Official Title: Effect of combined acoustic ripples and transcranial direct current stimulation on the symptoms of new-onset subjective tinnitus

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Study Protocol – Version 2 – Updated 14/03/2025
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This protocol is a summary of procedures rather than a comprehensive guide. The activities in the protocol should only be undertaken by an appropriately trained and skilled individual. The study is intended to be performed solely by the named researchers above, but under certain circumstances another individual might need to be trained. If you are not independently competent in any procedure listed in the protocol, do not undertake it, and seek the advice of the Chief Investigator.

Recruitment

Recruitment advertising will be performed with online search engine sponsored links, such as Google Ads.

Ads should be targeted to a geographical region comprising Newcastle upon Tyne and the immediately surrounding area, so as to only make it visible to people likely to be able to make the journey the required number of times.

Ads should be paused whenever there will be any period of insufficient availability of researcher or research facilities to permit new volunteers to complete Visits 1-10 of the study protocol uninterrupted. This might include a period of annual leave, for instance. Any anticipated unavailability for 7 days or longer should prompt suspension of the study either side of this period, noting that this part of the protocol lasts one month.

Pre-screening

Potential participants will make contact via email or a web form. Both inboxes must be checked daily on weekdays during the time the study is running, and ideally over weekends also. They should receive an initial reply within one working day, and ideally within one calendar day. The reply should include a copy of Form 1 and Form 2.

Ensuing discussion will usually be by email, but potential participants should be offered the option of a telephone call instead or as well.

The researcher should answer questions any questions posed, and reply in a manner that satisfies all of the below criteria:

- Information provided is factually accurate
- Replies acknowledge uncertainties, and do not involve speculation
- No direct or inadvertent pressure to participate is applied
- The potential volunteer considers realistically whether they can manage the number of study visits, without it becoming problematic or burdensome for them
- That any information given does not constitute a medical opinion, and should not be taken in place of seeking medical help for their tinnitus if required

- The entire process of questions, answers and pre-screening should be time-efficient for the potential participant

Form 1 should be destroyed once they have either made a decision to participate, or once they have decided to participate, and their eligibility has been confirmed. Before destroying the form, volunteers indicating they would like their contact details stored for contact about future studies should have these details added to the research group's secure volunteers database.

Inclusion and exclusion criteria

These should be assessed primarily from the responses to Form 1, but also take into account information disclosed in written or verbal communication.

Inclusion criteria:

- The presence of tinnitus (persistent sound heard in one or both ears that is not coming from an external sound source or actual sounds being generated inside your body such as turbulent blood flow), which has persisted for at least 3 days, and began within the last 8 weeks. You do not need to be aware of the tinnitus all the time, but it must be persistent in the sense that is can always hear it if you listen out for it, and there is not enough other sounds around to mask it.
- Age 18 or over
- The ability to make and communicate an informed choice about whether to take part in the study
- The ability to sit still and comfortably in a comfortable chair for around 1 hour at a time.

Exclusion criteria:

- Tinnitus due to a physical sound source in the body, such as turbulent blood flow or muscle contractions in the middle ear.
- Presence of tinnitus over a period of 8 weeks
- Severe or profound hearing loss at high frequencies in the tinnitus ear(s), such that you could not properly hear the sounds used in the study
- Any implanted electronic device, such as a pacemaker, cochlear implant, bone-anchored hearing aid, nerve stimulator, deep brain stimulator or spinal cord stimulator
- Any areas of broken skin on the parts of the scalp where tDCS is applied
- Ménière's disease
- Any abnormality of brain structure (e.g. stroke, tumour), or other neurological disorder (e.g. multiple sclerosis or epilepsy)
- The ongoing use of sedating medications, or certain other nerve- or brain-acting medications
- A current mental health condition of sufficient severity to prevent certain activities of everyday life

In addition to these criteria, the researcher might have other reasons to suspect that participation is either contraindicated, or might be unsuitable. In such cases, the researcher should discuss these concerns with the potential participant and/or a senior member of the research team. Participation should only proceed if all those involved in these discussions agree it should.

Scheduling appointments

After passing pre-screening, and wanting to proceed in principle, potential participants should be booked in as soon as feasibly possible for their in-person visits. Visits can be booked during weekdays, evenings and weekends, at the researcher's discretion as per their own availability. In most cases, just the first visit will be booked at this stage, as the potential participant will not yet have consented to participate in the study. However, for volunteers whose participation would be contingent on knowing a longer schedule (or even the full schedule) of visits from the outset, the researcher can hold future appointments on a provisional basis for that individual.

Visit 1 (7-60 days following tinnitus onset)
Attendees are likely to want to discuss their tinnitus, given that this is a new issue for them, and may be associated with questions, uncertainty and in some cases distress. The researcher should make it clear that they can take a role in providing general information about tinnitus (of the sort that might, for instance, be found on a public information website or telephone helpline), but cannot provide any kind of medical opinion, diagnosis or instruction. They should be encouraged to seek these through usual medical channels, usually their GP initially, for any clinical input required. The researcher should provide what information is relevant, requested, and they know to be accurate, as long as it relates to tinnitus 'in general', rather than commenting on the individual's case.
The following procedures should take place, in the order listed. Participants should be encouraged to take comfort breaks, where needed, between procedures:

1) Informed consent discussion and consent form (Form 3) signing. Hard copy of participant information sheet (Form 2) given. Visit ends here if consent is not provided, or volunteer is deemed to be ineligible.
2) Generation of random participant ID code, and recording on link anonymisation form (Form 4)
3) Short narrative case history from participant. Researcher to confirm the history is consistent with subjective tinnitus.
4) Completion of volunteer questionnaire (Form 5)
5) Completion of additional standardised questionnaires: Tinnitus Handicap Inventory (THI), Tinnitus Functional Index (TFI), Hospital Anxiety and Depression Scale (HADS), Hyperacusis Questionnaire (HQ), Inventory of Hyperacusis Symptoms (IHS)
6) Pure tone audiogram (PTA)
7) Uncomfortable loudness levels (ULL). Stimuli should be presented at ascending intensity, starting at a quiet level not exceeding 30 dB SPL. Increments should be no more than 5 dB.

Participants should be instructed to indicate the first stimulus that induces and noticeable discomfort, rather than this being a test of the degree of discomfort they can endure.

8) Tinnitus frequency and loudness matching, with Matlab Script 'EAC_Matching'
9) Electroencephalography (EEG) recording. This should use the Biosemi ActiveTwo system, and be conducted in a dimply-lit, monitored, shielded, soundproof room. The 64 or 128 channel headcap can be used. Headshape and electrode position spatial localisation can be performed, optionally, with the Polhemus Patriot device. Signagel electrode gel should be used, applied sparingly with a blunt plastic syringe, without attempt to perform skin abrasion (which is unnecessary with this EEG system). Participants should be instructed to notify the researcher if any discomfort at all is noted during gel instillation. 10 minutes of EEG in total is recorded, with a mixture of eyes-open and eyes-closed conditions, using the Matlab script 'EAC_EEG'.
10) Randomisation should be run, once, using the Matlab Script 'EAC_Randomisation'. This will save the random group assignment in a way not inadvertently visible to the researcher or participant, but that will determine the stimulation parameters used throughout the study.
11) Generation of intervention sounds. This is performed using the script 'EAC_Sound_Generation'. The script customises the sounds based on the PTA result, tinnitus frequency match and group randomisation (which is loaded automatically). The participant then listens to the sound and customises their preferred volume level using the script 'EAC_Sound_Volume_Check'. The researcher should not listen to the sound, in case they hear cues that might allow them to determine whether the participant is receiving active or placebo intervention.
12) Booking of subsequent visit(s). As per the participant's preference, anywhere between one visit and all remaining visits can be booked at this stage. Visits 2-9 should be arranged with no two visits on non-consecutive days, and spaced out as evenly as can be managed over a period of 21 to 30 days. Visit 10 should be arranged exactly 7 days after Visit 9.
13) Instructions about home sound listening. The volunteer should be advised to listen to their personalised intervention sound for up to 60 minutes per day, where safely possible, and according to the '60/60' rule. They should be provided with Form 6 (appointment and listening diary), have any appointments recorded, and instructed how to record their daily sound listening.

Visits 2-9 (over 21 to 30 days, with no appointments on consecutive days, as evenly spaced as possible, and with Visit 9 no more than 90 days from tinnitus onset)

1) Enquire as to any issues with study since last visit, or changes in health
2) Inspect scalp and other skin stimulation sites
3) Combined tDCS and intervention sound session. This should be run with the Matlab script 'EAC_Stimulation'. This will load the participant's saved data, including randomisation group. Ensure the Digitimer DS5 constant current stimulator and Fireface UC external sound card are switched on. Ensure that the Digitimer DS5 has the display screen covered, to avoid inadvertent unblinding. Run the script, and apply headphones and stimulation electrode sponges as

prompted. The script will run two stimulation sessions, each at 2 mA for 20 minutes. The following indicated positions are based on the international 10-20 system. If the researcher is not suitably familiar with these and trained to practice this technique independently then they should not run this stage of the study. First session: anode C3-T5, and cathode either P4-P6 or right upper arm. Second session: Anode Fz, Cathode left cheek. Participants should be instructed to report if experiencing discomfort or other problems, and should be continuously monitored through the audiovisual links.

4) Inspect scalp and other skin stimulation sites after removal. Electrodes should be cleaned, disinfected and dried as per manufacturer's instructions.
5) Verbal confirmation with volunteer of suitability and desire to continue with study.
6) Booking of subsequent visit(s). As per the participant's preference, anywhere between one visit and all remaining visits can be booked at this stage. Visits 2-9 should be arranged with no two visits on non-consecutive days, and spaced out as evenly as can be managed over a period of 21 to 30 days. Visit 10 should be arranged exactly 7 days after Visit 9.

Visit 10 (7 days after Visit 9)

1) Completion of volunteer questionnaire (Form 5)
2) Completion of additional standardised questionnaires: Tinnitus Handicap Inventory (THI), Tinnitus Functional Index (TFI), Hospital Anxiety and Depression Scale (HADS), Hyperacusis Questionnaire (HQ), Inventory of Hyperacusis Symptoms (IHS)
3) Pure tone audiogram (PTA)
4) Uncomfortable loudness levels (ULL). Stimuli should be presented at ascending intensity, starting at a quiet level not exceeding 30 dB SPL. Increments should be no more than 5 dB. Participants should be instructed to indicate the first stimulus that induces and noticeable discomfort, rather than this being a test of the degree of discomfort they can endure.
5) Tinnitus frequency and loudness matching, with Matlab Script 'EAC_Matching', which also performs minimum masking level (MML) testing
6) Electroencephalography (EEG) recording. This should use the Biosemi ActiveTwo system, and be conducted in a dimply-lit, monitored, shielded, soundproof room. The 64 or 128 channel headcap can be used. Headshape and electrode position spatial localisation can be performed, optionally, with the Polhemus Patriot device. Signagel electrode gel should be used, applied sparingly with a blunt plastic syringe, without attempt to perform skin abrasion (which is unnecessary with this EEG system). Participants should be instructed to notify the researcher if any discomfort at all is noted during gel instillation. 10 minutes of EEG in total is recorded, with a mixture of eyes-open and eyes-closed conditions, using the Matlab script 'EAC_EEG'.
7) Stage 1 debriefing (Form 7) provided, and discussed with participant, including reminder about further contact 6 months after onset of tinnitus.

In between visits

Inboxes should be monitored regularly, as for recruitment purposes. Volunteers with questions should receive responses in the same timeframe. If a period of leave or sickness occurs or is anticipated, responsibility for responding to contact must be formally delegated to another member of the research team, and will default to the Chief Investigator if no alternative individual is available.

Six-month contact

The researcher must record in a calendar with reminders the dates on which they must contact participants to complete six-month questionnaires. If automated emails are used instead, the researcher must still verify that these have been sent. The email contact must follow a standardised text, identically worded to all participants, and attach a copy of the questionnaire (Form 5), or a link to the same questions hosted securely online. If a response is not received after 48 hours, the researcher may email again, and if a response has not been received after a further 48 hours then they may phone the participant between the hours of 8am and 8pm. Once the questionnaire has been completed, the researcher should thank the participant, and send a digital copy of the Stage 2 debrief form (Form 8). The appropriate version (8a or 8p) should be sent, based on whether the participant was in the Active or Placebo group. This is the first stage at which the researcher may see which group the participant was in. This can be displayed by running the Matlab Script 'EAC_Group_Reveal'.

If the participant was in the Placebo group, they should be sent their Active intervention sounds, which can be generated by running the script 'EAC_Active_Sound_Generation_Post_Placebo'. This will usually be sent with Newcastle University's File Drop Off service.

Participants should be reminded they can listen to their active intervention in their own time in future, if they wish.

Participants should be offered a final chance to ask questions of the research team by email or telephone at this stage.

Participant reimbursement

Participants should be reimbursed for travel expenses and participation time after each session. Participation time reimbursement is fixed at £20 per session. Travel expenses require a receipt, or details of journey start and end postcode for car mileage. Monetary reimbursements must follow University procedures, and require the requisite forms completing. Participants should be informed of the inherent delay, and asked to ensure they have their bank details available. For time reimbursement, participants may choose the option of Amazon vouchers instead of a monetary payment.

Data storage

All computer-generated data (including tinnitus matching and MML, and EEG data) are automatically stored on the secure group server, which is a safe storage location. These are non-identifiable.

Hard copy consent forms and link anonymisation forms should be stored in secure physical filing facilities within the laboratory's offices.
Hard-copy or emailed questionnaires should be turned into digital copies and stored on the secure group server, in non-identifiable form (containing only link-anonymisation ID).
Physical link anonymisation forms should be destroyed after the final debrief for that participant.