2017. Objective measurement of subjective tinnitus using the acoustic change complex. *PLOS ONE*, 12(11), p.e0188268. Available at: https://doi.org/10.1371/journal.pone.0188268.

Hazell, J.W.P., Wood, S.M., Cooper, H.R., Stephens, S.D.G., Corcoran, A.L., et al, 1985. A clinical study of tinnitus maskers. *British Journal of Audiology*, 19(2), p.65–146.

Henry, J.A., Rheinsburg, B., Zaugg, T., 2004. Comparison of custom sounds for achieving tinnitus relief. *Journal of the American Academy of Audiology*, 15(8), p.585–598. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15553658.

Henry, J.A., Schechter, M.A., Zaugg, T.L., Griest, S., Jastreboff, P.J., et al, 2006. Clinical trial to compare tinnitus masking and tinnitus retraining therapy. *Acta Oto-Laryngologica*, 126(sup556), p.64–69.

Hoare, D.J., Edmondson-Jones, M., Gander, P.E., Hall, D.A., 2014. Agreement and reliability of tinnitus loudness matching and pitch likeness rating. *PLOS ONE*, 9(12), p.e114553. Available at: https://doi.org/10.1371/journal.pone.0114553.

Hobson, J., Chisholm, E., El Refaie, A., 2012. Sound therapy (masking) in the management of tinnitus in adults. *Cochrane Database of Systematic Reviews*, (11). Available at: https://doi.org//10.1002/14651858.CD006371.pub3.

Holdefer, L., Oliveira, C.A., Venosa, A.R., 2013. The mismatch negativity test in ears with and without tinnitus-a path to the objectification of tinnitus. *International Tinnitus Journal*, 18(2).

Hong, S.K., Park, S., Ahn, M.-H., Min, B.-K., 2016. Top-down and bottom-up neurodynamic evidence in patients with tinnitus. *Hearing Research*, 342, p.86–100. Available at: http://www.sciencedirect.com/science/article/pii/S0378595516303148.

Houdayer, E., Teggi, R., Velikova, S., Gonzalez-Rosa, J.J., Bussi, M., et al, 2015. Involvement of cortico-subcortical circuits in normoacousic chronic tinnitus: A source localization

EEG study. *Clinical Neurophysiology*, 126(12), p.2356–2365. Available at: http://www.sciencedirect.com/science/article/pii/S1388245715000851.

Ito, J., Sakakihara, J., 1994. Suppression of tinnitus by cochlear implantation. *American Journal of Otolaryngology - Head and Neck Medicine and Surgery*, 15(2), p.145–148. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=24082952.

Joos, K., Gilles, A., Van de Heyning, P., De Ridder, D., Vanneste, S., 2014. From sensation to percept: The neural signature of auditory event-related potentials. *Neuroscience & Biobehavioral Reviews*, 42, p.148–156. Available at: http://www.sciencedirect.com/science/article/pii/S014976341400030X.

Juul Jensen, J., Callaway, S.L., Lunner, T., Wendt, D., 2018. Measuring the impact of tinnitus on aided listening effort using pupillary response. *Trends Hear*, 22, p.1–17. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30205768 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6136111/.

Li, Z., Gu, R., Zeng, X., Zhong, W., Qi, M., et al, 2016. Attentional bias in patients with decompensated tinnitus: Prima facie evidence from event-related potentials. *Audiology and Neurotology*, 21(1), p.38–44. Available at: https://www.karger.com/DOI/10.1159/000441709.

Mahmoudian, S., Farhadi, M., Mohebbi, M., Alaeddini, F., Najafi-Koopaie, M., et al, 2015. Alterations in auditory change detection associated with tinnitus residual inhibition induced by auditory electrical stimulation. *Journal of the american academy of audiology*, 26(4), p.408-422. Available at: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01069727/full.

Mahmoudian, S., Farhadi, M., Najafi-Koopaie, M., Darestani-Farahani, E., Mohebbi, M., et al, 2013. Central auditory processing during chronic tinnitus as indexed by topographical maps of the mismatch negativity obtained with the multi-feature paradigm. *Brain Research*, 1527, p.161–173. Available at: http://www.sciencedirect.com/science/article/pii/S0006899313008706.

Martin, B.A., Shafer, V., Wroblewski, M., An, L.J., 2012. Functional significance of the acoustic change complex, mismatch negativity, and P3a for vowel processing in native-English listeners and late learners of English. *The Journal of the Acoustical Society of America*, 132(3), p.1935–1935. Available at: https://doi.org/10.1121/1.4755113 [Accessed March 11, 2019].

McKerrow, W.S., Schreiner, C.E., Merzenich, M.M., Snyder, R.L., Toner, J.G., 1991. Tinnitus suppression by cochlear implants. *Annals of Otology, Rhinology & Laryngology*, 100(7), p.552–558.

McNicol, D., 2004. *A primer of signal detection theory*, Mahwah, New Jersey: Lawrence Erlbaum.

Mehlum, D., Grasel, G., Fankhauser, C., 1984. Prospective crossover evaluation of four methods of clinical management of tinnitus. *Otolaryngology—Head and Neck Surgery*, 92(4), p.448–453.

Mohebbi, M., Daneshi, A., Asadpour, A., Mohsen, S., Farhadi, M., et al, 2019. The potential role of auditory prediction error in decompensated tinnitus: An auditory mismatch negativity study. *Brain Behav*, 9(4), p.e01242–e01242. Available at: https://pubmed.ncbi.nlm.nih.gov/30895749.

Moore, B.C.J., 2012. *An introduction to the psychology of hearing, 6th Ed.*, Leiden, The Netherlands: Brill.

Näätänen, R., Petersen, B., Torppa, R., Lonka, E., Vuust, P., 2017. The MMN as a viable and objective marker of auditory development in CI users. *Hearing Research*, 353, p.57–75. Available at: http://www.sciencedirect.com/science/article/pii/S0378595516306074.

Neff, P., Michels, J., Meyer, M., Schecklmann, M., Langguth, B., et al, 2017. 10 Hz Amplitude modulated sounds induce short-term tinnitus suppression. *Frontiers in Aging Neuroscience*, 9, p.130. Available at: https://www.frontiersin.org/article/10.3389/fnagi.2017.00130.

Neff, P., Zielonka, L., Meyer, M., Langguth, B., Schecklmann, M., et al, 2019. Comparison of amplitude modulated sounds and pure tones at the tinnitus frequency: Residual tinnitus suppression and stimulus evaluation. *Trends in Hearing*, 23, p.2331216519833841. Available at: https://doi.org/10.1177/2331216519833841 [Accessed March 18, 2019].

Noreña, A.J., 2012. Stimulating the auditory system to treat tinnitus: From alleviating the symptoms to addressing the causes. In J. J. Eggermont, F. G. Zeng, A. N. Popper, & R. R. Fay, eds. *Tinnitus*. Springer Handbook of Auditory Research. New York: Springer, pp. 217–253.

Paul, B.T., Bruce, I.C., Bosnyak, D.J., Thompson, D.C., Roberts, L.E., 2014. Modulation of electrocortical brain activity by attention in individuals with and without tinnitus. *Neural plasticity*, 2014.

Pierzycki, R.H., Edmondson-Jones, M., Dawes, P., Munro, K.J., Moore, D.R., et al, 2016. Tinnitus and sleep difficulties after cochlear implantation. *Ear and hearing*, 37(6), p.e402–e408.

Quaranta, N., Fernandez-Vega, S., D'Elia, C., Filipo, R., Quaranta, A., 2008. The effect of unilateral multichannel cochlear implant on bilaterally perceived tinnitus. *Acta Oto-Laryngologica*, 128(2), p.159–163. Available at: https://doi.org/10.1080/00016480701387173.

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

Rao, R.P.N., Ballard, D.H., 1999. Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. *Nature neuroscience*, 2(1), p.79.

Reavis, K.M., Rothholtz, V.S., Tang, Q., Carroll, J.A., Djalilian, H., et al, 2012. Temporary suppression of tinnitus by modulated sounds. *Journal of the Association for Research in Otolaryngology*, 13(4), p.561–571. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22526737.

Rimmele, J.M., Morillon, B., Poeppel, D., Arnal, L.H., 2018. Proactive sensing of periodic and aperiodic auditory patterns. *Trends in Cognitive Sciences*, 22(10), p.870–882. Available at: http://www.sciencedirect.com/science/article/pii/S136466131830192X.

Ruckenstein, M.J., Hedgepeth, C., Rafter, K.O., Montes, M.L., Bigelow, D.C., 2001. Tinnitus suppression in patients with cochlear implants. *Otology & Neurotology*, 22(2). Available at: https://journals.lww.com/otology-neurotology/Fulltext/2001/03000/Tinnitus_Suppression_in_Patients_With_Cochlear.14.aspx.

Sameiro-Barbosa, C.M., Geiser, E., 2016. Sensory entrainment mechanisms in auditory perception: Neural synchronization cortico-striatal activation. *Frontiers in Neuroscience*, 10, p.361. Available at: https://www.frontiersin.org/article/10.3389/fnins.2016.00361.

dos Santos Filha, V.A.V., Matas, C.G., 2010. Late Auditory evoked potentials in individuals with tinnitus. *Brazilian Journal of Otorhinolaryngology*, 76(2), p.263–270. Available at: http://www.sciencedirect.com/science/article/pii/S1808869415306406.

Sedley, W., Alter, K., Gander, P.E., Berger, J., Griffiths, T.D., 2019. Exposing Pathological Sensory Predictions in Tinnitus Using Auditory Intensity Deviant Evoked Responses. *J. Neurosci.*, 39(50), p.10096. Available at: http://www.jneurosci.org/content/39/50/10096.abstract.

Sedley, W., Friston, K.J., Gander, P.E., Kumar, S., Griffiths, T.D., 2016. An integrative tinnitus model based on sensory precision. *Trends in Neurosciences*, 39(12), p.799–812. Available at: http://www.sciencedirect.com/science/article/pii/S0166223616301412.

Sendesen, E., Erbil, N., Türkyılmaz, M.D., 2021. The mismatch negativity responses of individuals with tinnitus with normal extended high-frequency hearing—is it possible to use mismatch negativity in the evaluation of tinnitus? *European Archives of Oto-Rhino-Laryngology*. Available at: https://doi.org/10.1007/s00405-021-07097-6.

Souliere, C.R.J., Kileny, P.R., Zwolan, T.A., Kemink, J.L., 1992. Tinnitus suppression following cochlear implantation: A multifactorial investigation. *Archives of Otolaryngology–Head & Neck Surgery*, 118(12), p.1291–1297. Available at: http://dx.doi.org/10.1001/archotol.1992.01880120017004.

Stefanics, G., Kremláček, J., Czigler, I., 2014. Visual mismatch negativity: a predictive coding view. *Frontiers in Human Neuroscience*, 8, p.666. Available at: https://www.frontiersin.org/article/10.3389/fnhum.2014.00666.

Tyler, R., Stocking, C., Secor, C., Slattery William, H., 2014. Amplitude modulated S-tones can be superior to noise for tinnitus reduction. *American Journal of Audiology*, 23(3), p.303–

308. Available at: https://doi.org/10.1044/2014_AJA-14-0009 [Accessed March 19, 2019].

Tyler, R.S., Owen, R.L., Bridges, J., Gander, P.E., Perreau, A., et al, 2018. Tinnitus suppression in cochlear implant patients using a sound therapy app. *Am J Audiol*, 27(3), p.316–323. Available at: http://europepmc.org/abstract/MED/30105356 https://doi.org/10.1044/2018_AJA-17-0105.

Van de Heyning, P., Vermeire, K., Diebl, M., Nopp, P., Anderson, I., et al, 2008. Incapacitating unilateral tinnitus in single-sided deafness treated by cochlear implantation. *Annals of Otology, Rhinology & Laryngology*, 117(9), p.645–652. Available at: https://doi.org/10.1177/000348940811700903 [Accessed October 23, 2018].

Yang, H., Xiong, H., Yu, R., Wang, C., Zheng, Y., et al, 2013. The characteristic and changes of the event-related potentials (ERP) and brain topographic maps before and after treatment with rTMS in subjective tinnitus patients. *PLOS ONE*, 8(8), p.e70831. Available at: https://doi.org/10.1371/journal.pone.0070831.

Yau, S.H., Bardy, F., Sowman, P.F., Brock, J., 2017. The magnetic acoustic change complex and mismatch field: a comparison of neurophysiological measures of auditory discrimination.

Yonehara, E., Mezzalira, R., Porto, P.R.C., Bianchini, W.A., Calonga, L., et al, 2006. Can cochlear implants decrease tinnitus? *International Tinnitus Journal*, 12(2), p.172.