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**Protocol**

# Protocol for a triple-blinded randomised sham-controlled pilot trial of multi-session transcranial direct current stimulation for tinnitus alleviation: the WHITBY study

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## ABSTRACT

**Background:** Tinnitus-the perception of sound in the absence of an external source is a common condition, highly impactful condition for which treatment options are limited. Based on the limited available evidence, transcranial direct current stimulation (tDCS) has shown promise for suppressing, or reducing, tinnitus salience. Unlike existing tinnitus interventions, which aim to help patients to better cope with tinnitus, tDCS has the potential to address the tinnitus percept itself.
**Methods:** Protocol for a triple-blinded randomised sham-controlled pilot trial, aimed at informing a future clinical trial for tDCS-based tinnitus treatment. 40 participants, will be randomised to receive ten sessions of either active or sham tDCS over a 2-week period. Proof of concept will be measured by protocol compliance, attrition, and tolerance. Tinnitus loudness, symptom severity, and other relevant outcomes will be measured using self-report measures and electroencephalography.
**Conclusions:** The study's primary aims are to assess the tolerability of multiple tDCS treatments in tinnitus patients by way of treatment adherence and satisfaction, devise an evidence-based protocol and derive a minimum sample size for a future controlled efficacy trial. Secondary aims are to compare different subjective measures of tinnitus, as well as electrophysiological measures of underlying brain activity and to explore the feasibility of individualised head and current flow modelling for the development of future individualised treatment regimens using structural magnetic resonance imaging data acquired in a subset of our patients. The results will yield new insights into tinnitus mechanism and treatment-related changes.
**Trial Registration:** This study is registered at ClinicalTrials.gov (NCTNCT06628414).

**Keywords:** Tinnitus, tDCS, EEG, Randomised controlled pilot study

## INTRODUCTION

Tinnitus is the perception of sound in the absence of an external sound stimulus. It affects around 14.4% of the global adult population and is often co-morbid with hearing loss.[1,2] The impact of tinnitus on an individual ranges from minimal to extremely distressing and can include impaired social and cognitive functioning, and reduced quality of life.[3] Current treatment options provide coping strategies, rather than addressing the tinnitus percept itself. The exact aetiology of tinnitus is unknown, however maladaptive plasticity due to sensorineural hearing loss is thought to play an important role.[4] Neuro- and electrophysiological studies have pointed to changes in spontaneous oscillatory activity within the central auditory system, including the auditory

cortex, and suggested a role of the frontal cortex through dysfunctional top-down modulation.[5-12]

tDCS is a non-invasive neuromodulation technique in which a weak electric current is delivered to the brain via electrodes positioned on the scalp surface, depolarising or hyperpolarising neurons in targeted regions of cortex. It has previously been used in the treatment of depression and anxiety, rehabilitation after stroke, and to enhance neurocognitive function in athletes and video gamers.[13-16] In tinnitus, neuromodulation therapies would be desired to afford a permanent, or long-term, reduction in tinnitus salience by driving the neuroplastic changes necessary to restore normal levels of spontaneous cortical activity. To the degree to which tinnitus distress is driven by tinnitus salience, this should also alleviate the psychological and life impact of tinnitus (tinnitus severity). Existing research has shown that tDCS is generally well-tolerated by people with tinnitus, usually resulting in no, or only mild adverse effects, including temporary fatigue or irritation of the skin underneath the electrodes.[13,17,18]

There is much interest in neuromodulation therapies for tinnitus and investigating the effectiveness of neuromodulation for tinnitus is one of the research recommendations in the UK National Institute for Health and Care Excellence tinnitus guidelines.[19] The existing evidence is limited to quasi-experimental and underpowered studies using widely varying stimulation parameters and outcome measures across studies, which yielded conclusions that were overlapping in general but inconsistent in detail. Recent systematic reviews reported improvements in tinnitus symptom severity following tDCS, as compared to sham, but noted that the available data comes from a limited number of studies, with varying stimulation parameters, suggesting that further research efforts, particularly in high-quality, controlled studies, could progress tDCS-based tinnitus treatment along the translational pipeline towards clinical application.[20,21] Specifically, a network meta-analysis has concluded that repeated administration of tDCS to dorsolateral prefrontal cortex (DLPFC) would likely be the most effective at reducing tinnitus salience and comorbid symptoms.[18] This is supported by a recent investigation of acute changes in brain activity during single applications of tDCS to DLPFC, which showed significant modulation in spontaneous oscillatory brain activity thought to be associated with tinnitus percept.[22]

Previous work has also established that single application of tDCS to DLPFC generally well-tolerated in otherwise healthy adult volunteers.[16] Current projects is a triple-blinded randomised sham-controlled pilot trial of repeated tDCS application to DLPFC for treatment of chronic tinnitus. Its primary aims to assess tolerability of multiple tDCS treatments in tinnitus patients by way of treatment adherence and satisfaction, devise an evidence-based protocol and derive a minimum sample size for a future controlled efficacy trial by collecting data on tinnitus symptom severity and other core outcome measures, identified through an international consensus exercise. This study further aims to compare different subjective measures of tinnitus (severity, loudness), as well as electrophysiological measures of underlying brain activity and to explore feasibility of individualized head and current flow modelling for the development of future individualized treatment regimens using structural magnetic resonance imaging data acquired in a subset of our patients.

## METHODS

### *Participants*

Forty participants, aged 18 years or over, with subjective idiopathic tinnitus will be recruited to take part in this triple-blinded randomised sham-controlled pilot trial. With the exception of MRI scanning, all primary data collection will take place in the Hearing Sciences department, University of Nottingham. Participants will be recruited from the National Institute for Health and Care Research (NIHR) Nottingham Biomedical Research centre (BRC) participant database, Tinnitus UK, and the general public. Information about the study will be sent via social media to people following the NIHR Nottingham BRC and Tinnitus UK accounts. Interested people can choose to enrol by contacting the investigators via email or telephone. Structural (T1-weighted) MRI scans will be acquired from a subset of 10 participants using the 3T wide-bore Phillips Ingenia scanner at the University of Nottingham's Sir Peter Mansfield Imaging Centre. Follow-up data will be collected 3 months after the final tDCS session online survey software.

Participants must be aged 18 or over, have chronic (>6 months) subjective idiopathic tinnitus, have sufficient understanding of English to be able to provide informed consent, and be able to safe undergo tDCS. Volunteers will be excluded from participating if they fail to meet these criteria or if they have taken part in research involving invasive procedures or an inconvenience allowance within 3 months prior to their participation. The subset of participants undergoing MRI scanning will be required to additionally meet the safety criteria for MRI scanning. Participants will receive a one-time set payment towards travel expenses and inconvenience allowance after completion of their final visit.

### *Intervention and comparator*

We will use a NeuroConn DC Stimulator Plus to administer tDCS via two 35-cm$^2$ rubber electrodes covered in saline-soaked sponges. The anode electrode will be positioned over EEG 10-20 coordinate F4, and the cathode over F3. A current of 2 mA will be applied for a total duration of 20 minutes per session. The sham condition will be identical to the treatment condition, except that stimulation will be ramped off after 30 seconds. In each condition, there will be a ramp-up and ramp-down of 10 seconds. All tDCS sessions will be conducted in Hearing Sciences department, University of Nottingham.

### *Randomisation and blinding*

Participants will be randomly allocated to receive either true tDCS or sham stimulation. Randomisation will be performed using computerised random sequence generation by a research assistant at NIHR Nottingham BRC who is not a member of the study team. Using the device's built-in "study mode", the parameters will be pre-programmed into stimulator, ensuring the participants and the experimenters administering the intervention and performing the outcome assessments are blinded. The study statistician will also be blinded to group allocation.

### *Outcomes and measures*

The primary outcome is proof of concept as measured by protocol compliance and attrition. Secondary outcomes are 1) tinnitus symptom severity as measured using the tinnitus functional index (TFI), 2) tinnitus loudness, measured using a 10-point visual analogue scale (VAS) as well as audiometric loudness matching, 3) depression and anxiety, measured using the patient health questionnaire (PHQ-9) and generalised anxiety disorder assessment (GAD-7), respectively, 4) treatment satisfaction, measured using the short assessment of patient satisfaction (SAPS) questionnaire, 5) adverse effects and effectiveness of blinding (treatment vs sham), measured using a self-devised in-house adverse effects questionnaire, and 6) resting-state brain activity, measured with EEG.[23-26]

These instruments cover the entirety of the core outcome domain set (CODS) for trials of electrical stimulation interventions for tinnitus.[27] All outcomes in this CODS will be measured by the TFI, with the exception of treatment satisfaction which will be measured by the SAPS, and adverse effects which will be measured using a self-devised adverse effects questionnaire.

## DISCUSSION

### *Procedure*

Figure 1 provides a schematic overview of the study timeline. Participants will attend 10 appointments over a 2-week period, with a 2-day gap between the fifth and sixth appointments. At the first appointment, eligibility will be confirmed and informed consent obtained. Hearing ability will be measured via pure-tone audiometry, conducted in accordance with the British Society for Audiology (BSA) guidelines, using a doubled-walled sound-insulating booth (International Acoustics Company, IAC) equipped with clinically certified and calibrated audiometric equipment (InterAcoustics, AC40).[28] Tinnitus symptom severity will be assessed using the TFI.Tinnitus loudness will be assessed using both the VAS and loudness matching. The loudness matching will be performed following an existing procedure, using the same audiometric equipment and soundproof room as the audiometric assessment.[29] Spontaneous oscillatory brain activity and coherence, as well as electrophysiological responses to sounds of different frequencies across the normal audiometric range will be measured using a 32-channel EEG system (Brain Products UK) in a double-walled sound-insulating and electrically shielded booth (IAC). Sound stimuli will be delivered via ER-2 insert earphones (Etymotics) and EEG responses will be recorded through Ag-AgCl ring electrodes mounted in an elasticated EEG cap (Easycap). Following this, participants will receive the first stimulation session (either genuine tDCS or sham, depending on random participant assignment). At the end of the appointment, participants will be queried for any adverse effects and for the effectiveness of blinding with a purpose-made questionnaire.

At the second through ninth appointments, participants will again undergo tDCS (or sham) stimulation. Following this, tinnitus loudness will be assessed using the VAS only, and participants will be queried for adverse effects and effectiveness of blinding. At the tenth and final appointment, a final tDCS (or sham) session will be delivered, following which all tinnitus-related outcomes that were assessed at the first appointment (VAS loudness assessment and audiometric loudness matching, TFI, PHQ-9, GAD-7, adverse effects and blinding effectiveness questionnaire, EEG) will be reassessed. In addition, participants will be asked to complete the SAPS questionnaire to probe their overall satisfaction with the treatment (or sham) process. Three months after the tenth appointment, an online follow-up data collection will be performed online, including the VAS tinnitus loudness assessment, TFI, PHQ-9, GAD-7 and SAPS. For a summary of the outcome measures and timing of administration see Table 1.

**Table 1: Schedule of outcomes measures.**

| Outcomes | Baseline | Appointments 2-9 | Appointment 10 | 3-month follow-up |
|---|---|---|---|---|
| **TFI** | X | | X | X |
| **Loudness VAS** | X | X | X | X |
| **Loudness match** | X | | X | |
| **PHQ-9** | X | | X | X |
| **GAD-7** | X | | X | X |
| **SAPS** | | | X | X |
| **Adverse effects and blinding** | X | X | X | |
| **EEG** | X | | X | |

Structural T1-weighted MRIs will be obtained of the brains of a subset of 10 participants following their final tDCS session. This data will be used to explore the feasibility of creating individualised head models for EEG source modelling and tDCS current flow modelling.

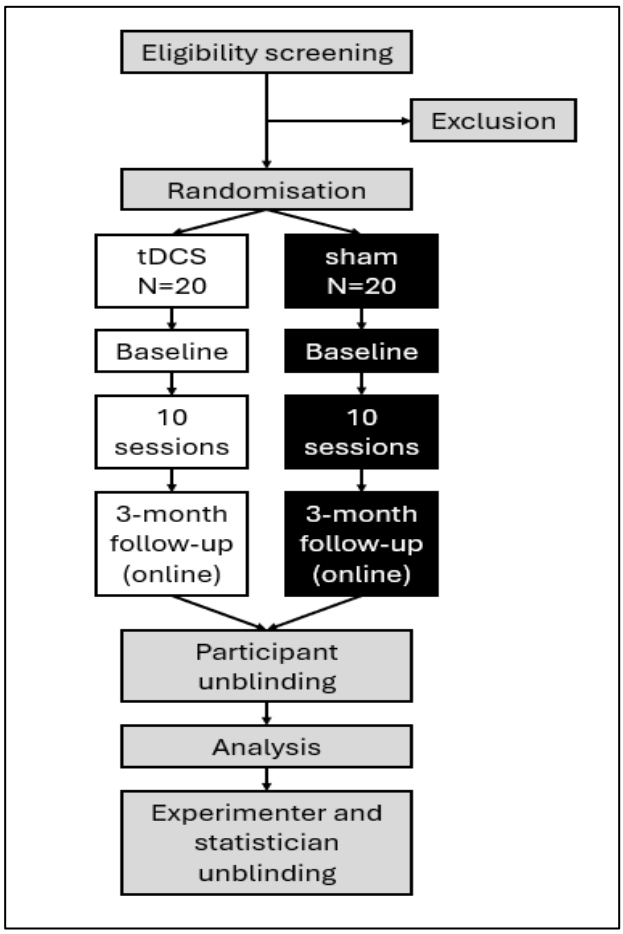


**Figure 1: Schematic overview of the study.**

***Planned analyses***

This study will be a pilot trial designed to provide proof of concept. As such, no power calculation was performed to determine sample size. Rather, a sample size of 40 was pragmatically decided upon based on previous studies of tDCS for tinnitus, and the availability of resources.

In line with previous feasibility studies of interventions for tinnitus, an adapted feasibility assessment will be used to determine whether a fully powered trial will be feasible.[30,31] This will be deemed feasible if 1) 80% of the recruitment target is achieved, (i.e. 32 participants provide informed consent), and 2) no more than 50% of in-person collected data is missing. The authors, considering the above criteria, will conclude that either a definitive RCT is not feasible, or a definitive RCT is feasible, possibly subject to optimisation of the experimental design.

Exploratory within and between-participant comparisons will be made using descriptive statistics Resting-state EEG data collected at baseline and after the final stimulation session will be compared in order to assess any physiological changes. EEG data will be processed in accordance with established analysis pipelines for resting state EEG, taking place in Matlab and/or other suitable analysis software.[32,33] This will help to devise a viable analysis pipeline for a full trial. Spontaneous activity at sensor level will be analysed using a generic (elliptical) head model to infer sources. We will assess to what degree each frequency band of oscillatory activity is measurable in the resting state and evoked data, and which analysis tool is best suited to separate the oscillatory activity. In the subset of 10 participants for whom T1 weighted anatomical images will be acquired, individualised realistic head models will be used to infer oscillatory source strengths within the prefrontal and auditory regions. Statistical processing will be conducted blind by the medical statistician of the hearing theme of the NIHR Nottingham BRC.

## CONCLUSION

This trial seeks to assess proof-of-concept towards a powered randomised sham-controlled trial to determine the efficacy of multiple sessions of tDCS to DLPFC in reducing tinnitus loudness and symptom severity. This will be an important step towards a viable device-based tinnitus treatment that is both safe and minimally invasive. Trial results will yield new insights into tinnitus mechanism and treatment-related changes.

The current literature on tDCS for tinnitus is affected by a risk of bias due to a lack of reporting in clinical trial registrations, protocols, and published study records. There is a large variability in the stimulation parameters (such as number of sessions, electrode montage, and current intensity) used in studies, making it difficult to pool data. When data from randomised controlled trials are pooled, the resulting meta-analyses tend to show an effect favouring tDCS over controls, but this effect is largely driven by one or two trials with large effect sizes. This trial seeks to provide a foundation for a future clinical trial of tDCS for tinnitus that will have a robust empirical basis that addresses the limitations of previous studies of tDCS for tinnitus. The selected outcome measures will also ensure a rich dataset to inform future trials. These include a recently established core outcome domain set for tinnitus trials involving electrical stimulation treatments, thus ensuring results will be meaningful to key stakeholders including people with tinnitus and the clinicians who care for them. The inclusion of MRI scanning on a subset of participants will allow for the feasibility of individualised head models for EEG source modelling and tDCS current flow modelling to be tested. Current modelling is an approach that has not previously been applied to neuromodulation in tinnitus. If feasible, this will be a powerful tool to standardise the dose of stimulation reaching target

regions of the brain by personalising the stimulation parameters used according to individual patient anatomy. This study will provide proof of concept for a future, powered randomised controlled trial of multiple tDCS sessions for tinnitus.

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